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Ref. 4: Briggs, et al., *Chem. Comm.* 749 (1970)

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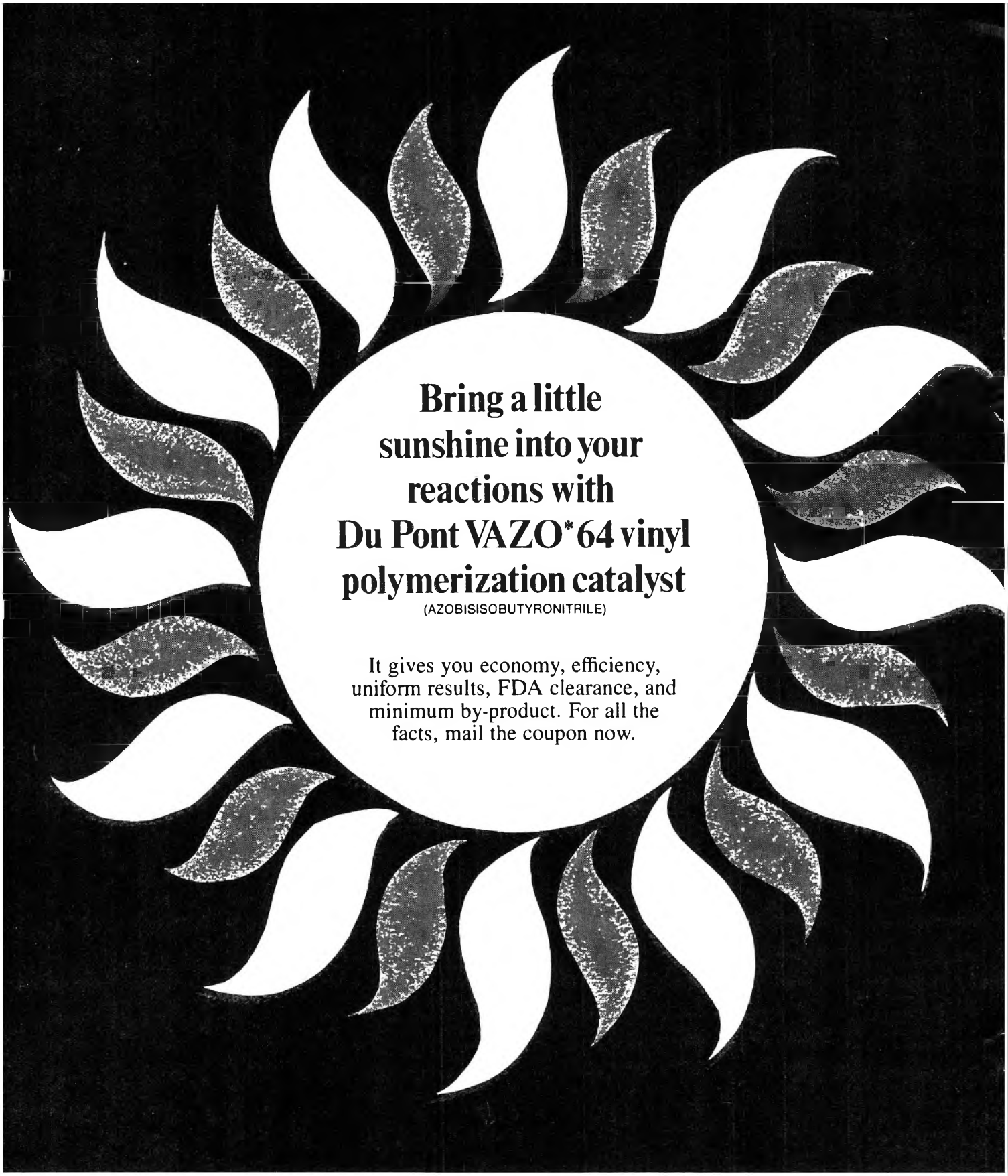

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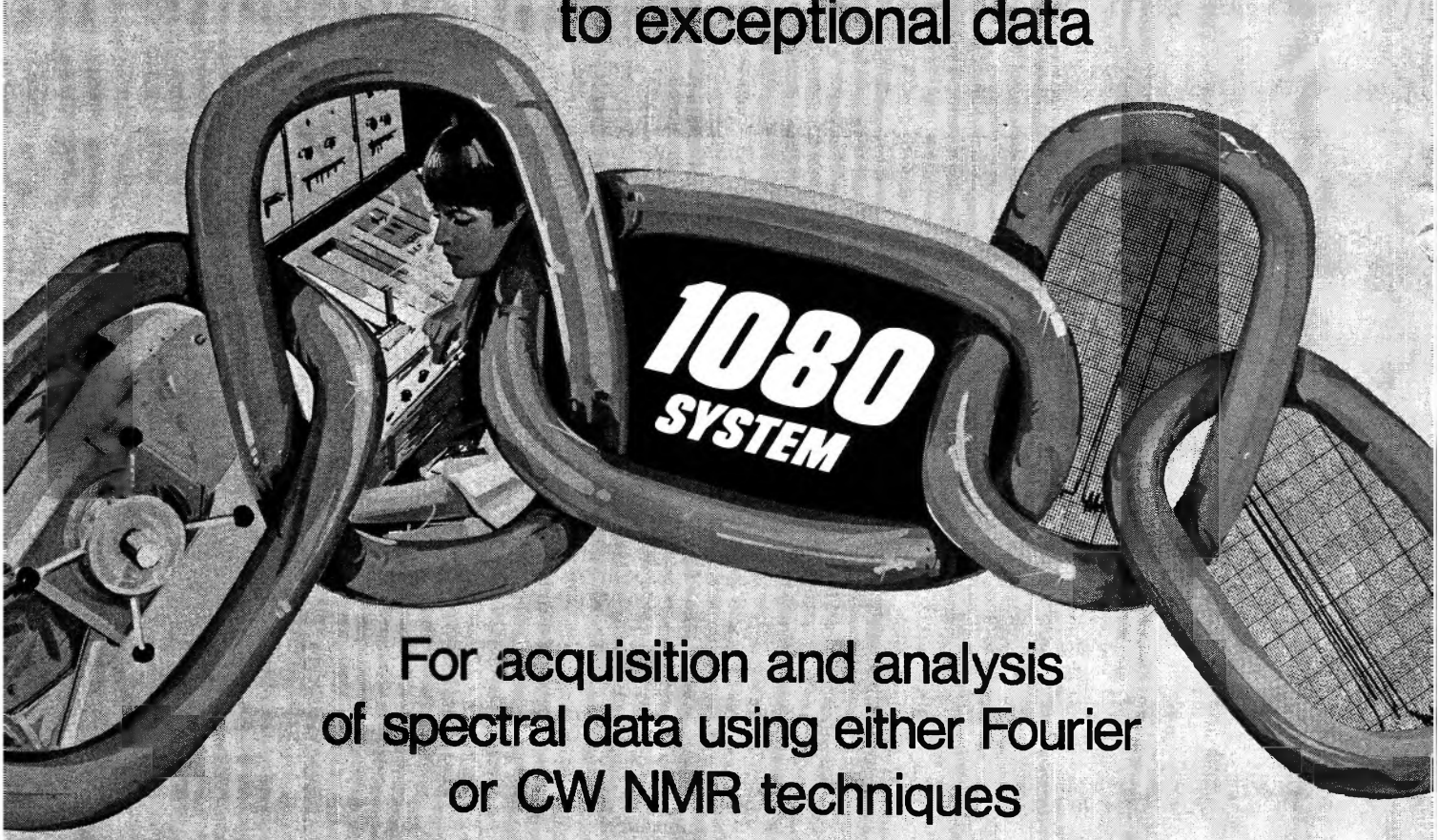

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NOTICE

In this and forthcoming issues of this journal, some papers will appear that are organized in two parts—an "initial core" section, Part A, which consists of a concise account (1–2 pages) of the principal findings and conclusions, and a Part B which contains supporting data, experimental details, and, in some instances, supplementary discussion and interpretation. These "two-part" papers have been prepared by authors at the invitation of the Editors as part of a program by the ACS Publication Office to explore improved communication of research findings.

The purpose of the "core" section is to convey the essentials of a paper in concise form, permitting a journal reader to use his time optimally. A complete account of a major investigation can rarely be compressed to 1–2 printed pages. It is usually possible, however, to present in this space the core of the work in a form that can be readily assimilated, and that will in all likelihood be read more widely than the full paper. This division of papers into two parts would also lend itself to publication of the journal in two editions if economics or reader demand so indicate. We welcome comments on these "two-part" papers both from the viewpoint of readers and authors. Authors interested in preparing a paper in this form are cordially invited to contact Dr. James A. Moore, Department of Chemistry, University of Delaware, Newark, Del. 19711, for further information.

FREDERICK D. GREENE, EDITOR

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Optical Rotatory Dispersion Studies. CXVIII.[1] Aliphatic *C*-Nitroso Compounds[2]

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Methods for synthesizing the unique blue *C*-nitroso chromophore attached to secondary aliphatic carbon atoms have been improved and the optical properties of this group in important steric environments (steroids and terpenoids) have been measured. The isolation of the pure blue monomers can be achieved in a few cases only, but measurement of circular dichroism spectra of the total reaction mixture gives absorption bands with value in diagnosing the orientation of the chromophore, since none of the other components absorbs in the visible region.

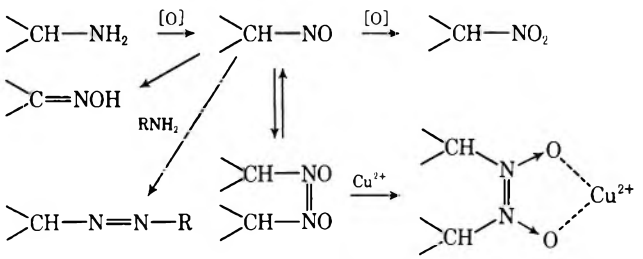
Part A

Monomeric aliphatic *C*-nitroso compounds are virtually unique in organic chemistry because of their deep color which results from absorption at 660–700 mμ.[4] Because of their ease of detection, nitroso derivatives were widely studied prior to 1920[5] but principally as tertiary *C*-nitroso compounds, which are incapable of tautomerization. Primary and secondary representatives have received only scant study because of difficulties in handling these very reactive (normally only transient) species.

The nitroso chromophore can be derived from aliphatic and alicyclic oximes,[4-6] amines,[4,7] and olefins[4,8] (by reaction with NOCl). Since none of these groups is readily amenable to optical investigations, whereas the long wavelength absorption of the nitroso function is readily distinguishable and may be measured in the presence of any other organic chromophore, we decided to examine the feasibility of employing *C*-nitroso compounds as "chromophoric derivatives."[9]

Nonhalogenated *C*-Nitroso Derivatives.—Those *C*-nitroso derivatives attached to a carbon atom carrying no further heteroatoms were synthesized by the sequence ketone → oxime → amine → nitroso. Following standard methods, the oxime reductions were carried out using sodium in alcohol to yield equatorial amines and by hydrogenation to yield axial amines.[10-12]

Nitroso monomers can be generated by oxidation of a primary amine,[7] but great care must be exercised, since, as summarized in the following scheme, overoxidation yields nitro derivatives, dimerization is facile, and tautomerization to oximes also can occur when the carbon carries a hydrogen atom[13] and the presence of



inorganic ions such as Cu^{2+} appears to lead to colored chelated forms of the nitroso dimer.

Results

Even with the improved methods of synthesis, it proved difficult in practice to get spectra with reproducible intensities because of the reactivity of the nitroso monomers, but qualitatively reproduction of the Cotton effects created no difficulties. Despite the manipula-

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(1) For part CXVII, see G. Barth, W. Voelter, H. S. Mosher, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **92**, 875 (1970).

(2) Financial assistance (Grant No. AM-12758) from the National Institutes of Health is gratefully acknowledged.

(3) National Institutes of Health Postdoctoral Fellow, Stanford University, 1968–1969.

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(6) D. C. Iffland and G. X. Criner, *J. Amer. Chem. Soc.*, **75**, 4047 (1953).

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(8) W. A. Tilden and J. J. Sudborough, *J. Chem. Soc.*, **63**, 479 (1893).

(9) C. Djerassi, *Proc. Chem. Soc.*, 314 (1964).

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(11) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *ibid.*, 1649 (1956).

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(13) C. H. Robinson, L. Milewich, and P. Hofer, *J. Org. Chem.*, **31**, 524 (1966).

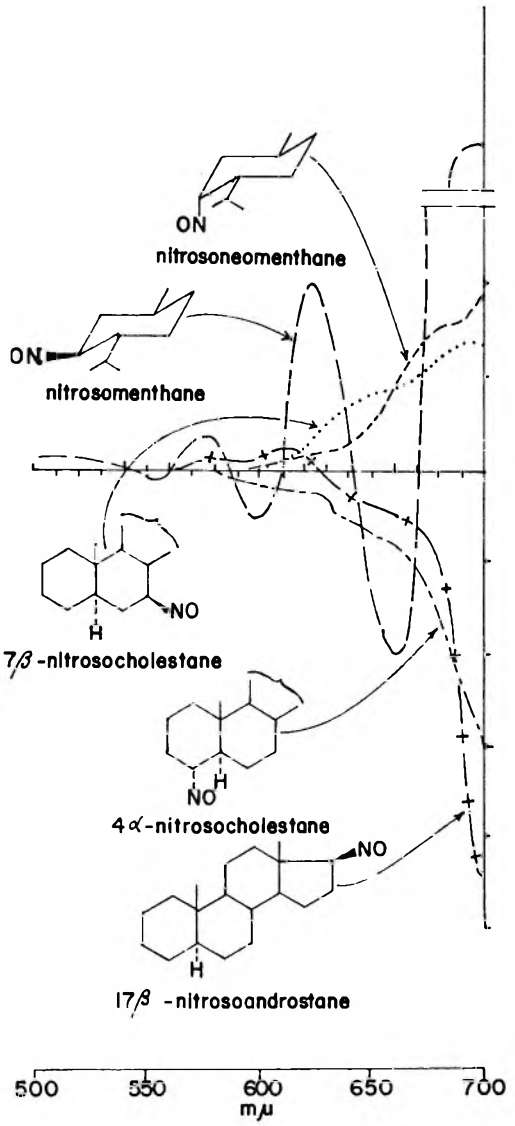
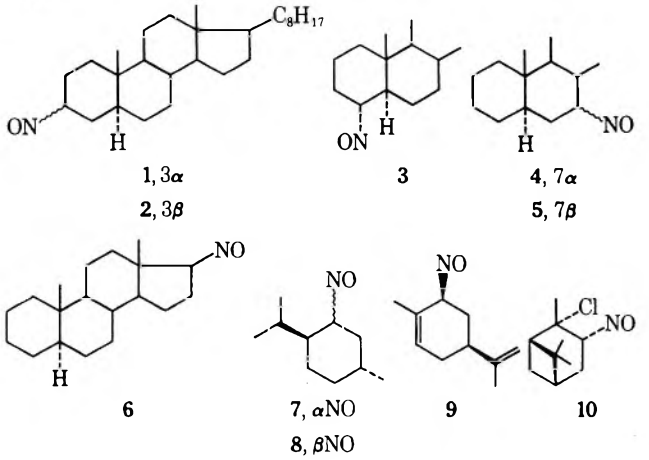


Figure 1.—Circular dichroism of nitroso derivatives in dichloromethane solution (amplitude differences between curves do not reflect molecular ellipticity differences).

tive complications, spectra of a representative group of optically active nitroso derivatives were obtained. The results are shown in Table I and a selection of spectra in Figure 1.



The spectra demonstrate that the nitroso chromophore is influenced by an optically active environment and can show sign inversions and differences in peak shape. Based on these findings, the *C*-nitroso chromophore holds definite promise for the conversion of amines to a readily observable, optically active group with a CD spectrum characteristic of the amine's environment. No amplitude information is determinable for the circular dichroism absorptions in Table I as the monomeric compounds are too unstable for isolation. Estimates of concentration from ultraviolet absorption studies were foiled by the inability to measure the absorption due to the weakness of the chromophore and our inability to concentrate the highly reactive monomers.

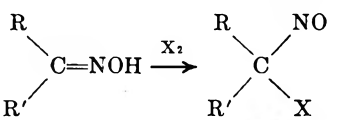
TABLE I

CIRCULAR DICHROISM OF OPTICALLY ACTIVE *C*-NITROSO COMPOUNDS

Compd	Sign	Position, mμ
3α-Nitrosocholestane[a] (1)	−	685
3β-Nitrosocholestane (2)	+	700
	−	675
4α-Nitrosocholestane[a] (3)	−	700
7α-Nitrosocholestane[a,b] (4)	+	690
	+	640
7β-Nitrosocholestane[a,b] (5)	+	695
	Inflection	650
17β-Nitroso-5α-androstane (6)	−	700
	−	650
	+	620
Nitrosomenthane (7)	+	690
	−	660
	+	625
	−	600
	+	575
	−	555
Nitrosoneomenthane (8)	+	700
	+	680
	+	625
Nitrosocarvodiene[c] (9)	−	700
	−	630
α-Pinene nitrosochloride (10)	+	695
	+	620

[a] The amines used to synthesize these derivatives were kindly supplied by Professor C. W. Shoppee, University of Sydney. [b] 7α- and 7β-nitrosocholestanes can be readily distinguished by their shorter wavelength CD absorptions; 7β shows minimum at 322 and maximum at 280 mμ, whereas 7α shows maximum at 330 and minimum at 294 mμ. [c] Synthesized from carvone *via* carvylamine.

α-Halogeno-*C*-nitroso Compounds.—The production of blue products (formulated as **11**) from oximes by the addition of bromine or chlorine has been known since the last century.[4] The bulkiness of the halogen atom represses dimerization and isomerization to oximes is inhibited in these compounds by the lack of a tautom-



11

X = Br, Cl, NO_2

erizable hydrogen atom. Since such α-halonitroso derivatives promised to overcome many of the difficulties associated with their unsubstituted counterparts covered in the previous section, a series of them was subjected to CD analysis.

The steroidal nitrosobromides were synthesized from the corresponding oxime by careful treatment of a cold

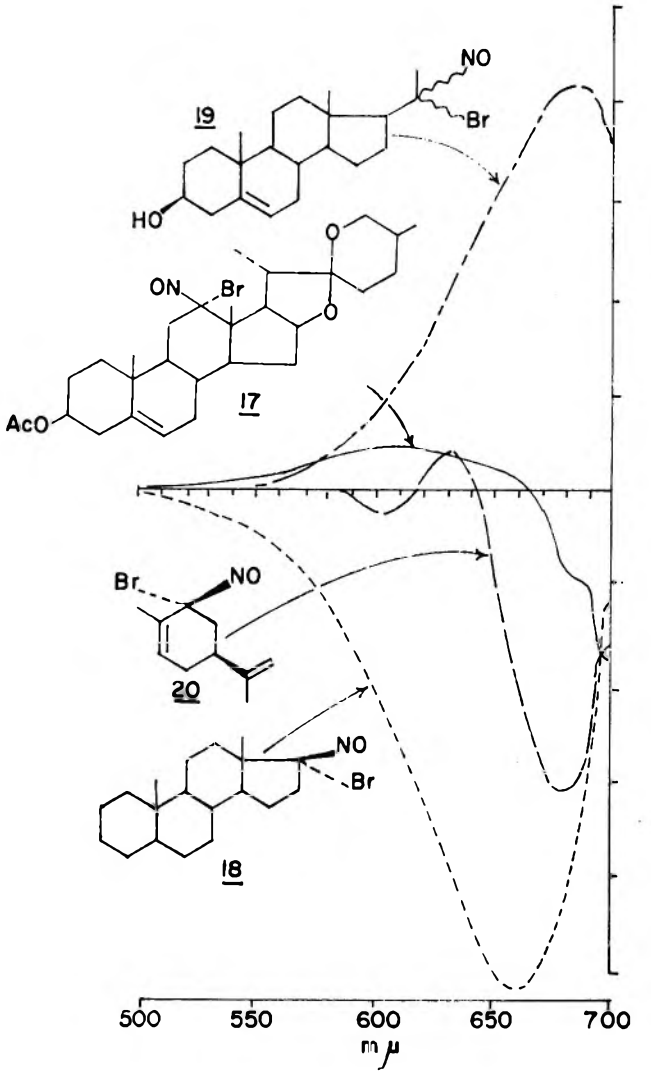


Figure 2.—Circular dichroism of geminal nitrosobromide derivatives in ethanol solution (amplitude differences between curves do not reflect molecular ellipticity differences).

pyridine–ethanol solution with a cold suspension of *N*-bromosuccinimide in ethanol. Spectra were run within 10 min of the addition and the solutions were filtered and maintained at 0° before measurement.

Bromination of oximes at the 7, 11, 12, 17, and 20 positions gave blue nitroso compounds, whose absorption band was readily discernible in the CD spectrometer. Normal work-up procedures, however, yielded colorless (and, in the case of C-20, rearranged) products. Cholestan-3-one ketoxime however yielded stable crystalline monomeric material on work-up. This material was isolated as deep blue crystals, unique for a steroid. Because of facile decomposition, however, even this compound could not be obtained in analytical purity.

The stereochemistry of these compounds is undoubtedly that in which the halogen atom occupies an axial position as the synthesis requires that the halogen approach the double bond of the oxime, and it is well known[14] that such approach is from the axial side in similar functional groups such as ketones.

CD Results.—Table II and Figures 2 and 3 show typical CD measurements for the products. The

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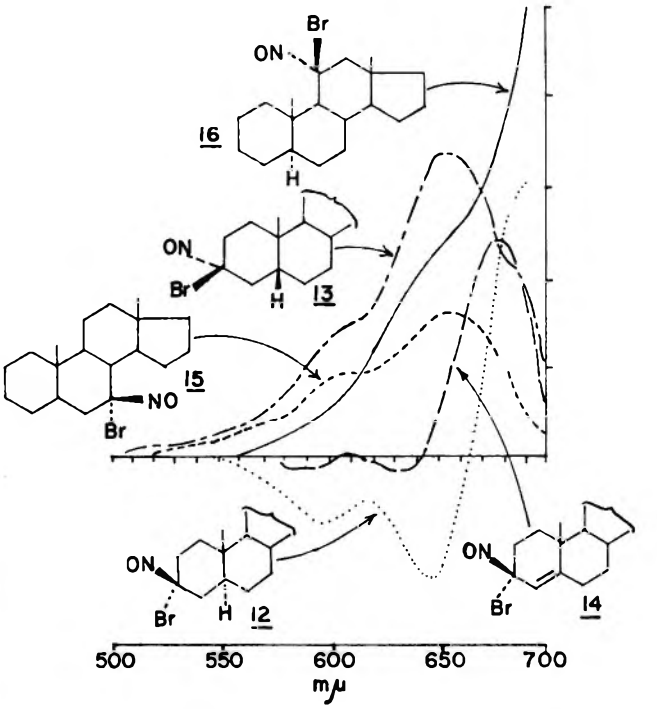


Figure 3.—Circular dichroism of geminal nitrosobromide derivatives in ethanol solution (amplitude differences between curves do not reflect molecular ellipticity differences).

Table II

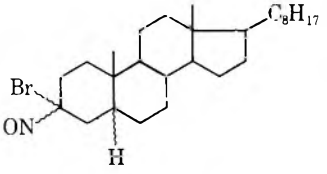
Circular Dichroism of *gem*-Nitroso Halogen Compounds

Compd	Sign of CD absorption	Position mμ
3α-Bromo-3β-nitroso-5α-cholestane (12)	+	694
	−	645
	Inflection	615
	Inflection	594
3β-Bromo-3α-nitroso-5β-cholestane (13)	Inflection	690
	+	655
	Inflection	620
	Inflection	570
17β-Hydoxy-3α-bromo-3β-nitroso-Δ⁴-androstene (14)	+	680
	−	635
	+	610
	−	590
7α-Bromo-7β-nitroso-5α-cholestane (15)	+	660
	Inflection	625
	+	610
	Inflection	570
11β-Bromo-11α-nitroso-5α-androstane (16)	+	700[a]
	Inflection	660
	+	640
	Inflection	610
12α-Bromo-12β-nitrosotigogenin acetate (17)	−	700[a]
	Inflection	690
	+	610
17α-Bromo-17β-nitroso-5α-androstane (18)	−	660[b]
3β-Hydroxy-20-bromo-20-nitroso-Δ⁵-pregnene (19)	+	685[b]
2-Bromo-2-nitrosocarvo-6,8-diene (20)	−	678
	+	632
	−	604

[a] Maximum absorption beyond the limits of our instrument. [b] Spectrum showed no fine structure.

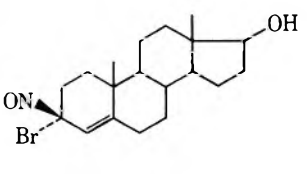
nitroso absorption shows shape and sign individuality characteristic of the position of the chromophore on the steroid nucleus, and the production of nitroso absorption promises to be useful in the examination of the asymmetric environment around a ketone group. Such analyses including synthesis and measurement can be carried out in less than 1 hr.

As with the nitroso derivatives obtained by oxidation of amines, no statement can be made about the intensities of the CD absorptions for the various compounds, as in most cases the monomeric materials are too transitory for isolation. This will probably continue to be the major drawback to this method of investigating asymmetry.



12, 5α H, 3α Br, 3β NO

13, 5β H, 3β Br, 3α NO



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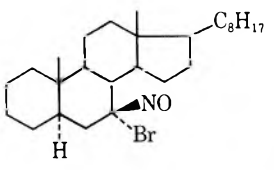

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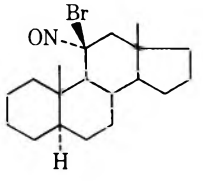

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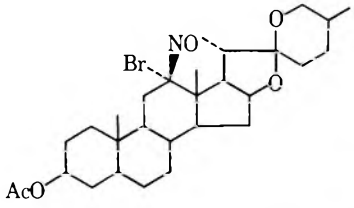

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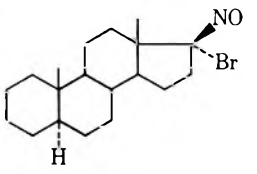

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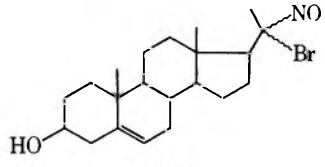

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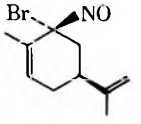

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Part B

Experimental Section

A Japan Spectroscopic Co. spectropolarimeter (Durrum-JASCO Model ORD-UV-5) was used for the CD measurements, which were measured by Mrs. Ruth R. Records.

Oxidation of *tert*-Butylamine.—When using 96% *m*-chloroperbenzoic acid[15] as an oxidant for *tert*-butylamine, satisfactory blue color was obtained using the following solvents: $CHCl_3$, CH_2Cl_2, CCl_4, dioxane, tetrahydrofuran, pyridine, dimethylformamide, acetone, 2,2-dimethoxypropane, nitromethane, 1-propanol, 2-propanol, 1-butanol. All of these solvents, however, gave cloudy precipitates of *m*-chlorobenzoic acid which made the solutions unsatisfactory for direct spectral measurement. Although solutions of nitroso compounds such as this *tert*-butyl example can be filtered without loss of color, the same is not true for compounds such as nitrosocyclohexane in which the nitroso function is attached to a secondary carbon.

The use of 40% peracetic acid as oxidant yielded more satisfactory product solutions as no precipitate was formed and strong colors were formed when *tert*-butylamine was treated as above with this reagent, particularly in alcohol solution. Water and the liberated acetic acid could be removed using solid anhydrous sodium carbonate in the reaction mixture.

The following example is typical of these experiments. To a 50-ml erlenmeyer flask was added 1 g (13.7 mmol) of *tert*-butylamine and 20 ml of *n*-propyl alcohol. The solution was stirred vigorously and chilled to −10° in an ice–methanol bath. To this cold solution was added 3.6 ml (28 mmol) of a similarly chilled solution of 40% peracetic acid and 5 ml of *n*-propyl alcohol. The reaction mixture turned deep blue and the color remained during several days of standing at room temperature.

Oxidation of Cyclohexylamine.—The oxidation of cyclohexylamine was carried out in the manner of the above sequence. Colors were found for all of the solvents used for the oxidation of *tert*-butylamine. In addition acetonitrile, ether, ethyl acetate, *tert*-butyl alcohol, and a mixed solvent with pyridine, the peracid, and methylene chloride could all be used as for the reaction solvent. The reaction was best carried out at between −10 and 0° and color was retained longest in *n*-propyl alcohol or acetonitrile. Oxidant could be added in solution or neat without significant difference in the depth of color produced.

Preparation of Oximes.—All oximes were prepared by refluxing (15 min) the corresponding ketone with 1.5 equiv of hydroxylamine hydrochloride in an alcohol solution containing about 1% pyridine. Steroidal oximes were concentrated to dryness and recrystallized. The solutions of oximes of lower molecular weight were concentrated, diluted with chloroform, washed with water and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated.

Reduction of Oximes with Sodium in Alcohol.—A standard procedure following Haworth[16] was used in all cases. The oxime in refluxing *n*-propyl alcohol was treated during 2 hr with a large excess (up to tenfold) of sodium spheres.[16] The cooled reaction mixture was then diluted with ether or chloroform, washed thoroughly with water, and, in the case of steroidal materials, evaporated, and recrystallized. Nonsteroidal amines were extracted from the organic layer using 10% hydrochloric acid solution and after washing with ether the acidic solution was treated with concentrated ammonia solution until basic and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to yield the free amine. Amine hydrochlorides were prepared by precipitation from an ether solution of the amine using dry hydrogen chloride gas.

3α-Amino-5α-cholestane and **3β-amino-5α-cholestane** were synthesized according to the literature directions.[10,11]

17β-Amino-5α-androstane.—Dihydrotestosterone was reduced to 5α-androstan-17β-ol by the method of Nagata and Itazaki.[17] Oxidation of this product by the method of Jones[18] yielded androstan-17-one, the oxime of which was reduced by sodium in alcohol to 17β-amino-5α-androstane.[19]

Neomenthylamine[20] was synthesized by treating menthyl tosylate with lithium azide[21] by the method of Smith[22] and reducing the azide produced with lithium aluminum hydride.

Menthylamine (3-amino-*p*-menthane)[20] **and carvylamine (3-amino-*p*-mentha-1,8-diene)**[23] were synthesized by the reduction of menthane and carvone oximes with sodium in alcohol.

α-Pinene nitrosocholoride[24] was synthesized from α-pinene [$[\alpha]_D$ +39.6° (neat)] by treatment with nitrosyl chloride.[8,24]

Bromination of Oximes for CD Measurement.—The following example is typical. To a 50-ml erlenmeyer flask was added 100 mg of carvone oxime (0.6 mmol), 150 μl. of pyridine (1.86 mmol), and 20 ml of ethanol. The solution was chilled to 0° and 220 mg (1.23 mmol) of *N*-bromosuccinimide added. The deep green solution was kept in an ice bath until ready for measurement (less than 1 hr). The solution was filtered through a small pad of cotton using a pipet immediately prior to adding to the spectrometer cell.

(15) Pilot Chemical Company, London Road, Ware, Herts., England.

(16) D. P. Dodgson and R. D. Haworth, *J. Chem. Soc.*, 67 (1952).

(17) W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964).

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

(19) C. W. Shoppee and J. C. P. Sly, *ibid.*, 345 (1959).

(20) J. Read and R. A. Storey, *ibid.*, 2761 (1930).

(21) R. L. Huisgen and I. Ugi, *Chem. Ber.*, **90**, 2914 (1957).

(22) (a) E. H. Massey, H. E. Smith, and A. W. Gordon, *J. Org. Chem.*, **31**, 684 (1966); (b) A. K. Bose, S. Harrison, and L. Farber, *ibid.*, **28**, 1223 (1963).

(23) A. Mailhe, *Bull. Soc. Chim. Fr.*, **33**, 83 (1923).

(24) E. V. Lynn, *J. Amer. Chem. Soc.*, **41**, 361 (1919).

Bromination of 5α-Cholestanone Oxime.—A sample of cholestanone oxime (1 g, 2.58 mmol) was synthesized in 1:1 ethanol–hexane solution containing a small amount of water by the addition of hydroxylamine hydrochloride, 180 mg (2.58 mmol), and 1.095 μl (7.74 mmol) of pyridine. The two-phase system was treated with 920 mg (5.06 mmol) of solid *N*-bromosuccinimide and stirred 15 min. The reaction product was diluted with pentane and the upper layer separated and concentrated on a steam bath. During the concentration acetone was added; cooling of the product solution in a refrigerator gave blue crystalline needles of 3α-bromo-3β-nitroso-5α-cholestane (**12**), mp 135–138° (three recrystallizations from methanol): nmr (δ ppm from TMS) 0.64 (methyl), 0.82 (methyl), 0.87 (methyl), 0.91 (methyl). Further purification of this product by preparative thin layer chromatography failed to yield an analytical sample because of its facile decomposition.

Results and Discussion

Nonhalogenated Nitroso Compounds.—In our initial experiments, we employed 96% *m*-chloroperbenzoic acid at −10° in methylene chloride solution, with solid calcium carbonate in order to neutralize the *m*-chlorobenzoic acid formed in the reaction. This standard[7b] reagent mixture was drastically changed during the course of our work because of the necessity of recording the spectra and circular dichroism of the nitroso compounds directly on the crude reaction solution. The chlorobenzoic acids both have low solubility in methylene chloride below 0° and cause fogging of the solution in the spectrometer. This could be overcome, however, by using peracetic acid as oxidant or by changing the solvent to an alcohol. Contrary to literature suggestions[4,25] that the tautomerism from nitroso to oxime is facilitated by polar solvents, it was found on test samples of nitrosocyclohexane that this chromophore could be prepared and maintained at −30° (ice–methanol bath) in chlorocarbon solvents, alcohols, ethers, benzene, pyridine, and dimethylformamide for 30 min without fading.

During attempts at measuring the CD absorption of the reaction solution containing nitrosomenthane at low temperature it was noticed that the brass cell imparted a deep blue color to the solution. This color could also be produced by the addition of cupric sulfate to the reaction mixture. The cause of the color (soluble in water and organic solvents) is possibly a chelate of the nitroso dimer. This product was stable (detection by color only) during 1 year in a refrigerator. This blue solution showed a broad diffuse CD absorption in the visible region and a sharp band at 370 mμ. The nitroso grouping has the ability to rotate freely and will do so in these saturated compounds, but the occurrence of the chelating phenomenon made low temperature analysis for rotation of the nitroso products impossible.

The configuration of the nitroso group is probably that of the parent amine, as the nitro groups produced by overoxidation in the same synthesis as used here have been shown to retain configurational identity.[13]

Strong bands occur at 300 mμ in the spectra of the reaction mixtures, but at this time it is not known if these are due to $\pi-\pi^*$ absorption in the monomer or in the dimer which is undoubtedly present also. The CD spectrum of the dimer from nitrosomenthane is shown in Figure 4 for reference purposes to illustrate the spectral characteristics of the pure dimer.

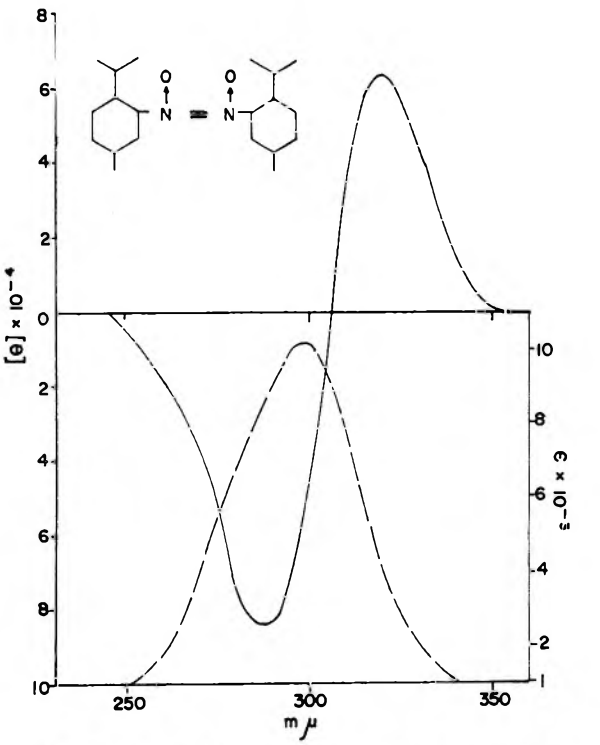
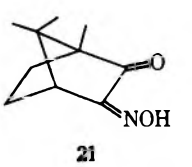


Figure 4.—Circular dichroism and ultraviolet spectrum of nitrosomenthane dimer in hexane solution.

Geminal Nitroso–Halogen Compounds.—Measurement of the geminal nitroso–halogen chromophores was first reported by Mitchell in 1940[26] with the curve of a menthol ester which showed very similar characteristics to those reported here.

We found that the synthesis of such derivatives can be conducted conveniently with *N*-bromosuccinimide, *N*-chlorosuccinimide, *N*-bromoacetamide, as well as fuming nitric acid and dinitrogen tetroxide (both of which give α-nitronitroso compounds). The reaction failed to yield visible blue color with iodine, *N*-iodosuccinimide, and cyanogen bromide. Isolation of the oxime is generally not necessary as the conversion of ketone to oxime can be carried out in virtually quantitative fashion. Syntheses of nitroso derivatives from acetone oxime (as a test material) could be carried out in alcohols, pyridine, ethers, and chlorocarbon solvents and were best carried out below 0°.

Cyclohexenone, carvone, benzophenone, salicylaldehyde, nitrosocamphor (**21**) propionaldehyde, and pentane-2,4-dione gave no blue coloration when they were reacted under the conditions used for the cyclohexanones. However, at temperatures below 0° carvone



21

(25) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 3rd ed, 1966, p 339.

(26) S. Mitchell and G. K. Simpson, *J. Chem. Soc.*, 784 (1940).

gave color distinguishable in the CD spectrometer, but warming to room temperature yielded only a yellow solution with no detectable CD absorption. On reducing the temperature of a solution containing **12** to −187°, the spectrum amplitude increased but no position changes were noticed.

Registry No.—**1**, 25630-12-0; **2**, 25630-11-9; **3**, 25558-52-5; **4**, 25630-13-1; **5**, 25558-53-6; **6**, 25554-40-9; **7**, 25554-41-0; **8**, 25554-42-1; **9**, 25554-43-2; **10**, 25554-44-3; **12**, 1912-59-0; **13**, 25554-46-5; **14**, 25554-47-6; **15**, 25554-48-7; **16**, 25554-49-8; **17**, 25554-50-1; **18**, 25554-51-2; **19**, 25554-52-3; **20**, 25554-53-4.

Azacoumarins[1]

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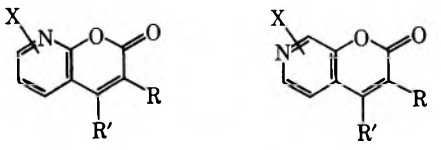
Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received March 5, 1970

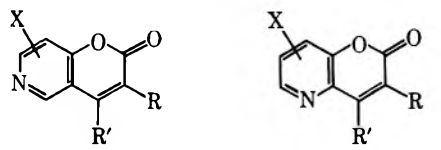
Eighteen azacoumarins were prepared by condensation of appropriate esters, acids, or anhydrides with *o*-hydroxypyridine aldehydes or ketones. This constitutes examples of all four possible types (I, II, III, and IV) of azacoumarins with N replacing CH of the benzene ring. Two 8-azaflavones and a number of intermediates and by-products are also reported.

Part A

Coumarins in which a CH group is replaced by a nitrogen can be called "azacoumarins." In a broad sense this could include the 2*H*-1,4-benzoxazin-2-ones[2] and 2*H*-1,3-benzoxazin-2-ones.[3] However, this paper comprises only those azacoumarins in which the nitrogen replaces a CH of the benzene ring (I, II, III, and IV). The literature contains only two references



I II



III IV

to 2*H*-pyranopyridin-2-ones,[4,5] both of which are of the [2,3-*b*] type, I. One of these[5] gives no information on the synthesis. Robinson and Watt[4] report the synthesis of 7-hydroxy-5-methyl-2*H*-pyrano[2,3-*b*]-pyridin-2-one (I, R and R′ = H; X = 7-OH, 5-CH_3) by the Pechmann synthesis from 2,6-dihydroxy-4-methylpyridine[6] and malic acid. This procedure was confirmed by our synthesis of the corresponding desmethyl analog **7**. However, in general, the Pechmann synthesis does not seem to work on monohydroxypyridines, doubtless because of the protonation of the pyridine ring by the strong acid used. The Kostanecki–Robinson modification of the Perkin reaction or the Knoevenagel reaction were found to be more generally applicable methods and examples of all four types of these azacoumarins were prepared. Types II, III, and IV appear to constitute new classes of compounds.

(1) Presented in part at the Great Lakes Regional Meeting of the American Chemical Society, Fargo, N. D., June 18–19, 1970.

(2) R. B. Moffett, *J. Med. Chem.*, **9**, 475 (1966).

(3) R. L. McKee, *Chem. Heterocycl. Compounds*, **17**, 351 (1962).

(4) R. Robinson and J. S. Watt, *J. Chem. Soc.*, 1536 (1934).

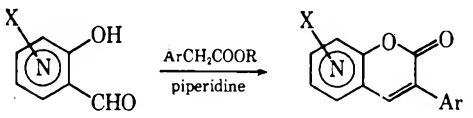
(5) K. v. Auwers, *J. Prakt. Chem.*, **150**, 166 (1938).

(6) Many 2- and 4-hydroxypyridines are known to exist in the pyridone form. However, in this article the pyridol nomenclature will be used since it is the hydroxy form that reacts in our syntheses.

Of the requisite pyridinol aldehydes or ketones only pyridoxal was available. 3-Hydroxy-2- (and -4-) pyridinecarboxaldehydes were prepared by the method of Heinert and Martell[7] and 3-acetyl-4-hydroxy-2,6-dimethylpyridine was made as described by Ziegler, Herbst, and Kappe.[8] 3-Acetyl-2-hydroxy-6- (and -4,6-di-) methylpyridines were prepared from the corresponding 3-nitriles by treatment with methyllithium in yields of 47–61%, respectively. Since this work was done the 4,6-dimethyl compound (**20**) has been reported by Bonsall and Hill[9] who prepared it by condensation of acetylacetone with acetoacetamide.

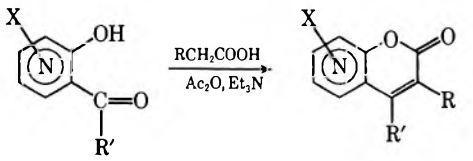
In general the Knoevenagel reaction (Scheme I) was

SCHEME I



used with the pyridol aldehydes employing an arylacetic ester and piperidine. Scheme I was not applicable with the pyridol ketones and so the Perkin reaction (Scheme II) was used.

SCHEME II



In the one case where a direct comparison was made, 3-phenyl-2*H*-pyrano[3,2-*b*]pyridin-2-one (**17**), about the same yield was obtained by both methods. Table I lists the azacoumarins prepared and their melting points.

An attempt was made to prepare the 4-hydroxy-8-azacoumarin **22** by condensation of the acetylpyridol **20** with diethyl carbonate in the presence of NaH.[10]

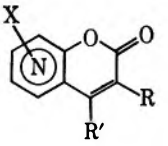
(7) D. Heinert and A. E. Martell, *J. Amer. Chem. Soc.*, **81**, 3933 (1959).

(8) E. Ziegler, I. Herbst, and Th. Kappe, *Monatsh. Chem.*, **100**, 132 (1969).

(9) C. Bonsall and J. Hill, *J. Chem. Soc. C*, 1836 (1967).

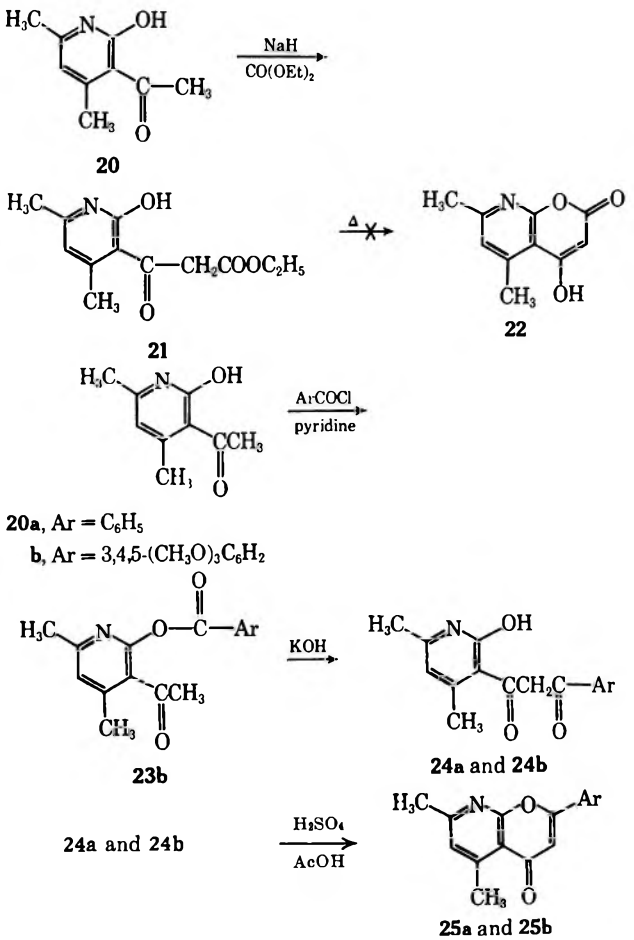
(10) Method described for 4-hydroxycoumarin: British Patent 705,316 (1954).

TABLE I



No.	Position of aza N	X	R	R′	Method of prepn[a]	Yield,[b] %	Mp, °C[c]
1	8	7-CH_3	*p*-BrC_6H_4	CH_3	B	65	226.5–228
2	8	7-CH_3	*m*-$CH_3OC_6H_4$	CH_3	B	56	158.5–159.5
3	8	5,7-Di-CH_3	C_6H_5	CH_3	B	49	163–164.5
4	8	5,7-Di-CH_3	*p*-FC_6H_4	CH_3	B	35	194.5–196
5	8	5,7-Di-CH_3	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	B	38	225.5–227.5
6	8	5,7-Di-CH_3	3-Pyridyl	CH_3	B	17	180–180.5
7	8	7-OH	H	H	C	8	293–297 dec
8	7	H	*p*-$CH_3OC_6H_4$	H	B	83	217.5–219.5
9	7	H	2-Pyridyl	H	A	49	150–152
10	7	5-CH_2OH, 8-CH_3	4-Pyridyl	H	A	44	188–197
11	7	5-CH_2OH, 8-CH_3	*p*-$NO_2C_6H_4$	H	A	26	233.5–235
12	6	5,7-Di-CH_3	C_6H_5	CH_3	B	36	166–168
13	6	5,7-Di-CH_3	*m*-$CH_3C_6H_4$	CH_3	B	24	125–126
14	6	5,7-Di-CH_3	*p*-ClC_6H_4	CH_3	B	49	206.5–208
15	5	H	H	H	D[d]	26	107.5–108.5
16	5	H	COOH	H	...[e]	68	192–193 dec
17	5	H	C_6H_5	H	A and B	12	156–157.5
18	5	H	4-Pyridyl	H	A	79	252–254
19	5	H	*p*-$NO_2C_6H_4$	H	A	86	243.5–244.5

[a] A = Knoevenagel reaction (Scheme I); B = Kostanecki–Robinson modification of the Perkin reaction (Scheme II); C = Pechmann synthesis;[4] D = Perkin reaction. [b] The yield is based on the pyridol aldehyde or ketone and is reported for material melting not less than 2° below the highest melting point obtained. [c] Elemental analyses and ir and uv spectra were obtained on all azacoumarins and nmr on selected examples. All were in accord with the proposed structures. Data are given in the Experimental Section for an example of each type of azacoumarin (compd no. 1, 10, 12, and 15). [d] Obtained both by the Perkin reaction (Ac_2O + KOAc) and along with 16 by heating (3-hydroxy-2-pyridyl)methylenemalonic acid, which was prepared from 3-hydroxypicolinaldehyde and malonic acid. [e] Prepared by heating (3-hydroxy-2-pyridyl)methylenemalonic acid with polyphosphoric acid.



However, the ring did not close, probably owing to the pyridone structure[6] of the intermediate, and only the β-keto ester **21** was isolated. The same acetylpyridol **20** was utilized in the preparation of two azaflavones (**25a** and **25b**).

Since completion of this work, the preparation of compounds **24a** and **25a** by slightly different methods have been reported by Bonsall and Hill.[9] Our melting points agree with theirs. All the compounds reported herein have been widely screened for biological activity but only minimal activity was found.

Part B

Experimental Section[11]

3-Acetyl-2-hydroxy-4,6-dimethylpyridine[9] (**20**).—Methyllithium was prepared from 21.0 g (3.0 g-atoms) of Li and 142.5 g (1.5 mol) of MeBr in 900 ml of Et_2O. To this was added with vigorous stirring under N_2 a suspension of 74.0 g (0.5 mol) of 3-cyano-2-hydroxy-4,6-dimethylpyridine in 900 ml of THF. Most of the ether was distilled through a fractionating column (to bp 60°) and then the solution was stirred under reflux for 2.5 hr. After cooling, the mixture was poured into ice water, acidified with HCl, and allowed to stand at room temperature for 1 hr. The solution was neutralized to pH 7–8 with NaOH and continuously extracted with Et_2O for 40 hr. Evaporation of the extract gave 76.4 g of orange colored solid. Recrystallization from 1.5 l. of

(11) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Nmr spectra were determined with a Varian A-60 spectrometer, ir spectra were on Nujol mulls, and uv spectra were in EtOH.

EtOH yielded 50.0 g (61%) of yellow solid, mp 215–216°. An additional 5 g, mp 209–210°, was obtained from the filtrate. A sample recrystallized from benzene gave mp 216–218°.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.54; H, 6.71; N, 8.48; O, 19.37. Found: C, 65.57; H, 6.31; N, 8.73; O, 19.32.

3-Acetyl-2-hydroxy-6-methylpyridine.—By a similar procedure this was prepared from 47 g (6.7 g-atoms) of Li, 320 g (3.36 mol) of MeBr, 2.1 l. of Et_2O, 150 g (1.12 mol) of 3-cyano-2-hydroxy-6-methylpyridine, and 3.4 l. of THF. The product was recrystallized twice from EtOH (with Darco G-60 treatment) yielding 78.3 g (47%) of light yellow crystals, mp 202–207°. A sample recrystallized for analysis had mp 208.5–209.5°.

Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.71; H, 6.09; N, 8.98.

3-(*p*-Bromophenyl)-4,7-dimethyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (1) (Example of Method B).—A solution of 7.5 g (0.05 mol) of 3-acetyl-2-hydroxy-6-methylpyridine, 15 g (0.07 mol) of *p*-bromphenylacetic acid, and 7 ml (0.05 mol) of Et_3N in 31.5 ml (0.35 mol) of Ac_2O was stirred under N_2 under reflux for 6 hr. After cooling the crystal containing mixture was poured into water and adjusted to pH 8 with NH_4OH. The solid was collected, washed with water, and boiled with EtOH. After cooling the solid was collected and dried giving 11.77 g of light brown crystals. Recrystallization from 100 ml of ethylene glycol monomethyl ether (filtered hot) yielded 10.6 g (64.6%) of tan crystals, mp 226.5–228°. Principal spectral bands: uv 222, 236, 274, and 317 mμ; ir C=CH at 3075, C=O/C=N at 1710, C=C at 1616, 1597, 1588, 1553, and 1487, C—H/C—O at 1145 and 1075, arom at 817 cm^{-1}; nmr (in $CDCl_3$) two Me singlets (integrating 3 each) at δ 2.33 and 2.67, and aromatic multiplets (integrating 6) between δ 7 and 8.

Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; Br, 24.20; N, 4.24. Found: C, 58.26; H, 3.65; Br, 24.11; N, 4.21.

3-(*m*-Methoxyphenyl)-4,7-dimethyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (2).—By a similar procedure this was prepared from 7.5 g (0.05 mol) of 3-acetyl-2-hydroxy-6-methylpyridine, 16.6 g (0.1 mol) of *m*-methoxyphenylacetic acid, 31.5 ml (0.35 mol) of Ac_2O, and 7 ml (0.05 mol) of Et_3N. The crude solid was recrystallized from 150 ml of EtOH (with Darco G-60 treatment) yielding 7.75 g (55.5%) of light tan solid, mp 158–160°. A sample recrystallized again from EtOH had mp 158.5–159.5°.

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.53; H, 5.42; N, 4.98.

4,5,7-Trimethyl-3-phenyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (3).—By a similar procedure this was prepared from 8.3 g (0.05 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 13.6 g (0.1 mol) of phenylacetic acid, 28.2 ml (0.3 mol) of Ac_2O, and 14 ml (0.1 mol) of Et_3N. The mixture was stirred under reflux for 22 hr and then the solvent was distilled, under N_2, from a bath at 190° during 2 hr. The crude solid was sublimed at 0.01 mm from a bath at 190° giving 6.9 g of light tan solid. This was recrystallized from 120 ml of EtOH yielding 6.53 g (49%) of white crystals, mp 163–164.5°.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.76; H, 5.53; N, 5.30.

3-(*p*-Fluorophenyl)-4,5,7-trimethyl-2*H*-pyrano[2,3-*b*]pyridin-2-one (4).—By a similar procedure this was prepared from 5.54 g (0.033 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 18.8 ml (0.2 mol) of Ac_2O, and 4.7 ml (0.33 mol) of Et_3N. The mixture was heated under reflux, under N_2, for 10 hr. The crude product was recrystallized from EtOH (with Darco G-60 treatment) yielding 3.28 g (35%) of light tan crystals, mp 194.5–196°.

Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; F, 6.71; N, 4.94. Found: C, 71.93; H, 4.59; F, 6.68; N, 4.85.

3-(3,4,5-Trimethoxyphenyl)-4,5,7-trimethyl-2*H*-pyrano[2,3-*b*]-pyridin-2-one (5).—By a similar procedure this was prepared from 16.6 g (0.1 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 27.2 g (0.12 mol) of 3,4,5-trimethoxyphenylacetic acid, 56.4 ml (0.6 mol) of Ac_2O, and 28 ml (0.2 mol) of Et_3N. After heating under reflux for 19 hr the solvent was distilled from a bath at 175° during 2 hr. The crude product was recrystallized twice from EtOH yielding 13.35 g (38%) of tan crystals, mp 225.5–227.5°.

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.62; H, 6.33; N, 4.10.

4,5,7-Trimethyl-3-(3-pyridyl)-2*H*-pyrano[2,3-*b*]pyridin-2-one (6).—By a similar procedure this was prepared from 16.6 g (0.1 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine, 14.6 g (0.12 mol) of 3-pyridylacetic acid, 56.4 ml (0.6 mol) of Ac_2O, and 28 ml (0.2 mol) of Et_3N. After heating under reflux for 24 hr the solvent was distilled from a bath at 200° during 2 hr. The crude gummy product was boiled with 400 ml of EtOH, filtered, and evaporated to dryness. The resulting gum was sublimed at 0.01 mm from a bath up to 250°. After removing a little white solid the product sublimed as a partly crystalline solid. This was recrystallized from 2-propanol yielding 4.55 g (17%) of yellow solid, mp 170–180°. A sample recrystallized from EtOH gave mp 180–180.5° after sintering at 173.5–175°.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.09; H, 5.36; N, 10.79.

3-(*p*-Methoxyphenyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (8).—By a similar procedure this was prepared from 1.23 g (0.01 mol) of 3-hydroxyisonicotinaldehyde,[7] 3.32 g (0.02 mol) of *p*-methoxyphenylacetic acid, 10 ml of Ac_2O, and 1.4 ml (0.01 mol) of Et_3N. The solution was heated under reflux for 5 hr. The crude product boiled with EtOH, cooled, collected, and dried giving 2.1 g (83%) of tan crystals, mp 217.5–219°. Recrystallization from 25 ml of ethylene glycol monomethyl ether gave 2.0 g of light tan crystals, mp 217.5–219.5°.

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.29; H, 4.34; N, 5.42.

4,5,7-Trimethyl-3-phenyl-2*H*-pyrano[3,2-*c*]pyridin-2-one (12).—By a similar procedure this was prepared from 5.0 g (0.03 mol) of 3-acetyl-4-hydroxy-2,6-dimethylpyridine,[8] 8.15 g (0.06 mol) of phenylacetic acid, 17 ml (0.16 mol) of Ac_2O, and 5 ml (0.36 mol) of Et_3N. The solution was stirred under reflux for 8 hr. The crude product was crystallized from 2-propanol and recrystallized from EtOH (with Darco G-60 treatment) yielding 2.9 g (36.4%) of nearly white crystals, mp 166–168°. Principal spectral bands: uv 206, 234, and 302 mμ; ir C=O at 1720, C=C/C=N at 1595, 1540, and 1495, C–O, C–N at 1180, 1090, and 985, arom at 735 and 710 cm^{-1}; nmr (in $CDCl_3$) three Me singlets (integrating 3 each) δ 2.40, 2.57, and 2.90, 8-H singlet (integrating 1) at δ 6.99, and aromatic multiplet (integrating 5) centered at δ 7.4.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.69; H, 5.69; N, 5.35.

4,5,7-Trimethyl-3-(*m*-tolyl)-2*H*-pyrano[3,2-*c*]pyridin-2-one (13).—By a similar procedure this was prepared from 8.0 g (0.048 mol) of 3-acetyl-4-hydroxy-2,6-dimethylpyridine,[8] 14.5 g (0.96 mol) of *m*-tolylacetic acid, 27 ml (0.256 mol) of Ac_2O, and 8 ml (0.058 mol) of Et_3N. The solution was stirred under N_2 under reflux for 8 hr. The crude product was crystallized from 2-propanol and recrystallized from MeOH (with Darco G-60 treatment) yielding 3.2 g (23.8%) of nearly white crystals, mp 125–126° (with sintering at 121–122°).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.14; N, 5.02. Found: C, 77.63; H, 6.43; N, 5.27.

3-(*p*-Chlorophenyl)-4,5,7-trimethyl-2*H*-pyrano[3,2-*c*]pyridin-2-one (14).—By a similar procedure this was prepared from 7.5 g (0.045 mol) of 3-acetyl-4-hydroxy-2,6-dimethylpyridine,[8] 15.3 g (0.09 mol) of *p*-chlorophenylacetic acid, 25 ml (0.24 mol) of Ac_2O, and 7.5 ml (0.054 mol) of Et_3N. The solution was heated under reflux, under N_2, for 8 hr. The crude product was boiled with 150 ml of 2-propanol and cooled, and the solid was collected giving 6.6 g (49%) of light brown solid, mp 202–206°. Recrystallization from EtOH (with Darco G-60 treatment) yielded 4.65 g of nearly white crystals, mp 206.5–208°.

Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; Cl, 11.83; N, 4.67. Found: C, 68.02; H, 4.80; Cl, 11.87; N, 4.76.

3-Phenyl-2*H*-pyrano[3,2-*b*]pyridin-2-one (17) (Method B).—By a similar procedure this was prepared from 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 2.72 g (0.02 mol) of phenylacetic acid, 10 ml of Ac_2O, and 1.4 ml (0.01 mol) of Et_3N. The product was extracted with Et_2O from the weakly basified aq mixture, containing much tar, washed (H_2O and satd NaCl), and dried (Na_2SO_4). After removal of the ether the gummy product was sublimed at 0.015 mm from a bath up to 194° and then crystallized from 2-propanol yielding 0.26 g (12%) of pink crystals, mp 152.5–154.5°. The infrared spectrum was identical with that of material prepared by method A (below).

3-Phenyl-2*H*-pyrano[3,2-*b*]pyridin-2-one (17) (Method A).—A solution of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 1.65 g (0.011 mol) of methyl phenylacetate, and 1 ml of piperidine in 25 ml of abs EtOH was heated under reflux for 4 hr. After filtration and evaporation, the dark tar was sublimed at 0.01 mm from a bath up to 193°. The sublimate was recrystallized from 2-propanol (with Darco G-60 treatment) yielding 0.27 g (12%) of white crystals, mp 156–157°. A sample for analysis was recrystallized again from 2-propanol, mp 156–157.5°.

Anal. Calcd for $C_{14}H_9NO_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.09; H, 4.02; N, 6.24.

3-(*p*-Nitrophenyl)-2*H*-pyrano[3,2-*b*]pyridin-2-one (19).—A solution of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 2.3 g (0.011 mol) of ethyl *p*-nitrophenylacetate, and 1 ml of piperidine in 25 ml of abs EtOH was heated under reflux for 0.5 hr. After cooling the resulting crystalline solid was collected, washed (EtOH), and dried giving 2.3 g (86%) of light tan crystals, mp 243–244°. Recrystallization from ethylene glycol monomethyl ether gave 2.15 g of fluffy cream colored needles, mp 243.5–244.5°.

Anal. Calcd for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.00; N, 10.43. Found: C, 62.33; H, 2.99; N, 10.52.

3-(4-Pyridyl)-2*H*-pyrano[3,2-*b*]pyridin-2-one (18).—A solution of 12.3 g (0.1 mol) of 3-hydroxypicolinaldehyde,[7] 15.1 g (0.1 mol) of methyl 4-pyridylacetate, and 5.8 ml of piperidine in 125 ml of abs EtOH was heated under reflux for 1 hr. After cooling the resulting crystalline solid was collected, washed (EtOH), and dried, giving 17.7 g (79%) of light brown solid, mp 245–252°. This was recrystallized from 140 ml of DMF yielding 16.6 g of brown crystals, mp 249–253°. A sample for analysis was sublimed at 0.05 mm from a bath up to 187° and recrystallized from DMF giving white needles, mp 252–254°.

Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.59; N, 12.50. Found: C, 69.87; H, 3.57; N, 12.36.

3-(2-Pyridyl)-2*H*-pyrano[2,3-*c*]pyridin-2-one (9).—A solution of 1.23 g (0.01 mol) of 3-hydroxyisonicotmaldehyde,[7] 1.66 g (0.011 mol) of methyl 2-pyridylacetate, and 0.3 ml of piperidine in 25 ml of abs EtOH was heated, under N_2, under reflux for 2 hr. The mixture was dissolved in more EtOH, treated with Darco G-60 at bp, filtered, and cooled, yielding 1.1 g (49%) of pink crystals, mp 150–152°.

Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.59; N, 12.50. Found: C, 69.36; H, 3.26; N, 12.39.

5-(Hydroxymethyl)-8-methyl-3-(4-pyridyl)-2*H*-pyrano[2,3-*c*]-pyridin-2-one (10).—A solution of 20.36 g (0.1 mol) of pyridoxal hydrochloride, 15.1 g (0.1 mol) of methyl 4-pyridylacetate, and 15.8 ml of piperidine, in 120 ml of abs EtOH was heated under reflux for 2 hr. After filtration the solution was evaporated *in vacuo* and the residue was shaken with water giving 13.5 g of pink solid, mp 187–192°. This was recrystallized from 160 ml of EtOH yielding 11.9 g (44.5%) of pink crystals, mp 188–197°. A sample dissolved in hot water and separated (still at bp) as fluffy needles, mp 192–197°. The infrared spectra indicated dimorphic forms. Principal spectral bands: uv 240, 295, and 346 mμ; ir OH at 3180, C=CH at 3070, C=O at 1728, C=C/C=N at 1628, 1542, and 1600, C–N/C–O at 1230, 1144, 1079, and 102 cm^{-1}; nmr (in deuterated DMSO) Me singlet at 2.57, CH_2 doublet centered at 4.82, OH broad triplet centered at 5.65, and vinyl and aromatic multiplets between δ 7 and 9.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44; O, 17.89. Found: C, 66.91; H, 4.63; N, 10.23; O, 17.82.

5-(Hydroxymethyl)-8-methyl-3-(*p*-nitrophenyl)-2*H*-pyrano-[2,3-*c*]pyridin-2-one (11).—A solution of 10.4 g (0.05 mol) of pyridoxal hydrochloride, 11.5 g (0.055 mol) of ethyl *p*-nitrophenylacetate, and 9.9 ml (0.1 mol) of piperidine in 30 ml of abs EtOH was heated under reflux for 2 hr. The dark solution was cooled and poured into water. The resulting orange-brown solid was dissolved in 100-ml of ethylene glycol monomethyl ether, treated with Darco G-60, filtered, diluted with 150 ml of ethanol, and cooled, yielding 4.1 g (26%) of cream colored fluffy needles, mp 233.5–235°.

Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.53; H, 3.87; N, 8.97. Found: C, 61.22; H, 3.75; N, 8.82.

2*H*-Pyrano[3,2-*b*]pyridin-2-one (15).—A mixture of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde,[7] 1 g (0.01 mol) of KOAc, and 4 ml (0.04 mol) of Ac_2O was heated under reflux for 2 hr. The dark mixture was distilled *in vacuo* in a short path apparatus. The distillate in EtOH was mixed with 2 g of $NaHCO_3$ and evaporated to dryness. The residue was sublimed at 0.02 mm from a bath up to 150°. The sublimate was recrystallized from EtOH yielding 0.39 g (26%) of white crystalline solid, mp 107.5–108.5°. Principal spectral bands: uv 230, 251, 257, 261, 308, 314, 328, and 335 mμ; ir C=CH at 3070, C=O at 1765 and 1725, C=C/C=N at 1655, 1610, 1583, and 1558, C–N/C–O at 1207, 1165, 1084, and arom at 792; nmr (in $CDCl_3$) showed only vinyl and aromatic multiplets between δ 6.5 and 8.7.

Anal. Calcd for $C_8H_5NO_2$: C, 65.30; H, 3.42; N, 9.52. Found: C, 65.19; H, 3.36; N, 9.79.

This same azacoumarin was obtained by twice subliming a sample of [(3-hydroxy-2-pyridyl)methylene]malonic acid (below) at 0.01 mm from a bath up to 200°. It was recrystallized from EtOH, mp 107.5–108.5°.

[(3-Hydroxy-2-pyridyl)methylene]malonic Acid.—A solution of 1.23 g (0.01 mol) of 3-hydroxypicolinaldehyde[7] and 1.56 g (0.015 mol) of malonic acid in 25 ml of abs EtOH was heated under reflux with stirring for 2 hr. Solid separated during the first 5 min. After cooling, the solid was collected and dried giving 0.94 g (54.4%) of yellow-tan crystals, mp 174.5–175.5° dec. A sample for analysis was dissolved in DMSO at room temp, filtered, and diluted with methanol giving yellow-tan solid melting with decomposition between 163° and 179.5° depending on the rate of heating.

Anal. Calcd for $C_9H_7NO_5$: C, 51.68; H, 3.37; N, 6.70. Found: C, 51.50; H, 3.38; N, 6.64.

2-Oxo-2*H*-pyrano[3,2-*b*]pyridine-3-carboxylic Acid (16).—A mixture of 5.1 g (0.03 mol) of [(3-hydroxy-2-pyridyl)methyl)-methylene]malonic acid and 20 g of polyphosphoric acid was heated with stirring in a bath at 125–130° for 20 min. After cooling the mixture was well mixed with 100 ml of H_2O and the resulting solid was collected, washed (H_2O), and dried yielding 3.77 g (68%) of white solid, mp 192–193° dec.

Anal. Calcd for $C_9H_5NO_4$: C, 56.55; H, 2.64; N, 7.33; equiv wt, 191.1. Found: C, 56.42; H, 2.68; N, 7.32. equiv wt, 189.

7-Hydroxy-2*H*-pyrano[2,3-*b*]pyridin-2-one (7).—To 23.6 g (0.16 mol) of 2,6-dihydroxypyridine hydrochloride was cautiously added 70 ml of concd H_2SO_4. After the evolution of HCl had ceased 22 g (0.164 mol) of malic acid was added and the solution was heated with stirring under N_2 on a steam bath for 5.75 hr. After cooling the solution was poured into 300 ml of ice water and allowed to stand at 0–5° for 3 days. The resulting crystalline solid was collected, washed (ice water), and dried giving 6.1 g of light brown solid. This was sublimed at 0.01 mm from a bath up to 262° giving 4 g of solid, mp 280–290° dec. This was recrystallized from 70% aq EtOH and then from ethylene glycol monomethyl ether (with Darco G-60 treatment) yielding 2 g (7.7%) of nearly white solid, mp 293–297° dec.

Anal. Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.69; H, 3.01; N, 8.51.

Ethyl β-(2-Hydroxy-4,6-dimethyl-3-pyridine)-β-oxopropionate (21).—To a warm mixture of 2.4 g (0.1 mol) of NaH (4.5 g of 54% suspension in mineral oil), 11.8 g (0.1 mol) of diethyl carbonate, and 60 ml of toluene was slowly added with stirring 8.3 g (0.05 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine. Solvent was slowly distilled through a short column to bp 109°. After cooling, water was added. The aqueous layer was washed with ether and acidified (pH 6) with AcOH. The resulting solid was collected, washed (H_2O), and dried giving 4.83 g of tan crystals, mp 127–129°. This was recrystallized from 40 ml of abs EtOH (with Darco G-60 treatment) yielding 4.05 g (34%) of light yellow crystals, mp 132–133°. Ir, uv, and nmr spectra confirm the proposed structure.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.67; H, 6.35; N, 5.91.

3-Acetyl-4,6-dimethyl-2-pyridyl 3,4,5-Trimethoxybenzoate (23b).—To a suspension of 82.5 g (0.5 mol) of 3-acetyl-2-hydroxy-4,6-dimethylpyridine in 500 ml of dry pyridine was slowly added during 25 min 138 g (0.6 mol) of 3,4-trimethoxybenzoyl chloride. After heating on a steam bath for 15 min and standing overnight the mixture was poured into ice water and extracted with ether. The ether solution was washed (cold dil NaOH and H_2O) and dried (Na_2SO_4), evaporated, and crystallized from 2-propanol giving 102.7 g (68%) of solid, mp 82–91°. This was recrystallized from 2-propanol yielding 86 g (48%) of yellow crystals, mp 85–88°. A sample recrystallized again from 2-propanol (with Darco G-60 treatment) had mp 87–90°.

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.37; H, 5.95; N, 4.16.

1-(2-Hydroxy-4,6-dimethyl-3-pyridyl)-3-(3,4,5-trimethoxyphenyl)propane-1,3-dione (24b).—To a solution of 21.7 g (0.06 mol) of the above ester (**23b**) in 150 ml of pyridine was slowly added with stirring 9 g of powdered 85% KOH. The mixture, containing gummy solid was placed on a mechanical shaker and shaken overnight. Most of the pyridine was distilled, under reduced pressure, and the residue was mixed with ice water and adjusted to pH 6.5 with AcOH. The resulting fluffy yellow solid was collected, washed (H_2O), and dried giving 12.9 g solid, mp 181–183°. This was recrystallized from a mixture of

700 ml of ethanol and 300 ml of methanol yielding 12.2 g (61%) of yellow crystals, mp 183.5–185°.

Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.32; H, 5.75; N, 3.92.

2-(3,4,5-Trimethoxyphenyl-5,7-dimethyl-4*H*-pyrano[2,3-*b*]pyridin-4-one (25b).—To a suspension of 7 g (0.0195 mol) of the above dione (**24b**) in 105 ml of AcOH was added with stirring 2.6 ml of concd H_2SO_4. After heating on a steam bath for 45 min the solution was cooled, poured into ice water, and neutralized with NaOH. The resulting solid was collected, washed (H_2O), and dried giving 6.73 g (100%) of solid, mp 203–206°. Recrystallization from 175 ml of benzene yielded 4.49 g of light yellow crystals, mp 204–206°.

Anal. Calcd for $C_{19}H_{19}NO_6$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.47; H, 5.69; N, 3.98.

1-(2-Hydroxy-4,6-dimethyl-3-pyridyl)-3-phenylpropane-1,3-dione[9] (24a).—This was prepared by a process similar to that used for **24b** above. The intermediate 3-acetyl-4,6-dimethyl-2-pyridylbenzoate was distilled, bp 150° (0.05 mm), but was not highly pure. The dione **24a** was obtained in a 62% yield (mp 199–210°) from 3-acetyl-2-hydroxy-4,6-dimethylpyridine on neutralization of the basic solution. After recrystallization of 8.84 g from ethylene glycol monomethyl ether and then from a large volume of methanol 4.6 g of fluffy needles was recovered, mp 220–227° (Bonsall and Hill[9] report mp 220–226°).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.82; N, 5.40.

5,7-Dimethyl-2-phenyl-4*H*-pyrano[2,3-*b*]pyridin-4-one[9] (25a).—This was prepared by a process similar to that used for **25b** above. A yield of 72.5% of yellow-tan crystals after recrystallization from EtOH, mp 182.5–184.5° (Bonsall and Hill[9] report mp 182–184°).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.58. Found: C, 76.57; H, 5.29; N, 5.88.

Registry No.—**1**, 25957-01-1; **2**, 25957-02-2; **3**, 25957-03-3; **4**, 25957-04-4; **5**, 25957-05-5; **6**, 25957-06-6; **7**, 25957-07-7; **8**, 25957-08-8; **9**, 25957-09-9; **10**, 25957-10-2; **11**, 25957-11-3; **12**, 25957-12-4; **13**, 25957-13-5; **14**, 25957-14-6; **15**, 25957-15-7; **16**, 25957-16-8; **17**, 25957-17-9; **18**, 25957-18-0; **19**, 25957-19-1; **20**, 25957-20-4; **21**, 25957-21-5; **23b**, 25957-22-6; **24a**, 25957-24-8; **24b**, 25957-25-9; **25b**, 25957-26-0; 3-acetyl-2-hydroxy-6-methylpyridine, 25957-23-7; [(3-hydroxy-2-pyridyl)methylene]malonic acid, 25957-27-1.

Dianions Derived from Glutarimide, 3,5-Morpholinedione, and 3,5-Thiomorpholinedione as Useful New Synthetic Intermediates[1]

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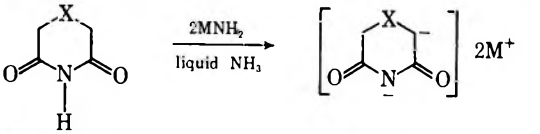
Glutarimide, 3,5-morpholinedione, and 3,5-thiomorpholinedione were converted to their respective dianions by means of slightly more than 2 mol equiv of sodium amide in liquid ammonia. Reactions of the dianions derived from glutarimide and 3,5-morpholinedione with alkyl halides and carbonyl compounds afforded α-substituted derivatives of the parent heterocycles. The dianion of 3,5-thiomorpholinedione gave a similar monosubstituted derivative on treatment with methyl benzoate but underwent a dicondensation reaction with benzophenone and polyalkylation with *n*-butyl bromide. Satisfactory monoalkylation at the α carbon of 3,5-thiomorpholinedione was accomplished when lithium amide was used to generate the dianion. Synthetically useful yields were obtained in a majority of the reactions of these new dianions.

Part A

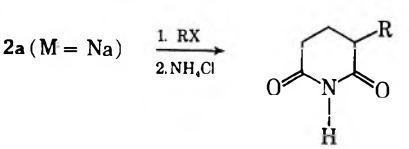
Conventional methods for introduction of substituents at one or both of the α carbons of glutarimide (**1a**), 3,5-morpholinedione (**1b**), and 3,5-thiomorpholinedione (**1c**) involve cyclization of appropriately substituted glutaric, diglycolic, and thiodiglycolic acid derivatives, respectively.[3] Such procedures require the preparation of a number of intermediates, with each member of a series requiring the synthesis of a separate acyclic precursor.

In the present study we have found that dianion **2a–c**,[4] prepared from **1a–c** by means of 2.3–2.4 mol equiv of alkali amide in liquid ammonia, can serve as convenient intermediates for the synthesis of a number of α-substituted derivatives of **1a–c** by virtue of their regiospecific reactions with electrophilic reagents.



1a, X = $-CH_2-$ **2a**, X = $-CH_2-$
b, X = $-O-$ **b**, X = $-O-$
c, X = $-S-$ **c**, X = $-S-$

Results with the Glutarimide Dianion (2a).—Alkylations of dianion **2a** (M = Na) with a series of primary halides produced monlsubstituted glutarimides of type **3** (Table I). Structural assignments for these compounds were based on nmr spectra (see Experimental Section), and acid-catalyzed hydrolysis to the appropriate 2-alkylglutaric acids in 80–90% yield.



3

* To whom correspondence should be addressed.

(1) (a) Supported by the Public Health Service, Research Grant No. GM 14340 from the National Institute of General Medical Sciences. (b) For a preliminary account of a porton of this work, see J. F. Wolfe and T. G. Rogers, *Chem. Commun.*, 1040 (1967).

(2) Abstracted from the Ph.D. Thesis of T. G. R., Virginia Polytechnic Institute, Aug 1968.

(3) For examples of such a synthetic procedure as applied to glutarimide derivatives, see (a) T. Kametani, W. Taub, and D. Ginsburg, *Bull. Chem. Soc. Jap.*, **31**, 357 (1958). (b) T. Y. Yu and M. Y. Huang, *Hua Hsueh Hsueh Pao*, **25**, 146 (1959); *Chem. Abstr.*, **54**, 4564*i* (1960). (c) For examples of the synthesis of substituted 3,5-morpholinediones, see F. A. Baron and C. A. Vanderwerf, *J. Med. Chem.*, **10**, 276 (1967). (d) See G. S. Skinner and R. M. MacNair, *J. Org. Chem.*, **25**, 1164 (1960), and references cited therein for examples of the synthesis of substituted 3,5-thiomorpholinediones.

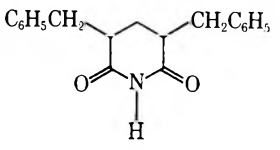
(4) See C. R. Hauser and D. R. Bryant, *J. Amer. Chem. Soc.*, **83**, 3468 (1961), and R. F. C. Brown, *Aust. J. Chem.*, **17**, 154 (1964), for what appear to be the only previous reports of dianions derived from cyclic imides.

TABLE I
ALKYLATIONS OF DIANION 2a (M = Na) TO FORM 2-ALKYLGLUTARIMIDES (3)[f]

Alkyl halide	R (no.)	Mp, °C	Yield, %
C_2H_5Br	Ethyl (3a)	101–102[a,b]	66
n-C_4H_9Br	n-Butyl (3b)	97–98[c]	77
n-$C_8H_{17}Br$	n-Octyl (3c)	104–105[a]	59
$C_6H_5CH_2Cl$	Benzyl (3d)	142–144[d,e]	80
p-$ClC_6H_4CH_2Cl$	p-Chlorobenzyl (3e)	158–159.5[d]	56
p-$CH_3OC_6H_4CH_2Cl$	p-Methoxybenzyl (3f)	152–153[d]	83
1-$C_{10}H_7CH_2Cl$	1-Naphthylmethyl (3g)	184–185[d]	65
CH_2=$CHCH_2Br$	Allyl (3h)	107–108[a]	78
$ClCH_2COONa$	Carboxymethyl (3i)	194–196[d]	23

[a] Recrystallized from heptane–acetone. [b] Lit.[3b] mp 103–104°. [c] Recrystallized from heptane. [d] Recrystallized from 95% ethanol. [e] Lit.[3b] mp 143–144.5°. [f] Satisfactory analytical values (±0.3%) were reported for all new compounds: Ed.

In an attempt to apply the present approach to the synthesis of 2,4-dialkylglutarimides, benzyl derivative **3d** was treated with 2.4 mol equiv of sodium amide in liquid ammonia followed by benzyl chloride to give dibenzyl derivatives **4**[5] (37%) and **5** (10%). The structure of **4** was confirmed by its hydrolysis to give the high-melting diastereomer of 2,4-dibenzylglutaric acid.[6]



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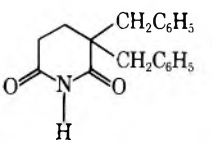

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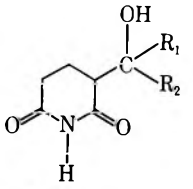
Next, reactions of dianion **2a** (M = Na) with several types of carbonyl compounds were investigated (Table III). This intermediate underwent addition with benzophenone (71%), fluorenone (55%), and cyclohexanone (8%)[7] to produce tertiary alcohols **6**, **7**, and **8**, respectively. Carbinols **6** and **7** were dehydrated



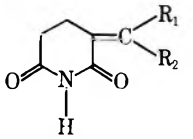
6, $R_1 = R_2 = C_6H_5$

7, R_1 and R_2 = 

8, R_1 and $R_2 = -(CH_2)_5-$

12a, $R_1 = H$; $R_2 = p$-$C_6H_4OCH_3$; mp 114–115°

12b, $R_1 = H$; $R_2 = p$-$C_6H_4OCH_3$; mp 154–155.5°



9, $R_1 = R_2 = C_6H_5$

10, R_1 and R_2 = 

13, $R_1 = H$; $R_2 = p$-$C_6H_4OCH_3$

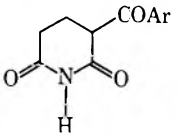
(5) The sharp melting point of this compound was indicative of a single diastereomer.

(6) L. Eberson, *Acta Chem. Scand.*, **12**, 314 (1958).

(7) The low yield obtained in this reaction was presumably due to appreciable ionization of an α-hydrogen of the ketone by dianion **2a**; see R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).

with p-toluenesulfonic acid in refluxing benzene to yield unsaturated derivative **9** and **10**, the former of which was hydrolyzed to give 2-(diphenylmethylene)-glutaric acid. Dianion **2a** reacted similarly with anisaldehyde to give in low yields the diastereomeric alcohols **12a** and **12b**, each of which was dehydrated to form **13**.

Treatment of dianion **2a** (M = Na) with the appropriate aromatic esters produced 2-aroylglutarimides **14a–c**, which were subsequently hydrolyzed to form 4-aroylbutyric acids **15a–c**.

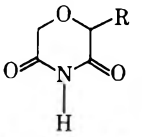


$\xrightarrow[-CO_2]{\text{acid}}$ $ArCOCH_2CH_2CH_2CO_2H$

15a, Ar = C_6H_4
b, Ar = p-$C_6H_4OCH_3$
c, Ar = p-C_6H_4Cl

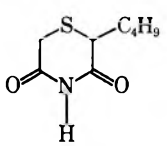
14a, Ar = C_6H_5
b, Ar = p-$C_6H_4OCH_3$
c, Ar = p-C_6H_4Cl

Results with the 3,5-Morpholinedione Dianion (2b).—Reactions of dianion **2b** (M = Na) with a representative series of electrophiles paralleled those of dianion **2a** (Table IV). Thus, treatment of **2b** with benzyl bromide, p-chlorobenzyl chloride, and n-butyl bromide produced C-alkyl derivatives **16a–c**. Dianion **2b** also underwent condensation with benzophenone to afford carbinol **16d** and aroylation with methyl benzoate to give β-keto imide **16e**.



16a, R = $CH_2C_6H_5$
b, R = p-$CH_2C_6H_4Cl$
c, R = n-C_4H_9
d, R = $-C(C_6H_5)_2$ (OH)
e, R = COC_6H_5

Results with the 3,5-Thiomorpholinedione Dianion (2c).—In contrast to the clean alkylations of dianions **2a** and **2b**, addition of n-butyl bromide to dianion **2c** (M = Na) afforded an oily mixture consisting of monobutyl derivative **17**, both diastereomers of 2,6-dibutyl derivative **18**, and 2,2,6-tributyl derivative **19** in a relative ratio of 7:6:1,[8] as determined by vapor phase chromatography (vpc). Formation of **18** and **19** was subsequently minimized by slow addition of **2c** (M = Li)



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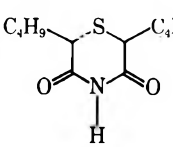
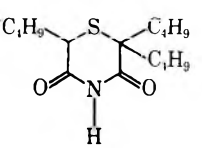


18



19

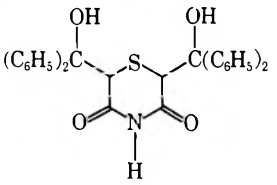
to excess n-butyl bromide in liquid ammonia. This procedure afforded predominately monobutyl derivative **17**, which was isolated in 42% yield by direct crystallization of the crude product mixture.

Dianion **2c** (M = Na) underwent a twofold reaction with benzophenone to form dialcohol **20**; none of the expected monoadduct was isolated. Interestingly, the

(8) The value assigned to dibutyl derivative **18** represents the total concentration of both diastereomers.

yield of **20** was critically dependent on reaction time. For example, a 45% yield of **20** was obtained when the reaction was neutralized after 3–5 min, whereas neutralization after 10 min lead to nearly quantitative recovery of benzophenone.

Finally, reaction of dianion **2c** (M = Na) with methyl benzoate afforded monobenzoyl derivative **21**, uncontaminated by higher benzoylation products.



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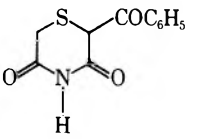


21

Part B

Experimental Section[9]

Formation and Deuteration of the Glutarimide Dianion (2a).—To 0.074 mol[10] of sodium amide,[11] prepared from 0.074 g-atom of sodium metal in 400 ml of commercial anhydrous liquid ammonia, contained in a 500-ml, three-necked flask equipped with an air-cooled condenser and a mechanical stirrer, was added 3.39 g (0.03 mol) of finely powdered glutarimide (**1a**).[12] After 30 min, the resulting thick white suspension was assumed to contain 0.03 mol of dianion **2a** (M = Na).

Similarly, addition of 0.03 mol of **1a** to a stirred suspension of 0.07 mol of potassium amide[13] produced a thick white suspension of **2a** (M = K).

A suspension of 0.03 mol of **2a** (M = Na) was prepared as described above, and the ammonia was than evaporated on a steam bath as an equal volume of anhydrous ether was added. To the resulting ethereal suspension was added 10 ml of 10 *N* deuterioacetic acid in deuterium oxide.[14] The acidified mixture was allowed to stir for 1 hr. The precipitate which formed was separated by filtration and washed with dry ether. The original ethereal solution and washing were combined, dried, and concentrated. The resulting solid was dried under vacuum and then sublimed twice to afford 1.87 g of deuterated **1a**, mp 154–156°. The nmr spectrum ($CDCl_3$) of this material had multiplets at δ 2.68 and 2.10 ppm for the C-2 and C-3 protons, respectively. The ratio of the intergrated intensities of these multiplets was 1.67:1, indicating incorporation of 0.66 of a deuterium atom at C-2 of imide **1a**. The spectrum of the deuterated material was devoid of NH absorption.

Alkylations of Dianion 2a.—To a stirred suspension of 0.03 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 0.033 mol of the appropriate halide as a solution in 20–30 ml of anhydrous ether. The reaction mixture was stirred for 1 hr, then neutralized with excess solid ammonium chloride. The liquid ammonia was evaporated (steam bath) as an equal volume of ether was added. To the resulting ethereal suspension was added a mixture of 75–100 ml of 6 *N* HCl and 250 g of crushed ice, and the resulting two-phase system was allowed to stir until the ice had melted. In reactions where the product separated between the aqueous and ethereal layers, it was collected by filtration and recrystallized from the appropriate solvent (Table I). The remaining ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal fractions were dried and concentrated; residues were recrystallized to afford additional product. In reactions where no solid appeared, the layers were separated and the aqueous layer was extracted with ether. The ethereal extracts were dried and concentrated to give the appropriate alkyl derivative, which was then recrystallized.

In the reaction of **2a** with sodium chloroacetate, the alkylating agent was added as a finely divided solid and the reaction was allowed to proceed for 3 hr. A reaction time of 3 hr was also required for optimum yields of octyl derivative **3c**. Highest yields of ethyl derivative **3a** were obtained by continuously extracting the aqueous layer with ether for 6 hr.

Yields and analytical data for alkylation products **3a–i** are presented in Table I. The ir spectra of these derivatives were characterized by NH adsorption at 3350–3400 and C=O absorption at 1700 cm^{-1}. All of the nmr spectra[15] had an NH singlet at 9.36–11.56 ppm. The spectra of **3d–g** had adsorption for the appropriate number of aromatic protons, with those of **3d** and **3e** appearing as singlets at 7.35 (5 H) and 7.62 (4 H), those of **3f** as a quartet at 7.50 (4 H), and those of **3g** as a multiplet at 8.20 ppm (7 H). The vinyl protons of **3h** appeared as multiplets at 5.82 (2 H) and at 6.0 ppm (1 H). The complex splitting patterns in the 1–3 ppm region of the spectra of alkyl derivatives **3a–c** and carboxymethyl derivative **3i** made it difficult to determine with certainty which of the signals were due to the hydrogens of the glutarimide ring, and which were attributable to the side-chain protons.

Reaction of 0.03 mol of dianion **2a** (M = Na) with 6.04 g (0.043 mol) of β-phenylethyl chloride afforded a clear oil with an ir spectrum very similar to that of styrene. Treatment of this oil with a solution of bromine in carbon tetrachloride until a color persisted, afforded 1.17 g of α,β-dibromoethylbenzene as white needles from 95% ethanol, mp 72.5–74° (lit.[16] 74–74.5°).

Attempted alkylation of dianion **2a** (M = Na) (0.03 mol) with 6.7 g (0.033 mol) of benzhydryl chloride produced 3.88 g (71%) of tetraphenylethylene, mp 222–224° (lit.[17] mp 222–224°). A mixture melting point with an authentic sample was not depressed.

Treatment of **2a** (M = Na) (0.03 mol) with isopropyl bromide (0.035 mol) as described above afforded only recovered **1a**.

Dipotassio derivative **2a** (M = K) (0.03 mol) was treated with benzyl chloride as described above to afford 4.0 g (65%) of benzyl derivative **3d**, mp 142–144°.

In one experiment imide **1a** (0.03 mol) was treated with 0.072 mol of freshly prepared lithium amide[18] in 400 ml of liquid ammonia for 1 hr to form presumably dilithio salt **2a** (M = Li). Subsequent addition of benzyl chloride (0.03 mol) was accompanied by the bright purple color associated with stilbene formation.[19] The reaction was processed in the usual manner to afford 0.9 g (15%) of **3d** and 1.04 g (35%) of stilbene, mp 121–123°, mmp (with an authentic sample)[19] 122–123°.

Hydrolysis of Alkylation Products 3a–e and 3g.—A 0.9–2.7-g sample of the appropriate alkylation product was refluxed for 24 hr with 100 ml of 6 *N* HCl. The reaction mixture was cooled and the 2-alkylglutaric acids were isolated either by filtration or extraction of the aqueous acid solution with ether. Several of the low-melting acids were slow to crystallize, but, once crystalline, their melting points were in excellent agreement with reported values. The results of these hydrolysis reactions are presented in Table II.

(9) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman Ir-5A infrared spectrophotomer; potassium bromide pellets were used for solids, and neat samples between sodium chloride plates were used for liquids. Nmr spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to internal tetramethylsilane, are measured to the center of a singlet or multiplet. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU spectrometer at 50 eV. Vapor phase chromatography (vpc) measurements were carried out on a Varian-Aerograph 90P chromatograph using a 5 ft × 0.25 in. stainless steel column packed with 20% SE-30 on 60–80 A/W DMSC Chromosorb W at 200–250° with helium as the carrier gas. Product ratios were determined by measuring peak areas using the method of triangulation. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and in our laboratories by Dr. C. S. Menon and Miss Q. H. Tan, using an F & M Model 185 C, H, and N analyzer. Unless otherwise specified, all chemicals were commercial reagent grade and were used without further purification. Anhydrous sodium sulfate was employed as a drying agent.

(10) This molar ratio of amide to starting imide **1a** consistently gave reproducible yields, whereas exactly 2 mol equiv of base led to erratic results in several instances.

(11) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

(12) G. Paris, L. Berlinguet, and R. Gaudry, *Org. Syn.*, **37**, 47 (1957).

(13) C. R. Hauser, and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

(14) This reagent was prepared by diluting 12.81 g of acetic anhydride to 25 ml with deuterium oxide (99.9% isotropic purity) and allowing the resulting solution to stir for 15 hr.

(15) The spectra of **3a–c** and **3h** were measured using $CDCl_3$ as the solvent The spectra of **3d–g** and **3i** were determined using DMSO-d_6 as the solvent.

(16) I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1938, p 644.

(17) L. J. Durham and H. S. Mosher, *J. Amer. Chem. Soc.*, **84**, 2811 (1962).

(18) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, **25**, 503 (1960).

(19) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Broadhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956).

TABLE II
HYDROLYSIS OF 2-ALKYLGLUTARIMIDES TO FORM 2-ALKYLGLUTARIC ACIDS ($HO_2CCHRCH_2CH_2CO_2H$)

2-Alkylglutarimide	Acid R	Yield, %	Mp, °C	Lit. mp, °C
3a	C_2H_5	84	59–61	58–60[a]
3b	n-C_4H_9	88	40–42	40[a]
3c	n-C_8H_{17}	73	50–52	50.5[b]
3d	$C_6H_5CH_2$	82	76–78	77–78[a]
3e	p-$ClC_6H_4CH_2$	93	141–142[c]	...[d]
3g	1-$C_{10}H_7CH_2$	91	145–147	144–146[a]

[a] M. F. Ansell and D. H. Hey, *J. Chem. Soc*, 1683 (1950). [b] L. Dubravkova, I. Jezo, P. Sefcovic, and Z. Voticky, *Chem. Zvesti*, **9**, 541 (1955); *Chem. Abstr.*, **50**, 16764*h* (1956). [c] Recrystallized from benzene–heptane. [d] *Anal.* Calcd for $C_{12}H_{13}ClNO_4$: C, 56.15; H, 5.10. Found: 56.37; H, 5.27.

Benzylation of 3d to Form Dibenzyl Derivatives 4 and 5.—To a stirred suspension of 0.048 mol of sodium amide in 400 ml of liquid ammonia was added 4.06 g (0.02 mol) of 2-benzylglutarimide (**3d**). After 1 hr, 2.53 g (0.02 mol) of benzyl chloride in 30 ml of anhydrous ether was added and the reaction mixture was allowed to stir for 1 hr before being processed as described for the alkylations of dianion **2a**. The ethereal extracts were concentrated to give a solid residue, which was recrystallized from 95% ethanol to produce 2.14 g (37%) of 2,4-dibenzylglutarimide (**4**): mp 138.5–140°; ir 3400 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.56 (s, 1, NH), 7.58 (m, 10 aromatic), 3.30 (m, 6, overlapping ring methine and CH_2Ph), and 1.71 ppm (t, 2, $-CH_2-$); mass spectrum, molecular ion peak at m/e 293 with abundant fragment peaks at m/e 174, 131, and 91.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.86; H, 6.39; N, 4.76.

The mother liquor from the above recrystallization was concentrated to afford a second crop of impure solid, which was recrystallized from heptane–chloroform to afford 0.56 g (10%) of 2,2-dibenzylglutarimide (**5**): mp 140–141.5°; ir 3400 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.04 (s, 1, NH), 7.60 (s, 10, aromatic), 3.19 (ABq, 4, CH_2Ph), 2.54 (m, 2, $-CH_2C=O$), and 1.90 ppm (m, 2, $-CH_2-$); mass spectrum, molecular ion peak at m/e 293 with abundant fragment peaks at m/e 202 and 91.

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.51; H, 6.47; N, 4.60.

A 2.27-g sample of **4** was refluxed for 36 hr with 150 ml of 6 *N* HCl. The precipitate which formed on cooling was recrystallized from 80% aqueous acetic acid to give 0.66 g of recovered **4** and three crops, totaling 1.40 g, of impure diacid, which was dissolved in chloroform and then extracted into aqueous $NaHCO_3$. The $NaHCO_3$ solution was acidified with concd HCl to precipitate 1.02 g (42%) of the pure, high-melting diastereomer of 2,4-dibenzylglutaric acid, mp 150–151.5° (lit.[6] mp 149–151°). The ir spectrum of this acid was identical with that of an authentic sample prepared by the method of Eberson;[6] a mixture melting point determination showed no depression.

Condensation of Dianion 2a with Ketones.—To a stirred suspension of 0.03 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 0.033–0.042 mol of the respective ketone in 30 ml of dry ether. After an appropriate time[20] the reaction mixture was neutralized by rapidly pouring it into a solution of excess ammonium chloride in 100 ml of liquid ammonia (inverse neutralization).[21] The ammonia was removed on the steam bath and replaced by 300–400 ml of ether. The resulting ethereal suspension was treated with 50 ml of 6 *N* HCl and 200 g of crushed ice. In the reactions with benzophenone and fluorenone, most of the product separated between the layers and was collected by filtration. The ethereal layers were also dried and concentrated to afford additional material. In the condensation with cyclohexanone the product was isolated entirely from the etheral layer. Yields and analytical data for products obtained in these reactions are given in Table III. The spectral characteristics of the products derived from these reactions were consistent with their assigned structures. Thus, **6**, **7**, and **8** had principal ir bands at 3250–3500 (NH and OH) and 1680–1700 cm^{-1} (C=O). The nmr spectrum of **6** had peaks (DMSO-d_6) at δ 11.20 (s, 1, NH), 7.94 (m, 10, aromatic), 5.80 (s, 1, OH),[22] 4.30 (t, 1, ring methine), 2.66 (m, 2, $-CH_2C=O$), and 1.80 ppm (m, 2, $-CH_2-$). The spectrum of **7** had peaks (DMSO-d_6) at δ 11.42 (s, 1, NH), 7.94 (m, 8, aromatic), 6.50 (s, 1, OH), 3.72 (m, 1, ring methine), 2.34 (m, 2, $-CH_2C=O$), and 1.38 ppm (m, 2, $-CH_2-$). The spectrum of **8** had peaks (DMSO-d_6) at δ 10.04 (s, 1, NH), 4.64 (s, 1, OH), 2.64 (m, 3, overlapping ring methine and $-CH_2C=O$), 2.10 (m, 2, $-CH_2-$), and 1.60 ppm (broad s, 10, cyclohexyl).

Condensation of Dianion 2a with Anisaldehyde.—To 0.05 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 9.53 g (0.07 mol) of anisaldehyde in 30 ml of dry ether. After 10 min the reaction mixture was neutralized inversely and processed as described for the condensation with ketones. The ethereal layer afforded a semicrystalline residue which was washed with petroleum ether (bp 40–60°) and recrystallized from heptane–acetone to give 1.36 g (11%) of high-melting diastereomer **12b**: ir 3200–3450 (NH and OH) and 1680 cm^{-1} (C=O; nmr (DMSO-d_6) δ 11.20 (s, 1, NH), 7.50 (q, 4, aromatic), 5.70 (s, 2, OH and side-chain CH), 3.90 (s, 3, OCH_3), 2.64 (m, 3, $-CH_2C=O$ and ring methine), and 1.76 ppm (m, 2, $-CH_2-$).

The mother liquor remaining from the recrystallization of **12b** was concentrated to dryness and the residue was recrystallized from benzene to give 0.97 g (8%) of low-melting diastereomer **12a**: ir 3200–3500 (NH and OH) and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 10.94 (s, 1, NH), 7.32 (q, 4, aromatic), 5.60 (d, 1, OH), 5.36 (t, 1, side-chain CH), 3.90 (s, 3, OCH_3), 2.96 (m, 1 ring methine), 2.48 (m, 2, $-CH_2C=O$), and 1.56 ppm (m, 2, $-CH_2-$).

Dehydration of Carbonyl Addition Products 6, 7, 12a, and 12b.—A 0.75-g sample of **6** was refluxed for 20 hr with 0.1 g of p-toluenesulfonic acid in 25 ml of benzene. The reaction mixture was cooled to afford a white solid, which was recrystallized from 95% ethanol to give 0.59 g (85%) of 2-diphenylmethyleneglutarimide (**9**): mp 197–198°; ir 3400 (NH), 1650, 1700, and 1710 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.02 (s, 1, NH), 7.54 (m, 10, aromatic), and 2.67 ppm (m, 4, $-CH_2C=O$ and $-CH_2-$).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.06; H, 5.34; N, 5.03.

Similarly, a 1.06-g sample of **7** afforded 0.58 g (58%) of 2-fluorenylideneglutarimide (**10**) as yellow plates from 95% ethanol: mp 201–202°; ir 3450 (NH), 1650 and 1700 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.96 (s, 1, NH), 8.20 (m, 8, aromatic), 3.64 (t, 2, $-CH_2C=O$), and 2.86 ppm (t, 2, $-CH_2-$).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.55; H, 4.73; N, 5.09. Found: C, 78.42; H, 4.99; N, 5.01.

Dehydration of 250 mg of **12a** with a few crystals of p-toluenesulfonic acid in 10 ml of refluxing benzene afforded 180 mg (78%) of 2-(p-methoxybenzylidene)glutarimide (**13**), as colorless needles from 95% ethanol: mp 171–172.5°; ir 3450 (NH), 1600 and 1670 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.40 (s, 1, NH), 8.18 (s, 1, vinyl), 7.72 (q, 4, aromatic), 4.04 (s, 3, OCH_3), 3.10 (m, 2, $-CH_2C=O$), and 2.74 ppm (m, 2, $-CH_2-$).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.55; H, 5.63; N, 6.06. Found: 67.80; H, 5.80; N, 6.04.

Similar treatment of a 1-g sample of **12b** produced 0.66 g (71%) of **13**, which had identical physical and spectral properties with those of a sample of **13** obtained by dehydration of **12a**.

Hydrolysis of Unsaturated Derivative 9.—A 1.0-g sample of unsaturated imide **9** was refluxed with 50 ml of a 1:1 v/v solution of 50% H_2SO_4–glacial acetic acid for 24 hr. The reaction mixture was cooled and extracted with ether. The ethereal extracts were dried and concentrated. Residual acetic acid was removed by vacuum distillation on a steam bath. The resulting red oil was triturated with a mixture of ether–petroleum ether (bp 40–60°) until crystallization occurred. The solid residue was then recrystallized from benzene–petroleum ether (bp 40–60°) to give 0.32 g (33%) of 2-diphenylmethyleneglutaric acid (**10**): mp 177–178°; ir 3100–3450 (COOH) and 1650 cm^{-1} (C=O); nmr (DMSO-d_6) δ 12.84 (s, 2, COOH), 7.40 (m, 10, aromatic), and 2.52 ppm (broad s, 4, $-CH_2CH_2-$).

(20) Reaction periods of 10 min, 0.5 hr, and 1 hr were employed with each ketone. Best yields were obtained with benzophenone, fluorenone, and cyclohexanone after 0.5 hr, 1 hr, and 10 min, respectively.

(21) This inverse neutralization procedure was employed to minimize possible reversion of the carbonyl addition; see ref 31.

(22) Signals arising from OH protons were assigned by adding several drops of deuterium oxide to the nmr sample and then rescanning the spectrum.

TABLE III

REACTIONS OF DIANION 2a (M = Na) WITH CARBONYL COMPOUNDS[d]

Carbonyl compound	Product	Mp, °C	Yield, %
Benzophenone	2-(α-Hydroxy-α,α-diphenylmethyl)-glutarimide (6)	184–187[a]	71
Fluorenone	2-(9-Hydroxy-9-flourenyl)-glutarimide (7)	210–211 dec[a]	55
Cyclohexanone	2-(1-Hydroxycyclohexyl) glutarimide (8)	158–159[b]	8
Anisaldehyde	2-(α-Hydroxy-p-methoxybenzyl)-glutarimide (12a)	114–115	8
Anisaldehyde	2-(α-Hydroxy-p-methoxybenzyl)-glutarimide (12b)	154–155.5	11
Methyl benzoate	2-Benzoylglutarimide (14a)	120.5–121.5[a]	72[c]
Methyl anisate	2-Anisoylglutarimide (14b)	169.5–170.5[a]	76[c]
Methyl p-chlorobenzoate	2-(p-Chlorobenzoyl)glutarimide (14c)	177–178[a]	67[c]

[a] Recrystallized from 95% ethanol. [b] Purified by sublimation at 130–150° (0.5–1.0 mm). [c] Yield based on ester. [d] Satisfactory analytical data (±0.3% in C, H, N) were submitted for all compounds: Ed.

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.18; H, 5.27.

Reaction of Dianion 2a with Aromatic Esters.—To a stirred suspension of 0.06 mol of dianion **2a** (M = Na) in 400 ml of liquid ammonia was added 0.03 mol of the appropriate ester in 20–30 ml of dry ether. The reaction mixture was stirred for 4–5 hr and then processed as in the alkylations of dianion **2a**. Yields and analytical data for the products from these reactions are given in Table III. The ir spectra of **14a–c** had NH absorption at 3450 and broad carbonyl absorption at 1610–1725 cm^{-1}. The nmr spectrum of **14a** had peaks (DMSO-d_6) at δ 11.46 (s, 1, NH), 8.20 (m, 5, aromatic), 5.14 (t, 1, ring methine), 2.64 (broad s, $-CH_2C{=}O$), and 2.32 ppm (m, 2, $-CH_2-$). The spectrum of **14b** had peaks (DMSO-d_6) at δ 11.38 (s, 1, NH), 7.84 (q, 4, aromatic), 5.04 (t, 1, ring methine), 4.0 (s, 3, OCH_3), 2.58 (broad s, $-CH_2C{=}O$), and 2.30 ppm (m, 2, $-CH_2-$). The spectrum of **14c** had peaks (DMSO-d_6) at δ 11.40 (s, 1, NH), 8.18 (q, 4, aromatic), 5.12 (t, 1, ring methine), 2.60 (broad s, 2, $-CH_2C{=}O$), and 2.30 ppm (m, 2, $-CH_2-$).

Hydrolysis of 2-Aroylglutarimides 14a–c.—A 1.0-g sample of **14a** was refluxed for 24 hr with 25 ml of 6 *N* HCl. The resulting solid was dissolved in ether, the ethereal layer was extracted with aqueous $NaHCO_3$, and the basic extracts were acidified with concd HCl to afford 0.84 g (87%) of 4-benzoylbutyric acid (**15a**), mp 128–130°. A mixture melting point determination with an authentic sample of this acid obtained from Aldrich Chemical Co. was undepressed; the ir spectra were identical. Similar hydrolysis of **14b** (0.5 g) gave 0.41 g (87%) of 4-anisoylbutyric acid, **15b**, mp 139.5–141° (lit.[23] 138–140°). Hydrolysis of **14c** (0.51 g) produced 0.46 g (99%) of 4-(p-chlorobenzoyl)butyric acid (**15c**), mp 125–126° (lit.[24] mp 123–125°).

Independent Synthesis of 2-Benzoylglutarimide (14a).—To a suspension of 20 g of a 60% mineral oil dispersion of sodium hydride[25] in 350 ml of 1,2-dimethoxyethane[26] (DME) contained in a 1-l. three-necked flask equipped with a condenser, mechanical stirrer, and pressure-equilizing addition funnel was added a solution of 11.3 g (0.10 mol) of 4-cyanobutyric acid[12] and 13.6 g (0.10 mol) of methyl benzoate in 75 ml of DME. The reactions mixture was refluxed under nitrogen for 70 hr. The DME was removed under vacuum to leave a pasty residue to which was added 150 ml of ether. The ethereal suspension was cooled in an ice bath and the excess sodium hydride was destroyed by cautious addition of 250 ml of cold water. The ethereal layer was separated and discarded. The aqueous layer was poured into a mixture of 100 ml of concd HCl and 600 g of crushed ice. The acidic solution was extracted with three 100-ml portions of ether. The extracts were dried and concentrated to give a red oil, which solidified after 2 days. The resulting crude solid was recrystallized from benzene to yield 12.2 g (56%) of 4-benzoyl-4-cyanobutyric acid (**27**): mp 98–99.5°; ir 3400 (COOH), 2500 (CN), and 1680 cm^{-1} (C=O); nmr (DMSO-d_6) δ 12.60 (s, 1, COOH), 8.18 (m, 5, aromatic), 5.46 (t, 1, PhCOCHCN), and 2.40 ppm (m, 4, $-CH_2-CH_2-$).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 4.10; N, 6.45. Found: C, 66.07; H, 5.12; N, 6.40.

A 1.0-g sample of **16** was heated with 5 ml of concd H_2SO_4 on a steam bath for 30 min. The resulting purple solution was poured cautiously onto crushed ice to precipitate 30 mg (4%) of 2-benzoylglutarimide (**14a**), mp 119–121°. A mixture melting point with a sample of **14a** prepared from dianion **2a** was not depressed.

Formation of the 3,5-Morpholinedione Dianion (2b).—To 0.07 mol of sodium amide in 400 ml of liquid ammonia was added 3.45 g (0.03 mol) of finely powdered 3,5-morpholinedione.[27] The resulting grey-green solution of dianion **2b** (M = Na) was allowed to stir for 30 min before being employed in the reactions described below.

Alkylations of Dianion 2b.—To 0.03 mol of dianion **2b** (M = Na), prepared as described above, was added 0.033 mol of the appropriate halide in 30 ml of dry ether. The reaction was allowed to proceed for 1 hr and was then processed as in the alkylations of dianion **2a**. Additional details are given in Table IV. Addition of benzyl bromide to **2b** produced none of the purple color characteristic of stilbene formation. Vpc analysis of crude butyl derivative **16c** showed <10% of polyalkylation products. The ir spectra of **16a–c** had principal bands at 3400 (NH) and 1700 cm^{-1} (C=O). The nmr spectrum of **16a** had peaks (DMSO-d_6) at δ 11.82 (s, 1, NH), 7.52 (s, 5, aromatic), 4.66 (q, 1, ring methine), 4.44 (s, 2, $-OCH_2C{=}O$), and 3.20 ppm (m, 2, $PhCH_2$). The spectrum of **16b** had peaks (DMSO-d_6) at δ 12.01 (s, 1, NH), 7.68 (s, 4, aromatic), 4.78 (q, 1, ring methine), 4.56 (s, 2, $-OCH_2C{=}O$), and 3.30 ppm (m, 2, $PhCH_2$). The spectrum of **16c** had peaks (Cl_3CCN) at δ 10.20 (s, 1, NH), 4.49 (ABq, 2, $-OCH_2C{=}O$), 4.21 (t, 1, ring methine), and 1.51 ppm (m, 9, n-C_4H_9).

Condensation of Dianion 2b with Benzophenone.—To 0.03 mol of dianion **2b** (M = Na) in 400 ml of liquid ammonia was added 6.20 g (0.034 mol) of benzophenone in 20 ml of dry ether over a period of 5 min. The reaction mixture was allowed to stir for 10 min, neutralized inversely, and then processed in the usual manner. The ir spectrum of **16d** had bands at 3450 (NH and OH) and 1690 cm^{-1} (C=O). The nmr spectrum had peaks (DMSO-d_6) at δ 11.98 (s, 1, NH), 7.76 (m, 10, aromatic), 6.42 (s, 1, OH), 5.72 (s, 1, $-OCHC{=}O$), and 4.58 ppm (AB q, 2, $OCH_2C{=}O$).

Reaction of Dianion 2b with Methyl Benzoate.—To 0.06 mol of dianion **2b** (M = Na) in 400 ml of liquid ammonia was added 4.08 g (0.03 mol) of methyl benzoate in 20 ml of anhydrous ether. The resulting olive-green suspension was stirred for 3 hr, neutralized directly with excess solid ammonium chloride, and worked up as in the aroylations of dianion **2a**. The ir spectrum of **16e** had peaks at 3450 (NH), 1640 and 1700 cm^{-1} (C=O). The nmr spectrum had peaks (DMSO-d_6) at δ 12.56 (s, 1, NH), 8.24 (m, 5, aromatic), 6.38 (s, 1, $-OCHC{=}O$), and 4.82 ppm (ABq, 2, $-OCH_2C{=}O$).

(23) M. G. Pratt, J. O. Hoppe, and S. Archer, *J. Org. Chem.*, **13**, 576 (1948).

(24) Dr. Ernst Berliner, Bryn Mawr College, personal communication, 1967.

(25) Obtained from Metal Hydrides Inc., Beverly, Mass.

(26) The DME was distilled from sodium ribbon immediately before use.

(27) This compound, mp 143–145°, was prepared by the method of W. Heintz, *Justus Liebigs Ann. Chem.*, **128**, 134 (1863): nmr (DMSO-d_6) δ 11.60 (s, 1, NH) and 4.37 ppm (s, 4, $-CH_2OCH_2-$).

TABLE IV

REACTIONS OF DIANION 2b (M = Na) WITH ALKYL HALIDES AND CARBONYL COMPOUNDS

Halide or carbonyl compound	Product	Mp, °C	Yield, %	Formula	Calcd, %			Found, %	
					C	H	N	C	H
Benzyl bromide	2-Benzyl-3,5-morpholinedione (16a)	92–93[a]	46	$C_{11}H_{11}NO_3$	64.38	5.40	6.83	64.08	5.50	6.62
p-Chlorobenzyl chloride	2-(*p*-Chlorobenzyl)-3,5-morpholinedione (16b)	135–136.5[a]	54	$C_{11}H_{10}ClNO_3$[d]	55.13	4.21	5.84	55.16	4.35	5.76
n-Butyl bromide	2-*n*-Butyl-3,5-morpholinedione (16c)	60–61.5[b]	67	$C_8H_{13}NO_3$	56.13	7.65	8.18	56.37	7.85	7.92
Benzophenone	2-(α-Hydroxy-α,α-diphenylmethyl)-3,5-morpholinedione (16d)	160–161.5[a]	45	$C_{17}H_{15}NO_4$	68.68	5.09	4.71	68.50	5.15	4.45
Methyl benzoate	2-Benzoyl-3,5-morpholinedione (16e)	135–136.5[a]	23[c]	$C_{11}H_9NO_4$	60.27	4.14	6.39	60.38	4.24	6.14

[a] Recrystallized from 95% ethanol. [b] Recrystallized from heptane. [c] Yield based on ester. [d] Calcd: Cl, 14.79. Found: Cl, 14.95.

Benzylation of 1b by Means of Sodium Hydride.—A mixture of 11.51 g (0.1 mol) of **1b**, 0.13 mol of methyl benzoate, and 20 g of sodium hydride dispersion in 450 ml of DME was refluxed under nitrogen for 115 hr. The DME was removed under vacuum and 150 ml of ether was added to the resulting red paste. To the ethereal suspension was cautiously added 150 ml of glacial acetic acid. The acidified mixture was filtered and the filtrate was dried and concentrated. The residue was washed with sufficient petroleum ether (bp 30–60°) to remove the mineral oil. The remaining yellow semisolid was dissolved in ether and the ethereal solution was washed with aqueous $NaHCO_3$, dried, and concentrated to afford, after initial recrystallization from benzene and then from 95% ethanol, 4.47 g (34%) of **16e**. The ir spectrum of this material was identical with that of a sample of **16e** prepared from dianion **2b**; a mixture melting point showed no depression.

Formation of the 3,5-Thiomorpholinedione Dianion (2c).—To 0.048 mol of sodium amide in 400 ml of liquid ammonia was added 2.62 g (0.02 mol) of finely powdered 3,5-thiomorpholinedione (**1c**).[28] After 30 min, the resulting dark green solution was presumed to contain 0.02 mol of dianion **2c** (M = Na).

Similarly, addition of 0.02 mol of **1c** to 0.048 mol of lithium amide in 400 ml of liquid ammonia afforded, after 30 min, a green solution of dilithio derivative **2c** (M = Li).

Alkylations of Dianion 2c. A. Benzyl chloride.—To 0.03 mol of dianion **2c** (M = Na), prepared as described above, was added 4.60 g (0.036 mol) of benzyl chloride in 30 ml of dry ether. No stilbene formation was evident. The reaction mixture was stirred for 1 hr and worked up as described for the alkylations of dianion **2a**. The resulting oil was shown by vpc to contain unreacted halide, starting imide **1c**, and at least three other components, which were assumed to be mono- and polyalkylation products.

B. *n*-Butyl Bromide.—Addition of an ethereal solution of 0.02 mol of this halide to 0.02 mol of dianion **2c** (M = Na) in 400 ml of liquid ammonia gave, after a reaction period of 1 hr, 2.38 g of red oil, which failed to crystallize. Vpc analysis revealed the presence of (in order of elution) 2-*n*-butyl-3,5-thiomorpholinedione (**17**), the two diasteromers of 2,6-di-*n*-butyl-3,5-thiomorpholinedione (**18**), and 2,2,6-tri-*n*-butyl-3,5-thiomorpholinedione (**19**) in a relative ratio of 7:6:1. A sample of monobutyl derivative **17**, collected from the chromatograph column at 200°, had mp 61–62.5°; ir 3450 (NH) and 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.20 (s, 1, NH), 3.76 (sharp s superimposed on broad m, 3, $-SCH_2C{=}O$ and ring methine), and 1.64 ppm (m, 9, *n*-C_4H_9).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48; S, 17.12. Found: C, 51.19; H, 6.97; N, 7.48; S, 17.03.

A sample of tributyl derivative **19** collected at 200° for spectral analysis, had nmr peaks ($CDCl_3$) at δ 8.48 (s, 1, NH), 3.90 (m, 1, ring methine), and 1.50 ppm (m, 27, *n*-C_4H_9); mass spectrum, molecular ion peak at *m/e* 299 with abundant fragment peaks at *m/e* 243 and 242. The two diastereomers of dibutyl derivative **18** were separated and collected from the chromatography column at 175°. The more volatile diastereomer had nmr peaks ($CDCl_3$) at δ 9.14 (s, 1, NH), 3.76 (m, 2, –CHSCH–), and 1.64 ppm (m, 18, *n*-C_4H_9); mass spectrum, molecular ion peak at *m/e* 243 with abundant fragment peaks at *m/e* 187 and 55. The less volatile diastereomer had nmr peaks ($CDCl_3$) at δ 9.00 (s, 1, NH), 4.00 (m, 2, –CHSCH–), and 1.82 (m, 18, *n*-C_4H_9); mass spectrum, molecular ion peak at *m/e* 243 with abundant fragment peaks at *m/e* 187 and 55.

A solution of 0.02 mol of **2c** (M = Li) in 300 ml of liquid ammonia was prepared in a 500-ml three-necked flask, equipped with a mechanical stirrer, air-cooled condenser, and an outlet tube at the bottom, which was connected *via* a ball and socket stopcock adapter to the center neck of a second 500-ml three-necked flask. The lower flask, which was equipped with an air-cooled condenser and magnetic stirrer, was charged with 0.06 mol of *n*-butyl bromide in 100 ml of liquid ammonia. The contents of the upper flask were added to the solution of halide in the lower flask over a period of 1 hr. The resulting mixture was stirred for an additional 30 min, neutralized with excess solid ammonium chloride, and processed in the usual fashion to give 3.07 g of a yellow oil. Analysis of the oil by vpc revealed the presence of **17**, **18**, and **19** in a ratio of 100:20:1. Dissolution of

(28) This compound, mp 129–131°, was prepared according to the method of C. Barkenbus and P. S. Landis, *J. Amer. Chem. Soc.*, **70**, 684 (1948): nmr (acetone-d_6) δ 3.96 ppm (s, $-CH_2SCH_2-$).

the oil in heptane, followed by cooling and seeding with a sample of **17** collected by vpc, produced 1.55 g (42%) of monobutyl derivative **17**, mp and mmp 59–61°.

Condensation of Dianion 2c with Benzophenone.—To a stirred solution of 0.02 mol of dianion **2c** (M = Na) in 400 ml of liquid ammonia was added 4.0 g (0.022 mol) of benzophenone in 30 ml of anhydrous ether. The resulting navy-blue solution was stirred for 4–5 min then poured rapidly into a solution of excess ammonium chloride in 100 ml of liquid ammonia. The ammonia was replaced by ether and the ethereal suspension was treated with enough cold dilute HCl to acidify the mixture. The resulting thick organic precipitate was collected by suction filtration and recrystallized from heptane–acetone to give 1.74 g (45% based on dianion **2c**) of 2,6-bis(α-hydroxy-α,α-diphenylmethyl)-3,5-thiomorpholinedione (**20**): mp 150–151°; ir 3400 (NH and OH) and 1680 cm^{-1} (C=O); nmr (DMSO-d_6) δ 11.24 (s, 1, NH), 7.68 (m, 20, phenyl), and 6.0 ppm (broad s, 4, OH and -CHSCH-).

Anal. Calcd for $C_{30}H_{25}NO_4S$: C, 72.71; H, 5.08; N, 2.83; S, 6.47. Found: C, 72.60; H, 4.82; N, 2.73; S, 6.54.

In another experiment, the reaction mixture was neutralized inversely after 10 min to afford a quantitative recovery of benzophenone, which was isolated as its 2,4-dinitrophenylhydrazone, mp 239°.

Reaction of Dianion 2c with Methyl Benzoate.—To a solution of 0.02 mol of dianion **2c** (M = Na), prepared as described above, was added 1.36 g (0.01 mol) of methyl benzoate in 30 ml of dry ether. The reaction mixture was allowed to stir for 4 hr and was then processed in the usual manner to give a crude yellow solid, which was recrystallized from benzene to furnish 1.51 g (45% based on ester) of 2-benzoyl-3,5-thiomorpholinedione (**21**) as yellow platelets: mp 134–136°; ir 3450 (NH), 1625 and 1680 cm^{-1} (C=O). The nmr spectrum of **21** was obtained in two solvents of different polarity. In DMSO-d_6, peaks were observed at δ 12.50 (s, 1, NH), 8.50 (m, 5, aromatic), 6.42 (s, 1, ring methine), and 3.84 ppm (ABq, 2, $-SCH_2C=O$). In $CDCl_3$ peaks were observed at δ 15.70 [s, $-SC=C(OH)Ph$], 9.26 (s, 1, NH), 8.06 (m, 5, aromatic), 5.44 (s, ring methine), and 3.62 ppm (ABq, 2, $-SCH_2C=O$).

Benzoylation of 1c by Means of Sodium Hydride.—A mixture of 2.62 g (0.02 mol) of **1c**, 2.73 g (0.02 mol) of methyl benzoate, and 8.0 g of sodium hydride dispersion in 350 ml of DME was refluxed under nitrogen for 22 hr. The reaction was processed as in the sodium hydride benzoylation of **1b** to produce 3.81 g (81%) of **21**: mp 127–129°, and 134–136° after two recrystallizations from benzene. The infrared spectrum of this material was identical with that of a sample prepared by benzoylation of dianion **2c**.

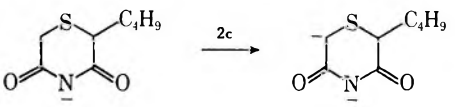
Discussion

Certain additional comments concerning the chemistry of dianions **2a–c** are now presented in this section.

As mentioned above, alkylations of dianion **2a** (M = Na) with the primary halides listed in Table I proceeded smoothly. However, attempted alkylations with β-phenylethyl chloride and benzhydryl chloride afforded styrene and tetraphenylethylene, respectively. Apparently dianion **2a** served as a base rather than a nucleophile in these two instances to effect elimination in the case of the former halide and dimerization of the latter.[29] Competitive elimination may also have been responsible for the failure of dianion **2a** to undergo satisfactory alkylation with isopropyl bromide. When dianion **2a** (M = K) was prepared by means of potassium amide and alkylated with benzyl chloride, the yield (65%) of benzyl derivative **3d** was comparable to that (80%) obtained with sodium amide. In a similar experiment employing lithium amide, **3d** was obtained in only 15% yield and stilbene (35%) was isolated, indicating that the twofold ionization of **1a** to form **2a** (M = Li) was incomplete.[30]

(29) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960), have observed similar elimination and dimerization reactions on treatment of acetylacetone dianion with these halides.

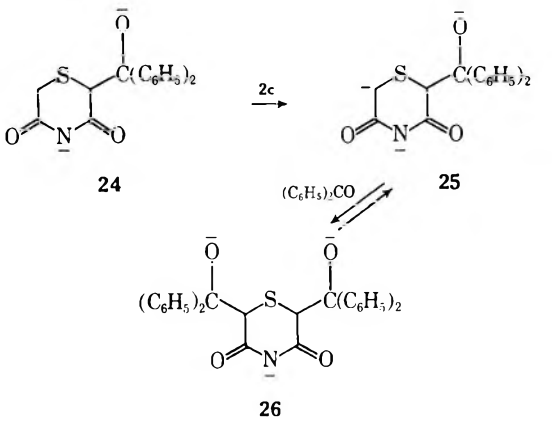
The tendency for dianion **2c** (M = Na) to yield appreciable amounts of polyalkylation products is undoubtedly caused by rapid proton–metal exchange between this intermediate and alkylated monoanion **22** to produce dianion **23**, which then undergoes further alkylation. When the more covalent dilithio derivative of **2c** is employed, the exchange reaction is inhibited and monoalkylation predominates. In addition, inverse mixing of the reactants serves to suppress the formation of alkylated dianion **23** by keeping the concentration of original dianion **2c** low throughout the reaction.



22 **23**

Formation of dialcohol **20** in the reaction of **2c** (M = Na) with benzophenone evidently involves a similar proton–metal exchange in which the initially formed intermediate **24** loses a methylene proton to dianion **2c** to form trianion **25**. Reaction of **25** with a second molecule of benzophenone then produces trianion **26**, which affords dicondensation product **20** on neutralization (Scheme I). The fact that the yield of **20** decreased dramatically, while the recovery of benzophenone increased, when neutralization was delayed, implies that this reaction represents an example of kinetic *vs.* thermodynamic control in which the kinetically favored intermediate **26** is eventually converted to the thermodynamically more stable monanion of **1c** and the sodium amide adduct of benzophenone.[31]

SCHEME I



24 **25**

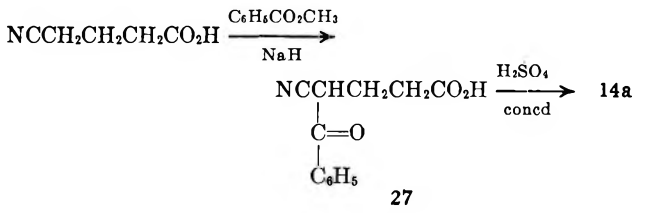
26

During the course of the present work, several alternative methods for the preparation of α-benzoyl derivatives **14a**, **16e**, and **21** were investigated. Thus, **14a** was synthesized through cyano keto acid **27** as shown in Scheme II, but the overall yield was quite low. Direct introduction of a benzoyl group at the α position of **1b** and **1c** was accomplished satisfactorily on treatment of these compounds with methyl benzoate and excess sodium hydride in refluxing 1,2-dimethoxyethane (DME). However, sodium hydride was not suitable

(30) See R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967), and references cited therein.

(31) For a discussion of kinetic *vs.* thermodynamic control in the addition of benzophenone to 1,3-dialkali salts of phenylacetamide in liquid ammonia, see E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3317 (1966).

Scheme II



for alkylations and carbonyl addition condensations involving **1a–c**, presumably because dianion formation was incomplete with this reagent.[32]

The present dianion route to α-substituted derivatives of **1a–c** permits the synthesis of a variety of such compounds in a single operation under mild conditions. Condensation at the carbanion site of dianions **2a–c** followed by hydrolysis of the imide function also offers a facile two-step method for the preparation of certain acyclic compounds, *e.g.*, the synthesis of 2-alkylglutaric and 4-aroylbutyric acids *via* dianion **2a**. Even in reactions where yields were low the dianion method may still be perferred over more circuitous procedures because of its greater convenience and the ease with which the water soluble heterocyclic precursors to dianions **2a–c** can be separated from the desired products.

(32) See J. F. Wolfe, G. B. Trimitsis, and C. R. Hauser, *Can. J. Chem.*, **43**, 2561 (1968).

Registry No.—**3b**, 19450-21-6; **3c**, 24866-78-2; **3e**, 24866-79-3; **3f**, 24866-80-6; **3g**, 24866-81-7; **3h**, 24866-82-8; **3i**, 24866-83-9; **4**, 24866-84-0; **5**, 24866-85-1; **6**, 19450-22-7; **7**, 24929-21-3; **8**, 24866-87-3; **9**, 24866-88-4; **10**, 24866-89-5; **12**, 24866-90-8; **13**, 24866-91-9; **14a**, 24866-92-0; **14b**, 19450-23-8; **14c**, 24866-94-2; **16a**, 24866-95-3; **16b**, 24866-96-4; **16c**, 24866-97-5; **16d**, 24866-98-6; **16e**, 24866-99-7; **17**, 24867-00-3; **18**, 24929-22-4; **20**, 24867-01-4; **21**, 24867-02-5; **27**, 24867-03-6; 2-(*p*-chlorobenzyl)glutaric acid, 24867-04-7.

Acknowledgment.—We are pleased to acknowledge the National Science Foundation for providing funds to aid in the purchase of the Perkin-Elmer Hitachi RMU-6E mass spectrometer used in this research. We also wish to thank Dr. John G. Dillard for obtaining the mass spectral data and Dr. Harold M. Bell for helpful discussions concerning this work.

Optically Active Adamantanes *via* Microbiological Hydroxylation. Absolute Configuration and the "Anti-octant" Effect of the Axial 3-Methyl Group of Cyclohexanone[1]

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Oxygenation of *N*-benzoyl-4β,*N*-dimethyl-1-adamantanamine (**3**) with *Sporotrichum sulfurescens* (ATCC 7159) gave *N*-benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,7-diol (**5**) and (1*S*)-*N*-benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,6α-diol (**6**). Oxygenation of the epimeric substrate, *N*-benzoyl-4α,*N*-dimethyl-1-adamantanamine (**4**), gave (1*R*)-*N*-benzoyl-6α,*N*-dimethyl-1-adamantanamine-4α-ol (**11**). Diol **6** readily formed a cyclic sulfite ester (**7**), proving the 1,3 diaxial relationship of the two hydroxyl groups and also establishing the relative configuration of the methyl substituent in all compounds. Nmr established that diol **6** was substituted at the 4,6 positions. Optical activity was demonstrated by circular dichroism (CD) spectra of ketones **8** and **12**, derived from **6** and **11**, respectively. The absolute configuration of the optically active molecules was assigned on the basis of the CD curve of (1*R*)-*N*-benzoyl-*N*-methyl-6-methylene-1-adamantanamine-4-one (**9**), derived from **8**. The two series of products were correlated by reduction of **9** to a mixture of **12** and its epimer, **10**. Ketone **12**, which contains an axial 3-methyl cyclohexanone system, demonstrates a weak "anti-octant" effect for this system in its CD spectrum.

Part A

Optically active adamantanones have been prepared[2] in order to test the effects of certain substituents on the octant rule.[3] Other optically active adamantanes have been prepared[4] in order to assess the effect of distance upon the optical rotatory power of various functional groups in chiral molecules.[5] In every case, resolution was achieved by the classical method of fractional crystallization of the appropriate carboxylic acid salt. We have recently found that optically active products may be obtained from the microbiological oxygenation of either achiral molecules[6] or racemic mixtures of chiral molecules[7] by the mold *Sporotrichum sulfurescens* (ATCC 7159). We have also found that the same microorganism gives good yields of hydroxylated products when *N*-acyl-1-adamantanamines are used as substrates.[8] The possibility of preparing an optically active adamantane by a microbial reaction therefore was of interest, since this would provide an alternate route to such molecules and would also further test the ability of the microbial reagent to achieve stereoselective reactions. The hydroxylation of the

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(1) Stereochemistry of Microbiological Hydroxylation. Part V.

(2) (a) W. S. Briggs, M. Suchý, and C. Djerassi, *Tetrahedron Lett.*, 1097 (1968); (b) G. Snatzke and G. Eckhardt, *Chem. Ber.*, **101**, 2010 (1968); (c) G. Snatzke and G. Eckhardt, *Tetrahedron*, **24**, 4543 (1968).

(3) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(4) (a) H. Hamil and M. A. McKervey, *Chem. Commun.*, 864 (1969); (b) J. Applequist, P. Rivers, and D. E. Applequist, *J. Amer. Chem. Soc.*, **91**, 5705 (1969).

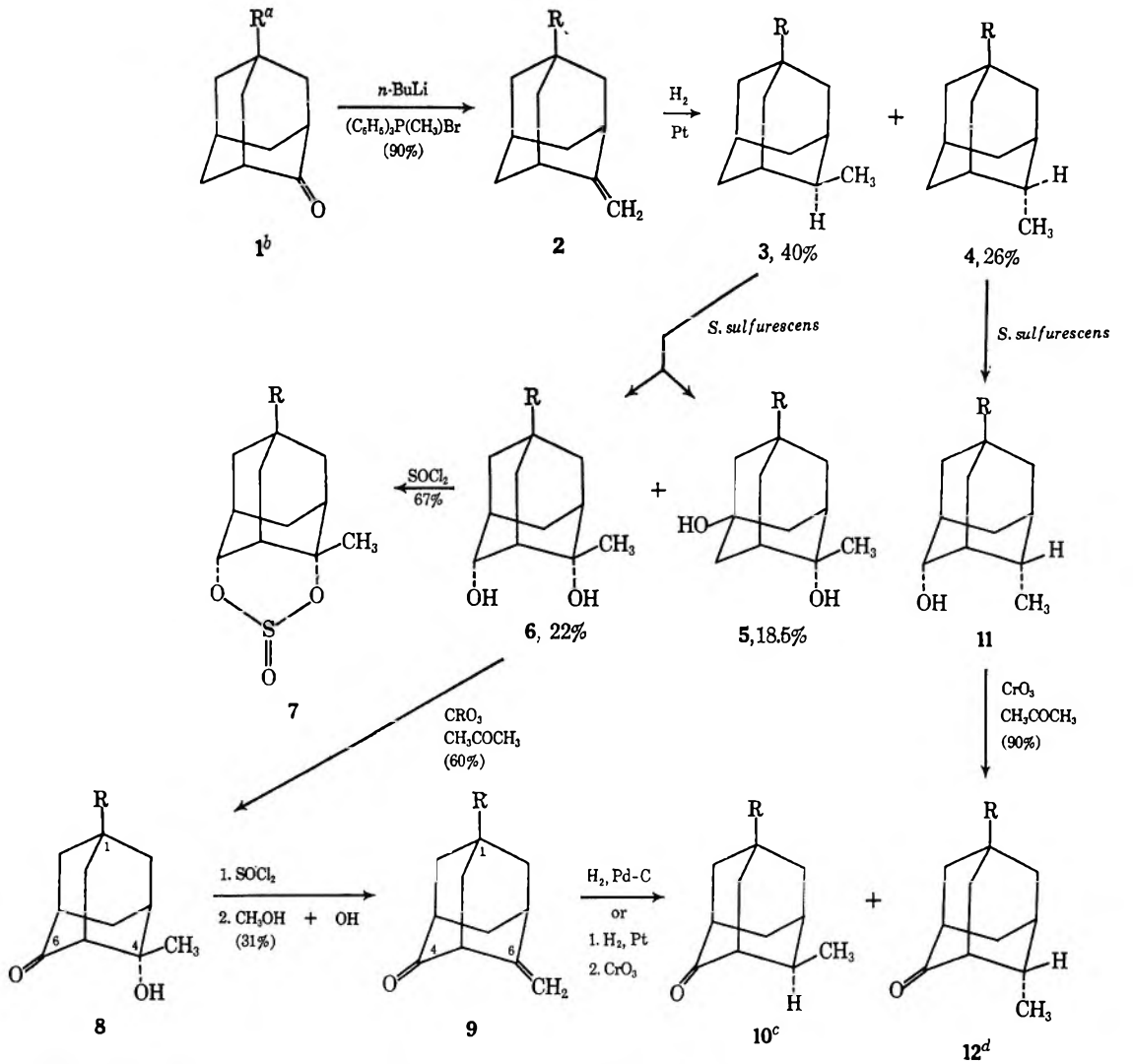
(5) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).

(6) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(7) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **34**, 2279 (1969), and references cited therein.

(8) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3201 (1968).

SCHEME I



[a] R = $-N(CH_3)COC_6H_5$ in all compounds. [b] Reference 8. [c] Not isolated. [d] 58% from 9.

epimeric *N*-benzoyl-4,*N*-dimethyl-1-adamantanamines (**3** and **4**) by *S. sulfurescens* and further chemical modifications of the products are outlined in Scheme I.

The stereoselective nature of the hydroxylations of **3** and **4** was demonstrated by the circular dichroism (CD) curves of ketones **8**–**10**, **12**,[9] all of which demonstrated significant carbonyl n → π* Cotton effects (see Table I). The absolute configuration of this series of compounds has been assigned on the basis of the CD curve of ketomethylene **9**, which shows a positive n → π* Cotton effect. The rotational characteristics of β,γ-unsaturated ketones, such as **9**, are critically dependent upon the relative disposition of double bond and carbonyl group.[10] However, for suitable orientations, the double bond perturber alone determines the sign of the carbonyl n → π* Cotton effect and absolute configurations can be assigned on the basis of the octant rule.[10] An excellent model for the present determination is cholest-5-en-3-one, which is known to give an n → π* Cotton curve consistent with the octant rule[11] and which has the same disposition of ketone and

TABLE I

CIRCULAR DICHROISM DATA FOR ADAMANTANES[a]

Compd	CD maxima (mμ) and molecular ellipticity ([θ], deg cm² decimol⁻¹)
8	307.5 (1540), 298 (2300), 290 (2200)
9	314 (6570), 303 (9290), 295 (7930)
12 (from 3)	313.5 (−210), 303 (−310), 294 (−220)
12 (from 4)	314 (−220), 303 (−310), 294 (−230)
10 and 12[b] (mixture)	310 (420), 300 (600), 292 (570)
2(e)-methyladamantan-4-one[c]	310 (1750), 300 (2570), 292.5 (2310)
2(a)-methyladamantan-4-one[d]	313 (−230), 303 (−310), 294 (−230), 284i (−110)

[a] All CD spectra were obtained on a Cary 60-CD spectropolarimeter in dioxane using 1- or 5-cm pathlength cells and a concentration of about 0.5 mg/ml. [b] A mixture, estimated from the nmr spectrum to be approximately 2:3 in 10 and 12. [c] Reference 2c. The solvent is dioxane. [d] Reference 13. The solvent is dioxane.

(9) We are indebted to Professor W. Klyne, Westfield College, for bringing to our attention the possibility that ketonic derivatives, such as **8**, would be more likely to have measurable optical rotation in their CD spectra than would compounds **6** or **11**. CD spectra of the latter, necessarily carried out on dilute solutions due to the strong absorbance of the benzamide chromophore, demonstrated no measurable optical activity. Other optically active adamantanes have also shown extremely low optical rotation.[4]

(10) A. Moscowitz, K. Mislow, M. A. W. Glass, and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1945 (1962).

(11) R. Grinter, S. F. Mason, and G. W. Vane, *Trans. Faraday Soc.*, **60**, 285 (1964).

methylene as does **9**. Both cholest-5-en-3-one and **9** give positive n → π* Cotton effects with almost identical fine structure and molar ellipticity maxima, $[\theta]_{296m\mu}$ = +9750 for the former and $[\theta]_{303m\mu}$ = +9300 for **9**. This establishes the absolute configuration of **9** as (1*R*)-*N*-benzoyl-*N*-methyl-6-methylene-1-adamantanamin-4-one and of the other optically active adamantanes as shown in Scheme I. The close agreement of the Cotton effect magnitudes of **9** and cholest-5-en-3-one and the sharp melting points observed suggest that the optical purity of the compounds in the present study is very high.

The stereochemical correlations outlined in Scheme I also enabled us to consider the question of the existence of an "anti-octant" effect for an axial 3-methyl group of cyclohexanone. This question was raised by the results of Pao and Santry in their development of a self-consistent field molecular orbital (SCF MO) approach to the calculation of optical rotatory strengths, and their signs, for methyl cyclohexanones.[12] Their results were generally consistent with those expressed by the octant rule[3] except for their prediction that the sign of rotation for an axial 3 substituent on the cyclohexanone ring should be opposite and approximately equal in magnitude to that predicted by the octant rule.[12]

Ketones **8** and **10** show positive Cotton effects (Table I), consistent with the octant rule. However, ketone **12** shows a weak, negative Cotton effect, consistent in sign but having an intensity of about one-tenth that predicted by the SCF MO theory or of that observed for the equatorial 3-methyl derivative, (1*R*)-2-methyladamantan-4-one.[2c] Subsequent to the completion of this work, the preparation and CD spectra of both enantiomers of 2-methyladamantan-4-one having the methyl substituent in the axial configuration were reported.[13] Our results are in excellent agreement with those reported (see Table I) and confirm the abnormal contribution of an axial 3-methyl group to the CD spectrum of cyclohexanones. It therefore appears that, except for magnitude, the "anti-octant" effect shown by the various axial 3 perturbers, which have been examined to the present,[14] is a consequence of the position rather than of the nature of the perturber.

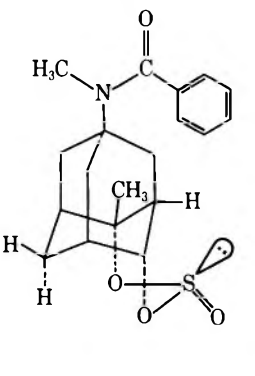
Part B

Interest in the stereochemistry of microbiological hydroxylation has led us to prepare as substrates the epimeric *N*-benzoyl-4,*N*-dimethyl-1-adamantanamines, **3** and **4**. Both are achiral compounds, but substitution at any position other than C-4 or C-7 is sufficient to introduce chirality into either molecule. This fact, combined with our previous experience with the hydroxylation of *N*-acyl-1-adamantanamines by *S. sulfurescens*,[8] held promise for the use of **3** and **4** as oxygenation substrates. If optically active products could be obtained in this manner, they would be of potential value for the study of substituent effects on the optical rotation of inherently symmetric chromophores, such as the carbonyl group. We here describe in greater detail the structural and stereochemical relationships of the products and their modifications; the optical properties of these having been summarized in Part A.

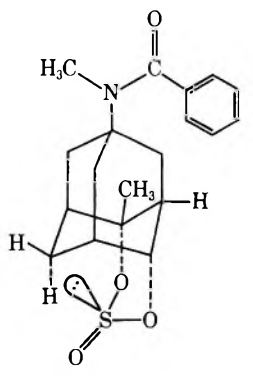
The two substrate molecules, **3** and **4**, were obtained from the reduction of the olefin **2**, which was formed in excellent yield from ketone **1**.[8] Chromatographic analyses of the reduction mixture indicated roughly equivalent amounts of the two 4-methyl derivatives; however separation of the two was extremely difficult and resulted in the lower and unequal yields shown in Scheme I.

Oxygenation of **3** with *S. sulfurescens* gave two diols, **5** and **6**, as products. One of these (**5**) failed to undergo chromic acid oxidation[15] and therefore must have two tertiary hydroxyl groups. One hydroxyl group must be at C-4 (nmr shows a singlet for the C-4 methyl group) and the other is tentatively assigned to the C-7 bridgehead position. The second diol (**6**) contained one secondary hydroxyl group, which could be oxidized to a ketone (**8**) by chromic acid. A singlet for the methyl signal in the nmr spectrum of **6** placed the tertiary hydroxyl group at the C-4 position. The two hydroxyl groups in **6** were shown to have a 1,3-diaxial relationship by the formation of the cyclic sulfite ester **7** from **6**. Only at positions C-2 ar C-6 can hydroxyl groups be placed so that they would be in a 1,3-diaxial relationship with a C-4 alcohol. The nmr spectrum (100 Mc) of **7** in deuteriobenzene showed a triplet (δ 3.92 $J \simeq 4$ Hz) for the secondary carbinol proton, which collapsed to a doublet (δ 3.95) upon irradiation of the C-5 proton. Only a C-6 carbinol proton has two adjacent protons capable of producing the observed triplet splitting. The possibility that the cyclic sulfite ester was formed from a 2,4-diol is thereby eliminated. Also, as a consequence of these observations, the stereochemistry of the methyl group in **6** can be assigned a cis configuration with respect to the *N*-methylbenzamido group. The stereochemistry of the methyl group in all molecules which have been chemically related to **6** is therefore also established.

The nmr spectrum of cyclic sulfite ester **7** is deserving of further comment. The signal for the C-5 proton at δ 3.39 at first appears extremely far downfield until the structure of the product is examined in detail. Two conformations, **7a** and **7b**, are possible for the sulfite



7a



7b

ester portion of the molecule; however examination of molecular models suggests that conformation **7b** will be

(12) Y. H. Pao and D. P. Santry, *J. Amer. Chem. Soc.*, **88**, 4157 (1966).

(13) G. Snatzke, B. Ehrig, and H. Klein, *Tetrahedron*, **25**, 5601 (1969).

(14) Snatzke and Eckhardt have previously prepared 4-chloro-, 4-bromo-, 4-iodo-, 4-azido-, and 4-carboxyadamantan-2-ones in which the 4 substituent is in an axial 3 position with respect to the cyclohexanone ring.[2b] They found that these groups also have signs of rotation opposite to those expected from the octant rule.[2a]

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

highly unfavorable from consideration of steric interactions. Conformation **7a** is much more favorable and in this conformation it can be seen that considerable deshielding of the C-5 proton will occur due to the proximity of either the oxygen or the electron pair (presumably the latter) on the sulfur atom.

Oxygenation of substrate **4** gave a monohydroxylated product (**11**) in low yield. Oxidation of **11** with chromic acid gave ketone **12**, showing that the hydroxyl group of **11** was secondary. The position of the hydroxyl group was determined in the following way. Dehydration of keto alcohol **8** by treatment with thionyl chloride followed by methanolic potassium hydroxide provided the ketomethylene compound **9**. Reduction of the methylene group gave a mixture of two methyl ketones from which one could be isolated in pure form. This ketone was identical to ketone **12**, establishing that the hydroxyl group of **11** was at the C-6 position. Additionally, the identity of the two ketones establishes the relative configurations of the methyl groups in the reduction products obtained from **9**. The configuration of the hydroxyl group in **11** is presumed to be trans with respect to the benzamido group, since hydroxylation to give such an orientation of functional groups has been found to occur almost exclusively in a number of alicyclic benzamides.[16] In fact, whereas hydroxylation at the methyl substituted C-4 carbon is the one feature common to both products obtained from **3**, oxygenation at C-4 in **4** is apparently blocked by the trans methyl group at this position.

The chemical conversion of ketone **8** into ketone **12** was also necessary in order to allow assignment of absolute configurations to all of the optically active compounds obtained. It was not clear what effect the axial (with respect to the cyclohexanone ring) hydroxyl group might have on the sign of rotation in the CD curve of **8** nor was it certain that hydroxylation of the two substrates would necessarily give products of the same enantiomeric series. However, negative Cotton effects for samples of **12** obtained from both series of compounds demonstrated that the same enantiomeric form was being dealt with throughout.

Experimental Section

***N*-Benzoyl-*N*-methyl-4-methylene-1-adamantanamine (2).**—A solution of 100 ml of 1.6 *M* *n*-butyllithium in hexane was added with stirring under a nitrogen atmosphere, to a mixture of 57.3 g (0.16 mol) of methyl triphenylphosphonium bromide in 500 ml of benzene. While continuing to stir under nitrogen and maintaining the temperature at 50°, a solution of 45.4 g of *N*-benzoyl-*N*-methyl-1-adamantanamine-4-one[8] in 150 ml of benzene was added during 30 min. The mixture was heated at 60–70° for 2 hr, allowed to stand at room temperature overnight, and stirred with 300 ml of water for 2 hr, and the layers were separated. The organic layer was concentrated under reduced pressure to 200 ml and filtered. The filtrate was chromatographed over a 1200-g silica gel column which has been prepared with cyclohexane–ethyl acetate (1:1). The column was eluted in 600-ml fractions with the same solvent mixture. The residues from fractions 2–5 were recrystallized from methylene chloride–hexane to give 40 g of product: mp 94–96°; ir (Nujol) 1630, 1380, 1285, 1070, 900, 804, 728, 704 cm^{-1}; nmr ($CDCl_3$) δ 4.56 (s, 2, C=H_2), 2.79 (s, 3, N–CH_3).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.01; H, 8.31; N, 4.88.

***N*-Benzoyl-4β,*N*- and -4α,*N*-dimethyl-1-adamantanamine (3, 4, Respectively).**—A mixture of 25.0 g of **2**, 250 ml of methanol, and 1.0 g of platinum oxide catalyst prepared under nitrogen was shaken with hydrogen (54.5 psig) for 1 hr. The catalyst was removed by filtration through Celite and the filtrate was concentrated to dryness under reduced pressure. The solid residue was separated into its two component isomers by three chromatographs over a silica gel column, 100 g of silica gel per gram of substrate. The solvent system for elution was 10% ethyl acetate in Skellysolve B hydrocarbons and the cuts were 100 ml each. After each chromatograph, the residues were examined by silica gel tlc; the residues containing the individual isomers were pooled and those containing mixtures were rechromatographed. Recrystallization of the less polar isomer from Skellysolve B gave 10.30 g of product **3**: mp 69–71°; ir (Nujol) 1630, 1380, 1068, 1062, 1023, 803, 732, 706 cm^{-1}; nmr ($CDCl_3$) δ 2.82 (s, 3, NCH_3), 1.10 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.50; H, 8.94; N, 4.94.

The more polar isomer was recrystallized from Skellysolve B to give 7.19 g of product **4**: mp 94–97°; ir (Nujol) 1620, 1378, 1078, 1060, 1023, 803, 730, 706 cm^{-1}; nmr ($CDCl_3$) δ 2.83 (s, 3, NCH_3), 1.07 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.20; H, 8.93; N, 4.98.

Biotransformation Process.—The culture used in these experiments was *Sporotrichum sulfurescens* v. Beyma (ATCC 7159). The process has been described previously,[17] with the exception that we have now added a dispersing agent Ultrawet DS-30 (2.5 ml/l.) to the fermentations.

Isolation of Products from the Microbiological Oxygenations.—The general procedure was to extract the fermentation beers with methylene chloride and evaporate to dryness to give a crude extract residue, which was processed for pure products as described in the experiments below.

Bioconversion of *N*-Benzoyl-4β,*N*-dimethyl-1-adamantanamine (3) to *N*-Benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,7-diol (5) and (1*S*)-*N*-Benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,6α-diol (6).—The extract residue from a 2.0 g fermentation of **3** was chromatographed over 200 g of Florisil, eluting with 4 l. of solvent Skellysolve B containing increasing proportions of acetone from 0 to 50%, and collecting fractions of 60 ml each. The residues were examined by tlc and fractions 36–42 (0.73 g) were combined (pool A) and fractions 45–50 (0.63 g) were combined (pool B).

Pool A was recrystallized from methylene chloride–ether to give 0.49 g of **6**: mp 175–178°; ir (Nujol) 3300 (OH), 1610 cm^{-1} (amide); nmr ($CDCl_3$) δ 4.06 (m, 1, CHOH), 2.83 (s, 3, NCH_3), 1.45 (s, 3, $COHCH_3$).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 71.93; H, 7.96; N, 4.27.

Pool B was recrystallized from methanol–benzene to give 0.41 g of **5**: mp 221–223°; ir (Nujol) 3400 (OH), 1650 cm^{-1} (amide); nmr (DMF-d_7) δ 2.88 (s, 3, NCH_3), 1.40 (s, 3, $COHCH_3$).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 71.95; H, 7.90; N, 4.65.

Bioconversion of *N*-Benzoyl-4α,*N*-dimethyl-1-adamantanamine (4) to (1*R*)-*N*-Benzoyl-6α,*N*-dimethyl-1-adamantanamin-4α-ol (11).—The extract residue from a 2.0-g conversion was subjected to gradient chromatography over 150 g of Florisil eluting in fractions of 85 ml each with 4 l. of solvent Skellysolve B plus increasing proportions of acetone from 0 to 25%. Examinations of the fraction residues by tlc resulted in the pooling of fractions 31–34; this residue (120 mg) was recrystallized from methylene chloride–ether; yield of **4** was 70 mg: mp 181–182°; ir (Nujol) 3500 (OH), 1600 cm^{-1} (amide); nmr ($CDCl_3$) δ 2.83 (s, 3, NCH_3), 1.02 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.33; H, 8.21; N, 4.71.

(1*R*)-*N*-Benzoyl-6α,*N*-dimethyl-1-adamantanamine-4-one (12).—(1*R*)-*N*-Benzoyl-6α,*N*-dimethyl-1-adamantanamin-4α-ol (**11**) (13 mg) in acetone was oxidized by the Jones method and the product was recrystallized from dioxane–water to give **12**: mp 136–137°; ir (Nujol) 1740 (C=O), 1625 cm^{-1} (amide).

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80. Found: C, 76.47; H, 7.98.

(1*R*)-*N*-Benzoyl-4β,*N*-dimethyl-1-adamantanamine-4,6α-diol Cyclic Sulfite (7).—A mixture of 100 mg of **6** and 1.0 ml of thionyl

(16) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3217 (1968); *ibid.*, **35**, 622 (1970).

(17) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *ibid.*, **33**, 3187 (1968).

chloride was allowed to stand for 20 min and the excess reagent was removed under reduced pressure. The residue was chromatographed over 20 g of Florisil, gradient elution with Skellysolve B–acetone, to give 80 mg of product **7**. Recrystallization from ether–Skellysolve B gave the analytical sample: mp 152–154°; nmr (benzene-d_6) δ 3.87 (t, 1, J = 6 Hz, $\begin{matrix}CH\\CH\end{matrix}>CHOS$), 3.38 (m, 1, $O{=}S<\begin{matrix}OCH\\OC\end{matrix}>CHCH_2$), 1.87 (s, 3, NCH_3), 1.13 (s, 3, $OCCH_3$) (see Discussion for spectrum at 100 Mc).

Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; S, 8.87. Found: C, 63.28; H, 6.41; S, 8.89.

(1*R*)-*N*-**Benzoyl**-*N*,4β-**dimethyl-1-adamantanamin-4-ol-6-one** (**8**).—Compound **6** (140 mg) in acetone was oxidized by the Jones method and the crude was recrystallized from aqueous acetone to give **8**: mp 179–182°; ir (Nujol) 3500 (OH), 1725 (C=O), 1620 cm^{-1} (amide); nmr ($CDCl_3$) δ 2.84 (s, 3, NCH_3), 1.55 (s, 3, $COHCH_3$).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.81; H, 7.40. Found: C, 72.88; H, 7.40.

(1*R*)-*N*-**Benzoyl**-*N*-**methyl-6-methylene-1-adamantanamin-4-one** (**9**).—Compound **8** (0.900 g) and 10.0 ml of thionyl chloride was warmed on a steam bath for 5 min and the excess reagent was removed under reduced pressure. The residue was triturated with water to give 0.72 g of solid. The nmr spectrum of this material indicated a mixture of about $^2/_3$ methylene-C-6 and about $^1/_3$ chloro compound; so it was taken up in 12 ml of methanol and 5.0 ml of 10% aqueous potassium hydroxide solution and heated at reflux for 3 hr. Dilution with water and concentrating gave a crude solid product which was recrystallized from acetone–water: yield of 9, 0.26 g; mp 162–163°; ir (Nujol) 1730 (C=O), 1625 cm^{-1} (amide); nmr ($CDCl_3$) δ 4.75 (m, 2, $C{=}CH_2$), 2.84 (s, 3, NCH_3).

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.78; H, 7.62; N, 4.76.

(1*R*)-*N*-**Benzoyl-6**α,*N*-**dimethyl-1-adamantanamine-4-one** (**12**) **and the 6**β-**Methyl Isomer** (**10**).—A mixture of 155 mg of **9**, 25 ml of methanol, and 40 mg of 10% palladium on carbon was shaken with hydrogen (35 psig) for 110 min. The catalyst was removed by filtration and the residue from the filtrate was examined by nmr. The spectrum indicated a mixture of two parts of **10** to three parts of **12**. We were unable to separate the two isomers by chromatography, but pure **12** (90 mg) was obtained by direct crystallization from methanol–water: mp 138–139°; ir (Nujol) identical with **12** prepared by oxidation as described above and the mixture melting point was not depressed; nmr ($CDCl_3$) δ 2.85 (s, 3, NCH_3), 0.97 (d, 3, J = 7 Hz, $CHCH_3$). The filtrate residue from **12** was rich in **10** and melted at 83–112°, but we were unable to obtain this compound pure.

Registry No.—**2**, 25934-87-6; **3**, 25934-88-7; **4**, 25934-89-8; **5**, 25934-70-1; **6**, 25934-91-2; **7**, 25934-92-3; **8**, 25934-93-4; **9**, 25934-94-5; **11**, 25934-95-6; **12**, 25934-96-7

Reactive Intermediates in the Anodic Oxidation of Cycloalkanecarboxylic Acids[1,2]

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Anodic oxidations of a series of α-deuteriocycloalkanecarboxylic acids (I-*n*-*d*) in aqueous solution and at carbon anodes produce mixtures containing bicycloalkanes, cycloalkene, cycloalkanol, cycloalkyl cycloalkanecarboxylate, and bicycloalkyl. The extents of internal hydrogen rearrangement accompanying the formation of alkene and alcohol products have been measured by nmr techniques. The alcohols are formed from intermediates that have undergone more hydrogen shifts than are the alkenes, with the maximum difference being found for the cyclooctane derivatives. Thermal decompositions of *tert*-butyl cyclooctaneperoxycarboxylate (II and II-*d*) and of dicyclooctylmercury in aqueous solvents produced, presumably from cyclooctyl radical intermediates, cyclooctane, cyclooctene, and cyclooctanol. The α-D peroxy ester (II-*d*) gave cyclooctene without detectable rearrangement of the deuterium label. The interpretation of these data has focused on the nature of the intermediates from which most products are formed in the electrolyses. We conclude that alcohol formation is not a dependable indication of a cationic process in aqueous solution, but still cationic rather than radical pathways account for most (if not all) of the cycloalkene, cycloalkanol, and bicycloalkane products obtained from these anodic oxidations.

Part A

The Kolbe electrolysis of salts of carboxylic acids has been known for over 100 years, and the process has been usefully employed for the synthesis of radical coupling products.[3] Renewed interest in these electrolyses has been spurred recently, however, by observations of products presumed to be formed from cationic rather than radical intermediates.[4] Although these reactions appear quite unpromising for general synthetic applications, they do appear to be reasonably convenient sources of high energy, probably poorly solvated, cationic intermediates of theoretical interest. We have investigated the anodic oxidation of a series

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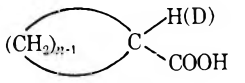
(1) (a) Based in part upon the Ph.D. Dissertation of E. E. Green, Louisiana State University, May 1969; (b) presented in part at Southwest Regional Meetings of the American Chemical Society, Little Rock, Arkansas, Dec 1967, Abstracts, No. 171, and Austin, Texas, Dec 1968, Abstracts, No. 175.

(2) Grateful acknowledgment is made to the National Science Foundation (Grant GP-8228) for partial financial support of this research, and to the Dr. Charles E. Coates Memorial Fund of the LSU Foundation donated by George H. Coates for financial aid toward the preparation of the Ph.D. Dissertation of E. E. G.

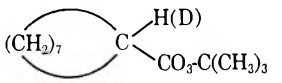
(3) For reviews, see (a) B. C. L. Weedon in "Advances in Organic Chemistry," Vol. I, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience, New York, N. Y., 1960, pp 1–34; (b) G. W. Thiessen, *Rec. Chem. Progr.*, **21**, 243 (1960); (c) A. K. Vijh and B. E. Conway, *Chem. Rev.*, **67**, 623 (1967).

(4) (a) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *J. Amer. Chem. Soc.*, **82**, 2645 (1960); (b) W. J. Koehl, Jr., *ibid.*, **86**, 4686 (1964); (c) L. Rand and A. F. Mohar, *J. Org. Chem.*, **30**, 3885 (1965); (d) P. H. Reichenbacher, M. Y. C. Liu, and P. S. Skell, *J. Amer. Chem. Soc.*, **90**, 1816 (1968); (e) P. S. Skell and P. H. Reichenbacher, *ibid.*, **90**, 2309 (1968); (f) P. H. Reichenbacher, M. D. Morris, and P. S. Skell, *ibid.*, **90**, 3432 (1968); (g) P. S. Skell and P. H. Reichenbacher, *ibid.*, **90**, 3436 (1968); (h) J. T. Keating and P. S. Skell, *ibid.*, **91**, 695 (1969); (i) L. Eberson, *ibid.*, **91**, 2402 (1969); (j) J. T. Keating and P. S. Skell, *J. Org. Chem.*, **34**, 1479 (1969); (k) W. B. Smith and Y. H. Yuh, *Tetrahedron*, **24**, 1163 (1968); (l) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68**, 497 (1968); (m) G. Atherton, M. Fleischmann, and F. Goodridge, *Trans. Faraday Soc.*, **63**, 1468 (1967); (n) A. A. Humffray and L. F. G. Williams, *Chem. Commun.*, 616 (1965); (o) L. Eberson, *Acta Chem. Scand.*, **17**, 1196, 2004 (1963); (p) N. A. Bonner and R. D. Mango, *J. Org. Chem.*, **29**, 430 (1964); (q) J. G. Traynham and J. S. Dehn, *J. Amer. Chem. Soc.*, **89**, 2139 (1967); (r) K. Sasaki, K. Uneyama, and S. Nagaura, *Electrochim. Acta*, **11**, 891 (1966).

of α-deuteriocycloalkanecarboxylic acids[5] (I-*n*-*d*) (at carbon anodes) to ascertain the extent of intramolecular hydrogen rearrangements[6] occurring in the high-energy intermediates. We have also investigated, for comparison, two nonelectrolytic radical reactions (thermolyses of *tert*-butyl cyclooctaneperoxycarboxylate, II, and of dicyclooctylmercury) in aqueous solutions,



I-*n* (I-*n*-*d*)



II (II-*d*)

since information on product formation from alkyl radical intermediates in aqueous solutions, apart from polymerization, is meager.[7] Although bicycloalkanes (formed by the anodic oxidation but not by the nonelectrolytic processes) appear to be formed from cycloalkyl cations[4q] but not from cycloalkyl radicals under the reaction conditions, both anodic oxidation and nonelectrolytic radical reactions of cyclooctane derivatives in aqueous solutions produce cyclooctene and cyclooctanol. Nonetheless, hydrogen rearrangements (revealed by deuterium-label scrambling) in the anodic oxidation products make it unlikely that cycloalkene and cycloalkanol are formed to significant extents from radical intermediates during electrolysis.

The product distribution data for the electrolyses are summarized in Table I. Analysis of deuterium

TABLE I

RELATIVE PRODUCT PROPORTIONS FROM AQUEOUS ELECTROLYSES OF α-DEUTERIOCYCLOALKANECARBOXYLIC ACIDS (CYCLOALKANOL = 1)

Acid ring size	Gc[a] column, temp, °C	Bicycloalkane	Cycloalkane	Cycloalkene	Cycloalkanol	Ester[b] + bicycloalkyl
6	A, 86	0.0	0.05	0.5	1	~1
	B, >100					
8	A, 120	0.5[c]	Trace	2.0	1	~1
9	C, 100	0.2	Trace	2.0[d]	1	~1
10	D	0.1	0	5.0[d]	1	

[a] Gc specifications; see ref 12. [b] Cycloalkyl cycloalkanecarboxylate. [c] Bicyclo[3.3.0]- and -[5.1.0]octanes. [d] cis + trans.

content of starting acids and content and rearrangement in alkene and alcohol products were accomplished by nmr spectroscopy. These rearrangement data are summarized in Table II.

Thermolyses of compounds containing the cyclooctyl ring system were carried out to obtain comparable radical product distribution and rearrangement data. Thermal decomposition of II-*d*[8] in aqueous solution yielded cyclooctene with no rearrangement of the deuterium label detectable by nmr analysis. The product distribution data for thermal decomposition of the unlabeled peroxy ester and dicyclooctylmercury[9] in aqueous solution are shown in Tables III and IV.

TABLE II

EXTENTS OF DEUTERIUM REARRANGEMENT IN ELECTROLYSIS PRODUCTS

	% rearrangement	
Ring size	Cycloalkene	Cycloalkanol
6	0	0[a]
8	5	40
9	16	25
10	0	

[a] Hydrolysis of the ester product gave unrearranged cyclohexanol.

TABLE III

THERMAL DECOMPOSITIONS OF II IN AQUEOUS SOLVENTS

Conditions			
Temp, °C	105	80	80
Concn of solute (*M*)	0.06	0.5	2.5
Atmosphere	N_2	Air	Air
H_2O:*tert*-BuOH, mol %	85:15	60:40	60:40
Products[a,b]			
Cyclooctane	0.4	0.5	1
Cyclooctene	1	1	1
tert-Butyl cyclooctyl ether		2	4.5
Cyclooctanone	0.1	0.5	3.0
Cyclooctanol	0.2	1.9	3.5

[a] Mole ratios within one reaction mixture, relative to cyclooctene = 1. A secondary deuterium isotope effect was not detected in comparisons between labeled and unlabeled peroxy ester decompositions. [b] Acetone, 2-methylpropene, and uncharacterized high-molecular-weight materials were also products of the decompositions. Control experiments with cyclooctene and cyclooctanol under conditions similar to the thermal decompositions produced no hydration or dehydration, respectively. *tert*-Butyl alcohol heated in water and under pressure did yield 2-methylpropene.

TABLE IV

THERMAL DECOMPOSITIONS OF DICYCLOOCTYLMERCURY IN AQUEOUS SOLVENT[a,b]

	Atmosphere	
Product	N_2	Air
Cyclooctane	0.5	0.3
Cyclooctene	1.0	1.0
Cyclooctanol	0.6	0.6
Cyclooctanone	0.4	0.5

[a] Water:*tert*-butyl alcohol, 85:15 mol %; 80°. [b] Mole ratios of products, relative to cyclooctene = 1.

Of special interest is the large proportion of oxygenated products formed in these reactions. Particular care was taken to exclude oxygen from some of these thermolyses,[10] and it seems improbable that enough oxygen was present to account for the yields of cyclooctanol and cyclooctanone.[11] Even though it is

(5) See ref 4q for a report on unlabeled acids, I-*n*.

(6) For reviews see (a) V. Prelog and J. G. Traynham, in "Molecular Rearrangements," P. de Mayo, Ed., Vol. 1, Wiley-Interscience, New York, N. Y., 1963, Chapter 9; (b) A. C. Cope, M. M. Martin, and M. A. McKervey, *Quart. Rev. (London)*, **20**, 119 (1966).

(7) See, for example, W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966.

(8) Thermal decomposition of *tert*-butyl alkaneperoxycarboxylates leads to *tert*-butoxy and alkyl radicals: ref 7, p 105.

(9) Photolysis and pyrolysis of dicyclooctylmercury in pentane solvent have been reported: A. C. Cope and J. Englehart, *J. Amer. Chem. Soc.*, **90**, 7092 (1968).

(10) (a) Reactions of organomercury compounds with oxygen are reviewed by T. G. Brilkina and V. A. Shushunov, "Reactions of Organometallic Compounds with Oxygen and Peroxides," A. G. Davies, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1969, pp 58–63. (b) Because of the decomposition of solvent water during the electrolyses, the anode was probably a continuing source of oxygen in those reactions. We, nonetheless, took care to exclude oxygen from the thermolyses in order to obtain information about the behavior of alkyl radicals in aqueous systems.

(11) Oxidations of cyclooctanol or *tert*-butyl cyclooctyl ether to cyclooctanone by radical reactions are examples of reactions which are well documented: (a) ref 7, p 12; (b) E. Staude and F. Patat, in "The Chemistry of the Ether Linkage," S. Patai, Ed., Wiley-Interscience, London, 1967, p 74; (c) G. A. Rasunajew, in "Vistas in Free Radical Chemistry," W. A. Waters, Ed., Pergamon Press, New York, N. Y., 1959, pp 225 ff.

difficult to rationalize an apparent reaction between cyclooctyl radical and water to give cyclooctanol with previously summarized data on the behavior of radical intermediates, it does seem that the formation of alcohol product is not a sure indicator of a cationic intermediate in the anodic oxidation of carboxylic acids.[4a,b] In the case of medium ring systems, bicycloalkane products appear to be the more dependable indicator of cationic intermediates.

Part B

Experimental Section

The compounds used in all syntheses were reagent grade commercial chemicals or materials on hand from previous work in these laboratories[4q] and, unless indicated otherwise, required no further purification. The infrared (ir) spectra were obtained with a Perkin-Elmer Infracord Model 137 spectrometer and with thin films on sodium chloride plates. The nuclear magnetic resonance (nmr) spectra were obtained with a Varian Associates Model A-60A nmr spectrometer, usually with chloroform-*d* solutions containing tetramethylsilane (TMS) as internal reference (negative chemical shift indicates downfield). Mass spectra (ms) were obtained from a Varian Associates M-66 mass spectrometer by Cheryl White, and element microanalyses were performed by R. Seab, both members of the technical staff of these laboratories. Several different instruments were used for gas chromatographic (gc) analyses.[12]

Deuterium Labeling of Cycloalkanecarboxylic Acids.[13]—A mixture of cycloalkanecarboxylic acid, sulfuric acid-d_2, and water-d_2 (1:2:1 mol ratio) was stirred at 90–100° for 5–7 days in a sealed vessel. The dark reaction mixture was extracted with pentane, and the pentane solution was washed with 1 *M* sodium hydroxide solution. The deuterated carboxylic acid was obtained by acidifying the basic wash with dilute hydrochloric acid, extracting into pentane, and removing the solvent at reduced pressure. The extent of deuterium incorporation was always less than that calculated for complete equilibration and was determined by nmr and ms techniques. The acids prepared, mole fraction of α-deuterium incorporated by one exchange, and yield were I-6-*d*, 0.20, 90%; I-8-*d*, 0.60, 91%; I-9-*d*, 0.78, 85%; I-10-*d*, 0.90, 60%.

Electrolyses[4q] of α-Deuteriocycloalkanecarboxylic Acids. General.—A Kontes, K-25005, 125-ml Universal Electrode Vessel was fitted with the appropriate graphite (+) and copper (−) electrodes, nitrogen inlet and exit, and magnetic stirring bar. The graphite anode had a surface area of about 3 cm², smaller than the copper cathode.

For each electrolysis, the current was initially adjusted to give an anode current density of about 0.05 A/cm² of exposed surface. This current was supplied either with a bank of lead–acid storage batteries (22 V) through a variable resistor, or with a direct current power supply that allowed variation of the voltage applied across the electrolysis cell. Normally the current through the cell varied during the course of the electrolysis as the resistance of the solution changed and substrate was consumed. The electrolysis was always initiated with slightly acidic solution. As the reaction proceeded, the solution became more basic (sometimes reaching a pH of 9). Product distributions did not vary significantly with differences in the duration of the electrolysis, (always greater than 20 V across the cell), or concentration of substrate.

To help remove evolved carbon dioxide and volatile hydrocarbons, nitrogen was introduced in a gently bubbling stream. After leaving the apparatus, the gas flowed through a drying tube (calcium chloride or Drierite), then through a small cold finger condenser immersed in an acetone–solid carbon dioxide bath (−78°), and finally through a preweighed U tube filled with number 8 mesh Ascarite.

After the electrolysis had continued for 9 hr, dilute hydrochloric acid was very quickly added to the basic reaction mixture (to displace dissolved carbon dioxide), and the system was resealed to force the gases to flow on through the system of traps. After bubbling had ceased and the mixture had been purged for a few minutes by the nitrogen stream, the U tube was weighed to determine the amount of carbon dioxide evolved. Based on the number of coulombs passed through the respective electrolysis solutions, the following yields of carbon dioxide were obtained: from I-6, 25%; I-8, 20%; I-10, 200%.[14]

The acidic reaction mixture was made basic with 1 *M* sodium hydroxide solution and removed to a separatory funnel. The reaction vessel was washed with distilled water and ethyl ether (100 ml of each), and these washings were also added to the separatory funnel. The basic aqueous layer was removed and set aside for recovery of unreacted acid. The ether layer was extracted twice with 50-ml portions of distilled water, and these washings plus the first aqueous basic layer were mixed, acidified with dilute hydrochloric acid, and extracted with ether. This second ether solution was dried over Drierite and concentrated under reduced pressure to give the following yields of recovered α-deuteriocycloalkanecarboxylic acids: I-6-*d*, 37%; I-8-*d*, 36%; I-9-*d*, 24%; and I-10-*d*, 86%.

The first ether layer containing the neutral products of the electrolysis was dried and concentrated by rotary evaporation. The residual liquid was analyzed by gas chromatographic (gc) and distillation techniques. Cycloalkane, cycloalkenes, bicycloalkanes, and cycloalkanol[15] were determined in the total mixture by gc; the amounts of the less volatile cycloalkyl cycloalkanoate and bicycloalkyl were estimated by distillation of the reaction mixture. These individual products were identified by comparisons of their ir, nmr, and gc data with those of authentic samples. The product distribution data are summarized in Table I.

Samples of cycloalkene and cycloalkanol, obtained by distillation of the reaction mixture, were examined by nmr techniques. The extents of hydride shifts accompanying formation of these products were established by comparing the relative intensity of the HC=C or HCOH absorptions with those of the rest of the alkene or alcohol molecule, respectively.[16] These data are summarized in Table II.

Electrolysis of Cyclooctanecarboxylic Acid in Binary Solvent.—Cyclooctanecarboxylic acid (6.2 g, 0.04 mol), sodium hydroxide (1.3 g, 0.035 mol), and 28 g of mixed solvent (60 mol % water, 40 mol % *tert*-butyl alcohol) were mixed in the electrolysis cell previously described. The electrolysis was run at about 0.06 A (total current) and 80 V. The current density at the anode, 0.02 A/cm², was lower than in the previously described electrolyses because of greater resistance of the cell when the binary solvent was employed. The electrolysis was run as described. After 17 hr, about 30% (0.50 g, 0.011 mol) of the theoretical amount of carbon dioxide, based on coulombs passed through the solution, had been collected.

The usual work-up of the reaction was carried out except that more water washings were employed to remove the *tert*-butyl alcohol. The neutral portion was analyzed by gc (D,[12] 180°) and found to contain cyclooctene, *tert*-butyl cyclooctyl ether, cyclooctanone, and cyclooctanol in relative amounts 0.25:7:0.15:1, respectively.

***tert*-Butyl Cyclooctaneperoxycarboxylate** (II).—The peroxy ester was prepared by the reaction of acyl chloride with sodium

(12) A, Micro Tek Model GC 1600 instrument, flame ionization detector (FID), ⅜ in. × 18 ft column, 10% tricresyl phosphate on 60–80 mesh Chromosorb P. B, Aerograph Autoprep Model A-700 instrument, ⅜ in. × 12 ft column, 17% ethylene glycol adipate on 80–100 mesh Chromoport XX. C, Barber–Colman IDS Model 20 instrument, FID, 100-ft capillary column, GE-96 silicone. D, Beckman CC-5 instrument, FID, ⅛ in. × 10 ft column, 10% Carbowax 20M on 60–80 mesh Chromosorb P. E, Hewlett–Packard 700 instrument, FID, ⅛ in. × 9.5 ft column, 10% Carbowax 20M on 80–100 mesh Chromosorb P.

(13) A. Murray, III, and D. L. Williams, "Organic Syntheses with Isotopes," Part II, Interscience, New York, N. Y., 1958, p 1311.

(14) Several other apparently difficult electrolyses in these laboratories have produced unexpectedly high yields of CO_2, probably from oxidation of the graphite anode by oxygen formed from the electrolysis of solvent water.

(15) (a) In a control experiment simulating electrolysis conditions, a mixture of cyclooctanecarboxylic acid (0.01 mol) and cyclooctene (0.001 mol) in 7 g of mixed solvent (60 mol % water, 40 mol % *tert*-butyl alcohol) did not generate any cyclooctanol, even after being refluxed for 3 days. (b) Although actual yields were seldom determined, the combined amount of product was always substantial and roughly equivalent to the amount of carboxylic acid consumed in the electrolysis.

(16) In a control experiment simulating electrolysis conditions, a mixture of cyclohexanecarboxylic acid (0.02 mol), D_2O (5 ml, 0.25 mol), and a few drops of 30% sodium deuterioxide (in D_2O) solution was heated at 50° for 14 hr. The nmr spectrum of the recovered acid gave no evidence for α-hydrogen exchange. It is, therefore, improbable that any loss of D label by exchange in the acid (or anion) occurred during electrolysis.

tert-butyl peroxide.[17] Cyclooctanecarboxylic acid,[4q] both with and without α-D label, was converted to acyl chloride[18] [bp 99–100° (8 mm)] by refluxing with thionyl chloride. The nmr spectrum of the unlabeled acyl chloride included absorptions centered at −2.95 ppm (α-H) and at −1.9 ppm (β-H), but in the spectrum of the labeled chloride the absorption at −2.95 ppm was nearly absent and the one at −1.9 ppm was appreciably sharper. The unlabeled peroxy ester (II) was obtained in 57% yield by removal of ethyl ether solvent on a rotary evaporator and was not distilled: ir (film) 5.63 (ester C=O), 7.25, 8.4, and 9.3 μ; nmr ($CDCl_3$) −2.4 (m, 1, $CHCO_3$), −1.75 (m, 4, CH_2CCO_3R), −1.4 (m, 10, $CH_2CH_2CH_2$), and −1.2 ppm (s, 9, CH_3). *Anal.* Calcd for $C_{13}H_{24}O_3$: C, 68.3; H, 10.6. Found: C, 67.8; H, 10.6.

The α-D labeled peroxy ester (II-*d*) was obtained in 73% yield from pentane solution; it exhibited little nmr absorption at −2.4 ppm and a sharper one at −1.75 ppm than did the unlabeled ester.

Thermal Decomposition of II.—A solution (0.056 *M* in solute) of II (5.1 g, 0.022 mol) in 40 ml of mixed solvent (40 mol % *tert*-butyl alcohol, 60 mol % water) was refluxed for 8 hr without protection from the air. The mixture then gave a negative potassium iodide test for peroxides.[19] The reaction mixture was diluted with pentane (50 ml) and washed with dilute sodium hydroxide solution. The organic layer was washed with five 50-ml portions of water to remove *tert*-butyl alcohol, the remaining organic solution was dried over Drierite, and the solvent was removed to yield about 1 g of neutral products. The sodium hydroxide wash solution was acidified, extracted with pentane, and concentrated to yield 1.7 g (0.011 mol, 50%) of I-8. Analysis of the neutral products by gc (D,[12] 100–180°), showed cyclooctane, cyclooctene,[20] *tert*-butyl cyclooctyl ether, cyclooctanone, and cyclooctanol[20] present in the relative amounts 0.5:1:2:0.5:1.9, respectively.

Other decompositions of this peroxy ester at different pressures, under different atmospheres, or for different lengths of reaction time produced no significant variations in product distribution. Decompositions at higher and lower concentration of substrate (see Table III) did suggest an influence on the product distributions.

A solution (about 0.03 *M* in solute) of II-*d* (14.4 g, 0.063 mol) in 200 g of solvent (85 mol % water, 15 mol % *tert*-butyl alcohol) was heated in a Parr medium-pressure autoclave under nitrogen at 118° for 18 hr. The same products as above were obtained in only slightly different ratios. Nmr analysis of the cyclooctene isolated from the decompositions of labeled peroxy ester gave no indication of rearrangement of the deuterium atom label.

Decomposition of Dicyclooctylmercury.—For 3 hr, nitrogen was bubbled through 21 g of refluxing solvent (85 mol % water, 15 mol % *tert*-butyl alcohol) to remove dissolved oxygen. The solvent was allowed to cool slightly. The flask was covered with aluminum foil, and, while the flask was being flushed with nitrogen, freshly prepared dicyclooctylmercury[9] (1.0 g, 2.4 mmol) was added. While a nitrogen atmosphere in the flask was being maintained, the mixture was stirred and heated at 80° (reflux) for 40 hr. Extraction of the mixture with pentane, washing the pentane extract with water 4 times, drying over Drierite, and removal of solvent by rotary evaporation yielded 0.2 g of products. (Some metallic mercury was observed in the reaction vessel after 40 hr.) The products were analyzed by ir, nmr, and gc (E,[12] 60 and 150°) methods. Cyclooctane, cyclooctene, cyclooctanone, and cyclooctanol were detected in the relative amounts of 0.5:1.0:0.4:0.6, respectively. No bicycloalkanes were detected.

Another experiment, duplicating that above except for the use of air instead of nitrogen, gave a product mixture almost identical with that above (see Table IV). In some other experiments for which a nitrogen atmosphere was used, the proportions of oxygenated products were even higher (*e.g.*, cyclooctene:cyclooctanol, 1:3 and 1:12).

Discussion

Anodic oxidation of the cycloalkanecarboxylic acids gives more hydrocarbon than oxygenated products, and, like solvolysis reactions which have been studied,[6] product formation from the medium-ring systems, but not the cyclohexane system, is accompanied by internal hydrogen rearrangements. The medium-ring alcohols are formed with more extensive intramolecular rearrangement of deuterium than are the alkenes (Tables I and II). These relative rearrangement data are similar to those obtained in the deamination of ^{14}C-labeled cyclononyl- and cyclodecylamines.[21] The deuterium label in cyclooctene obtained from radical decomposition of II-*d* was not rearranged. This result almost certainly ensures that (rearranged) alkene product from the electrolysis reaction was not formed directly from a radical precursor.

These data support the suggestion that the alcohol and alkene electrolysis products are formed from cationic intermediates. There is probably a common intermediate which reacts, by pathways having different energy requirements, to give alkene, alcohol, rearranged intermediate, and, to a substantially lesser degree, bicycloalkane. The fact that alcohol is formed with more extensive rearrangement than is the alkene indicates that the energies of the transition states for reaction of the cycloalkyl cation fall in the order: alkene formation < alcohol formation < rearrangement of cation.

Alternatively, of course, the possibility of different intermediates, possibly different charge types, leading to different products must be considered. Reactions presumably involving cyclooctyl radicals in aqueous solution yielded cyclooctane, cyclooctene, and unexpectedly substantial amounts of oxygenated products (but no bicyclooctane). Since data from II-*d* reveal no rearrangement in the cyclooctene product, and electrolytic cyclooctanol is more extensively rearranged than electrolytic cyclooctene, both electrolytic products must come from (nonradical) intermediates capable of internal hydrogen rearrangements.

Some product formation directly from cycloalkyl radicals must accompany the cationic processes during anodic oxidations, however. Radical mechanisms for the formation of cyclooctane and bicycloalkyl are quite reasonable. Disproportionation of cycloalkyl radicals, or other hydrogen abstraction reactions, will lead to cyclooctane (a trace product), and dimerization of the radicals will produce bicycloalkyl. Still, the amount of cyclooctane produced during electrolysis is too small for disproportionation alone to be responsible for the difference in extents of apparent rearrangement in the cyclooctene and cyclooctanol products, and most of the cyclooctene must come from cationic intermediates.

In summary, we conclude that cycloalkyl radical and cationic processes in aqueous solution can produce

(17) P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *J. Amer. Chem. Soc.*, **87**, 2590 (1965). We modified the published procedure by using ethyl ether rather than tetrahydrofuran as solvent.

(18) Use of cyclooctanecarbonyl chloride as an intermediate has been reported previously: A. C. Cope, M. Burg, and S. W. Fenton, *ibid.*, **74**, 173 (1952); A. O. Hellwig and H. Schubert, *Z. Chem.*, **4**, 227 (1964).

(19) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p 161.

(20) In a control experiment simulating peroxy ester decomposition conditions, a mixture of cyclooctanol (4 g, 0.031 mol), crude II (1 g, 0.045 mol), and 100 g of solvent (85 mol % water, 15 mol % *tert*-butyl alcohol) was heated for 2 days at 125° (50 psig) in a Paar medium-pressure apparatus. Analysis (nmr and gc) of the reaction mixture provided no evidence for the dehydration of cyclooctanol to cyclooctene.

(21) See ref 6a. The extents of ^{14}C rearrangement in alkene and alcohol products from solvolysis of cyclononyl toluenesulfonate were essentially equal.

quite similar product mixtures. Anodic oxidation of carboxylic acids at a carbon anode produces products from both radical and cationic intermediates, but the cationic pathway is the major one. With cycloalkyl systems, the cations undergo internal hydrogen rearrangements and competitive product formation similar to those from amine deaminations.

Registry No.—II, 25023-19-2: cyclooctanecarboxylic acid, 4103-15-5; dicyclooctylmercury, 21406-57-5.

Heterocyclic Studies. 33. 5-Methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-2,6-heptadien-4-one. Thermolysis to 4-Methyl-5-phenylpyridazine[1]

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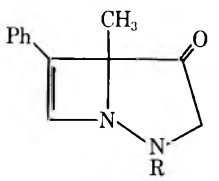
Received June 4, 1970

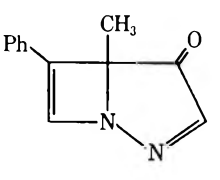
The preparation and properties of the title dienone **2** are described. The dienone is quite stable to hydrolysis; addition occurs with borohydride and methyllithium to give dienols. Thermolysis of **2** at 475° gives 4-methyl-5-phenylpyridazine; a mechanism involving a diazatropone intermediate is discussed. The thermal stability of **2** and the related diazabicyclo[3.2.0]-6-heptenone **1** and diazabicyclo[3.2.0]heptanone **19**, prepared by hydrogenation of **1** (R = Ac), are compared. The dimer of 2-methyl-3-phenylcyclopentadienone is described.

Part A

As previously reported,[2] the 1,2-diazabicyclo[3.2.0]-heptadienone **2** is obtained as a by-product in the photochemical preparation of **1a** and can be prepared by the base-catalyzed elimination of toluenesulfinic acid from **1b**. In this paper are described the details of the preparation and the chemical properties of **2**. This strained polyfunctional dienone appeared at the outset to offer possibilities for reactions of several types. Compounds containing the transoid cyclic unit –N=C–C=O are not well known, and the few examples that have been described are quite prone to solvolysis[3] or dimerization,[4] particularly in the absence of a substituent on the central carbon atom. The monomeric structure of **2**, which is consistent with the solubility and volatility of the compound, was confirmed by the mass spectrum, which contained no peaks above *m/e* 200 (P + 2).

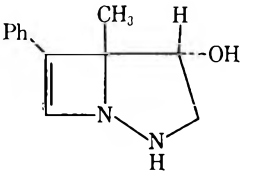


1a, R = H
b, R = *p*-$CH_3C_6H_4SO_2$

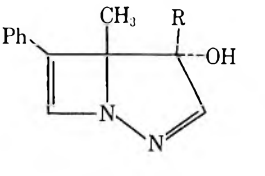


2

Contrary to expectation, **2** proved to be relatively inert; the dienone was recovered largely unchanged after refluxing for 16 hr with methanolic sodium methoxide or with methanolic hydrochloric acid. Treatment of **2** with sodium borohydride at room temperature leads to the saturated alcohol **3**.[5] At −40°, reduction with borohydride gave a small amount of **3** and, as the major product, the secondary alcohol **4a**, which was not further reduced to **3** at higher temperature, suggesting that **3** may arise from **2** by 1,4 addition. Methyllithium at −70° also added selectively to the carbonyl group to give **4b**. The *endo*-hydroxyl configuration in **4a,b** is assumed on the basis of exo attack of hydride; this has been established in the reduction of **1a** to **3**. Reactions with acetic anhydride, Grignard reagents, a phosphorus ylide, or organolithium compounds at higher temperature gave mixtures of starting material and several products which were not resolved. From this survey of the reactivity of **2**, the only clearly defined pathway observed is nucleophilic addition at the C-4 carbonyl group; the azetine and –N=C–C=O systems are surprisingly resistant to solvolytic attack.



3



4a, R = H
b, R = CH_3

One of the main points of interest in the chemistry of **2** was the possibility of thermal conversion to a diazatropone by ring opening analogous to the isomerization of bicyclo[3.2.0]-2,6-heptadienone to tropone.[6] The dienone **2** decomposed slowly in refluxing toluene to give a mixture containing apparently polymeric material. Heating **2** in higher boiling solvents or in sealed ampoules, or sublimation through a glass coil at temperatures up to 320° similarly caused incomplete conversion to material showing broad featureless nmr absorption. However, mixtures from pyrolysis at higher temperature showed evidence of two products, and these were isolated from a preparative scale pyrolysis in which a benzene solution of **2** was vaporized into a helix-packed column heated to 475°. After

* To whom correspondence should be addressed.

(1) Supported by Grant No. GP-9322 from the National Science Foundation.

(2) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 1369 (1968).

(3) 3-Oxo-2-phenylindolenine, R. J. Richman and A. Hassner, *J. Org. Chem.*, **33**, 2548 (1968); 1-alkyl-1,2-diazepin-4-one, J. A. Moore and W. J. Theuer, *ibid.*, **30**, 1887 (1965); imidazolinedione, E. Goldstein and D. Ben-Ishai, *Tetrahedron Lett.*, 2631 (1969).

(4) E. D. Hannah, W. C. Peaston, and G. R. Proctor, *J. Chem. Soc. C*, 1280 (1968), and earlier papers.

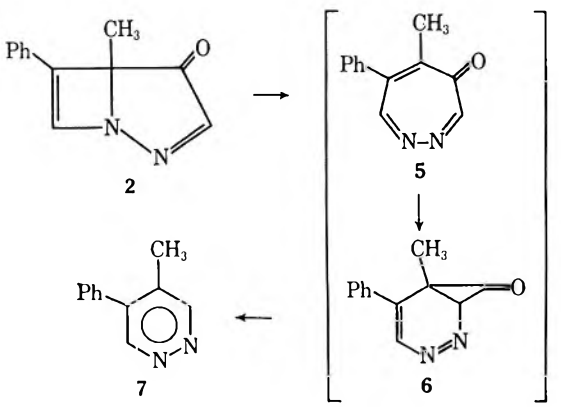
(5) J.-L. Derocque, W. J. Theuer, and J. A. Moore, *J. Org. Chem.*, **33**, 4381 (1968).

(6) P. R. Story and S. R. Fahrenholtz, *J. Amer. Chem. Soc.*, **87**, 1623 (1965).

removal of hydrocarbons derived from the solvent, a crystalline solid A was isolated in 3% yield and, as the main product, 4-methyl-5-phenylpyridazine (7) was obtained in 30% yield. These two products accounted for all of the clearly resolved peaks in the nmr spectrum of the total reaction mixture. The structure of the minor product A, $C_{24}H_{20}O_2$, is not known (see Part B).

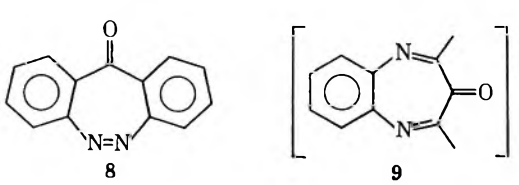
In an attempt to effect valence isomerization at a lower temperature, the dienone **2** was refluxed with excess silver tetrafluoroborate in dioxane and with methanolic cuprous chloride. These transition metal salts have been found to catalyze the thermal ring opening of fused cyclobutene systems when a concerted disrotatory process is sterically inaccessible.[7] No significant reaction was observed with **2** under these conditions, however.

Although no intermediates or other direct evidence are available, we presume that the pyridazine **7** is formed by ring opening of **2** at 350–400° (discussed in Part B) followed by valence isomerization of the diazatropone **5** and extrusion of CO. These steps have been observed with carbocyclic compounds. Bicyclo-[3.2.0]-2,6-heptadien-4-one rearranges quantitatively to tropone at 300°,[6] and the conversion of tropones to benzenes, presumably *via* bicyclo[4.1.0] intermediates, occurs at 600–700°.[8] The possibility that **2** undergoes thermal rearrangement directly to **6** is not excluded.



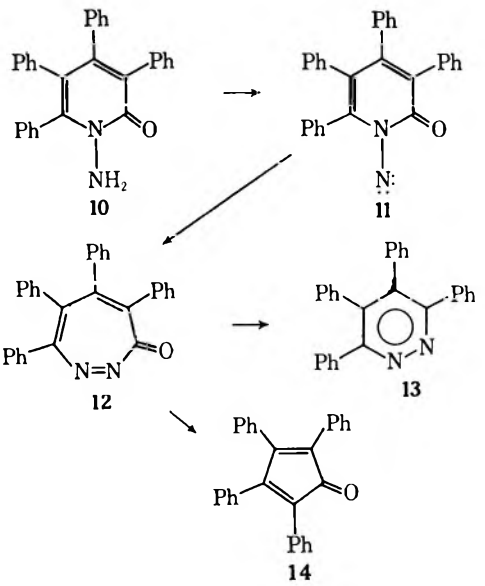
Part B

The Stability of Azatropones.—If the diazatropone **5** is the precursor of **7**, it must be considerably less stable than carbocyclic tropones. This inference is consistent with the limited data that have been reported on aza- or diazatropones comparable to **5**, containing only sp^2 nitrogen atoms. The dibenzo[*c,f*]-1,2-diazepinone **8**



has been characterized,[9] but a compound to which a dibenzo[*b,d*]azepinone structure was assigned has recently been found to be a dimer,[4,10] and attempts to obtain the benzodiazatropone **9**[11] or a monocyclic azatropone[12] were unsuccessful.

Rees and Yelland recently observed the formation of tetraphenylpyridazine (60%) and tetraphenylcyclopentadienone (1%) in the oxidation of 1-aminotetraphenyl-2-pyridinone at room temperature, and consider it likely that these products arise by thermal elimination of CO and N_2, in respectively concerted and nonconcerted processes, from the 2,3-diazatropone **12**.[13] The nature and relative amounts of products suggest a similarity in mechanism between this reaction and the thermolysis of **2**. If these reactions proceed *via* diazatropones, it seems quite remote, from the formation of **13** at 25°, that a diazatropone could be isolated from any reaction requiring elevated temperatures.



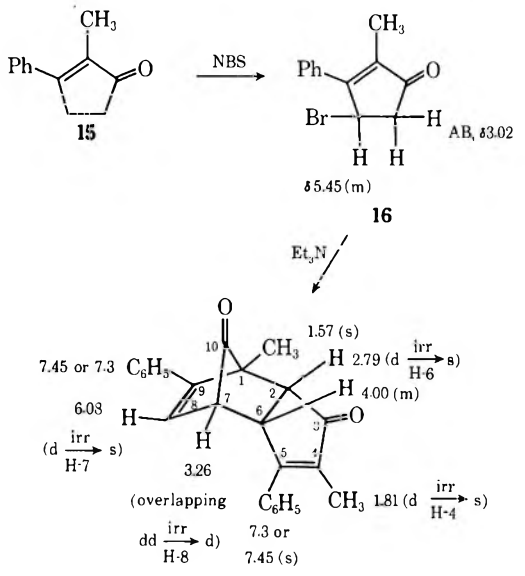
Minor Pyrolysis Product (A).—The characterization of this compound was limited by the small quantity available. Analysis and nmr data indicated a composition $C_{24}H_{20}O_2$, corresponding to loss of both nitrogen atoms from **2** and dimerization. The spectra of A [ir ν_{CO}^{KBr} 1770, 1680 cm^{-1}; nmr δ 1.61 (s, 3), 1.78 (s, 3), 2.78 (d, J = 4.9 Hz, 1), 3.37 (d, J = 1.8 Hz, 1), 3.73 (dd, J = 1.8, 4.9 Hz, 1), 6.56 (s, 1), 7.33 (s, 5), 7.4–7.8 (m, 5) ppm] were in part similar to those expected for a methylphenylcyclopentadienone dimer. These limited data, and the possible parallel with the dienone **14** isolated from the presumed diazatropone **12**,[13] prompted comparison with an authentic sample of the dimer of 2-methyl-3-phenylcyclopentadienone, which would arise by extrusion of N_2 from the diazatropone **5**.

2-Methyl-3-phenylcyclopentenone[14] (**15**) was brominated with NBS; the nmr data establish the 4-bromo structure **16**. Treatment of **16** with boiling triethylamine gave the dimer **17**. The spectral data, including all of the coupling constants, can be compared with those reported recently for several cyclopentadi-

(7) W. Merk and R. Pettit, *J. Amer. Chem. Soc.*, **89**, 4788 (1967).
(8) T. Miyashi, M. Nitta, and T. Mukai, *Tetrahedron Lett.*, 3433 (1967); T. Mukai, T. Nakazawa, and K. Okayama, *ibid.*, 1695 (1968).
(9) R. B. Johns and K. R. Markham, *J. Chem. Soc.*, 3712 (1962).
(10) R. G. Cooke and I. M. Russell, *Tetrahedron Lett.*, 4587 (1968).
(11) J. A. Barltrop, C. G. Richard, D. M. Russell, and G. Ryback, *J. Chem. Soc.*, 1132 (1959).
(12) N. A. Evans, R. B. Johns, and K. R. Markham, *Aust. J. Chem.*, **20**, 713 (1967).
(13) C. W. Rees and M. Yelland, *Chem. Commun.*, 377 (1969).
(14) H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).

enone dimers,[15] and uniquely define the *endo*-3,10-dione structure **17**.

The synthetic dimer **17** was distinctly different from the thermolysis product A. Although the ir stretching frequencies and the nmr proton groupings are very similar for the two substances, the single low field signal and the rather simple proton couplings in the nmr spectrum of A rule out a homodimer of any of the six isomeric methylphenylcyclopentadienones. The unlikely possibility that compound A arose from a subsequent thermal rearrangement of **17** was ruled out by pyrolysis of **17** at 350°. The product was not fully characterized, but the ir suggested decarbonylation, as expected;[15] compound A was not detected.

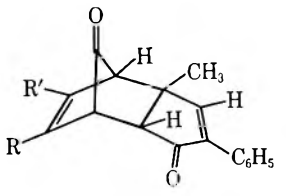


$J_{2,6} = 6.3$ Hz, $J_{6,7} = 4.5$ Hz, $J_{7,8} = 3.9$ Hz, $J_{4\,CH_3,\,6} = 1.6$ Hz

ir: C-3, ν_{CO} 1680 cm^{-1}, C-10, ν_{CO} 1770 cm^{-1}

$\frac{\text{irr}}{\text{H-6}}$ = spin decoupling by irradiation of H-6

The spectrum of A would be best accommodated by structure **18**, but the structure cannot be specified from the evidence available, nor can it be stated whether this product arises from the diazatropone **7** or by some other decomposition process of the dienone **2**.

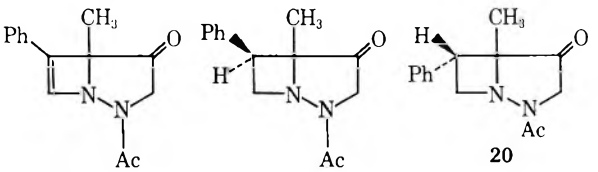


18, R, R′ = CH_3 and C_6H_5

The Mechanism of Ring Opening of Dienone 2 and Related Diazabicyclo[3.2.0]heptanones.—The results of the thermolysis of **2** indicate a significant activation barrier for ring opening of this [3.2.0] system, and invite comparison of the thermal stability of **2** with that of some related compounds. Of particular interest are the diazabicyclo[3.2.0]heptenones **1**, R = H, or CH_3, which rapidly isomerize to the diazepinones **22** at room temperature.[5]

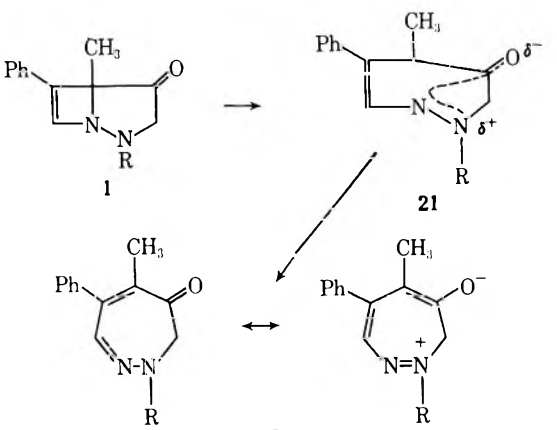
(15) E. W. Garbisch, Jr., and R. F. Sprecher, *J. Amer. Chem. Soc.*, **91**, 6785 (1969).

To extend this series, the diazabicycloheptanones **19** and **20** were prepared by hydrogenation of **1**, R = Ac, with a palladium catalyst. Approximately equal amounts of the stereoisomeric ketones, **19** and **20**, were obtained and were readily separated by crystallization. Configurational assignments were based on the large upfield nmr shift of the CH_3 in **19** due to the eclipsing 5-*exo*-phenyl group.[5] Hydrogenation of the unstable ketones **1**, R = H and CH_3, led to air-sensitive mixtures which could not be separated.



The stabilities of the unsaturated ketone **1** (R = Ac), dienone **2**, and the saturated ketone **19** were compared at 80° in chloroform solution. Isomerization of **1** (R = Ac) to the diazepinone **22** (R = Ac) was 30% complete after 48 hr and over 90% after 310 hr. The diazadienone **2** decomposed, probably by polymerization, to the extent of 40–50% in 300 hr; **19** was unchanged.

It has been suggested[16] that the facile isomerization of the enones **1** to **22** may occur by orbital symmetry allowed conrotatory thermal ring opening, permitted by inversion of the bridgehead nitrogen atom. We have viewed the lability of **1** (R = H or Me) as a consequence of interaction of the unshared electron pair at N-2 with the carbonyl group in a dipolar transition state (**21**).[5] The rates of isomerization are dependent on solvent and on the electron-releasing ability of the R group; the rate of isomerization of **1**, R = Ac, is many times slower than that of **1**, R = CH_3. Furthermore, debridging does not occur with the corresponding alcohols. In this mechanism, the Δ^6 double bond is required for dissipation of charge as the product develops.

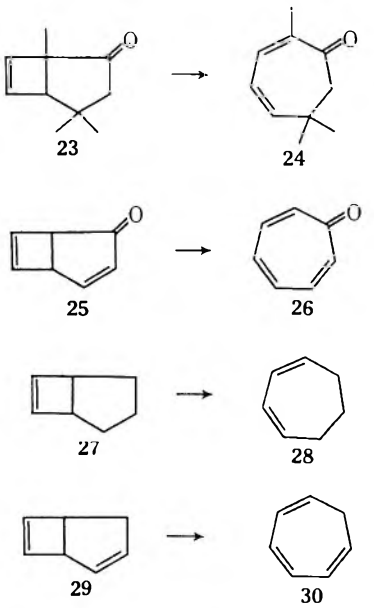


The thermal isomerization of eucarvone (**23**)[17] and the dienone **25**[6] have been carried out at 320 and 300°, respectively; these qualitative data suggest no major effect in the activation barrier for ring opening of these ketones due to the second double bond in **25**.

(16) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 51.

(17) G. Buchi and E. M. Burgess, *J. Amer. Chem. Soc.*, **82**, 4333 (1960).

Kinetic measurements of the isomerization of **27** and **29** have shown that the second double bond lowers the activation energy for the disrotatory ring opening by 6 kcal, the difference being attributed to allylic stabilization of a diradical intermediate.[18] Ring opening of bicyclo[*n*.2.0]alkenes such as **27** has more recently been suggested to occur by initial concerted conrotatory electrocyclic reaction followed by 1,5-hydride shift.[19]



In contrast to the ring opening of these carbocyclic-[3.2.0]heptenes and heptadienes, the Δ^2 double bond in **2** has a profound stabilizing effect in the 1,2-diazaheptenone series, indicating an entirely different mechanism for the thermolysis of **1** and **2**. Neither nitrogen inversion nor participation of N-2 is available in the diazadienone **2**; ring opening to **5** must occur by a pathway with an activation energy comparable to that of the dienone **25**.

Experimental Section

5-Methyl-6-phenyl-2-*p*-toluenesulfonyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-one (1b).—A solution of 0.50 g of dihydrodiazepinone **22** in 250 ml of MeOH was irradiated in sunlight[5] for 30 min and evaporated *in vacuo* to a homogeneous (tlc) pale yellow oil. Treatment of this oil with 4.5 ml of pyridine and 520 mg of *p*-toluenesulfonyl chloride for 2 hr followed by addition of water and the usual isolation gave 707 mg (80%) of **1b** in two crops. Recrystallization from methanol gave white needles: mp 151–152° dec; λ_{max}^{MeOH} 224 mμ (ε 21,000), 266 (19,000); ν^{KBr} 1750, 1340, and 1165 (SO_2); δ^{CDCl_3} 1.12 (s, 3), 2.45 (s, 3), 4.60 (d, J = 4 Hz, 2), 6.72 (s, 1), 7.2–8.0 ppm (m, 9).

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.25; H, 5.05; N, 7.69.

5-Methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-2,6-heptadien-4-one (2).—To a suspension of 2.13 g (0.04 mol) of sodium methoxide in 150 ml of toluene (Na dried) was added a solution of 2.05 g of **1b** (0.0055 mol) in 100 ml of toluene. The mixture was stirred for 24 hr under nitrogen at 25° and water was added. The toluene layer was washed, dried, and evaporated to a yellow oil. Crystallization from hexane gave pale yellow prisms of **2**: 0.99 g (85%); mp 70°; λ_{max}^{MeOH} 265 mμ (ε 17,000), 342 (370); ν^{KBr} 1730 cm^{-1}; δ^{CDCl_3} 1.73 (s, 3), 7.20 (s, 1), 7.37 (s, 5), 7.83 ppm (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 198 (57), 170 (9), 143 (10), 129 (4), 116 (19), 115 (32), 102 (100).

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.86; H, 5.02; N, 13.82.

The experiment described was the best run. In other runs, longer reaction times (up to 48 hr) were required for complete reaction of **1b** (by ir). Poor yields were sometimes obtained, perhaps due to inferior methoxide. A lower boiling solvent would probably be suitable.

The semicarbazone of **2** was prepared with semicarbazide acetate in the usual way: yellow crystals from methanol; mp 222–225° dec.

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.28; H, 5.18; N, 27.15. Found: C, 61.06; H, 5.13; N, 27.44.

Reduction of 2 with Sodium Borohydride. A. Room temperature.—Solutions of 100 mg (0.5 mmol) of **2** in 4 ml of ethanol and 35 mg of $NaBH_4$ in 0.6 ml of 2:1 EtOH–H_2O were mixed and allowed to stand at 25°. After 8 hr, excess hydride was decomposed with HCl and the mixture was neutralized with bicarbonate. The white solid was then collected, giving 74 mg (72%) of the carbinol **3**, mp 208–210° dec; ir matched with sample prepared by reduction of **1** (R = H).[5]

B. At −40°.—A solution of 500 mg of dienone **2** in 40 ml of methanol was cooled to −40° and a solution of 97 mg of $NaBH_4$ in methanol was added, with stirring, during 30 min. After stirring at −40–50° for 30 min, acetic acid was added and the solution was warmed to room temperature and concentrated. Water and CH_2Cl_2 were added and an insoluble solid was removed; this was 34 mg (7%) of the saturated alcohol **3**. The organic phase was washed, dried, and evaporated. Dilution of the oil with pentane gave 164 mg (32%) of **4a**, mp 161–163°. Recrystallization from methylene chloride gave white crystals: mp 163–164°; ν^{KBr} 3300 cm^{-1}; δ^{CDCl_3} 1.76 (s, 3), 2.42 (broad, 1), 4.72 (broad, 1), 7.09 (s, 1), 7.29 (m, 1), 7.35 ppm (s, 5).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.65; H, 6.28; N, 13.82.

4-*exo*-5-Dimethyl-6-phenyl-1,2-diazabicyclo[3.2.0]-2,6-heptadien-4-ol (4b).—To a solution of 600 mg of **2** in 30 ml of ether at −80° was added 3.4 mmol of methyllithium in ether. After stirring for 7 hr at −80°, the solution was warmed and treated with aqueous ammonium chloride. After washing and drying, the organic layer was evaporated to give 400 mg (62%) of colorless crystals of **4b**, mp 153–155°. This material was recrystallized from methylene chloride–ether: mp 154–155°; δ^{CDCl_3} 1.52 (s, 3), 1.66 (s, 3), 7.01 (s, 1), 7.14 (s, 1), 7.34 ppm (s, 5).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.75; H, 6.66; N, 12.96.

Thermolysis of Dienone 2.—The apparatus consisted of a helix-packed 1 × 15 cm Pyrex tube with a heating coil and outer jacket filled with sand. The tube was heated to 450–475° (thermometer in sand). A solution of 3 g of the dienone in 3 l. of benzene was dropped into the heated tube during a period of about 20 hr; the effluent was condensed in ice. After filtration to remove particles of dark solid, the solution was evaporated and the residual dark oil, in benzene–ether solution was poured through a short column of 16 g of silicic acid.

The initial fractions from this chromatogram, containing 1.7 g of material, were chromatographed on a column of 120 g of alumina. Evaporation of the initial hexane eluate gave 0.9 g of biphenyl, mp 65°, and 0.3 g of yellow oil. This oil was chromatographed again on 22 g of silicic acid to give 160 mg of crystals, mp 88–89°, corresponding to 3% of compound "A". Recrystallization from methylene chloride–pentane gave crystals with mp 88–95°; from ether–pentane, the mp was 127–130°; for spectral properties, see discussion.

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.57; H, 6.69.

The residue from the later fractions from the first silicic acid column, 1.7 g, was rechromatographed in benzene solution on 36 g of silicic acid. The main fractions were evaporated to give 900 mg (33%) of colorless solid, mp 81–84°. Recrystallization from ether–pentane followed by sublimation, gave colorless crystals of **4-methyl-5-phenylpyridazine**: mp 81–82°; δ^{CDCl_3} 2.36 (s, 3), 7.35–7.55 (m, 5), 9.00 (s, 1), 9.07 ppm (s, 1) (the two low field singlets were somewhat broadened, $W_{1/2}$ = 2 Hz).

Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.35; H, 6.02; N, 16.45.

The **picrate** was crystallized from alcohol, mp 136–137°. The ir spectrum was identical with that of a previously prepared sample.[20]

(18) M. R. Willcott and E. Goerland, *Tetrahedron Lett.*, 6341 (1966).

(19) J. J. Bloomfield, J. S. McConaghy, Jr., and A. G. Hartmann, *ibid.*, 3723 (1969).

(20) R. K. Bly, E. C. Zoll, and J. A. Moore, *J. Org. Chem.*, **29**, 2128 (1964).

4-Bromo-2-methyl-3-phenyl-2-cyclopentenone (16).—A solution of 100 mg of 2-methyl-3-phenyl-2-cyclopentenone in 3 ml of carbon tetrachloride was treated with 103 mg of *N*-bromosuccinimide. After 1 hr refluxing, a rapid reaction was observed; the succinimide which separated was collected and the filtrate was evaporated to an oil which crystallized to give 140 mg (96%) of off-white solid, mp 68–75°. Recrystallization from ether–pentane and sublimation gave **16** as white crystals: mp 89–91°; ν^{KBr} 1705 cm^{-1}; δ^{CCl_4} 1.88 (d, 3, J = 1.5 Hz), 3.01 (m, 2), 5.45 (m, 1), 7.45 ppm (s, 5).

Anal. Calcd for $C_{12}H_{11}BrO$: C, 57.61; H, 4.27. Found: C, 57.39; H, 4.41.

2-Methyl-3-phenylcyclopentadienone Dimer (17).—A solution of 46 mg of bromo ketone **16** in 2 ml of triethylamine was refluxed for 1 hr. The mixture was diluted with benzene and 32 mg of triethylammonium bromide was collected by filtration. Removal of solvent gave a colorless oil which crystallized from ether–pentane to give 12 mg (38%) of colorless crystals, mp 161–163°. Recrystallization from methylene chloride–ether gave the dimer **17**, mp 163–164°; for spectral data, see structure.

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.86; H, 5.90.

Hydrogenation of 2-Acetyl-5-methyl-6-phenyl-1,2-diazabicyclo[3.2.0]-6-hepten-4-one.—A solution of 900 mg of ketone **1** (R = Ac) in 90 ml of ethyl acetate and 90 mg of 10% Pd–C catalyst was shaken with hydrogen at atmospheric pressure until the uptake of 1 mol of H_2 (1 hr). After filtering off the catalyst, the solution was evaporated to a colorless oil. The nmr spectrum of this oil showed that the starting ketone was absent; the C-5 methyl peaks of the two isomeric dihydro ketones were of essentially equal size. The oil was seeded with a crystal of product from a previous hydrogenation (the initial crystallization required several weeks). A first crop of 380 mg, mp 103–105°, was collected. Recrystallization twice from ether and then sublimation at 105° (1 mm) gave colorless crystals of 2-acetyl-5-methyl-6-*exo*-phenyl-1,2-diazabicyclo[3.2.0]heptanone (**19**): mp 114–115°; ν^{KBr} 1750, 1670 cm^{-1}; δ^{CCl_3D} 0.89 (s, 3), 2.30 (s, 3), 3.5–4.7 (m, 5), 7.42 ppm (s, 5).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.97; H, 6.56; N, 11.52.

The mother liquor from **19** was concentrated, and 290 mg of crystals, mp 94–96°, was obtained after standing at 0°. Recrystallization of this material and final sublimation gave 2-acetyl 5-methyl-6-*endo*-phenyl-1,2-diazabicyclo[3.2.0]-4-heptanone (**20**) as white crystals: mp 94–96°; ν^{KBr} 1760 cm^{-1}; δ^{CDCl_3} 1.47 (s, 3), 2.21 (s, 3), 3.6–4.6 (9 lines, combination of C-3 CH_2, H-6 and C-7 CH_2), 6.9–7.4 ppm (m, 5).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.08; H, 6.78; N, 11.37.

Thermal Behavior of 1 (R = Ac), 2, and 19.—Solutions of 15 mg of the three ketones in 0.3 ml of $CDCl_3$ were sealed under nitrogen in nmr tubes and then heated in an 80° bath and spectra were recorded at intervals. **1** (R = Ac): After 48 hr, conversion to the diazepinone **22** (R = Ac), was 30% complete; after 90 hr, conversion was about 50%; after 310 hr the spectrum was essentially that of **22** (R = Ac) with about 5% of **2** (R = Ac) and negligible impurity peaks. **2**: After 260 hr, the only sharp peaks in the spectrum were those of unchanged **2**; very broad signals comprising about half of the total integral were present at δ 1.8–2.2 and 7.2–7.6. **19**: The spectrum was unchanged after 270 hr at 80°.

Registry No.—**1b**, 26439-91-8; **2**, 21039-49-6; **2** semicarbezone, 26439-93-0; **3**, 17831-34-4; **4a**, 26439-95-2; **4b**, 26439-96-3; **7**, 26439-97-4; **16**, 26439-98-5; **17**, 26439-99-6; **19**, 26440-00-6; **20**, 26440-01-7.

Models for the Stepwise Solvolysis of Unsaturated Ditosylates

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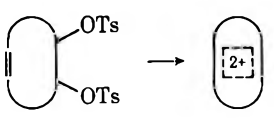
The solvolytic behavior of *cis*-4,5-cyclohexanediol ditosylate (I) has been studied as a model for the stepwise ionization of unsaturated ditosylates. Double ionization to form a bishomocyclobutenium ion is stereoelectronically prohibited in I. For comparison, the solvolyses of *trans*-4,5-cyclohexanediol ditosylate (II), *cis*-1,2-cyclohexanediol ditosylate (III), *trans*-1,2-cyclohexanediol ditosylate (IV), 4-cyclohexenyl tosylate (V), and cyclohexyl tosylate (VI) have also been studied. The rates of all the compounds are compared at 160°. Activation parameters and product analyses are reported. It is found that the double bond in I or II conveys no significant acceleration relative to III or IV, and that the unsaturated *cis*-ditosylate I reacts even more slowly than the *trans*-ditosylate II. These results are taken to be characteristic of the stepwise mechanism. Properties required of a mechanism involving double ionization to a dication are discussed.

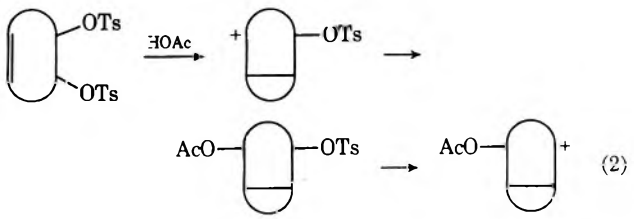
Part A

In this series of papers,[2] it has been our object to examine systems that could give rise to a doubly charged species as a transient intermediate under normal solvolytic conditions. The two positive charges are to be produced by solvolysis of adjacent tosylate groups, and the requisite stabilization is to be provided by an appositely positioned double bond (eq 1). The



(1)

novel intermediate so formed would be termed a bishomocyclobutenium ion and would receive its stabilization by possession of a planar bishomocyclic structure with $4n + 2$ electrons (n = 0). We have previously studied a system[2] that is stereochemically ideal for formation of a bishomo dication, but the kinetic data could not differentiate between the double ionization mechanism of eq 1 and pathways exemplified



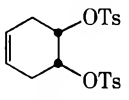
(2)

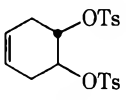
by eq 2, in which ionization is stepwise and an acetoxy tosylate intermediate intervenes. In the present work, we have examined the solvolysis of *cis*-4,5-cyclo-

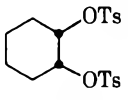
(1) (a) Alfred P. Sloan Foundation Fellow, 1968–1970. This work was supported by the National Science Foundation, Grant GP-9257, and by the Petroleum Research Fund, administered by the American Chemical Society, Grant 2970-A4,5. To whom correspondence should be addressed. (b) National Science Foundation Trainee, 1968–1969; NDEA Fellow, 1969–1970. (c) NDEA Fellow, 1967–1969.

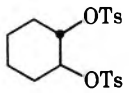
(2) For the first paper, see J. B. Lambert and A. G. Holcomb, *J. Amer. Chem. Soc.*, **91**, 1572 (1969).

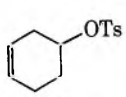
hexenediol ditosylate (I), in which participation of the double bond in a double ionization is conformationally disfavored. Examination of the solvolytic properties of I and the related compounds II–VI should therefore

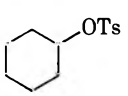

I


II


III


IV


V


VI

produce data characteristic of the stepwise pathway (eq 2). This information will serve to clarify the mechanistic analysis of those systems that do offer a stereoelectronically favorable relationship for production of a bishomo dication.

The solvolyses of compounds I–VI were carried out in acetic acid containing an equivalent amount of potassium acetate. Kinetic studies were performed for at least three temperatures in order to obtain activation parameters. The rates adjusted to 160° for all compounds are given in Table I. Products were

TABLE I
SOLVOLYTIC RATES FOR CYCLOHEXYL TOSYLATES (160°)

Compd	Rate, $sec^{-1} \times 10^5$
I	3.92[a]
II	10.0[b]
III	4.15[b]
IV	6.07[b]
V	9420[a]
VI	11900[a]

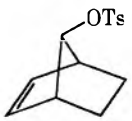
[a] Calculated from the Arrhenius plot. [b] Measured at 160°.

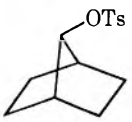
isolated after acetolysis at 170° for 24 hr (100° for VI) and identified by their spectrometric and chromatographic properties.

Comparison of the saturated (III) and unsaturated (I) *cis*-ditosylates shows that the double bond slows the reaction by a factor of I/III = 0.94. The deceleration for the monotosylates is similar (V/VI = 0.79). Introduction of the second tosylate group in a cis position slows the reaction with respect to that of the monotosylate by a factor of V/I = 2400 for the unsaturated pair or VI/III = 2900 for the saturated pair. The cis compound solvolyzes more slowly than the trans compound in both the unsaturated (I/II = 0.39) and the saturated (III/IV = 0.68) series. These rate comparisons show that (1) the double bond produces a small inductive retardation of the rate, so there is little anchimeric assistance; (2) the second tosylate group produces the expected large decelerative effect; (3) a cis relationship between the two leaving groups does not convey a rate acceleration. It would have been expected of a dication mechanism that the double bond produce a rate enhancement, the cis relationship a rate enhancement, and the second tosylate group only a small rate retardation. The observed results are considered to define the behavior of the stepwise mechanism.

Part B

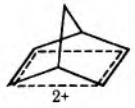
Solvolysis of *anti*-7-norbornenyl tosylate (VII) occurs


VII

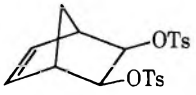

VIII

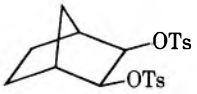
about eleven powers of ten more rapidly than that of the corresponding saturated tosylate (VIII).[3] This acceleration has been attributed to transition state stabilization leading to the bishomocyclopropenium ion intermediate IX. Isoelectronic to IX


IX

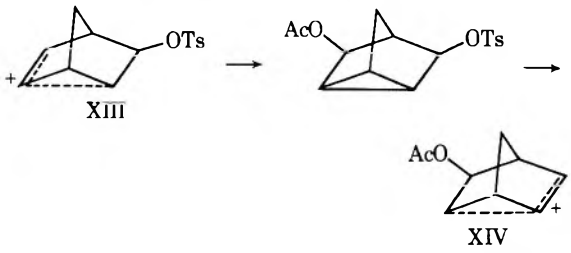

X

is the bishomocyclobutenium dication X, which could be formed by solvolysis of the ditosylate XI. A recent study, however, showed that XI acetolyzes


XI


XII

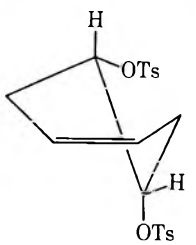
only 500 times more rapidly than the saturated analog XII. The kinetic and product analysis could not differentiate between a concerted or nearly concerted pathway proceeding to the dication X and a stepwise pathway (eq 3), which contains only monocationic intermediates such as XIII and XIV.


XIII

XIV

(3)

In the most favorable situation for formation of a bishomo dication, the two tosylate groups must be cis to each other and anti to the double bond. The molecule XI was chosen for the initial studies because the bicyclic structure rigidly maintains these requirements. In the present study, we have examined the solvolytic behavior of *cis*-4,5-cyclohexenediol ditosylate (I), in which the stereoelectronic requirements for formation of a bishomocyclobutenium dication are not fulfilled. The conformation probably resembles structure Ia. Because the double bond is positioned for


Ia

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

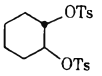
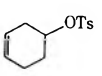
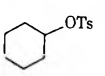
assistance with the leaving of no more than one tosylate group, the reaction must proceed by the stepwise pathway. The conformation obtained by reversal of the cyclohexene ring is the mirror image of Ia, and identical considerations apply. Compound I differs from XI only in the absence of the methano bridge. Since inductive effects should be almost the same in the two systems, compound I can serve as a model for the stepwise mechanism in analyzing the behavior of XI. The present studies were therefore initiated to characterize the properties of the stepwise mechanism.

For a complete investigation of the cyclohexyl system, the cis-unsaturated ditosylate should be compared to the cis-saturated ditosylate (III), the trans-unsaturated ditosylate (II), and the unsaturated monotosylate (V) in order to define the effect of the double bond, of the cis stereochemistry, and of the second tosylate group in I. To complete the series, the trans-saturated ditosylate (IV) and the saturated monotosylate (VI) have also been included. Previous studies have been reported on the acetolysis and hydrolysis of V[4] and on the acetolysis of the brosylates corresponding to III and IV.[5] In order to ensure common conditions, we have examined the solvolytic properties of the entire series I–VI. A study of analogous cyclooctyl brosylates has been reported by Closson, *et al.*[6]

Results and Discussion

The acetolyses of compounds I–VI were carried out at three temperatures. The kinetics are given in Table II and the activation parameters in Table III.

TABLE II
RATE CONSTANTS FOR ACETOLYSIS

Compd	Temp, °C	Rate, $sec^{-1} \times 10^6$
I 	169.7	8.29
	174.8	12.1
	180.8	18.9
II 	154.2	6.03
	160.0	10.0
	165.4	14.2
III 	154.2	2.92
	160.0	4.15
	169.6	10.5
IV 	154.2	3.54
	160.0	6.07
	165.4	9.15
V 	77.3	4.75
	90.2	19.7
	100.2	54.1
VI 	91.2	28.9
	96.2	46.1
	100.2	72.4

Rates measured or calculated for a common temperature (160°) are listed in Table I. Product studies are described in the Experimental Section.

TABLE III
ACTIVATION PARAMETERS FOR ACETOLYSIS

Compd	E_a, kcal/mol	log A	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$ (25°), kcal/mol	$\Delta S^{\ddagger}$, eu
I	29.7	10.6	29.1	32.7	−12.2
II	28.5	10.4	28.0	31.8	−13.0
III	31.8	11.7	31.2	33.3	−7.1
IV	31.6	11.7	31.0	33.1	−6.9
V	27.6	12.9	27.0	27.5	−1.4
VI	27.5	12.9	28.9	27.3	−1.4

The ratio of the solvolysis rate for an unsaturated tosylate to that for the corresponding saturated tosylate gives some indication of the anchimeric assistance provided by the double bond. A double bond that is two carbon atoms removed from the reaction site inductively reduces the rate by a factor of 5 or 10.[4] The extent of π participation, which is superimposed upon this inductive retardation, depends on the geometry of the system, with large accelerations observed in favorable cases such as VII. There is little evidence for double bond participation in the present cases, presumably because the double bond is poorly oriented with respect to the leaving group. The unsaturated/saturated ratios are 0.94 for I/II, 0.79 for V/VI, and 1.65 for II/IV. In the stepwise mechanism for I or II, the inductive retardation and the participative acceleration must approximately cancel each other. The dication mechanism would have exhibited a considerable anchimeric acceleration by the double bond.

Introduction of a second tosylate group should be appreciably rate retarding, since any electron-deficient intermediate will be destabilized by the electron-withdrawing group. Thus the monotosylate/ditosylate ratios are 2900 for VI/III, 2000 for VI/IV, 940 for V/II, and 2400 for V/I. These ratios would become much smaller in a dication mechanism.

For a double ionization to occur, the leaving groups must be cis to each other and equivalently oriented with respect to the double bond. In the trans form a stepwise mechanism is therefore obligatory. If in the cis isomer the double ionization is to occur more rapidly than the stepwise mechanism, it must convey a rate enhancement. Operationally, the presence of the double ionization therefore requires that the cis isomer react more rapidly than the trans isomer. The cis/trans ratios are 0.39 for I/II and 0.68 for III/IV. The cis isomers thus do not display a rate acceleration. Of the cases examined in the present study, none were expected to show double ionization; so these low cis/trans ratios are in accord with a stepwise mechanism in all cases.

Since little or no anchimeric acceleration is observed in I, II, and V, a participative k_Δ component of the rate is probably small, though not negligible. Limiting carbonium ion behavior (k_c) with neither solvent nor neighboring-group participation is unlikely in these simple secondary systems.[7] The relative contributions of the k_Δ (double bond participation) and k_s (solvent displacement) mechanisms cannot be assessed. The

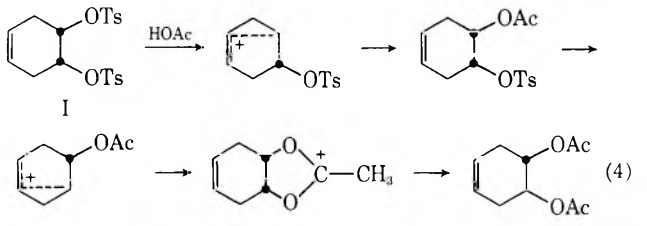
(4) M. Hanack and K. Keberle, *Ber.*, **96**, 2937 (1963); M. Hanack and H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.*, **6**, 674 (1967).

(5) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

(6) W. D. Closson, J. L. Jernow, and D. Gray, *Tetrahedron Lett.*, 1141 (1970). We are endebted to Professor Closson for informing us of his results prior to their publication.

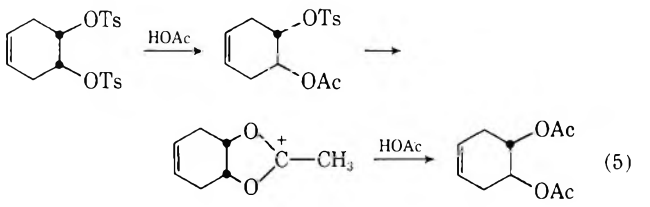
(7) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2538 (1970).

k_Δ component of the rate for the unsaturated compounds would derive from a process such as that in eq 2, or in particular for I, eq 4. The frequent occur-



(4)

rence of *trans*-diacetate products may be suggestive of acetoxonium ion intermediates in the final stages of the reaction.[8] For the k_s component, the first stage of the stepwise mechanism would be modified so that the acetoxy tosylate is produced directly from the ditosylate (eq 5).



(5)

Experimental Section

Nmr spectra were taken on Varian Model A-60 and T-60 spectrometers; infrared spectra were recorded on Beckman IR-5 and IR-10 spectrophotometers. Gas chromatographic analyses were performed on F & M Model 700 and Varian Model 1520B chromatographs. Elementary analyses were provided by Micro-Tech Laboratories, Skokie, Ill.

Tosylates were prepared by the usual treatment of alcohols with recrystallized *p*-toluenesulfonyl chloride in dry pyridine at 0°. Purification was effected by crystallization from ethanol or methanol. Rates were measured in dry acetic acid containing an equivalent of potassium acetate. Aliquots were titrated with standardized perchloric acid in acetic acid with crystal violet indicator. Temperatures were read from a Beckman thermometer calibrated against an Anschütz thermometer. The temperature was constant within 0.1 degree for any run. For product studies, about 2 g of a tosylate was treated with 10 ml of acetic acid 1 *N* in KOAc, and this solution was diluted with acetic acid to 100 ml. This solution was heated in a sealed tube at 170° (100° for cyclohexyl tosylate) for 24 hr. The tube was opened and the contents diluted with about 5 vol of H_2O. This mixture was extracted five times with ether. The extracts were shaken with saturated $NaHCO_3$ solution and dried over $MgSO_4$–Na_2CO_3. After the ether was removed, the products were separated by preparative gas chromatography. Diacetates were isolated from a $^1/_2$ in. × 10 ft silicone column and monoacetates from a $^3/_8$ in. × 12 ft Carbowax column. Various acetates were prepared for comparative purposes by treatment of the corresponding alcohol with acetic anhydride.

cis-**Cyclohexene-4,5-diol** was prepared in four steps from cyclohexadiene by the method of Ali and Owen.[9] The product was recrystallized from hexane (mp 79.5–80.5°) and converted to the ditosylate (I, mp 90–91°). *Anal.* Calcd for $C_{20}H_{22}O_6S_2$: C, 56.84; H, 5.26; O, 22.72; S, 15.18. Found: C, 56.83; H, 5.33. The major component (>70%) of the solvolysis was *trans*-4,5-cyclohexenediol diacetate. The nmr and ir spectra were identical with those of an authentic sample.

trans-**Cyclohexene-4,5-diol** was prepared in two steps from cyclohexadiene by the method of Ali and Owen.[9] The material was recrystallized from heptane and converted to the ditosylate (II, mp 80–81°). *Anal.* Calcd for $C_{20}H_{22}O_6S_2$: C, 56.84; H, 5.26; O, 22.72; S, 15.18. Found: C, 57.25; H, 5.25. Over 80% of the acetolysis product was *trans*-4,5-cyclohexenediol acetate. There were no other major components.

cis-**Cyclohexane-1,2-diol** was prepared by treatment of cyclohexene with $KMnO_4$. The product was recrystallized twice from toluene (mp 99–100°) and converted to the ditosylate (III, mp 128–129°). *Anal.* Calcd for $C_{20}H_{24}O_6S_2$: C, 56.57; H, 5.71; O, 22.61; S, 15.11. Found: C, 56.18; H, 5.65. The major components (~50%) of the acetolysis products were *cis*- and *trans*-1,2-cyclohexane diacetates.

trans-**Cyclohexane-1,2-diol** was obtained from Aldrich Chemical Co. The ditosylate IV was recrystallized from ethanol (mp 110–112°). *Anal.* Calcd for $C_{20}H_{24}O_6S_2$: C, 56.57; H, 5.71; O, 22.61; S, 15.11. Found: C, 55.93; H, 5.51. The major acetolysis product (~50%) was the *trans* diacetate. Other products included unsaturated monoacetates.

Cyclohexene-4-ol was prepared by the dehydration of cyclohexane-1,4-diol (Aldrich Chemical Co.) with sulfuric acid or alumina. The product was purified by fractional distillation, with the desired material boiling at 160–163°. Product studies from the solvolysis of the tosylate have been discussed elsewhere.[4]

Cyclohexanol was purchased from Aldrich Chemical Co. The only major ester product from the solvolysis of the tosylate was cyclohexyl acetate.

Registry No.—I, 26431-17-4; II, 26419-16-9; III, 5433-22-7; IV, 5433-21-6; V, 26431-20-9; VI, 953-91-3.

(8) S. Winstein, C. Hanson, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *ibid.*, **70**, 816 (1948).

(9) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 1066 (1958).

Stable Free Radicals. VIII.[1] New Imino, Amidino, and Carbamoyl Nitroxides

EDWIN F. ULLMAN,* LUDWIG CALL,[2] AND JEANNE H. OSIECKI

Contribution No. 20 from Synvar Research Institute, Palo Alto, California 94304

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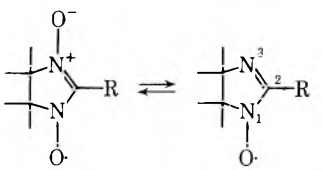
A new group of cyclic nitroxides **2**, **9**, and **10** are described. Many of these radicals are highly stable and undergo reactions at sites of high spin density without decomposition. Hyperfine splittings of the two ring nitrogens are changed in opposite directions by changes in the substituent. Hammett σ_p and σ_p^+ correlations are obtained. The new radicals are basic and the conjugate acids undergo proton exchange that is rapid on the esr time scale except in very acidic solutions. In bromo and iodo substituted derivatives, infrequently observed coupling to halogen was resolved.

Part A

Recently there has been described a new class of stable chemically versatile free radicals, the nitronyl nitroxides **1**.[1,3] In this paper we describe the preparation, chemistry, and spectral properties of related highly stable imino, amidino, and carbamoyl nitroxides. Although the esr spectra of some related linear radicals have been reported, the compounds were unstable and could not be chemically characterized.[4,5]

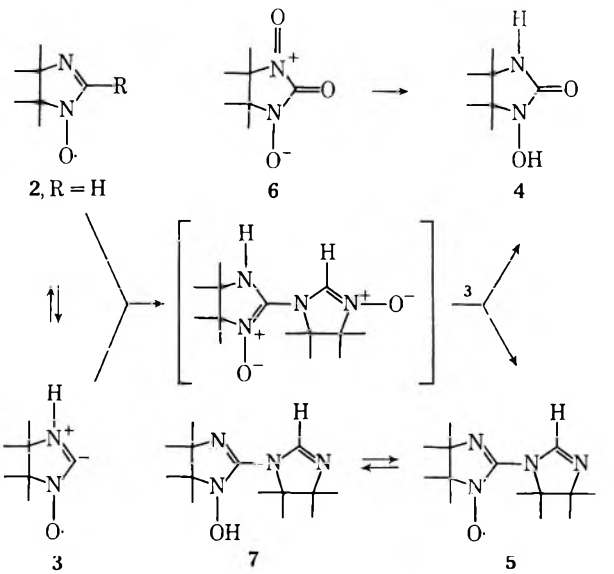
Heating nitronyl nitroxides **1** with triphenylphosphine in benzene or treatment with nitrous acid affords 4,4,5,5-tetramethylimidazoline-1-oxyls **2** in high yields. Most of these compounds are stable, low-melting orange solids which, in several cases, R = C_6H_5, CH_3, and $CH(CH_3)_2$, have been reconverted to the starting nitronyl nitroxides with *m*-chloroperbenzoic acid. The compounds are weak bases by virtue of the imino nitrogen



1 **2**

and may be reversibly protonated without decomposition or disproportionation; pK_a (**2**, R = C_6H_5) = 1.9 ± 0.1.

The unsubstituted derivative **2**, R = H, undergoes deuterium exchange at C_2 within 6 hr at pH 7. The absence of a dramatic rate increase up to pH 13 suggests a nonbase-catalyzed exchange process possibly involving the radical zwitterion intermediate **3**. Similar nonradical intermediates have recently been implicated in exchange reactions of other heterocycles.[6] Formation of **3** may also account for the spontaneous decomposition of **2**, R = H, which occurs when the pure solid is permitted to stand for 24 hr at room temperature. Two products were obtained, both in 70% yield. Identification of the hydroxyurea **4** [ν_{KBr} 1700 cm^{-1} (C=O)] was confirmed by an independent synthesis



2, R = H **6** **4**

3 **7** **5**

through reduction of the zwitterion **6**[3b] with triphenylphosphine in methanol. The radical product **5** showed esr coupling similar to the other imino nitroxides **2** (Table I). Despite the absence of coupling with the nonradical ring nitrogens, attachment of the nonradical ring in **5** through a nitrogen atom is supported by the

TABLE I

HYPERFINE SPLITTING (GAUSS) OF IMINO AND AMIDINO NITROXIDES IN BENZENE

Compd	$a_{N(1)}$	$a_{N(3)}$	a_R
2, R = $NHCH(CH_3)_2$	10.80	3.15	
2, R = $N(CH_3)_2$	10.44	3.12	
2, R = NH_2	10.40	3.38	
5	10.25	3.25	
2, R = OCH_3	9.55	3.20	
2, R = $C(CH_3)_3$	9.48	3.94	
2, R = CH_3	9.25	3.9	1.95 (CH_3)
2, R = $CH_2CH(CH_3)_2$	9.24	4.00	1.50 (CH_2)
2, R = $CH(CH_3)_2$	9.25	4.00	1.25 (CH)
2, R = C_6H_5	9.10	4.37	
2, R = H	8.80	4.40	1.5 (H)
2, R = I	8.90[a]	4.18[a]	3.9 (I)[b]
2, R = Br	8.80	4.25	1.9 (Br)
2, R = $COOCH_3$	8.50	4.33	
2, R = CN	8.00	4.63	

[a] Determined from a seven-line pattern in toluene at −70°. [b] Separation of the two lines due to iodine at 77° in benzene (see text).

* To whom correspondence should be addressed.

(1) Paper VII: P. W. Kopf, R. Kreilick, D. G. B. Boocock, and E. F. Ullman, *J. Amer. Chem. Soc.*, **92**, 4531 (1970).

(2) Synvar Postdoctoral Fellow, 1969–1970.

(3) (a) J. H. Osiecki and E. F. Ullman, *ibid.*, **90**, 1078 (1968); (b) D. G. B. Boocock and E. F. Ullman, *ibid.*, **90**, 6873 (1968); (c) D. G. B. Boocock, R. Darcy, and E. F. Ullman, *ibid.*, **90**, 5945 (1968); (d) E. F. Ullman and D. G. B. Boocock, *Chem. Commun.*, 1161 (1969).

(4) H. G. Aurich, *Ber.*, **101**, 1761, 1770 (1968).

(5) (a) A. L. Buchachenko, "Stable Radicals," Consultants Bureau, New York, N. Y., 1965, p 123; (b) *ibid.*, p 128; (c) V. S. Griffiths and G. R. Parlett, *J. Chem. Soc. B*, 997 (1969).

(6) R. A. Cofburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, **26**, 685 (1970).

TABLE II

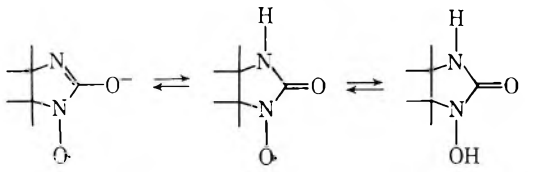
EFFECT OF pH ON HYPERFINE SPLITTING (GAUSS) OF IMINO, AMIDINO, AND CARBAMOYL NITROXIDES IN WATER

Compd	pH	$a_{N(1)}$	$a_{N(3)}$	$a_{N(exo)}$	$a_{H(3)}$	$a_{X(exo)}$
2, R = $NHCH(CH_3)_2$[a]	9	11.45	3.06	<0.5		
	b	12.97[c]	1.75[d]	<0.5		
2, R = $N(CH_3)_2$	9	11.03	3.12	<0.5		
	2	8.9	1.7	1.3[e,f]	2.0[e,f]	1.7 (CH_3)[e,f]
2, R = NH_2	9	11.00	3.31	<0.5		
	2	8.7	2.0	<0.5	3.8[f]	1.0 (H)[f]
	b	12.55[c]	2.1[d]	<0.5		
2, R = C_6H_5	7.6	9.90	4.35			
	−0.8	6.60	4.60		4.6	
9	7	10.4	1.60		1.90[f]	
	13	12.08	2.64			

[a] Spectrum in acid complex and uninterpreted. [b] Dimethyl sulfoxide–potassium *tert*-butoxide. [c] Based on solvent shifts of neutral compound a solvent correction of 0.45 G must be added to obtain coupling in water. [d] Coupling of neutral compound nearly solvent invariant. [e] Determined from spectrum of 2, R = $^{15}N(CH_3)_2$. [f] Determined from spectra taken in D_2O.

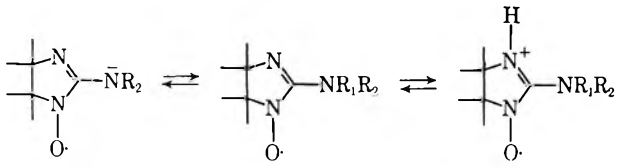
appearance of an olefinic proton in the nmr spectrum of its hydrogenation (Pd–C) product **7**.

Treatment of **2**, R = H, with sodium methoxide in methanol in the presence of air gave **2**, R = OCH_3, in 26% yield. This radical formed in higher yield (62%) from methoxide treatment of **2**, R = Br. Similarly, aqueous potassium hydroxide converted **2**, R = Br, to the radical anion **8** which on neutralization afforded the unisolated carbamoyl nitroxide **9** ($pK_a \simeq 11.0$). The identity of **9** was established by hydrogenation to give **4** from which it could be regenerated with sodium periodate.



8 **9** **4**

Stable amidino nitroxides **10** were prepared by refluxing **2**, R = Br, with aqueous amines followed by lead dioxide reoxidation of the partially reduced products. Nitrous acid reduction of amino nitronyl nitroxides **1**, R = NR_1R_2,[7] also gave the amidino nitroxides **10**. These orange radicals are moderately strong bases (**10**, $R_1 = R_2 = H$, pK_a 6.4; **10**, $R_1 = R_2 = CH_3$, pK_a 6.8) which reversibly form stable yellow radical cations **11**. It is also possible to form blue radical anions **12** from **10**, R_1 = H, by treatment with potassium *tert*-butoxide in dimethyl sulfoxide.



12 **10** **11**

The esr spectra of the new radicals (Tables I and II) display several interesting characteristics. Rarely observed coupling with heavy halogen atoms is present in the spectra of **2**, R = Br and I. Prior reports of bromine and iodine coupling are confined to some σ-iminoxyl radicals[8] and the π radical **1**, R = Br.[3b] The spectrum of **2**, R = Br, is fully resolved in most solvents at room temperature except in water and dimethyl sulfoxide where only two of the four bromine lines (I = 3/2) are observed. The spectrum of **2**, R = I, is highly sensitive to solvent and temperature. Only two of the six lines expected due to iodine coupling (I = 5/2) are observed even under the best conditions for spectral resolution (Table I). The ability to resolve halogen hyperfine interactions in these and other halo radicals may be related to d orbital bonding which may reduce the electric field gradients at the halogen nuclei.

Hyperfine coupling of the ring nitrogens in **2** and **10** correlate with the electronic properties of the 2 substituents. Coupling with the nitroxide nitrogen decreases with substituent electron-withdrawing capacity (σ_p) due to coulombic destabilization of the $\overset{+}{N}-\overset{-}{O}$ resonance form. On the other hand, electron-donating capacity of the substituents decreases coupling to the imino nitrogen through reduction of the C=N bond order. The approximate fraction of nitrogen spin density located on N_3 [*vis.*, $a_{N(3)}/(a_{N(1)} + a_{N(3)})$] correlates best with σ_p^+.

The esr spectra of the amidino nitroxides **5** and **10** are unusual in that only two nitrogens show coupling. The dependence of N_3 coupling on C=N bond order and the absence of coupling with substituents on the exocyclic nitrogen suggest that coupling occurs only with the ring nitrogens. Surprisingly, even when there is multiple bond character toward both N_3 and the exo nitrogen as in the ions **11**, $R_1 = R_2 = H$, and **12**, R_2 = H and $CH(CH_3)_2$, there is coupling to only two nitrogens. Although coupling to all nitrogens occurs in the cations **11**, $R_1 = R_2 = CH_3$ and R_1 = H, $R_2 = CH(CH_3)_2$ (Table II) at least in the former, coupling is weaker to the exo nitrogen than to N_3. The reason for weak exo nitrogen coupling in **11** and **12** is uncertain. Possibly angular distortions at C_2 and N_3 imposed by the five-membered ring have a strong influence on the distribution of spin density although transannular spin transmission through space or through σ bonds cannot be ruled out.

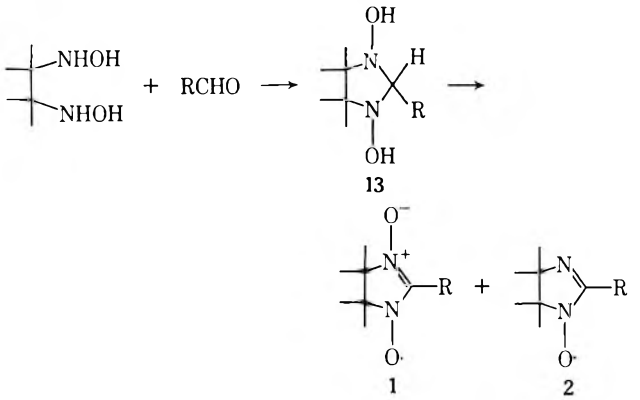
Part B

Preparation and Chemical Properties.—Members of the new class of imino nitroxides **2** were first observed

(7) Unpublished observations of L. Call.

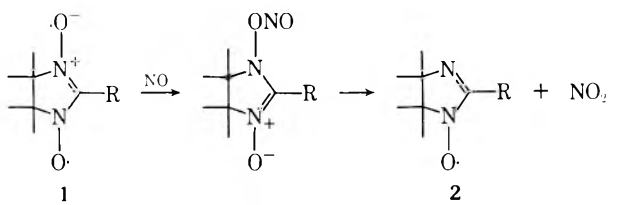
(8) (a) W. M. Fox and W. A. Waters, *J. Chem. Soc.*, 4628 (1965); (b) R. O. C. Norman and B. C. Gilbert, *J. Phys. Chem.*, **71**, 14 (1967); (c) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc., B*, 981 (1967); (d) *ibid.*, 123 (1968).

as by-products during the synthesis of nitronyl nitroxides[3] **1** from lead dioxide or sodium periodate oxidation of *N,N'*-dihydroxyimidazolidines **13**. These compounds are the first examples of stable imino nitroxide radicals. Chemical evidence for their structures is provided by ready interconversions with the



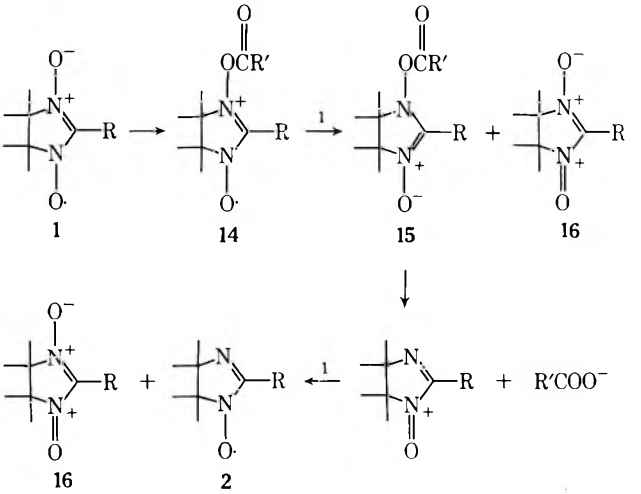
corresponding nitronyl nitroxides **1** which occur under a variety of conditions. Thus, in addition to the above described deoxygenation of **1** with triphenylphosphine or nitrous acid, the imino nitroxides **2** are also formed from **1** with active acid derivatives such as acid chlorides or anhydrides or sulfonylisocyanates, with lead dioxide and acetic acid in dimethylformamide, and occasionally simply by heating. The absence of rearrangement during these reactions is confirmed by reoxidation of the imino nitroxides **2** to nitronyl nitroxides **1** with *m*-chloroperbenzoic acid or with hydrogen peroxide and a catalytic amount of phosphotungstic acid.

Except for the use of triphenylphosphine, none of the above conditions had been predicted to lead to the formation of imino nitroxides, and only limited evidence is available concerning the course of the reactions. Although the formation of imino nitroxides during oxidation of the imidazolidines **13** obviously requires a dehydration step, the mechanistic details are uncertain. On the other hand, partial evidence for the active species in the deoxygenation of nitronyl nitroxides **1** with nitrous acid is available from the observation that nitric oxide alone effects this reaction.



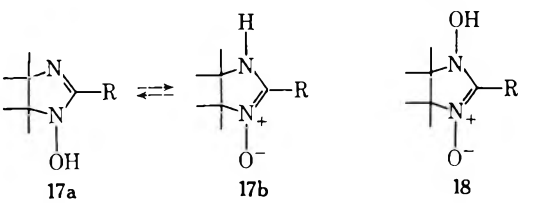
The ability of active acid derivatives to deoxygenate nitronyl nitroxides **1** is consistent with the weak basic properties of these compounds.[3a] Thus an acyl derivative **14** may initially be formed which could then accept an electron from unreacted **1** with formation of the known cation **16**.[3a] Heterolytic cleavage of the acyl product **15** followed by a second electron transfer could account for the imino nitroxide product.

Partial evidence in support of the latter mechanism was obtained from room temperature reaction of **1**, R = C_6H_5, with *p*-toluenesulfonyl isocyanate in methylene chloride to give a 48% conversion to **2**, R = C_6H_5. When this reaction was stopped prior to completion a



yellow, highly polar intermediate was observed. Since this intermediate underwent reaction with ethers and alcohols to give **1**, R = C_6H_5, it was very probably the cation **16**, R = C_6H_5.[3a] The latter compound is a very strong oxidizing agent and even reacts slowly with water to give back the nitronyl nitroxide **1**, R = C_6H_5. The formation of the imino nitroxide **2**, R = C_6H_5, in greater than 33% yield may be due to slow reduction of **16**, R = C_6H_5, by solvent impurity or by the as yet undefined product derived from the sulfonyl isocyanate reagent.

The imino nitroxides **2** have equal or greater thermal stability than the nitronyl nitroxides **1**, and many of them survive heating above 100° in neutral or alkaline solutions without appreciable decomposition. Like the nitronyl nitroxides **1**, imino nitroxides **2** can be quantitatively reduced by catalytic hydrogenation with the uptake of one atom equivalent of hydrogen. The resulting reduced modifications can in principle exist in two tautomeric forms. The phenyl derivative **17**, R = C_6H_5, has been studied in this regard. It appears to exist principally in the amidino oxide form **17b**, R = C_6H_5, since in dilute solutions its ultraviolet absorption is nearly identical with that of the reduced nitronyl nitroxide **18**, R = C_6H_5. However, as its solutions do not obey Beer's Law, the distinction between the two forms



in concentrated solution may be obscured by intermolecular hydrogen bonding. The reduced imino nitroxides **17** are less readily reoxidized than their nitronyl nitroxide counterparts **18**[3a] as demonstrated by their relative stability in air and the inability of **17b**, R = C_6H_5, to reduce the phenyl nitronyl nitroxide **1**, R = C_6H_5.

Esr Spectra.—The imino nitroxides **2** and **10** display coupling to both nitrogens. These couplings give rise to nine major lines which frequently overlap to give a seven-line pattern (Figures 1–3). Coupling with the *gem*-methyl hydrogens is weak (~0.2 G) and usually unresolved. Alkyl substituents at the 2 position display α-hydrogen coupling which decreases in the order

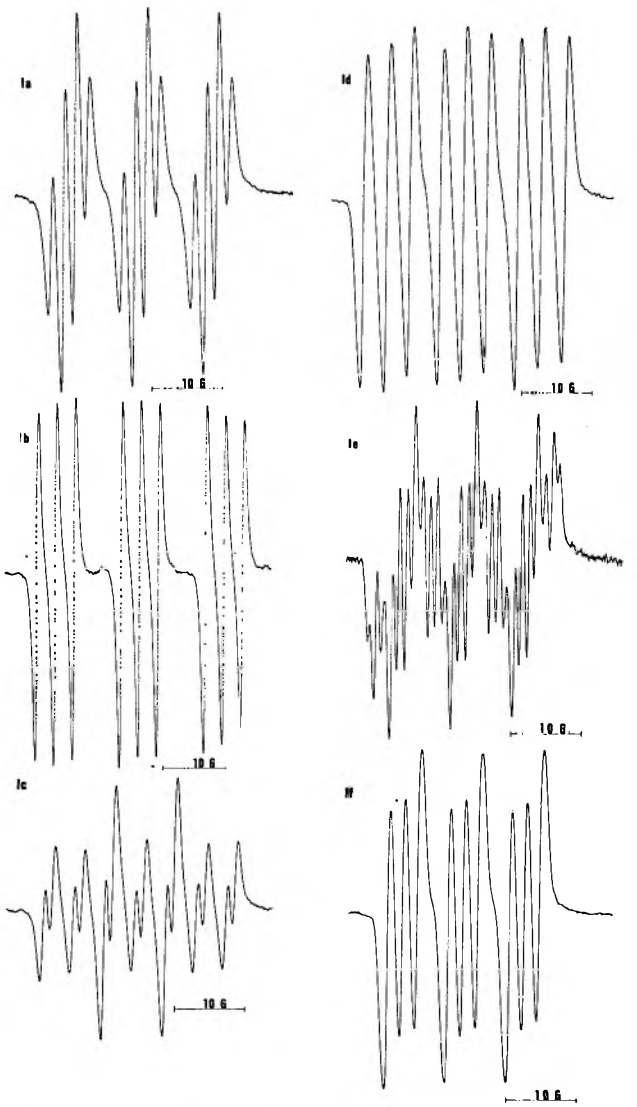


Figure 1.—Esr spectra of (a) carbamoyl nitroxide **9** in water; (b) **9** in 0.1 *N* NaOH; (c) imino nitroxide **2**, R = H in benzene; (d) **2**, R = NH_2 in pH 9 buffer; (e) **2**, R = NH_2 in pH 2 buffer; (f) **2**, R = NH_2 in pD 2 buffered D_2O.

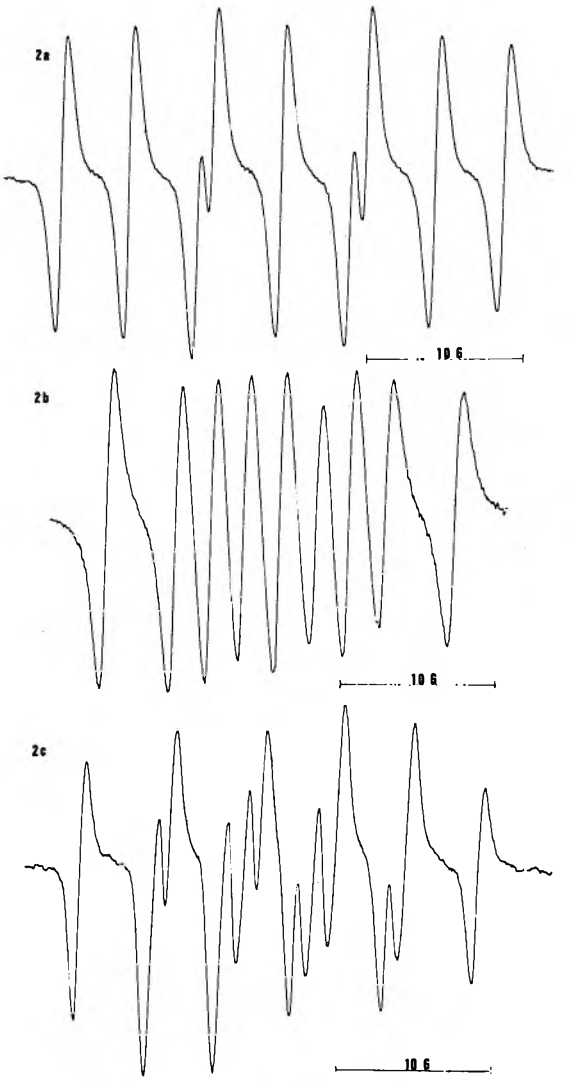


Figure 2.—Esr spectra of imino nitroxide **2**, R = C_6H_5, in (a) pH 7.6 buffer; (b) pH 1.4 buffer; (c) 6 *N* HCl.

methyl > methylene > methine (Table I) due undoubtedly to increased steric hinderance to overlap of the C–H bonds with the C_2 π orbital.

Previously reported spectra of linear imino nitroxides[4] also display coupling with both nitrogens. In these less stable derivatives, the nitrogen coupling constants are strongly affected by steric factors which interfere with coplanarity of the system. Previously reported linear amidino[5a] and carbamoyl[5c] nitroxides display coupling with only one nitrogen presumably for similar reasons. In the present cyclic compounds, coplanarity is assured and the effects of substituents and solvents can be attributed primarily to their electronic properties. Examination of these effects reveals that **2** and **10**, like simple nitroxides,[9] show an increase in the nitroxide nitrogen coupling constants $a_{N(1)}$ with increasing solvent polarity (Table III). This is consistent with the expected increase in stabilization of $\dot{N}-\overset{+}{O}$ resonance contributors in more polar media. With the exception of the amino derivatives **10**, increased solvent polarity produces a similar effect on $a_{N(3)}$ due to partial resonance delocalization of the increased N_1 spin density (*cf.* Tables I–III). The effect of introduction of electron-donating substituents at the 2 position also is to increase $a_{N(1)}$, but now there is a decrease in N_3 coupling (Table I).

Interpretation of these results is simplified by assuming that the spin density in **2** is distributed only on

TABLE III

EFFECT OF SOLVENTS ON NITROGEN HYPERFINE COUPLING (GAUSS) IN **2**, R = $C(CH_3)_3$

Solvent	E_T[a]	$a_{N(1)}$	$a_{N(3)}$
Water[b]	63.1	10.20	4.23
Formamide	56.6	9.84	4.12
Ethanol[b]	51.9	9.47	4.08
Acetonitrile	46.3	9.70	3.93
Methylene chloride	41.1	9.65	3.98
Chloroform	39.1	9.65	3.98
Ethyl ether	34.6	9.40	3.80
Benzene	34.5	9.48	3.94
Carbon tetrachloride	32.5	9.32	3.90
n-Hexane	30.9	9.30	3.87

[a] Solvent polarity parameter: see C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, **4**, 29 (1965). [b] Protonic solvents may have unrepresentative coupling due to hydrogen bonding to N_3 which shifts free spin density away from N_1.

(9) A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals," Academic Press, New York, N. Y., 1968, p 198.

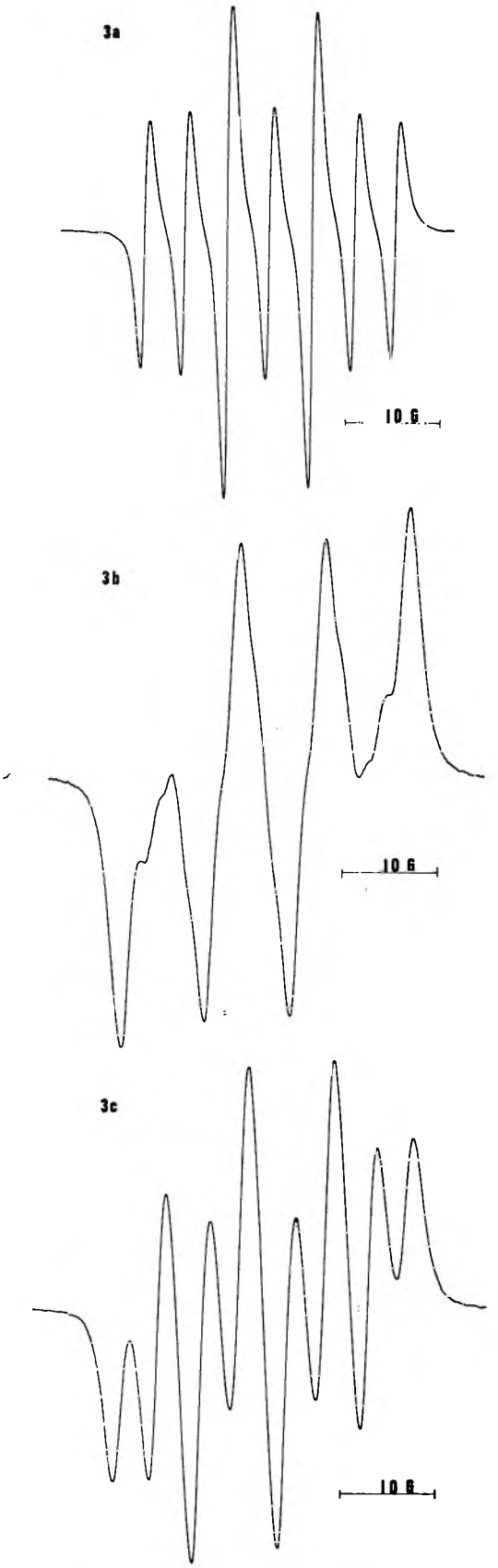


Figure 3.—Esr spectra of imino nitroxide **2**, R = I in toluene at (a) −70°; (b) 18°; (c) 77°.

O, N_1, and N_3. Based on the simplified Karplus–Fraenkel expression (eq 1),[10,11] coupling to N_1 is given

$$a_N = Q^N_N \rho_N + \sum_i Q^N_{X(i)} \rho_{X(i)} \quad (1)$$

$$a_{N(1)} = Q^N_{N(1)} \rho_{N(1)} + Q^N_{ON} (1 - \rho_{N(1)} - \rho_{N(3)}) \quad (2)$$

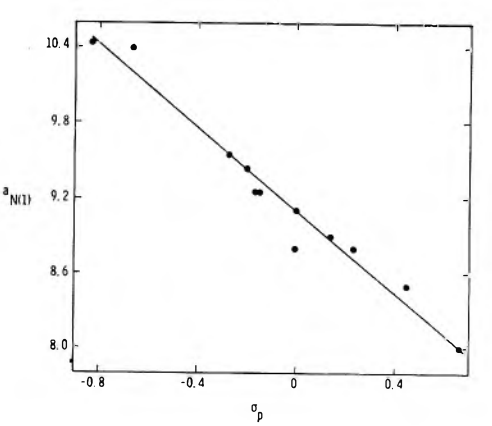


Figure 4.—Effect of substituents on hyperfine coupling of N_1 in the imino nitroxides **2**. σ_p values taken from H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

by eq 2. Since $Q^N_{N(1)}$ is 10–20 times[12] greater than Q^N_{ON}, and $\rho_{N(1)}$ is expected to be greater than $\rho_{N(3)}$, coupling to N_1 should be approximately proportional to its spin density $\rho_{N(1)}$. The observed correlation of $a_{N(1)}$ with σ_p values of the 2 substituents (Figure 4) is consistent with this relationship and suggests that spin density at N_1 is controlled by substituent inductive effects.[13]

Distribution of spin density to N_3 might, on the other hand, be expected to depend primarily on the C=N bond order. This should be reduced by resonance interactions with the 2 substituents. The effect is exemplified by the substituent effects given in Table I, the reduction in the $a_{N(3)}$ coupling of **10** on either protonation or deprotonation, and the increase in $a_{N(3)}$ of the carbamoyl nitroxide **9** upon deprotonation (Table II). The small $a_{N(3)}$ solvent dependence of the amino derivatives **10** (*cf.* Tables I and II) also fits this picture. Higher N_3 spin density in more polar solvents would be expected by partial distribution of the increased N_1 spin. This is offset by transmission of a smaller fraction of the spin to N_3 because the same solvents increase resonance delocalization of the amino group and reduce the C=N bond order.

The spin density $\rho_{N(3)}$ is expected to be approximately proportional to $a_{N(3)}$ (eq 3).[11,12] Since spin

$$a_{N(3)} = Q^N_{N(3)} \rho_{N(3)} \quad (3)$$

$$a_{N(1)} = Q^N_{N(1)} \rho_{N(1)} \quad (4)$$

distribution to N_3 will be reduced by the donation of electrons into the C=N bond, we might expect a correlation of $a_{N(3)}$ with σ_p^+. Although $a_{N(3)}$ does indeed correlate better with ρ_p^+ than with other Hammett parameters, the correlation is only fair (correlation coefficient 0.847). It is found that the ratio $a_{N(3)}/[a_{N(1)} + a_{N(3)}]$ correlates significantly better (Figure 5). The result is rationalized by use of eq 4 where the small Q^N_{ON} terms in (eq 2) have been neglected. If we assume that $Q^N_{N(1)} \cong Q^N_{N(3)}$, then $a_{N(3)}/[a_{N(1)} + a_{N(3)}]$ becomes a measure of the spin distribution between N_1

(10) E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **39**, 1635 (1963).
(11) P. H. Rieger and G. K. Fraenkel, *ibid.*, **39**, 609 (1963).
(12) (a) A. Carrington and J. dos Santos-Veiga, *Mol. Phys.*, **5**, 21 (1962); (b) P. B. Ayscough and F. P. Sargent, *J. Chem. Soc. B*, 907, (1966).
(13) For a discussion of correlations of nitrogen coupling constants with Hammett parameters, see E. G. Janzen, *Accounts Chem. Res.*, 279 (1969).

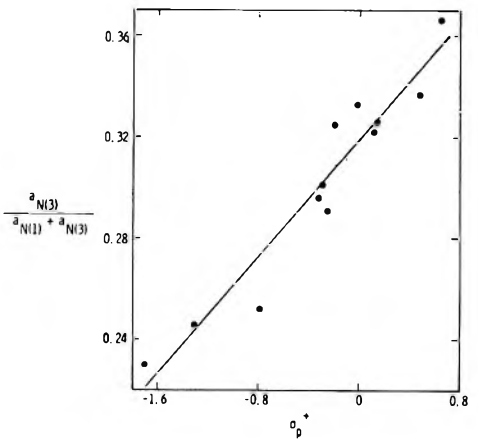


Figure 5.—Effect of substituents on the hyperfine coupling ratio $a_{N(3)}/[a_{N(1)} + a_{N(3)}]$ in the imino nitroxides **2**. σ_p^+ values taken from H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

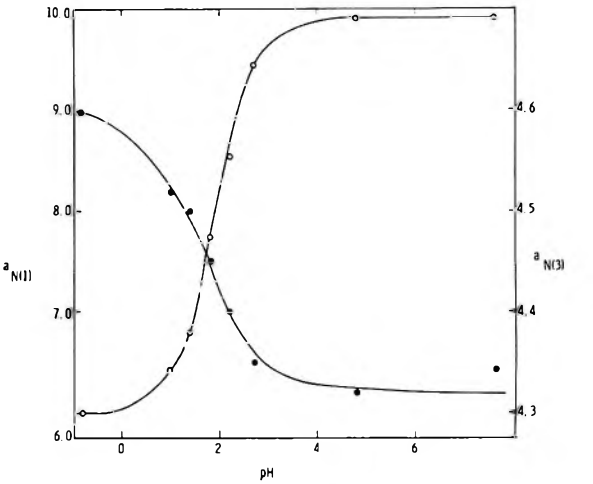


Figure 6.—Effect of pH on hyperfine coupling of **2**, R = C_6H_5: $a_{N(1)}$, open circles; $a_{N(3)}$, closed circles.

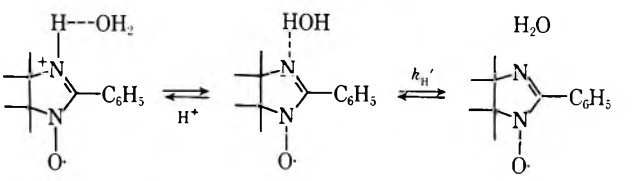
and N_3 and should be sensitive to the C=N bond order.[14]

Halogen Coupling.—The esr coupling to halogen in the imino nitroxides **2**, R = Br and I, will be described in detail elsewhere.[16] Failure to observe halogen hyperfine coupling in most bromo and iodo radicals arises from the large halogen nuclear quadrupole moments. Fluctuations in the electric field gradients at the halogen nuclei due to molecular tumbling generally produce nuclear spin relaxation rates that are greater than the hyperfine splitting, and spectral averaging of the nuclear spin states occurs. Structural features that reduce electric field gradients at the halogen nuclei should favor the observation of halogen coupling. In the present examples the nuclear field gradients caused by the asymmetric halogen σ bonds are possibly partially offset by back bonding of the symmetrical halogen d orbitals with the π system or bonding through space with the nitroxide oxygen. A similar explanation could account for the halogen coupling in the iminoxyl radicals.[8]

pH Dependence.—The imino nitroxides **2** are weak bases which can be protonated without loss of free-radical character. The esr spectrum of **2**, R = C_6H_5, was studied as a function of pH. Resolved spectra showing coupling to both nitrogens but not to the added proton were obtained above pH 1.0. At lower pH line broadening was observed and in 6 *N* hydrochloric acid coupling to the added proton became resolved (Figure 2). The coupling constants $a_{N(1)}$ and $a_{N(3)}$ changed gradually with pH giving typical titration plots from which was obtained the pK_a 1.9 ± 0.1. On lowering the pH the N_1 coupling decreased and the N_3 coupling increased (Figure 6).

The change in a_N with pH suggests that protonation occurs on the imino nitrogen. The inductive effect should reduce coupling to N_1 and increased N_3 coupling should occur by additional resonance delocalization of spin to N_3. By contrast, protonation of simple nitroxides occurs on oxygen and is known to produce increased nitroxide nitrogen coupling.[17] The observed gradual changes in nitrogen coupling without the appearance of two spectroscopically identifiable species require that the protonated and unprotonated radicals are in rapid equilibrium. Spectroscopic averaging is expected when $1/\tau \gg \sqrt{2}\,\pi\delta\nu$ where τ is the mean lifetime of the two species and $\delta\nu$ is the line separation in hertz.[18] Since $a_{N(1)}$ undergoes an overall change of 3.9 G on protonation, both protonation and deprotonation can be estimated to proceed with first-order rate constants of $\gg 5 \times 10^7$ sec^{-1}. The base causing deprotonation is not imino nitroxide since spectral averaging occurs even at very low concentrations (10^{-6} *M*). Hydroxide ion also cannot act as the base as its low concentrations also cannot account for the fast exchange rates. Accordingly, the acid counterion or water probably acts as the base.

The absence of proton coupling in protonated **2**, R = C_6H_5, at pH > 1 is also consistent with a rapid exchange process. However, the appearance of proton coupling at pH < 0 requires a mechanism which permits acid inhibition of the proton exchange despite high counterion and water concentrations. Similar inhibition of proton exchange in very acidic solutions of ammonia and amines has previously been observed.[19] The behavior has been attributed to a reduction in the equilibrium concentration of hydrogen bonded free base which is the species postulated to undergo exchange. A similar explanation where acid lowers the concentration of the hydrogen bonded species **20** may account for the present observation. This mechanism is supported by the similar magnitudes of k_H' for the amines[19] and that



20

(14) This assumption is consistent with estimates of Q_N^N of 23–28 G for imino nitrogens[15] and 23–36 G for nitroxide nitrogens.[5b,12]

(15) J. R. Bolton in "Radical Ions," E. T. Kaiser and L. Kevan, Ed., Interscience, New York, N. Y., 1968.

(16) E. F. Ullman and L. Call, *J. Amer. Chem. Soc.*, in press.

(17) B. M. Hoffman and T. B. Eames, *ibid.*, **91**, 2169 (1969).

(18) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 223.

(19) M. T. Emerson, E. Grunwald, M. L. Kaplan, and R. A. Kromhout, *J. Amer. Chem. Soc.*, **82**, 6307 (1960).

TABLE IV

PHYSICAL PROPERTIES OF IMINO NITROXIDES 2

Substituent	Mp, °C[a]	ν (cm^{-1})[b]	λ_{max}, mμ (ϵ)[c] (l. mol^{-1} cm^{-1})
$NHCH(CH_3)$[d,e]	46–48	($CHCl_3$) 1641, 1367	(EtOH) 232 (6080), 464 (1230)
$N(CH_3)_2$[d,e]	*f*	($CHCl_3$) 1610, 1370	(EtOH) 246 (3700), 465 (510)
NH_2[d,e]	141–144	(KBr) 1685, 1367	(EtOH) 238 (4080), 440 (1100)
OCH_3[d,e]	58–59	($CHCl_3$) 1630, 1370	(C_6H_{14}) 243 (6500), 372 (1220)
$CH(CH_3)_2$	*f*	($CHCl_3$) 1590, 1370	
$CH_2CH(CH_3)_2$[e]	*f*	(CCl_4) 1588, 1365	
$C(CH_3)_3$[d,e]	44–46	(CCl_4) 1576, 1365	(C_6H_{12}) 263 (7850), 371 (660), 530 (26)
C_6H_5[d,e]	27–28	($CHCl_3$) 1600, 1370	(C_6H_{14}) 230 (16,200), 273 (3500), 304 (4300), 442 (440), 502 (190)
H[d]	53–54		
I[d,e]	95–97	($CHCl_3$) 1500, 1368	(C_6H_{12}) 267 (3800), 399 (345), 522 (19)
Br[d,e]	54	(KBr) 1520, 1370	(C_6H_{12}) 274 (6150), 387 (550), 521 (23)
CN[e]	110–113	($CHCl_3$) 1545, 1370, 2245 (C≡N)	(C_6H_{12})[g] 300, 346, 436, 496
	70–71	($CHCl_3$) 1600, 1370	

[a] Sublimation accompanies melting in most compounds. [b] Peaks for C=N and N–O stretching, respectively, are given. [c] Shoulders and vibrational structure not recorded. [d] Satisfactory elemental analysis for C, H, and N (>0.3% error). [e] Empirical formula confirmed by mass spectroscopy. [f] Oil, freezes below room temperature. [g] Accurate extinction coefficients not obtained due to slow intensity changes on dilution. Association product probably diamagnetic since the esr spectra were not distorted.

estimated for **20** (5×10^9 sec^{-1}) by determining the pH (−0.7) that produces line coalescence.

The base strengths of the amidino nitroxides **10** were determined from optical spectroscopy (see Part A). At pH's where these compounds were only partially protonated, averaging of the nitrogen coupling in the esr was again observed. At lower pH's coupling to the added proton was also resolved. Analysis of the spectra of acidic solutions of **10**, $R_1 = R_2 = H$ and $R_1 = R_2 = CH_3$, was achieved by use of deuterium oxide solvent, and in the latter case by the incorporation of ^{15}N at the 2 position (Table II). It has not been possible to interpret the spectra of acidic solutions of **10**, $R_1 = CH(CH_3)_2$, $R_2 = H$.

Optical and Mass Spectra.—The infrared spectra of **2** and **10** display strong characteristic absorption at 1365–1378 cm^{-1} attributable to the nitroxyl stretching frequency.[20] The C=N stretching peaks appear at 1576–1600 cm^{-1} in the alkyl and phenyl derivatives but move higher with the amino and methoxy substituents and lower with electron-withdrawing substituents. The ultraviolet and visible spectra of these compounds are quite variable. The strongest absorption maximum is generally found in the range 230–300 mμ with a second weaker maximum in the 370–470 mμ range. Resolution of additional maxima seems to depend strongly on substitution, and many of the spectra display long wavelength tails extending to near 600 mμ. The halo, *tert*-butyl, and phenyl derivatives give well resolved spectra with long wavelength maxima at 500–530 mμ ($\epsilon \sim 20$) and longer wavelength shoulders which may be due to n,π^* transitions (see Table IV).

Mass spectral fragmentation patterns of **2** and **10** display molecular ion peaks plus characteristic major fragments at *m/e* 114 and 84. These may be accounted for by loss of RCN followed by loss of NO.

(20) A. K. Hoffman and A. T. Henderson, *J. Amer. Chem. Soc.*, **83**, 4671 (1961), report the N–O frequency at 1345 cm^{-1} for di-*tert*-butyl nitroxide.

Experimental Section

Representative procedures are given below for the preparation of imino nitroxides, **2**. The triphenylphosphine and nitrous acid reductions of nitronyl nitroxides **1** have general applicability, and the physical properties of the imino nitroxide products of these reactions are given in Table IV. Catalytic hydrogenation of the imino nitroxides to their reduced modifications **17** and reoxidation with lead dioxide or sodium periodate also have general utility.

The esr spectra were recorded using a Varian E3 spectrometer which operates at 9.5 G Hz. Several imino nitroxide spectra were distorted with abnormally intense outermost lines. The behavior was dependent on concentration, temperature, and solvent and could be avoided by sufficient dilution. Association of these radicals in solution was also detected by deviations from Beer's Law at high concentrations.

2-Phenyl-4,4,5,5-tetramethylimidazoline 3-Oxide (17b, R = C_6H_5).—To a solution of 1.0 g of 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide[3a] (**1**, R = C_6H_5) in 100 ml of absolute ethanol was added 7.5 ml of concentrated HCl over 15 min at room temperature. The solution was warmed on a steam bath until it became colorless (~1 hr). It was evaporated *in vacuo;* the residue was taken up in methanol and neutralized with sodium carbonate. Evaporation of the solvent and extraction of the residue with chloroform yielded 0.43 g (46%) of the product: mp 189–190° dec; nmr (DMSO) τ 2.26 (5 Ar H, m), 5.97 (NH, s), and 8.85 (4 CH_3, s); λ_{max}^{EtOH} 238 mμ (ϵ ~15,000) and 325 (~5000) (concentration dependent).

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 71.51; H, 8.31; N, 12.83. Found: C, 71.37; H, 8.25; N, 12.70.

2-Phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = C_6H_5).

A.—2-Phenyl-4,4,5,5-tetramethylimidazoline 3-oxide (**17b**, R = C_6H_5), 0.200 g, in 100 ml of benzene was treated with 4 g of lead dioxide with vigorous stirring at room temperature for 35 min. After filtration, the solution was evaporated *in vacuo* and the orange-brown oil chromatographed on silica gel with benzene. The orange band was collected, and evaporation of the solvent yielded the pure crystalline product (75%).

B.—2-Phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide (**1**, R = C_6H_5), 47 mg, was dissolved in 5 ml of dry dimethylformamide, and 0.25 g of sodium nitrite and 3 drops of concentrated hydrochloric acid were added. On heating the mixture on a steam bath for 10 min, the original blue color changed to orange brown. After cooling, the solution was diluted with 35 ml of benzene and stirred with 2 g of lead dioxide for 5 min at room temperature in order to reoxidize the partially reduced product. After filtration and concentration *in vacuo*, the residue was

chromatogaphed on silica gel with 1:1 benzene–ether to yield 40 mg (91%) of the radical.

This product could be reconverted to the starting nitronyl nitroxide 1, R = C_6H_5, by stirring in a methylene chloride solution containing *m*-chloroperbenzoic acid for a few minutes at room temperature. Alternatively the imino nitroxide 2, R = C_6H_5, was stirred for 3 days in 3% hydrogen peroxide containing a catalytic amount of phosphotungstic acid (5% of the weight of 2, R = C_6H_5). However, the conversion is slow and incomplete under the latter conditions.

C.—To a solution of 112 mg of 2-phenyl-4,4,5,5-tetramethylimidazolidine-1-oxyl 3-oxide (1, R = C_6H_5) in 10 ml of dry methylene chloride was added 95 mg of *p*-toluenesulfonyl isocyanate. The reaction mixture was stirred for 16 hr under nitrogen at room temperature. The brown residue obtained by evaporation of the solvent *in vacuo* was chromatographed on silica gel with ether. The imino nitroxide 2, R = C_6H_5, was obtained in 48% yield (50 mg).

Interruption of the reaction before completion and thin layer chromatography of the reaction solution on silica gel gave a yellow spot which did not migrate with methylene chloride, acetonitrile, or hydrocarbon solvents. However, it became blue with alcohols and ethers. This blue product was indistinguishable from the starting nitronyl nitroxide 1, R = C_6H_5.

2-*tert*-Butyl-4,4,5,5-tetramethyl-2-imidazoline-1-oxyl [2, R = $C(CH_3)_3$].—2,3-(Bishydroxylamino)-2,3-dimethylbutane (1.48 g) and 2.20 ml of pivalaldehyde in 10 ml of methanol were allowed to stand at room temperature for 1 day. Evaporation of the mixture *in vacuo* yielded a partly crystalline residue which was suspended in 500 ml of water containing 2.0 g of $NaHCO_3$. A solution of 3.20 g of $NaIO_4$ in 50 ml of water was added to this solution with cooling in an ice bath. After the addition was complete, the mixture was stirred for 30 min in the dark at room temperature and then extracted with four 100-ml portions of methylene chloride. The combined organic phases were dried over Na_2SO_4 and evaporated and the crystalline residue chromatographed on silica with ether. In addition to the isolation of 1.0 g of 2-*tert*-butyl-4,4,5,5-tetramethyl-2-imidazoline-1-oxyl 3-oxide [1, R = $C(CH_3)_3$], there was obtained 400 mg (19%) of a brown-red oil. Sublimation *in vacuo* at 30° gave 370 mg of 2, R = $C(CH_3)_3$.

4,4,5,5-Tetramethylimidazoline-1-oxyl (2, R = H). A.—To a benzene solution (125 ml) of 1.57 g of 4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide (2, R = H) was added 3 g of triphenylphosphine. The reaction mixture was boiled for 15 min by which time the deep purple color was replaced by orange. The solvent was removed *in vacuo* and the residue chromatographed over silica gel, first by elution with CH_2Cl_2 and then with ether. The solvent was removed *in vacuo* from the pure orange product, 0.675 g (48%) which could be stored in ether solution at Dry Ice temperature. The product was completely decomposed upon standing overnight at room temperature.

B.—To 1 ml of a benzene solution containing several milligrams of 4,4,5,5-tetramethylimidazolidine-1-oxyl 3-oxide (1, R = H) was added two drops of pyridine and one drop of methanesulfonyl chloride. This mixture was maintained at 70° for 5 min and then allowed to stand for 1 hr at room temperature. The resulting solution was washed several times with water. The above product was separated by tlc.

1-Hydroxy-4,4,5,5-tetramethylimidazolidin-2-one (4). A.—A sample of 0.35 g of 4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = H) which was allowed to stand overnight at room temperature was extracted with ether to leave a white ether-insoluble crystalline compound. Recrystallization from methanol–ether gave the product in 70% yield (92 mg): mp 225–230°; ν_{KBr} 1700 (C=O), 3210 cm^{-1} (NH, OH); nmr (DMSO) τ 8.93 and 8.98 (4 CH_3, d), 3.36 (1 H exchanged with D_2O, s), 1.47 (1 H exchanged with D_2O, s).

Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92; N, 17.71; mol wt, 158. Found: C, 53.01; H, 8.81; H, 17.50; *m/e* 158 (M^+).

B.—A solution of 4,4,5,5-tetramethylimidazolidin-2-one-1-oxyl anion (8) was prepared by heating 55 mg of 2-bromo-4,4,5,5-tetramethylimidazolidine-1-oxyl (2, R = Br) in 10 ml of 2 *N* KOH at 70° for 20 min. Potassium borohydride (10 mg) was added and the solution stirred for 3 min at room temperature. The reaction mixture was then neutralized with 2 *N* HCl and taken to dryness *in vacuo*. Continuous extraction of the residue with ethyl acetate and evaporation of the extracts yielded 25 mg of the product.

Alternatively, a solution of the anion 8 was brought to pH 7 with HCl and extracted with ethyl acetate. This solution of radical 9 was dried over $MgSO_4$ and hydrogenated at atmospheric pressure over palladium on charcoal to give the hydroxyurea product.

C.—4,4,5,5-Tetramethylimidazolidin-2-one 1,3-dioxide (6)[3b] (86 mg) was dissolved in 5 ml of methanol and 131 mg of triphenylphosphine was added at 0°. The orange color of 6 faded very rapidly. The unreacted triphenylphosphine was removed by filtration and the solution concentrated *in vacuo*. The residue was purified by preparative tlc on silica gel with ether to give 25 mg (32%) of 1-hydroxy-4,4,5,5-tetramethylimidazolidin-2-one (4).

2-(4,4,5,5-Tetramethylimidazolidine-1-yl)-4,4,5,5-tetramethylimidazolidine-1-oxyl (5).—A sample of 0.35 g of 4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = H) which was allowed to stand overnight at room temperature was extracted with ether. The residue was nearly pure 1-hydroxy-4,4,5,5-tetramethylimidazolidine-2-one. The extracts were concentrated *in vacuo* and purified by chromatography on silica gel with ether. The solid orange product was obtained in 70% yield (0.152 g) by evaporation of the solvent and recrystallization from chloroform.

Anal. Calcd for $C_{14}H_{25}N_4O$: C, 63.36; H, 9.50; N, 21.11; mol wt, 265. Found: C, 62.85; H, 9.52; N, 20.65; *m/e* 265 $(M)^+$, 266 $(M + 1)^+$.

Reduction of 30 mg of this compound in 5 ml of ethyl acetate with hydrogen and palladium on charcoal yielded a white diamagnetic solid 7. The nmr spectrum (CCl_4) showed signals at τ 8.9, 8.84, and 8.62 (8 CH_3) which obscured a one-proton signal (NOH) that disappeared on addition of D_2O. An additional singlet at τ 2.38 (N=CH) was unaffected by D_2O. On stirring a benzene solution of this product (7) with lead dioxide for a few minutes at room temperature, the radical 5 was regenerated.

4,4,5,5-Tetramethylimidazolidin-2-one-1-oxyl (9).—Several milligrams of 1-hydroxy-4,4,5,5-tetramethylimidazolidinone (4) dissolved in methylene chloride were shaken with aqueous sodium periodate solution. The yellow organic layer, after drying over $MgSO_4$ displayed a strong characteristic esr spectrum of the radical $a_{N(1)}$ 10.15 G, $a_{N(3)}$ 1.60, a_H 1.65. (For coupling in water, see Table II.) In alkaline solutions the proton coupling disappeared (Figure 1a and 1b).

Alternatively, solutions of 9 could be prepared by stirring solutions of 4 with lead dioxide or by heating 2-bromo-4,4,5,5-tetramthylimidazolidine-1-oxyl (2, R = Br) in base, as described above, followed by neutralization with acetic or hydrochloric acid. The radical decomposed on attempted isolation.

2-Methoxy-4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = OCH_3). A.—To 0.11 g of 2-bromo-4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = Br) dissolved in 8 ml of methanol was added 0.10 g of sodium methoxide. After 1 hr the solvent was removed *in vacuo* and the residue was chromatographed on silica gel with ether to yield 0.052 g (62%) of the crystalline product. The sample was purified by recrystallization from ether–chloroform.

B.—A methanol solution containing 0.16 g of sodium methoxide and 0.30 g of 4,4,5,5-tetramethylimidazolidine-1-oxyl (2, R = H) was boiled for 40 min. The solution was then neutralized with 1 *N* HCl and evaporated to dryness *in vacuo*. Chromatography on silica gel with ether–chloroform gave 93 mg (26%) of the nearly pure radical.

2-Bromo-4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = Br).[21]—2-Bromo-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide (1, R = Br)[3b] (5 g) was dissolved in 200 ml of dimethylformamide and stirred at room temperature with 20 g of solid sodium nitrite. The color almost immediately turned from purple to orange without addition of acid. The solid sodium nitrite was filtered off and 500 ml of benzene was added to the filtrate. After stirring for 4 min with 50 g of lead dioxide, the solution was filtered and concentrated *in vacuo*. The orange solution was diluted with 700 ml of water and extracted with benzene. Removal of the benzene *in vacuo* and chromatography of the residue on silica gel with ether gave 3.73 g (80%) of the product.

2-Amino-4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = NH_2).—2-Bromo-4,4,5,5-tetramethylimidazoline-1-oxyl (2, R = Br) (1.0 g) was heated at reflux in 100 ml of ammonium hydroxide while bubbling ammonia gas into the solution. The solution was heated for 5 hr, cooled, partially concentrated *in vacuo*, and then stirred for 15 min with 20 g of lead dioxide. After filtration

(21) We thank Dr. D. G. B. Boocock for the preparation of this compound.

through Celite and extraction of the solution with five 50-ml portions of methylene chloride, the combined organic phase was dried and evaporated *in vacuo*. The semicrystalline residue recrystallized from hexane to give 500 mg (70%) of the nearly pure product.

This compound displayed the following absorption maxima: λ_{H_2O} (pH 8) 232 mμ (ε 4200), 451 (1050); λ_{H_2O} (pH 1) 233 mμ (ε 3920), 383 (1070); λ_{DMSO} (KO-*tert*-bu) 668 mμ (ε 590).

2-Dimethylamino-4,4,5,5-tetramethylimidazoline-1-oxyl [2, R = $N(CH_3)_2$].—2-Bromo-4,4,5,5-tetramethylimidazoline-1-oxyl (**2**, R = Br) (500 mg) was heated under gentle reflux with 20 ml of 40% aqueous dimethylamine. After 90 min the solution was almost colorless. Most of the excess amine was removed by evaporation *in vacuo* and the residual solution was reoxidized by stirring for 15 min with 10 g of PbO_2. After filtration through Celite and extraction with three 50-ml portions of CH_2Cl_2, the combined extracts were dried over Na_2SO_4 and evaporated to leave 230 mg of the brown liquid radical. An analytical sample was obtained by molecular distillation at 0.05 mm.

This compound displayed absorption maxima at: λ_{H_2O} (pH 8) 246 mμ (ε 4200), 475 (600); λ_{H_2O} (pH 1) 244 mμ (ε 3800), 427 (900).

2-Isopropylamino-4,4,5,5-tetramethylimidazoline-1-oxyl [2, R = $NHCH(CH_3)_2$].—2-Bromo-4,4,5,5-tetramethylimidazoline-1-oxyl (**2**, R = Br) (250 mg) dissolved in 25 ml of isopropylamine and 25 ml of water were heated under gentle reflux (55–60°) for 4 hr. The almost colorless solution showed only a very weak esr signal. After cooling to room temperature the solution was concentrated *in vacuo* and then stirred for a few minutes with 10 g of PbO_2. The solution was filtered through Celite and the filtrate extracted with five 50-ml portions of CH_2Cl_2. The combined organic phases were dried and evaporated *in vacuo* to leave a brown oil. Chromatography of this residue on silica gel with ether yielded 100 mg (44%) of the pure radical.

This compound displayed absorption maxima at: λ_{H_2O} (pH 8) 233 mμ (ε 5250), 268 (sh) (2200), 480 (1020); λ_{H_2O} (pH 1) 235 mμ (ε 5670), 270 (sh) (1970), 401 (1270); λ_{DMSO} (KO-*tert*-bu) 698 mμ (ε 430).

2-Amino-1-hydroxy-4,4,5,5-tetramethylimidazoline (17, R = NH_2).—2-Amino-4,4,5,5-tetramethylimidazoline-1-oxyl (**2**, R = NH_2) (70 mg) in 50 ml of methanol containing 5 mg of platinum oxide was stirred under a hydrogen atmosphere at room temperature until the solution became colorless. It was then filtered through Celite and evaporated *in vacuo*. The slightly yellow residue was recrystallized from methanol–acetone to give 20 mg of the product, mp 141–144°. The compound reoxidized slowly to the starting radical on standing in air. A satisfactory analysis was not obtained.

2-Dimethylamino-1-hydroxy-4,4,5,5-tetramethylimidazoline [17, R = $N(CH_3)_2$].—2-Dimethylamino-4,4,5,5-tetramethylimidazoline-1-oxyl [**2**, R = $N(CH_3)_2$] (50 mg) in 50 ml of methanol containing 5 mg of platinum oxide was stirred under a hydrogen atmosphere at room temperature until the solution became colorless. The solution was then rapidly filtered through Celite and evaporated *in vacuo*. The residue was recrystallized from acetone to give 15 mg of product (sublimes without melting above 190°). The compound displayed characteristic infrared absorption at ν_{KBr} 3100 (OH) and 1605 cm^{-1} (C=N).

Anal. Calcd for $C_9H_{19}N_3O$: C, 58.34; H, 10.34; N, 22.68. Found: C, 58.33; H, 10.27; N, 22.47.

2-Cyano-4,4,5,5-tetramethyl-2-imidazoline-1-oxyl (2, R = CN).—A finely ground mixture of 300 mg of sodium cyanide and 300 mg of 2-bromo-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide[3b] was heated in 3 ml of dry dimethylformamide at 70° for 15 min. The solution was then diluted with ether, filtered, and evaporated *in vacuo*. The residue was purified by preparative tlc (silica gel–ether) to give 66 mg (31%) of the radical.

Registry No.—**2** (R = NH_2), 26682-07-5; **2** [R = $N(CH_3)_2$], 26682-08-6; **2** [R = $NHCH(CH_3)_2$], 26682-09-7; **2** (R = OCH_3), 26682-10-0; **2** [R = $C(CH_3)_3$], 26682-11-1; **2** (R = CH_3), 26682-12-2; **2** [R = $CH_2CH(CH_3)_3$], 26682-13-3; **2** [R = $CH(CH_3)_2$], 26682-14-4; **2** (R = C_6H_5), 26731-64-6; **2** (R = H), 26682-15-5; **2** (R = I), 26682-16-6; **2** (R = Br), 26682-17-7; **2** (R = $COOCH_3$), 26682-18-8; **2** (R = C≡N), 26682-19-9; **4**, 26682-20-2; **5**, 26682-21-3; **9**, 26682-22-4; **17** (R = NH_2), 26682-23-5; **17** [R = $N(CH_3)_2$], 26682-24-6; **17b** (R = C_6H_5), 18390-03-0.

Iminophosphoranes from the Reaction of Ylides with Nitriles

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Benzonitrile and α-(triphenylphosphoranylidene)toluene react to give the stable iminophosphorane α-[(triphenylphosphoranylidene)amino]stilbene (**3**) which was also prepared by reaction of *cis*- or *trans*-α-azidostilbene with triphenylphosphine. A wide variety of resonance-stabilized phosphoranes and iminophosphoranes, while not reacting with unactivated nitriles, undergo the analogous reaction with cyanogen and trifluoroacetonitrile. The resulting iminophosphoranes (*e.g.*, **4** and **20**) are air stable and quite resistant to hydrolysis. Two isomers are formed in a number of cases. The reaction of nitriles with phosphoranes is believed to proceed by a mechanism analogous to that of the reaction of phosphoranes with activated acetylenes.

Part A

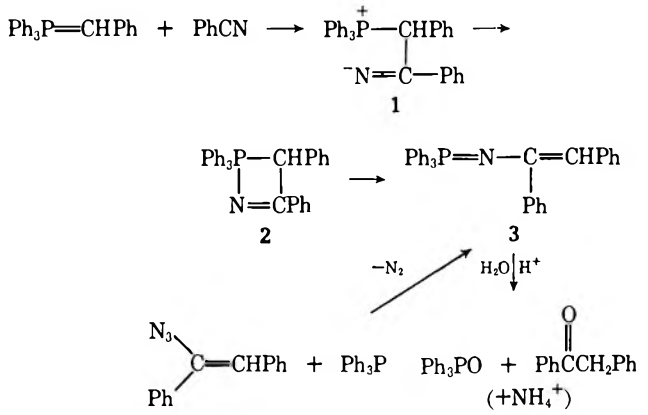
The nucleophilic character of phosphorus ylides has long been recognized and reactions of this class of compounds with a wide variety of electrophilic reagents have been reported.[1] Among these, however, reactions with nitriles have received less attention. McEwen and coworkers[2] found that nonresonance-stabilized ylides[1a,b] react with aliphatic and aromatic nitriles to give ketones after hydrolysis of the unidentified intermediates. We have isolated and characterized the intermediate in one such case and extended the scope to include reactions between resonance-stabilized[1a,b] ylides and the activated nitriles, cyanogen and trifluoroacetonitrile.

α-(Triphenylphosphoranylidene)toluene and benzonitrile reacted slowly in refluxing ether–benzene to give a 1:1 adduct in 68% yield. It was identified as α-[(triphenylphosphoranylidene)amino]stilbene (**3**) by independent synthesis from triphenylphosphine and either *cis*- or *trans*-α-azidostilbene. On hydrolysis, **3** gave deoxybenzoin and triphenylphosphine oxide as reported previously.[2] Attempts to add nitriles to resonance-stabilized ylides, *i.e.*, those carrying electron-withdrawing groups on the ylide carbon, were unsuccessful. How-

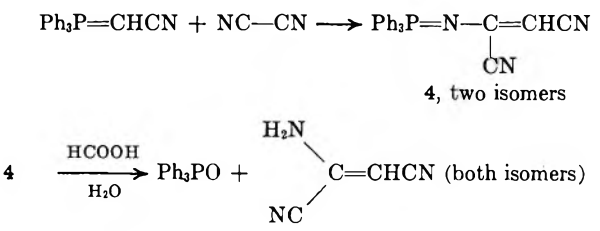
(1) (a) A. Maercker, *Org. React.*, **14**, 270 (1965); (b) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966; (c) H. J. Bestmann, *Angew. Chem.*, **77**, 850 (1965), and preceding reviews.

(2) (a) R. G. Barnhardt, Jr., and W. E. McEwen, *J. Amer. Chem. Soc.*, **89**, 7009 (1967); (b) A. Bladé-Font, W. E. McEwen, and C. A. VanderWerf, *ibid.*, **82**, 2646 (1960); (c) A. Bladé-Font, Ph.D. Thesis, University of Kansas, 1960.

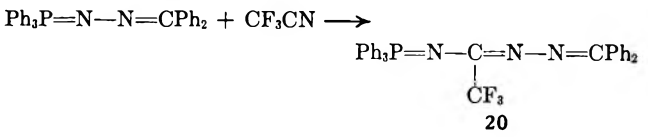
ever, the much more strongly electrophilic nitriles, cyanogen and trifluoroacetonitrile, reacted readily under mild conditions with a large number of such ylides to give iminophosphoranes analogous to **3** in high yields, as



exemplified by the reaction of (triphenylphosphoranylidene)acetonitrile with cyanogen. Hydrolysis of **4**

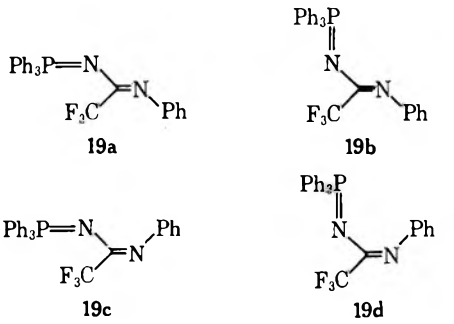


gave a mixture of aminomaleonitrile and aminofumaronitrile, the enamines in this case being resistant to further hydrolysis. Iminophosphoranes, including phosphazines, also reacted readily with cyanogen and trifluoroacetonitrile to give compounds such as **20**.[3] The

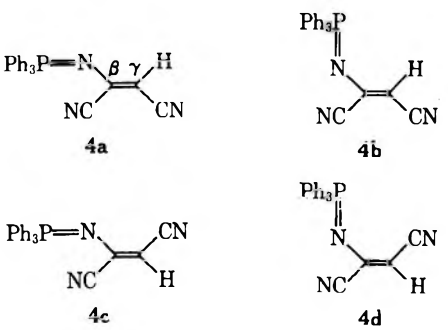


reactions are summarized in Table I. No pure products could be isolated from the reactions of cyanogen or trifluoroacetonitrile with the more strongly basic nonresonance stabilized ylides, polymerization of the nitriles probably occurring to the exclusion of formation of simple adducts. Attempts to add these nitriles to selected nitrogen, arsenic, and sulfur[4] ylides also were unsuccessful.

Two isomers were formed in most but not all cases (Table I). These can differ in the arrangement of the substituents on the phosphorus–nitrogen or carbon–carbon double bonds as exemplified for **4**; the four possible isomers of the iminophosphorane adducts are illustrated for the case of compound **19**. Existence of four isomers presupposes restricted rotation around the



N–C$_\beta$ bond, since **4a–4b** and **4c–4d** are pairs of rotamers. Restricted rotation around the C$_\alpha$–C$_\beta$ bond has been observed in the case of alkoxycarbonylmethylenetriphenylphosphoranes[5] with rotation barriers as high as 18 kcal/mol.[5b] Substituents on C$_\gamma$ capable of delocalizing a negative charge (*e.g.*, the cyano group in **4**) should increase the double bond character of the N–C$_\beta$ bond and consequently increase the barrier of rotation around that bond. The data available do not allow a choice of which of these isomers are present in the products **4–20**. The isomer ratios seemed to be dependent on minor changes in reaction conditions since the values listed in the Table were not always exactly reproducible. In most cases the isomer predominating in the crude sample was also the major component of the purified material, although there were some exceptions. Thus, crystallization of the crude isomer mixture **7** from hot ethyl acetate produced the minor isomer exclusively; similarly, the adduct **10** consisted mainly of the less stable isomer, since heating of the crude reaction product in isopropyl alcohol gave a product in which the isomer ratio was reversed (both in the crystals and in the mother liquor); this ratio remained unchanged on further crystallization. Isomerization on crystallization was observed in other but not all cases. Thus, the major and minor isomers in adduct **4** could be almost completely separated by crystallization from hot isopropyl alcohol or acetonitrile. Since conditions for isomerization were determined for only three sets of isomers (**5** in addition to **7** and **10**), a statement as to which isomers are the thermodynamically more stable ones cannot be made in most cases. The isomer ratio in the formation of **5** from methyl (triphenylphosphoranylidene)acetate and cyanogen was solvent dependent; the equilibrium mixture (*ca.* 80:20) was formed in acetonitrile, toluene, and acetone whereas a mixture containing the two isomers in equal amounts was obtained in methylene chloride. A rationalization of this



(3) The reaction of activated nitriles with Ph$_3$P=NH to give iminophosphoranes, Ph$_3$P=N–C(R)=NH, has recently been reported: A. S. Shtepanek, E. N. Tkachenko, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **39**, 1475 (1969). Although these products are probably formed by simple addition of the phosphineimine across the nitrile triple bond as suggested by these authors, the possibility that a four-membered ring intermediate analogous to **2** is involved cannot be ruled out completely.

(4) The reaction of trichloroacetonitrile with carboethoxymethylenedimethylsulfurane has been reported to give a complex mixture of products, neither of which was an iminosulfurane analagous to **3**: G. B. Payne, *J. Org. Chem.*, **33**, 3517 (1968).

(5) (a) For a brief summary see "Organophosphorus Chemistry," S. Trippett, Ed., Vol. 1, The Chemical Society, London, 1970, pp 288–289. (b) H. I. Zelinger, J. P. Snyder, and H. J. Bestmann, *Tetrahedron Lett.*, 2199 (1969).

TABLE I[a]

$$R^1CN + Ph_3P{=}YR^2R^3 \longrightarrow Ph_3P{=}N{-}\underset{\displaystyle R^1}{\underset{|}{C}}{=}YR^2R^3$$

No.	Y	R^1	R^2	R^3	Conditions[b]	Yield, %	Mp, °C[c]	Isomer ratio (crude product)	δ_H[d,e]	J_{PH}[e,f]
4	C	CN	CN	H	25 (16)	87[g]	228–230	72:28	5.2, 5.3	6.1, 0.6
5	C	CN	COOMe	H	25 (16)	90[g]	173–174	77:23	4.5, 4.5	0.5, 5.0
6	C	CN	COPh	H	25 (16)	77[g]	198–200	...[i]	3.6	<1
7	C	CN	COOMe	Me	25 (16)	100[h]	178–179[k]	76:24	7.9, 7.8[j]	1.9, 0.7[j]
8	C	CN	$-COOCH_2CH_2CH_2-$		80 (0.5)	100[h]	218–200	?		
9	C	CN	9-fluorenylidene		106 (1)	63[g]	272–273	?		
10	C	CF_3	CN	H	25 (16)	84[g]	162–166[l]	80:20	6.1, 5.2	<1, <1
11	C	CF_3	COOMe	H	25 (90)	94[g]	114–115	...[i]	4.5	<1
12	C	CF_3	COPh	H	70 (1)	81[g]	163–165	...[i]	3.6	<1
13	C	CF_3	COOMe	Me	25 (18)	100[h]	88–90[m]	71:29	6.7, 6.3[n]	
14	C	CF_3	$-COOCH_2CH_2CH_2-$		80 (0.5)	97[h]	165–169	93:7		
15	C	CF_3	9-fluorenylidene		82 (68)	98[h]	253–254	?		
16	N	CN	Ph		25 (1)	82[g]	197–198	...[i,o]		
17	N	CN	*tert*-Bu		25 (16)	90[h]	150–151	50:50	8.5, 8.9[p]	
18	N	CN	$N{=}CPh_2$		25 (70)	60[g]	219–221	?		
19	N	CF_3	Ph		40 (3)	81[h]	122–124	80:20		
20	N	CF_3	$N{=}CPh_2$		90 (6)	47[g]	223–224[m]	82:18		

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds in the table; analyses for P were reported for **4**, **5**, **11**, and **17**. Ed. [b] Solvent CH_3CN in all cases except for **9**, which was run in CH_2Cl_2; numbers are temperature and time (hr) in that order; see Experimental Section (Part B) for typical procedures. [c] Melting point of analytical sample of isomer mixture unless indicated otherwise. [d] Chemical shift of vinyl proton (R^3) in τ units, measured in $CDCl_3$ solution with TMS as externally substituted standard. [e] Parameters for the major isomer are listed first. [f] Coupling constant between phosphorus and the vinylic proton (R^3) from the splitting of the proton nmr spectra. [g] Yield of crystallized product. [h] Yield of crude product. [i] Only one isomer formed. [j] Parameters for the methyl group (R^2). [k] Melting point of pure minor isomer which is obtained on crystallization of the crude product mixture. [l] Melting point of a mixture containing 78% of the previously minor isomer and 22% of the major isomer obtained on crystallization from isopropyl alcohol. [m] Melting point of the pure major isomer. [n] Parameters for the COOMe group (R^2). [o] Only one phosphorus resonance at −19.7 ppm from H_3PO_4 was observed. [p] Parameters for the *tert*-butyl groups (R^2).

solvent effect requires knowledge of the as yet unknown stereochemistry of the isomers. However, the fact that of the four solvents tried only methylene chloride produced a different isomer mixture indicates that the ability of the latter to form strong hydrogen bonds may be of importance.

The mechanism of the addition of nitriles to ylides probably involves initial formation of an adduct such as **1** followed by ring closure to the dihydrophosphazete **2**; the final product (**3**) then results by opening of the four-membered ring. Such a mechanism has been proposed for the addition of activated acetylenes to ylides,[6–8] in which products exactly analogous to the nitrile adducts are formed. The formation of isomers was also noted in these reactions.[6]

The phosphoranes **4** to **20** are stable to air and quite resistant to hydrolysis. Their diminished nucleophilic character is demonstrated by their reluctance to react with alkylating and acylating agents and to undergo further reaction with activated nitriles or a normal Wittig reaction with aldehydes or ketones.

Part B

Scope of the Reaction of Nitriles with Ylides.—The results presented above make it likely that iminophosphoranes corresponding to **3** are formed in all the reactions of trialkyl- and triarylphosphoranes with aromatic and aliphatic nitriles studied by McEwen and coworkers.[2] It appears that resonance-stabilized ylides do not react with unactivated nitriles, since (triphenylphosphoranylidene)acetonitrile was recovered unchanged after heating in neat acetonitrile, benzonitrile, and phthalonitrile to 200° for 8 hr. Addition of lithium iodide[2a] failed to promote the reaction. Similarly, *N*-(triphenylphosphoranylidene)aniline and acetonitrile did not react at 150° during 3 days. Cyanogen and perfluoroalkylnitriles will probably form adducts of type **4**–**20** with most resonance-stabilized phosphoranes provided that the nucleophilic character of the latter is not too drastically diminished by the presence of two electron-withdrawing substituents on the ylide carbon. Thus, methyl (triphenylphosphoranylidene)cyanoacetate gave no adduct with cyanogen at 120°; *N*-(triphenylphosphoranylidene)benzamide also failed to react under these conditions. In the following combinations, reaction did occur but pure products could not be isolated: (triphenylphosphoranylidene)methane with cyanogen or trifluoroacetonitrile; α-(triphenylphosphoranylidene)toluene, (triphenylphosphoranylidene)cyclopentadiene, pyridinium benzoylmethylide, and (methoxycarbonylmethylene)triphenylarsenic with cyanogen; and methyl (triphenylphosphoranylidene)acetate with trichloroacetonitrile. Methyl (triphenylphosphoranylidene)acetate catalyzed the trimerization[9] of malononitrile. Methyl cyanoformate underwent a normal Wittig reaction with (triphenylphosphoranyli-

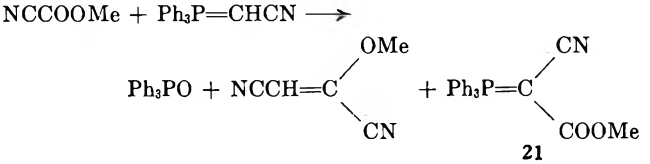
(6) H. J. Bestmann and O. Rothe, *Angew. Chem.*, **76**, 569 (1964).

(7) G. W. Brown, R. C. Cookson, and I. D. R. Stevens, *Tetrahedron Lett.*, 1263 (1964).

(8) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.*, **86**, 107 (1964); J. B. Hendrickson, C. Hall, R. Rees, and J. F. Templeton, *J. Org. Chem.*, **30**, 3312 (1965).

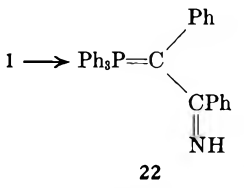
(9) Various structures have been assigned to the trimer of malononitrile; *cf.* J. D. Atkinson and M. C. Johnson, *J. Chem. Soc. C*, 2181 (1969).

dene)acetonitrile; a small amount of the acylation product **21** was also isolated.



21

Structures.—Only one isomer of **3** was isolated from the addition of benzonitrile to α-(triphenylphosphoranylidene)toluene as well as from the reaction of either *cis*- or *trans*-α-azidostilbene with triphenylphosphine. This probably indicates that the barrier for interconversion between the four possible isomers of **3** is lower than in the case of the phosphoranes **4**–**20**. Phosphorane **3** exists in two crystal forms having slightly different infrared spectra in the solid but identical infrared and nmr spectra in solution. The previous workers[2] suggested structure **22** for the intermediate of the reaction between benzonitrile and α-(triphenylphosphoranylidene)toluene, although the correct structure **3** was also mentioned[2c] as a possibility.

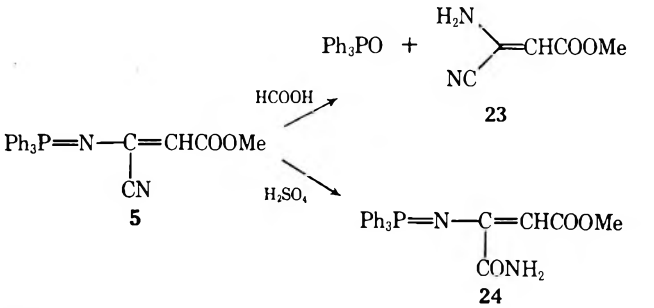


22

Although only one or two isomers were formed in most reactions of activated nitriles with phosphoranes, there were indications in two cases for the presence of three isomeric species in the products: the nmr spectra of the crude adduct of trifluoroacetonitrile to *N*-(triphenylphosphoranylidene)-*tert*-butylamine showed three trifluoromethyl groups and three *tert*-butyl groups. Similarly, three carbomethoxy peaks were observed in the nmr spectrum of the crude adduct of cyanogen to methyl (triphenylphosphoranylidene)phenylacetate. No attempts were made to isolate these isomers. The isomers listed in Table I could in some cases be separated by chromatography on Florisil (*e.g.*, **10**); others either isomerized (*e.g.*, **5**) or hydrolyzed (*e.g.*, **7**) under these conditions. The only case where the position of the equilibrium was determined is that of **5**. Slow room temperature crystallization from ethyl acetate of the 1:1 mixture of isomers obtained on carrying out the reaction in methylene chloride (see above) gave crystals containing a 77:23 mixture of the major and minor isomers of **1**. The mother liquor contained these isomers in the ratio of 25:75, but on chromatography on Florisil the 77:23 equilibrium mixture was again obtained. A pure sample of the major isomer was accidentally obtained when the isomer mixture was treated with acetyl chloride and triethylamine in an abortive attempt at acetylation. Crystallization from hot acetonitrile again resulted in formation of the 77:23 equilibrium mixture.

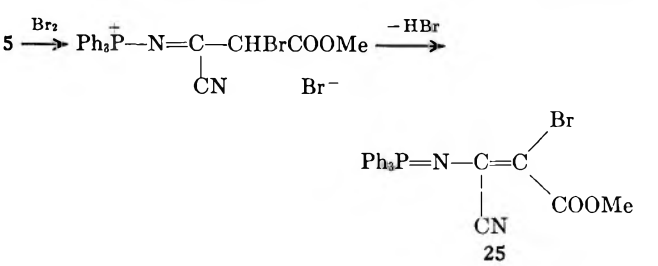
The two isomers of **4**, each containing about 10% of the other, were obtained by fractional crystallization. Their ultraviolet spectra are very similar but they differ in their infrared and proton and phosphorus nmr spectra. Thus, the long-range coupling between the vinylic proton (R^3) and phosphorus is 0.5 Hz in the major, and 5.0 Hz in the minor isomer (Table I); the phosphorus resonances occur at −13.7 and −15.1 ppm (from 85% H_3PO_4). Interestingly, the magnitude of the P–H coupling constants is reversed in the case of the isomers **5**, whereas both isomers of **10** have $J_{HP} < 1$ Hz. The phosphorus resonances in **10** are found at −13.4 (major isomer) and −8.5 ppm; the ^{19}F nmr spectrum shows P–F coupling of 5 Hz in the major and of 1 Hz in the minor isomer, but little or no H–F coupling. On the other hand, the fluorines in both isomers of **13** are coupled to the methyl protons (3 and 2 Hz, respectively) but very little to phosphorus; the methyl protons of the major isomer of **13**, however, are coupled to phosphorus (5 Hz); this parameter could not be determined in the minor isomer of **13**. The phosphorus resonances in the two isomers of the iminophosphorane adduct **19** occur at −1.5 and −19.7 ppm, that of the single isomer of **16** at −19.7 ppm. The somewhat conflicting nmr data seem to indicate that different combinations of the four possible types of isomers (*e.g.*, **4a**–**4d** and **19a**–**19d**) may occur in the adducts **4**–**20**.

Reactions.—The iminophosphoranes **4**–**20** are quite resistant to hydrolysis as evidenced by the fact that **5** was recovered unchanged on heating in methanol to 150°, on refluxing in 20% aqueous acetonitrile, and on stirring with potassium carbonate or potassium hydroxide in methanol at room temperature. Some hydrolysis to triphenylphosphine oxide and methyl 3-amino-3-cyanoacrylate (**23**) occurred on heating **5** to



23 **5** **24**

160° in 80% aqueous methanol for 6 hr, but hydrolysis to **23** was much more readily and conveniently carried out with 90% formic acid at room temperature. Only a single isomer of **23** was obtained whereas both aminomaleonitrile and aminofumaronitrile were obtained from **4** under similar conditions. Quenching a solution of **5** in concentrated sulfuric acid with base resulted mainly in conversion of the cyano to an amide group to give **24**. Bromination of **5** followed by treatment with base gave a single isomer of **25**. Unchanged **5** was recovered after heating with neat methyl iodide to 70°; reaction did occur at 100° but no pure products could be isolated. Adduct **5** did not react with acetyl chloride and base at room temperature, or with cyanogen chloride at 70°, nor could it be hydrogenated with a palladium catalyst at room temperature. Pyrolysis of **5** at



25

275° gave a complex mixture of products. No reaction occurred between **5** and acetone at 120° or between **5** and a large excess of cyanogen at room temperature.

Experimental Section

Reaction of (Triphenylphosphoranylidene)acetonitrile with Cyanogen.—Cyanogen (7.38 g) was transferred at liquid nitrogen temperature to a Carius tube containing 20.27 g of (triphenylphosphoranylidene)acetonitrile[10] and 70 ml of acetonitrile. The tube was sealed under vacuum and the contents were allowed to come to room temperature with magnetic stirring. On reaching room temperature, the phosphorane dissolved and a new precipitate formed. It was collected after standing at room temperature overnight, washed with acetonitrile, and dried to give 17.33 g of a product (A) containing 82% of the major isomer and 18% of the minor isomer of 1-[(triphenylphosphoranylidene)-amino]-1,2-dicyanoethylene (**4**) as indicated by nmr spectroscopy. The mother liquors, on concentration to dryness gave 3.46 g of a solid (B) containing 77% of the minor and 23% of the major isomer, combined yield 20.77 g (87%). Two crystallizations of A from acetonitrile gave a sample of the major isomer, still containing 10% of the minor isomer: mp 228–230°; ^{1}H nmr ($CDCl_3$) τ 1.9–2.8 (m, 15, Ph) and 5.2 (d, J = 6.0 Hz, 1, CH); ^{31}P nmr (CH_2Cl_2, shift from internally substituted 85% H_3PO_4) −13.7 ppm; uv max (MeCN) 314 mμ (ϵ 18,300), 275 (8300), 268 (7500), and 225 (sh, 23,100); ir max (KBr) 2205, 1545 cm^{-1} (vs), among others.

One crystallization of B from acetonitrile gave a sample composed of 82% of the minor and 18% of the major isomer of **4**: mp 162–166° (a small amount remained solid to 210°); ^{1}H nmr ($CDCl_3$) τ 2.0–2.7 (m, 15, Ph) and 5.3 (d, J = 0.6 Hz, 1, CH); ^{31}P nmr (CH_2Cl_2, shift from internally substituted 85% H_3PO_4) −15.1 ppm; uv max (MeCN) 314 mμ (ϵ 18,100), 275 (8000), 268 (7300), and 225 (sh, 24,600); ir max (KBr) 2200, 1550 (vs), 930 cm^{-1} (s), among others; the band at 930 cm^{-1} is absent in the spectrum of the major isomer.

Anal. Calcd for $C_{22}H_{16}N_3P$: C, 74.78; H, 4.57; N, 11.89. Found: C, 74.42; H, 4.22; N, 12.09.

Hydrolysis of 1-[(Triphenylphosphoranylidene)amino]-1,2-dicyanoethylene (4).—A mixture of 2.00 g of 1-[(triphenylphosphoranylidene)amino]-1,2-dicyanoethylene (product A, above) and 10 ml of 90% formic acid was stirred at room temperature for 1 hr. The solvent was removed under vacuum and the residue was sublimed at 90° bath temperature (0.1 μ) to give 0.19 g (39%) of a mixture of aminomaleonitrile and aminofumaronitrile in the ratio of 55:45 as judged by the nmr spectrum (in CD_3CN): broad band at τ 4.5 (2 H) and singlets at 5.2 and 5.5 (1 H) in the ratio of 45:55. The infrared spectrum was identical with that of a mixture of aminomaleonitrile and aminofumaronitrile (see below).

Aminomaleonitrile from Ammonia and Dicyanoacetylene.—To a mixture of 1.36 g of anhydrous ammonia and 150 ml of ethyl ether was added, at −80° over 30 min, a solution of 5.35 g of dicyanoacetylene[11] in 100 ml of ether. The mixture was allowed to come to room temperature slowly. Removal of the solvent from the filtered solution gave 6.08 g of a tan solid. Sublimation of 5.51 g of this material at 80° (0.1 mm) overnight gave 5.20 g of colorless crysals. Crystallization from 10 ml of isopropyl alcohol gave 3.86 g of aminomaleonitrile: mp 135–136° (lit.[12] mp 131°); nmr (CD_3CN) τ 4.4 (broad, 2) and 5.5 (s, 1). The stereochemical assignment is based on the chemical shift of the vinylic proton, which in aminomaleonitrile might be expected to occur at higher field, and on the fact that amines add to activated acetylenes predominantly in a cis fashion.[13] Concentration of the mother liquors and crystallization of the residue from dichloroethane gave 0.67 g of tan crystals, mp 121–124°, the nmr spectrum of which showed it to be a mixture of 75% aminomaleonitrile and 25% aminofumaronitrile (singlets at τ 5.5 and 5.2 in a ratio of 3:1). Since the latter was absent in the nmr spectrum of the crude reaction product, the isomerization must have occurred during the crystallization.

Reaction of Methyl (Triphenylphosphoranylidene)acetate with Cyanogen.—In a Carius tube was placed 22.02 g of methyl (triphenylphosphoranylidene)acetate and 80 ml of acetonitrile. Cyanogen (6.0 g) was distilled in at liquid nitrogen temperature. The tube was sealed under vacuum and placed in a Dry Ice–acetone bath which was allowed to come to room temperature slowly overnight. The tube was cooled to −10° and opened. The precipitate was collected by filtration, washed with acetonitrile, and dried to give 22.81 g (90% yield) of methyl 3-[(triphenylphosphoranylidene)amino]-3-cyanoacrylate (**5**, two isomers, the ratio of the two isomers was 77:23 as determined by nmr spectroscopy). An analytical sample, prepared by recrystallization from acetonitrile, had mp 173–174°. The nmr spectrum showed the ratio of the two isomers to be unchanged: uv max (MeCN) 322 mμ (ϵ 18,700) 375 (6500), 268 (6000), and 225 (sh) (23,300); ir max (KBr) COOMe at 1710 cm^{-1}, CN very weak; nmr ($CDCl_3$) major isomer [τ 1.9–2.7 (m, 15), 4.5 (d, J = 0.5 Hz, 1), and 6.3 (s, 3)], minor isomer [1.9–2.6 (m, 15), 4.5 (d, J = 5 Hz, 1), and 6.2 (s, 3)].

Hydrolysis of Methyl 3-[(Triphenylphosphoranylidene)amino]-3-cyanoacrylate (5) with Formic Acid.—A solution of 5.19 g of methyl 3-[(triphenylphosphoranylidene)amino]-3-cyanoacrylate in 33 ml of 90% formic acid was allowed to stand at room temperature for 50 min. Removal of the solvent at room temperature under high vacuum left a semisolid which on addition of acetonitrile deposited 0.39 g of methyl 3-amino-3-cyanoacrylate (**23**). Concentration of the mother liquor and addition of methylene chloride gave another 0.32 g of the product, combined yield 0.71 g (42%). Crystallization from ethyl acetate gave an analytical sample: mp 163–164°; uv max (MeCN) 289 mμ (ϵ 13,400);[14] ir max (KBr) 3400, 3320, 2240, 1670, 1625, and 1575 cm^{-1} among others; nmr (CD_3CN) τ 3.0–4.5 (broad, s, 2), 5.0 (s, 1), and 6.5 (s, 3).

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.61; H, 4.77; N, 22.57.

Hydrolysis of Methyl 3-[(Triphenylphosphoranylidene)amino]-3-cyanoacrylate (5) with Sulfuric Acid.—To a solution of 2.07 g of methyl 3-[(triphenylphosphoranylidene)amino]-3-cyanoacrylate in 10 ml of methylene chloride was added, at room temperature, 2 ml of concentrated sulfuric acid. The mixture became warm and two layers formed; the lower sulfuric acid layer was yellow. The mixture was stirred at room temperature for 5 min and poured into a cold solution of 5.3 g of sodium hydroxide and 25 ml of water. Methylene chloride was added, the layers were separated, and the aqueous layer was extracted twice with methylene chloride. The extracts were washed with concentrated sodium chloride solution and dried. Removal of the solvent gave 2.06 g of a yellow glass. Addition of 5 ml of methanol and filtration gave 1.43 g (66%) of methyl 3-[(triphenylphosphoranylidene)amino]-3-carbamoylacrylate (**24**), mp 163–164°. An analytical sample, prepared by crystallization from isopropyl alcohol, had mp 164–165°: uv max (MeCN) 313 mμ (ϵ 11,200), 274 (6200), 267 (74,000), 225 (sh, 25,200); ir (KBr) 3450, 3400, 3270, 1660, 1625, 1580, 1560, and 1540 cm^{-1}, among others; nmr ($CDCl_3$) τ 1.9–2.7 (m, 17), 4.0 (s, 1), and 6.2 (s, 3).

Anal. Calcd for $C_{23}H_{21}N_2O_3P$: C, 68.30; H, 5.24; N, 6.93. Found: C, 68.31; H, 5.28; N, 7.08.

Bromination of Methyl 3-[(Triphenylphosphoranylidene)amino]-3-cyanoacrylate (5).—Bromine (1.16 g) was added with cooling to a solution of 2.66 g of methyl 3-[(triphenylphosphoranylidene)amino]-3-cyanoacrylate in 30 ml of methylene chloride. The mixture was stirred at room temperature for 5 min. Triethylamine (3 ml) was added, and stirring was continued for another 10 min. Water was added, the layers were separated, and the aqueous layer was extracted once with methylene chloride. The combined extracts were washed with concentrated sodium chloride solution and dried. Removal of the solvent gave a tan solid which was washed several times with water and dried. Crystallization from isopropyl alcohol gave methyl 3-[(triphenylphosphoranylidene)amino]-2-bromo-3-cyanoacrylate (**25**), mp 158–159°, as pale yellow crystals: uv λ_{max} (MeCN) 334 mμ (ϵ 21,300), 275 (5500), 268 (5500), 262 (sh, 4700), 225 (sh, 25,200); ir (KBr) 2220, 1700, 1625 cm^{-1}, among others; nmr τ 1.8–2.6 (m, 15) and 6.1 (s, 3).

Anal. Calcd for $C_{23}H_{18}BrN_2O_3P$: C, 59.37; H, 3.90; N, 6.02. Found: C, 59.53; H, 4.14; N, 6.11.

Reaction of Methyl 2-(Triphenylphosphoranylidene)propionate with Trifluoroacetonitrile.—To a Carius tube containing 10.54 g

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

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

(12) C. Moureu and J. C. Bongrand, *Ann. Chim. (Paris)*, **14**, 5 (1920); no stereochemical assignments were made.

(13) For a review, see E. Winterfeld, *Angew. Chem.*, **79**, 389 (1967).

(14) M. Atkinson and A. H. Horsington, *J. Chem. Soc. C*, 2186 (1969), report uv max (EtOH) 305 mμ (ϵ 11,640) for ethyl 3-amino-3-cyano-2-methylacrylate.

of methyl 2-(triphenylphosphoranylidene)propionate[15] and 40 ml of acetonitrile was transferred 9.70 g of trifluoroacetonitrile. The tube was sealed under vacuum at liquid nitrogen temperature and allowed to come to room temperature with internal agitation (magnetic stirrer). After stirring at room temperature overnight, the tube was cooled in liquid nitrogen, opened, and rinsed out with methylene chloride. Removal of the solvent gave 13.95 g of the crude mixture of isomeric products. To a solution of 6.18 g of this mixture in 50 ml of methanol was added water to the cloud point, followed by sufficient methanol to produce a homogeneous solution. Crystals deposited on standing for 3 hr. They were collected by filtration, washed with aqueous alcohol, and dried, giving 2.87 g of a single isomer of methyl 3-[(triphenylphosphoranylidene)amino]-2-methyl-4,4,4-trifluorocrotonate(**13**), mp 86–89°. An analytical sample, prepared by crystallization from hexane, had mp 88–90°: uv max (MeCN) 295 mμ (sh, ε 6500), 273 (7800), 266 (8100), and 225 (sh, 23,000); ir max (KBr) 1690 and 1560 cm^{-1}, among others; ^{1}H nmr ($CDCl_3$) τ 2.0–2.8 (m, 15, Ph), 6.8 (s, 3, COOMe), and 8.1 [doublet (J = 5 Hz), of quartets (J = 3 Hz), 3, Me]; ^{19}F nmr ($CDCl_3$, shift from external Freon® 11) +62.2 ppm (q, J = 3 Hz, CF_3). The minor isomer had the following nmr data as deduced from the spectra of the crude mixture: ^{1}H nmr ($CDCl_3$) τ 2.0–2.8 (m, 15, Ph), 6.4 (s, 3, COOMe), and 8.1 (m, 3, Me); ^{19}F nmr ($CDCl_3$, shift from external Freon® 11) +63.4 ppm (q, J = 2 Hz, CF_3).

Reaction of (Triphenylphosphoranylidene)aniline with Cyanogen.—To a Carius tube containing 11.12 g of (triphenylphosphoranylidene)aniline[16] and 50 ml of acetonitrile was transferred, at liquid nitrogen temperature, 4.36 g of cyanogen and the tube was sealed under vacuum. The mixture became homogeneous shortly after reaching room temperature whereupon internal stirring was discontinued. Crystals started to form soon. After standing at room temperature for 1 hr, the tube was cooled in ice and opened, and the crystals were collected, washed with cold acetonitrile, and dried to give 11.02 g (82%) of *N*-(triphenylphosphoranylidene)-*N'*-phenylcyanoformamidine (**16**), mp 197–198, unchanged on further recrystallization: uv max (MeCN) 310 mμ (ε 7000), 273 (sh, 11,400), 267 (11,900), and 225 (sh, 31,800); ir max (KBr) 2210 (w) and 1575 cm^{-1} (vs), among others.

Reaction of Benzophenone Triphenylphosphazine with Trifluoroacetonitrile.—A sealed Carius tube, containing 6.0 g of benzophenone triphenylphosphazine,[17] 6.0 g of trifluoroacetonitrile, and 15 ml of acetonitrile was heated, with internal stirring, to 90° for 6 hr. It was cooled to liquid nitrogen temperature, opened, and rinsed out with methylene chloride. Removal of the solvent gave 7.43 g of a tan semisolid. The ^{19}F nmr spectrum showed a doublet (J = 7.5 Hz) at +69.0 ppm (from Freon® 11) and a broadened singlet at +70.0 ppm in the ratio of 82:18. Crystallization from ethyl acetate gave 3.36 g (47% yield) of the major isomer of *N*-(triphenylphosphoranylidene)trifluoroacetamide diphenylmethylenehydrazone (**20**), mp 220–224°. An analytical sample (1,2-dichloroethane) had mp 223–224°: uv max (MeCN) 331 mμ (ε 12,300) and 225 (sh, 35,000); ir max (KBr) 1575 cm^{-1} (vs), among others; ^{19}F nmr ($CDCl_3$, shift from external Freon® 11) +69.0 ppm (d, J = 7.5 Hz, CF_3).

Reaction of α-(Triphenylphosphoranylidene)toluene with Benzonitrile.—To a slurry of 23.17 g (49 mmol) of benzyltriphenylphosphonium iodide in 25 ml of anhydrous benzene was added, under nitrogen, 28 ml of a 2.3 *M* solution of methyllithium (65 mmol) in ether. The clear red solution was heated to reflux; a precipitate formed before the boiling point was reached. Benzonitrile (21.7 g) was added, and the mixture was stirred under reflux for 44 hr. The mixture was cooled and filtered. Removal of the solvents from the filtrate gave 39.0 g of a brown oil. Addition of 20 ml of methanol to 5.1 g of this product, heating the mixture under reflux for a short time, and cooling gave 1.95 g (68% yield) of pale yellow crystals, which according to their infrared spectrum were a mixture of the two crystal forms of α-[(triphenylphosphoranylidene)amino]stilbene (**3**). Crystallization from ethyl acetate gave a mixture of pale yellow cubes (crystal form A) and yellow needles (B), which was separated mechanically. The melting points and mixture melting point of A and B were identical (156–157°). The infrared spectrum (in Nujol) of A was identical with that of the authentic sample prepared by reaction of α-azidostilbene with triphenylphosphine (see below). The spectrum of crystal form B (in Nujol) is quite similar to that of A, the main differences being as follows: A has a doublet at 1240 cm^{-1}, B only a singlet; bands at 1160 and 1100 cm^{-1}, and the region of 690–770 cm^{-1} show differences in the relative intensities; A has a band at 800 cm^{-1}, not present in B; B has a band at 820 cm^{-1}, not present in A. In solution, A and B have identical ir, uv, and nmr spectra (in tetrahydrofuran, cyclohexane, and deuteriochloroform, respectively). The uv spectra of A and B in the solid phase both show maxima at 322 mμ. The two crystal forms could be interconverted by dissolution in hot acetonitrile and seeding with a crystal of pure A or B.

Reaction of α-Azido-*trans*-stilbene with Triphenylphosphine.—To a solution of 8.91 g of α-azido-*trans*-stilbene[18] in 50 ml of ether was added 11.75 g of triphenylphosphine. Nitrogen evolution began after a while, the mixture started to reflux, and a precipitate formed. After heating under reflux for 1 hr, the solvents were removed. There was no evidence for the presence of crystal form B (see above) in the infrared spectrum of the crude product. Crystallization from 50 ml of ethyl acetate gave 11.09 g (61% yield) of α-[(triphenylphosphoranylidene)amino]stilbene (**3**, crystal form A) as yellow crystals, mp 156–156.5°. An analytical sample, obtained by crystallization from ethyl acetate, had mp 157–157.5°: uv max (cyclohexane) 317 mμ (ε 18,500), 275 (sh, 11,500), and 267 (sh, 10,500); ir (KBr) 1595, 1565 and 1390 cm^{-1}, among others; ^{1}H nmr ($CDCl_3$) τ 1.8–3.4 (m, 25, phenyl) and 4.3 (d, 1, J = 4 Hz, β-H); ^{31}P nmr ($CDCl_3$) + 0.3 ppm (from 85% H_3PO_4).

Anal. Calcd for $C_{32}H_{25}NP$: C, 84.37; H, 5.76; N, 3.08; P, 6.81. Found: C, 84.03; H, 5.71; N, 3.05; P, 7.10.

The same product was obtained from the reaction of triphenylphosphine with α-azido-*cis*-stilbene[18]; again, there was no evidence for the presence of crystal form B in the infrared spectrum of the crude product.

Reaction of (Triphenylphosphoranylidene)acetonitrile with Methyl Cyanoformate.—A mixture of 1.78 g of (triphenylphosphoranylidene)acetonitrile, 2.84 g of methyl cyanoformate, and 3 ml of acetonitrile was heated under reflux for 10 min. Removal of the solvent and short-path distillation of the residue at 120° bath temperature (0.5 mm) gave 470 mg (90% yield) of a colorless liquid which according to its infrared and nmr spectra and its gas chromatogram was a 1:1 mixture of methoxymaleonitrile and methoxyfumaronitrile.[19] The residue was crystallized from 4 ml of ethyl acetate to give 0.99 g of triphenylphosphine oxide, identified by its infrared spectrum. The mother liquors were concentrated to dryness and the residue was chromatographed over Florisil. Elution with a mixture of methylene chloride and tetrahydrofuran (98:2) gave 77 mg (4% yield) of methyl (triphenylphosphoranylidene)cyanoacetate, identified by comparison of its infrared spectrum with that of an authentic sample.[20]

Registry No.—**3**, 26740-23-8; **4**, 26740-24-9, 26740-25-0; **5**, 26740-26-1, 26740-27-2; **6**, 26740-28-3; **7**, 26740-30-7, 26740-31-8; **8**, 26740-32-9; **9**, 26740-33-0; **10**, 26740-34-1, 26740-35-2; **11**, 26740-29-4; **12**, 26740-36-3; **13**, 26740-37-4, 26740-38-5; **14**, 26740-39-6, 26740-40-9; **15**, 26740-41-0; **16**, 26740-42-1; **17**, 26740-43-2, 26740-44-3; **18**, 26740-45-4; **19**, 26740-46-5, 26740-47-6; **20**, 26740-48-7, 26740-49-8; **23**, 26740-50-1; **24**, 26740-51-2; **25**, 26740-52-3.

(15) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).
(16) H. Zimmer and G. Singh, *ibid.*, **28**, 483 (1963).
(17) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 619 (1919).
(18) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967).
(19) E. Winterfeld, W. Krolin, and H. Preuss, *Chem. Ber.*, **99**, 2572 (1966).
(20) L. Horner and H. Oediger, *ibid.*, **91**, 437 (1958).

Jacobsen-Type Rearrangements in Aromatic Trichloromethylations[1]

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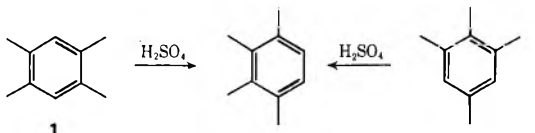
Trichloromethylation of 2-X-1,3,5-trimethylbenzenes by CCl_4–$AlCl_3$, followed by methanolysis, affords substituted methyl benzoates in >90% yields. When X = H, no alkyl rearrangement occurred, methyl 2,4,6-trimethylbenzoate being the sole product. But when X = F, Cl, or Br, there was formed in addition to methyl 3-X-2,4,6-trimethylbenzoate a minor product, methyl 4-X-2,3,5-trimethylbenzoate. Electrophilic attack by CCl_3^+ para to the halogen, followed by a Wagner–Meerwein 1,2-methyl migration, accounts for the rearrangement products. Their amount increases (Br, 7%; Cl, 12%; F, 30%) as the ability of the halogen to stabilize an adjacent positive charge in the intermediate benzenonium ion increases. The trichloromethylation reaction is a good, nonreversible model for study of Jacobsen-type rearrangements.

Part A

Despite its venerability[3] the Jacobsen rearrangement is still poorly understood by modern mechanistic standards.[4] The reaction is typified by the isomerization of durene (**1**) or isodurene (**2**) to prehnitene (**3**) in the presence of concentrated sulfuric acid. The products are usually vicinally substituted; the hydrocarbons are



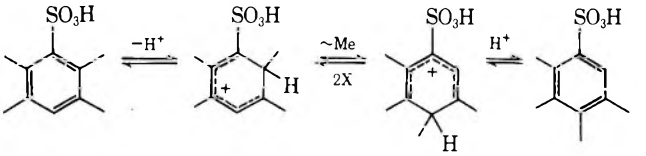
recovered from the actual products, which are sulfonic acids, by steam distillation. Methyl, ethyl, and methylene groups migrate, but secondary and tertiary alkyl groups (*i.e*, isopropyl and *tert*-butyl) are eliminated. Halogens (except F[4a]) may also migrate.[4,5] Disproportionation of halogens[4,6] and alkyl groups[4,5,7] also occurs; with methyl groups, this reaction may proceed *via* diarylmethane intermediates.[8]

Though numerous mechanisms for the Jacobsen rearrangement have been suggested,[4b-d] none is firmly established. Those most frequently proposed are summarized in Chart I,[9-11] using the conversion of **1** → **3** as an example.

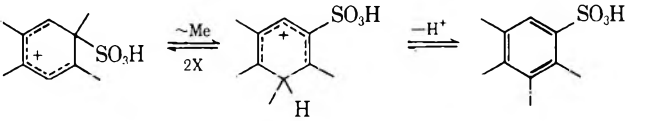
Of these, A and/or B are the most likely.[12] C requires that the desulfonation of prehnitenesulfonic acid be slow relative to the isomeric sulfonic acids; S^{35} labeling experiments[11] show this not to be the case. D rests mainly on the detection of SO_2 and oxidation products (from

CHART I

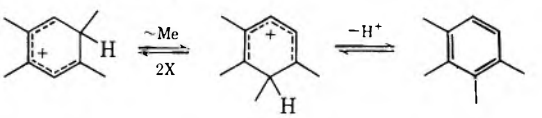
A. Protonation of the Sulfonic Acid[9]



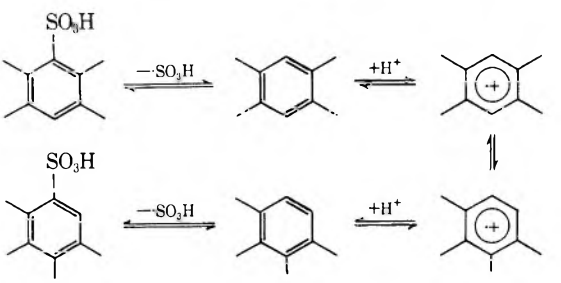
B. Sulfonation at a Substituted Position[4b]



C. Protonation of the Hydrocarbon[4d,10]

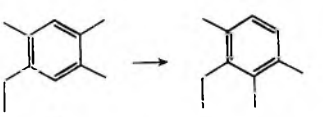


D. Radical–Cation Intermediate[11]



$\cdot SO_3H \rightarrow SO_2 + \cdot OH$?), and of esr signals due to hydrocarbon cation radicals. The mechanism by which the latter are presumed to isomerize is obscure, and the experimental observations have not been demonstrated to be associated with the main reaction path.

Some very basic mechanistic information is often lacking, even for mechanisms A and B. Frequently it is not even clear which group is migrating. For example, in the isomerization of **4** → **5**, it has been asserted[4c]



that the ethyl group migrates in preference to methyl, but this has not been established experimentally.[13]

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(1) We express appreciation to the National Science Foundation for financial support of this research.

(2) Du Pont Teaching Fellow, M. S. U., 1965–1966.

(3) O. Jacobsen, *Chem. Ber.*, **19**, 1209 (1886).

(4) For reviews, see (a) L. I. Smith, *Org. React.*, **1**, 370 (1942); (b) M. J. S. Dewar in "Molecular Rearrangements," Part I, P. deMayo, Ed., Interscience, New York, N. Y., 1963, pp 299–306; (c) H. J. Shine, "Aromatic Rearrangements," Elsevier Publishing Co., Amsterdam, 1967, pp 23–32, 48–55; (d) H. Suzuki, *Bull. Chem. Soc. Jap.*, **36**, 1642 (1963).

(5) L. I. Smith and C. L. Moyle, *J. Amer. Chem. Soc.*, **58**, 1 (1936).

(6) J. Herzig, *Monatsh. Chem.*, **2**, 192 (1881); for recent examples, see R. Goto and H. Suzuki, *Nippon Kagaku Zasshi*, **84**, 167 (1963); H. Suzuki and R. Goto, *ibid.*, **84**, 284 (1963); H. Suzuki, K. Maruyama, and R. Goto, *Bull. Chem. Soc. Jap.*, **38**, 1590 (1965).

(7) O. Jacobsen, *Chem. Ber.*, **20**, 896 (1887); L. I. Smith and A. R. Lux, *J. Amer. Chem. Soc.*, **51**, 2994 (1929).

(8) H. Suzuki and Y. Tamura, *Chem. Commun.*, 244 (1969); H. Suzuki, Y. Tamura, and A. Sera, *Bull. Chem. Soc. Jap.*, **42**, 851 (1969); H. Suzuki, *ibid.*, **42**, 2618 (1969).

(9) E. N. Marvell and B. M. Graybill, *J. Org. Chem.*, **30**, 4014 (1965).

(10) M. Kilpatrick and M. Meyer, *J. Phys. Chem.*, **65**, 1312 (1961).

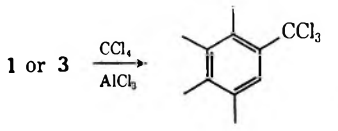
(11) F. Bohlmann and J. Riemann, *Chem. Ber.*, **97**, 1915 (1964).

(12) An alternative to A, sulfonation of the sulfonic acid, cannot be ruled out.

(13) A. Tohl and D. von Karchowski, *Chem. Ber.*, **25**, 1530 (1892); L. I. Smith and M. A. Kiess, *J. Amer. Chem. Soc.*, **61**, 989 (1939).

The major stumbling blocks to mechanistic studies on the Jacobsen reaction as usually considered are (a) the well-known reversibility of sulfonations, (b) the presence of two electrophiles, H^+ and a sulfonating species (SO_3, SO_3H^+, etc.), with the resulting uncertainty about which is required at what stage of the mechanism, and (c) oxidation, which may lead to SO_2, tars, and a less than clean reaction.

To avoid these difficulties, we have begun a systematic study of aromatic trichloromethylation[14] which also gives Jacobsen-like rearrangements.[15] For example, durene (1) or isodurene (2) gives mainly trichloromethylprehnitene (6). The reaction has the advantage that a new carbon–carbon bond is formed with the



6

electrophile (CCl_3^+), a process likely to be less reversible than sulfonation. The initial product $ArCCl_3$ reacts with the Lewis acid, used in excess, to form $ArCCl_2^+$, thus being effectively removed from further reaction.[14,16] Work-up by methanolysis gives esters readily separated and analyzed by vpc and spectroscopic methods.

In this paper we describe the trichloromethylation of **7** (X = H, CH_3, F, Cl, and Br); the substituents, particularly the halogens, serve as a label to determine the position of electrophilic attack and identify the migrating group.

Results and Discussion

Each compound **7** was added, in CCl_4 solution, to a twofold excess of $AlCl_3$ slurried in CCl_4, at 40°. After 2 hr the trichloromethyl compounds were isolated and methanolyzed, and the resulting methyl esters were separated (vpc), analyzed, and identified by comparison with authentic samples. Isolated yields of esters were 90% or greater; no tars or undesirable side products were produced.

The structures and percentages of products are summarized in Chart II.

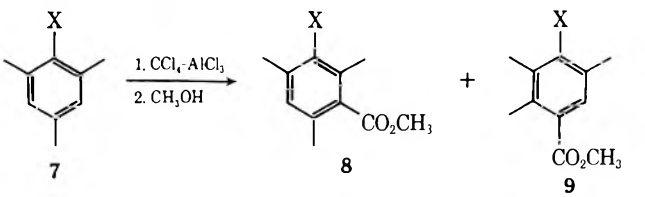
The product from mesitylene (**7-H**) was pure methyl 2,4,6-trimethylbenzoate, but the halomesitylenes and isodurene gave, in addition to the expected product **8**, a Jacobsen-like rearrangement product **9**. The structure of **9** was proved conclusively by independent synthesis when X = CH_3 and F (for the latter, see Part B), but is assumed by analogy for X = Cl and Br.

The reaction is assumed to involve an electrophilic substitution by CCl_3^+, or its equivalent, say

$$\overset{\delta+}{CCl_3}\cdots Cl\cdots\overset{\delta-}{AlCl_3}$$

The preferred intermediate in all cases is structure A, in which the positive charge is stabilized by three

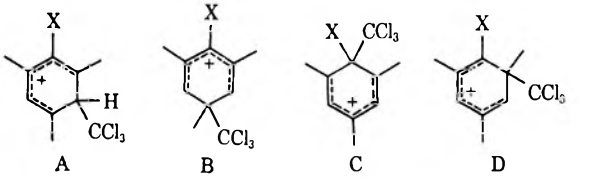
CHART II



X	%, product	
	8	9
H	100	0
CH_3	73[a]	25[a]
F	70	30
Cl	88	12
Br	93	7

[a] These yields are normalized from 90 to 100%. Some disproportionation (10%) to methyl 2,4,6-trimethylbenzoate and methyl pentamethylbenzoate occurred. The third isomerization product, 2%, was methyl 2,3,5,6-tetramethylbenzoate. No disproportionation or other isomerization products were observed in any of the other cases.

methyl groups in the ortho and para positions. Proton loss leads, after methanolysis, to **8**. Intermediate C is



also stabilized by three methyls and may be important when X is methyl, but not when X is halogen, since the halogen-bearing ring carbon should be electron deficient and a poor site for electrophilic attack.[17] Intermediate D is excluded when X = halogen or H, since no products expected from this intermediate were observed. When X = halogen, the minor products (**9**) are derived from intermediate B, by 1,2-methyl migration, proton loss, and methanolysis. The percentage of **9** decreases as the ability of the halogen to stabilize an adjacent carbonium ion decreases, being greatest as expected[18,19] when X = F. Competitive rate experiments show that **7-F** reacts at approximately the same rate (k_{rel} = 1.0 ± 0.1) as **7-CH₃**, whereas the rate falls off for **7-Cl** (0.36 ± 0.05) and **7-Br** (0.21 ± 0.03).

We conclude that the Jacobsen-like rearrangement in these trichloromethylations occurs by attack of the electrophilic CCl_3^+ on an already substituted aromatic ring position, followed by 1,2-methyl migration and proton loss (perhaps most analogous to mechanism B in the introduction).

Part B

Structures of the Major Products (8).—Compounds **8-H** and **8-CH₃** were identified by comparison (ir, nmr, and retention time) with authentic samples synthesized

(14) H. Hart and R. W. Fish, *J. Amer. Chem. Soc.*, **82**, 5419 (1960); H. Hart and R. W. Fish, *ibid.*, **83**, 4460 (1961); H. Hart, J. A. Hartlage, R. W. Fish, and R. R. Rafos, *J. Org. Chem.*, **31**, 2244 (1966).

(15) Suzuki[4d] has generalized the term Jacobsen rearrangement beyond the usual sulfonations, to include a variety of anomalous electrophilic substitutions which involve inter- and/or intramolecular group migrations.

(16) H. Volz and M. J. Volz de Lecca, *Tetrahedron Lett.*, 3413 (1965).

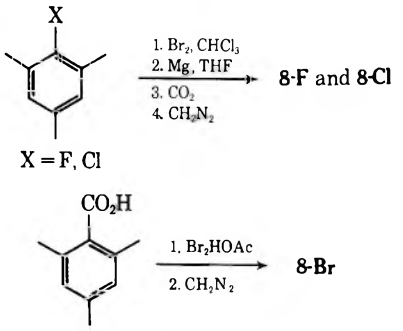
(17) One cannot, from the present work, exclude the possibility that **8** arises in part from C followed by two migrations of X, though, in the second step, X (halogen) would have to migrate exclusively in preference to CH_3. This seems unlikely, and no product with X ortho to the carbomethoxy group was observed.

(18) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 168.

(19) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **89**, 5692 (1967); G. A. Olah and T. E. Kiovsky, *ibid.*, **90**, 2583 (1968).

by literature procedures.[20,21] Compounds **8-F**, **8-Cl**, and **8-Br**, previously unknown, were synthesized by the sequence in Scheme I. The ir and nmr spectra were

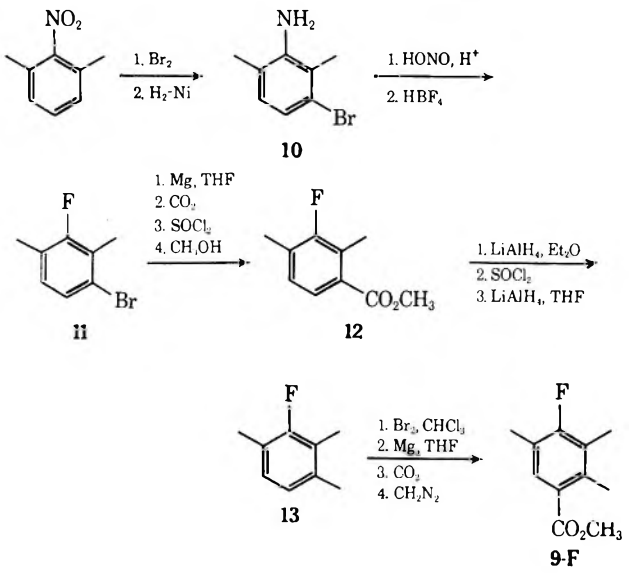
SCHEME I



unexceptional and identical with those of the major trichloromethylation–methanolysis products.

Structures of the Minor Products (9).—Compound **9-CH$_3$** from the trichloromethylation of isodurene was identical (ir, nmr) with authentic[21] methyl 2,3,4,5-tetramethylbenzoate. Compound **9-F**, previously unknown, was synthesized from 2-nitro-1,3-dimethylbenzene, according to Scheme II. Bromination gave

SCHEME II



4-bromo-2-nitro-1,3-dimethylbenzene; the position of the bromine was clearly ortho, para to the methyls, and meta to the nitro, as shown by the AB aromatic proton pattern (doublets at τ 2.21 and 2.79, J = 6 Hz). This pattern was also evident in the amine **10**. The nmr spectrum of the bromination product of **13** showed that the bromine had entered the ring para to the fluorine, because the remaining aromatic proton appeared as a doublet at τ 3.00, J_{HF} = 7.8 Hz (characteristic of meta, not para J_{HF}).[22] Similarly, the aromatic proton in **9-F** appeared as a doublet at τ 2.60, J_{HF} = 8.1 Hz. Synthetic **9-F** and that obtained from the trichloromethylation–methanolysis of **7-F** were identical in all respects.

Because of the length of this synthesis, it was not repeated for X = Cl or Br; the structures of the minor products from **7-Cl** and **7-Br** are assumed to be analogous to that from **7-F**.

Further Discussion.—As stated in Part A, trichloromethylation (in contrast to sulfonation) is probably irreversible. The reactions are heterogeneous. Normally a dilute CCl_4 solution of the aromatic compound is added to a stirred suspension of a twofold excess of $AlCl_3$ in CCl_4. The mixture almost immediately develops a red-orange color, which changes to deep purple as the reaction proceeds. The color resides in a lower, semisolid phase (often spread on the vessel walls by the stirrer). The upper, CCl_4 layer remains almost colorless. All of the reaction product appears to be complexed with the $AlCl_3$ in the colored layer, because separate hydrolysis of the colorless layer affords no trichloromethylation product whatever. Therefore, it appears that as soon as $ArCCl_3$ is produced, it reacts with the excess $AlCl_3$ present to form $ArCCl_2^+ AlCl_4^-$.

Hydrolysis of the lower layer gives mainly $ArCCl_3$; in this step, chloride competes effectively with water, and very little $ArCO_2H$ is formed.

Evidence for interaction between CCl_4 and $AlCl_3$ has been presented by Willard,[23] who found rapid Cl^{36} exchange between liquid CCl_4 and solid $AlCl_3$, even at −21°. Since no exchange occurred between the vapors (140°, 9 hr), an $AlCl_3$ surface is essential. The authors favor an exchange mechanism in which an induced dipolar CCl_4 molecule is adsorbed on the $AlCl_3$ lattice at a charge site. This adsorption may furnish an incipient source of CCl_3^+ needed for the trichloromethylations.

Experimental Section[24]

Starting Materials.—Fluoromesitylene was prepared from the amine *via* the diazonium tetrafluoborate:[25] nmr τ 3.47 (d, 2, J_{HF} = 6.8 Hz, arom), 7.86 (br m, 9, CH_3's). Chloromesitylene was prepared by chlorination of mesitylene:[25a] nmr τ 3.41 (s, 2, arom), 7.81 (s, 6, *o*-CH_3's), 7.92 (s, 3 H, *p*-CH_3). Bromomesitylene was prepared by brominating mesitylene:[26] nmr τ 3.25 (s, 2, arom), 7.72 (s, 6, *o*-CH_3's), 7.91 (s, 3, *p*-CH_3).

General Trichloromethylation Procedure.—A solution of the aromatic compound in carbon tetrachloride was added dropwise to a stirred slurry of aluminum chloride (anhydrous, twice the molar amount of aromatic compound) in carbon tetrachloride, at 40.0 ± 0.1°. After addition, the mixture was stirred for 2 hr and then hydrolyzed by pouring it into ice water. The organic layer was dried ($MgSO_4$) and concentrated to half its volume, methanol was added, and the mixture was refluxed overnight. Evaporation of the solvent left a residue of substituted methyl benzoate(s) which was analyzed directly by vpc (usually 5 ft × 0.25 in. 20% SF-96 on Chromosorb W, He carrier gas, 40 psi, 175°). Products were also isolated by vacuum distillation or recrystallization. In the following specific cases, amounts are given, and conditions are stated only if they deviate from those given in the general procedure.

(20) M. L. Bender and R. S. Dewey, *J. Amer. Chem. Soc.*, **78**, 317 (1956).

(21) The tetramethylbenzoic acids were prepared by procedures analogous to that given for mesitoic acid in "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 533; the acids were converted to methyl esters with diazomethane or by methanolysis of the acid chlorides. Melting points agreed with those in the literature: see L. I. Smith and J. J. Rosenbaum, *J. Amer. Chem. Soc.*, **73**, 3843 (1951).

(22) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 349.

(23) C. H. Wallace and J. E. Willard, *J. Amer. Chem. Soc.*, **72**, 5275 (1950); M. Blau and J. E. Willard, *ibid.*, **73**, 442 (1951).

(24) All melting points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were calibrated against polystyrene and nmr spectra against tetramethylsilane as an internal reference.

(25) (a) E. T. McBee and R. E. Leech, *Ind. Eng. Chem.*, **39**, 393 (1947); (b) G. Balz and G. Schiemann, *Chem. Ber.*, **60**, 1186 (1927).

(26) L. I. Smith, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 95.

Trichloromethylation of Mesitylene (7-H) and Subsequent Methanolysis.—Mesitylene (4.76 g, 0.039 mol) in 200 ml of CCl_4, aluminum chloride (10.58 g, 0.079 mol) in 200 ml of CCl_4, 500 ml of ice water, 150 ml of methanol. A single vpc peak (150°, ret. time 5.3 min) was observed. Distillation gave 6.31 g (90%) of methyl 2,4,6-trimethylbenzoate, bp 72–73° (0.15 Torr), identical in ir, nmr, and retention time with an authentic sample.[20]

Trichloromethylation of Isodurene (7-CH_3), and Subsequent Methanolysis.—Isodurene (6.7 g, 0.05 mol) in 100 ml of CCl_4, aluminum chloride (13.3 g, 0.1 mol) in 100 ml of CCl_4, 100 ml of methanol. The crude product (9.10 g, 95%) gave vpc peaks assigned as follows (ret. time in min, %): methyl 2,4,6-trimethylbenzoate (5.3, 3–5), methyl 2,3,4,6- and 2,3,5,6-tetramethylbenzoates (10.3, 66 and 2%, respectively, as determined by nmr), methyl 2,3,4,5-tetramethylbenzoate (13.9, 22), and methyl pentamethylbenzoate (16.0, 5–7). All products were identified by comparison of ir, nmr, and retention times with those of authentic samples.

Trichloromethylation of Fluoromesitylene (7-F), and Subsequent Methanolysis.—Fluoromesitylene (1.38 g, 0.01 mol) in 75 ml of CCl_4, aluminum chloride (2.68 g, 0.02 mol) in 75 ml of CCl_4, 100 ml of ice water, 100 ml of methanol. The vpc peaks (ret. time in min, %) were assigned as follows: methyl 3-fluoro-2,4,6-trimethylbenzoate (7.8, 70) and methyl 4-fluoro-2,3,5-trimethylbenzoate (9.3, 30). The compounds were identical (ir, nmr, retention time) with authentic samples prepared as described below.

Methyl 3-Fluoro-2,4,6-trimethylbenzoate (8-F).—A solution of 2-bromo-4-fluoro-1,3,5-trimethylbenzene[27] (3.0 g, 0.014 mol) in 25 ml of dry tetrahydrofuran was added to a stirred suspension of magnesium (0.34 g, 0.014 g-atom) in 10 ml of THF. The mixture was refluxed (1 hr); CO_2 was passed in until the mixture became white. The mixture was acidified (6 *N* HCl), extracted with ether, dried ($MgSO_4$), and evaporated. The residue of **3-fluoro-2,4,6-trimethylbenzoic acid** was recrystallized from aqueous acetone to yield 0.51 g (20%), mp 140.5–141.0°.

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.95; H, 6.04; neut equiv, 182. Found: C, 65.94; H, 6.13; neut equiv, 180.7.

The acid was converted, *via* diazomethane, to methyl 3-fluoro-2,4,6-trimethylbenzoate which was purified by vpc: mp 12.0–12.5°; ir 1724 cm^{-1}; nmr τ 3.27 (d, 1, J_{HF} = 7.1 Hz, arom), 6.19 (s, 3, OCH_3), 7.82–7.87 (m, 9, CH_3's).

Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.32; H, 6.69. Found: C, 67.25; H, 6.72.

4-Bromo-2-fluoro-1,3-dimethylbenzene (11).—A solution of 3-bromo-2,6-dimethylaniline[28] (33.2 g, 0.166 mol) in 200 ml of water containing 25 ml of 18 *M* sulfuric acid was cooled to 3° and solid sodium nitrite was added until an excess was indicated (starch–iodide). The solution was filtered, 55 g of 47% fluoroboric acid was added, and the white precipitate was collected, washed successively (100 ml) with water, ethanol, and ether, and dried in a vacuum desiccator over P_2O_5 for 5 hr. The dry powder was gently heated in a large flask fitted with an efficient condenser. The solid decomposed smoothly, to leave a liquid which was dissolved in ether, washed (20% NaOH, water), and dried ($MgSO_4$). Evaporation of the ether and distillation of the residue gave 25.8 g (0.127 mol, 77%) of **4-bromo-2-fluoro-1,3-dimethylbenzene**: bp 38–39° (0.8 Torr); nmr τ 2.6–3.3 (m with peaks at 2.68, 2.91, 3.01, 3.16, and 3.29, 2, arom), 7.74 (d, 3, J_{HF} = 2.6 Hz), 7.92 (d, 3, J_{HF} = 2.3 Hz).

Anal. Calcd for C_8H_8BrF: C, 47.31; H, 3.98. Found: C, 47.41; H, 4.09.

Methyl 3-Fluoro-2,4-dimethylbenzoate (12).—A solution of 11 (37.6 g, 0.185 mol) in 50 ml of anhydrous tetrahydrofuran was added dropwise to a stirred slurry of magnesium (4.5 g, 0.185 g-atom) in 50 ml of THF. When the Grignard reagent was completely formed, the solution was poured over excess crushed Dry Ice. Work-up gave 29.0 g (0.172 mol, 93%) of crude **3-fluoro-2,4-dimethylbenzoic acid**. Two recrystallizations from aqueous acetone gave needles, mp 140.5–141.0°.

Anal. Calcd for $C_9H_9FO_2$: C, 64.27; H, 5.40; neut equiv, 168. Found: C, 64.32; H 5.27; neut equiv, 166.6.

The acid (20 g, 0.119 mol) was refluxed for 1 hr with thionyl chloride (30 g, 0.252 mol), excess thionyl chloride was removed by distillation, methanol (100 ml) was added, and the mixture was refluxed for 1 hr. Work-up gave 18.4 g (0.101 mol, 85%) of **methyl 3-fluoro-2,4-dimethylbenzoate**: bp 53–54° (0.15 Torr); ir 1718 cm^{-1}; nmr τ 2.21 (d, 1, J = 7.8 Hz, arom 6-H), 2.82 (t, 1, J_{HH} and J_{HF} = 7.8 Hz, arom 5-H), 6.06 (s, 3, OCH_3), 7.46 (d, 3, J_{HF} = 2.7 Hz, methyl at C-2), 7.70 (d, 3, J_{HF} = 2.3 Hz, methyl at C-4).

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.91; H, 6.10. Found: C, 65.80; H, 6.13.

3-Fluoro-1,2,4-trimethylbenzene (13).—A solution of 12 (14 g, 0.077 mol) in 50 ml of anhydrous ether was added dropwise to a slurry of $LiAlH_4$ (5.85 g, 0.154 mol) in 300 ml of ether, after which the mixture was refluxed (1 hr). Customary work-up gave a liquid residue which solidified on standing. Distillation gave 9.45 g (0.063 mol, 80%) of **3-fluoro-2,4-dimethylbenzyl alcohol**, bp 74–75° (0.3 Torr). Recrystallization from petroleum ether yielded platelets: mp 37–38°; ir 3320 (br) cm^{-1}; nmr τ 3.00, 3.05 (s, 2, arom), 5.55 (s, 2, CH_2), 5.82 (s, 1, OH), 7.75 (d, 3, J_{HF} = 2.1 Hz, arom CH_3), 7.88 (d, 3, J_{HF} = 2.2 Hz, arom CH_3).

Anal. Calcd for $C_9H_{11}FO$: C, 70.10; H, 7.20. Found: C, 70.16; H, 7.11.

The alcohol (9.3 g 0.062 mol) was treated cautiously with 25 ml of thionyl chloride. When the spontaneous reaction subsided, the mixture was refluxed (1 hr). Work-up gave 8.1 g (0.047 mol, 76%) of **3-fluoro-2,4-dimethylbenzyl chloride**: bp 49–50° (0.35 Torr); nmr τ 2.90, 2.94 (s, 2, arom), 5.43 (s, 2, CH_2), 7.71 (t, from overlapping doublets, 6, J_{HF} = 2.4 Hz, arom CH_3's).

Anal. Calcd for $C_9H_{10}ClF$: Cl, 20.53. Found: Cl, 20.38.

A solution of the benzyl chloride (8.0 g, 0.046 mol) in 25 ml of dry THF was added dropwise to a stirred suspension of $LiAlH_4$ (0.95 g, 0.025 mol) in 25 ml of THF. Addition was followed by 1 hr reflux. Work-up gave 5.79 g (0.042 mol, 91%) of **3-fluoro-1,2,4-trimethylbenzene**: bp 54–55° (15 Torr); $n^{25}D$ 1.4858; nmr τ 3.03 (d, 1, J_{HF} = 6 Hz, arom 5-H), 3.08 (s, 1, arom 6-H), 8.65–8.90 (m, 9, arom CH_3's).

Anal. Calcd for $C_9H_{11}F$: C, 78.21; H, 8.04. Found: C, 78.24; H, 8.15.

Methyl 4-Fluoro-2,3,5-trimethylbenzoate (9-F).—To a solution of 13 (5.0 g, 0.037 mol) in 50 ml of chloroform was added dropwise with stirring a solution of bromine (5.9 g, 0.037 mol) in 50 ml of chloroform. After 3 hr at room temperature, excess bromine was removed with 10% sodium bisulfite. The clear mixture was washed (H_2O), dried ($MgSO_4$), and distilled to yield 6.83 g (0.030 mol, 81%) of **6-bromo-3-fluoro-1,2,4-trimethylbenzene**: bp 95–96° (10 Torr); $n^{25}D$ 1.5365; nmr τ 3.00 (d, 1, J_{HF} = 7.8 Hz, arom), 7.79 (s, 3, arom CH_3), 7.89 (br s, 6, arom CH_3's).

Anal. Calcd for $C_9H_{10}BrF$: C, 49.78; H, 4.65. Found: C, 49.88; H, 4.66.

A solution of the bromofluoride (3.0 g, 0.014 mol) in 10 ml of dry THF was added to a suspension of magnesium (0.34 g, 0.014 g-atom) in 25 ml of THF. After 1 hr reflux, the mixture was poured over crushed Dry Ice. Customary work-up gave crude **4-fluoro-2,3,5-trimethylbenzoic acid** (1.29 g, 50%) which, after two sublimations (0.1 Torr, 100°), was pure, mp 167–168°; ir 3300–2400 cm^{-1} (br).

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.91; H, 6.10; neut equiv, 182. Found: C, 65.93; H, 6.08; neut equiv, 182.5.

An ether solution of the acid (0.5 g, 0.003 mol) was treated with diazomethane. The ester was purified by vpc (5 ft × 0.25 in. 20% SE-30, 180°) to give **methyl 4-fluoro-2,3,5-trimethylbenzoate (8-F)**: mp 19.0–19.5°; ir 1725 cm^{-1}; nmr τ 2.60 (d, 1, J_{HF} = 8.1 Hz), 6.25 (s, 3, OCH_3), 7.62 (s, 3, C-2 methyl), 7.80–7.92 (m with 3 peaks due to HF coupling, 6, C-3 and C-5 methyls).

Anal. Calcd for $C_{11}H_{13}FO_2$: C, 67.32; H, 6.69. Found: C, 67.26; H, 6.65.

Trichloromethylation of Chloromesitylene (7-Cl) and Subsequent Methanolysis.—Chloromesitylene (15.5 g, 0.10 mol) in 100 ml of CCl_4, aluminum chloride (26.6 g, 0.2 mol) in 100 ml of CCl_4, 500 ml of ice water. The crude trichloromethyl product weighed 25.7 g (0.094 mol, 94%). After methanolysis (100 ml of methanol) the product was analyzed by vpc using a 20% Carbowax 20 M on Chromosorb W column, 175°. The vpc peaks (ret. time in min, %) were assigned as follows: methyl 3-chloro-2,4,6-trimethylbenzoate (54.6, 88) and methyl 4-chloro-2,3,6-trimethylbenzoate (71.4, 12). The former was identical (ir, nmr, retention time) with an authentic sample prepared as described below.

(27) G. Grassini, G. Illuminati, and G. Marino, *Gazz. Chim. Ital.*, **86**, 1138 (1956).

(28) K. Auwers, and T. Markovits, *Chem. Ber.*, **41**, 2332 (1908); E. Noelting, A. Braun, and G. Thesmar, *ibid.*, **34**, 2261 (1901).

Methyl 3-Chloro-2,4,6-trimethylbenzoate (8-Cl).—To a solution of chloromesitylene (31.0 g, 0.20 mol) in 100 ml of chloroform was added, at room temperature, a solution of bromine (35 g, 0.22 mol) in 50 ml of chloroform, in an apparatus equipped with an HBr trap. After being stirred for 3.5 hr, the mixture was washed ($NaHSO_3$, H_2O) and dried ($MgSO_4$). Distillation afforded 33.1 g (0.14 mol, 71%) of **2-bromo-4-chloro-1,3,5-trimethylbenzene**, bp 128–129° (10.5 Torr). The distillate solidified and, after recrystallization from pentane, yielded crystals: mp 57.5–58°; nmr τ 3.13 (s, 1, arom), 7.50, 7.72, 7.86 (s, 3 each, arom CH_3's).

Anal. Calcd for $C_9H_{10}BrCl$: C, 45.89; H, 4.29. Found: C, 46.38; H, 4.51.

A solution of the bromochloride (30 g, 0.129 mol) in 150 ml of dry ether was added dropwise to a suspension of magnesium (3.15 g, 0.129 g-atom) in 150 ml of ether. Reaction was initiated with ethylmagnesium iodide. After Grignard formation was complete, the mixture was poured over crushed Dry Ice. The usual work-up afforded, after two recrystallizations from aqueous acetone, 16.8 g (0.085 mol, 66%) of 3-chloro-2,4,6-trimethylbenzoic acid, mp 145–146° (lit.[29] value 143.5–144.0°).

The acid (5 g, 0.025 mol) in ether was treated with diazomethane. Work-up gave 5.15 g (0.024 mol, 96%) of crude **methyl 3-chloro-2,4,6-trimethylbenzoate (8-Cl)**. Two recrystallizations from petroleum ether (30–60°) gave pure ester: mp 34–34.5°; ir 1725 cm^{-1}; nmr τ 3.19 (s, 1, arom), 6.20 (s, 3, OCH_3), 7.73 (br s, 6, arom CH_3's), 7.83 (s, 3, arom CH_3).

Anal. Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.17. Found: C, 62.10; H, 6.11.

Trichloromethylation of Bromomesitylene (7-Br) and Subsequent Methanolysis.—Bromomesitylene (2.01 g, 0.010 mol) in 50 ml of CCl_4, aluminum chloride (2.70 g, 0.020 mol) in 50 ml of CCl_4, 500 ml of ice water, 100 ml of methanol, 20% SE-30 column. In addition to some recovered starting material (ret. time 6.4 min, 8%), two products were obtained, methyl 3-bromo-2,4,6-trimethylbenzoate (24.8 min, 93%) and 4-bromo-2,3,5-trimethylbenzoate (27.8 min, 7%). The former was identical (ir, nmr, retention time) with an authentic sample prepared as described below.

Methyl 3-Bromo-2,4,6-trimethylbenzoate (8-Br).—An ether solution of 3-bromo-2,4,6-trimethylbenzoic acid[29] was treated with diazomethane. The usual work-up afforded a 96% yield of **methyl 3-bromo-2,4,6-trimethylbenzoate**: mp (30–60° petroleum ether) 42.5–43°; ir 1713 cm^{-1}; nmr τ 3.21 (s, 1, arom), 6.22 (s, 3, OCH_3), 7.70 (br s, 6, arom CH_3's), 7.86 (s, 3, arom CH_3).

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.36; H, 5.06. Found: C, 51.49; H, 5.21.

Relative Trichloromethylation Rates.—A suspension of aluminum chloride (2.68 g, 0.020 mol) in 75 ml of carbon tetrachloride was allowed to thermally equilibrate at 40.0 ± 0.1°. A mixture of 0.005 mol each of isodurene and 1 mol of the halomesitylenes in 75 ml of carbon tetrachloride was similarly brought to temperature; the solutions were quickly mixed, stirred for 5 min, and quenched by adding 100 ml of ice water. Solvent was evaporated from the organic layer and the residue was refluxed (2 hr) with 100 ml of aqueous acetone (1:1). The mixture was made strongly alkaline, and unreacted aromatics were extracted with ether and analyzed by vpc.

Registry No.—**8-Br**, 26584-20-3; **8-Cl**, 26584-21-4; **8-F**, 26584-22-5; **8-F** (acid), 26584-23-6; **9-F**, 26584-24-7; **9-F** (acid), 26584-25-8; **11**, 26584-26-9; **12**, 26584-27-0; 12 (acid), 26583-81-3; **13**, 26630-72-8; 3-fluoro-2,4-dimethylbenzyl alcohol, 26583-82-4; 3-fluoro-2,4-dimethylbenzyl chloride, 26583-83-5; 6-bromo-3-fluoro-1,2,4-trimethylbenzene, 26583-84-6; 2-bromo-4-chloro-1,3,5-trimethylbenzene, 26583-85-7.

(29) F. M. Beringer and S. Sands, *J. Amer. Chem. Soc.*, **75**, 3319 (1953).

Reduction with Metal-Ammonia Combinations. III.[1] Synthesis of β- and γ-Alkylthiomercaptans from 1,3-Dithiolanes and 1,3-Dithianes

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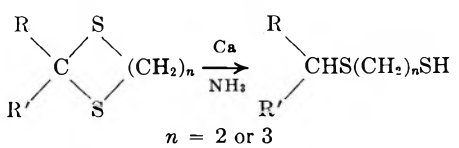
Eleven 1,3-dithiolanes and four 1,3-dithianes have been reduced with calcium in liquid ammonia to give β- and γ-alkylthiomercaptans, $RS(CH_2)_nSH$ (n = 2 or 3), respectively, in high yields.

Part A

Recently, the calcium–ammonia reduction of 1,3-oxathiolanes and 1,3-oxathianes has been reported[1] as a fairly general preparative method for β- and γ-alkoxy mercaptans, respectively. It is evident that selective cleavage of the C–S bond of 1,3-dithiolanes and 1,3-dithianes (Scheme I) would provide a convenient route

SCHEME I



to β-alkylthioethyl and γ-alkylthiopropyl mercaptans. *A priori*, it was not evident whether cleavage of only one of the four C–S bonds in the starting materials shown in Scheme I could be achieved and at the inception of this work there was only one report[2] of such a selective reduction (of 2,2-dimethyl-4-hydroxymethyl-1,3-dithiolane), whereas there were several known instances where reduction led to complete desulfurization[3] or to more complicated products.[4] While this work was in progress,[5] Owen and coworkers[6] published additional examples involving selective cleavage of 2,2-dimethyl-1,3-dithiolanes (Scheme I, R = R′ = CH_3) whereas total cleavage (Scheme II) occurred with 2-methyl- and 2-phenyl-1,3-dithiolanes (R = R′ = H or R = C_6H_5; R′ = H).

As the data in Table I show, reduction according to

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(1) Paper II [E. L. Eliel and T. W. Doyle, *J. Org. Chem.*, **35**, 2716 (1970)] contains an extensive survey of the background literature.

(2) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 2938 (1950).

(3) (a) L. A. Stocken, *ibid.*, 592 (1947); (b) R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.*, **80**, 4604 (1958); (c) N. S. Crossley and H. B. Henbest, *J. Chem. Soc.*, 4413 (1960); (d) R. D. Stolow and M. M. Bonaventura, *Tetrahedron Lett.*, 95 (1964). These reports refer either to benzylic (a) or allylic (b) thioacetals or -ketals or involve reduction with lithium in ethylamine (c, d).

(4) Q. F. Soper, W. E. Buting, J. E. Cochran, and A. Pohland, *J. Amer. Chem. Soc.*, **76**, 4109 (1954); A. Schönberg, E. Petersen, and H. Kaltschmitt, *Ber.*, **66B**, 233 (1933); the latter report involves sodium in ether.

(5) Preliminary report: E. L. Eliel, T. W. Doyle, R. A. Daignault, and B. C. Newman, *J. Amer. Chem. Soc.*, **88**, 1828 (1966).

(6) E. D. Brown, S. M. Iqbal, and L. N. Owen, *J. Chem. Soc. C*, 415 (1966).

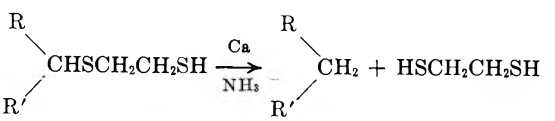
TABLE I

REDUCTION OF 1,3-DITHIOLANES AND 1,3-DITHIANES WITH CALCIUM IN AMMONIA

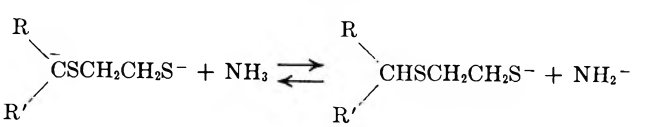
Method[a]	Starting material, ethylene dithioacetal or dithioketal of	Product, R in $RSCH_2CH_2SH$	Yield, %[b] Anal	Isold
B	Formaldehyde	Methyl	...[c]	85
A	Acetaldehyde	Ethyl[d]	93, 90	81
A	Propionaldehyde	*n*-Propyl	99, 100	91
A	Isobutyraldehyde	Isobutyl	95, 96	85
A	3-Pentanone	3-Pentyl	97, 98	90
A	Pinacolone	3,3-Dimethyl-2-butyl	98, 99	97
A	*n*-Heptaldehyde	*n*-Heptyl	90 (93), 51 (94)[e]	82
A	Cyclohexanone	Cyclohexyl	92, 93	85
B	Phenylacetaldehyde	2-Phenylethyl	...[c]	94
B	Phenylacetone	1-Phenyl-2-propyl	...[c]	91
A	Hydrocinnamaldehyde	3-Phenyl-1-propyl	98, 99	94
A	Formaldehyde	H	90	60
A	Phenylacetaldehyde	H	97	71
		and ethylbenzene		71
A	Phenylacetone	H	92	76
		and *n*-propylbenzene		79
A	Phenylpentadeuteriopropanone	H	...[c]	...[f]
		and 1-phenyl-1,1,3,3,3-pentadeuteriopropane		65
B	Benzaldehyde	H	...[c]	16
		and toluene		18
	Trimethylene dithioacetal or dithioketal of	R in $RSCH_2CH_2CH_2SH$	Anal	Isold
B	Formaldehyde	Methyl	...[c]	86
A	Isobutyraldehyde	Isobutyl	95, 98	85
A	Cyclohexanone	Cyclohexyl	90, 93	84
A	Formaldehyde	H	97, 98	90
A	α-Hydroxypropionaldehyde	$CH_3CHOHCH_2$–	...[c]	83

[a] Method A, normal addition of an ethereal solution of the 1,3-dithiolane or 1,3-dithiane to an excess of calcium in ammonia. Method B, inverse addition of a limited amount of calcium to an ethereal solution of the 1,3-dithiolane or 1,3-dithiane in ammonia. [b] First column gives analytical yield determined by iodine titration. Second column gives yield of compound isolated. [c] No attempt made to analyze compound. [d] Contaminated with a small amount of an unidentified compound, apparently a mercaptan, not 1,2-ethanedithiol, from thin layer chromatography. [e] The mercaptan is very susceptible to disulfide formation; figures in parentheses refer to the % yields obtained after reduction of disulfide with zinc amalgam (see Experimental Section). [f] No attempt made to isolate compound.

SCHEME II



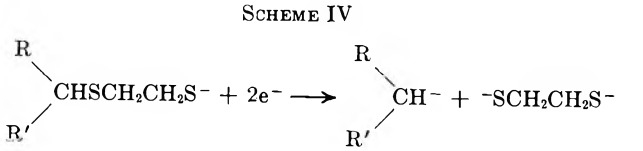
SCHEME III



Scheme I was achieved in the present investigation in almost all cases in nearly quantitative analytical yield; the yields of isolated products ranged from 69 to 97%. In only four cases was overreduction (Scheme II) observed, and in three of these (R = R′ = H and R = $C_6H_5CH_2$; R′ = H or CH_3) it could be effectively prevented by limiting the amount of calcium to the theoretical 2 equiv per mole of thioacetal or thioketal and adding the metal rapidly. Apparently the second reduction stage (Scheme II) is sufficiently slower than the first (Scheme I) in these instances to enable one to achieve high selectivity. Only in the case of benzaldehyde ethylene dithioketal (R = C_6H_5; R′ = H) were we unable to prevent reduction to toluene, ethanedithiol, and other products, presumably because the second stage of reduction is considerably faster than the first in this instance.

In accordance with the previously postulated[1,7] mechanism, we assume that reduction of dithioacetals or -ketals proceeds *via* a two-stage electron transfer involving the dianion shown in Scheme III. The carbanion moiety is stabilized by the adjacent sulfur atom (d-orbital resonance) which may account for its reluctance to undergo further reduction as well as for the much higher yields generally achieved in the reduction of dithioacetals or -ketals to alkylthiomercaptans compared to the yields of alkoxy mercaptans previously obtained[1] from monothioacetals and -ketals.[6] Only when the carbanion formed in the second stage of cleavage (Scheme IV) is particularly stable, *e.g.*, when it is a methyl or

SCHEME IV



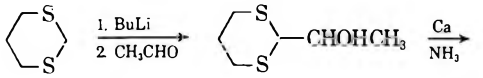
benzyl anion[6] or when it is inductively stabilized by an electron-withdrawing group (*e.g.*, R = $C_6H_5CH_2$), will overreduction occur readily.

The present procedure provides a convenient route to β- and γ-alkylthiomercaptans; its versatility is en-

(7) See also R. Gerdil and E. A. C. Lucken, *J. Chem. Soc.*, 2857, 544 (1963); 3916 (1964).

hanced by the availability of a wide variety of functionally 2-substituted 1,3-dithianes by the elegant procedure of Corey and Seebach.[8] Thus (last entry in Table I), the reduction of 2-(1-hydroxyethyl)-1,3-dithiane, synthesized from 1,3-dithiane and acetaldehyde,[8] produced 1-(3-mercaptopropylthio)-2-propanol (Scheme V) in 83% yield.

SCHEME V



$CH_3CHOHCH_2SCH_2CH_2CH_2SH$

The reduction of 2-isopropyl-1,3-dithiolane is described as typical of those in which an excess of calcium is employed. Additional experimental techniques, tables of starting materials and products, syntheses of authentic samples, and a more detailed discussion of the reaction mechanism are found in Part B.

Reduction of 2-Isopropyl-1,3-dithiolane.—To 300 ml of liquid ammonia in a 500-ml three-necked flask equipped with an addition funnel, mechanical stirrer, and venting tube was added 2.7 g (0.067 g-atom) of calcium turnings. When the metal had dissolved (5 min), a solution of 4.70 g (0.034 mol) of 2-isopropyl-1,3-dithiolane in 50 ml of anhydrous ether was added over a period of 5–10 min. After an additional 10 min, the excess calcium (blue solution) was destroyed by addition of solid ammonium chloride. The ammonia was allowed to evaporate in the hood and the residual slurry treated with 100 ml of 1 *N* hydrochloric acid. The layers were separated and the aqueous layer three times extracted with 50-ml portions of ether. The combined ether solution was dried over $MgSO_4$ and concentrated to give 4.57 g of an oil, a small aliquot of which was titrated with iodine for mercaptan content;[9] the remainder of the oil was distilled, bp 92° (15 mm), yield 4.04 g (85%). The infrared and nmr spectra were compatible with the assigned structure, $(CH_3)_2CHCH_2SCH_2CH_2SH$.

Part B

The starting 1,3-dithiolanes and 1,3-dithianes for this investigation were generally formed from the appropriate aldehydes or ketones and ethane-1,2-dithiol or propane-1,3-dithiol in the presence of an acid catalyst.[10] Properties and yields of starting materials are indicated in Table II. The yields in the reductions (Table I), usually determined by iodimetry[9] in duplicate reactions, generally exceeded 90% although in one run, involving *n*-heptyl mercaptan as the product, disulfide formation lowered the yield to 51%; the disulfide was readily reconverted to mercaptan by treatment with zinc amalgam in the presence of acid,[9] however.

Reduction of the dithiolanes derived from formaldehyde, phenylacetaldehyde, phenylacetone, and benzaldehyde and of the dithiane derived from formaldehyde with excess calcium in ammonia led to double cleavage (Scheme II), the products being ethane-1,2-dithiol or propane-1,3-dithiol, respectively, and ethylbenzene, *n*-propylbenzene, and toluene (methane, presumably formed from the formyl derivatives, was not isolated). In the case of the formaldehyde, phenylacetaldehyde, and phenylacetone derivatives, it was established that hydrocarbon formation did, in fact, occur in two sequential steps (Scheme I followed by Scheme II), for not only could the desired single cleavage (Scheme I) be achieved by limiting the amount of calcium to 2 equiv per mole of starting thioacetal or -ketal, but in addition, the initial products, $CH_3SCH_2CH_2SH$ and $C_6H_5CH_2CH_2SCH_2CH_2SH$, were further reduced to $HSCH_2CH_2SH$ and (in the second case) $C_6H_5CH_2CH_3$ by treatment with 3 equiv of calcium in ammonia. Only in the case of the benzaldehyde derivative 2-phenyl-1,3-dithiolane did we fail to arrest the reduction at the intermediate stage, the only products isolated being toluene and ethane-1,2-dithiol in low yield (other, unidentified and more complex products are also formed). The last result confirms previous reports in the literature;[2,3a] it is well known that benzyl sulfides, the expected initial products according to Scheme I, are readily cleaved by metal–ammonia combinations, the benzyl group often serving as a protective group in such instances.

Overreduction of the formaldehyde and benzaldehyde derivatives is readily explained in terms of the high stability of the methyl and benzyl carbanions formed in the second stage of cleavage (Scheme IV). That similar stabilization accounts for the overreduction of the phenylacetaldehyde and phenylacetone derivatives (Schemes I, II, IV; R = $C_6H_5CH_2$; R′ = H or CH_3) was not immediately obvious, since only an inductive electron withdrawal by the benzyl group can be invoked as stabilizing the corresponding carbanions (Scheme IV). Alternative pathways in these cases were considered (Scheme VI). One of these (i) involves formation of a

SCHEME VI

(i) $C_6H_5CH_2CHR'SCH_2CH_2S^- \xrightarrow[-NH_3]{NH_2^-} C_6H_5C^-HCHR'SCH_2CH_2S^- \longrightarrow {}^-SCH_2CH_2S^- + C_6H_5CH{=}CHR' \xrightarrow[NH_3]{Ca} C_6H_5CH_2CH_2R' + {}^-SCH_2CH_2S^-$

(ii) Reduction occurring *via* Scheme IV with stabilization of the homobenzylic carbanion as a phenanion

R′ = H or CH_3

benzylic carbanion followed by an E2cB elimination to give the ethanedithiolate dianion and a styrene which is known to be further reduced to an alkylbenzene by metal–ammonia.[11] The other hypothesis (ii) provides for stabilization of the intermediate of Scheme IV as a phenanion.

Both alternatives were ruled out by a study of the reduction of the ethylene dithioketal of 1-phenyl-2-propanone-1,1,3,3,3-d_5, $C_6H_5CD_2COCD_3$. Reduction of the thioketal proceeded *without* loss of deuterium (as established by nmr spectroscopy) to give pentadeuterated $C_6H_5CD_2CH_2CD_3$. It is clear that pathway i, Scheme

(8) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075, 1077 (1965). See also D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968), and references there cited.

(9) D. P. Harnish and D. S. Tarbell, *Anal. Chem.*, **21**, 968 (1949).

(10) R. H. Jones, G. E. Lukes, and J. I. Bashour, U. S. Patent 2,690,988 (1954); *Chem. Abstr.*, **49**, 9868*d* (1955).

(11) C. B. Wooster and J. F. Ryan, *J. Amer. Chem. Soc.*, **56**, 1133 (1934).

TABLE II

STARTING MATERIALS (1,3-DITHIOLANES AND 1,3-DITHIANES)

Ethylene dithioacetal or dithioketal[l] of	Yield, %	Bp, °C (mm)	$n^{20}D$	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found
Formaldehyde[a]	94	77 (23)	1.5988				
Acetaldehyde[b]	81	75 (23)	1.5637	39.96	39.64	6.70	6.83
Propionaldehyde[c]	83	87 (21)	1.5496				
Isobutyraldehyde	84	84 (9)	1.5382	48.60	49.00	8.16	8.16
3-Pentanone	85	53 (0.7)	1.5331	51.80	51.84	8.69	8.66
Pinacolone	84	...[d]		54.49	54.71	9.15	9.11
n-Heptaldehyde[b]	84	100.5–101 (1.1)	1.5189	56.78	56.88	9.53	9.66
Cyclohexanone[e]	94	86.5 (1.2)	1.5664				
Benzaldehyde[b,f]	95	109.5 (0.7)	1.6368	59.29	58.81	5.53	5.53
Phenylacetaldehyde[b]	92	122 (0.7)	1.6159	61.17	61.45	6.16	6.38
Phenylacetone	91	108 (0.7)	1.6010	62.81	62.67	6.71	6.65
1-Phenylpentadeuteriopropanone	94	104 (0.3)	1.6001				
Hydrocinnamaldehyde	85	130 (0.5)	1.5994	62.81	62.80	6.71	6.71
Trimethylene dithioacetal or dithioketal[m] of							
Formaldehyde[g]	93	...[h]					
Isobutyraldehyde[i]	82	69.5 (1.2)	1.5435				
Cyclohexanone[j]	98	90 (0.3)[k]					

[a] D. T. Gibson, *J. Chem. Soc.*, 12 (1930), reports bp 61° (11 mm), $n^{15}D$ 1.5975. [b] Reported in ref 10 without physical constants. [c] S. Oae, W. Tagaki, and A. Ohno, *Tetrahedron*, 20, 427 (1964), report bp 68° (10 mm). [d] Solid, mp 61–62°. [e] E. E. Reid and A. Jelinek, *J. Org. Chem.*, 15, 448 (1950), report bp 107° (5 mm), $n^{25}D$ 1.5650. [f] Reported by B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, 41, 2671 (1963), without physical constants. [g] J. R. Meadow and E. E. Reid, *J. Amer. Chem. Soc.*, 56, 2177 (1934), report mp 53.3°. [h] Solid, mp 52.5–53°. [i] S. Oae, W. Tagaki, and A. Ohno (footnote c) report bp 134° (35 mm). [j] H. Hauptmann and M. M. Campos, *J. Amer. Chem. Soc.*, 72, 1405 (1950), report bp 148–148.5° (17 mm), mp 40.5–41.5°. [k] Solid, mp 39–40°. [l] Respective registry numbers follow: 4829-04-3, 5616-51-3, 6008-80-6, 26733-24-4, 26733-25-5, 26785-73-9, 6008-84-0, 177-16-2, 5616-55-7, 26785-74-0, 20137-72-8, 26733-30-2, 14505-46-5. [m] Respective registry numbers follow: 505-23-7, 6007-25-6, 180-96-1.

VI, would have led to $C_6H_5CHDCH_2CD_3$ (*via* $C_6H_5CD{=}CHCD_3$). Pathway ii should presumably have given rise to isopropylbenzene as well as *n*-propylbenzene in the reduction of the undeuterated analog 1-phenyl-2-propanone by protonation at the CH_2 group of the cyclic intermediate. Pathway ii was disproved still more convincingly by reduction of ethyl 2-phenylethyl-1-*d* sulfide, $C_2H_5SCHDCH_2C_6H_5$, with calcium in ammonia which gave 1-phenylethane-2-*d*, $C_6H_5CH_2CH_2D$, in 71% yield, the position of the deuterium being exclusively in the 2 position as shown by nmr spectroscopy. Reduction thus proceeded by the anion $C_6H_5CH_2CHD^-$ and not by the corresponding phenanion (Scheme VI, ii, R = D) which should have produced nearly equal amounts of $C_6H_5CH_2CH_2D$ and $C_6H_5CHDCH_3$.

The method here described provides a much more convenient route to β- and γ-alkylthiomercaptans than known procedures: the slow addition of hydrogen sulfide to vinyl sulfides under pressure,[12] the conversion of β- or γ-hydroxy sulfides[13,14a] to chlorides and thence to mercaptans by treatment with NaSH,[14] or the reaction of mercaptans with thiiranes.[15] The last method was used here to obtain a comparison sample of 2-cyclohexylthioethanethiol in only 34% yield, contaminated with a considerable amount of oligomeric material. An authentic sample of $CH_3CHOHCH_2SCH_2CH_2CH_2SH$ (*cf.* Scheme V) was prepared in 36% yield from 1,3-propanedithiol and propylene oxide in the presence of sodium hydroxide.[16]

Experimental Section

Melting points, determined on a Kofler block, and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Nuclear magnetic resonance spectra were recorded with a Varian Associates Model V-4311 HR-60 spectrometer at 60 MHz by Mr. D. Schifferl. Carbon tetrachloride was used as solvent, with tetramethylsilane as an internal standard. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Starting Materials.—1,3-Dithiolane, 2-methyl-1,3-dithiolane, and 1,3-dithiane were prepared by the method of Corey and Seebach.[8] Dimethoxymethane or acetaldehyde was allowed to react with the appropriate dimercaptan with boron trifluoride etherate as catalyst. The remaining 1,3-dithiolanes and 1,3-dithianes were prepared by the method of Jones, *et al.*,[10] employing the appropriate dimercaptan, aldehyde, or ketone, except for phenylacetaldehyde, where the dimethyl acetal was used, and *p*-toluenesulfonic acid as catalyst. The yields and physical properties of starting materials are listed in Table II. Known starting materials agreed in their physical properties with samples previously prepared and described in the literature.

Reductions.—The reduction of 2-isopropyl-1,3-dithiolane has been described above as typical of reductions employing method A (see Table I), where mercaptan is the sole product, the reduction of 2-benzyl-1,3-dithiolane is described as typical of reductions employing method A (see Table I), where hydrocarbon is also isolated, and the reduction of 2-benzyl-2-methyl-1,3-dithiolane with a limited amount of calcium is described as typical of reductions employing method B (see Table I). Yields of reduction products are listed in Table I and their properties in Table III. Known reduction products agreed in their physical properties with samples previously prepared and described in the literature.

(12) M. F. Shostakovsky, E. N. Prilezhaeva, and N. I. Uvarova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 447 (1954).

(13) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962).

(14) (a) S. E. Livingstone, *J. Chem. Soc.*, 437 (1956). NaSH is erroneously called "sodium ethyl sulphide" in this paper. (b) R. C. G. Moggridge, *ibid.*, 1105 (1946); L. J. Goldsworthy, G. F. Harding, W. L. Norris, S. G. P. Plant, and B. Selton, *ibid.*, 2177 (1948).

(15) W. Reppe and A. Freytag, German Patent 696,774 (1940); *Chem. Abstr.*, **35**, 5909 (1941); E. M. Meade and F. N. Woodward, *J. Chem. Soc.*, 1894 (1948); C. C. J. Culvenor, W. Davies, and N. S. Heath, *ibid.*, 282 (1949); E. P. Adams, F. P. Doyle, D. L. Hatt, D. O. Holland, W. H. Hunter, K. R. L. Mansford, J. H. C. Nayler, and A. Queen, *ibid.*, 2649 (1960); W. Reppe and coworkers, *Justus Liebigs Ann. Chem.*, **601**, 127 (1956); H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Amer. Chem. Soc.*, **69**, 2675 (1947).

(16) *Cf.* R. D. Schuetz, *ibid.*, **73**, 1881 (1951).

TABLE III
REDUCTION PRODUCTS (β- AND γ-ALKYLTHIOMERCAPTANS)

R in $RSCH_2CH_2SH$[d]	Bp, °C (mm)	$n^{20}D$	% carbon Calcd	% carbon Found	% hydrogen Calcd	% hydrogen Found
Methyl[a]	69.5 (26)	1.5409				
Ethyl[b]	92.5–93 (41)	1.5264				
n-Propyl[c]	95 (24)	1.5175				
Isobutyl	92 (15)	1.5084	47.95	48.29	9.39	9.38
3-Pentyl	57 (0.4)	1.5087	51.16	51.04	9.81	9.93
3,3-Dimethyl-2-butyl	68 (0.9)	1.5059	53.87	53.64	10.17	10.06
n-Heptyl	95 (0.7)	1.5001	56.19	56.17	10.48	10.68
Cyclohexyl	85 (0.6)	1.5420	54.49	54.72	9.15	8.99
2-Phenylethyl	114.5 (0.5)	1.5847	60.55	60.82	7.11	7.23
1-Phenyl-2-propyl	117 (0.7)	1.5735	62.21	62.39	7.59	7.81
3-Phenyl-1-propyl	130.5 (0.4)	1.5747	62.21	62.15	7.59	7.70
R in $RSCH_2CH_2CH_2SH$[e]						
Methyl	79 (18)	1.5278	39.30	39.60	8.25	8.36
Isobutyl	73 (1.5)	1.5028	51.16	51.07	9.81	9.87
Cycohexyl	100.5 (0.7)	1.5347	56.78	56.97	9.53	9.55

[a] E. M. Meade and F. N. Woodward, *J. Chem. Soc.*, 1894 (1948), report bp 82° (40 mm). [b] Reference 12 reports bp 60° (9 mm), $n^{20}D$ 1.5273. [c] L. J. Goldsworthy, G. F. Harding, W. L. Norris, S. G. P. Plant, and B. Selton, *J. Chem. Soc.*, 2177 (1948), report bp 75–77° (11 mm). [d] Respective registry numbers follow: 22322-43-6, 26750-44-4, 26733-37-9, 10160-80-2, 26718-03-6, 26718-04-7, 26718-05-8, 10160-81-3, 26785-75-1, 26718-07-0, 26718-08-1. [e] Respective registry numbers follows: 26718-09-2, 26718-10-5, 26718-11-6.

Reduction of 2-Benzyl-1,3-dithiolane with Calcium in Ammonia. Method A.—By the procedure described in Part A above, 6.09 g (0.031 mol) of 2-benzyl-1,3-dithiolane in 50 ml of ether was treated with 4.5 g (0.11 g-atom) of calcium in 300 ml of liquid ammonia; then ammonium chloride was added to destroy excess calcium. After the ammonia had evaporated, the resulting slurry was acidified with 150 ml of 2 *N* hydrochloric acid. The layers were separated; the aqueous layer was extracted three times with 50-ml portions of ether. The combined ether solutions were extracted four times with 40-ml portions of 2 *N* potassium hydroxide. The ether solution was dried over anhydrous magnesium sulfate and concentrated to give a clear colorless oil. Distillation afforded 2.34 g (71%) of ethylbenzene, bp 134.5–135° (755 mm), having an infrared spectrum identical with that of an authentic sample. The combined basic extracts were acidified with 90 ml of 5 *N* hydrochloric acid and extracted three times with 50-ml portions of ether. The combined ether solutions were dried over anhydrous magnesium sulfate and partially concentrated to give 4.03 g of a clear yellow oil. A small aliquot of this oil was removed and titrated for mercaptan content with iodine;[9] the yield of mercaptan was 97%. The remainder was distilled to give 2.06 g (71%) of 1,2-ethanedithiol, bp 42.5° (15 mm), having an infrared spectrum identical with that of an authentic sample.

Method B.—To 300 ml of liquid ammonia contained in the apparatus described above was added 6.31 g (0.030 mol) of 2-benzyl-2-methyl-1,3-dithiolane in 50 ml of anhydrous ether. Then, 1.31 g (0.033 g-atom)[17] of calcium turnings was added as quickly as possible (*ca.* 2 min). The ammonia was allowed to evaporate and the residual slurry was treated with 100 ml of 1 *N* hydrochloric acid. The layers were separated and the acidic aqueous layer extracted three times with 50-ml portions of ether. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to give a clear yellow oil. Distillation afforded 5.79 g (91%) of 2-(1-phenyl-2-propylthio)ethanethiol, bp 117° (0.7 mm). The infrared and nmr spectra were compatible with the assigned structure.

Reduction of 2-Phenyl-1,3-dithiolane (Method B).—The reduction of 5.47 g (0.03 mol) of 2-phenyl-1,3-dithiolane was effected as described in the previous experiment. The solution turned black, the color changing to brown during the evaporation of the ammonia. The product was separated into neutral and acidic fractions as indicated under method A above. The neutral fraction weighed 2.26 g and yielded *ca.* 0.5 g (18%) of toluene, bp 110° (750 mm) upon distillation; its infrared spectrum was identical with that of an authentic sample. The acidic material was a red oil weighing 3.85 g. Distillation afforded *ca.* 0.45 g (16%) of 1,3-ethanedithiol, bp 59.5–60.5° (34 mm), whose infrared spectrum was identical with that of an authentic sample. The remaining material (2.65 g) distilled with much difficulty and some decomposition at 100–200° (0.5 mm) and yielded 0.33 g of sulfur and 1.75 g of an unidentified semisolid material which was not extractable into aqueous potassium hydroxide.

Deuteration of Phenylacetone.—Phenylacetone (25 g) was treated with 10 g of anhydrous potassium carbonate in 100 g of deuterium oxide at reflux for 24 hr.[18] After cooling, the reaction mixture was extracted with three 50-ml portions of ether, previously saturated with deuterium oxide. The combined ether solutions were dried over anhydrous magnesium sulfate and concentrated to give 24.6 g of a clear yellow oil. Distillation afforded phenylpentadeuteriopropanone: bp 100° (15 mm); yield 21.8 g (84%); nmr spectrum multiplet 109.5–121.5 Hz (0.24 H) (3 H in undeuterated compound, hence 92% D at C-3), multiplet 206.5–213.5 Hz (0.20 H) (2 H in undeuterated compound, hence 90% D at C-1), multiplet 418–441 Hz (5 H).

Reduction of Ethylene Dithioketal of 1-Phenyl-2-propanone-1,1,3,3,3-d_5. A.—To a solution of 5.51 g (0.04 mol) of phenylpentadeuteriopropanone and 4.15 g (0.044 mol) of 1,2-ethanedithiol in 80 ml of benzene was added *ca.* 50 mg of *p*-toluenesulfonic acid and the mixture refluxed for 2 hr, water being removed azeotropically by means of a Dean and Stark trap.[10] The reaction mixture was cooled and poured into a solution of sodium carbonate in deuterium oxide. The basic solution was extracted three times with 50-ml portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, concentrated, and distilled to give the ethylene dithioketal of phenylpentadeuteriopropanone, bp 104° (3 mm), yield 8.0 g (94%). The infrared spectrum was compatible with the assigned structure. Nmr spectrum: broad singlet 92.5 Hz (0.62 H) (3 H in undeuterated species, hence 79% D at C-3), multiplet 167–203.5 Hz (4.64 H; 0.64 H attributed to C_1 position) (6 H in undeuterated species, hence 68% D at C-1), multiplet 420–444.5 Hz (5 H).

B.—The ethylene dithioketal of phenylpentadeuteriopropanone was reduced and the reaction mixture worked up according to the procedure for 2-methyl-2-benzyl-1,3-dithiolane (method A). Distillation of the neutral fraction afforded 1-phenylpropane-1,1,3,3,3-d_5: bp 55.5° (20 mm); nmr spectrum multiplet at 38.5–63 Hz (0.63 H) (3 H in undeuterated species, hence 79% D at C-3), broad singlet at 90.5 Hz (2 H), multiplet at 137–160.5 Hz (0.59 H) (2 H in undeuterated species, hence 70% D at C-1), singlet at 424.5 Hz (5 H).

Reduction of 2-(2-Phenylthio)ethanethiol and 2-Methylthioethanethiol.—The conditions of method A were used, starting with 5.95 g (0.030 mol) of $C_6H_5CH_2SCH_2CH_2SH$ and employing an excess of calcium (*ca.* 1.97 g, 0.049 g-atom). The work-up was as in method B (partition between ether and aqueous KOH).

(17) To determine the optimum amount of calcium to be used, 5.23 g (0.030 mol) of 2-cyclohexyl-1,3-dithiolane was similarly treated, adding small portions of calcium, slowly, till a permanent blue color resulted. This required 1.31 g of calcium, thus a 10% excess of Ca seems desirable.

(18) A. C. Cope and D. M. Gale, *J. Amer. Chem. Soc.*, **85**, 3747 (1963).

The neutral fraction, upon distillation, afforded 2.08 g (65%) of ethylbenzene, bp 134–135° (745 mm), whose infrared spectrum was identical with that of an authentic sample. The acidic fraction, 4.11 g of a yellow oil, was shown by iodine titration[9] to contain 93% of mercaptan calculated as 1,2-ethanedithiol. Distillation gave 2.45 g (86%) of ethanedithiol, bp 59° (33 mm), identified by infrared spectrum.

Similar reduction of 2.74 g (0.025 mol) of $CH_3SCH_2CH_2SH$ with 1.61 g of calcium yielded 94% of mercaptan,[9] isolated in 79% yield [1.98 g, bp 59.5–60° (34 mm)] identified as 1,2-ethanedithiol by infrared spectrum.

2-Phenylethyl-1-*d* *p*-Toluenesulfonate.—2-Phenylethanol-1-*d* was prepared by LAD reduction of the aldehyde[19] in 95% yield: bp 67° (0.6 mm); $n^{20}D$ 1.5317 [lit.[19] bp 55–57° (0.7 mm), $n^{20}D$ 1.5315)]; nmr spectrum doublet at 160 Hz (J = 7 Hz, 2 H), triplet at 214.5 Hz (J = 7 Hz, 1 H), singlet at 224.5 Hz (1 H), singlet at 425.5 Hz (5 H). The *p*-toluenesulfonate was prepared in the usual manner[19–21] from 10 g of *p*-toluenesulfonyl chloride dissolved in 15 ml of pyridine added to 5.45 g of the alcohol in 10 ml of pyridine at −10°. The mixture was left at 0° for 3 hr before work-up and yielded 10.94 g (89%) of the *p*-toluenesulfonate: mp 38–40° (lit.[19] 38–40°); nmr spectrum 138.5 Hz (s, 3 H), 169 Hz (d, J = 7 Hz, 2 H), 244.5 Hz (t, J = 7 Hz, 1 H), multiplet at 406.5–469 Hz (9 H).

Ethyl 2-Phenyl-1-monodeuterioethyl Sulfide.—A solution of 10.0 g (0.036 mol) or 2-phenyl-1-monodeuterioethyl tosylate in 20 ml of ether was treated with 45 ml of 6 *N* sodium hydroxide and 8.5 g (0.14 mol) of ethyl mercaptan at 25°, with constant stirring under nitrogen for 70 hr.[22] A further quantity of 7 g (0.11 mol) of ethyl mercaptan was then added and the reaction continued for an additional 50 hr. After the addition of 20 ml of water, the product was extracted with three 50-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated. By treatment with hexane, the crude product was divided into a hexane-soluble and a hexane-insoluble fraction. From the latter, by purification on neutral alumina, was obtained 4.37 g (44%) of unreacted tosylate. Distillation of the hexane-soluble extract afforded 2.51 g (42%) of the sulfide: bp 80° (0.8 mm); $n^{20}D$ 1.5411 [lit.[23] for the undeuterated species, bp 92–94° (3 mm); $n^{20}D$ 1.5420]; nmr spectrum 72 Hz (t, J = 7.5 Hz, 3 H), 146.5 Hz (q, J = 3.5 Hz, 2 H), 155–178 Hz (multiplet, 3 H), 427 Hz (s, 5 H).

Reduction of Ethyl 2-Phenyl-1-deuterioethyl Sulfide with Calcium in Ammonia.—Using method A, 1.67 g (0.01 mol) of $C_6H_5CH_2CHDSC_2H_5$ was reduced with 0.5 g (0.013 g-atom) of calcium in 100 ml of ammonia to give 0.76 g (71%) of 1-phenylethane-2-*d*: bp 44° (27 mm); $n^{20}D$ 1.4948; nmr spectrum 70 Hz (triplet of triplets, J_1 = 7.5 Hz, J_2 = 2 Hz, 2 H), 152.5 Hz (t, J = 7.5 Hz, 2 H), 425.5 Hz (s, 5 H).

Reduction of 2-Heptyl-1,3-dithiolane with Calcium in Ammonia.—Using method A, 2.87 g (0.015 mol) of 2-hexyl-1,3-dithiolane was reduced with 3.0 g (0.075 g-atom) of calcium in 300 ml of ammonia to give 2.84 g of semisolid crude material. A small aliquot (*ca.* 0.1 g) was removed and titrated for mercaptan content with iodine.[9] The yield of mercaptan was 51%. A similar aliquot was then removed and dissolved in 20 ml of absolute ethanol with 0.5 ml of 10 *N* hydrochloric acid and treated with 2 g of zinc amalgam. The decanted solution was again titrated for mercaptan content with iodine,[9] the yield of mercaptan now being 94%.

2-(1-Hydroxyethyl)-1,3-dithiane.[8]—To a solution of 7.25 g (0.060 mol) of 1,3-dithiane in 200 ml of tetrahydrofuran at −30°, stirred under nitrogen, was added 48 ml (0.061 mol) of a 1.27 *M* solution of *n*-butyllithium in hexane, at the rate of 2 ml/min. A clear yellow solution was obtained. After stirring for 1.5 hr at −30°, the solution was allowed to warm to −5°, 3.3 g (0.075 mol) of acetaldehyde was added, and the mixture was stirred for 14 hr at 0°, under nitrogen. It was then poured into 750 ml of water, acidified to pH 5–6, and extracted with five 150-ml portions of ether. The combined extracts were washed once with 50 ml of 2 *N* potassium hydroxide and dried over anhydrous magnesium sulfate, and the solvents evaporated to give 9.11 g of a clear yellow oil. Treatment with hexane afforded 8.15 g of a hexane-insoluble fraction and 0.6 g of a hexane-soluble fraction. From the latter was isolated *ca.* 0.4 g (6%) of unreacted 1,3-dithiane. Distillation of the hexane-insoluble fraction gave an additional 0.2 g (3%) of 1,3-dithiane and 6.39 g (65%) of crude 2-(1-hydroxyethyl)-1,3-dithiane, bp 90–98° (0.4 mm). The product was redistilled to afford 4.8 g of the pure material: bp 93° (0.55 mm); $n^{20}D$ 1.5759; nmr spectrum 79.5 Hz (d, J = 6 Hz, 3 H), 99.5–145 Hz (multiplet, 2 H), 145–183.5 Hz (multiplet, 4 H), 186 Hz (s, 1 H), 220.5–252.5 Hz, (multiplet, 2 H).

Anal. Calcd for $C_6H_{12}OS_2$: C, 43.86; H, 7.37. Found: C, 43.82; H, 7.51.

1-(3-Mercaptopropylthio)-2-propanol. 1.—Using method A, 2.40 g (0.015 mol) of 2-(1-hydroxyethyl)-1,3-dithiane was reduced with 0.8 g (0.02 g-atom) of calcium in 150 ml of ammonia to give 2.69 g of crude 1-(3-mercaptopropylthio)-2-propanol; yield by iodine titration,[9] 91%. Distillation afforded 2.00 g (83%) of pure product: bp 99.50 (0.6 mm); $n^{20}D$ 1.5318; nmr spectrum 72.5 Hz (d, J = 6 Hz, 3 H), 78.5 Hz (t, J = 7.5 Hz, 1 H), 94.5–126 Hz (multiplet, 2 H), 140.5–173 Hz (multiplet, 6 H), 204 Hz (s, 1 H), 228 Hz (sextet, J = 6 Hz, 1 H).

2.—To 21.7 g (0.2 mol) of 1,3-propanedithiol was added 1.0 g of 30% sodium hydride in mineral oil, under nitrogen, with stirring, at 25°. The mixture was cooled to 0° and 17 ml (0.24 mol) of propylene oxide added over 1 hr.[15] Stirring was continued for an additional hr at 0°, and then the reaction mixture acidified with 3% hydrochloric acid. The product was extracted with two 50-ml portions of ether and the combined ether extracts were washed with three 20-ml portions of water and then dried over anhydrous magnesium sulfate. The ether was removed and distillation gave 5.87 g (22%) of unreacted 1,3-propanedithiol, bp 77–78° (23 mm), and 14.1 g of a second fraction, bp 115–128° (0.8 mm). Some higher boiling material (6.54 g) remained. A solution of the second fraction in 100 ml of ether was extracted with three 50-ml portions of 5 *N* potassium hydroxide solution. The combined extracts were acidified with 200 ml of 5 *N* hydrochloric acid and extracted with three 100-ml portions of ether. After drying over anhydrous magnesium sulfate, concentration yielded 12.1 g (36%) of crude 1-(3-mercaptopropylthio)-2-propanol. Distillation afforded 11.5 g (34%) of the pure product, bp 99° (0.5 mm), $n^{20}D$ 1.5321, having infrared and nmr spectra identical with those for the product obtained above.

Anal. Calcd for $C_6H_{12}OS_2$: C, 43.33; H, 8.48. Found: C, 43.11; H, 8.56.

2-(Cyclohexylthio)ethanethiol.—To a solution of 9.9 g (0.085 mol) of cyclohexyl mercaptan in alcoholic sodium ethoxide (1.6 g of sodium and 75 ml of ethanol) at 0° was added, dropwise, 3.3 g (0.055 mol) of ethylene sulfide at −10°. The reaction mixture was allowed to warm to 25° over a period of 40 min, 250 ml of 5% acetic acid then added, and the product extracted with three 50-ml portions of anhydrous ether. After drying over anhydrous magnesium sulfate, concentration left 12.9 g of an oil. Distillation afforded 4.48 g (46%) of crude 2-(cyclohexylthio)ethanethiol, bp 71–78° (0.08 mm). Redistillation gave 3.3 g (34%) of purer material, bp 84–85° (0.5 mm), $n^{20}D$ 1.5419, whose infrared spectrum was identical with that of the product prepared from the calcium–ammonia reduction of 2-cyclohexyl-1,3-dithiolane.

Registry No.—2-Phenylethyl-1-*d* *p*-toluenesulfonate, 26718-12-7; ethyl 2-phenyl-1-monodeuterioethyl sulfide, 26785-76-2; 1-phenylethane-2-*d*, 1861-04-7; 2-(1-hydroxyethyl)-1,3-dithiane, 14947-48-7; 1-(3-mercaptopropylthio)-2-propanol, 26718-15-0; 2-(cyclohexylthio)-ethanethiol, 10160-81-3.

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Organic Disulfides and Related Substances. XXX. Preparations and Reactions of Mercaptoterephthalic Acids and Derivatives[1]

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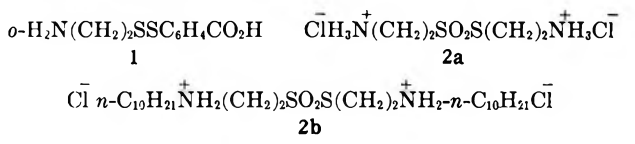
2,5-Dimercaptoterephthalic acid was prepared by four routes to permit assessment of their relative merits for a bifunctional system and to permit confirmation of structures of useful intermediates through interconnections of the routes (Scheme I). The routes were: (I) conversion of the phenol to the *O,O*-bisthiocarbamate, rearrangement of this to the *S,S*-bisthiocarbamate, then saponification; (II) cleavage of 2,5-bisbenzyl thioether moieties of the terephthalate diester, then saponification; (III) reaction of potassium hydrosulfide with 2,5-dibromoterephthalic acid; and (IV), route II but with the acid instead of the ester. 2-Mercaptoterephthalic acid was prepared by similar routes for the same reasons. Both the mono- and dimercapto acids reacted with aminoalkyl thiolsulfonates to give unsymmetrical aminoalkyl disulfides (Scheme II). Several products of Schemes I and II are of interest for further chemical studies and, particularly, for biological evaluation as antiradiation drugs, against histoplasmosis, or against schistosomiasis.

Mercaptoterephthalic acids were desired for two reasons: (1) *o*-(2-Aminoethyldithio)benzoic acid (**1**) and



o-$H_2N(CH_2)_2SSC_6H_4CO_2H$ (**1**)

$Cl^-H_3\overset{+}{N}(CH_2)_2SO_2S(CH_2)_2\overset{+}{N}H_3Cl^-$ (**2a**)

$Cl^-\ n\text{-}C_{10}H_{21}\overset{+}{N}H_2(CH_2)_2SO_2S(CH_2)_2\overset{+}{N}H_2\text{-}n\text{-}C_{10}H_{21}Cl^-$ (**2b**)

related compounds have shown activity as antiradiation drugs.[2a-c] Bis and 4-carboxy analogs of **1** were needed for assessing the effects that structural changes of these kinds would have on antiradiation activity and toxicity. Furthermore, arenethiols and aryl disulfides seem promising classes for testing against *Histoplasma capsulatum*,[2d] the causative organism of histoplasmosis, and possibly against schistosomiasis.[2e] Since **1** was prepared by thioalkylating *o*-mercaptobenzoic acid with the thiolsulfonate **2a**,[2a] the use of **2a** and **2b** with 2,5-dimercaptoterephthalic acid and 2-mercaptoterephthalic acid (**12** and **15**, respectively, of Scheme I) seemed likely to give bis and 4-carboxy analogs of **1** (**23**–**25** of Scheme II). (2) The 1,4-benzenedithiol system has quite interesting chemical possibilities. Oxidation of 2,5-dimercaptoterephthalic acid or its ester (**12** and **19** of Scheme I) might give thioquinones, tetrathia[2.2]paracyclophanes, or polymers; Parekh and Guha oxidized 1,4-benzenedithiol to a solid they thought might be tetrathia[2.2]paracyclophane, but the insolubility of their product also suggests it may have been polymeric.[3] Furthermore, reaction of 1,4-diethoxybenzene with sulfur monochloride gave a large-ring crystalline polysulfide,[4] which has attracted considerable interest;[4b] **12** should afford further entries into such systems.

Scheme I shows approaches to the synthesis of 2,5-dimercaptoterephthalic acid (**12**) and 2-mercaptoterephthalic acid (**15**) by four routes, I–IV. Interconnections between routes I–IV, made primarily to buttress the structure of intermediates, also provide conversions useful for connecting the routes during other work with mercaptoarenecarboxylic acids. The four routes are: (I) conversion of phenols to thiophenols *via* thiocarbamates; (II) cleavage of benzyl (alkoxycarbonyl)aryl sulfides; (III) reaction of potassium hydrosulfide with bromoterephthalic acids; and (IV) cleavage of benzyl carboxyaryl sulfides.

2,5-Dibromoterephthalic acid (**3**) was the starting material for all routes. For preparation of **3**, oxidation failed of 2,5-dibromo-*p*-xylene with nitric acid[5] and with potassium dichromate in sulfuric acid[6] or acetic acid. Oxidation of *p*-xylene with bromine[7] or of 2,5-dibromo-*p*-xylene with permanganate gave **3**, but in low yield. Sodium dichromate,[8] however, oxidized 2,5-dibromo-*p*-xylene to acid **3** in yields of 57–64%.

Route I.—Route I was the best of the four for the preparation of dithiol **12**. After the salt of acid **3** (from **3** in ethanolic sodium ethoxide, 97%) had been heated with sodium acetate and copper powder, acidification gave 2,5-dihydroxyterephthalic acid (**4**, 97% yield),[9] which was converted to the diester **5** (57% yield);[10] substitution of the commercially available 2,5-dichloroterephthalic acid led only to diethyl 2,5-dichloroterephthalate.

A modification of the elegant conversion of Newman and Karnes of phenols to thiophenols[11] next was used. The dihydroxy ester (**5**) gave the *O,O*-bisthiocarbamate **6** in 88% yield; **6** had ir bands characteristic for C(=S)N and C(=S) and two nmr singlets for NMe_2 (δ 3.43, 3.48). The rearrangement of **6** to the *S,S*-bisthiocarbamate **13** went smoothly at 230° (76%); higher temperatures led to unnecessary decomposition. The

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(1) (a) Paper XXIX: N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts No. DA-49-193-MD-2030 and DADA17-69-C-9128. (c) Abstracted from the Ph.D. Dissertation of P. R. E. (Vanderbilt University, May 1970), which may be consulted for further details. (d) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967.

(2) (a) R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965). (b) L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970); the "proto" nomenclature used for **1** and analogs in this earlier paper was less well adapted to the present paper. (c) L. Field and H. K. Kim, *ibid.*, **9**, 397 (1966). (d) I. McVeigh, Z. Evans, L. Field, and W. Hanley, *Mycopathol. Mycol. Appl.*, **37**, 349 (1969). (e) We are indebted to Dr. E. A. Steck of the Walter Reed Army Institute of Research for this suggestion.

(3) V. C. Parekh and P. C. Guha, *J. Indian Chem. Soc.*, **11**, 95 (1934).

(4) (a) Z. S. Ariyan and R. L. Martin, *Chem. Commun.*, 847 (1969). (b) *Cf. Chem. Eng. News*, **47** (No. 48), 40 (Nov 17, 1969).

(5) *Cf.* A. Eckert and F. Seidel, *J. Prakt. Chem.*, **102**, 338 (1921).

(6) *Cf.* R. Fittig, W. Ahrens, and L. Mattheides, *Justus Liebigs Ann. Chem.*, **147**, 15 (1868).

(7) J. E. McIntyre and D. A. S. Ravens, *J. Chem. Soc.*, 4082 (1961).

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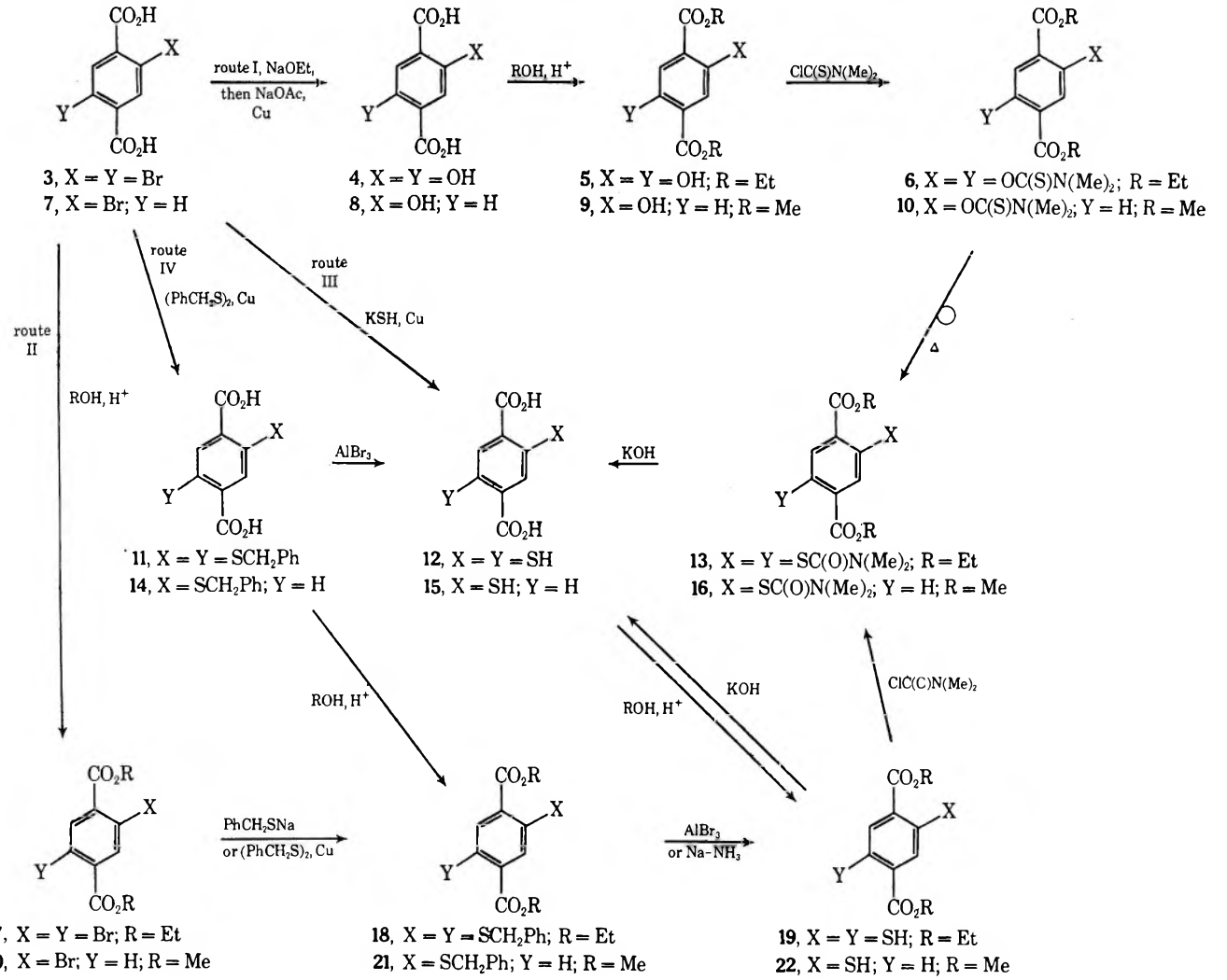
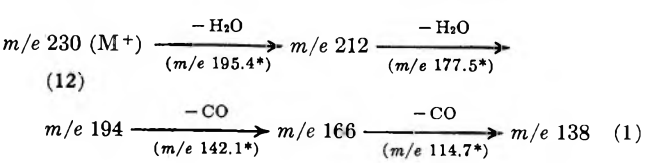
SCHEME I



S,S-bisthiocarbamate **13** had an ir band typical of an amide and only an nmr singlet for NMe_2 (δ 3.1, two nmr peaks for the *N*-methyl groups of *O*-aryl compounds, but only one for those of *S*-aryl compounds, were observed previously).[11]

The last step in route I was saponification of **13** to the dithiol **12**. Newman and Karnes effected saponification of *S*-aryl thiocarbamates in hot aqueous methanol under nitrogen, but, when **13** was similarly heated for 9 hr (when iodine uptake became constant), the product appeared to be oxidized **12**, iodine titration indicating that only one thiol group of **12** had survived. Eventually, we learned that heating of the *S,S*-bisthiocarbamate **13** with potassium hydroxide (in slight excess of six molar proportions) at 120–130° for 20 min would give the dithiol **12** in 100% yield. This rather critical time of heating was determined by titrating aliquots with acid until a plot of acid consumption reached a minimum; after 20 min the acid increased, suggesting that oxidation was taking place.

The structure of **12** was confirmed by iodine titration. The ir spectrum was consistent. The nmr spectrum, done in *N,N*-dimethylacetamide (DMA) because of sparing solubility in the usual solvents, showed a singlet (δ 8.2) for the ring protons, with the acid and thiol protons either obscured in the base line or buried beneath the solvent peaks; exchange with D_2O, however, led to a peak at δ 4.8 for HOD and a 2:1 ratio for the integrals at δ 4.8 and 8.2 which supported the dithiol structure for **12**. The mass spectrum of **12** showed the molecular ion at *m/e* 230, with peaks and metastables (*) consistent with the events formulated in eq 1; *o*-



mercaptobenzoic acid shows similar behavior.[12] Consistent with the strong yellow color of **12** (and of about a third of the other compounds in Schemes I and II) is a low order of absorption of **12** at 435–470 nm (**12** also had λ_{max} at 276 and 375 nm).

Toward the preparation of the monomercapto acid **15** by route I, sodium 2-bromoterephthalate gave 2-hydroxyterephthalic acid (**8**, 99%), which was converted to the ester **9** (77% yield; the dimethyl ester was used because it was known).[13] *N,N*-Dimethylthiocarbamoyl chloride converted **9** to the monothiocarbamate **10**. Although **10** did not precipitate as had the bisthiocarbamate **6**, addition of water gave a 92–97% yield, but the

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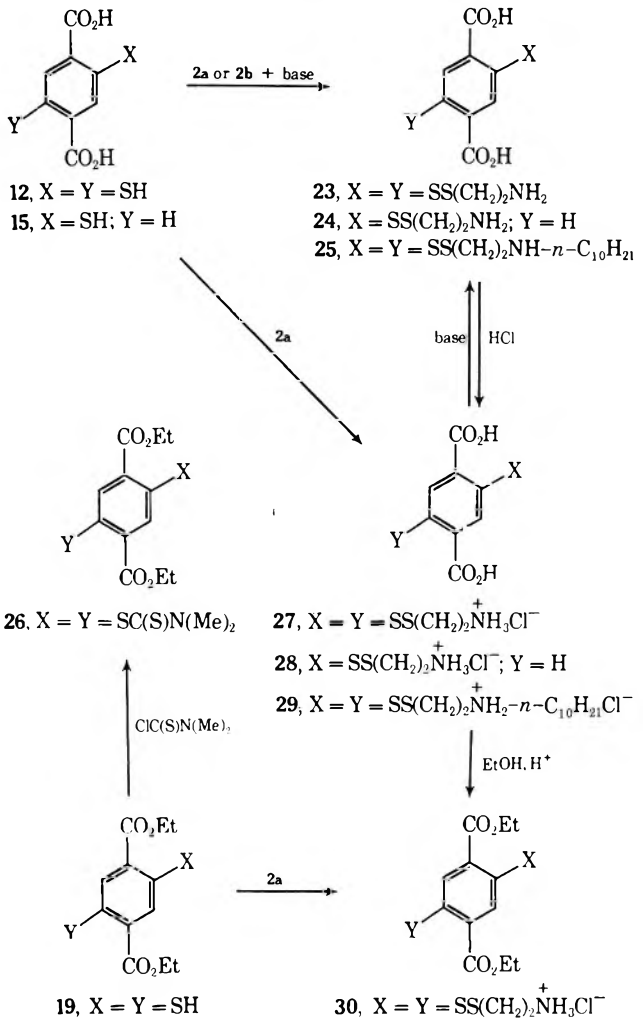
(13) R. Wegscheider and K. Bittner, *Monatsh. Chem.*, **21**, 638 (1900).

SCHEME II



carbamoyl chloride then had to be removed by recrystallization. The ir spectrum of **10** indicated C(=S)N and C(=S), and the nmr spectrum again showed two singlets (δ 3.42, 3.47). Rearrangement of **10** to **16** was accomplished as with **6**. Conversion of **16** to the acid **15** was not tested because **16** was not obtained completely pure and because by this time route II to **15** was considered better than route I; the successful conversion of **13** to **12** suggests that conversion of **16** to **15** should present no difficulties.

Route II.—In route II to the dithiol **12** and thiol **15** bromine atoms were replaced with benzyl thioether moieties, and the benzyl groups then were removed. Preparation of the benzyl sulfides **18** and **21** by the usual use of cuprous phenylmethanethiolate with the bromo esters **17** and **20** was precluded because, unlike other cuprous thiolates, cuprous phenylmethanethiolate decomposes into benzyl sulfide and stilbene before reacting with an aryl halide.[14] We therefore turned to two procedures of Campbell.[15,16] The first involves direct action of a disulfide on an aryl halide in the presence of copper[15] and the second heating of an alkali-metal thiolate with the halide.[16] When the dibromo diester **17** was heated with benzyl disulfide and copper, yields of the bisbenzyl sulfide **18** were 29–33% and, on a larger scale, even dropped to 5%. As a prelude to the more promising second approach, the stability of sodium phenylmethanethiolate in DMA was tested. At 100°, the solution soon darkened and, after 7 hr, failed to decolorize iodine. Hence the ester **17** and the thiolate were heated only at 75° (24 hr); the yield of **18** was 50%. Substitution of the commercially available 2,5-dichloroterephthalic acid (same molar proportions) for **3** in route II led to **18** in overall yields nearly as good as those from **3**.

Removal of the benzyl groups of **18** was accomplished in two ways. Use of sodium in liquid ammonia[17] gave **19**, which decolorized iodine and had appropriate ir and nmr spectra, but no way could be found to purify it. Hence cleavage with aluminum bromide in dry toluene was used.[18] Ultimately, **18** was cleaved thus to the dithiol **19** in 76% yield; substitution of chlorobenzene[19] for toluene resulted in a yield of 60%. In early work, the ir spectrum of crude **19** showed the presence of both carboxyl and benzyl groups, suggesting partial hydrolysis of the ester and incomplete cleavage of the sulfide. Purification of the aluminum bromide[20] failed to prevent the hydrolysis (but even so is desirable because it leads to purer thiol), but predistillation of the toluene from phosphorus pentoxide did so.

The structure of the dimercapto diester **19** was confirmed by ir absorption for SH, by iodine titration, and by the mass spectrum. The mass spectrum is consistent with the events of eq 2, which resemble those of

$$m/e\ 286\ (M^+) \xrightarrow[(m/e\ 201.4^*)]{-\text{EtOH}} m/e\ 240 \xrightarrow[(m/e\ 156.8^*)]{-\text{EtOH}} \underset{(19)}{} \quad m/e\ 194 \xrightarrow[(m/e\ 142.1^*)]{-\text{CO}} m/e\ 166 \xrightarrow[(m/e\ 114.7^*)]{-\text{CO}} m/e\ 138 \quad (2)$$

eq 1 for the diacid **12**; similar behavior has been reported for methyl *o*-mercaptobenzoate.[12] For further substantiation, route II was connected with route I by converting the dimercapto diester **19** of route II to the *S*,*S*-bisthiocarbamate **13** (69%).

The final step in route II was saponification of **19** to the diacid **12** (quantitative yield); when saponification was incomplete, purification was very difficult. The overall yield of **12** from **3** by the four steps of route II was about 32%; although there is also a somewhat better yield, route I (overall yield from **3** about 36%) was recommended above, despite its six steps, mainly because all steps are easily done and the overall process seems easier.

Route II seems that of choice for preparation of the monomercaptoacid **15** because it is shorter than route I and involves products usually easier to purify (overall yield from **7**, 18%). For the preparation of **15** by route II, dimethyl 2-bromoterephthalate (**20**)[13] was converted to the sulfide **21** with sodium phenylmethanethiolate. Cleavage of **21** with aluminum bromide always gave both the diester **22** and acid, despite distillation of the toluene from phosphorus pentoxide and other precautions to exclude moisture and irrespective of the amount of aluminum bromide or of whether it was purified;[20] probably the unhindered 4-carboxylate moiety of **21** is more susceptible to attack by aluminum bromide

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(15) J. R. Cambell, *J. Org. Chem.*, **27**, 2207 (1962).
(16) J. R. Campbell, *ibid.*, **29**, 1830 (1964).
(17) A. Ferretti, *Org. Syn.*, **42**, 54 (1962).
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(19) D. S. Tarbell and D. P. Harnish, *ibid.*, **74**, 1862 (1952).
(20) C. F. H. Tipper and D. A. Walker, *J. Chem. Soc.*, 1352 (1959).

than the more hindered carboxylate moieties of **18**. Saponification of the mixture of monomercapto ester and acid gave the thiol **15** (55% from **21**).

Route III.—Route III to the dimercapto acid **12** involved the single reaction of eight molar proportions of potassium hydrosulfide with the dibromo acid **3** in the presence of copper. It was based on an early patent for synthesis of *o*-mercaptobenzoic acid.[21] We had avoided use of this deceptively simple route until information about **12** was available to permit its separation and identification. A principal complication which was foreseen was that equilibria of thiol moieties with potassium hydrosulfide would lead to metal thiolates of **12**, which could react with the aryl bromide to form bisaryl sulfides, oligomers, and polymers. In route III, the dibromo acid **3** gave a product which showed no Beilstein test and had an ir spectrum identical with that of **12** from route I. Tlc showed a series of spots, however, although the dominant one did have the R_f value of **12**. Iodine titration showed only 67% of the thiol content expected for **12**. Ethanol roughly separated fractions with iodine titers ranging from 60–90% of expectation for **12**. One fraction gave an elemental analysis consistent with **12**, had an iodine titer of 90%, and was confirmed as **12** by converting it to ester **19** (identical with **19** from route II). Route III thus does afford a one-step synthesis for dithiol **12** but, since it gives a grossly impure product, the longer routes are preferred.

Route III was even less promising for the monothiol **15** than for the dithiol **12**. Conditions identical with those used in the bis series (for **12** from **3**) converted the monobromo acid **7** to a product which showed only 55% of the thiol content expected for **15** (iodine titration). Tlc showed two spots, even after recrystallizations, suggesting the impracticability of purification.

Route IV.—In a procedure based on one of Campbell,[15] **3** gave two products, **11** and **14**. We at first thought it surprising that reduction to **14** occurred, when we had not observed reduction of the dibromo diester **17**; however, *o*-bromobenzoic acid is reduced by copper to benzoic acid although its ester is unaffected;[22a,23] in suitable instances the aryl halides themselves may act as hydrogen donors.[22b,23]

The dibenzyl sulfide (**11**) was separated from the monobenzyl one (**14**) by the sparing solubility of its salt in 10% KOH (the dipotassium salt of **11** will dissolve, however, in very dilute base). The structure of **11** was confirmed by converting it to **18** (47%). Attempts using aluminum bromide to cleave both benzyl groups from **11** to give **12** invariably led to mixtures containing nondebenzylated products, perhaps because the reaction mixture was heterogeneous; in route II (homogeneous reaction mixture), the ester **18** was cleaved smoothly to **19**. The mixture could not be purified, but mass spectrometry showed that acid **12** and acid **11** with one benzyl group remaining were present.

Attempts also were made to debenzylate the monosulfide **14** to **15** with sodium in liquid ammonia.[14] The **14** was readily soluble, but the product was difficult to purify. Aluminum bromide in toluene was equally unpromising, perhaps because of sparing solubility; again, intractable mixtures of **14** and **15** resulted. No pure dithiol **12** or monothiol **15** could be isolated by route IV.

Reactions of Thiols (Scheme II).—Uses made of the thiols are summarized in Scheme II. Of the bisdisulfides prepared, the most important to us was 2,5-bis(2-aminoethyldithio)terephthalic acid (**23**), the bis analog of **1**.

Although route III (*via* the hydrosulfide) gave impure **12**, there seemed a possibility that this **12** could be converted to **23**, which might be purified, so that route III would afford a two-step synthesis of **23**. Reaction of this impure **12** in 4 equiv of aqueous alkali with thiosulfonate **2a** did indeed give bisdisulfide **23** (33%); use of **12** with 4 equiv of alkali will be referred to as route V. This **23** dissolved in acid and base, failed to decolorize iodine, and gave a negative nitroprusside test; later, it proved to be identical with **23** obtained by other routes. Use of route III thus *can* give a two-step synthesis of **23** from **3**. This **23** may be sufficiently pure for some purposes, but since it contained a persistent impurity which precluded a satisfactory elemental analysis the two-step advantage may be dubious.

Because of the low yield, conditions were tried such as those which were successful for **1**,[2a] but with DMF for ethanol (in which **12** is sparingly soluble) and DABCO for neutralization; such use of **12** in DMF with 4 mol of DABCO will be referred to as route VI. To test route VI, *o*-mercaptobenzoic acid and the thiolsulfonate **2a** were stirred for 4 hr in DMF–H_2O; neutralization of the homogeneous mixture with DABCO gave **1** in 60% yield. With pure dithiol **12** from route I, route VI gave the bisdisulfide **23** (85%), which could be purified nicely through its hydrochloride.

We felt that with this purer dithiol **12** from route I, the conditions of route V might produce further improvement; the yield of **23** became quantitative when route V was used, but the gain in yield was offset since analytically pure **23** again could not be obtained. Route VI, with purification *via* the hydrochloride, thus seems to be the best choice.

The product from the reaction of dithiol **12** with thiolsulfonate **2a** can hardly be other than bisdisulfide **23**. It dissolves in both dilute acid and base (but not in water), and formol titration gave a neutralization equivalent of 211 (calcd, 190). Furthermore (Scheme II), a dihydrochloride precipitated (93%) during the reaction of **12** with **2a** identical with **27** prepared from **23** (mentioned below). The ir spectrum of **23** met expectation (and resembled that of **1**). Neither **23** nor its salts were sufficiently soluble in D_2O for nmr analysis. Efforts to obtain a mass spectrum of **23** or **27** resulted in thermal decomposition.

In the synthesis of the 4-carboxy analog (**24**) of disulfide **1** a new problem arose; the second carboxyl group was not neutralized by an amine moiety. The reaction of monothiol **15** with thiolsulfonate **2a**, essentially by route VI, gave **24** in 24% yield. In an improvement (route VII, minimum DMF), the yield was increased to 67%. Compound **24** had ir absorption consistent with both carboxyl and carboxylate functions.

(21) L. Cassella and Co., Ltd., German Patent 189,200 (1906); *Chem. Abstr.*, **2**, 607 (1908).

(22) (a) W. R. H. Hurtley, *J. Chem. Soc.*, 1870 (1929). (b) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev. (London)*, **19**, 110 (1965).

(23) We are indebted to Professor Joseph F. Bunnett of the University of California, Santa Cruz, for bringing the work of ref 22 to our attention.

Also prepared from dithiol **12** was an analog of **23** with *n*-decyl groups on the nitrogen atoms (**25**); **25** was desired for testing for the same reason as an earlier *n*-decyl analog of **1**.[2a] The chief synthetic problem was that the requisite thiolsulfonate (**2b**) is virtually insoluble in water and DMF. It was circumvented, in a modification of route VI, by dissolving **2b** in ethanol–methylene chloride (66% yield).

The hydrochlorides **27**, **28**, and **29** were obtained from the presumed zwitterionic structures **23**, **24**, and **25**, respectively, by treating aqueous slurries with hydrochloric acid (Scheme II). Dihydrochloride **27** was more soluble than its parent (**23**) and was purified by dissolution in methanol, filtration, and precipitation with ether. Hydrochloride **28** could be purified by recrystallization from ethanol. When **29** was heated in ethanol, however, **25** soon precipitated, and attempted dissolution in ethanol even without heating still resulted in **25**; **29** could not be purified as such.

The ester **30** of the key carboxy bisdisulfide **23**, of interest for comparison biologically with the ester of **1**,[2a] was also sought because its synthesis from both **23** and **19** would further confirm the structure of **23**. Acid **27** gave ester **30**. In the independent synthesis, **19** was treated with thiolsulfonate **2a**. For its isolation, **30** was converted to the free base, which was extracted with chloroform and then quickly reextracted into acid, because such bases usually are quite subject to disproportionation to the two symmetrical disulfides. Compound **30** was identical in ir and tlc behavior (one spot) with **30** obtained from **27**.

Since the dihydrochloride **27** had precipitated directly in the reaction of **12** with **2a**, the possibility was tested that **30** also might precipitate directly in the reaction of **19** with **2a** and thus provide a simpler preparation; **30** did indeed so precipitate, but only in 26% yield.

Since a number of dithiocarbamates are active as antiradiation drugs,[24] the bisdithiocarbamate **26** also was of interest. As Scheme II shows, dithiol **19** gave **26** (41% yield).

Evaluations are in progress at the Walter Reed Army Institute of Research, Washington, D. C., for antiradiation drug activity (thus far, **27** has shown LD_{50} > 450 mg/kg and inactivity at 75–150 mg/kg; *cf.* ref 2b for procedures) and also for inhibition of schistosomiasis. Tests for inhibition of *Histoplasma capsulatum in vitro* are being performed by Dr. Ilda McVeigh of the Department of General Biology, Vanderbilt University;[2d] thus far, **12** and **19** have proved inactive.

Experimental Section[25]

Starting Materials.—2,5-Dibromo-*p*-xylene[26] and 2-bromoterephthalic acid (**7**)[27] were purchased and also were prepared by the procedures cited in respective yields of 59% and 71%; 2,5-dihydroxyterephthalic acid (**4**, 97%),[9] diethyl 2,5-dihydroxyterephthalate (**5**, 57%),[10] diethyl 2,5-dibromoterephthalate (**17**, 83%),[28] benzyl disulfide (method I of ref 29), dimethyl 2-hydroxyterephthalate (**9**, 77%),[13] and dimethyl 2-bromoterephthalate (**20**, 94%)[13] were prepared by the procedures cited; properties agreed well with those reported. Sodium phenylmethanethiolate was freshly made by adding α-toluenethiol to a 1.0 molar proportion of NaOEt (from Na in absolute EtOH protected by a soda lime trap) and removing excess EtOH (a wash of Et_2O then removed any disulfide formed), and KSH was prepared by saturating an aqueous solution of KOH with H_2S, removing H_2O, and washing with EtOH and then Et_2O. The $AlBr_3$ was purified as described,[20] was broken up and stored over P_2O_5, and was weighed in a nitrogen-filled glove bag. Toluene used in cleavages with $AlBr_3$ was a technical grade dried by distillation from P_2O_5. The following were used as purchased: *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), diethylene glycol (Chromatoquality), Cu powder (150 mesh), *N*,*N*-dimethylcarbamyl, and thiocarbamoyl chlorides, 1,4-diazabicyclo[2.2.2]-octane (DABCO), and 2-bromo-*p*-xylene. Thiolsulfonate **2a** was prepared as before,[30] and thiolsulfonate **2b** was kindly provided by Dr. E. A. Steck of the Walter Reed Army Institute of Research.

2,5-Dibromoterephthalic Acid (3).—In a procedure based on one of Friedman, Fishel, and Shechter,[8] 2,5-dibromo-*p*-xylene (17.16 g, 65 mmol), sodium dichromate dihydrate (46.50 g, 156 mmol), and H_2O (186 ml) were sealed in a Magne-Drive autoclave and were heated at 250° for 5 hr. The mixture was filtered, and the chromic oxide was washed with H_2O until the filtrate was colorless. The filtrates were combined, treated with decolorizing carbon, filtered, and acidified with 6 *N* HCl to precipitate colorless **3**, yield 11.96 g (57%), mp 315–318° (lit.[31] mp ~320°); material of this quality was used. Recrystallization from glacial HOAc gave 7.69 g (37% overall), mp 317–318°.

Larger scale preparations were carried out by E. I. DuPont de Nemours and Co. through the kindness of Dr. R. G. Downing. Optimum conditions seemed to be with 0.9 mol of dichromate and 0.3 mol of dibromoxylene in 560 g of H_2O at a temperature of 230° for 10 hr (59–64% conversion of the 2,5-dibromo-*p*-xylene). At 280° for 5 hr, degradation occurred; our conditions reportedly gave somewhat lower yields and less pure product.

Two other methods gave **3** only in very low yield. The reaction of Br_2, water, and *p*-xylene (sealed tube, 180°, 2 hr)[7] gave **3** in 12% yield, mp 317–318°, and oxidation of 2,5-dibromo-*p*-xylene with $KMnO_4$ using the Morton high-speed stirring technique[32] gave **3** in 16% yield, mp 318–320°.

2-Hydroxyterephthalic Acid (8).—In method based on that for **4**,[9] disodium 2-bromoterephthalate (13.01 g, 45 mmol, prepared by neutralizing the acid **7** and removing water completely), sodium acetate (8.12 g, 99 mmol) and Cu powder (0.0572 g, 0.9 mg-atom) were placed in H_2O (206 ml) with a little phenolphthalein solution. The mixture then was heated at reflux for ~10 hr. It slowly became acidic, and 5% aqueous KOH was occasionally added dropwise to maintain *ca.* pH 8. During the last hour of reflux, the solution remained basic. The alkaline solution then was filtered and was acidified with 10% HCl until precipitation of **8** as white solid was complete, yield of **8**, 8.13 g (99%), mp 320–322° dec (lit.[33] mp >330°).

1,4-*O*,*O*-2,5-Bis(ethoxycarbonyl)phenylene Bis(*N*,*N*-dimethylthiocarbamate) (6) and 1-*O*-2,5-Bis(methoxycarbonyl)phenyl *N*,*N*-Dimethylthiocarbamate (10).—Diethyl 2,5-dihydroxytereph thalate (**5**, 0.51 g, 2 mmol), DABCO (1.35 g, 12 mmol), and *N*,*N*-dimethylthiocarbamoyl chloride (1.48 g, 12 mmol) were stirred in DMF (9 ml) for 30 min. White solid which precipitated was washed with H_2O to remove DMF and amounted to 0.755 g (88%) of **6**, mp 206–209°. Recrystallization from absolute EtOH gave colorless **6** with a constant mp of 210–211°: ir

(24) L. Field and J. D. Buckman, *J. Org. Chem.*, **33**, 3865 (1968).

(25) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were obtained using a Beckman Model IR-10 with KBr pellets; bands reported were of at least medium intensity unless w (weak) is indicated. Nmr spectra were obtained using a Varian Model A-60 spectrometer (TMS). Mass spectra were kindly determined by C. T. Wetter at 70 eV using the direct inlet system on an LKB Model 9000 instrument, which was obtained through NSF Science Development Program Grant GU-2057. Moist extracts were dried using anhydrous $MgSO_4$, and solvents then were evaporated under reduced pressure with a rotary evaporator. Tlc was done on polyamide (Brinkman MN-Polygram 66 10 12) using AcOH or on silica gel (Eastman Chromagram 6060) with benzene, CH_2Cl_2, 95% EtOH, or 95% EtOH–H_2O–NH_4OH (25:3:4), with location of spots by a uv lamp or by I_2 vapor.

(26) P. Ruggli and F. Brandt, *Helv. Chim. Acta*, **27**, 274 (1944).

(27) S-H. Yen, *Chlorine Alkali News*, **11**, 44 (1953); *Chem. Abstr.*, **49**, 7523 (1955).

(28) A. S. Wheeler and E. W. Constable, *J. Amer. Chem. Soc.*, **45**, 1999 (1923).

(29) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *ibid.*, **73**, 3627 (1951).

(30) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *ibid.*, **83**, 4414 (1961).

(31) A. Claus and C. Wimmel, *Ber.*, **13**, 902 (1880).

(32) A. A. Morton, B. Darling, and J. Davidson, *Ind. Eng. Chem., Anal. Ed.*, **14**, 734 (1942).

(33) H. Fischli, *Ber.*, **12**, 615 (1879).

(KBr) 1720, 1545 [C(S)N],[34] 1385, 1255, 1180 [-C(S)-],[34] and 870 (w) cm^{-1}; nmr ($DCCl_3$) δ 1.33 (t, 6), 3.43 (s, 6), 3.48 (s, 6), 4.3 (q, 4), and 7.78 (s, 2).

Anal. Calcd for $C_{18}H_{24}N_2O_6S_2$: C, 50.45; H, 5.65; N, 6.54; S, 14.96. Found: C, 50.35; H, 5.68; N, 6.64; S, 14.93.

When DABCO was added to a solution of 2,5-dihydroxyterephthalic acid (4) in DMF, a solid precipitated (probably the salt of 4). Addition of *N,N*-dimethylthiocarbamoyl chloride to this mixture, followed by heating at 70° for 5 hr, failed to give the acid of 6.

Much the same procedure used for 6 converted the monohydroxy diester 9 to its thiocarbamate 10: dimethyl 2-hydroxyterephthalate (9, 2.48 g, 12 mmol), DABCO (4.04 g, 36 mmol), and *N,N*-dimethylthiocarbamoyl chloride (4.44 g, 36 mmol) were stirred in DMF (18 ml) at ~25° for 5 hr. The homogeneous mixture then was poured into H_2O (72 ml) to precipitate yellow 10, yield 3.30 g (94%), mp 80–105°. Two recrystallizations from MeOH gave colorless 10: yield 2.03 g (58%); constant mp 113–114°; ir (KBr) 1720, 1540 [C(S)N],[34] 1400, 1280, 1240 [-C(S)-],[34] 1110, 890 (w), and 820 (w) cm^{-1}; nmr ($DCCl_3$) δ 3.42 (s, 3), 3.47 (s, 3), 3.85 (s, 3), 3.93 (s, 3), 7.78 (m, 1), and 8.0 (m, 2).

Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71; S, 10.78. Found: C, 52.92; H, 5.29; N, 4.80; S, 10.66.

1,4-*S,S*-2,5-Bis(ethoxycarbonyl)phenylene Bis(*N,N*-dimethylthiocarbamate) (13) and 1-*S*-2,5-Bis(methoxycarbonyl)phenyl *N,N*-Dimethylthiocarbamate (16).[35] A. *S,S*-Bisthiocarbamate (13) from *O,O*-Bisthiocarbamate 6 (Route I).—Compound 6 (9.25 g, 22 mmol) was heated neat at 230° for 30 min (Wood's metal). Cooling gave 9.00 g (97%) of 13, mp 107–140°. One recrystallization from absolute EtOH gave 7.07 g (76%), mp 135–145°, and further recrystallization gave white 13 with a constant mp of 143–146° (on a large scale, 6 and 13 were less soluble in EtOH and were recrystallized from benzene): ir (KBr) 1710, 1660 [-SC(O)NR_2],[36] 1360, 1330, 1270 (w), 1220, 1130, 1095, 895 (w), and 860 (w) cm^{-1}; nmr ($DCCl_3$) δ 1.35 (t, 6), 3.08 (s, 12), 4.33 (q, 4), and 8.10 (s, 2).

Anal. Calcd for $C_{18}H_{24}N_2O_6S_2$: C, 50.45; H, 5.65; N, 6.54; S, 14.96. Found: C, 50.44; H, 5.74; N, 6.57; S, 14.80.

When the *O,O*-bisthiocarbamate (6) was heated at 280° for 30 min, the melt darkened; tar resulted. At 230° decomposition seemed slight.

B. The *S,S*-Bisthiocarbamate 13 from the Dimercapto Diester 19.—DABCO (0.335 g, 3 mmol) and 19 (0.143 g, 0.5 mmol) were dissolved in DMF (8 ml). A red solution and a precipitate quickly resulted. *N,N*-Dimethylcarbamyl chloride (~0.5 ml) was added rapidly with stirring. The solution became colorless, and white solid precipitated. Stirring was continued for 1 hr, and the solid then was collected by filtration. This solid, soluble in water, evidently was DABCO·HCl. Addition of H_2O (30 ml) to the filtrate and cooling gave 13 as white solid, yield 0.147 g (69%), mp 130–137°. One recrystallization from absolute EtOH gave 0.106 g (50%) of 13, mp 142–146°, identical in its ir spectrum with the 13 from A.

C. The *S*-Monothiocarbamate 16 from the *O*-Monothiocarbamate 10 (Route I).—In a procedure much like that of A, 10 (1.45 g, 4.9 mmol) was heated neat at 230° for 0.5 hr. An oil resulted (even after 5 days), but it solidified when rubbed under hexane, yield of 16 0.70 g (48%), mp 65–68°. This 16 was recrystallized from benzene, then twice from MeOH–H_2O, to give colorless 16 having a constant mp 67–68°. Analysis indicated the presence still of a persistent impurity (Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71; S, 10.78. Found: C, 53.34; H, 5.05; N, 4.78; S, 11.63), so identification was made by the spectra: ir (KBr) 1730, 1665 [-SC(O)NR_2],[36] 1440, 1370, 1300, 1260, 1100, 1060, 870 (w), and 820 (w) cm^{-1}; nmr ($DCCl_3$) δ 3.05 (s, 6), 3.88 (s, 3), 3.92 (s, 3), and 8.08 (m, 3); mass spectrum *m/e* (rel intensity) 297 (31), 266 (18), 225 (13), 210 (8), 194 (7), 178 (6), 166 (3), 163 (4), 135 (12), 108 (5), 107 (6), 72 (100), 63 (12), and 42 (11).

Lower temperatures than 230° resulted in incomplete rearrangement and higher ones in unnecessary decomposition.

2,5-Dimercaptoterephthalic Acid (12) and 2-Mercaptoterephthalic Acid (15). A. Dimercapto Acid 12 from the *S,S*-Bisthiocarbamate 13 (Route I).—A 1.74 *N* solution (23.4 ml) of KOH in diethylene glycol was heated to 120–130°; 2.50 g (5.8 mmol) of 13 was added in one portion. The solution was heated under N_2 at 120–130° for 20 min; solid appeared. The solution was cooled and diluted with H_2O (234 ml), thus dissolving the solid. The solution was acidified with 10% HCl until precipitation of yellow solid was complete, yield of 12 1.35 g (100%), mp >350°. Titration with I_2 showed 90% of expectation for 2 SH groups; the ir spectrum showed this 12 to be of good quality and, owing to large losses on recrystallization, it was used as such for subsequent reactions. Two recrystallizations from glacial HOAc gave 0.146 g of deep yellow 12 (11%): mp >350°; ir (KBr) 3300–2500, 1680, 1480, 1410, 1300, 1250, 1090, 900, and 785 cm^{-1}; nmr as described in the discussion; mass spectrum *m/e* (rel intensity) 230 (32), 212 (45), 194 (100), 166 (25), 138 (15), and 69 (22); uv max (95% C_2H_5OH) 276 nm (ϵ 11,110), 375 (2722), and 435–470 (560–110, hence a yellow color);[37] tlc in HOAc on polyamide gave only one spot, R_f 0.39.

Anal. Calcd for $C_8H_6O_4S_2$: C, 41.73; H, 2.63; S, 27.85. Found: C, 41.86; H, 2.77; S, 27.47.

B. Dimercapto Acid 12 from Diester 19 (Route II).—Much as in A, 19 (1.43 g, 5 mmol) was placed in 17.82 ml of a 1.40 *N* solution of KOH in diethylene glycol at 120–130°. The solution was heated under N_2 (20 min) and then was diluted with H_2O (85 ml). Acidification with 10% HCl to pH 1 precipitated 12 of good quality (ir), yield 1.24 g (108%), mp >350°. Two recrystallizations from glacial HOAc gave 0.129 g (11%) of deep yellow 12, mp >350°; the ir spectrum and tlc in HOAc on polyamide were identical with those of 12 from A.

Anal. Calcd for $C_8H_6O_4S_2$: C, 41.73; H, 2.63; S, 27.85. Found: C, 41.97; H, 2.75; S, 27.87.

In two previous attempts to prepare diacid 12 from diester 19 impurity observed was believed (tlc) to be the monoester.

C. Dimercapto Acid 12 from Dibromo Acid 3 (Route III).—In a procedure based on one for *o*-mercaptobenzoic acid,[21] KSH (42.52 g, 589 mmol), Cu powder (0.609 g, 9.58 mg-atoms), and 3 (23.84 g, 73.6 mmol) were placed in diethylene glycol (136 ml); N_2 was bubbled through the mixture for 30 min to purge air. The stream of N_2 then was stopped, and the mixture was heated at 175° for 3 hr. It then was cooled. Water (1360 ml) was added, and the solution was treated with decolorizing carbon and filtered. The filtrate, acidified to pH 1, gave a yellow compound 12, 19.09 g (113%), mp >350°. The Beilstein test (hot copper wire) was negative (strongly positive for 3). Extraction of the crude 12 with 95% EtOH in a Soxhlet extractor gave seven fractions. Fraction 7, recrystallized twice from glacial HOAc, gave a deep yellow compound 12, mp >350°, identical in its ir spectrum and tlc behavior with 12 from A, iodine titer 90% of expectation for 12.

Anal. Calcd for $C_8H_6O_4S_2$: C, 41.73; H, 2.63; S, 27.85. Found: C, 42.10; H, 2.45; S, 27.80.

This procedure is not the best for the dimercapto acid 12 because the 12 is impure; the seven fractions varied in iodine titer from 60–90%. Attempts to separate pure 12 using benzylisothiuronium chloride or DABCO failed.

D. Monomercapto Acid 15 from Monomercapto Ester 22 (Route II).—In a procedure much like that in B, 22 (7.64 g, 33.8 mmol, somewhat crude as reported later for 22) was placed in 80 ml of a 1.40 *N* solution of KOH in diethylene glycol at 120–130°. The solution was heated as before, H_2O (400 ml) was added, and the solution was acidified with 10% HCl to pH 1 to precipitate 15 as cream-colored solid: yield 3.85 g (57%); mp >320°. This 15 by ir was of good purity and because of large losses on recrystallization was used for subsequent reactions; 0.734 g was recrystallized twice from glacial HOAc to give 0.188 g (26% yield) of a pale yellow compound 15: mp >320°; tlc on silica gel in 95% EtOH–H_2O–NH_4OH (25:3:4) gave one spot, R_f 0.27; ir (KBr) 3200–2300, 1675, 1480, 1410, 1260, 890, 775, and 745 cm^{-1}; mass spectrum *m/e* (rel intensity) 198 (20), 180 (100), 152 (8), 135 (36), 69 (8), and 45 (7).

Anal. Calcd for $C_8H_6O_4S$: C, 48.48; H, 3.05; S, 16.18. Found: C, 48.59; H, 3.12; S, 16.30.

Diethyl 2,5-Bis(benzylthio)terephthalate (18) and Dimethyl 2-(Benzylthio)terephthalate (21). A. The Bissulfide 18 from the Dibromo Ester 17 (Route II).—A mixture of sodium phenylmethanethiolate (6.43 g, 44 mmol) and 17 (8.36 g, 22 mmol) in DMA (83 ml) was heated at 75° for 24 hr. DMA was removed

(34) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 350.

(35) These procedures were based on the method of Newman and Karnes.[11]

(36) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 255.

(37) C. R. Noller, "Chemistry of Organic Compounds," W. B. Saunders, Philadelphia, Pa., 1965, p 737.

by vacuum distillation until a thick slurry remained. Benzene (100 ml) and H_2O (100 ml) were added, and the H_2O layer was extracted repeatedly with benzene until an extract was colorless. The benzene extracts were combined, dried, and concentrated to give **18**, yield 10.35 g (100%), mp 75–101°. Compound **18**, recrystallized from absolute EtOH, gave 5.17 g (50%), mp 137–140°. Further recrystallization gave yellow **18** with constant mp 140–142°; ir (KBr) 1710, 1460, 1370, 1300, 1225, 1075, 885 (w), 775, 710, and 690 cm^{-1}; nmr ($DCCl_3$) δ 1.35 (t, 6), 4.13 (s, 4), 4.35 (q, 4), 7.32 (m, 10), and 7.87 (s, 2); mass spectrum *m/e* (rel intensity) 468 (8), 467 (26), 92 (11), 91 (100), and 65 (13).

Anal. Calcd for $C_{26}H_{26}O_4S_2$: C, 66.92; H, 5.62; S, 13.74. Found: C, 66.93; H, 5.73; S, 13.58.

The ester was used instead of the sodium salt of acid **3** because the salt led to a solid that gave a positive Beilstein test and a negative sulfur test (sodium fusion) indicating little reaction. Reaction under the conditions of A of the known diethyl 2,5-dichloroterephthalate gave **18** in 29–46% yield, mp 137–140°, identical with that from **17** (ir).

B. The Diester 18 from the Bis(benzylthio) Acid 11.—A mixture of concentrated H_2SO_4 (1 ml) and crude **11** (41.0 mg, 0.1 mmol) in absolute EtOH (20 ml) was heated at reflux for 12 hr. The solution was neutralized with a KOEt solution to pH 7, and the EtOH was evaporated. The residue was extracted with Et_2O, and the solution was washed with H_2O. The Et_2O solution was dried and evaporated to give **18** as yellow solid, 22.0 mg (47%). One recrystallization from absolute EtOH gave 8.0 mg (17% overall) of **18**, mp 133.5–135°, identical in ir spectrum with the **18** from **17** and sodium phenylmethanethiolate.

C. The Monosulfide 21 from the Monobromo Ester 20 (Route II).—Much as in A, the bromo ester **20** (3.55 g, 13 mmol) and sodium phenylmethanethiolate (1.90 g, 13 mmol) in DMA (48 ml) were heated at 75° for 24 hr. DMA was removed, benzene and H_2O were added, and benzene extracts then were combined, dried, and evaporated to give 1.40 g of **21** (34%). Two recrystallizations from MeOH gave 0.415 g of colorless **21** (10% from **20**): constant mp 94–96°; ir (KBr) 1710, 1435, 1250, 1060, 850 (w), 810 (w), 740, 710, and 690 cm^{-1}; nmr ($DCCl_3$) δ 3.93 (s, 6), 4.22 (s, 2), 7.5–7.2 (m, 5), 7.84 (m, 1), 7.95 (m, 1), and 8.1 (m, 1); mass spectrum *m/e* (rel intensity) 316 (18), 285 (6), 284 (11), 225 (16), 92 (8), 91 (100), and 65 (9); tlc in benzene on silica gel gave a single spot, R_f 0.26.

Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10; S, 10.13. Found: C, 64.64; H, 5.19; S, 9.97.

Diethyl 2,5-Dimercaptoterephthalate (19) and Dimethyl 2-Mercaptoterephthalate (22). A. The Dimercapto Diester 19 from the Bisbenzyl Sulfide 18 (Route II).—A solution of $AlBr_3$ (0.59 g, 2.2 mmol) in dry toluene (10 ml) was placed in a 25-ml three-necked flask equipped with a drying tube ($CaCl_2$). Addition of **18** (0.467 g, 1 mmol) immediately led to a red precipitate. The mixture was heated at 60° for 6 hr with stirring. Water (1 ml) then was added to the cooled mixture during 30 min with stirring. Then more H_2O (1.5 ml) was added at one time, and the mixture was stirred for 20 min. The mixture was extracted with 5% aqueous KOH, and the basic solution was filtered into concentrated HCl, yield of **19** which precipitated 0.217 g (76%), mp 133–135°. Recrystallization from absolute EtOH gave yellow **19** having a constant mp 131–133°: ir (KBr) 2500, 1710, 1460, 1360, 1290, 1235, 1130, 1080, 1010, 890 (w), 860 (w), and 770 cm^{-1}; nmr [$D_3CC(O)CD_3$] δ 1.40 (t, 6), 4.40 (q, 4), 5.03 (s, 2), and 8.06 (s, 2); mass spectrum *m/e* (rel intensity) 286 (33), 240 (33), 194 (100), 166 (15), 138 (11), 95 (22), and 69 (19); titration with I_2, 99% for 2 SH moieties; uv max (95% C_2H_5OH) 276 (ϵ 12,110), 303 (1556), 378 (3110), and 435–450 nm (220–110, hence a yellow color).[37]

Anal. Calcd for $C_{12}H_{14}O_4S_2$: C, 50.33; H, 4.93; S, 22.39. Found: C, 50.17; H, 4.84; S, 22.50.

The toluene in the above reaction must be dry; otherwise hydrolysis of the ester groups leads to a mixture (containing acids and *S*-benzyl compounds) that is almost impossible to separate.

Bisbenzyl sulfide **18** (1.00 g, 2.14 mmol) also was cleaved with Na using liquid NH_3 (250 ml), which gave a heterogeneous mixture. Sodium (0.9 g, 39 mg-atoms) was added until the solution became blue and the blue color persisted for 30 min; NH_4Cl (0.79 g, 15 mmol) then was added. After evaporation of the NH_3, addition of H_2O, and acidification to pH 1, solid precipitated; extraction into Et_2O and evaporation gave 0.527 g (86%) of **19** as yellow semisolid; the ir (neat) and nmr spectra were essentially identical with those (ir, KBr) of the **19** formed with $AlBr_3$; addition of D_2O caused a nmr peak at δ 5.07 to disappear; **19** decolorized I_2.

B. The Dimercapto Diester 19 from the Diacid 12.—Concentrated H_2SO_4 (0.4 ml) and **12** (0.23 g, 1 mmol, from route III) were heated under reflux in absolute EtOH (8 ml) for 4 hr. The solution was cooled, neutralized with KOEt solution, and K_2SO_4 was separated by filtration. Evaporation of the filtrate gave 0.220 g (77%) of yellow **19**, mp 62–120°. One recrystallization from absolute EtOH gave 0.100 g (35%), mp 133–135° (ir spectrum identical with that of **19** obtained under A).

C. Monomercapto Diester 22 from Monobenzyl Sulfide 21 (Route II).—In essentially the procedure of A, **21** (0.95 g, 3 mmol) was heated in dry toluene containing $AlBr_3$ (1.76 g, 6.6 mmol) at 60° for 3 hr, the mixture was cooled, and H_2O (3 ml) was added (30 min) followed by 4.5 ml more of H_2O in one portion. The mixture was stirred for 20 min, Et_2O was added to dissolve solid, and the solution was extracted as before with 5% aqueous KOH. The basic extract was treated with decolorizing carbon and filtered, and the filtrate was acidified with 10% HCl to pH 1 to precipitate white **22**, yield 0.655 g (97%), mp 202–212°. The ir spectrum of this **22** indicated presence of carboxyl groups; since recrystallization from MeOH failed to give pure **22**, the mixture therefore was saponified directly to acid **15**.

2,5-Bis(benzylthio)terephthalic Acid (11) and 2-(Benzylthio)-terephthalic Acid (14) (Route IV).—Acid **3** (25.92 g, 80 mmol), benzyl disulfide (19.71 g, 80 mmol), and Cu powder (10.17 g, 160 mg-atoms) in DMA (480 ml) were heated to 70–75°. Solid appeared and the solution became green. The solution was heated at 70–75° with vigorous stirring for 2 hr and then at reflux (~165°) for 10 hr. DMA was removed by vacuum distillation until a thick slurry remained. The slurry was made basic with 10% aqueous NaOH. Solid was removed by filtration, and the filtrate was acidified with 10% HCl to pH 1; 35.58 g of a yellow mixture of **11** and **14** precipitated.

This yellow solid was stirred with 10% aqueous KOH to leave undissolved 6.11 g of sparingly soluble potassium 2,5-bis(benzylthio)terepthalate. This white salt of **11** was collected by filtration and dried. When it then was stirred with 10% HCl, yellow solid precipitated: yield of **11** 4.03 g (12%); mp 309–316° dec; ir (KBr) 1690, 1250, 1230, 715, and 690 cm^{-1}; tlc in HOAc on polyamide showed 3 spots, and no purification was attempted. The structure of **11** was confirmed by preparing the bisbenzylthio ester **18** (*vide supra*).

The basic solution (in which the potassium salt of **11** had been sparingly soluble) was acidified to precipitate a second solid. This solid, collected by filtration and dried, gave 8.55 g (37%) of yellow **14**, mp ~246° dec (sublimation). The **14** was recrystallized from *tert*-BuOH–H_2O to a constant ir spectrum: (KBr) 1690, 1480, 1410, 1290, 1250, 780, 745, 710, and 690 cm^{-1}.

Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.49; H, 4.19; S, 11.12. Found: C, 62.23; H, 4.08; S, 11.14.

2,5-Bis(2-aminoethyldithio)terephthalic Acid (23) and 2-(2-Aminoethyldithio)terephthalic Acid (24). A. Bisdisulfide 23 from the Dimercapto Acid 12 (Route VI).—A solution of **12** from route I (0.921 g, 4 mmol) in DMF (38 ml) was added with stirring to a solution of thiolsulfonate **2a** (2.06 g, 8 mmol) in 5.03 ml of H_2O–DMF (7:1). Yellow solid began to precipitate after 5 min. The mixture was stirred for 5.5 hr and then was neutralized at 0° with a cold solution of DABCO (1.79 g, 16 mmol) in H_2O (6.3 ml). The yellow solid immediately became white. Filtration separated 1.29 g (85%) of **23**, mp 243–245° dec. Purification was effected by dissolution in 0.258 *N* HCl, filtration, and neutralization with 0.250 *N* NaOH to pH 7. Three repetitions gave white **23** having a constant mp 251.5–252.5° dec: ir (KBr) 3400, 3100–2500, 1630, 1560, 1445, 1370, and 810 cm^{-1}; too sparingly soluble for an nmr spectrum.

Anal. Calcd for $C_{12}H_{16}N_2O_4S_4$: C, 37.88; H, 4.24; N, 7.36; S, 33.70; neut equiv, 190. Found: C, 37.64; H, 4.32; N, 7.17; S, 33.55; neut equiv (formol), 211.[38]

Use of the tetrasodium salt of **12** was less satisfactory (route V). Thus, when **12** (from route I, 0.921 g, 4 mmol) was dissolved in a solution of NaOH (0.64 g, 16 mmol) in H_2O (1.28 ml) and added to a solution of thiolsulfonate **2a** (2.06 g, 8 mmol) in H_2O (5 ml), white solid precipitated. Filtration separated 1.57 g (103%) of **23**, mp 241–243° dec, which, twice purified by dis-

(38) In the formol titration (*cf.* ref 2a), a 37% formaldehyde solution was neutralized (phenolphthalein end point) and added to an aqueous slurry of **23**. This mixture then was neutralized (phenolphthalein end point).

solution in HCl, filtration, and neutralization as before, gave white **23** with a constant mp of 250–251° dec. The ir spectrum was identical with that of the **23** from route VI, but a satisfactory analysis could not be obtained (Found: C, 36.29; H, 4.42). When an nmr spectrum of this **23** was attempted in D_2O–H_2SO_4, yellow solid appeared immediately; the ir spectrum suggested the solid was a salt of **23** with H_2SO_4 since there was a strong broad band at 1075 cm^{-1} (**23**·HCl also was too sparingly soluble to give an nmr spectrum; *vide infra*).

Variations of route V were less promising. Use of crude **12**, prepared by the one-step reaction of KSH with acid **3** (route III), with thiolsulfonate **2a** gave the desired **23** but in yields of 25–33%.

B. The Monodisulfide 24 from the Monomercapto Acid 15 (Route VII).—A solution of **15** (0.198 g, 1 mmol) in 95% EtOH (3.68 ml), with barely enough DMF to effect solution at boiling, was added to a solution of thiolsulfonate **2a** (0.257 g, 1 mmol) in 0.63 ml of H_2O–95% EtOH (7:1). The mixture was stirred for 4 hr and cooled at 5°, and a cooled solution of DABCO (0.224 g, 2 mmol) in H_2O (0.8 ml) was added. In ~20 min a white precipitate began to appear. The mixture was stirred for 1 hr and then cooled overnight. The solid was collected and washed with EtOH and Et_2O, yield of a white compound **24** 0.183 g (67%), mp 265–267° dec. Two recrystallizations from H_2O gave 0.0424 g (16%) of a white compound **24** with a constant mp 263–264° dec: ir (KBr) 1690, 1620, 1510, 1410, 1370, 1240, 1130, 1030, 940, 875, 780, and 760 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_4S_2$: C, 43.95; H, 4.04; N, 5.13; S, 23.47; neut equiv, 137. Found: C, 44.13; H, 4.16; N, 4.99; S, 23.10; neut equiv (formol), 130.[38]

The use of DMF–H_2O, essentially route VI, gave disulfide **24** in 24% yield, ir similar but not identical with that of **24** from route VII; loss through excessive solubility of **24** apparently occurred, and the ir suggested less satisfactory **24**.

2,5-Bis(2-aminoethyldithio)terephthalic Acid Dihydrochloride (27) and 2-(2-Aminoethyldithio)terephthalic Acid Hydrochloride (28).—Concentrated HCl (0.5 ml) was added to a suspension of **23** (0.250 g, 0.66 mmol) in H_2O (3 ml) to give a yellow solid, yield 0.218 g (73%), mp 283–286°. This, after two recrystallizations from MeOH by addition of Et_2O, gave the yellow compound **27**: yield 0.091 g (30%), having a constant mp 280–281° dec; ir (KBr) 3200–2500, 1690, 1460, 1410, 1310, 1250, 1080, 890, and 790 cm^{-1}; **27** was too sparingly soluble for a nmr spectrum in D_2O.

Anal. Calcd for $C_{12}H_{18}Cl_2N_2O_4S_4$: C, 31.78; H, 4.00; Cl, 15.64; N, 6.18; S, 28.29. Found: C, 32.02; H, 4.17; Cl, 15.43; N, 6.01; S, 28.01.

In the preparation of bisdisulfide **23** by route VI, the yellow solid which precipitated before the neutralization with DABCO proved to be the dihydrochloride **27** (mp 278–281°, 93% yield); the ir spectra of the two samples of **27** were identical.

Disulfide **24** (0.300 g, 1.1 mmol) was placed in H_2O (5 ml) and and concentrated HCl (1 ml) was added. Part of the hydrochloride dissolved, so the solution was evaporated to leave 0.294 g (86%) of **28**, mp >320°. Two recrystallizations from absolute EtOH gave 0.0697 g (20%) of white **28**, mp >320°: ir (KBr) 3200–2500, 1675, 1470, 1400, 1250, 920, 880, 780, and 740 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}ClNO_4S_2$: C, 38.77; H, 3.90; N, 4.52; S, 20.70. Found: C, 39.14; H, 3.98; N, 4.82; S, 21.20.

2,5-Bis(2-*n*-decylaminoethyldithio)terephthalic Acid (25).—A solution of dithiol **12** (0.461 g, 2 mmol) in DMF (3.76 ml) was added to one of thiolsulfonate **2b** (2.15 g, 4 mmol) in 80 ml of 1:1 CH_2Cl_2–EtOH (this solution of **2b** was prepared at the boiling point and then cooled to ~25°). The mixture was stirred for 4 hr, during which it remained homogeneous, after which DABCO (0.897 g, 8 mmol) in DMF (7 ml) was added (essentially route VI). A copious amount of white solid precipitated immediately and did not increase significantly upon storage at 0° overnight. The solid, washed with EtOH and Et_2O, amounted to 0.87 g (66%) of **25**, mp 202–205° dec. The **25** was purified by stirring 0.205 g with 14 ml of 0.0966 *N* aqueous HCl for 20 min. The solid, then presumably largely **25**·HCl, was virtually insoluble in H_2O and was extracted, by shaking, into a solution of DMF–CH_2Cl_2–EtOH (1:1:1). This solution then was neutralized with one of DABCO (0.067 g, 0.6 mmol) in absolute EtOH (7 ml) to pH 7 to give **25**, 0.139 g (68% recovery), mp 211–213° dec. Repetition of the procedure gave 0.095 g (46% recovery of a white powdery compound **25**: mp 212–214° dec; ir (KBr) similar to **23** but simpler, 3400 (w), 2920, 2850, 1610, 1560, 1450 (doublet), 1360, 815, 795, and 725 (br, w) cm^{-1}. The **25** was too sparingly soluble for nmr or neutral equivalent (formal) studies.

Anal. Calcd for $C_{32}H_{56}N_2O_4S_4$: C, 58.14; H, 8.54; N, 4.24. Found: C, 58.44; H, 8.97; N, 4.25.

Diethyl 2,5-Bis(2-aminoethyldithio)terephthalate Dihydrochloride (30). A. Ester 30 from Bisdisulfide 27.—Hydrochloride **27** (0.628 g, 1.4 mmol) and *p*-toluenesulfonic acid·H_2O (12.43 g, 65 mmol) were heated in absolute EtOH (314 ml) at reflux for 14 hr. The EtOH was evaporated to a volume of ~25 ml, and H_2O (25 ml) was added. The solution was made basic (pH 9) with 5% aqueous KOH and extracted with $CHCl_3$. The $CHCl_3$ extracts were combined and rapidly extracted with 0.0966 *N* HCl. The acid extracts were combined, evaporated to dryness, and the residue was rubbed with acetone to give 0.648 g (88%) of **30**·H_2O, mp 235–240° dec. This procedure was repeated to give white **30**·H_2O, yield 0.212 g (29%), mp 268–270° dec. Two recrystallizations from absolute EtOH gave white **30**·H_2O: yield 0.064 g (9%) with a constant mp 267–268°; ir (KBr) 3200–2500, 1710, 1450, 1290, 1230, and 1070 cm^{-1}. A satisfactory analysis could not be obtained, evidently because of a persistent impurity associated with disproportionation, complicated by uncertain solvation (Found: C, 38.52; H, 4.88; S, 22.50), but **30** was identical with that from B (*vide infra*) in its ir spectrum and in its tlc behavior (identical single spots when both samples and a mixture were done concurrently).

In other efforts to convert **27** to **30**, **27** (5.9 mmol) was heated under reflux with PCl_5 (17.6 mmol) in AcCl (64 ml) for 24 hr, but cooling and filtration gave only **27** (91% recovery, ir spectrum identical with that of pure **27**). When **27** (0.800 g, 1.8 mmol) was heated in 1200 ml of boiling absolute EtOH with vigorous stirring for 6 hr, removal of excess **27** showed that 0.500 g (1.1 mmol) of **27** had dissolved; the solution was refluxed while HCl was bubbled in during 24 hr (tlc then showed that ester **30** might be present), the EtOH was evaporated, and residual solid was dissolved in water, basified, and extracted with $CHCl_3$; the $CHCl_3$ solution was extracted with 0.0966 *N* HCl, and the acid extract was evaporated to give 0.0288 g (5%) of **30**·H_2O, mp 248–252° dec. Recrystallization from absolute EtOH gave 0.010 g (2%) of **30**·H_2O, mp 265–268°, which was identical (ir) with **30** prepared using *p*-toluenesulfonic acid.

B. The Ester 30 from Dithiol 19.—A solution of **19** (0.2214 g, 0.77 mmol) in 5.6 ml of 0.270 *N* NaOH was added dropwise during 30 min to a stirred solution of **2a** (0.792 g, 3.08 mmol) in H_2O (10 ml). The solution was cooled overnight at 5°, and 5% aqueous KOH then was added to pH 11. The alkaline solution was extracted twice with $CHCl_3$, and the $CHCl_3$ extract was acidified by shaking with 10% HCl to pH 1. Evaporation of the aqueous layer to dryness gave 0.157 g (39%) of **30**·H_2O, mp 263–265° dec. Recrystallization from absolute EtOH gave 0.0834 g (20%) of the white compound **30**·H_2O: mp 267–268° dec; tlc (silica gel, 95% EtOH) showed only one spot (R_f 0.12); ir (KBr) 3200–2500, 1710, 1450, 1290, 1230, and 1070 cm^{-1}; too sparingly soluble for a nmr spectrum.

Anal. Calcd for $C_{16}H_{26}Cl_2N_2O_4S_4 \cdot H_2O$: C, 36.43; H, 5.35; S, 24.31; H_2O, 3.41. Found: C, 36.26; H, 5.41; H_2O, 1.72.[39]

1,4-*S*,*S*-2,5-Bis(ethoxycarbonyl)phenylene Bis(*N*,*N*-dimethyldithiocarbamate) (26).—*N*,*N*-Dimethylthiocarbamoyl chloride (23.73 g, 192 mmol), DABCO (21.54 g, 192 mmol), and **19** (9.26 g, 32 mmol) were stirred in DMF (144 ml) at ~25° for 2 hr. Solid which precipitated was collected, washed with H_2O, and dried, yield of **26** 4.17 g (28%), mp 197–202°. Addition of H_2O to the filtrate precipitated more **26** (12.53 g, 84%). The solids were combined and recrystallized from CH_3NO_2–EtOH to give 6.19 g (41%) of **26** as fine yellow needles, mp 197–202°. Three recrystallizations from benzene and one from benzene–EtOH gave white **26** with a constant mp 215–217°; ir (KBr) 1725, 1640, 1500, 1370, 1240, 1130, 1070, 970, and 850 cm^{-1}; nmr ($DCCl_3$) δ 1.37 (t, 6), 3.55 (s, 12), 4.32 (q, 4), and 8.17 (s, 2).

(39) The **30**·H_2O was dried for 6 hr at 100° (0.5 mm) before submission for analysis (presumably with partial loss of H_2O), after which the analyses reported for H_2O was based on further drying for 24 hr at 100° (0.5 mm); the analysis after the latter drying was unsatisfactory for anhydrous **30**, probably because of decomposition during the vigorous drying [Calcd for (anhydrous) $C_{16}H_{26}Cl_2N_2O_4S_4$: C, 37.71; H, 5.14; S, 25.17. Found: C, 36.43; H, 5.09]. It seems clear that **30** is a hydrate, but whether or not it is a monohydrate is unclear.

Anal. Calcd for $C_{18}H_{24}N_2O_4S_4$: C, 46.93; H, 5.25; N, 6.08; S, 27.84. Found: C, 47.23; H, 5.40; N, 6.15; S, 27.79.

Registry No.—**6**, 25906-63-2; **10**, 25906-64-3; **11**, 25906-65-4; **12**, 25906-66-5; **13**, 25906-67-6; **14**, 25906-68-7; **15**, 25906-69-8; **16**, 25906-70-1; **18**, 25906-71-2; **19**, 25906-72-3; **21**, 25906-73-4; **22**, 25906-74-5; **23**, 25906-75-6; **24**, 25906-76-7; **25**, 25906-77-8; **26**, 25902-98-1; **27**, 25902-99-2; **28**, 25957-59-9; **30**, 25903-00-8.

The Stereochemistry of Oxidation at Sulfur. Oxidation of 2-Methylthiolane[1,2]

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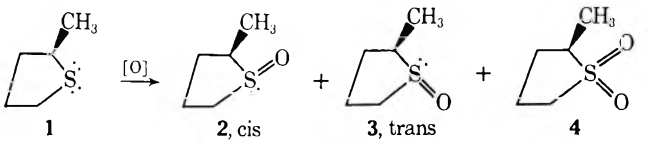
Pure samples of the diastereomeric 2-methylthiolane 1-oxides were isolated and characterized by chromatographic retention time and nmr spectroscopy. The cis isomer exhibits the shorter retention times on chromatography. The methyl resonance of the trans isomer shows the greater benzene-induced shift. The stereochemistry of oxidation of 2-methylthiolane by a variety of reagents is recorded.

Oxidation of sulfides is likely to remain the foremost method for the preparation of sulfoxides. The availability of stereochemical data on this transformation is useful from both mechanistic and synthetic standpoints. In earlier papers we have examined the details of the conversion of 4-substituted thianes[4] and 2-thiabicyclo[2.2.1]heptane[5] to the diastereomeric S-oxides. We now record a related study on the oxidation of 2-methylthiolane (2-methyltetrahydrothiophene) (**1**).



1 **2**, cis **3**, trans **4**

Assignment of Configuration.—Pure samples of the isomeric sulfoxides **2** and **3** were obtained by careful elution chromatography on acid-washed alumina beginning, most conveniently, with mixtures in which one isomer was significantly more abundant. The structural assignments were based on three main lines of evidence: chromatographic retention times, nmr studies, and oxidation studies. The sulfoxides are highly hygroscopic liquids.

The isomer which exhibited the higher retention time on both column and vapor phase chromatography was assigned the trans structure **3**. Experience in our laboratories and others has shown that in the absence of complicating effects the isomer with the more sterically accessible sulfoxide oxygen has the higher retention time. Perhaps the most rigorous proof of structure comes from nmr studies summarized in Table I.

It is obvious from an inspection of the data of Table I that arguments based on the magnitude of chemical shifts would be ineffective for structural assignments. It has been assumed for some time that the anistropy of the S=O bond approximates that of the carbon–carbon triple bond. This assumption is probably a valid one, but the utility is limited by the less well understood screening by the free electron pair. The most effective data is provided by the benzene-induced shifts.[6,7] Ledaal[8] has recently proposed that benzene–polar solute collision complexes are best represented by a model with the positive end of the dipole of the polar functional group located along the sixfold axis of the benzene molecule. In the case of the sulfoxides in question, the deshielding of the methyl by the aromatic solvent should be more dramatic in the trans sulfoxide than in the cis (Figure 1). The interested reader is referred to an excellent group of recent articles dealing with penicillin sulfoxides.[9] The stereochemical assignment made here is entirely in line with arguments presented in detail in these papers concerning the steroechemistry of penicillin sulfoxides.

TABLE I

SOLVENT EFFECTS IN THE NMR SPECTRA OF 2-METHYLTHIOLANE AND DERIVATIVES[a]

Compd	Concn, mmol/ml	Solvent	δ_{CH_3}	J (Hz)	$(\delta' - \delta_{C_6H_6})$
1 (sulfide)	1.70	CCl_4	1.27	7.0	+0.11
		C_6H_6	1.16	7.0	
2 (cis sulfoxide)	1.70	DMSO-d_6	1.22	6.7	+0.04
		CCl_4	1.28	7.0	+0.10
		$CDCl_3$	1.40	6.5	+0.22
		C_6H_6	1.18	6.2	
3 (trans sulfoxide)	1.70	DMSO-d_6	1.13	7.3	+0.39
		CCl_4	1.19	7.0	+0.45
		$CDCl_3$	1.23	7.1	+0.49
		C_6H_6	0.74	7.2	
4 (sulfone)		CCl_4	1.27	7.0	+0.23
		C_6H_6	1.04	7.0	

[a] The spectra were run at ambient temperature using TMS as standard.

Infrared analysis of the 2-methylthiolane 1-oxides showed very minor differences outside the sulfoxide

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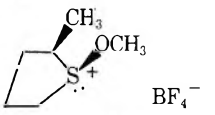
TABLE II

EQUILIBRATION OF 2-METHYLTHIOLANE 1-OXIDES[a]

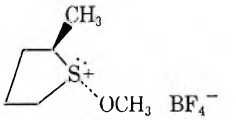
Sulfoxides before reaction, cis:trans	Reaction conditions	Sulfoxides after reaction, cis:trans
19:81	HCl–dioxane, 20 min, 25°	76:24
64:36	HCl–dioxane, 2–3 min, 25°	78:22
62:38	Sulfuric acid–water, 2 min, 25°	79:21
75:25	N_2O_4, 30 min, 0°	62:38

[a] All reactions gave trace amounts of unidentified products.

promoted hydrolysis of these salts occurred with complete inversion of configuration at the sulfonium sulfur.[12] Hydrolysis of **5** led to pure **3** and hydrolysis of **6** gave pure **2**.



5, cis



6, trans

TABLE III

OXIDATION OF 2-METHYLTHIOLANE

Reagent	Conditions, °C	2-Methylthiolane 1-oxides, cis:trans	4-*t*-Butylthiane 1-oxides,[b] cis:trans
Dinitrogen tetroxide	0	62:38	81:19
Sodium metaperiodate	H_2O, 0	43:57	75:25
Hydrogen peroxide	CH_3COCH_3, 0	56:44	37:63[a]
m-Chloroperbenzoic acid	CH_2Cl_2, 0	54:46	36:64
m-Chloroperbenzoic acid	H_2O–dioxane pH 12, 0	30:70[b]	
Chromic acid	C_6H_5N, 0–25[c]	16:84	27:73
Iodosobenzene	C_6H_6, 68	58:38[d]	46:54[e]
Iodobenzene dichloride	C_5H_5N, H_2O, 0	26:74[b]	...[f]
Ozone	CH_2Cl_2, −78	22:70[g]	10:90[h]
Ozone	CH_2Cl_2, 25	23:77	
tert-Butyl hypochlorite	$(CH_3)_2CHON$, −78	65:35	100:0[i]
Isopropyl hypochlorite	CH_2Cl_2, −78	6:94	

[a] Reaction run at 25°. [b] Traces of sulfone. [c] Run at 0° for 1 hr, then 1 hr at 25°. [d] Sulfone, 4%. [e] Run at 80°. [f] Oxidation of 4-*p*-chlorophenylthiane at room temperature afforded 10% cis:90% trans sulfoxides; at −40°, 5% cis:95% trans (ref 17). [g] Sulfone, 8%. [h] Run at −40°. [i] Run in ethanol at −78°.

region. No unambiguous way of correlating solvent effects on sulfoxide band shapes and positions with geometry appeared possible. Infrared data in several solvents are reported in the experimental section. The mass spectra of the diastereomeric sulfoxides did not reveal significant differences.

Equilibration of Sulfoxides.—The stereomutation of sulfoxides can be achieved by numerous methods.[10] The equilibration methods used and results obtained in the present system are given in Table II.

The result that cis oxides are more stable than the trans is not out of line with our earlier observation that cis axial oxides are more stable than equatorial in the 4-substituted thianes.[4] In the latter case we suggested that attractive interaction between the oxygen and the ring accounts for this result. Recent theoretical studies substantiate this suggestion.[11] Along these same lines it is interesting to note the similarities in nonbonded distances labeled in Figure 1.

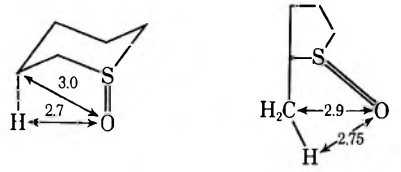


Figure 1. Comparison of nonbonded distances (Å) in cyclic sulfoxides. Distances estimated from Drieding models.

The sulfoxides were characterized additionally by the preparation of crystalline salts by O-alkylation with trimethyloxonium fluoroborate. As anticipated, base-

Chloride ion is known to equilibrate alkoxysulfonium salts.[13] When a sample of the pure trans salt **6** was exposed to hydrogen chloride, equilibration was complete in less than 1 min. The equilibrium composition was 70% cis and 30% trans based on integration of the nmr resonances of the methoxy groups. Note from Table II that this value is very close to that observed for the hydrogen chloride catalyzed equilibration[14] of the free sulfoxides.

Oxidation Studies.—Table III shows the percentages of cis and trans sulfoxides produced under a variety of oxidation conditions; previous results obtained for 4-*tert*-butylthiane are included for comparison.[4] Due care was exercised to prevent or minimize oxidation to the sulfone state. In general, less stereoselectivity of oxidation was found in the case of 2-methylthiolane than in the 4-substituted thianes. This is somewhat surprising in view of the close proximity of the methyl substituent on the thiolane to the sulfur reaction site.

In an earlier paper[4] the stereochemical results of oxidations of cyclic sulfides were considered to be the outcome of thermodynamic control, steric approach control, or product development control. Since the present results are not significantly out of line with earlier discussions, additional commentary on the relationship of stereochemistry and mechanism is not in order at this time.

In connection with these oxidation studies, it was noted that in competitive reactions the cis sulfoxide **2** was oxidized to the sulfone by *m*-chloroperbenzoic acid somewhat faster than the trans sulfoxide **3**. It seems logical that the electron pair trans to the methyl group

(10) For a review, see K. Mislow, *Rec. Chem. Progr.*, **28**, 217 (1967).
(11) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).
(12) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965).
(13) C. R. Johnson and J. J. Rigau, *ibid.*, **91**, 5398 (1969).
(14) J. Jacobus and K. Mislow, *ibid.*, **89**, 5228 (1967).

would be more accessible to electrophilic attack by the peracid.

Experimental Section

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 621 spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

2-Methylthiolane was prepared in 60% yield by reaction of 1,4-dibromopentane with sodium sulfide nonahydrate in aqueous ethanol, bp 132° (lit.[15] 132°).

General Methods of Oxidation.—The procedures employed for the oxidations summarized in Table III are generally those previously reported for the oxidation of thianes.[4] Exceptions are noted below. In this work, where necessary, the sulfoxides were extracted from aqueous solutions with chloroform. The aqueous phase was then saturated with sodium chloride and the chloroform extraction repeated. The ratio of sulfoxide extracted by this procedure was identical with that present in water as shown by extracting known mixtures from water.

A. *m*-Chloroperbenzoic Acid (pH 12).[16]—The peracid (0.85 mmol) was added to 21 ml of a potassium chloride–sodium hydroxide buffer solution (pH 12) in water–dioxane (60:40). This solution was added over a 5-min period to 1 mmol of the sulfide in 10 ml water–dioxane cooled in an ice bath. The mixture was stirred at ice-bath temperature for 5 hr prior to work-up.

B. Iodobenzene Dichloride.[17]—A solution of iodobenzene dichloride (1 mmol) in anhydrous pyridine (3 ml) was added dropwise during 5 min to a stirred solution of the sulfide (1 mmol) in 3 ml of pyridine–water (20:80) and cooled in an ice bath. After 30 min at 0° the mixture was allowed to warm to 25°. The mixture was diluted with water prior to extraction.

C. *tert*-Butyl Hypochlorite.—To 1 mmol of the 1-methylthiolane in 10 ml of isopropyl alcohol at −78° was added 1 mmol of *tert*-butyl hypochlorite. After 30 min at that temperature 100 ml of 0.1 *N* aqueous sodium hydroxide was added and the mixture was shaken vigorously prior to extraction.

D. Isopropyl Hypochlorite.—A methylene chloride solution of isopropyl hypochlorite (1 equiv) was cooled to −78° and rapidly added to 1 equiv of the sulfide dissolved in methylene chloride and cooled to −78°. The reaction was worked up as described above for *tert*-butyl hypochlorite.

Analysis of Mixtures.—Percentage composition of mixtures were ascertained by planimetric integration of curves obtained from an F & M Model 720 chromatograph employing an 8 ft × 1/4 in. 20% Carbowax 20M on Chromosorb W column at 170°, a flow rate near 60 ml/min; retention times were 17 min for **2** and 21 min for **3**.

Separation of *cis*- and *trans*-1-Methylthiolane 1-Oxide.—Mixtures of sulfoxides were chromatographed on a 14 in. × 3/8 in. column of Fisher Scientific Co. alumina acid, activity I, employing ether, methylene chloride, and methanol as eluents. The fractions were monitored by vapor phase chromatography.

Registry No.—**1**, 1795-09-1; **2**, 25859-44-3; **3**, 25859-45-4; **4**, 1003-46-9.

(15) E. W. Whitehead, R. A. Dean, and F. A. Fidler, *J. Amer. Chem. Soc.*, **73**, 3632 (1951).

(16) For other examples of oxidations by peracids at high pH, see R. Curci, A. Giovini, and G. Modina, *Tetrahedron*, **4**, 1227 (1966).

(17) G. Barbieri M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. C*, 659 (1968).

3-Substituted Thietanes. Synthesis and Oxidation to Sulfoxides[1,2]

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A method is reported which appears to be general for the synthesis of 3-aryl and 3-alkylthietanes from the readily available aryl methyl and alkyl methyl ketones. The cycloaddition product of sulfene and the appropriate enamine is reduced to the desired 3-aryl- or 3-alkylthietane in three steps. Thietanes deuterated in the α position could be prepared by exchange under mild conditions at the sulfone stage. The oxidation of 3-alkylthietanes to the isomeric sulfoxides was examined with a variety of oxidants; the thietane system appears to be less sensitive to the nature of the oxidant than the previously examined thiane system. Isomeric cis and trans sulfoxides could be separated by chromatography on silica gel; the cis isomer was eluted prior to trans in each of six 3-substituted thietane systems examined.

With the increasing sophistication of the organic chemistry of sulfur has come the postulation of tetracovalent sulfur reaction intermediates of trigonal bipyramid geometry.[4] For intermediates of such geometry the ligands about sulfur must subtend an angle of either 90 or 120 degrees; thus the thietane ring system, in which the C-S-C angle is close to 90°, becomes an important model. Substituted thietane 1-oxides are also pertinent models for studying the intramolecular neighboring group effect of sulfinyl oxygen,[5] and for studying the competitive stereochemical requirements of sulfinyl oxygen and the nonbonded electron pair on trigonal sulfur.[6,7] It was our interest in the latter of these which established our need for a 3-substituted thietane system the isomeric sulfoxides of which could be identified stereochemically.

To simplify a study of the conformational preference of sulfinyl oxygen it was necessary to "anchor" the conformation of the thietane ring. The puckering of thietane rings is well documented.[8] By analogy to examples in cyclobutane chemistry, it is reasonable to hypothesize that a thietane molecule with a relatively bulky substituent at the 3 position would exist predominantly in a puckered conformation with the bulky substituent equatorial.[9] Thus, if the substituent at C_3 exerts a decided equatorial preference, a substituent

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(2) We gratefully acknowledge support by the National Science Foundation (Grant No. GP-8648).

(3) National Aeronautics and Space Administration Trainee, 1966–1969.

(4) (a) S. Oae, M. Yokoyama, M. Kise, and N. Furukawa, *Tetrahedron Lett.*, 4131 (1968); (b) B. M. Trost, W. L. Schinski, and I. B. Mantz, *J. Amer. Chem. Soc.*, **91**, 4320 (1969); (c) R. Tang and K. Mislow, *ibid.*, **91**, 5644 (1969); (d) C. R. Johnson and J. J. Rigau, *ibid.*, 5398 (1969); (e) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 5404 (1965).

(5) (a) S. M. Kotin, Ph.D. Dissertation, University of Pennsylvania, 1962; (b) J. J. Ubel, Ph.D. Dissertation, University of Illinois, 1964.

(6) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(7) (a) C. R. Johnson and W. O. Siegl, *ibid.*, **91**, 2796 (1969); (b) *Tetrahedron Lett.*, 1879 (1969).

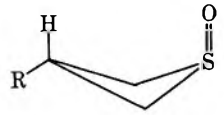
(8) (a) B. Z. Zrbuzov, O. N. Nuretdinova, and A. N. Vereshchagin, *Dokl. Akad. Nauk SSSR*, **172**, 591 (1967); (b) W. D. Keller, T. R. Lusebrink, and C. H. Sederholm, *J. Chem. Phys.*, **44**, 782 (1966); (c) S. Allenmark, *Ark. Kemi*, **26**, 73 (1966); (d) D. O. Harris, H. W. Harrington, A. C. Luntz, and W. D. Gwinn, *J. Chem. Phys.*, **44**, 3467 (1966).

(9) J. Lillien and R. A. Doughty, *J. Amer. Chem. Soc.*, **89**, 155 (1967).

introduced at sulfur (*e.g.*, oxygen) is required to be either axial (trans isomer) or equatorial (cis somer) in a conformational fixed system. The *p*-chlorophenyl group was chosen because its dipole would allow assignment of cis and trans stereochemistry to the isomeric sulfoxides **2a** and **3a** from dipole moment determinations.[6] The *tert*-butyl substituent was also desired for its ability to anchor a ring conformation and for its lack of a significant dipole contribution which might influence geometry and chemistry.

1

2 (cis)



3 (trans)

4

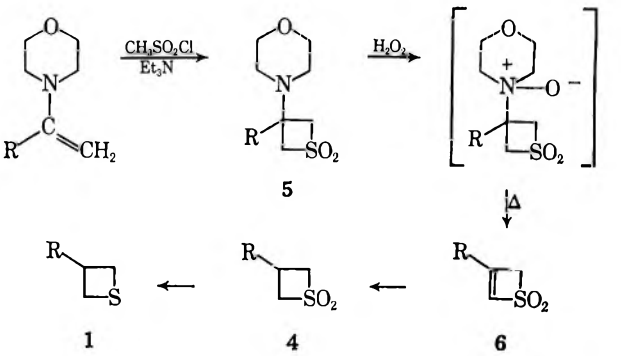
a, R = *p*-ClC$_6$H$_4$
b, R = *t*-C$_4$H$_9$
c, R = C$_6$H$_5$
d, R = Cl
e, R = OCOCH$_3$
f, R = CH$_3$

Only one synthesis of a 3-arylthietane (unsubstituted at C_2 and C_4) appears in the literature, the preparation of 3-hydroxy-3-phenylthietane by the treatment of 3-thietanone with phenylmagnesium bromide.[10] Syntheses[11] of 3-alkylthietanes have been limited to the methyl and ethyl cases. The cycloaddition of enamines with sulfene (CH_2=SO_2) provides a convenient entry to substituted thietane 1,1-dioxide systems but the sulfoxides can only be obtained by reduction of the sulfone to the sulfide stage and selective back oxidation to the sulfoxide. Conceptually, the cycloaddition of sulfine (CH_2=SO) to an enamine would eliminate these last two steps, but to date no one has successfully carried out this reaction.[12,13]

We report here an application of the enamine–sulfene cycloaddition for the synthesis of 3-substituted thietanes (Scheme I). The method appears general for 3-aryl- and certain 3-alkylthietanes. Stereochemistry was assigned to **2a** and **3a** from the dipole moments and to other 3-substituted thietane 1-oxides from spectral data as reported in our preliminary communications.[7] Continuing our interest in the stereochemical course of the oxidation of sulfides to sulfoxides, data are presented for the oxidation of 3-*tert*-butylthietane and 3-methylthietane to their sulfoxides.

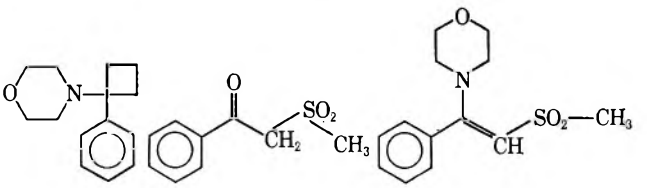
Synthesis.—Scheme I was first attempted on the enamine of morpholine and acetophenone,[14] to yield the crystalline 1:1 cycloaddition product (**5c**) (46% yield

SCHEME I



1 **4** **5** **6**

from acetophenone). The nmr spectrum of **5c** contained a four proton singlet for the ring methylene hydrogens of which there are clearly two nonequivalent pairs. Even in benzene, which often accentuates the nonequivalence of protons, the thietane ring hydrogens appear as a singlet. The sulfone **5c** was reduced with lithium aluminum hydride to 3-morpholino-3-phenylthietane (**7**) in which the thietane ring hydrogens appear as the expected AB quartet.



7 **8** **9**

The adduct **5c** could be converted to 3-phenylthiete 1,1-dioxide (**6c**) in almost quantitative yield by oxidation with hydrogen peroxide in acetic acid–acetic anhydride and subsequent pyrolysis of the amine oxide. The olefinic double bond of **6c** was considerably less reactive than reported for the unsubstituted thiete 1,1-dioxide.[15] Although **6c** would add bromine[16] and undergo the expected hydrolysis in aqueous base,[15,17] it failed to add secondary amines. The hydrolysis of **6c** to benzoic acid and dimethyl sulfone probably occurs *via* the β-keto sulfone **8** which is subsequently cleaved by hydroxide. If the amino sulfone **5c** is subjected to similar conditions, the enamine **9** is obtained. When the reaction is acidified before extraction, **8** is isolated.

The conversion of **6c** to 3-phenylthietane 1,1-dioxide (**4c**) could be accomplished by treatment with sodium borohydride in isopropyl alcohol at 60° (65% yield) or in dimethylformamide at 60–70° (37% yield). Catalytic hydrogenation of the olefinic double bond of **6c** with palladium on carbon or platinum oxide proceeded only in very low yield.

The sulfone **4c** was reduced to the volatile sulfide **1c** with lithium aluminum hydride. Attempts to reduce **6c** directly to 3-phenylthietane (**1c**) with lithium aluminum hydride were unsuccessful, yielding only what was believed to be 2-phenylpropanethiol from the spectral data.

Scheme I was repeated with the enamine from morpholine and *p*-chloroacetophenone as the starting material; experimental conditions were kept the same. The yield of 3-*p*-chlorophenyl-3-morpholinothietane 1,1-

(10) A. Luettringhaus, S. Kabuss, H. Prinzbach, and F. Langenbucher, *Ann Chem.*, **653**, 195 (1962).

(11) The synthesis of thietanes has been reviewed: M. Sanger, *Chem. Rev.*, **66**, 341 (1966); Y. Etienne, R. Soulas, and H. Lumbroso in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part Two, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter 5; L. L. Muller and J. Hamer, "1,2-Cycloaddition Reactions," Interscience, New York, N. Y., 1967.

(12) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3231 (1963); W. A. Sheppard and J. Diekmann, *ibid.*, **86**, 1891 (1964); A. M. Hamid and S. Trippett, *J. Chem. Soc. C*, 1612 (1968).

(13) A sulfine has recently been trapped in a 1,4 cycloaddition reaction: B. Zwanenburg, L. Thijs, and J. Strating, *Tetrahedron Lett.*, 4461 (1969).

(14) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(15) D. C. Dittmer and M. E. Christy, *ibid.*, **84**, 399 (1962).

(16) C. R. Johnson and G. A. Dutra, unpublished results.

(17) J. N. Wells and F. S. Abbott, *J. Med. Chem.*, **9**, 489 (1966).

dioxide (**5a**), from the cycloaddition of sulfene and the morpholine enamine of *p*-chloroacetophenone, was higher (52 *vs.* 37%) when benzene replaced ether as the solvent. The conversion of **5a** to 3-*p*-chlorophenylthiete 1,1-dioxide (**6a**) was almost quantitative. The double bond of **6a** resembled that of **6c** in its lack of reactivity and it was necessary to employ the reaction conditions mentioned above to effect the desired reduction. Base hydrolysis of **6a** produced *p*-chlorobenzoic acid and dimethyl sulfone.

With some slight modification Scheme I was employed for the synthesis of 3-*tert*-butylthietane (**1b**). Because of the sterically hindered carbonyl function of pinacolone, its dimethylamine enamine was prepared by the procedure of White and Weingarten.[18] The sulfene–enamine adduct, 3-dimethylamino-3-*tert*-butylthietane 1,1-dioxide,[19] was prepared and converted to 3-*tert*-butylthiete 1,1-dioxide (**6b**) by experimental procedures analogous to those described above. The olefinic double bond of **6b** was more reactive than that of **6a** or **6c**; it underwent catalytic hydrogenation and reacted with sodium borohydride in 2-propanol at 25° to yield 3-*tert*-butylthietane 1,1-dioxide (**4b**). The sulfone **4b** was reduced to the volatile 3-*tert*-butylthietane (**1b**) with lithium aluminum hydride.

When attempting to extend the stereochemical assignments from **2a** and **3a** to the sulfoxides of **1b** and **1c** it became necessary to prepare the α-tetradeuterated sulfoxides in order that the chemical shift values of the β-ring hydrogens be more accurately assigned. This was accomplished by treating the sulfones **4a** and **4b** with sodium deuterioxide in deuterium oxide–dioxane at 50°. Complete exchange of the sulfone α-methylene hydrogens could be effected under these conditions, whereas the corresponding sulfoxides were inert. The deuterated sulfones were converted to the α-tetradeuterated sulfides with lithium aluminum hydride and were subsequently oxidized to the tetradeuterated sulfoxides.

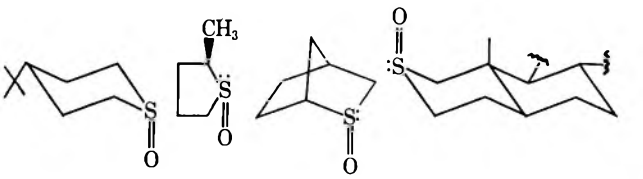
Sulfoxides. Separation and Assignment of Configuration.—To draw conclusions about the nature of cis and trans sulfoxides resulting from the oxidation (see below) of 3-substituted thietanes it was first necessary to separate the sulfoxide isomers, to ascertain their isomer purity, and to assign stereochemistry. Although Backer and Keuning in 1933 reported[20] the first separation of two isomers of a thietane 1-oxide (isomerism due to configuration at sulfur), by fractional crystallization of diastereomeric platinum complexes of the optical isomers of **10**, no other reports were published in the years between their work and the start of our studies.

10

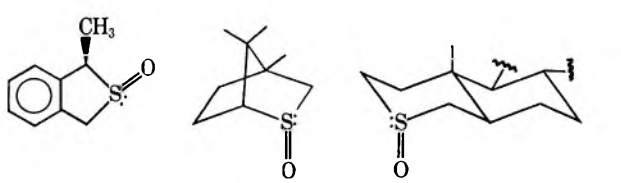
Preparative column chromatography over silica gel offered an effective method for separating the cis and trans isomers with little noticeable isomerization. Isomer purity for the sulfoxides of **1b** and **1f** was determined by vapor phase chromatography, the isomers eluting in the same order as from silica gel. For the sulfoxides of **1a**, **1c**, **1d**, and **1e** purity was determined from the nmr signals of the α-methylene hydrogens.[7b]

Dipole moment values of 3.22 ± 0.09 and 2.80 ± 0.03 D obtained for the sulfoxides of **1a** in their order of elution from silica gel were in fair agreement with values of 2.99 and 2.47 calculated from models of a puckered (37°) thietane 1-oxide, for **2a** and **3a**.[7a] From such models it is apparent that the β-ring hydrogen has a cis-diaxial relationship to the S=O bond in the trans isomer and thus should appear at significantly lower field in the nmr spectrum than the β hydrogen in the cis sulfoxide.[21] Experimentally, the β hydrogen signal for the isomer eluted first, assigned structure **2a**, appears at higher field than its counterpart in the isomer of longer retention time. Assignments for the sulfoxides of systems **1b–f** were made on this basis.[7b] For the sulfoxides assigned cis stereochemistry (**2a–f**) on the basis of the β hydrogen chemical shift, each has an α-methylene proton signal which is considerably broader than the signal for the trans isomer.[22] These assignments are supported by the recent configuration assignment made to **3d** from a dipole moment study.[8a]

The property of chromatographic retention times have been employed for the assignment of configuration to cyclic sulfoxides.[6,23–26] Elution rates from silica gel in particular have been employed, but to our knowledge the order or elution from silica gel for isomeric sulfoxides usually agrees with the order of elution from vpc columns. It is certainly noteworthy that for the six 3-substituted thietane 1-oxide systems examined the cis isomer was in each case eluted prior to the trans. The cyclic sulfoxides **11**,[6] **12**,[26] **13**,[24] **14**,[23a] and **15**[23b] are reported in the literature to have shorter retention times than their diastereomers. Retention times were also employed to distinguish **16** and **17** from their isomers; although not stated explicitly by the authors,[23b,25] it is assumed that the isomers shown here were eluted first. The apparent stereochemical feature which



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



16 **17** **15**

(18) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

(19) The thietane ring hydrogens of this material (as with **5a** and **5c**) appears as a singlet in the nmr spectrum. Thus offsetting proximity effects of the proton cis to the α-nitrogen atom and of the proton cis to the phenyl group of **7** are not a satisfacoty explanation.

(20) H. Backer and K. Keuning, *Recl. Trav. Chim. Pays-Bas*, **53**, 808 (1934).

(21) A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 1086 (1968), and previous papers.

(22) The significance of these nmr spectra will be discussed in more detail in a subsequent paper.

(23) (a) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *Chem. Commun.*, 552 (1967); (b) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *ibid.*, 550 (1967).

(24) C. R. Johnson, H. Diefenbach, J. E. Keiser, and J. C. Sharp, *Tetrahedron*, **25**, 5649 (1969).

(25) F. A. L. Anet, L. M. Sweeting, T. A. Whitney, and D. J. Cram, *Tetrahedron Lett.*, 2617 (1968).

(26) J. J. Rigau, C. C. Bacon, and C. R. Johnson, *J. Org. Chem.*, **35**, 3655 (1970).

TABLE I

OXIDATION OF 3-METHYLTHIETANE AND 3-*tert*-BUTYLTHIETANE

Reagent	Conditions solvent (°C)	3-Methylthietane 1-oxides, cis/trans	3-*tert*-Butylthietane 1-oxides, cis/trans
Dinitrogen tetroxide	(0)	75/25	82/18
Sodium metaperiodate	H_2O–MeOH (0)	59/41	51/49
tert-Butyl hypochlorite	MeOH (0)	55/45	59/41
Chromic acid	C_5H_5N (25)	54/46	70/30
Hydrogen peroxide (30%)	HOAc (0)	46/54	43/57
Hydrogen peroxide (30%)	CH_3COCH_3 (0)	46/54	43/57
m-Chloroperbenzoic acid	CH_2Cl_2 (0)	45/55	45/55
Ozone	CH_2Cl_2 (25)	41/59	
N-Chlorotriazole	MeOH (−78)	33/67	
Nitric acid	Ac_2O (0)	Sulfone	Sulfone

these isomers hold in common is a more sterically hindered sulfinyl oxygen. That is, the negative end of their S–O dipole is less accessible for association with the absorbant. Thus the axial oxygen of trans 3-substituted thietane 1-oxides must be more accessible for interaction with the absorbant than the equatorial oxygen of the cis isomer. This is apparently a result of the bulk effect of the substituent.

Although the 1200–1000 cm^{-1} region of the infrared spectra of the cis and trans 3-substituted thietane 1-oxides differ significantly in each case, the differences do not appear to follow a simple pattern which might be useful in determining stereochemistry.

Stereochemistry of Oxidation.—Our study of the stereochemical course of oxidation to sulfoxides was limited to the oxidations of the **1b** and **1f** systems for which the cis/trans ratios of products could be determined rapidly and quantitatively by vpc analysis. Our results for a variety of oxidants are presented in Table I.

The oxidation with dinitrogen tetroxide, known to occur *via* thermodynamic product control,[6] gave a predominance of the cis isomer from 3-methylthietane. This supports our earlier report that sulfinyl oxygen in a 3-substituted thietane 1-oxide has an equatorial preference.[7a] Attempts to equilibrate a mixture of **2f** and **3f** with hydrogen chloride led to decomposition.

Oxidations with peroxy reagents usually involve steric approach control,[6] yielding the isomer in which oxygen is bonded to the least hindered side of the sulfur. The less stable isomer predominates in the oxidation of both **1b** and **1f** with peroxy reagents. Thus, approach to the sulfur atom of a puckered 3-alkylthietane must be less hindered from the side trans to the substituent at C_3. If the degree of ring puckering changes little upon oxidation, the axial oxygen of the trans isomer would be least hindered for association with a chromatography absorbant, in agreement with the greater retention time observed for the trans isomer.

In general, the 3-alkylthietane systems appear to be less sensitive to the nature of the oxidant than the 4-alkylthiane system.[6]

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. The microanalyses were performed by Midwest Microlabs Inc., Indianapolis, Ind. The ir spectra were recorded on Perkin-Elmer infrared spectrophotometers, Models 137B and 621. The nmr spectra were taken on a Varian A-60A spectrometer. Vapor phase chromatography (vpc) was performed on an F and M Model 5750 (thermal conductivity) chromatograph with 0.25 in. columns. The mass spectral data was obtained on either an Atlas CH4 or an AEI MS9 mass spectrometer.

α-Morpholinostyrene.—A solution of 60 g (0.5 mol) of acetophenone, 65 g (0.75 mol) of redistilled morpholine, 45 mg of *p*-toluenesulfonic acid, and 150 ml of benzene was refluxed over a water separator until no further separation of water was observed (10–14 days). After concentration of the solution to a yellow oil vpc analysis indicated a mixture (~1/3) of acetophenone and a material of higher retention time. Reduced pressure distillation of the oil afforded 16.0 g of pure enamine, bp 85° (0.08 mm) [lit.[27a] bp 86–89° (0.1 mm)], ir (film) strong absorption at 1540 and 1590 cm^{-1}.

3-Phenyl-3-morpholinothietane 1,1-Dioxide (5c).—This reaction was run under nitrogen using either the pure enamine or a crude enamine–acetophenone mixture. Morpholinostyrene (0.5 mol), 51.0 g (0.5 mol) of triethylamine, and 200 ml of solvent (ether or benzene) were cooled to 0° in a 1-l. three-necked flask. Methanesulfonyl chloride (57.2 g, 0.5 mol) was added dropwise with stirring over a 45-min period. The ice bath was removed and the stirring was continued for 12 hr at room temperature. The yellow slurry was filtered and the residue washed with solvent. The residue was swirled with 400 ml of water (to remove triethylamine hydrochloride), filtered, and recrystallized from ethanol to yield white crystals: mp 193.5–194°; ir ($CHCl_3$) 1120 and 1320 cm^{-1} (sulfone); nmr ($CDCl_3$) δ 2.25 (m, 4), 3.70 (m, 4), 4.45 (s, 4), and 7.27 (m).

Anal. Calcd for $C_{13}H_{17}O_3NS$: C, 58.40; H, 6.41. Found: C, 58.33; H, 6.57.

The combined filtrate and organic washes from above were concentrated *in vacuo*; 50 ml of ethanol was added and on cooling white crystals, mp 86–89°, were obtained. Recrystallization from ethanol yielded *N*-methanesulfonylmorpholine as white plates: mp 91–93.5° (lit.[27b] mp 90–91°); ir ($CHCl_3$) 960, 1075, 1110, 1158, and 1345 cm^{-1}; nmr ($CDCl_3$) δ 2.78 (s, 3), 3.17 (m, 4), and 3.90 (m, 4).

The yield of **5c** from the reaction with pure enamine in benzene was 74% and from crude enamine in benzene or ether it was 33 or 46%, respectively.

When pure enamine was employed in this reaction α-methylsulfonylacetophenone was obtained in low yield as a by-product, crystallizing from solution after the cycloaddition product. After two recrystallizations from ethanol white crystals were obtained: mp 106.5–107° (lit.[28] mp 106–107°); ir ($CHCl_3$) 1675, 1324, 1277, 1151, and 1122 cm^{-1}; nmr ($CDCl_3$) δ 3.12 (s, 3), 4.61 (s, 2), and 7.5–8.1 (m, 5).

3-Phenylthiete 1,1-Dioxide (6c).—To a solution of 0.02 mol of **5c** in 10 ml of glacial acetic acid and 10 ml of acetic anhydride at ice bath temperature, was added dropwise with stirring 4.6 g (an excess) of 30% hydrogen peroxide solution. The reaction mixture was stirred over night at room temperature and then cooled again to ice bath temperature and neutralized with a concentrated solution of sodium hydroxide. Pyrolysis of the amine oxide was effected by heating the reaction mixture *in vacuo* on a rotary evaporator at ~65° for 2 hr or until dry. The residue was washed thoroughly with 60 ml of water, filtered, and recrystallized from ethanol to yield white crystals: mp 145–147°;

(27) (a) S. Huenig, K. Hiebner, and E. Benzing, *Chem. Ber.*, **95**, 926 (1962); (b) A. G. Kostsova, E. I. Kozachenko, O. M. Osina, V. P. Volokhova, and L. D. Maslova, *Zh. Org. Khim.*, **1**, 728 (1965).

(28) H. D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1897 (1963).

yields 90–97.5%; ir ($CHCl_3$) 1125, 1310, 1563 (w), 1600 cm^{-1}; nmr ($CDCl_3$) δ 4.47 (s, 2), 7.00 (s, 1), 7.45 (s, 5).

Anal. Calcd for $C_9H_8O_2S$: C, 59.98; H, 4.47. Found: C, 60.18; H, 4.66.

3-Phenylthietane 1,1-Dioxide (4c). Procedure A.—A solution of 3.0 g (17.3 mmol) of **6c** and 0.70 g (~35 mmol) of sodium borohydride in 10 ml of dimethylformamide was heated with stirring for 1 hr at 60–70°. Stirring was continued at room temperature for an additional 8 hr. The solution was cooled in an ice bath and acidified with 1 *N* sulfuric acid. A white precipitate was collected and recrystallized from methanol to yield 1.12 g (37%) of white crystals: mp 101–102°; ir ($CHCl_3$) 1130, 1324, and 1600 cm^{-1}; nmr ($CDCl_3$) δ 3.93–4.75 (m, 5), and 7.38 (s, 5).

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.39; H, 5.74.

Procedure B.—To 1.2 g (an excess) of sodium borohydride in 50 ml of isopropyl alcohol at 60° was added 1.0 g of sulfone **6c** in small amounts over a 2-hr period. Stirring was continued at 60° for 4 days; an additional 100 mg of sodium borohydride was added the first day and again after the second. The reaction mixture was cooled, made slighlty acidic by dropwise addition of dilute sulfuric acid, and evaporated *in vacuo* to dryness. The residue was extracted with hot ethyl acetate. The extract was concentrated *in vacuo* to an oil which was placed on a short column of silica gel. Elution with ethyl acetate yielded 0.65 g (65%) of pure **4c**.

3-Phenylthietane (1c).—To 400 mg (~10 mmol) of lithium aluminum hydride in 30 ml of anhydrous ether at ice bath temperature was added dropwise with stirring a solution of 600 mg (3.42 mmol) of **4c** in 100 ml of ether. After stirring for 1 hr at ice bath temperature, saturated sodium sulfate solution was added dropwise until the reaction mixture turned white. The ether layer was decanted and the residue was washed with methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield 389 mg of colorless oil. Chromatography over silica gel with methylene chloride as eluent yielded 150 mg (31%) of a colorless oil which produced only one peak on vpc analysis; ir, no sulfone bands; nmr ($CDCl_3$) δ 3.15–3.75 (m, 4), 4.3–4.9 (m, 1), and 7.3 (s, 5).

The mercuric chloride adduct was a white solid, mp 147–149°.

Anal. Calcd for $C_9H_{10}Cl_2HgS$: C, 25.63; H, 2.39. Found: C, 25.53; H, 2.42.

***cis*- and *trans*-3-Phenylthietane 1-Oxides (2c and 3c).**—To 330 mg of crude sulfide **1c** in 12 ml of reagent acetone at ice bath temperature added 160 mg (1.4 mmol) of 30% hydrogen peroxide. The solution was stirred at room temperature for 11 hr. The reaction mixture was concentrated *in vacuo* to a yellow oil. Chromatography of the oil over silica gel (elution by hexane, methylene chloride, and 1:1 (v/v) methylene chloride and chloroform) yielded 106 mg of the cis sulfoxide (**2c**) as white crystals, mp 91–91.5°, and 150 mg of the trans sulfoxide (**3c**) as a colorless oil. The cis isomer was eluted prior to the trans. The ir spectra of the two isomers differed in the 1250–950 cm^{-1} region. From the nmr spectra stereochemical assignments could be made and the isomer purity could be determined.[7b]

Anal. Calcd for $C_9H_{10}OS$ (cis isomer, **2c**): C, 65.02; H, 6.06. Found: C, 64.78; H, 6.09.

A mercuric chloride adduct (3:2) of the trans sulfoxide (**3c**) was prepared, white solid, mp 119–120°.

Anal. Calcd for $C_{18}H_{20}Cl_6Hg_3O_2S_2$: C, 18.85; H, 1.76. Found: C, 19.23; H, 1.90.

3-Morpholino-3-*p*-chlorophenylthietane 1,1-Dioxide (5a).—Crude *p*-chloro-α-morpholinostyrene was treated with triethylamine and methanesulfonyl chloride under conditions identical with those described for the preparation of **5c**. Higher yields were obtained (52% based on starting ketone) when benzene (*vs.* ether) was employed as the solvent. Recrystallization of the crude product from ethanol yielded white crystals: mp 193–194°; ir ($CHCl_3$) 1120, 1325, 1600 cm^{-1}; nmr ($CDCl_3$) δ 2.27 (m, 4), 3.70 (m, 4), 4.41 (s, 4), and 7.27 (q, 4).

Anal. Calcd for $C_{13}H_{16}ClNO_3S$: C, 51.74; H, 5.34. Found: C, 51.59; H, 5.63.

3-*p*-Chlorophenylthiete 1,1-Dioxide (6a).—The oxidation and amine oxide pyrolysis were conducted as described for the preparation of 3-phenylthiete 1,1-dioxide. The crude product was recrystallized from ethanol to yield white needles: mp 244.5–246°; yields were 90% or better; ir ($CHCl_3$) 1095, 1130, 1310, and 1600 cm^{-1}.

Anal. Calcd for $C_9H_7ClO_2S$: C, 50.36; H, 3.29. Found: C, 50.52; H, 3.49.

3-*p*-Chlorophenylthietane 1,1-Dioxide (4a). Procedure A.—A solution of 5.0 g (23.2 mmol) of unsaturated sulfone **6a** and 5.0 g (132 mmol) of sodium borohydride in 25 ml of dimethylformamide was heated with stirring at 60–65° for 3 to 4 hr. The solvent was removed under reduced pressure with gentle heating. To the residue was added 15 ml of water and the mixture was quickly acidified (dilute sulfuric acid) and filtered. The white residue was washed with water and recrystallized from methanol to yield 2.27 g (45%) of white plates: mp 116.5–118°; ir ($CHCl_3$) 1015, 1095, 1135, 1320, 1395, and 1490 cm^{-1}.

Anal. Calcd for $C_9H_9ClO_2S$: C, 49.89; H, 4.19. Found: C, 49.72; H, 4.33.

Procedure B.—The reduction of **6a** to **4a** could also be effected with sodium borohydride in isopropyl alcohol as described above for synthesis of **4c**; the yield of **4a** was 65% by this method.

3-*p*-Chlorophenylthietane (1a).—The saturated sulfone (**4a**) was reduced with lithium aluminum hydride in ether by a procedure analogous to that employed in the synthesis of **1c**. After chromatography of the crude product over silica gel (eluting with benzene) a yield (33%) of colorless oil was obtained which exhibited only one peak on vpc analysis; ir ($CHCl_3$) 1009, 1090, and 1489 cm^{-1} (no SO_2 bands).

Anal. Calcd for C_9H_9ClS: C, 58.53; H, 4.91. Found: C, 58.73; H, 5.06.

***cis*- and *trans*-3-*p*-Chlorophenylthietane 1-Oxides (2a and 3a).**—To 680 mg (3.64 mmol) of sulfide **1a** in 40 ml of reagent methylene chloride at 0° was added dropwise with stirring 700 mg (~3.6 mmol) of *m*-chloroperbenzoic acid in 20 ml of methylene chloride. After stirring at 0° for 12 hr the reaction mixture was filtered and the residue washed with methylene chloride. The filtrate was washed with saturated sodium hydrogen carbonate solution, dried, dried ($MgSO_4$), and concentrated *in vacuo* to an oil which crystallized on standing. The mixture could be resolved by chromatography over silica gel [eluting with hexane, methylene chloride, and a 1:1 (v/v) mixture of methylene chloride and chloroform]. The cis sulfoxide was eluted first as white crystals, mp 89–89.5°, the trans isomer as white crystals, mp 87–88.5°. The ir spectra differ significantly in the 1250–950 cm^{-1} region. Stereochemical assignments were based on dipole moments and were substantiated by the nmr spectra.

Anal. Calcd for C_9H_9ClOS (a mixture of the two isomers): C, 53.86; H, 4.52. Found: C, 53.91; H, 4.64.

Dipole Moments of *cis*- and *trans*-3-*p*-Chlorophenylthietane 1-Oxide (2a and 3a).—The dipole moments were measured with a Dipolemeter DM01 manufactured by Wissenschaftlich-Technische Werkstatlen using the measurement of the dielectric constant by the Heterodyne Beat Method according to the procedure of Allinger and Allinger.[29] The dipole moments were measured in benzene solution at 25 ± 0.01°. The dipole moment data for **3a** are α = 11.4557, β = 0.8331, e_1 = 2.27485, P_2 = 211.35, d_1 = 0.873011, R_D = 50.81, giving a dipole moment of 2.80 ± 0.03 D; for **2a** the data are α = 15.2567, β = 0.9656, e_1 = 2.27430, P_2 = 263.20, d_1 = 0.872929, R_D = 50.81, giving a dipole moment of 3.22 ± 0.09 D.

3-*tert*-Butyl-3-dimethylaminothietane 1,1-Dioxide.—This reaction was run in benzene using crude 2-dimethylamino-3,3-dimethylbutene[18] and employing the procedure described earlier for the synthesis of **5c**. The reaction mixture was filtered and the residue washed with benzene. The combined filtrate and washes were concentrated *in vacuo* to a brown oil. The oil was dissolved in 10% hydrochloric acid and the insolubles were discarded. Neutralization of the acid solution precipitated the crude product. After several recrystallizations from hexane a 31% yield of white needles, mp 104–104.5°, was obtained: ir ($CHCl_3$) 1135 and 1300 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 1.05 (s, 9), 2.60 (s, 6), and 4.10 (s, 4).

Anal. Calcd for $C_9H_{19}NO_2S$: C, 52.59; H, 9.34. Found: C, 52.61; H, 9.31.

3-*tert*-Butylthiete 1,1-Dioxide (6b).—The oxidation and amine oxide pyrolysis were carried out as described in the preparation of **6c**. Recrystallization of the crude product from hexane gave an 80% yield of white crystals: mp 65–65.5°; ir ($CHCl_3$) 1150, 1305, (SO_2), 1590 cm^{-1} (C=C); nmr (CCl_4) δ 1.20 (s, 9), 4.25 (s, 2), and 6.25 (s, 1).

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.46; H, 7.56. Found: C, 52.40; H, 7.39.

(29) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

3-*tert*-Butylthietane 1,1-Dioxide (4b).—To a solution of 8.0 g (0.05 mol) of 3-*tert*-butylthiete 1,1-dioxide in 70 ml of absolute ethanol was added 500 mg of 5% palladium on carbon. The mixture was placed on a Parr hydrogenation apparatus with hydrogen pressure of 40 psi for 2.5 days. The hydrogenation mixture was then filtered and concentrated *in vacuo* to a yellow oil. Vpc analysis showed only one component, which had a retention time shorter than that of starting material. Recrystallization from hexane gave 7.1 g (88%) of hydroscopic yellow-white crystals: mp 37–39°; ir (CCl_4) 1140, 1320 cm^{-1} (SO_2); nmr (CCl_4) δ 0.95 (s, 9), 2.50 (m, 1), and 3.92 (d, 4).

Anal. Calcd for $C_7H_{14}O_2S$: C, 51.81; H, 8.71. Found: C, 51.74; H, 8.73.

3-*tert*-Butylthietane (1b).—To 1.85 g (47 mmol) of lithium aluminum hydride in 70 ml of anhydrous ether at ice bath temperature was added dropwise with stirring a solution of 1.85 g (11.4 mmol) of sulfone (4b) in 100 ml of ether. Stirring was continued at ice bath temperature for 1 hr. An additional 100 ml of ether was added and the normal work-up procedure with saturated sodium sulfate solution was followed to yield 1.26 g of colorless oil. Chromatography over silica gel (eluting with hexane) yielded 842 mg (56%) of a colorless volatile oil for which vpc analysis showed only one peak. The infrared spectrum was void of sulfone absorption bands: nmr (CCl_4) δ 0.87 (s, 9), and 3.03 (m, 5).

The mercuric chloride adduct was obtained as a white solid, mp 177.5–178.5°.

Anal. Calcd for $C_7H_{14}Cl_2HgS$: C, 20.93; H, 3.51. Found: C, 21.08; H, 3.57.

***cis*- and *trans*-3-*tert*-Butylthietane 1-Oxides (2b and 3b).**—To 775 mg (3.7 mmol) of sodium metaperiodate in 8 ml of water at ice bath temperature was added 470 mg (3.7 mmol) of crude sulfide in 6 ml of methanol. The mixture was stirred at ice bath temperature for 12 hr. The reaction mixture was filtered and the filtrate extracted with chloroform. The dried (Na_2SO_4) extract was concentrated *in vacuo* to a yellow oil. Vpc analysis indicated approximately equivalent amounts of the two sulfoxides and a small amount of sulfone. The sulfoxide mixture could be resolved by elution chromatography over silica gel, eluting first with methylene chloride followed by 1:1 (v/v) methylene chloride and chloroform. The cis sulfoxide was eluted first (both sulfoxides are oils). Stereochemical assignments were based on the nmr spectra.[7b] The isomer purity was determined by vpc analysis on a 5-ft FFAP (on Chromosorb W) column at 145°. The ir spectra of the two sulfoxides differed in the region of 1200–1000 cm^{-1}. Oxidation of the sulfoxides yielded the sulfone 4b. Mass spectra for 2b (70 eV): *m/e* (relative intensities for *m/e* above 40) 41 (62), 43 (10), 55 (34), 57 (100), 69 (27), 83 (11), 97 (11), and 146 (30); for 3b, 41 (65), 43 (15), 55 (34), 57 (100), 69 (26), 83 (12), 97 (10, and 146 (25). The calculated molecular weight is 146.

3-Chlorothietane (1d).—This oil was prepared from 3-thietanol[30] according to the procedure of Kotin.[5a] A yield of 33% was obtained.

***cis*- and *trans*-3-Chlorothietane 1-Oxides (2d and 3d).**—To 1.09 g (10 mmol) of sulfide 1d in 29 ml of methylene chloride stirring at ice bath temperature was added 2.0 g (10 mmol) of *m*-chloroperbenzoic acid in 35 ml of methylene chloride. After stirring for 8 hr at ice bath temperature the mixture was filtered. The filtrate was diluted with chloroform and washed with saturated sodium hydrogen carbonate solution. The dried (Na_2SO_4) filtrate was concentrated *in vacuo* to 1.07 g of yellow oil. The two sulfoxides could be separated by chromatography over silica gel (eluting with 1:2 chloroform and methylene chloride). The cis isomer was eluted first, white crystals with mp 92–94° (lit.[5a] mp 91–93°). The trans isomer, white crystals, had mp 74–76° (lit. mp 70–72°[5a] or 74–75°[8a]). A stereochemical assignment is reported in the literature[8a] and is substantiated by the nmr spectra.[7b]

3-Acetoxythietane (1e).—The procedure of Adams, *et al.*,[31] was employed to convert 3-thietanol to the acetate 1e: nmr (CCl_4) δ 1.97 (s, 3), 3.33 (m, 4), and 5.53 (m, 1).

***cis*- and *trans*-3-Acetoxythietane 1-Oxide (2e and 3e).**—To 2.43 g (11.4 mmol) of sodium metaperiodate in 30 ml of water at ice bath temperature was added with stirring 1.50 g (11.4 mmol) of sulfide 1e in 3 ml of methanol. The mixture was stirred at ice bath temperature overnight and then filtered. The filtrate was extracted with chloroform and methylene chloride and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to 1.85 g of light yellow oil. Elution chromatography over silica gel with 1:1 (v/v) chloroform–methylene chloride followed by pure chloroform separated the two sulfoxides. The cis isomer was eluted prior to the trans. The ir spectra differed in the 1250–950 cm^{-1} region but isomer purity was best determined from the nmr spectra.[7b] Stereochemistry was assigned from the nmr spectra also.[7b] The cis isomer 2e was a colorless oil: mass spectrum (70 eV) *m/e* (relative intensities for *m/e* above 40) 43 (54) 46 (13), 57 (25), 60 (13), 63 (32), 88 (100), 106 (12), 147 (0.9), and 148 (0.5). The calculated mol wt is 148. The trans isomer (3e) was recrystallized from ether to yield white crystals, mp 50–52.5°.

Anal. Calcd for $C_5H_8O_3S$: C, 40.53; H, 5.44. Found: C, 40.61; H, 5.45.

3-Acetoxythietane 1,1-Dioxide (4e).—Treatment of the sulfide 1e with excess 30% hydrogen peroxide in acetone yielded the corresponding sulfone, a white crystalline solid, mp 117–117.5°.

Anal. Calcd for $C_5H_8O_4S$: C, 36.58; H, 4.91. Found: C, 36.49; H, 4.80.

3-Methylthietane (1f).—This volatile sulfide was prepared from 2-methyl-3-chloropropene according to the method of Bordwell and Hewett.[32]

***cis*- and *trans*-3-Methylthietane 1-Oxide (2f and 3f).**—These sulfoxides were recently reported by Tang and Mislow.[4c] Our samples were likewise prepared by the oxidation of 3-methylthietane and subsequent chromatography of the sulfoxide mixture over silica gel. The cis isomer was eluted prior to the trans; the stereochemical assignments have been reported.[4c] Cis/trans ratios could be determined by vpc on a 17 ft × 0.25 in. column of 7.5% Versamid on Diaport S at 126° with a helium flow of 1.5 ml/sec.

3-Methylthietane 1,1-Dioxide (4f).—Oxidation of 1f with an excess of hydrogen peroxide yielded the corresponding sulfone 4f, a colorless oil: ir (film) 2950, 1395, 1310, 1220, 1195 (sh), and 1160 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (d, 3), 2.65 (m, 1), 3.95 (m, 4).

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71. Found: C, 39.79; H, 6.83.

3-Morpholino-3-phenylthietane (7).—To 7.00 g (26.2 mmol) of sulfone 5c and 3.8 g (100 mmol) of lithium alumuminum hydride was added dropwise 200 ml of anhydrous ether, keeping the reaaction flask in an ice bath. Stirring was continued at 0° for 10 hr after which time the excess lithium aluminum hydride was decomposed by dropwise addition of ethanol. The reaction mixture was made slightly acidic with 20% hydrochloric acid and the ether layer was decanted. The aqueous residue was extracted with ether and the combined ether extracts were dried ($MgSO_4$) and concentrated *in vacuo* to 4.4 g of an oil which crystallized in ethanol–hexane. Recrystallization from ethanol yielded 2.35 g (38%) of white crystals: mp 104–105°; ir ($CHCl_3$) no sulfone bands; nmr ($CDCl_3$) δ 2.25 (m, 4), 3.3–3.8 (m, 8), 7.35 (s, 5).

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.22; H, 7.29; N, 5.79.

Base Hydrolysis of 5c.—A mixture of amino sulfone 5c (0.5 g), sodium hydroxide (3.0 g), water (30 ml), and methanol (30 ml) was heated on a steam bath for 2 hr and the methanol was allowed to evaporate. On cooling 0.25 g of unreacted starting material was collected by filtration. The aqueous filtrate was extracted with methylene chloride and the dried ($MgSO_4$) extract was concentrated *in vacuo* to 0.15 g of white solid. Recrystallization from ether–petroleum ether yielded 0.06 g of white crystals identified as the enamine 9: ir ($CHCl_3$) 1552, 1320, 1145, and 1118 cm^{-1}; nmr ($CDCl_3$) δ 3.0 (s, 3), 3.0–3.15 (m, 4), 3.6–3.8 (m, 4), 5.45 (s, 1), and 7.5 (m, 5). A second crop of crystals, 0.02 g, was identified as dimethyl sulfone, a mixture melting point showed no depression.

If the aqueous filtrate above was acidified before extraction with methylene chloride, the β keto sulfone 8, identified earlier, was isolated; a mixture melting point showed no depression.

Base Hydrolysis of 3-Phenylthiete 1,1-Dioxide (6c).—A mixture of sulfone 6c (0.5 g), sodium hydroxide (3.0 g), water (30 ml), and methanol (30 ml) was heated on the steam bath for 2 hr. After cooling and acidification with dilute sulfuric acid a white solid precipitated. The white solid, 0.18 g, was collected

(30) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961).

(31) E. P. Adams, K. N. Ayad, E. P. Doyle, D. O. Holland, W. H. Hunter, J. H. C. Nyler, and A. Queen, *J. Chem. Soc.*, 2665 (1960).

(32) F. G. Bordwell and W. A. Hewett, *J. Org. Chem.*, **27**, 292 (1962).

by filtration, dried, and compared with an authentic sample of benzoic acid. The ir spectra were superimposable and a mixture melting point showed no depression. The aqueous layer was extracted with methylene chloride and the dried extract was concentrated *in vacuo* to ~0.3 g of white solid. After recrystallization this solid was identified as dimethyl sulfone by ir and a mixture melting point. Under the conditions described above 3-*p*-chlorophenylthiete 1,1-dioxide was converted to *p*-chlorobenzoic acid and dimethyl sulfone.

Reduction of 3-Phenylthiete 1,1-Dioxide (6c) with Lithium Aluminum Hydride.—A solution of lithium aluminum hydride (1.0 g) in 50 ml of freshly distilled THF was refluxed for 30 min. To this was added dropwise with stirring 1.0 g of sulfone (6c) in 50 ml of THF; addition time was 45 min. Stirring was continued at room temperature for 12 hr after which the excess hydride was decomposed with a 20% ammonium chloride solution. The organic layer was filtered and the residue was washed with ether. The dried ($MgSO_4$) organic solution was concentrated *in vacuo* to a foul smelling oil which was analyzed as predominantly a single component on vpc. This major component, a colorless oil, was collected from vpc and tentatively identified as 2-phenylpropanethiol: ir (film) 3000–2850, 1600, 1490, 1440, 1365 (w), 1060 (w), 1010 (w), 905 (w), 755, and 690 cm^{-1}; nmr (CCl_4) δ 1.0 (t, 1), 1.35 (d, 3), 2.5–2.9 (m, 3), and 7.17 (s, 5). On shaking the nmr sample with D_2O the triplet at δ 1.0 disappeared and the multiplet at δ 2.5–2.9 became less complex.

H–D Exchange of α-Methylene Protons of Thietane 1,1-Dioxide.—Sodium (60 mg, 2.5 mg-atoms) was added to 2.60 g (130 mmol) of deuterium oxide; to that solution was added 2.75 mmol of sulfone **4a** or **4b** in 6 ml of dioxane. The mixture was heated with stirring at 40–50° for 24 hr; stirring was continued at room temperature for an additional 24 hr. Concentrated hydrochloric acid (2.5 ml) was added with stirring. The reaction mixture was evaporated *in vacuo* to dryness and the residue was extracted with ethyl acetate. The extract was concentrated and the residue was recrystallized from methanol to yield 88% of the α-tetradeuterated sulfone. The melting point and ir spectrum remained very similar to that of starting material. In the nmr spectrum the signal for the α-methylene protons had disappeared and the multiplet for the methine proton collapsed to a broad singlet.

The α-tetradeuterated thietane derivatives were reacted under the same conditions as their hydrogen analogs.

Oxidation of Thietanes.—The general methods of oxidation employed for the oxidation study were reported earlier.[6] The use of *N*-chlorotriazole as an oxidant for sulfides has been reported in a more recent communication from this laboratory.[33] Special care was observed to avoid over oxidation to sulfone, less than 1 equiv of oxidant per mole of sulfide was employed. The ratios given in Table I were obtained from planimetric integration of the vpc graphs.

Registry No.—**1a**, 25903-01-9; **1b**, 25903-02-0; mercuric chloride adduct of **1b**, 25903-03-1; mercuric chloride adduct of **1c**, 25957-63-5; **1f**, 22438-40-0; **2a**, 25902-65-2; **2b**, 25902-66-3; **2c**, 25902-67-4; **3a**, 25902-68-5; **3b**, 25902-69-6; mercuric chloride adduct of **3c**, 25902-70-9; **3e**, 25902-71-0; **4a**, 25903-04-2; **4b**, 25903-05-3; **4c**, 25636-64-0; **4e**, 25903-14-4; **4f**, 25903-07-5; **5a**, 25903-08-6; **5c**, 25957-61-3; **6a**, 25903-15-5; **6b**, 25903-16-6; **6c**, 25903-17-7; **7**, 25903-18-8; 3-*tert*-butyl-3-dimethylaminothietane 1,1-dioxide, 25957-62-4.

Acknowledgment.—We gratefully acknowledge the very able technical assistance of Mr. A. Geertsema with the synthesis of 3-*tert*-butylthietane and of Mr. H. Levin with the oxidation study of 3-methylthietane. We are also grateful to Mr. J. Sprague for the dipole moment determinations.

(33) W. D. Kingsbury and C. R. Johnson, *Chem. Commun.*, 365 (1969).

The Stevens Rearrangements of *N,N,N*-Trimethylneopentylammonium Iodide[1]

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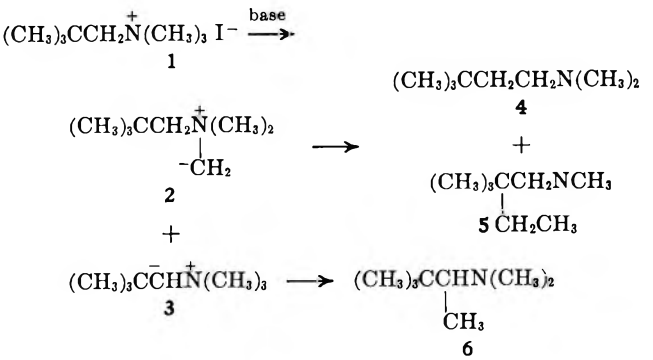
The Stevens rearrangements of *N,N,N*-trimethylneopentylammonium iodide (**1**) have been investigated using a series of base–solvent systems. In all cases 3,3,*N,N*-tetramethyl-1-butylamine (**4**) is the major rearrangement product, with *N*-ethyl-*N*-methylneopentylamine (**5**) and 3,3,*N,N*-tetramethyl-2-butylamine (**6**) being formed in low yields. In addition, *N,N*-dimethylneopentylamine (**7**) from a displacement reaction becomes the major product in more acidic solvents. Thermal decomposition (294°) leads to **7** and methyl iodide. An ion-pair rearrangement pathway is proposed consistent with the minor side products, *N,N*-dimethylbenzylamine (**10**), from phenyllithium, *N,N*-dimethyl-1-pentylamine (**11**) from *n*-butyllithium, and neopentane (**9**).

Although the Stevens rearrangement[2] of quaternary ammonium salts has been the subject of many studies since its discovery in 1932,[3] very little work has been reported using simple alkylammonium systems.[4] As a continuation of our interest in this area, we have studied the Stevens rearrangements of *N,N,N*-trimethylneopentylammonium iodide (**1**) with a series of base–solvent systems. The quaternary ammonium salt **1** has the characteristic of being the potential precursor for three different Stevens rearrangement products, **4**, **5**, and **6**, through ylides of similar carbanion stability,[5] **2** and **3**,



but differing steric requirements. In the following we report the results of this study and their relevance to the mechanism of the Stevens rearrangement.

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(1) The authors thank the National Science Foundation and the donors of the Petroleum Research Fund for partial support of this work.

(2) T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.*, 3193 (1928).

(3) For leading references, see S. H. Pine, *Org. React.*, **18**, 403 (1970).

(4) (a) H. Daniel and J. Paetsch, *Chem. Ber.*, **101**, 1445 (1968); (b) W. K. Musker, *J. Org. Chem.*, **32**, 3189 (1967); (c) G. Wittig and D. Krauss, *Justus Liebigs Ann. Chem.*, **679**, 34 (1964).

(5) D. J. Cram in "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 21.

Results

N,N,N-trimethylneopentylammonium iodide (**1**) was allowed to react with a series of base–solvent systems under dry nitrogen. Products were separated into basic and nonbasic fractions for analysis by gas chromatography. The basic products were positively identified by separation through preparative gas chromatography and comparison of the nmr and ir spectra of the recovered samples with the spectra of independently synthesized materials. The average results of many runs are compiled in Table I.

TABLE I
STEVENS REARRANGEMENTS OF *N,N,N*-TRIMETHYLNEOPENTYLAMMONIUM IODIDE

Base–solvent	Basic products, % 4	5	6	7
n-C_4H_9Li–hexane[a]	86	5.1	0[b]	9.3
n-C_4H_9Li–hexane, TMEDA[c]	81	2.1	1.3	16
n-C_4H_9Li–HMPA[a]	73	1.2	0.4	25
C_6H_5Li–HMPA[a]	77	2.5	1.2	19
C_6H_5Li–$(C_2H_5)_2O$, C_6H_6	97	1.0	0	1.7
n-C_4H_9Li–DMSO[a]	0	0.7	0	99
$NaNH_2$–NH_3 (liquid)	*d*			*d*
$KOC(CH_3)_3$–$(CH_3)_3COH$				*e*

[a] Average of runs. [b] In one case a trace peak with the retention time of **6** was observed. [c] Tetramethylethylenediamine. [d] Low yield provided only qualitative data, **4**:**7** ≈ 1:5. [e] Only basic product observed.

All three potential rearrangement products are found, with 3,3,*N*,*N*-tetramethyl-1-butylamine (**4**) predominant in all cases. In less basic systems the rearrangements are notably inhibited and the nonrearranged tertiary amine, *N*,*N*-dimethylneopentylamine (**7**), pre-

$(CH_3)_3CCH_2N(CH_3)_2$
7

dominates. Additional basic materials, *N*,*N*-dimethylbenzylamine (**10**) and *N*,*N*-dimethyl-1-pentylamine (**11**), are also observed when the base used is phenyllithium or n-butyllithium, respectively.

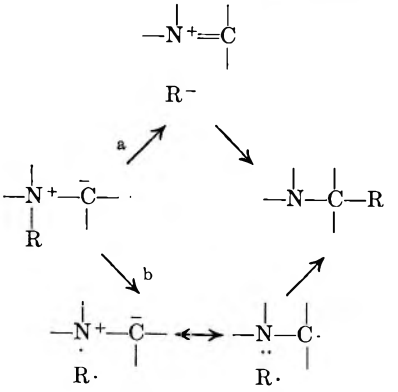
Discussion

The observation that **4** is the major rearrangement product suggests that the relief of internal nonbonded interactions is significant in directing the reaction pathway. In a related study only the product analogous to **4** was obtained from *N*,*N*,*N*-trimethyl-2,2,2-triphenylethylammonium iodide. In this case the authors suggested that a combination of steric and electronic factors may be involved.[6] (It is interesting to note, however, that the reductive cleavage of **1** with sodium–ammonia results principally in methyl cleavage, a result which does not appear to involve significant steric acceleration.[6]) Consistent with this is the formation of only small amounts of **5** which also originates from the ylide **2**, but provides little relief of strain. We would not expect electronic factors to be important in directing the rearrangement of ylide **2** in this case, although such control would probably favor methyl over neopentyl migration.

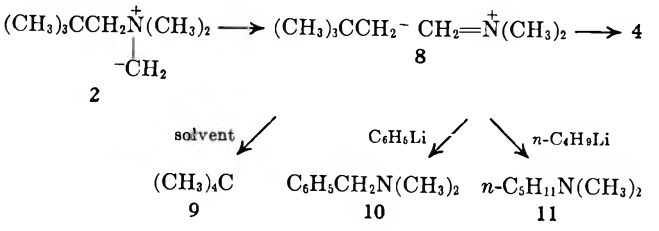
The detection of only minor amounts of **6** in some of the rearrangement system is not surprising since formation of the ylide **3** is expected to be sterically quite hindered. In fact, **6** is observed only with the base–solvent systems generally found to be particularly reactive. This is exemplified by the formation of **6** on the addition of tetramethylethylenediamine (TMEDA) to an n-butyllithium–hexane run. TMEDA is known to depolymerize the reagent and markedly increase its activity.[7]

The relatively greater yield of **7** in hexamethylphosphoramide (HMPA), presumably from a methyl displacement, reflects an expected enhancement of nucleophilic reactivity of the base in this polar aprotic solvent. This is further indicated by the comparison of the phenyllithium and n-butyllithium results where n-butyl is the better nucleophile. Although **1** is thermally stable under our reaction conditions, it does decompose at its melting point (294°) to give **7** and methyl iodide. In the more acidic solvents, dimethyl sulfoxide, ammonia, and *tert*-butyl alcohol, formation of the requisite ylides (**2** or **3**) is not favored and displacement to give **7** becomes the major pathway. *tert*-Butyl methyl ether from such a displacement was detected when potassium *tert*-butoxide was the base.

Two dissociation–recombination mechanisms are currently being considered for the Stevens rearrangement. The ion-pair pathway (a) initially proposed by Stevens[8] and reintroduced by Jenny,[9] and the radical-pair pathway (b) suggested by Schöllkopf.[10]



We believe that the ion-pair mechanism is most consistent with our results. Neopentane (**9**) has been found as a nonbasic product from the rearrangement as expected from collapse of the carbanion portion of the ion-pair **8** with solvent. In addition, the amines **10** and **11**, presumed to arise by reaction of the methylene immonium cation portion of **8** with the base, were also detected. Although these products were found in low



(6) E. Grovenstein, Jr, and L. C. Rogers, *J. Amer. Chem. Soc.*, **86**, 854 (1964).

(7) C. G. Screttas and J. F. Eastham, *ibid.*, **87**, 3276 (1965).

(8) (a) T. S. Stevens, *J. Chem. Soc.*, 2107 (1930); (b) T. Thomson and T. S. Stevens, *ibid.*, 55 (1932).

(9) E. F. Jenny and J. Druey, *Angew. Chem., Int. Ed. Engl.*, **1**, 155 (1962).

(10) U. Schöllkopf and U. Ludwig, *Chem. Ber.* **101**, 2224 (1968).

yield, their relevance to the major reaction pathway seems reasonable. The Stevens rearrangement is known to be highly stereospecific[11] and intramolecular[12] and probably occurs within a tight solvent cage. It is not surprising, therefore, that only a small degree of escape from the cage is observed.

The dimer **12** expected from a radical-pair intermediate[13a] was shown not to be present by gas chromatographic analysis. An attempt to observe chemically induced dynamic polarization (CIDNP) evidence for a radical pathway[13] was unsuccessful. This may, however, be due to experimental difficulties in this system.

$(CH_3)_3CCH_2CH_2C(CH_3)_3$
12

Although the recent observations of CIDNP during product formation in some Stevens rearrangements suggest the involvement of a radical pair,[13] the application of this data to a mechanistic sequence is not clear since substituent effect studies may be consistent with an ionic mechanism.[8b] A competition between the ionic (a) and radical (b) pathways which would result in significant contributions from both seems thermodynamically unreasonable. Possibly both pathways are involved in a sequential rather than competitive pathways. We are currently involved in studies in an attempt to determine the importance of these two potential pathways to the base-promoted rearrangements of quaternary ammonium salts.

Experimental Section

Nmr spectra were obtained using a Varian A-60 spectrometer. Chemical shifts are reported as downfield from internal TMS. Melting points were taken using a Hoover apparatus and are not corrected. Gas chromatographic analyses were obtained on an F & M Model 700 or 720 instrument using a Carbowax 20M or in some cases a Chromosorb 103 column. Peak areas were measured using a Disc integrator and predetermined correction factors for each rearrangement product. Rearrangement products were identified by separation using gas chromatography and comparison of retention times and spectral data with independently synthesized materials.

n-Butyllithium was obtained from Foote Mineral Co. as a solution in hexane. Phenyllithium was obtained from Alfa Chemical Co. as a solution in benzene–ether or was prepared[14] as needed. Potassium *tert*-butoxide was obtained from MSA Corp. Sodium amide was prepared as needed.[15] Solvents were dried and distilled.

***N,N,N*-Trimethylneopentylammonium Iodide (1).**—The reaction of neopentylamine with formic acid–formaldehyde[16] overnight gave a 46% yield of *N,N*-dimethylneopentylamine (**7**): bp 90–95°; nmr (CCl_4) δ 0.90 [s, 9, $(CH_3)_3C$], 2.02 (s, 2, CH_2N), 2.28 [s, 6, $(CH_3)_2N$]. *N,N*-Dimethylneopentylamine (**7**) was also prepared from pivalyl chloride and dimethylamine[6] in 52% yield.

To 3.0 g (0.026 mol) of tertiary amine in 15 ml of anhydrous acetone was added 8 ml of methyl iodide. After stirring for 24 hr, the solid was recovered by filtration and recrystallized from absolute ethanol to give 6.7 g of **1** as white crystals: mp 293–294° dec; nmr ($CDCl_3$) δ 1.28 [s, 9, $(CH_3)_3C$], 3.58 [s, 9, $(CH_3)_3N$] 3.70 (s, 2, CH_2N).

Anal. Calcd for $C_8H_{20}NI$: C, 37.37; H, 7.84; N, 5.45. Found: C, 37.41; H, 8.16; N, 5.27.

3,3,*N,N*-Tetramethyl-1-butylamine (4).—To a 100-ml flask equipped with a Dry Ice condenser, stirrer, and dropping funnel, was added *tert*-butylacetyl chloride [prepared from 10.0 g (0.086 mol) of *tert*-butylacetic acid and thionyl chloride] and 20 ml of tetrahydrofuran. The solution was cooled to 0°, and then a solution of 13.0 g (0.29 mol) of dimethylamine in 25 ml of tetrahydrofuran was added dropwise. After stirring an additional 20 min, the solid was recovered by filtration and washed further with solvent. The total solvent was removed under reduced pressure and the resulting liquid distilled to give 8.6 g (71%) of *N,N*-dimethyl-*tert*-butylacetamide: bp 94–97° (23 mm).

To a flask equipped with a stirrer, reflux condenser, and dropping funnel was added 25 ml of anhydrous ether and 2.1 g (0.054 mol) of lithium aluminum hydride (all under nitrogen). *N,N*-Dimethyl-*tert*-butylacetamide (8.6 g, 0.06 mol) in 10 ml of anhydrous ether was added dropwise at a rate to maintain gentle reflux. After refluxing an additional 1 hr, the mixture was cooled and hydrolyzed with 2.1 ml of water, 2.1 ml of 15% sodium hydroxide, and 6.2 ml of water, added in that order.[17] The solids were removed by filtration and washed further with ether. The total ether phase was dried over anhydrous magnesium sulfate and distilled to give 4.5 g (58%) of **4**: bp 128–130°; nmr (CCl_4) δ 0.90 [s, 9, $(CH_3)_3C$], 1.12–1.57 (m, 2, CH_2), 2.04–2.38 (m, 2, CH_2N), 2.13 [s, 6, $N(CH_3)_2$]; HCl salt mp 260–261° dec.

Anal. Calcd for $C_8H_{20}NCl$: C, 57.99; H, 12.17; N, 8.45. Found: C, 57.43; H, 11.93; N, 8.24.

***N*-Ethyl-*N*-methylneopentylamine (5).**—*N*-Methylpivalamide was prepared as above from 70.0 g (0.58 mol) of pivalyl chloride[18] and methylamine to give, after recrystallization from petroleum ether (bp 30–60°)–tetrahydrofuran, 53.9 g (81%) of a white solid: nmr (CCl_4) δ 1.17 [s, 9, $(CH_3)_3C$], 2.73 (d, 3, NCH_3, J = 5 Hz), 7.27 (s, 1, NH).

The amide (4.25 g, 0.042 mol) was reduced using 3.66 g (0.094 mol) of lithium aluminum hydride as above. After stirring for 144 hr, work-up and distillation gave 2.41 g (57%) of *N*-methylneopentylamine: bp 88–90°; nmr (CCl_4) δ 0.60 (s, 1, NH), 0.89 [s, 9, $(CH_3)_3C$], 2.27 (s, 2, CH_2), 2.40 (s, 3, NCH_3).

To 2.4 g (0.024 mol) of *N*-methylneopentylamine in 25 ml of anhydrous acetone was added 1.9 ml (0.024 mol) of ethyl iodide. After stirring for 72 hr, the volume was reduced to 5 ml, and then 25 ml of dilute sodium hydroxide was added and the mixture extracted with pentane. The pentane was dried over anhydrous magnesium sulfate. Distillation yielded 1.1 g (37%) of *N*-ethyl-*N*-methylneopentylamine: bp 110–118°; nmr (CCl_4) δ 0.84 [s, 9, $(CH_3)_3C$], 0.98 (t, 3, CH_2CH_3, J = 7 Hz), 2.05 (s, 2, NCH_2), 2.24 (s, 3, NCH_3), 2.38 (q, 2, CH_2CH_3, J = 7 Hz); methiodide mp 261.0–262.0°.

Anal. Calcd for $C_9H_{22}NI$: C, 39.86; H, 8.18; N, 5.16. Found: C, 40.04; H, 8.28; N, 5.13.

3,3,*N,N*-Tetramethyl-2-butylamine (6).—3,3-Dimethyl-2-butylamine was prepared[19] in 17% yield: bp 102–103°; nmr (CCl_4) δ 0.82 [s, 9, $(CH_3)_3C$], 0.95 (d, 3, CH_3, J = 6 Hz), 1.28 (s, 2, NH_2), 2.56 (q, 1, CH, J = 6 Hz).

Treatment of the primary amine with formic acid–formaldehyde[16] gave a 50% yield of **6**: bp 120–126°; nmr (CCl_4) δ 0.87 (d, 3, CH_3, J = 7 Hz), 0.87 [s, 9, $(CH_3)_3C$], 2.17 (q, 1, CH, J = 7 Hz), 2.20 [s, 6, $N(CH_3)_2$]; methiodide mp 241–242°.

Anal. Calcd for $C_9H_{22}NI$: C, 39.86; H, 8.18; N, 5.16. Found: C, 40.14; H, 8.22; N, 4.82.

Neopentane (9) was obtained commercially from Cal Biochem.

***N,N*-Dimethylbenzylamine (10)** was obtained commercially from Eastman.

***N,N*-Dimethyl-1-pentylamine (11)** was prepared from 1-pentylamine using formic acid–formaldehyde[16] in 56% yield: bp 118–124°; nmr (CCl_4) δ 0.8–1.1 (m, 3, CH_3), 1.2–1.6 [m, 6, $(CH_2)_3$], 2.18 [s, 6, $N(CH_3)_2$], 2.1–2.3 (m, 2, NCH_2).

2,2,5,5-Tetramethylhexane (12).—A mixture of 2 g (0.013 mol) of neopentyl bromide and 0.09 g (0.013 g-atom) of lithium metal in 15 ml of anhydrous ether was refluxed for 4 hr, and then stirred for an additional 16 hr. Addition of water followed by separation of the organic phase, drying ($MgSO_4$), and distillation gave the crude product, bp 95–105°. Preparative gas chromatography was used to separate starting material from the major product **12**: nmr ($CHCl_3$) δ 0.84 [s, 18, $(CH_3)_3C$], 1.12 (s, 4, CH_2).

(11) B. J. Millard and T. S. Stevens, *J. Chem. Soc.*, 3397 (1963).
(12) R. A. Johnstone and T. S. Stevens, *ibid.*, 4487 (1955).
(13) (a) U. Schöllkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 3415 (1969); (b) A. R. Lepley, *Chem. Commun.*, 1460 (1969).
(14) A. I. Vogel, "Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1957, p 931.
(15) Reference 14, p 197.
(16) S. H. Pine, *J. Chem. Educ.*, **45**, 118 (1968).
(17) B. M. Micovic and M. L. J. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).
(18) H. C. Brown, *J. Amer. Chem. Soc.*, **60**, 1325 (1938).
(19) M. L. Moore, *Org. React.*, **5**, 321 (1949).

Typical Rearrangement.—To a constricted tube with a small magnetic stirrer was added 0.26 g (0.001 mol) of **1** followed by 5 ml of dry hexane and 1.3 ml of 1.6 *N* (0.002 mol) *n*-butyllithium–hexane. The tube was purged with nitrogen, sealed and placed in a bath at 75 ± 2° with stirring for 48 hr. Water (3 ml) was added to the reaction mixture, and the organic layer was separated and extracted with 3 *N* HCl. The remaining nonbasic phase was retained for further analysis. The acid extracts were made basic with 50% sodium hydroxide and the basic products extracted with pentane. Careful distillation to concentrate the product resulted in 0.1–0.2 ml of a products–pentane solution which was analyzed by gas chromatography. In one run as above, 0.2 ml of TMEDA was added and the reaction time reduced to 1 hr. Controls were also run on solvent plus salt **1** or solvent plus base and analyzed as above.

Registry No.—**1**, 26154-20-1; **4**, 15673-04-8; **4** HCl, 26153-93-5; **5**, 26153-85-5; **5** MeI, 26153-94-6; **6**, 4474-61-7; **6** MeI, 26153-95-7; **7**, 10076-31-0; **11**, 26153-88-8; **12**, 1071-81-4; *N*,*N*-dimethyl-*tert*-butylacetamide, 26153-90-2; *N*-methylneopentylamine, 26153-91-3; 3,3,*N*,*N*-tetramethyl-2-butylamine, 3850-30-4.

o-Quinone Methides. II. Trapping with Production of Chromans

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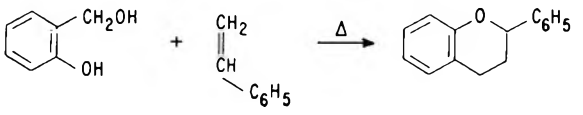
The first paper[1] demonstrated that phenoxy radicals are a precursor to the formation of the trimer **2**. They must pass through an *o*-quinone methide which could not be observed. This work demonstrates that the *o*-quinone methide can be trapped by reactive dienophiles and nucleophilic agents. A convenient synthesis of a variety of chromans results from this reaction. Only one isomer is obtained which suggests the similarity to usual diene reactions.

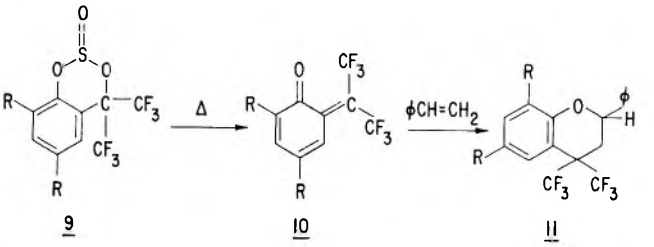
The first paper in this series[1] showed that the oxidation of 2,6-dimethylphenols (**1**) with metal oxides or basic potassium ferricyanide gave as a product a trimer. The trimer was shown to have the rather complex structure **2**. An examination of the structure suggests that it results from a diene–dienophile addition of three *o*-quinone methides **5**. However, spectroscopic evidence demonstrated that both the phenoxy radical **3** and its dimeric *o*-quinol ether dimer **4** were present and were part of the sequence of reactions that resulted in the formation of the trimer. Direct evidence of the existence of the *o*-quinone methide was lacking. It was felt that it should be possible to demonstrate the existence of an *o*-quinone methide by intercepting it with a dienophile more reactive than itself.

There have been a few examples of the presence of an *o*-quinone methide being demonstrated by its being trapped. Hultzsch[2] heated saligenin in the presence of styrene to form the chroman **8**. Other reactions of



this type have been reported[3,4] but all involve the application of heat to convert the phenol precursor to the *o*-quinone methide.

Near the end of this work, an *o*-quinone methide which is stabilized by trifluoromethyl groups was reported by Sheppard.[5] This was prepared by pyrolysis of the sulfite ester **9**. The quinone methide **10** was not isolable but reacted with styrene to give the chroman **11**.



There is another method of trapping quinone methides. This involves the addition of nucleophiles to the conjugated system. Filar and Winstein[6] have studied this addition to *p*-quinone methides, but they had no examples of an *o*-quinone methide. Very little work has been done where *o*-quinone methides have been studied in solution.

With this background of previous work, it was decided to concentrate on the generation of the sus-

(1) D. A. Bolon, *J. Org. Chem.*, **35**, 715 (1970).

(2) K. Hultzsch, *Chem. Ber.*, **74**, 898 (1941), *J. Prakt. Chem.*, **158** 275 (1941).

(3) G. R. Sprengling, *J. Amer. Chem. Soc.*, **74**, 2937 (1952).

(4) M. Wakselman and M. Vilkas, *C. R. Acad. Sci., Ser. C*, **258**, 1526 (1964).

(5) W. A. Sheppard, *J. Org. Chem.*, **33**, 3297 (1968).

(6) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).

pected *o*-quinone methide in solution in the presence of various trapping agents.

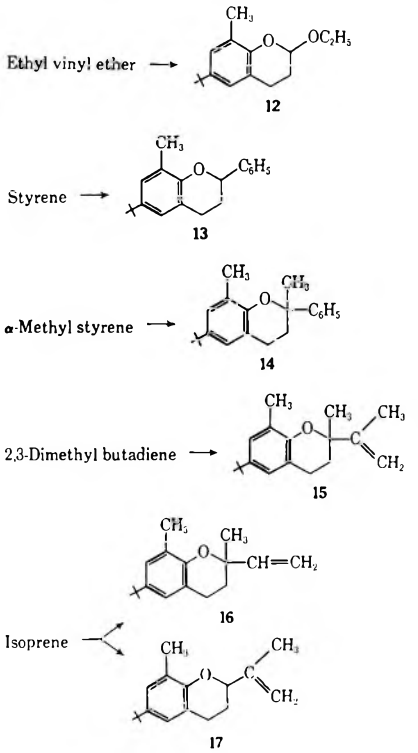
o-Quinone Methides.—The bulk of the work in this paper was done with the readily available 4-*tert*-butyl-2,6-dimethylphenol (**1**, R = *tert*-butyl). Other phenols such as 4-methoxy-2,6-dimethylphenol and 4-phenyl-2,6-dimethylphenol were used on occasion to convince us that the reaction was general but the bulk of the work was done on **1** (R = *tert*-butyl).

The first step in the metal oxide oxidation of the phenol **1** is the removal of the phenolic hydrogen to yield a phenoxy radical **3**. These radicals dimerize to yield an *o*-quinol ether **4**, which exists in equilibrium with the radical.[1] This system disproportionates to yield an *o*-quinone methide **5** and the phenol **1**. In an inert solvent the fate of the *o*-quinone methide is normally trimerization to **2**.

It was believed that **5** should have an appreciable lifetime. Previously attempts had been made to observe the group by spectroscopic means but its lifetime was too short for the methods used.

The oxidation of **1** in the presence of a variety of electron-rich dienophiles was then carried out. In Table I are shown the chromans obtained by this

TABLE I
CHROMANS FROM 4-*tert*-BUTYL-2,6-XYLENOL



method. This confirmed our belief that *o*-quinone methides were present. The reaction with ethyl vinyl ether was run using the ether as a solvent and in a 1:1 mol ratio with the phenol and using benzene as a solvent. In both cases the chief product was the chroman **12**. This reaction is a competition as the yield of the chroman is substantially lower where a 1:1 ratio of inert solvent to dienophile is used than when the dienophile is used as the solvent. When the yield of the chroman is reduced by diluting the dienophile, the other product that is obtained is the trimer corresponding to **2**.

This is demonstrated also in the case where 4-methoxy-2,6-dimethylphenol was oxidized in ethyl vinyl ether. The chief product in this reaction is the trimer **2** (R = CH_3O).

Another class of dienophile that was tried was the styrenes. Both styrene and α-methylstyrene were successful in trapping the *o*-quinone methide and gave chromans like **13** and **14**. These reagents were not so successful as the vinyl ethers and consequently the chromans had to be distilled from the trimer as well as some thermally polymerized styrene. The yields were low.

A third set of dienophiles were used and these were the dienes. One of the bonds in a conjugated diene acts as a dienophile and traps the *o*-quinone methide giving a vinylchroman like **15**. The presence of the vinyl group was demonstrated by ir and nmr spectral data and by catalytic reduction of the vinyl group in **15**.

In the case of an unsymmetrical diene like isoprene, two chromans are formed. Both result from an addition to the two different bonds of the isoprene rather than from a difference in orientation of one of the olefinic bonds. The isomer which results from the more stable intermediate **16** is favored over the one that yields **17** by a 2:1 ratio.

In Table II are listed some of the dienophiles that

TABLE II
DIENOPHILES THAT YIELD CHROMANS UPON REACTION WITH *o*-QUINONE METHIDES

Dienophile	Amount, ml	Chroman, %
None	...	...[a]
Isoprene	5	30[b]
2,3-Dimethylbutadiene	5	24
Butadiene	5	10[c]
Cyclohexadiene-1,3	5	8
Ethyl vinyl ether	5	100
Isobutyl vinyl ether	5	65[c]
α-Methylstyrene	5	13
Diethyl ketene acetal	5	20[c]
n-Propyl methylacrylate	5	6[c]
Isoprene	1	12
Isoprene	5	30
Isoprene	10	85

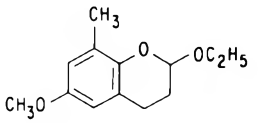
[a] The blank run showed 10% recovery of phenol indicating the silver oxide is only 90% effective or that some of the silver oxide is oxidizing something other than the phenol. [b] 20% of **10**, 10% of **11**. [c] These materials were trapped off the vpc and identified by mass spectrometry.

successfully trap the *o*-quinone methide. These were run in a standard fashion where equimolar amounts of 4-*tert*-butylxylenol and silver oxide were reacted in benzene. The dienophile was added in the amount indicated and the products then analyzed by gas chromatography. The per cent composition given under the chroman then is a measure of the trapping efficiency of the dienophile. It is evident that the most effective are the dienes. The three isoprene samples show the large effect that the concentration of the trapping agent has upon the rate of trapping. This is a measure of the competition of the *o*-quinone methide with itself.

Some of these chromans were not preparatively made but were collected from the vpc and identified by ir and by mass spectra.

There also were some olefins that would not compete for the *o*-quinone methide. Some of these are 3,3-dimethylbutene-1, isoquinoline, cyclooctadiene-1,3, vinylbenzoate, norbornene, acrylonitrile, *N*-vinylpyrrolidone, and 1-pyrrolidinocyclohexene. Isolated double bonds and those substituted with deactivating groups are not reactive enough to interfere with the trimerization. Cyclooctadiene is puzzling because it should be active enough and it may even be expected to react in view of the success of cyclohexadiene. It is possible that the flexibility of the eight-member ring offers some sort of steric hindrance.

Several other phenols were used in place of the 4-*tert*-butyl-2,6-xylenol in a similar reaction. When ethyl vinyl ether was used as a solvent both 4-methoxy-2,6-dimethylphenol and 2-methyl-4,6-di-*tert*-butylphenol yielded the corresponding chromans **18** and **19**.



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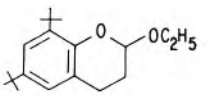
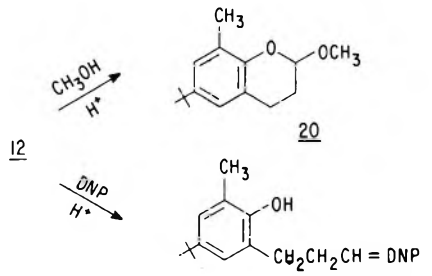


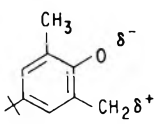
19

Several reactions were performed on the chroman **12**. The acetal linkage was thought to be susceptible to hydrolysis. However, prolonged refluxing in acidified aqueous ethanol resulted in recovery of the chroman. When the solvent was switched to methanol, the recovered material was the chroman **20** demonstrating the stability of the chroman ring even after an acid-catalyzed cleavage. When the same reaction was carried out in the presence of an aldehyde trap such as 2,4-dinitrophenylhydrazine (DNP), the β-phenol propionaldehyde derivative **21** was obtained demonstrating the ring opening equilibrium.



12 **20** **21**

The trapping reaction is obviously a cycloaddition of a diene (the *o*-quinone methide) to a dienophile. These experiments do not distinguish between a two-step or a concerted process. The very specific orientation as obtained here suggests some sort of prior complexation of the reactants allowing polar effects to direct the addition. All of the products can be accounted for by assigning the polarized form **22** to the *o*-quinone methide and then using this to predict the orientation.

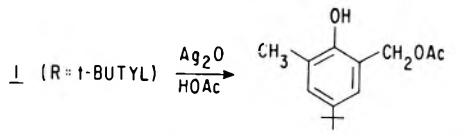


22

Any dienophile that has some stabilizing effect on the developing benzylic carbonium ion should preferentially add in a single orientation. In addition, other agents should add to this developing charge separated species.

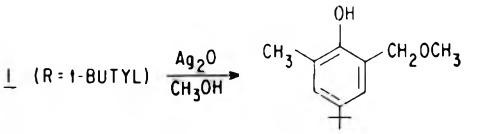
***o*-Quinone Methides and Nucleophiles.**—Several nucleophiles were also found to be capable of intercepting the *o*-quinone methide. When 4-*tert*-butyl-2,6-xylenol is oxidized in the presence of acetic acid, the chief product formed is the 2-(α-acetoxymethyl)-6-methyl-4-*tert*-butylphenol **23.** This material could not be isolated directly because upon heating it split out acetic acid and regenerated the *o*-quinone methide which trimerized.

The phenol **23** was isolated by converting it to the trimethylsilyl ether by use of bis(trimethylsilyl)acetamide.[7] This ether could be distilled and the free phenol then reisolated by hydrolysis of the trimethylsilyl ether.



23

Another nucleophile that would trap the *o*-quinone methide was methanol. If the oxidation of **4**-*tert*-butyl-2,6-xylenol is run in methanol with an excess of the phenol over the oxidizing agent, the primary product formed is 4-*tert*-butyl-2-methoxymethyl-6-methylphenol **24**.



24

The methoxy group is not deactivating enough and if a higher oxidant:phenol ratio than 1 is used the primary product **24** is itself oxidized and adds another molecule of methanol. This has been shown in the work of Orlando[8] where the second methoxy attaches to the same methyl as the first methoxy. The phenol with two methoxy groups was not isolated but was identified by mass spectrum. Because of this spectrum of possible products, this particular reaction is not a good preparative method.

These trapping reactions demonstrate that an *o*-quinone methide is present in the oxidation of 4-*tert*-butyl-2,6-xylenol and that it is susceptible to trapping. A variety of 2-methyl substituted phenols yield the *o*-quinone methide with the only proviso being that there be no α hydrogen on the 4 position. In addition, a variety of dienes and nucleophilic reagents can intercept the *o*-quinone methide on its way to self-trimerization. This offers a new route to a variety of substituted chromans. The specific orientation observed in these reactions is expected of diene reactions and offers little suggestion as to whether the reaction is concerted or two step.

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Experimental Section

4-*tert*-Butyl-2,6-Xylenol.—This material was prepared by alkylation of 2,6-dimethylphenol with isobutylene.

Measurement of the Efficiency of Quinone Methide Trapping.—A standard solution was prepared in benzene containing 1 mol of 4-*tert*-butyl-2,6-xylenol and 0.1 mol of *m*-terphenyl as an internal standard per 25 ml of solution. In individual runs, the appropriate trapping dienophile was mixed with 25 ml of the standard solution and oxidized with 0.232 g (1 mol) of silver oxide.

After 1 hr, a sample of the solution was silylated with bis(trimethylsilyl)acetamide[7] and analyzed on a vpc using a 2-ft silicon rubber column with a 60 ml/min flow of helium and 100–300° at 10°/min programming. The various peaks were integrated and compared with the standard. Duplicate runs agreed with each other ±5%.

In those cases where the prepared chroman was not one of the materials in Table III, the material was collected from the vpc and identified by ir, nmr, and mass spectrometry. The results of this experiment are given in Table II.

2-Ethoxy-6-*tert*-butyl-8-methylchroman 12.—This is a general reaction for the preparation of chromans. It is written for the specific preparation of **12**, but can be used for all of the chromans listed in Table III.

In a magnetically stirred, water-cooled flask were placed 4-*tert*-butyl-2,6-dimethylphenol (8.9 g, 0.05 mol), ethyl vinyl ether (10 ml), and silver oxide (15 g, 0.06 mol). The mixture was stirred until the dark color of the silver oxide turned to the light grey of reduced silver in about 0.5 hr.

The slurry was filtered and the filtrate distilled. After a forerun of ethyl vinyl ether, the chroman **12** was obtained as a pale yellow oil, bp 103–110° (0.65 mm), 9.9 g (80% yield). Redistillation gave pure chroman [bp 106–107° (0.6 mm.)].

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7; mol wt, 248. Found: C, 77.2; H, 9.8; mol wt, 241.

2,8-Dimethyl-2-isopropyl-6-*tert*-butylchroman.—Absolute ethanol (100 ml), 2,8-dimethyl-2-isopropenyl-6-*tert*-butylchroman **15** (1.92 g, 0.0074 mol) and platinum oxide (0.1 g) were shaken in a hydrogenation apparatus. Hydrogen uptake was very rapid until 1 equiv was absorbed. The reaction was stopped and the solvent evaporated after filtration of the catalyst. The oil that was left was distilled and virtually all of the material distilled at 113° (0.4 mm): ir (CCl_4) C=C at 1646 cm^{-1} is not present.

Anal. Calcd for $C_{18}H_{28}O$: C, 83.1; H, 10.8; mol wt, 260. Found: C, 82.9; H, 10.8; mol wt, 265.

Exchange of the Ethoxy Group on 2-Ethoxy-8-methyl-6-*tert*-butylchroman (12). Acetal Exchange.—2-Ethoxy-8-methyl-6-*tert*-butylchroman (0.5 g, **12**) was heated to reflux in methanol (20 ml) containing a trace of HCl. After 20 hr the solvent was removed and the residual oil examined by nmr which showed the absence of the ethyl and the presence of a methoxy at 3.37 ppm (TMS). The oil was distilled, bp ~145° (11 mm), $M^{20}D$ 1.5156 giving a pure sample of 2-methoxy-8-methyl-6-*tert*-butylchroman (**20**).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.9; H, 9.4; mol wt, 234. Found: C, 77.3; H, 9.9; mol wt, 234.

Hydrolysis of 2-Ethoxy-8-methyl-6-*tert*-butylchroman (12).—Several attempts were made to hydrolyze the ethoxychroman with ethanol–water mixtures but only starting material was recovered. The chroman (2.83 g, 0.012 mol) was dissolved in 95% ethanol (200 ml) containing 2,4-dinitrophenylhydrazine (0.198 g, 0.01 mol) and concentrated sulfuric acid (0.1 ml). The solution was refluxed 3 hr and then water was added to the cloud point, and the reaction cooled. A red oil was obtained which upon further crystallization from ethanol–water yielded yellow crystals (0.8 g, 20% mp 154–156°) of **21**.

Anal. Calcd for $C_{20}H_{24}N_4O_5$: C, 60.0; H, 6.0; N, 14.0; mol wt, 400. Found: C, 60.0; H, 6.1; N, 14.1; mol wt, 398.

2-Methyl-4-*tert*-butyl-6-acetoxymethyl Phenyl Trimethylsilyl Ether.—To a solution of 4-*tert*-butyl-2,6-xylenol (17.8 g, 0.1 mol) in glacial acetic acid (150 ml) powdered potassium permanganate (6.4 g, 0.2 equiv) was added slowly and with stirring. After 2 hr, the permanganate color was gone and the pale yellow solution was poured into water. The organic layer was extracted with ether and the extracts were washed with bicarbonate solution and dried ($MgSO_4$). The ether was distilled and the residue titrated with bis(trimethylsilyl)acetamide[7] (22 g, 0.11 mol) to convert the phenol to the trimethylsilyl ether.

TABLE III

PREPARATION OF CHROMANS

No.	Chroman prepared	Phenol	Dienophile	Solvent	Yield, %	Bp° (mm)		Calcd, %			Found, %		
								C	H	Mol wt	C	H	Mol wt
12	2-Ethoxy-6-*tert*-butyl-8-methylchroman	...[a]	Ethyl vinyl ether	None	80	106–107 (0.6)	$C_{16}H_{24}O_2$	77.4	9.7	248	77.2	9.8	241
13	2-Phenyl-6-*tert*-butyl-8-methylchroman	...[a]	Styrene	None	40	158 (0.5)	$C_{20}H_{24}O$	85.7	8.6	280	85.5	8.8	297
14	2,8-Dimethyl-2-phenyl-6-*tert*-butylchroman	...[a]	α-Methylstyrene	C_6H_6, 75 ml	12[b]	162–166 (0.5)	$C_{21}H_{26}O$	85.6	8.8	294	85.9	9.0	297
15	2,8-Dimethyl-2-isopropenyl-6-*tert*-butylchroman	...[a]	2,3-Dimethylbutadiene	None	26	113 (0.5)	$C_{18}H_{26}O_2$	83.8	10.1	258	83.4	10.4	245[h]
17	2-Isopropenyl-8-methyl-6-*tert*-butylchroman	...[a]	Isoprene	None	62[c]	105–110 (0.5)	$C_{17}H_{24}O$	83.7	9.8	244	83.6	10.0	246[i]
16	2,8-Dimethyl-6-*tert*-butyl-2-vinylchroman	...[a]	Isoprene	None	62[c]	105–110 (0.5)	$C_{17}H_{24}O$	83.7	9.8	244	83.7	10.0	250[j]
18	2-Ethoxy-6-methoxy-8-methylchroman	...[d]	Ethyl vinyl ether	None	12[e]	...[f]	$C_{13}H_{18}O_3$	70.3	8.1	222	70.0	8.3	222
19	2-Ethoxy-6,8-di-*tert*-butylchroman	...[g]	Ethyl vinyl ether	None	80	134 (0.7)	$C_{19}H_{30}O_2$	78.7	10.4	290	78.4	10.6	301

[a] 4-*tert*-Butyl-2,6-dimethylphenol. [b] Chromatographed on alumina. [c] **16** and **17** were obtained as a mixture. They were separated by preparative vpc and gave 20% of **16** and 12% of **17** as isolated yield. [d] 4-Methoxy-2,6-dimethylphenol. [e] A trimer **2** (R = methoxy) of the *o*-quinone methide was obtained in 25% yield. [f] Purified by preparative vpc. [g] 2,4-Di-*tert*-butyl-6-methylphenol. [h] Ir (CCl_4) C=C 1646 cm^{-1}. [i] Ir (CCl_4) C=C 1652 cm^{-1}, 12%. [j] Ir (CCl_4) C=C 1642 cm^{-1}, 20%.

The material was distilled and after a forerun of silylating by-products the trimethylsilyl ether was obtained [113–114° (0.9 mm), 12.9 g, 42%). Redistillation gave the pure ether, bp 140° (3.5 mm).

Anal. Calcd for $C_{17}H_{28}O_3Si$: C, 71.2; H, 8.5; mol wt, 236. Found: C, 71.0; H, 8.7; mol wt, 243.

Pyrolysis of 2-Acetoxymethyl-4-*tert*-butyl-6-methylphenol.—A small sample (100 mg) of the title compound was heated at 150° for 18 hr under nitrogen. The deep yellow residue was examined by thin layer chromatography (silica gel–benzene–hexane) and was found to consist of recovered phenol, the trimer **2** (R = *tert*-butyl) and tars. The trimer was identified by comparison with authentic[1] in R_f values and in ir spectrum.

Registry No.—**12**, 25966-85-2; **13**, 25966-86-3; **14**, 25966-87-4; **15**, 25966-88-5; **16**, 25966-89-6; **17**, 25966-90-9; **18**, 25966-91-0; **19**, 25966-92-1; **20**, 25966-93-2; **21**, 25966-94-3; 2,8-dimethyl-2-isopropyl-6-*tert*-butylchroman, 25966-95-4; 2-methyl-4-*tert*-butyl-6-acetoxymethylphenyl trimethylsilyl ether, 25957-28-2.

Selective Solvation of Hydrophobic Ions in Structured Solvents. Azo–Hydrazone Tautomerism of Azo Dyes in Aqueous Organic Solvents

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The azo–hydrazone tautomerism of a series of 4′-substituted 2- and 4-arylazo-1-naphtholsulfonates was studied spectrophotometrically in a wide range of protic and aprotic polar solvents with dielectric constants varying from 24.3 (ethanol) to 182.4 ($HCONHCH_3$). The effect of solvents on the position of the equilibrium between the tautomers does not correlate with bulk solvent properties but depends upon the solvent structure and the microscopic environment of the dye in the solvent matrix. For solvent-sensitive dyes, the hydrazone form is predominant in those neat solvents capable of forming a three dimensional structure, whereas the azo form is favored by neat solvents that form a two dimensional structure or are unstructured. In binary mixtures of water with methanol, ethanol, and *tert*-butyl alcohol, the shift from hydrazone to azo is most pronounced in the predominantly aqueous compositions, *tert*-butyl alcohol having the greatest effect. At alcohol levels associated with reduction of solvent structure, the shift is gradual and nearly independent of the nature of the alcohol. Pronounced shifts from hydrazone to azo also occur in aqueous compositions of DMF– and DMSO–water mixtures. The results are interpreted in terms of selective solvation of the hydrophobic dyes by the organic cosolvent within the water structure. The tautomerism becomes progressively less exothermic as organic solvent is added to the aqueous binaries.

A number of spectroscopic methods have established that 4-phenylazo-1-naphthols can exist in solution as hydroxy azo or as quinone hydrazone tautomers.[1–8] The hydrazone is favored by polar solvents[2a,5,8] and by electron-withdrawing substituents in the phenyl ring.[2a,5,9] No systematic studies of the tautomerism have been made in structured solvents or in solvents of high dielectric constants, and no quantitative data are available on the effects of solvent dielectric constant or of specific solvation on the tautomeric equilibrium. We have studied the tautomerism of several water-soluble dyes in a number of neat solvents and in binary aqueous organic solvent mixtures and find that the equilibrium is sensitive to specific solvation and to the hydrogen bonded structure of the solvent.

Results

The neat solvents studied and their dielectric constants at 25° are ethanol (24.3), methanol (32.6), *N*,*N*-dimethylformamide (DMF, 36.7), acetonitrile (37.5), dimethyl sulfoxide (DMSO, 46.4), propylene carbonate (65.1), water (78.5), formamide (109.5), and *N*-methylformamide (182.4).

Structure **2** dyes (X = H, OCH_3, Cl, SO_3^-, and CF_3) give more stable hydrazones than the isomeric structure **1** dyes. Whereas the equilibrium concentrations of all the **1** dyes except **1e** can shift with changes in solvent or solvent composition, the **2** dyes exist predominantly as the hydrazones in all solvents studied. The order of stability of the hydrazones of the **1** dyes in a given solvent is **1e** > **1b** ≃ **1c** > **1a** > **1d**. The hydrazone of **1e** was the predominant tautomer in all our solvents and solvent mixtures, whereas the azo form of **1d** was preponderant in all solvents. We estimate that aqueous solutions of **1a** contain equal amounts of both tautomers at 25°, with a shift to the azo form in all other solvents. Dyes **1b** and **1c** exist as greater than 95% hydrazone in water at 25° and as pure azo tautomers in ethanol, *tert*-butyl alcohol, and the aprotic dipolar solvents.

The estimation of the predominant tautomer in the neat solvents was qualitative and was based on the relative preponderance of the two absorption bands. The predominance of one tautomer was so great in a given solvent with **1b** and **1c** that a qualitative approach was sufficient for evaluating solvent properties and for separating solvent types. The only neat solvents in which the hydrazones of **1b** and **1c** were predominant were water and formamide. These dyes were present almost exclusively as the azo tautomers in all the other neat solvents, including *N*-methylformamide.

There is no correlation of the position of the equilibrium with the dielectric constant of the neat solvent,

* To whom correspondence should be addressed.

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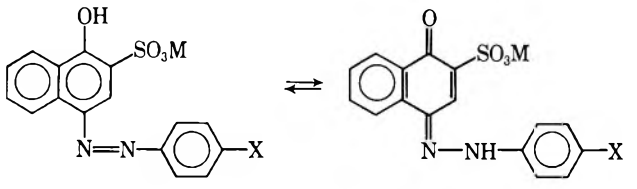
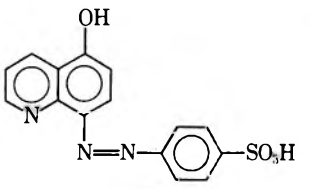


1a, X = H; M = K
b, X = SO_3Na; M = Na
c, X = CF_3; M = K
d, X = OCH_3; M = K
e, X = NO_2; M = K



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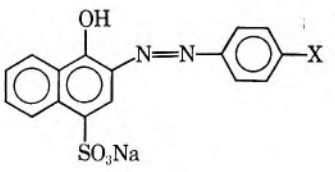

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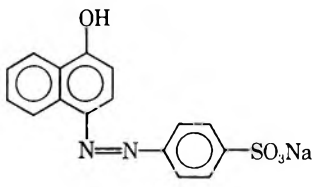

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with the Kosower "Z" value,[10] or with the fact that a solvent is protic or aprotic. The most important factor seems to be the degree and kind of structuring of the solvent and the manner in which this structuring influences the solvation of the dye. The unique property of water and formamide is the capability of these solvents to form three dimensional hydrogen-bonded regions[11–15] with lifetimes in the case of water of the order of 10^{-11} sec.[13a] There is little agreement at present on how regular or extensive the structured regions are, but it is agreed that in the limit each oxygen atom can be nearly tetrahedrally bonded to four nearest neighbor hydrogens. On the other hand, X-ray studies indicate that the liquid alcohols associate to give linear, two dimensional polymeric structure.[16,17] *N*-Methylformamide is also believed to exist as linear polymers in the liquid state.[18] Thus, protic solvents with two dimensional structure have the same effect on the equilibrium as aprotic solvents. The stabilization of a given tautomer must be associated with the energetics of forming cavities in the various solvent structures and with the way in which the solvent molecules order themselves around the dye for minimum energy of the system.

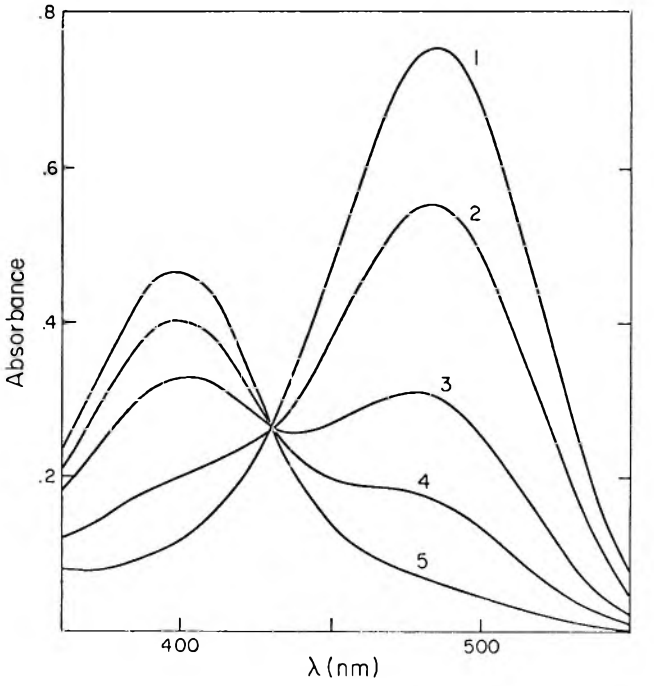

Figure 1.—Spectra of **1b** in ethanol–water at 25°. Curve numbers (1–5) correspond to x_2 = 0, 0.088, 0.175, 0.320, and 0.734 to 1.00, respectively.

Figure 1 shows the spectral changes accompanying the shift in the tautomeric equilibrium of **1b** in water–ethanol mixtures. Similar changes occur with **1b** and **1c** in aqueous binaries with DMSO, DMF, methanol, and *tert*-butyl alcohol. The fact that the position of the equilibrium can be shifted between the extreme forms of **1b** and **1c** made these dyes most valuable for studying the effect of solvent on the tautomerism.

Tautomer ratios were determined in mixtures of water with *tert*-butyl alcohol, ethanol, methanol, DMF, DMSO, and *N*-methylformamide, and in formamide–*N*-methylformamide mixtures. The ratios were calculated using eq 1 where the ϵ's are absorptivities and the

$$K_T = \frac{[\text{hydrazone}]}{[\text{azo}]} = \frac{\epsilon_M - \epsilon_A}{\epsilon_H - \epsilon_M} \quad (1)$$

subscripts refer to pure azo, pure hydrazone, and mixtures of the two. We used the wavelength where the hydrazone absorbs (480–500 nm), because the absorptivity in this region was less subject to small medium effects than was the absorptivity of the azo band. The value of ϵ_A was determined from absorption curves such as curve 5 in Figure 1, after the curve ceased to change with further addition of the organic component.

The absorptivity of the hydrazone bands of **1b** and **1c** in water increased on lowering the temperature from 35 to 10°. These curves were replotted on a frequency scale and folded through the wavelength of maximum absorption to give an isolated symmetric band for each temperature. The integrated areas increased 8 and 4%, respectively, for **1b** and **1c** between 35 and 10° and then became independent of temperature. We took this to mean that the azo form makes negligible contribution to the observed curve at temperatures below 10°, so that ϵ_H could be evaluated. The values are 3.32×10^4 and 3.18×10^4 for **1b** and **1c**, respectively.

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(15) R. J. DeSando and G. H. Brown, *J. Phys. Chem.*, **72**, 1088 (1968).
(16) F. Franks and D. J. G. Ives, *Quart. Rev.*, **20**, 1 (1966).
(17) (a) W. H. Zachariasen, *J. Chem. Phys.*, **3**, 158 (1935). (b) G. G. Harvey, *ibid.*, **6**, 111 (1938); **7**, 878 (1939).
(18) G. R. Leader and J. F. Gormley, *J. Amer. Chem. Soc.*, **73**, 5731 (1951).

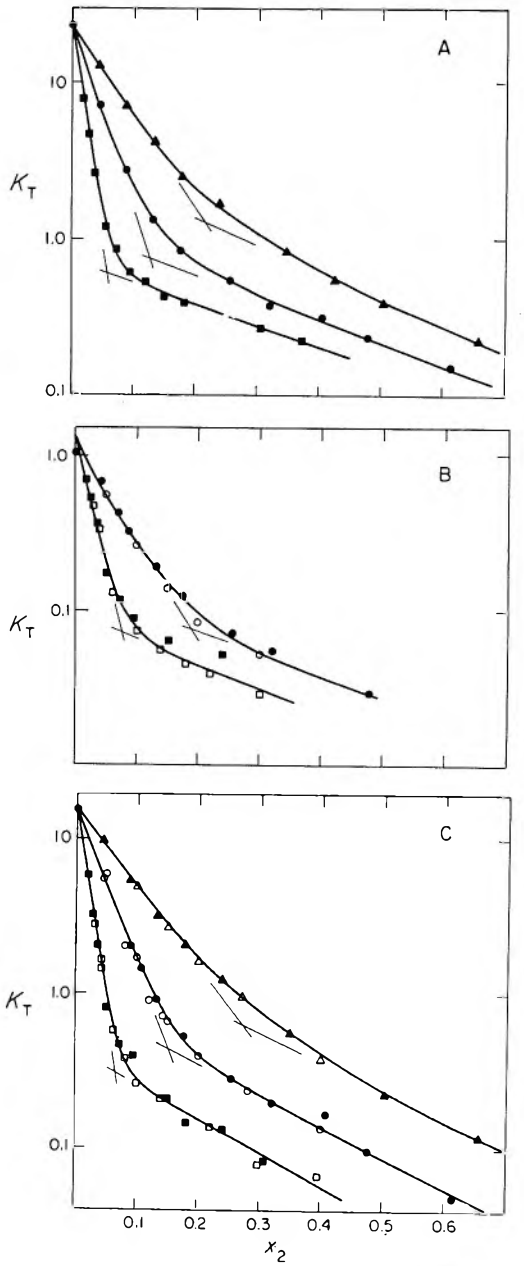


Figure 2.—Semilog plots of K_T at 25° *vs.* mol fraction of alcohol. Open data points, [dye] = 2.5×10^{-5} *M*; closed points, [dye] = 2.5×10^{-6} *M*; ■, *tert*-BuOH; ●, EtOH; ▲, MeOH; A, dye **1c**; B, dye **1a**; C, dye **1b**.

We assumed that ϵ_A and ϵ_H were constant in all the aqueous organic binaries. Dye **3** exists as the hydrazone in all water–alcohol mixtures. The values of ϵ_H for this dye deviated from the mean by less than 1.5% over the whole range of ethanol–water compositions. Dye **1d** exists as pure azo in ethanol–water at ethanol levels above 0.25 mol fraction. The range of absorptivity values at the hydrazone wavelength was only twice the experimental error in reading absorbances between mol fractions 0.25 and 0.50. Absorptivities may not be as constant in aqueous DMF and DMSO. In these solvent mixtures, there were small changes in band shapes and positions, so that the isosbestic points were more diffuse than with the water–alcohol mixtures. The values of ϵ_A for a given dye were the same in DMF, DMSO, and ethanol.

Because the value of ϵ_H for **1a** was experimentally inaccessible, we used the measured value for **1b**, assuming the inductive polar effect of the sulfo group did not effect ϵ_H. Neither extreme form could be obtained in the formamide–*N*-methylformamide mixtures. We had to assume that ϵ_H was the same as the value in water at 10°, and that ϵ_A was the same as the value measured in DMF.

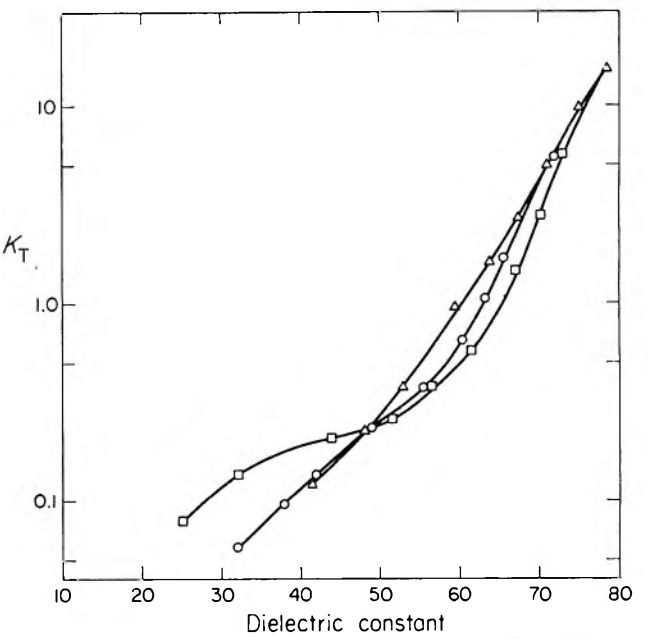


Figure 3.—Semilog plots of K_T for dye **1b** *vs.* solvent dielectric constant at 25° in □, *tert*-BuOH; ○, EtOH; △, MeOH.

Figure 2 shows plots of K_T on a semilog scale *vs.* solvent composition for two concentrations of **1a–c** in aqueous *tert*-butyl alcohol, ethanol, and methanol, where the organic component is regarded as the solute. The plots show that the greatest shift in the tautomeric equilibrium occurs in the predominantly aqueous compositions. The two linear segments of the plots were extended to the points of intersection to obtain the solvent composition corresponding to the break points. The break points occur at x_2 = 0.06–0.07, 0.14–0.16, and 0.24–0.27 in aqueous *tert*-butyl alcohol, ethanol, and methanol, respectively, and are independent of dye structure or the position of the equilibrium at the break. The plots show that, on the water side of the breaks, the shift in K_T depends on the nature of the added alcohol, but is nearly independent of the alcohol on the alcohol side of the breaks. Plots (not shown) of log K_T *vs.* volume fraction of alcohol gave three separate curves falling in the same order as those in Figure 2, although the separation is reduced and the breaks are less sharp. This shows that the three alcohols are specific in their effects on K_T, over and above the differences in molecular volume.

Figure 3 shows a plot of log K_T for dye **1b** *vs.* solvent dielectric constant at 25° for the aqueous alcohols. The plots not only show the lack of correlation of log K_T with dielectric constant, but also that each alcohol is rather specific in its effect.

Figure 4 shows plots of K_T *vs.* x_2 for aqueous DMSO, DMF, and *N*-methylformamide and for *N*-methylformamide in formamide. *N*-Methylformamide is considered the solute in formamide. The binary mixture of amides was chosen to see whether the addition of one amide having two dimensional solvent structure to an

TABLE I
EFFECT OF TEMPERATURE ON K_T VALUES OF DYE **1b**

Solvent	x_2	K_T 15°	K_T 25°	K_T 35°	$-\Delta H^0$, kcal/mol	$-\Delta S^0$ (25°), cal deg^{-1} mol^{-1}
EtOH–H_2O	0		15.2	6.90	14	40
	0.05	11.0	4.90	2.25	13.7	43.0
	0.10	3.59	1.68	1.01	11.0	35.9
	0.15	0.838	0.642	0.519	4.1	14.4
	0.20	0.413	0.392	0.340	1.8	8.0
	0.40	0.127	0.128	0.123	0	4.0
tert-BuOH–H_2O	0.02	5.22	4.59	2.72	5.8	16.4
	0.04	1.83	1.48	1.16	3.9	12.4
	0.06	0.712	0.518	0.474	3.5	13.1
	0.10	0.300	0.294	0.276	0.8	5.0
	0.18	0.192	0.169	0.170	0	3.4
	0.30	0.087	0.092	0.082	0	4.7
DMF–H_2O	0.05	2.40	1.68	1.32	5.2	16.4
	0.10	0.800	0.654	0.530	3.5	12.4
	0.20	0.193	0.172	0.148	2.2	10.7

amide possessing three dimensional structure would have the same effect on K_T as the addition of alcohols to water. Figure 4 shows that it does not. The effect of adding DMF and DMSO to aqueous solutions of **1b** is similar in magnitude to the effect of added alcohols in the predominantly aqueous mixtures. DMF has nearly the same effect as *tert*-butyl alcohol, and DMSO is similar in effect to ethanol. The main difference between the aqueous solutions of the protic and aprotic cosolvents is the presence or absence of a break in the log K_T–x_2 plots.

Tautomer ratios of **1b** were measured at 15, 25, and 35° in various mixtures of water with ethanol, *tert*-butyl alcohol, and DMF. Table I gives the values of K_T and the derived standard enthalpies and entropies for the conversion of the azo tautomer to the hydrazone. The enthalpies were calculated using the Van't Hoff equation. Compositions of the water–alcohol mixtures were chosen to give points on either side of the break points in the log K_T–x_2 profiles. The conversion from azo to hydrazone is exothermic in each case on the water side of the break point, but ΔH^0 becomes less negative as the alcohol content increases. On the alcohol side of the break point, changing temperature did not alter K_T by measurable amounts, *i.e.*, $\Delta H^0 \simeq 0$. It is significant that addition of increments of DMF to water also causes the conversion to hydrazone to become progressively less exothermic. Thus, in all respects there appear to be no basic differences between DMF and the alcohols in the effect on K_T except for the shape of the log K_T–x_2 profiles.

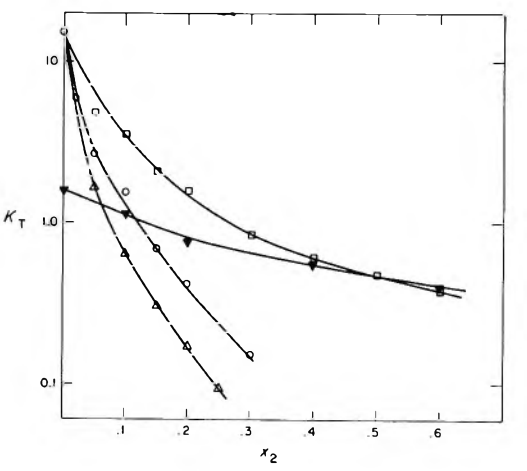


Figure 4.—Semilog plot of K_T for dye **1b** at 25° *vs.* mol fraction of added solvent. △, DMF in H_2O; ○, DMSO in H_2O; □, *N*-methylformamide in H_2O; ▼, *N*-methylformamide in formamide.

Discussion

The significant findings of this work are (1) the most profound shifts in the tautomeric equilibrium occur in the predominantly aqueous compositions and are out of proportion to changes in the bulk solvent properties; (2) the shift is not caused by preferential hydrogen bonding solvation by organic cosolvent to one of the tautomeric pairs, since similar effects are caused by protic and aprotic solvents; (3) there is a high correlation between changes in the three dimensional structure of the solvents and the position of the equilibrium. We believe that the results can be interpreted in terms of selective solvation of the dyes by the organic cosolvents, whereby the solute accumulates around the hydrophobic regions of the dye in microscopic concentrations that are higher than the concentration in the bulk solvent. In our interpretation, the nonpolar moieties of the organic cosolvent are oriented toward the hydrophobic portion of the dye, giving a diffuse interface between dye and bulk solvent with a polarity that is considerably lower than that of the bulk solvent.

In water, the sulfo group is strongly hydrated through hydrogen bonds, giving rise to "positive" hydration.[19] By analogy with the effect of adding small amounts of other hydrophobic solutes to water,[20] it is expected that the hydrophobic moiety of the dye would enhance the hydrogen bonded structure of the water in its vicinity relative to that which exists in bulk water. This structure formation, which has been designated as "negative hydration,"[19] is a high energy condition that is partly offset by the positive hydration of the ionic solubilizing group. It has been estimated that the net solvation of the naphthalenesulfonate ion is negative in water.[19] Since the hydrophobic volume of our dyes is even greater, the energy of the systems must be quite high so that the balance between positive and negative hydration is barely sufficient to maintain the dye in

(19) H. Uedaira and H. Uedaira, *Zh. Fiz. Khim.*, **42**, 1612 (1968).
(20) D. N. Glew, H. D. Mak, and N. S. Rath, *Chem. Commun.*, **264** (1968)

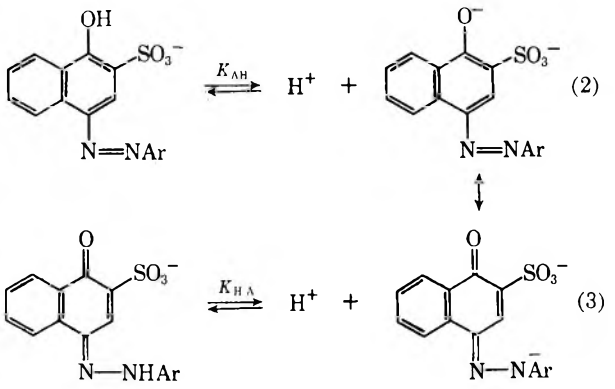
molecular dispersion. This is reflected in the strong tendency of the dyes to associate into aggregates and to be salted out of aqueous electrolyte solutions.[21] By our model, the energy at the microscopic dye–water interface is decreased by replacement of water molecules by molecules of organic cosolvents so that there is excess concentration of organic molecules in the interface. Our results show that the hydrazone form is stabilized by the negative solvation characteristic of the hydrogen bonded three dimensional solvent structures, and the azo form by the condition where the adjacent environment consists of nonpolar alkyl groups.

The compositions of the water–alcohol mixtures at which the breaks in the log K_T–x_2 plots occur correspond to the compositions where the three dimensional structure of the solvent is believed to change.[16,22,23] These compositions are at about 5, 15, and 30 mol % for *tert*-butyl alcohol, ethanol, and methanol, respectively. Thus, the most dramatic shifts in the tautomeric equilibrium occur in the predominantly aqueous compositions where the alcohol is thought to promote hydrogen bonded solvent structure. This is consistent with the view that selective solvation by the organic solute results because of the existence of three dimensional structure around the dye. In these compositions, the OH group of the alcohol may be incorporated into the water structure, with the alkyl group oriented into the dye–solvent interface. On the alcohol side of the breaks, the typical water structure is destroyed. In this region the solvation shell is apparently not altered greatly with increasing alcohol concentration, perhaps because it is already near saturation with respect to alcohol.

The similarities in the log K_T (ΔF), ΔH, and ΔS changes in the aqueous aprotic solvents and the aqueous alcohols suggest that similar solute–solvent interactions are occurring with changes in solvent composition in all cases. Arnett and McKelvey have shown that the partial molar heat of solution of sodium tetraphenylboron shows an endothermic maximum in water–DMSO mixtures at 15 mol % DMSO which is similar to the maxima found in water–*tert*-butyl alcohol and in water–ethanol.[23] Their finding that aqueous DMSO and aqueous ethanol solutions show similar interactions with a large solute are in agreement with our results. We believe that our results show that aprotic solvents accumulate around the hydrophobic moiety of the dye in the same way as the alcohols. The absence of breaks in the log K_T–x_2 plots may indicate that the aprotic solvents do not cause abrupt changes in the solvent structure.

The chaotic state of our understanding of the structure of water around hydrophobic solutes precludes any description of the hydration shell of our dyes. The decrease in entropy accompanying the conversion of the azo tautomer to the hydrazone in water is consistent with an increased solvent orientation around the hydrazone. Thermodynamics, however, give no clues as to why a structured water environment should stabilize one tautomer. It is possible that the nature of the dye–water interface permits specific hydrogen bonding of a water molecule to a heteroatom in the dye in a way that stabilizes the hydrazone. Replacement of the water environment with the nonpolar environment of the organic cosolvent apparently destroys this stabilization, even when the bulk solvent is still largely aqueous. The fact that dye **4** also shows the same tautomeric shift in alcohol–water mixtures rules out an intramolecular hydrogen bond between the –OH and $-SO_3^-$ groups as an important stabilizing factor.

The fact that K_T is sensitive to the solvation changes implies that the relative acidities of the protons on the OH oxygen and on the NH nitrogen are also sensitive to the same changes. The tautomerization can be written in terms of the two dissociations to a common anion (eq 2 and 3). The effect of adding alcohols,



$$K_T = [HA]/[AH] = K_{AH}/K_{HA}$$

DMF, or DMSO to water is to decrease K_{AH} relative to K_{HA} and to make the NH proton relatively more acidic.

The type of specific solvation we have discussed here seems general for other types of ionic dyes that are soluble in water and aqueous mixtures of organic solvents. We have found pronounced spectral and kinetic effects from such solvation. It is probable that the phenomenon is general for any large organic ion where most of the volume of the ion is hydrophobic.

Experimental Section

Dyes.—The dyes were prepared in the usual way and were recrystallized as the sodium salts from water or ethanol–water. Dyes **2b–c** were samples used in an earlier study.[24] Final purification of all the dyes except **1b** and **2b** was accomplished by chromatography on Sephadex G-25,[25] followed by recrystallization as the potassium salts. Dye **1b** was chromatographed on polyamide using DMF as eluent. The dihydrate of **1b**, and monohydrates of the other dyes were obtained after drying at 120° under water-pump vacuum. Elemental analyses and spectral data are given in Table II.

Solvents.—Commercially available "absolute" ethanol showed no absorption between 240 and 300 nm and was found free of impurities by glpc analysis. This solvent and Eastman Grade methanol were used without further purification. Eastman Grade *tert*-butyl alcohol was fractionated through a Vigreux column and the first and last thirds were discarded. Two separate runs contained 0.29 and 0.31% water by Karl Fischer analysis. Correction for the water content was made in preparing the mixtures with water.

N-Methylformamide and DMF (Eastman Grade) were distilled under vacuum at low temperature and the center third was retained. The solvents were stored over Linde 4A molecular sieves. Eastman Grade formamide was fractionated twice under vacuum through a Vigreux column and a variable take-off still

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(22) F. Franks, in "Physico-chemical Processes in Mixed Aqueous Solvents," F. Franks, Ed., American Elsevier, New York, N. Y., 1967, p 50.
(23) E. M. Arnett, ref 22, p 105.
(24) R. L. Reeves, *J. Amer. Chem. Soc.*, **88**, 2240 (1966).
(25) R. L. Reeves, R. S. Kaiser, and K. T. Finley, *J. Chromatogr.*, **47**, 217 (1970).

TABLE II

ANALYTICAL AND SPECTRAL DATA FOR DYES

Dye	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Solvent	λ_{max} (nm)	$10^{-4}\epsilon$ (M^{-1} cm^{-1})[a]
1a	50.0	3.4	7.3	50.4	3.4	7.4	H_2O	492	1.74
							EtOH	390	1.67
1b	40.8	2.6	6.0	41.0	2.6	6.1	H_2O	485	2.96
							EtOH	400	1.85
1c	45.1	2.7	6.2	45.0	2.6	6.1	H_2O	479	3.06
							EtOH	406	1.78
1d	51.3	3.8	7.0	[b]	3.9	6.9	H_2O	458, 400	1.22, 1.15
							72% EtOH	400	1.86
1e	44.8	2.8	9.8	[b]	3.0	9.7	H_2O	493	3.07
							80% EtOH	493	2.77
2a	52.2	3.7	7.6	52.4	3.3	7.4	H_2O	494	2.10
							EtOH	489	1.62
3	48.8	3.3	11.4	49.0	3.5	11.0	H_2O	455	4.25
							EtOH	453	4.30

[a] 25°. [b] Replicate analyses from three microanalytical laboratories on the same sample gave divergent values for % C.

head. A sizable forerun and residue were discarded each time. The final distillate was crystallized twice from the melt. All liquid freezing below 2.5° was discarded. The final product froze sharply at 2.5° (lit. 2.45–2.51°).[26] Samples of formamide that were not purified rigorously showed variable results and indicated the presence of basic impurities capable of ionizing the OH groups of some dyes.

To 3 kg of DMSO (Matheson Coleman and Bell) was added 500 ml of benzene which had been dried over 4A molecular sieves. The benzene was distilled from the mixture at atmospheric pressure, and the residue was distilled under reduced pressure. A center cut [bp 58° (5 mm)] amounting to half the total volume was distilled directly into a receiver containing 4A molecular sieves.

Eastman Grade acetonitrile containing less than 0.01% water was stored over 4A molecular sieves and was used without further purification. Eastman Practical Grade propylene carbonate was fractionated twice under reduced pressure. Foreruns and residues were discarded.

The binary mixtures of solvents were prepared by mixing weighed amounts of the two solvents. The volume fractions of the alcohols in the mixtures with water at 25° were calculated from the partial molal volumes. We used the density data of Chapas for methanol–water mixtures,[27] data from the International Critical Tables for ethanol–water,[28] and the data of Nakanishi, Kato, and Maruyama for *tert*-butyl alcohol–water.[29]

(26) G. R. Leader, *J. Amer. Chem. Soc.*, **73**, 856 (1951).

(27) G. Chapas, *ibid.*, **74**, 6275 (1952).

(28) "International Critical Tables," Vol. III, McGraw-Hill, New York, N. Y., 1928, p 116.

(29) K. Nakanishi, N. Kato, and M. Maruyama, *J. Phys. Chem.*, **71**, 814 (1967).

Spectral Measurements.—Absorption curves were obtained on a Beckman DK-2A recording spectrophotometer at dye concentrations of 2.5×10^{-5} M and 2.5×10^{-6} M. For the higher concentrations, individual weighed samples were dissolved directly into the solvent and the solutions measured in 1-cm cells. The lower concentrations were obtained by adding aliquots of a stock solution in water to an alcohol–water mixture of known composition and density and then correcting for the added water. The more dilute solutions were measured in 10-cm cells. The solutions were thermostated at the desired temperature in a constant temperature bath. A thermostated cell holder was used with the 1-cm cells, and all the temperature variations were made on the more concentrated dye solutions so that the desired temperature could be maintained in the solution while the absorption curve was recorded. The thermostated cell block could not be used with the 10-cm cells. We made all measurements in the very dilute solutions by equilibrating the solutions at 25° and working rapidly after transferring them to the cells.

Registry No.—**1a** azo, 26156-91-2; **1a** hydrazone, 26156-92-3; **1b** azo, 26156-93-4; **1b** hydrazone, 26156-94-5; **1c** azo, 26156-95-6; **1c** hydrazone, 26156-96-7; **1d** azo, 26156-97-8; **1d** hydrazone, 26156-98-9; **1e** azo, 26156-99-0; **1e** hydrazone, 26157-00-6; **2a** azo, 669-05-6; **2a** hydrazone, 26157-02-8; **3** azo, 26157-03-9; **3** hydrazone, 26157-04-0.

Acknowledgment.—We are indebted to Mr. John R. Abbott of the Kodak Research Laboratories for purifying some of the solvents.

Photolysis and Pyrolysis of the Episulfoxide of Dibenzoylstilbene[1-3]

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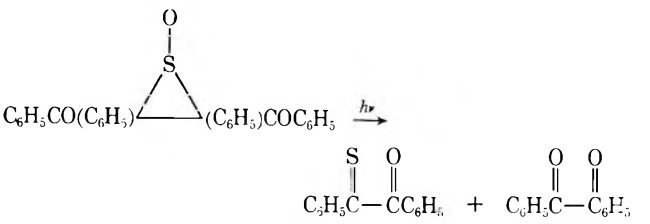
Photolysis or pyrolysis of the episulfoxide of dibenzoylstilbene (2,3-dibenzoyl-2,3-diphenylthiirane 1-oxide) yields monothiobenzil and benzil. Triplet sensitizers have no effect on the products of photolysis except as internal filters. A mechanism which involves ring expansion of the sulfoxide is suggested for the formation of the products.

Oxidation of the yellow episulfide of dibenzoylstilbene (believed to be the cis isomer) by hydrogen peroxide in acetic acid yields two episulfoxides.[4] Oxidation of a cis isomer would yield two meso episulfoxides, a trans and a pair of enantiomorphs. The low melting episulfoxide (mp 165–167°) shows in the mass spectrum much more intense fragments formed by loss of SO_2 and $C_6H_5CO_2$ than the high melting isomer (mp 184–186°). This indicates that in the low melting isomer the sulfoxide oxygen may be cis to the two benzoyl groups, there being more opportunity for the loss of an oxygen from a benzoyl group to the sulfoxide group or *vice versa* in this configuration. The relative integrated intensity of the carbonyl absorption to the phenyl absorption in the infrared is less for the low melting isomer. This favors a cis configuration for the low melting isomer in accord with the effect of nearby polar substituents on the stretching frequency of carbonyl groups.[5] The episulfoxides form unstable complexes with anhydrous cobalt(II) bromide and nitrate. The bromide forms a complex with 4 mol of episulfoxide and the nitrate with 2. The complexes appear to be too unstable for use in characterization.

Oxidation of an episulfide to an episulfoxide in an acidic medium is rare and until 1965 only a patent claimed such a synthesis.[6] Several examples of the oxidation of episulfides to episulfoxides have been reported since, but these episulfoxides are unstable in acid.[7] This paper reports on the photolysis and pyrolysis of the episulfoxide of dibenzoylstilbene. Some of the results of photolysis experiments were reported in preliminary form.[8]

Photolysis.—Previous investigations of the photochemistry of sulfoxides have been limited to the photosensitized oxidation of sulfoxides to sulfones,[9] the photochemical rearrangement of 2,2-dimethylthiachromane 1-oxide,[10] the photochemical racemization of optically active sulfoxides,[11] and the photodesulfurization of a thiaphenalene sulfoxide.[12]

Solutions of the episulfoxides[13] were irradiated in benzene at 6–11° with a water-cooled, internal mercury arc lamp (wavelength at maximum output was 366 nm) through filters of quartz, Vycor, or Pyrex. The products were monothiobenzil and benzil, obtained in comparable amounts.



Although there are carbonyl groups in the episulfoxides no carbonyl n → π* absorption band is discernable in the ultraviolet spectrum. The tail of the π → π* absorption obscures the n → π* band in *cis*-dibenzoylstilbene,[14] and the n → π* absorption in the episulfoxides likewise may be obscured.

The photochemical decomposition of the episulfoxide mixture may proceed through either a singlet or triplet state. Triplet sensitizers or quenchers had no effect on the photolysis except that occasionally a decrease in the yield of products was observed, caused by internal filtering of light by the added compound. The results are given in Table I. Relatively small amounts of anthracene noticeably decrease the yield of monothiobenzil. Anthracene, which absorbs strongly around 366 nm, may be acting as an internal filter.

An excited triplet state probably is not involved in the rearrangement unless the rearrangement through this state occurs faster than its quenching. The greater than normal yield of benzil obtained when piperylene was present in the reaction mixture may be caused by removal of the monothiobenzil by a diene addition or by a photochemical 2 + 2 addition.[15] Re-

* To whom correspondence should be addressed.

(1) This work was aided by National Science Foundation Grant GP-5513 for which we are grateful.

(2) Reported in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Abstracts of Papers, P-19.

(3) For complete details, see G. E. Kuhlmann, Ph.D. Thesis, Syracuse University, 1968.

(4) D. C. Dittmer and G. C. Levy, *J. Org. Chem.*, **30**, 636 (1965).

(5) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952).

(6) S. B. Soloway, U. S. Patent 2,694,073; *Chem. Abstr.*, **49**, 3465 (1955). However, a rearrangement to a four-membered thietane sulfoxide may have occurred: F. K. Lautenschlaeger, *J. Org. Chem.*, **34**, 3998 (1969). The structure proof for the compound claimed in the patent was not given.

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(8) D. C. Dittmer, G. C. Levy, and G. E. Kuhlmann, *J. Amer. Chem. Soc.*, **89**, 2793 (1967).

(9) G. O. Schenck and H. Krauch, *Chem. Ber.*, **96**, 517 (1963).

(10) R. A. Archer and B. S. Kitchell, *J. Amer. Chem. Soc.*, **88**, 3462 (1966).

(11) G. S. Hammond, H. Gotthardt, L. M. Coyne, M. Axelrod, D. R. Rayner, and K. Mislow, *ibid.*, **87**, 4959 (1965); K. Mislow, M. Axelrod, D. R. Rayner, H. Gotthardt, L. M. Coyne, and G. S. Hammond, *ibid.*, 4958 (1965); R. S. Cooke and G. S. Hammond, *ibid.*, **90**, 2958 (1968); R. A. Archer and P. V. DeMarco, *ibid.*, **91**, 1530 (1969).

(12) A. G. Schultz, C. D. DeBoer, and R. H. Schlessinger, *ibid.*, **90**, 5314 (1968).

(13) Mixtures of the two isomeric sulfoxides were used since the results are the same with either isomer alone (Pyrex filter). The proportion of each isomer in the mixtures was not determined for all experiments. In several experiments with approximately equimolar amounts of the two isomers the results were the same within experimental error as the results from the mixtures used in the runs in Table I.

(14) H. E. Zimmerman, H. G. Dürr, R. S. Givens, and R. G. Lewis, *J. Amer. Chem. Soc.*, **89**, 1863 (1967).

(15) Both types of addition are known: A. Schönberg and B. König, *Chem. Ber.*, **101**, 725 (1968); K. Yamada, M. Yoshioka, and N. Sugiyama, *J. Org. Chem.*, **33**, 1240 (1968); Y. Omote, M. Yoshioka, K. Yamada, and N. Sugiyama, *ibid.*, **32**, 3676 (1967).

TABLE I

EFFECT OF SENSITIZERS AND QUENCHERS ON THE PHOTOLYSIS OF THE MIXTURE OF EPISULFOXIDES OF DIBENZOYLSTILBENE (PYREX FILTER)[a]

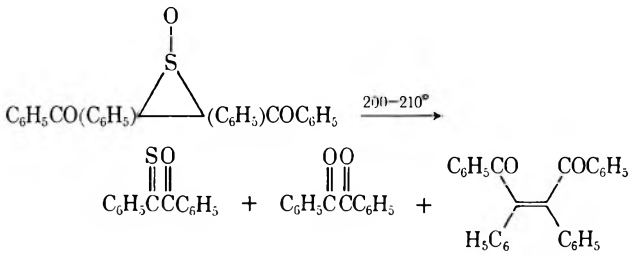
Compound added, 10^2 mol	E_T,[b] kcal mol^{-1}	Episulfoxide, 10^4 mol	Product	Mol %[c]
		8.30	Monothiobenzil	62.8[d]
		5.65	Monothiobenzil	69.3[d]
		3.27	Monothiobenzil	74.7[d]
		5.60	Monothiobenzil	54.3
Acetophenone, 1.02	74	6.88	Monothiobenzil	51.8
Benzophenone, 13.8	69	11.6	Monothiobenzil	49.2[e]
Biphenyl, 0.507	65	5.40	Monothiobenzil	54.8
Phenanthrene, 0.142	62	7.57	Monothiobenzil	54.4
Naphthalene, 10.5	61	10.4	Benzil	42.4
			Monothiobenzil	40.8
Piperylene, 100[f]	55–60	9.57	Benzil	64
Biacetyl, 96.8[g]	55	8.35	Monothiobenzil	34.2
Anthracene, 0.0102	42	7.94	Monothiobenzil	51.8
Anthracene, 0.0484	42	5.71	Monothiobenzil	43.0
Anthracene, 0.100	42	6.00	Monothiobenzil	33.3

[a] Solvent benzene, 500 ml; irradiation time 60 min unless otherwise noted; temperature between 6.3 and 10.7°. [b] N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965, p 132. [c] Yield of deep blue monothiobenzil determined spectrophotometrically. [d] Irradiation time, 90 min. [e] By difference from the amount of starting material recovered. [f] In 400 ml of benzene. [g] In 350 ml of benzene.

moving the monothiobenzil removes an internal quencher which retards the reaction.[16]

When relatively large amounts of biacetyl or naphthalene are added, efficient sensitization or quenching of singlet states is not apparent. The somewhat lower yields that are observed may be caused by internal filtering or by incomplete quenching of excited singlets.

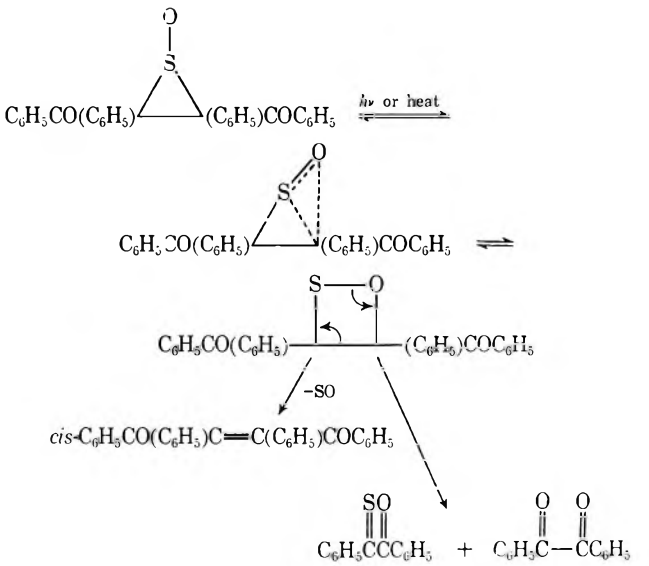
Pyrolysis.—Pyrolysis of a mixture of the two isomeric episulfoxides in a vacuum at 200–210° for 90 min gives a green sublimate and a brown residue. The sublimate consists of benzil (51%) and monothiobenzil (11%), and the residue contains *cis*-dibenzoylstilbene (3%), a trace of *trans*-dibenzoylstilbene, and three other unknown compounds detected by thin layer chromatography. The yield of monothiobenzil represents a lower limit because the compound is susceptible to conversion to benzil either by hydrolysis or oxidation.



This pyrolysis of an episulfoxide differs from that investigated by Hartzell and Paige who observed the loss of sulfur monoxide with the formation of 89% *cis*-2-butene and 11% *trans*-2-butene when the episulfoxide of *cis*-2-butene was pyrolyzed at 150°.[17]

Discussion.—Because the pyrolysis of the episulfoxide of dibenzoylstilbene yields essentially the same products as the photochemical decomposition, a common intermediate may be involved. The products may arise by way of a 1,2-oxathietane (cyclic sulfenate or monothiaperoxide),[18] which was suggested previously to account for the products from photolysis.[8] The oxathietane may decompose analogously to 1,2-dioxetanes (oxaoxetanes, cyclic four-membered peroxides).[19] Strain in the three-membered ring will dispose it to opening, but the electrophilic benzoyl and phenyl groups may require the opening to occur in such a way that some residual bonding (*i.e.*, electron density) remains at the site of bond breaking. This requirement can lead to the formation of the four-membered ring which is less strained than its precursor.

The role of the carbonyl groups in the episulfoxides in possible photochemical sensitization is unclear. They certainly play no unique photochemical role because the thermal decomposition leads to the same products. No dramatic effect is observed for relatively large amounts of added acetophenone or benzophenone but these external sensitizers may be of greatly decreased efficiency relative to the internal benzoyl groups.



Sulfenates are probable intermediates in the pyrolytic decomposition of dibenzyl sulfoxide or benzyl methyl sulfoxide.[20] The reverse reaction, the rearrangement of sulfenates to sulfoxides, is known.[21]

Absorption of light by the mixture of episulfoxides probably is followed quickly by decay of the initially formed electronically excited state to a vibrationally excited ground state from which rearrangement occurs. This excited ground state also may be attained by heating the episulfoxides. The recent discovery of the transfer of energy from a 1,2-dioxetane to organic mole-

(16) For examples of self-quenching of photochemical reactions by products, see H. D. Becker, *J. Org. Chem.*, **32**, 2124 (1967); F. D. Lewis and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **90**, 3828 (1968)

(17) G. E. Hartzell and J. N. Paige, *J. Org. Chem.*, **32**, 459 (1967).

(18) Expansions of cyclic sulfones to cyclic sulfinates (sultines) are known: D. C. Dittmer, R. S. Henion, and N. Takashina, *J. Org. Chem.*, **34**, 1310 (1969), and references cited therein; J. F. King, K. Piers, D. J. H. Smith, C. L. McIntosh, and P. deMayo, *Chem. Commun.*, 31 (1969).

(19) For recent examples, see K. R. Kopecky and C. Mumford, *Can. J. Chem.*, **47**, 709 (1969); C. S. Foote and J. Lin, *Tetrahedron Lett.*, 3267 (1968); J. E. Huber, *ibid.*, 3271 (1968); H. H. Wasserman, K. Stiller, and M. B. Floyd, *ibid.*, 3277 (1968). A 1,2-oxathiolane intermediate is alleged to decompose in a somewhat similar manner: Q. E. Thompson, *J. Org. Chem.*, **30**, 2703 (1965).

(20) E. Fromm and O. Achert, *Ber.*, **36**, 534 (1903); W. Carruthers, I. D. Entwistle, R. A. W. Johnstone, and B. J. Millard, *Chem. Ind. (London)*, 342 (1966).

(21) D. R. Rayner, E. G. Miller, P. Bickart, A. J. Gordon, and K. Mislow, *J. Amer. Chem. Soc.*, **88**, 3138 (1966); E. G. Miller, D. R. Rayner, and K. Mislow, *ibid.*, 3139 (1966).

cules (*e.g.*, *trans*-stilbene)[22] suggests that the presence of the postulated 1,2-oxathietane intermediate might be revealed by observation of an energy transfer from excited molecules produced from the intermediate.

Experimental Section

Melting points were obtained on a Fisher-Johns melting point apparatus (corrected). Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn., or at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All Chemicals were either "Chromatoquality" or reagent grade.

Infrared spectra were taken on either a Perkin-Elmer Model 137 infrared spectrophotometer or on a Perkin-Elmer Model 521 grating spectrophotometer. The infrared absorptions are reported as weak (0–20%, w), medium (20–80%, m), and strong (80–100%, s). Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 ultraviolet spectrophotometer. The absorptions are reported in nm and the intensity (ϵ) of the absorptions in l./mol cm. Proton nuclear magnetic resonance (nmr) spectra were obtained on a Varian Model A-60 nuclear magnetic resonance spectrometer. The nmr absorptions are reported as cycles per second (Hz) and tetramethylsilane was used as an internal standard. Molecular weight determinations were done by vapor pressure osmometry in an appropriate solvent or by mass spectrometry. Mass spectra were obtained on a Perkin-Elmer Hitachi Model RMU-6E single focusing spectrometer. Thin layer chromatography (tlc) was performed according to standard methods with apparatus from Brinkman Instruments, Inc., Westbury, N. Y., and either Merck silica gel GF_{254} or HF_{254}. Visualization was effected by the use of ultraviolet light and the compounds were identified as dark spots over the silica gel.

Dibenzoylstilbene Episulfoxides.—A solution of the yellow episulfide[4] (13.8 g, 0.0326 mol) in 250 ml of ethyl ether was treated with 10.5 ml of peracetic acid (40% in acetic acid, FMC Corp.) to yield a mixture of episulfoxides (11.8 g, 0.0272 mol, 86%). The episulfoxide isomers (mp 165–167°, 184–186°) may be precipitated fractionally from ethyl acetate. The yield of each isomer is about 10% for each recrystallization; the major portion of product remains in solution as a mixture. The two isomers have a mixture melting point of about 145°, and a mixture apparently was obtained in an earlier investigation.[4]

The infrared spectrum of the lower melting episulfoxide isomer (KBr disk) exhibits bands at 3050 (w), 1680 (s), 1615 (m), 1595 (m), 1570 (m), 1485 (m), 1440 (s), 1315 (m), 1300 (m), 1260 (s), 1210 (s), 1175 (m), 1150 (w), 1110 (m), 1100 (m), 1055 (s), 1040 (m), 1020 (m), 1000 (m), 970 (w), 945 (w), 935 (w), 875 (w), 850 (m), 815 (w), 780 (m), 770 (s), 755 (s), 735 (s), and 690 cm^{-1} (s). The infrared spectrum of the higher melting episulfoxide isomer (KBr disk) exhibits bands at 3050 (w), 1680 (s), 1615 (m), 1595 (m), 1570 (m), 1485 (m), 1440 (s), 1315 (m), 1300 (m), 1240 (s), 1205 (s), 1175 (m), 1160 (w), 1100 (m), 1055 (s), 1045 (s), 1020 (m), 1000 (s), 995 (m), 955 (m), 930 (m), 920 (m), 900 (m), 835 (w), 795 (w), 775 (m), 765 (s), 750 (s), 740 (s), and 685 cm^{-1} (s).

The proton nmr spectrum (60 MHz in $CDCl_3$) of each isomer was determined. The lower melting episulfoxide had two complex multiplets centered at 475 and 445 Hz relative to tetramethylsilane. The higher field multiplet had one strong peak at 438 Hz. The higher melting episulfoxide had two complex multiplets centered at 473 and 440 Hz. The higher field multiplet had three strong peaks at 447, 439, and 430 Hz.

Beer's Law is obeyed by the ultraviolet maxima of each episulfoxide.

Isomer mp, °C	Solvent	λ_{max}, nm	$10^4\epsilon$, l./mol cm	λ_{max}, nm	$10^4\epsilon$ l./mol cm
165–167	Acetonitrile	225	2.30	256	2.05
	95% ethanol	225	2.40	256	2.20
184–186	Acetonitrile	233	2.70	255[a]	2.30
	95% ethanol	233	2.75	260[a]	2.00

[a] Shoulder.

The mass spectrum of the high melting isomer of the episulfoxide of dibenzoylstilbene showed no parent ion and ions at *m/e* (rel intensity) 388 [0.049, $C_6H_5CO(C_6H_5)C{=}C(C_6H_5)COC_6H_5$], 372 (0.016, tetraphenylfuran), 284 (0.019), 283 (0.052), 226 (6.31, $C_6H_5CSCOC_6H_5$), 210 (2.52, $C_6H_5COCOC_6H_5$), 178 (0.040, $C_6H_5C{\equiv}CC_6H_5$), 165 (1.13), 152 (0.75), 123 (1.53), 122 (5.74), 121 (7.48, $C_6H_5CO_2$), 106 (11.4), 105 (100, C_6H_5CO). The mass spectrum of the low melting isomer also showed no parent ion and fragments at *m/e* 388 (1.56), 372 (1.32), 284 (4.09), 283 (1.51), 226 (5.88), 210 (2.78), 179 (2.94), 178 (3.32), 176 (2.30), 165 (3.12), 152 (2.74), 123 (2.33), 122 (12.4), 121 (27.4), 106 (8.46), 105 (100).

Table II

Yields of Benzil Obtained by Photolysis of Mixtures of Episulfoxides of Dibenzoylstilbene

Filter	Time, min	Episulfoxides, 10^4 mol	Benzil, 10^4 Mol	Benzil, Mol, %
Quartz	30	12.9	3.78	30.0[a]
	45	15.2	6.51	42.8[a]
	90	11.1	9.18	82.5[b]
	105	8.39	7.16	85.4[a]
Vycor	40	11.7	4.72	40.2[b]
	90	11.1	8.78	70.0[a]
Pyrex	60	5.60	2.94	52.5[a]
	90	10.8	5.80	53.7[b]
	120	10.0	5.19	51.9[a]

[a] Determined spectrophotometrically at 258 nm, ϵ (95% C_2H_5OH) 2.15×10^4. [b] Determined by weight.

Complexes of the episulfoxides with anhydrous cobalt(II) bromide and cobalt(II) nitrate were obtained by treatment of the episulfoxide with the cobalt salt in dry dichloromethane. Analyses were not satisfactory but they indicated that cobalt(II) bromide complexes with four molecules of episulfoxide and that cobalt(II) nitrate complexes with two. In the complex with cobalt nitrate, the absorption in the infrared caused by the nitrate groups are at 1490 and 1275 cm^{-1}, being shifted from 1380 and 1350 cm^{-1}, the absorptions in cobalt(II) nitrate itself, and indicating that the nitrate ions are acting as ligands. The episulfoxide band was at 945 cm^{-1} as compared with 1055 cm^{-1} in the uncomplexed ligand. Because of the instability of these complexes to light and to moist air and because of their extreme insolubility, they were not investigated further.

Pyrolysis of the Isomeric Episulfoxides of Dibenzoylstilbene.—Pyrolysis of the mixed episulfoxides (0.643 g, 0.00147 mol) at 200–210° for 1.5 hr under vacuum (<1 mm) gave a green sublimate and a brown residue. The entire apparatus was wrapped in aluminum foil to keep out light. After the reaction mixture was cool, dry nitrogen was admitted and 15 ml of toluene was used to dissolve the green sublimate.

The solution was chromatographed on silicic acid under nitrogen with chloroform to give monothiobenzil[8,23] (0.000161 mol, 11% calculated from the visible spectrum) and 0.156 g (0.000744 mol, 51%) of benzil, mp 92–93°, mmp 92–94°. The visible and ultraviolet spectrum of monothiobenzil in chloroform was identical with that of the monothiobenzil produced in the photolysis of the episulfoxides.

The addition of 10 ml of toluene to the brown residue afforded a yellow solution and *cis*-dibenzoylstilbene, mp 209–211° (0.0184 g, 0.0000473 mol, 3%). An infrared spectrum of the *cis*-dibenzoylstilbene was the same as that of an authentic sample.[24] Analysis by tlc showed the yellow solution contained benzil, a trace of *trans*-dibenzoylstilbene, *cis*-dibenzoylstilbene, and at least three other compounds.

Photolysis of Dibenzoylstilbene Episulfoxide.—An internal mercury arc lamp (Hanovia Type L, 450 W) which emits light with a maximum at 366 nm was used in a water-cooled quartz immersion well. The benzene solvent (Baker and Adamson) was dried with sodium ribbon and distilled. The silicic acid (Baker and Adamson) used for chromatography was dried overnight at 115°. All solvents and flasks used with monothiobenzil were flushed with Linde high purity dry nitrogen and the flasks were wrapped in aluminum foil to keep out light.

The benzene solutions of mixtures of the two episulfoxides were photolyzed at 6–11°. The deep blue-green solutions obtained after irradiation were chromatographed on silicic acid as de-

(22) E. H. White, J. Wiecko, and D. F. Roswell, *J. Amer. Chem. Soc.*, **91**, 5194 (1969); E. H. White, J. Wiecko, and C. C. Wei, *ibid.*, **92**, 2167 (1970).

(23) D. C. Dittmer and G. E. Kuhlmann, *J. Org. Chem.*, in press.

(24) N. M. Bikales and E. I. Becker, *ibid.*, **21**, 1405 (1956).

scribed in the section on the pyrolysis. The chromatography column was wrapped in aluminum foil to keep out light.

The course of the reaction usually was followed by the production of benzil, and the concentration of monothiobenzil can be determined spectrophotometrically. Benzil was recovered by the flash evaporation of the chloroform at room temperature followed by extraction with hot 95% ethanol and filtration. The benzil yield was determined either by weight or by ultraviolet spectroscopy. Data on yields are given in Table I and Table II and results with various quenchers and sensitizers are summarized in Table I.

Registry No.—2,3-Dibenzoyl-2,3-diphenylthiirane 1-oxide, 988-04-5.

Photolysis of Bis[*p*-(1,1,3,3-tetramethylbutyl)phenyl] Terephthalate

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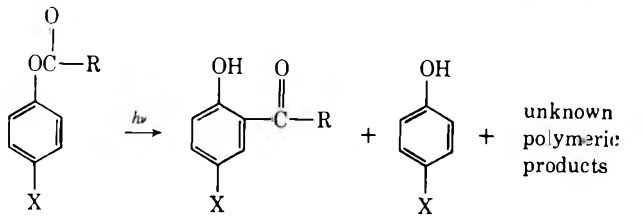
The photolysis of bis[*p*-(1,1,3,3-tetramethylbutyl)phenyl] terephthalate in various solvents resulted in two consecutive photo-Fries rearrangements, whose quantum efficiencies were much lower than for simple aryl esters. Changes in solvent polarity and moderate changes in viscosity had little effect on the photolysis, but the efficiency in a rigid matrix was lowered considerably. In aqueous dioxane, the chief reaction was a photohydrolysis to give *p*-(1,1,3,3-tetramethylbutyl)phenol and terephthalic acid.

The photolysis of aryl esters has recently been reviewed.[1] The course of the reaction is well established, but whether the photo-Fries rearrangement involves a separated free-radical intermediate[2] or a 1,3-sigmatropic shift[3] is not known. The quantum efficiency for ketone formation,[3,4] ϕ_k, is usually 0.15–0.20,

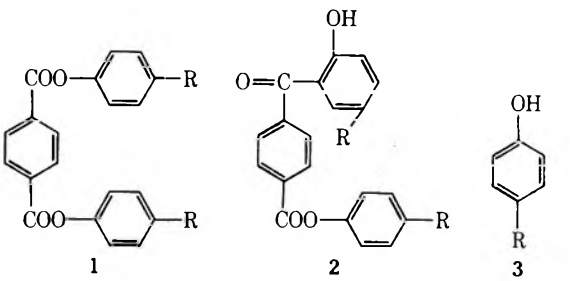


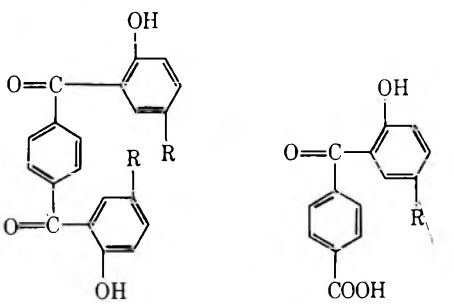
and the quantum efficiency, ϕ_p, for phenol production, is about 0.05–0.15 in nonviscous, inert solvents.[3] The effect of solvents on this photolysis is poorly understood. An increase in solvent polarity was reported to be without effect on either ϕ_k or ϕ_p in the photolysis of *p*-tolyl acetate[3] but was reported to increase both ϕ_k and ϕ_p in the photolysis of 3,5-di-*tert*-butylphenyl benzoate.[5] Increased solvent viscosity reduced ϕ_p.[3] In fluid solvents the yield of ketone is only 10–50%, and much of the ester is converted to unknown products; however, photolysis of aryl benzoates in a polymeric matrix has been reported to proceed without side reactions.[6,7] Many aryl esters of aromatic monocarboxylic acids have been studied; however, the photo-Fries rearrangement of nonpolymeric esters of aromatic dicarboxylic acids has not been reported. Photolysis of polymeric esters such as poly(isopropylidenedi-*p*-phenylene isophthalate) resulted in the formation of 2-hydroxybenzophenone moieties in the polymer.[6]

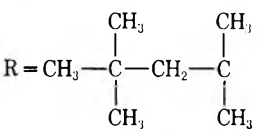
We report here the results of the photolysis of a nonpolymeric diester, bis[*p*-(1,1,3,3-tetramethylbutyl)-phenyl] terephthalate (**1**), in a number of fluid solvents and in a rigid, polymeric matrix.

Results and Discussion

Photolysis of **1** in anhydrous solvents gave four products which could be separated by glc: **2**, **3**, **4**, and **5**.







Each of these was also isolated and characterized by other means. In the presence of water, terephthalic acid was also a major product. Table I gives the product distribution, as determined by glc, for photolysis of **1** in various solvents.

Approximate quantum efficiencies for some of the reactions are given in Table II. These values were determined by using polychromatic light; loss of **1** was 10% or less. Because of the complexity of the mixture, the values are not corrected for absorption of light by the products.[4]

For further information on the effect of solvent polarity and viscosity, photolyses were carried out in mixtures of dioxane and acetonitrile. The results are shown in Table III.

* To whom correspondence should be addressed

(1) D. Belluš and P. Hrdlovič, *Chem. Rev.*, **67**, 599 (1967).
(2) H. Kobsa, *J. Org. Chem.*, **27**, 2293 (1962).
(3) M. R. Sandner, E. Hedaya, and D. J. Trecker, *J. Amer. Chem. Soc.*, **90**, 7249 (1968).
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(5) R. A. Finnegan and D. Knutson, *Tetrahedron Lett.*, 3429 (1968).
(6) S. B. Maerov, *J. Polym. Sci.*, **3**, 487 (1965).
(7) G. M. Coppinger and E. R. Bell, *J. Phys. Chem.*, **70**, 3479 (1966).

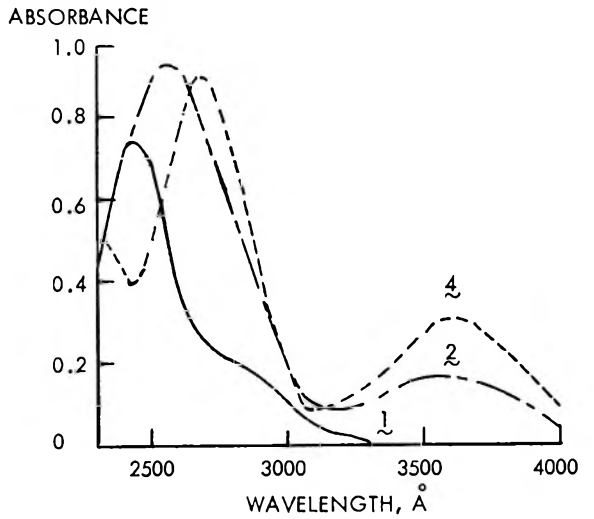


Figure 1.—Absorption spectra in methylene chloride of **1** (0.07 g/l.), **2** (0.10 g/l.), and **4** (0.07 g/l.). Cell length, 0.25 cm.

TABLE I

DISTRIBUTION OF PRODUCTS FROM PHOTOLYSIS OF **1** IN VARIOUS SOLVENTS

Solvent	Time, hr	Compd, 10^{-5} mol 1[a]	2	3	4	5
Benzene	4	6.7	2.6	2.6	0.4	0.2
	12	*b*	4.9	3.3	2.3	1.1
	75	*b*	0.6	4.5	6.2	1.9
Dioxane[c]	4	6.0	3.5	2.5	0.7	*b*
	12	*b*	1.7	4.8	4.6	0.4
	75	*b*	*b*	8.2	6.5	0.4
Dioxane–water,[d] 50:1	4	7.3	3.9	4.7	1.3	*b*
	12	0.1	1.0	23.6	3.6	0.5
	75	*b*	*b*	23.8	3.8	0.9
Dioxane–1-octanol, 1:1	12	1.0	3.1	15.2	3.7	*b*
Polystyrene[e]	48	6.6	2.6	*b*	1.0	*b*
Benzene[e]	20	8.0				

[a] Initial charge of **1** was 19.4 × 10^{-5} mol. [b] Not detected by glc. [c] Contained 50–75 ppm of water. [d] Terephthalic acid found in significant quantity. [e] Irradiation in Rayonet reactor.

TABLE II

APPROXIMATE QUANTUM EFFICIENCIES FOR PHOTOLYSIS OF **1**

Solvent	Quantum efficiency[a] ϕ_2	ϕ_3	ϕ_4
Benzene	0.02	0.004	0.01
Dioxane	0.02	0.010	*b*
Dioxane–water, 50:1	0.01	0.034	*b*

[a] ϕ_2 is for appearance of **2**; ϕ_3 is for appearance of **3**; ϕ_4 is for **2** → **3** in the absence of **1**. [b] Not determined.

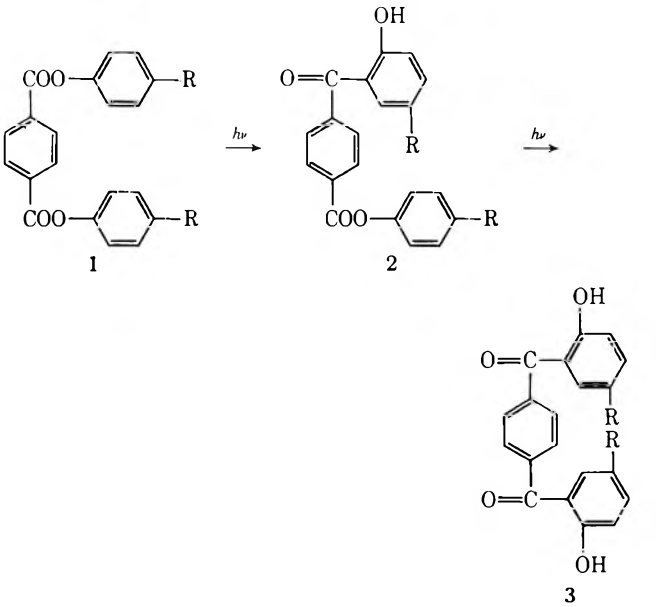
TABLE III

PRODUCTS FROM PHOTOLYSIS[a] OF **1** IN DIOXANE–ACETONITRILE SOLUTION

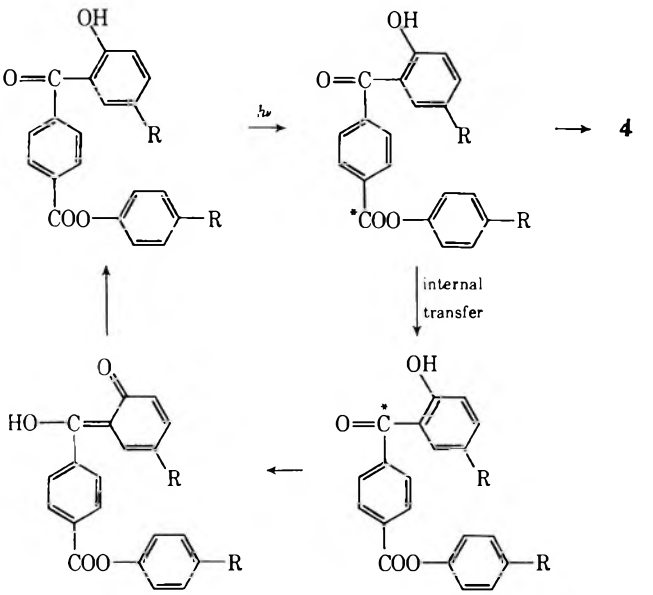
Acetonitrile, vol %	Viscosity, cp (30°)	Compd, 10^{-5} mol 1[b]	2	3	4	5
0	1.087	2.7	5.0	7.6	3.3	0.9
1		3.0	5.3	8.2	3.5	1.0
5		2.8	5.0	8.2	3.5	1.0
10		2.2	4.7	8.0	3.5	1.1
20	0.793	2.2	4.7	9.5	3.3	1.2

[a] Time was 9.4 hr. [b] Initial charge of **1** was 22 × 10^{-5} mol.

Aryl terephthalates can undergo two consecutive photo-Fries rearrangements. Because there appears to be no appreciable substituent effect in the photo-Fries rearrangement, the first reaction (**1** → **2**) should



proceed as efficiently as the rearrangement of an aryl benzoate. However, **2** has a possible means of self-stabilization by energy transfer between the two chromophores. If excitation energy were transferred from the ester moiety to the 2-hydroxybenzophenone moiety, **2** should be resistant to further photochemistry.[8]



When **2** was irradiated at 360 nm (Rayonet reactor, 360-nm lamps), where only the 2-hydroxybenzophenone carbonyl absorbs, as seen in Figure 1, it was recovered unchanged; hence, only light absorbed by the ester group leads to rearrangement. The absorption of polychromatic ultraviolet light by **2** will be divided between the two chromophores and, in the absence of efficient energy transfer from the ester carbonyl to the ketone carbonyl, the quantum efficiency for rearrangement of **2** would be somewhat lower than that for **1**.

(8) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1967, p 150.

However, if energy is efficiently transferred in this direction, the quantum efficiency for rearrangement of **2** would be greatly decreased. The observed value is about half that for the rearrangement of **1** and supports the hypothesis that energy transfer from the ester carbonyl to the ketone carbonyl is not an efficient process.

Both ϕ_2 and ϕ_3 are about an order of magnitude lower than ϕ_k and ϕ_p for aryl benzoates. We believe that the inefficiency of the photoreactions of **1** results from the extended conjugation of the terephthalate system, which may offer facile routes for internal conversion.[9]

In accord with the findings of Sandner, Hedaya, and Trecker,[3] solvent polarity was without effect on either the photo-Fries reactions of **1** or its cleavage to the phenol. Photolysis in dioxane–acetonitrile mixtures of varying polarity gave identical product ratios. Solvent viscosity, over a moderate range in fluid solvents, was also without effect on the photolysis of **1**. However, in a rigid medium, polystyrene, the production of the phenol **3** was completely suppressed, as would be expected in a highly viscous medium.[3] Unexpectedly, the rate of the photo-Fries rearrangement was reduced twofold in this rigid matrix. Earlier workers[3] reported that ϕ_k for the photolysis of *p*-tolyl acetate was the same in Carbowax 600 poly(ethylene glycol) as in ethanol, which differ in viscosity by a factor of 100. The bulky alkyl groups in **1** may hinder the mobility required for rearrangement in a rigid medium.

In anhydrous solutions, the conversion of **1** to the isolated products was low; less than half of the *p*-alkylphenyl content was accounted for. The nature of the major product of the photolysis of **1**, and of most other aryl esters reported, remains unknown. The data in Table I show that the production of **3** continues at a significant rate after its isolable precursors, **1** and **2**, have nearly disappeared; hence, the unknown product must retain the ester group.

The photolysis of **1** in polystyrene gave the same low conversion to the 2-hydroxybenzophenones as was obtained in fluid solvents. The major product of this reaction was an insoluble, fibrous, apparently polymeric, yellow substance. This finding is in contrast to previous reports[6,7] that no side reactions accompanied the the photo-Fries rearrangement in a polymeric matrix. In these earlier investigations, the hydroxybenzophenone product was determined by ultraviolet absorption analysis. Because an ultraviolet-absorbing major product of unknown structure was formed, ultraviolet analysis is unreliable in this application.

The most dramatic and unexpected solvent effect was that of water in dioxane. It was reported[3] that benzene and aqueous dioxane solutions gave the same results in the photolysis of *p*-tolyl acetate. However **1** showed a large increase in ϕ_3 for aqueous dioxane as compared to benzene. Furthermore, after 12 hr of irradiation, more than 60% of the *p*-(1,1,3,3-tetramethylbutyl)phenyl content was recovered as *p*-(1,1,3,3-tetramethylbutyl)phenol (**3**). Significantly, only 4.7×10^{-5} mol of **3** was formed in the first 4 hr of irradiation but about four times this amount, 18.9×10^{-5} mol, was produced in the next 8 hr, even though the precursors of **3** were decreasing *via* the photo-Fries rearrangement. A considerable amount of terephthalic acid was also produced in aqueous dioxane, but none was formed in anhydrous solvents. No hydrolysis occurred when solutions of **1** and its various photoproducts in aqueous dioxane were kept in the dark for several days. These results show that some photoexcited species is involved in the hydrolysis but direct reaction of an excited state of **1** with water does not occur. The first excited singlet of a phenol is a relatively strong acid;[10] hence, we believe the hydrolysis is catalyzed by the excited singlet of **3**. The effect of water is so pronounced that we believe the increased yield of **3** in "dry" dioxane (50–75 ppm water) is due to hydrolysis rather than to any effect of dioxane. Photolysis of **1** in dioxane–1-octanol solution also gave a considerably greater yield of **3** than expected. A similar result, attributed to a photochemical solvolysis, was observed[3] when *p*-tolyl acetate was photolyzed in ethanol. A catalyzed solvolysis, similar to the hydrolysis reported here, might also be involved when esters are photolyzed in alcohol solutions. Further work is under way to elucidate the mechanism of the apparent photochemical hydrolysis and solvolysis of **1**.

(9) We found that bis(2,4,6-trimethylphenyl) terephthalate, which cannot undergo a photo-Fries rearrangement, is very resistant to photolysis.

Experimental Section

Preparation of Bis[p-(1,1,3,3-tetramethylbutyl)phenyl] Terephthalate (1).—To a cooled solution of 20.6 g (0.1 mol) of *p*-(1,1,3,3-tetramethylbutyl)phenol and 4.0 g of sodium metal in 250 ml of ethanol was added slowly 10.2 g (0.05 mol) of terephthaloyl chloride dissolved in 150 ml of ether. The mixture was then chilled and filtered. The product was dissolved in isooctane, and the solution was filtered. The filtrate was cooled at 5°, and the precipitate was collected by filtration. The product was then dried to obtain 25 g (95%) of white crystals, mp 174–175°, ir (KBr) 1742 cm^{-1} (C=O).

Anal. Calcd for $C_{36}H_{46}O_4$: C, 79.68; H, 8.54: O, 11.80. Found: C, 79.56; H, 8.54; O, 11.90.

General Irradiation Procedure.—Solutions of **1** (1.0 wt %) in the appropriate solvent, contained in Vycor glass test tubes, were irradiated in a "merry-go-round" apparatus with a 550-W Hanovia medium-pressure arc light. Aliquots, 0.1 ml, were removed from time to time and treated with 0.9 ml of Tri-Sil trimethylchlorosilane. The mixture was allowed to stand 5 min, and then 40 μl of the resulting solution was injected onto a ¼ in. × 5 ft 15% SE-30 column. The column temperature was programmed from 85 to 340° at a rate of 10°/min and held at the upper limit until the last fraction was eluted. Actinometry for the photolysis was done with the uranyl oxalate actinometer solution of Masson, Boekelheide, and Noyes.[11]

The quantum efficiency for the photolysis of **2** was similarly determined by using a 1.0% solution of **2** in dioxane.

Attempted Photolysis of 2 with 3600-Å Light.—A 1.0% solution of **2** in dioxane was irradiated for 24 hr with a 3660-Å lamp (1.35×10^{-1} einstein/min). Only **2** was detected by glc.

Isolation of 2,2′-(p-Phenylenedicarbonyl)bis[p-(1,1,3,3-tetramethylbutyl)phenol] (4) and p-(1,1,3,3-Tetramethylbutyl)phenol (3).—A solution of 2.0 g of **1** in 150 ml of anhydrous dioxane was irradiated for 144 hr with a 2.5-W 2537-Å immersion lamp. The solution was evaporated to a paste. The residue was taken up in a small amount of acetone and cooled in dry ice. The yellow precipitate was collected and recrystallized twice from acetone–water to give a yellow crystalline product, mp 143–145°, identified as **4**: ir (KBr) 1627 cm^{-1} (C=O); nmr ($CDCl_3$) singlet at 11.7 ppm (2 H, OH).

Anal. Calcd for $C_{36}H_{46}O_4$: C, 79.68; H, 8.54: O, 11.80. Found: C, 79.00; H, 8.55; O, 12.45.

The acetone filtrate from the above precipitation was evaporated to a paste and sublimed at atmospheric pressure. Two recrystallizations of the sublimate from isooctane produced a white crystalline material, mp 73–75°, identified as **3** by mixture

(10) G. Jackson and G. Porter, *Proc. Roy. Soc., Ser. A*, **260**, 13 (1961).

(11) C. R. Masson, V. Boekelheide, and W. A. Noyes, Jr., in "Technique of Organic Chemistry," 2nd ed, Vol. II, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, pp 294–298.

melting point and comparison of its ir spectrum with that of an authentic sample.

Isolation of *p*-(1,1,3,3-Tetramethylbutyl)phenyl *p*-[2-Hydroxy-5-(1,1,3,3-tetramethylbutyl)benzoyl]benzoate (2).—A solution of 2.0 g of 1 in 150 ml of anhydrous dioxane was placed in a Pyrex glass test tube and irradiated with a 550-W Hanovia mercury arc for 37 hr. The yellow solution was evaporated to a paste, and the residue was taken up in acetone. The insoluble material, 1.0 g, was filtered out and the filtrate was concentrated, cooled in dry ice, and filtered. Five recrystallizations of the yellow precipitate from acetone–water produced a material, mp 156–157°, identified as 2: ir (KBr) 1631 (C=O), 1743 cm^{-1} (C=O); nmr ($CDCl_3$) singlet at 11.7 ppm (1 H, OH).

Anal. Calcd for $C_{36}H_{46}O_4$: C, 79.68; H, 8.54; O, 11.80. Found: C, 79.68; H, 8.54; O, 11.48.

Isolation of *p*-[2-Hydroxy-5-(1,1,3,3-tetramethylbutyl)benzoyl]benzoic Acid (5).—A solution of 12.0 g of 1 in 600 ml of dioxane (0.5% water) was irradiated for 26 hr with a 2.5-W 2537-Å immersion lamp. The yellow solution was evaporated to a paste and the residue was taken up in ether. The ether solution was filtered and then shaken with a 10% sodium hydroxide solution. The yellow precipitate formed was dissolved in warm water, and the resulting solution was acidified with hydrochloric acid. The precipitate was collected and sublimed at 0.5 mm pressure and 206° bath temperature. The initial fraction was discarded and the yellow, crystalline material, mp 196–197°, was identified as 5: ir (KBr) 1628 (C=O), 1692 cm^{-1} (C=O); nmr singlet at 11.8 ppm (2 H, OH and CO_2H).

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.70; H, 7.41; O, 17.89. Found: C, 74.92; H, 7.54; O, 17.54.

Isolation of Terephthalic Acid.—A solution of 1.0 g of 1 in 100 ml of 10:1 dioxane–water solution was irradiated for 48 hr in several Pyrex glass tubes with a 550-W Hanovia mercury arc. The solutions were combined and evaporated to dryness on a steam bath. The residue was extracted with warm sodium bicarbonate solution. The sodium bicarbonate solution was acidified with 6 *N* hydrochloric acid and filtered. The precipitate was washed with water and ether. The precipitate had a melting point greater than 300° and its ir spectrum was identical with that of a known sample of terephthalic acid.

Photolysis of 1 in Polystyrene.—A hot solution of 4.0 g of polystyrene and 0.08 g of 1 in 100 ml of methylene chloride was poured into a petri dish and allowed to stand until a hard film was obtained. The dish was then left overnight on a hot plate set at 50°. Half of the resulting film was irradiated in a Rayonet reactor (3100-Å lamps) for 48 hr. Samples (approximately 0.50 g) of the above films were dissolved in 50 ml of methylene chloride containing 4.0 ml of a 0.30% solution of *o*-hydroxybenzophenone (glc internal standard). The resulting solutions were cooled, diluted with 200 ml of acetone, filtered, and evaporated to dryness in a rotary evaporator. The residue was taken up in 2 ml of dioxane. A 0.2-ml portion of this solution was treated with 1.0 ml of Tri-Sil and chromatographed as previously described. As a control, a solution of 1 in benzene at the same concentration was photolyzed under the same conditions.

Registry No.—**1**, 3637-39-6; **2**, 26157-65-3; **4**, 26157-66-4; **5**, 26157-67-5.

Acknowledgment.—The authors gratefully acknowledge the help of Professor David Whitten, of the University of North Carolina, with whom many fruitful discussions of this work were held.

Photolysis of 2,2,5,5-Tetramethyldihydro-3-furanone[1,2]

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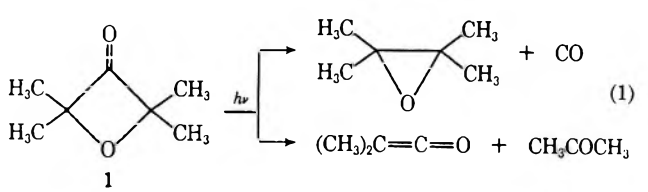
The photolysis of 2,2,5,5-tetramethyldihydro-3-furanone in methanol gives methyl 3-isopropoxy-3-methylbutanoate, methyl 3-methyl-2-butenoate, isopropyl 3-methyl-2-butenoate, methyl 3-methyl-3-butenoate, and isopropyl alcohol. These products are all considered to arise *via* the ketene formed by Norrish type I cleavage of the dihydrofuranone followed by intramolecular hydrogen abstraction. Corroboration for this view is provided by the observation that photolysis of 2,2,5,5-tetramethyldihydro-3-furanone-4-d_2 in methanol gives methyl 3-(isopropoxy-*1-d*)-3-methylbutanoate-*2-d* and methyl 3-methyl-2-butenoate-*2-d*.

Although the photolysis of cyclic ketones has been studied extensively, the only previous investigation of the photolysis of an oxacycloalkanone appears to be that of Hammond and coworkers,[3] who found that 2,2,4,4-tetramethyl-3-oxetanone (1) undergoes both decarbonylation and cleavage to a ketene and ketone (eq 1). These reactions are closely analogous to



1 (1)

reactions observed in the case of cyclobutanones,[4] and were interpreted as involving initial Norrish type I cleavage of the oxetanone.

We report now a study of the photolysis of the related 2,2,5,5-tetramethyldihydro-3-furanone (2) in methanol. This investigation was undertaken (1) to extend our knowledge of the photochemistry of oxacycloalkanones, and (2) as part of the search for new cases of the photochemical conversion of cyclic ketones to cyclic acetals.[2] With respect to the latter quest, it was considered that the absence of hydrogen atoms at the ring atoms bearing a β relationship to the carbonyl group might inhibit alkenal formation[5] and that the circumstance that the ring is five membered might inhibit ketene formation.[6] It was hoped that if these two pathways were thus made more difficult, an oxacarbene[2] might be formed, leading to the formation of a cyclic acetal. In the event, however, this goal was not achieved.

* Author to whom correspondence should be addressed.

(1) Taken from dissertations presented by J. P. Wasacz and G. R. Hagens in partial fulfillment of the requirements of the Ph.D. degree at the University of Pennsylvania, 1969, and the University of Toronto, 1970, respectively.

(2) Part of this work was discussed at the Second IUPAC Symposium on Photochemistry, Enschede, Holland, 1967; P. Yates, *Pure Appl. Chem.*, **16**, 93 (1968).

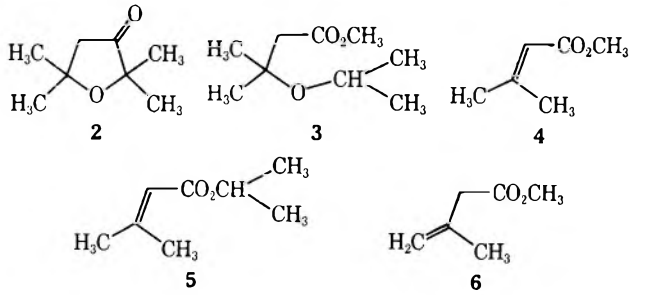
(3) P. J. Wagner, C. A. Stout, S. Searles, Jr., and G. S. Hammond, *J. Amer. Chem. Soc.*, **88**, 1242 (1966).

(4) N. J. Turro and R. M. Southam, *Tetrahedron Lett.*, 545 (1967); D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 4349 (1970).

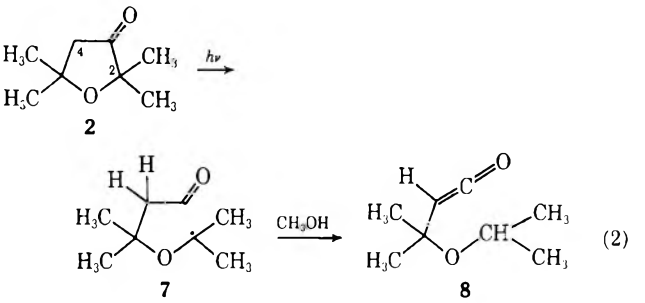
(5) R. Srinivasan, *ibid.*, **81**, 1546 (1959).

(6) G. Quinkert, *Pure Appl. Chem.*, **9**, 607 (1964).

Irradiation of dilute methanolic solutions of **2** in a Pyrex vessel with a medium-pressure mercury arc lamp gave methyl 3-isopropoxy-3-methylbutanoate (**3**), methyl 3-methyl-2-butenoate (**4**), and isopropyl 3-methyl-2-butenoate (**5**).[7] Vapor phase chromatography (vpc) indicated that the relative yields of these products were *ca.* 9:23:1; the formation of isopropyl alcohol was also detected by vpc. When the photolysis of **2** was carried out in the presence of sodium carbonate, the product mixture was greatly enriched in **3**. Photolysis of **2** in methanol containing a small amount of sulfuric acid gave **4** almost entirely. Photolysis of **2** in pentane gave **5** as the only significant volatile product. When the irrradiation of **2** in methanol was carried out by immersion of the lamp in the solution, the formation of **5** was not observed, but a new product, methyl 3-methyl-3-butenoate (**6**), was detected.

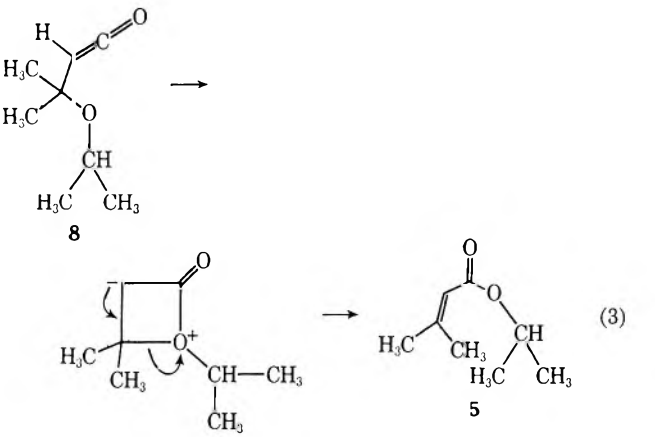


These observations can be interpreted in terms of the intermediacy of the ketene **8**, formed *via* Norrish type I cleavage of the more highly substituted[6] carbon–carbon bond adjacent to the carbonyl group of **2** to give **7** (eq 2). Reaction of this ketene with methanol in the normal fashion accounts for the formation of **3**.



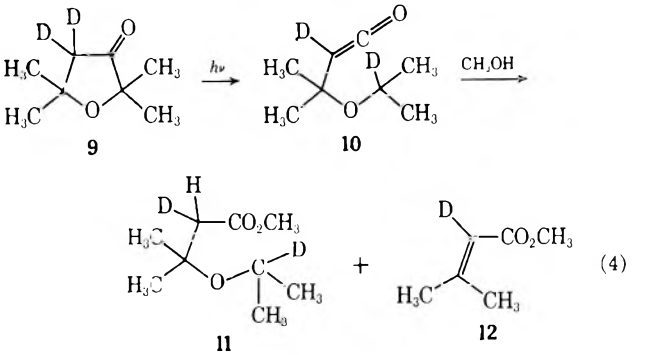
The formation of increased amounts of **4** when the reaction is carried out in the presence of acid and of increased amounts of **3** when the reaction is carried out in the presence of base indicates that **4** arises, at least in major part, by acid-catalyzed elimination of isopropyl alcohol from **3**. That such a reaction can occur in the dark was established by boiling a solution of **3** in methanol containing sulfuric acid for a brief period and demonstrating the formation of **4** and isopropyl alcohol.

The formation of **5** from **2** in methanolic solution might result from alcoholysis of **4** by the isopropyl alcohol eliminated in the formation of the latter. However, this is unlikely to be a significant pathway in dilute methanolic solution. Its formation is best interpreted as involving intramolecular attack of the ether oxygen atom on the ketene function in **8** (eq 3). Such a route can also account for the formation of **5** as the major volatile product from **2** in pentane.

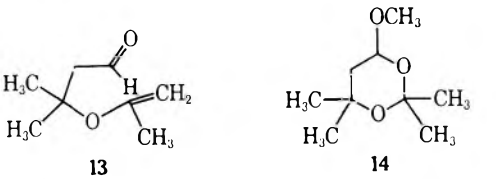


The formation of the β,γ-unsaturated ester **6** can be interpreted as involving the photoisomerization of the corresponding α,β-unsaturated ester **4**. Such isomerization has been reported previously by Jorgenson and Gundel,[8] and its occurrence in the present case was confirmed by irradiation of **4**. The fact that formation of **6** from **2** was observed only when the ultraviolet radiation was not filtered by a Pyrex vessel is in accord with expectation in that direct excitation of the α,β-unsaturated ester **3** would require radiation of shorter wavelength than that transmitted by Pyrex.

The postulated intramolecular transfer of a hydrogen atom from C-4 to C-2 in **7** in the formation of the intermediate ketene **8** (eq 2) has been confirmed by deuterium labeling at C-4. Irradiation of **9** gave **11** and **12**, the products anticipated from the ketene **10** (eq 4).



Thus, all the photoproducts obtained from **2** are most probably derived from the ketene **8**, formed by intramolecular hydrogen abstraction in the Norrish type I cleavage product **7**; no products derived *via* alternative hydrogen abstraction processes in **7**, *e.g.*, **13**, or *via* carbon–oxygen bond formation in **7**, *e.g.*, **14**, could be detected. The failure to form the unsaturated aldehyde



is not surprising, since its formation requires an unfavorable hydrogen abstraction from a methyl group in

(7) See Experimental Section for identification of products.

(8) M. J. Jorgenson and L. Gundel, *Tetrahedron Lett.*, 4991 (1968).

7. The exclusive formation of **8** is noteworthy, however, since it has previously been found that the hydrogen abstraction process leading to ketene formation is unfavorable in the case of the Norrish type I cleavage products formed from five-membered cyclic ketones.[6] The failure of oxacarbene formation to compete with ketene formation in this case reveals the very unfavorable nature of this reaction relative to ketene formation and places severe structural restrictions on those cyclic ketones that may be expected to undergo this reaction.

Experimental Section

The ultraviolet light source was a 450-W Hanovia Type L medium pressure mercury arc lamp; irradiation of solutions was carried out in Pyrex tubes placed close to the light source, unless otherwise specified. Infrared and nmr spectra were recorded in carbon tetrachloride solution. Analysis by vpc was carried out on a 10 ft × 0.25 in. column of 10% SE-30 on 80–100 Chromosorb W at 150°, unless otherwise specified. Preparative vpc was carried out on a 20 ft × 0.25 in. column of 10% silicone rubber on 45–60 Chromosorb W at 100–110° (injection port, 180°) with a helium flow rate of 120 ml/min; retention times are reported relative to air, coinjected as reference.

Photolysis of 2,2,5,5-Tetramethyldihydro-3-furanone (2). A.—A solution of 2,2,5,5-tetramethyldihydro-3-furanone (**2**)[9] (2.00 g) in methanol (100 ml) was irradiated for 5 days. Analysis by vpc showed that all the starting material had been consumed and that methyl 3-isopropoxy-3-methylbutanoate (**3**), methyl 3-methyl-2-butenoate (**4**), and isopropyl 3-methyl-2-butenoate (**5**) were formed in the ratio *ca.* 9:23:1; vpc analysis at 30° showed that isopropyl alcohol was also formed.

B.—To a solution of **2** (2.00 g) in methanol (50 ml) was added sodium carbonate (0.10 g). The mixture was irradiated for 75 hr, after which time vpc analysis revealed that 55% of **2** remained and that compounds **3** and **5** were formed in the ratio 24:1; no compound **4** was detected. Half of the methanol was distilled under reduced pressure, and the residual solution was added to a solution of Girard's-T reagent (1.00 g) in 10% acetic acid–ethanol (10 ml). The resulting solution was boiled for 30 min, after which time vpc analysis showed the complete removal of **2**. Water was added, and the mixture was extracted with ether. The ethereal solution was dried and stripped of solvent under reduced pressure, and the residual oil was molecularly distilled at 80–90° (15 mm) to give **3**.

C.—To a solution of **2** (2.00 g) in methanol (50 ml) was added 1 drop of concentrated sulfuric acid. The solution was irradiated for 75 hr, after which time vpc analysis revealed that 50% of **2** remained and that **4** represented 83% of the volatile photoproducts. A sample of the solution stored in the dark for several days showed no change in composition, as determined by vpc. After partial removal of methanol from the photolysis mixture, compound **2** was removed by treatment with Girard's-T reagent as in procedure B. The ether-soluble fraction was molecularly distilled at 60–80° (15 mm) to give **4**.

D.—A solution of **2** (3.00 g) in pentane (50 ml) was irradiated for 3 days, after which time the solution was brown in color and a gum had formed on the walls of the tube. Analysis by vpc revealed that no **2** remained and that the major volatile product was compound **5**; other products with longer retention times were present in small amount. The photolysis solution was stripped of solvent under reduced pressure, and the residual oil was molecularly distilled at 80–90° (15 mm) to give **5** (0.98 g, 33%).

E.—A solution of **2** (16.9 g, 0.119 mol) in methanol (300 ml) was irradiated by immersion of the lamp in the solution for 12 hr. After distillation of 290 ml of methanol, preparative vpc gave the following components of the photolysis mixture (retention times in parentheses): methanol (21 sec), isopropyl alcohol (43 sec), **6** (254 sec), **2** (415 sec), **4** (566 sec), and **3** (1667 sec).

Identification of Products from Photolysis of 2. Methyl 3-isopropoxy-3-methylbutanoate (3) gave the following: ν 1738 (ester C=O), 1379 (w), and 1364 (m) cm^{-1} [$(CH_3)_2C$]; δ 1.07 [d, J = 6 Hz, 6 H, $(CH_3)_2CH$–], 1.25 [s, 6 H, $(CH_3)_2C<$], 2.38 (s, 2 H, $-CH_2CO-$), 3.58 (s, 3 H, OCH_3), and 3.77 [septet, J = 6 Hz, 1 H, $(CH_3)_2CH$–]; *m/e* 159 (M − CH_3), 115 [$CH_3OOCCH_2\overset{+}{C}(CH_3)_2$], 101 [$(CH_3)_2CH\overset{+}{O}C(CH_3)_2$], 85 ($CH_3CO\overset{+}{C}H_2O$), 73 ($CH_3OOC\overset{+}{C}H_2$), and 43 ($\overset{+}{C}H(CH_3)_2$).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.37; H, 10.09.

Methyl 3-methyl-2-butenoate (4) gave the following: ν 1725 (conjugated ester C=O) and 1660 cm^{-1} (C=C); δ 1.86 (d, J = 1.5 Hz, 3 H, *trans*-CH_3C=CCO–), 2.15 (d, J = 1.5 Hz, 3 H, *cis*-CH_3C=CCO–), 3.60 (s, 3 H, OCH_3), and 5.70 [septet, J = 1.5 Hz, 1 H, $(CH_3)_2C$=CHCO–]; *m/e* 114 (M), 83 [$(CH_3)_2C=C\overset{+}{H}CO$], and 55 [$(CH_3)_2C=\overset{+}{C}H$].

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.27; H, 8.63.

The infrared and nmr spectra and the vpc retention time of the photolysis product were identical with those of an authentic sample of **4**, prepared by esterification of 3-methyl-2-butenoic acid with diazomethane.

Isopropyl 3-methyl-2-butenoate (5) gave the following: ν 1712 (conjugated ester C=O) and 1664 cm^{-1} (C=C); δ 1.20 (d, J = 6 Hz, 6 H, $(CH_3)_2CH$–], 1.86 (d, J = 1.3 Hz, 3 H, *trans*-CH_3C=CCO–), 2.16 (d, J = 1.3 Hz, 3 H, *cis*-CH_3C=CCO–), 5.02 [septet, J = 6 Hz, 1 H, $(CH_3)_2CHO$–], and 5.67 [m, 1 H, $(CH_3)_2C$=CH–]. The infrared and nmr spectra and the vpc retention time of the photolysis product were identical with those of an authentic sample of **5**, prepared by esterification of 3-methyl-2-butenoic acid with isopropyl alcohol in the presence of concentrated sulfuric acid.

Methyl 3-methyl-3-butenoate (6) gave the following: ν 3078 (C=CH_2), 1746 (ester C=O), and 1649 cm^{-1} (C=C); δ 1.80 (s, 3 H, CH_3C=C), 2.95 (s, 2 H, CH_2C=C), 3.63 (s, 3 H, OCH_3), and 4.82 (s, 2 H, C=CH_2).[10]

Isopropyl alcohol gave the following: δ 1.13 [d, J = 6 Hz, 6 H, $(CH_3)_2CH$–] and 3.92 [septet, J = 6 Hz, 1 H, $(CH_3)_2CH$-O–], corresponding to signals in the spectrum of an authentic sample.

Acid-Catalyzed Conversion of 3 to 4.—A solution of **3** in methanol was treated with a drop of concentrated sulfuric acid, and the solution was boiled under reflux for 10 min. Analysis by vpc showed that **3** was partially converted to **4**; vpc analysis at 30° showed that isopropyl alcohol was also formed. Both products were identified by comparison of their retention times with those of authentic samples.

Photoisomerization of 4 to 6.—A solution of **4** in methanol was irradiated in a quartz tube for 12 hr. Analysis by vpc (10% fluorosilicone on 60–80 Chromosorb W, 8 ft × 0.25 in., 125°) showed that no **4** remained and the **6**, as identified by its retention time, had been formed. Coinjection of this photolysis mixture with that from the photolysis of **2** in methanol confirmed that **6** was present in both mixtures.

2,2,5,5-Tetramethyldihydro-3-furanone-4-d_2 (9).—A mixture of 2,5-dimethyl-2,5-dihydroxyhex-3-yne (3.75 g, 0.026 mol), mercuric sulfate (0.75 g, 0.0025 mol), and deuterium oxide (15 ml) was stirred magnetically for 15 min and then distilled. The distillate, which separated into two layers, was saturated with potassium carbonate and the upper, organic layer was removed and dried with magnesum sulfate. This layer was distilled, and the fraction boiling at 150.5–152° was collected to give 2,2,5,5-tetramethyldihydro-3-furanone-4-d_2 (**9**) (3.5 g, 92%): ν 1757 cm^{-1} (ester C=O); δ 1.20 [s, 6 H, 2-$C(CH_3)_2$] and 1.33 [s, 6 H, 5-$C(CH_3)_2$].[11]

Anal. Calcd for $C_6H_{12}D_2O_2$: C, 66.63; H and D, 11.18. Found: C, 66.24; H and D, 11.26.

Photolysis of 2,2,5,5-Tetramethyldihydro-3-furanone-4-d_2 (9).—A solution of 2,2,5,5-tetramethyldihydro-3-furanone-4-d_2 (0.52 g, 0.0036 mol) in methanol (8.0 ml) was irradiated for 12 hr in a quartz tube. The methanol was removed from the reaction mixture by distillation, and the residue was subjected to preparative vpc to give **11** and **12** with retention times of 971 and 278 sec, respectively.

Analysis by vpc (10% fluorosilicone on 60–80 Chromosorb W, 8 ft × 0.25 in., 125°) showed the presence in the original photolysis mixture of 33% of **11** and 54% of **12**.

(9) H. Richet, *Ann. Chim.*, [12] **3**, 317 (1948); F. Leonard, A. Wajngurt, and H. Horn, *J. Org. Chem.*, **21**, 1400 (1956).

(10) This nmr spectrum was recorded on a solution in a microtube and fine splittings could not be observed.

(11) The assignment of the methyl proton signals are derived from those for **2**: P. M. Burke, Ph.D. Thesis, University of Toronto, 1966.

Identification of Products from Photolysis of 9. Methyl 3-methyl-3-(isopropoxy-*1-d*)butanoate-*2-d* (**11**) gave the following: ν 1733 cm^{-1} (ester C=O); δ 1.07 [m, 6 H, $(CH_3)_2CD$-], 1.25 [s, 6 H, $(CH_3)_2C<$], 2.39 (m, 1 H, -CHD-), and 3.61 (s, 3 H, OCH_3).

Anal. Calcd for $C_9H_{16}D_2O_3$: C, 61.33; H and D, 11.44. Found: C, 61.54; H and D, 11.34.

Methyl 3-methyl-2-butenoate-*2-d* (**12**) gave the following: ν 1718 (conjugated ester C=O) and 1643 cm^{-1} (C=C); δ 1.88 (s, 3 H, *trans*-CH_3C=CCO-), 2.15 (s, 3 H, *cis*-CH_3C=CCO-), and 3.62 (s, 3 H, OCH_3).

Anal. Calcd for $C_6H_9D_2O_2$: C, 62.53; H and D, 9.70. Found: C, 62.32; H and D, 10.08.

Registry No.—**2**, 5455-94-7; **3**, 25859-48-7; **4**, 924-50-5; **5**, 25859-51-2; **6**, 25859-52-3; **9**, 25859-53-4; **11**, 25907-97-5; **12**, 25859-50-1.

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Benzene Ring Substituted Indeno[1,2-*c*]pyrazol-4(1*H*)-ones

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The condensation of 4-substituted 2-acetyl-1,3-indandiones (**1a–d**) with hydrazine yielded the corresponding indandione α-hydrazones (**2a–c**), indeno[1,2-*c*]pyrazol-4(1*H*)-ones (**3** and **6**) or indeno[1,2-*c*]pyrazol-4(1*H*)-one hydrazones (**7a–c**), depending upon the nature of the substituents and the reaction conditions. Evidence is presented that the product of the reaction of 2-acetyl-4-nitro-1,3-indandione (**1a**) with hydrazine is 3-methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one (**6**), whereas the product from 2-acetyl-4-amino-1,3-indandione (**1b**) and hydrazine is 5-amino-3-methylindeno[1,2-c]pyrazol-4(1*H*)-one (**3**) and that the ring closure of the α-hydrazones of 4-amino- and 4-acetamido-2-acetyl-1,3-indandione (**2a** and **2b**) yields 5-amino- and 5-acetamino-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (**3** and **4**). 2-Acetyl-5-nitro-1,3-indandione (**12**) was treated with hydrazine to give 3-methyl-6- (or 7-) nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one hydrazone (**13**).

A number of indeno[1,2-*c*]pyrazol-4(1*H*)-ones with substituents in the pyrazole ring has been reported in several papers from this laboratory.[1,2] The interesting physiological properties of these compounds prompted us to investigate the syntheses and characteristics of benzene ring substituted 3-methylindeno[1,2-*c*]pyrazol-4 (1*H*)-ones **3**, **4**, **6**, **7**, and **13**, Scheme I).

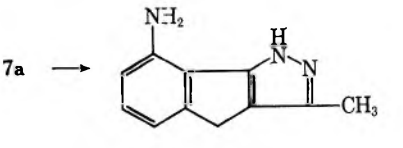
The preparation of 4- and 5-substituted 2-acetyl-1,3-indandiones (**1a–d** and **12**) necessary for this investigation was described in a previous paper.[3] The condensation of 4-amino- and 4-acetamido-2-acetyl-1,3-indandione (**1b** and **1c**) with 1 or 2 mol of hydrazine in refluxing ethanol for 0.5–1 hr yielded the α-hydrazones of the corresponding 2-acetylindandiones (**2a** and **2b**). When these hydrazones were refluxed in ethanol (in the case of **2a** catalytic amounts of hydrochloric acid were necessary) cyclization to the corresponding indeno-[1,2-*c*]pyrazol-4(1*H*)-ones **3** and **4** occurred. Whereas when **2a** and **2b** were refluxed in acetic anhydride the α-acetylhydrazone of 4-acetamido-2-acetyl-1,3-indandione (**5**) was formed.

The condensation of 4-amino-2-acetyl-1,3-indandione (**1b**) with hydrazine at 180–200° under the conditions of the Wolff–Kishner reaction gave directly 5-amino-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (**3**), whereas 4-nitro-2-acetyl-1,3-indandione (**1a**) yielded directly 8-nitro-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (**6**) by reacting with 1 mol of hydrazine in refluxing ethanol for 48 hr. When an excess of hydrazine was used, the nitroindandione **1a** gave the indenopyrazolone hydrazone **7a**. Under these last conditions 4-acetamido- and 4-hydroxy-2-acetyl-1,3-indandione (**1c** and **1d**) also gave the corresponding indenopyrazolone hydrazones **7b** and **7c**. All attempts to form the hydrazone of 5-amino-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one from **1b** failed.

The hydrazono group in the indandione hydrazones **2a–c** is on the side chain carbonyl, as demonstrated by a positive Tollens test[4] and by the formation of a red solution with aqueous sodium hydroxide.[4]

In the condensation of compounds **1** with hydrazine to form **3**, **6**, and **7** and in the cyclization of compounds **2** to form **3** and **4**, only one of the two possible isomers, the 5- or 8-substituted 3-methylindeno[1,2-*c*]pyrazol-4-(1*H*)-one, was formed. Theoretical considerations would lead one to predict that these reactions would give the 8-substituted rather than the 5-substituted isomer, when R is an electron-withdrawing group and the 5 rather than the 8 isomer, when R is an electron-donating group.

Evidence for the structure of the nitro derivative **7a** was obtained by treating it with hydrazine and palladium on charcoal to form the amino-1,4-dihydro-3-methylindeno[1,2-*c*]pyrazole (**8**). The melting point and infrared spectrum of **8** were found to be different from those of an authentic sample of 5-amino-1,4-dihydro-3-methylindeno[1,2-*c*]pyrazole (**10**, see below) and therefore the 8-nitro structure was assigned to com-



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(2) R. A. Braun and W. A. Mosher, *J. Org. Chem.*, **24**, 648 (1959).

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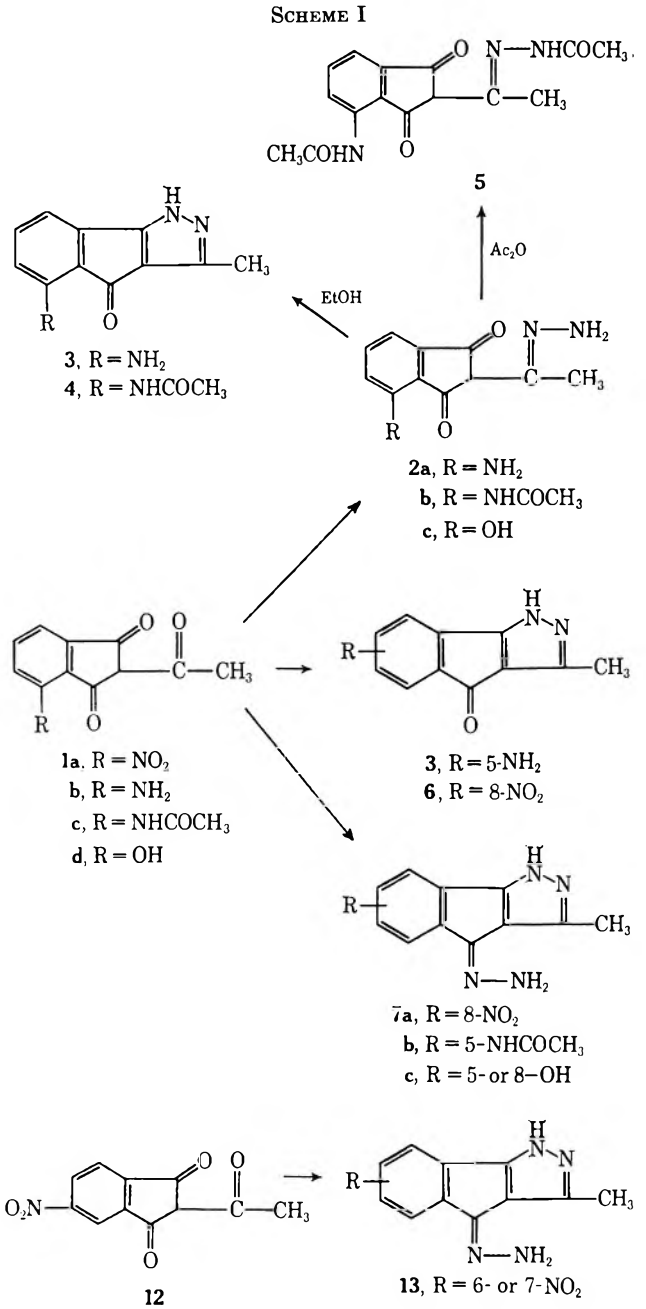
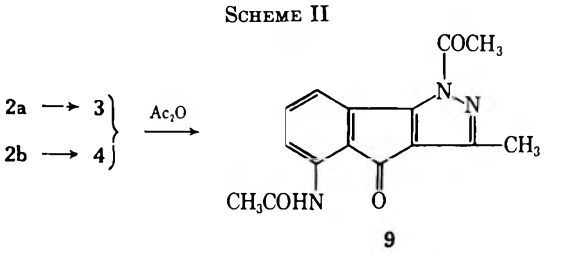
(4) R. A. Braun and W. A. Mosher, *J. Amer. Chem. Soc.*, **80**, 2749 (1958).

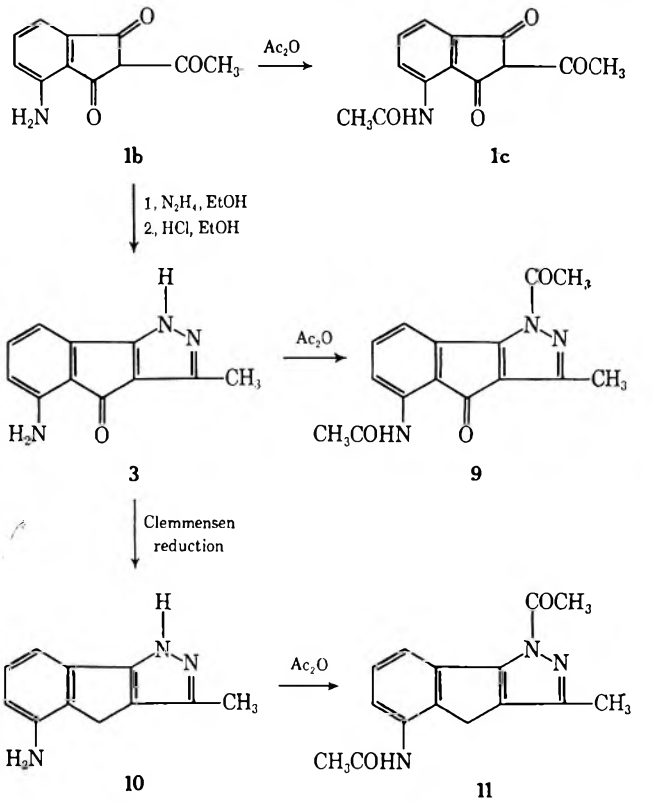
SCHEME I



SCHEME II



SCHEME III



pound **7a**. These results also support the structure assigned to compound **6**. Orientation of the acetamido group in **7b** was established by treating **7b** with hydrazine and potassium hydroxide under the conditions of the Wolff–Kishner reaction. The product obtained was identical with an authentic sample of 5-amino-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (**3**, see below).

Proof that the 5-substituted isomer was formed in the cyclization of compounds **2a** and **2b** was obtained by determining the positions of the amino and acetamido groups in compounds **3** and **4** respectively. First it was established that cyclization of **2a** and **2b** to form **3** and **4**, followed by acetylation (Scheme II), gave the same indenopyrazolone **9**, thus demonstrating that the amino group in **3** is in the same position as the acetamido group in **4**. Then compounds **1c**, **9**, and **11** were prepared as shown in Scheme III and their infrared spectra compared. These spectra show that the hydrogen atoms of the acetamido groups of **1c** and **9** exhibit similar intramolecular hydrogen–oxygen bonding (N—H stretching frequencies 3330 cm^{-1} for **1c** and 3335 cm^{-1} for **9**), whereas compound **11** exhibits an absorption frequency corresponding to a free N—H stretching (3435 cm^{-1}). These results demonstrate that the acetamido group in compound **9** must be in position 5 and therefore support the structures, 5-amino- and 5-acetamido-3-methyl[1,2-*c*]pyrazol-4-(1*H*)-one, assigned to compounds **3** and **4**, respectively. This structure proof of **3** is obviously also a proof for the structure **10** assigned to the amino-1,4-dihydro-3-methylindeno[1,2-*c*]pyrazole.

The condensation of 2-acetyl-5-nitro-1,3-indandione (**12**) with hydrazine in ethanol yielded directly the hydrazone of 3-methyl-6- (or 7-) nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one (**13**). Attempts to determine the position of the nitro group were unsuccessful.

The infrared spectra of the benzene ring substituted 3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-ones show a broad band at about 3200 cm^{-1} (N—H stretching of the pyrazole), a band at 1720 cm^{-1} (ketone carbonyl) when the benzene ring is substituted with a nitro group, and a band at 1690 cm^{-1} (ketone carbonyl) when the benzene ring is substituted with an amino or acetamido group. The band at 3200 cm^{-1} disappears upon acetylation of the pyrazole ring.

Experimental Section[5]

2-Acetyl-4-amino-1,3-indandione α-Hydrazone (2a).—Into a flask equipped with a mechanical stirrer and condenser were placed 50 ml of anhydrous ethanol and 0.7 g (0.02 mol) of 95% hydrazine. The mixture was heated to reflux and 2.03 g (0.01 mol) of 2-acetyl-4-amino-1,3-indandione[3] was added. The amine dissolved rapidly to give a red solution. After 7 min a yellow precipitate was formed. The mixture was refluxed for 1 hr, then was cooled and the precipitate was collected by filtration, washed with ethanol and dried to give 1.5 g (69%) of **2a** as small yellow needles, mp 220–222° (dimethylformamide–water).

Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.12; N, 19.35. Found: C, 61.05; H, 5.46; N, 20.09.

Prolonged refluxing and/or a large excess of anhydrous hydrazine led to the same product.

4-Acetamido-2-acetyl-1,3-indandione α-Hydrazone (2b).—Hydrazine hydrate 100% (1.2 g, 0.025 mol) was added to a stirred, refluxing solution of 4-acetamido-2-acetyl-1,3-indandione[3] (5 g, 0.02 mol) in ethanol (300 ml). The yellow solution turned red and shortly thereafter a mass of bright yellow needles separated. One 0.5 hr after the addition of the hydrazine, the mixture was cooled and the precipitate was collected by filtration, washed with ethanol, and dried to yield 4.5 g (79%) of **2b**, mp 264–265.5 (dimethylformamide–water). When the melting point is taken slowly, the product melts above 300°, probably because it cyclizes to the corresponding indenopyrazolone.

Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.02; N, 16.22. Found: C, 59.85; H, 5.19; N, 16.15.

2-Acetyl-4-hydroxy-1,3-indandione α-Hydrazone (2c).—Hydrazine hydrate 85% (1 ml, 0.022 mol) was added to a solution of 2-acetyl-4-hydroxy-1,3-indandione[3] (1.2 g, 0.006 mol) in ethanol (50 ml). After 5 min the precipitate was collected by filtration and washed with ethanol to give 0.7 g (55%) of **2c** as yellow needles, mp 260–262° dec (dimethylformamide–water).

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.76; H, 4.67; N, 13.09.

The hydrazone **2c** was also obtained when a solution of 4-acetoxy-2-acetyl-1,3-indandione[3] (0.1 g) in anhydrous ethanol (10 ml) was refluxed for 10 min with 95+% hydrazine (2 drops).

4-Acetamido-2-acetyl-1,3-indandione α-(Acetylhydrazone) (5). A.—A small amount of **2a** was dissolved in acetic anhydride and the solution refluxed for several minutes whereupon a heavy precipitate of thin white needles formed. The precipitate was collected by filtration, washed with ether, and dried to give **5**, as creamy white needles, mp 263.5–264.5° (ethanol), in almost quantitative yield.

Anal. Calcd for $C_{15}H_{13}N_3O_4$: C, 59.80; H, 4.98; N, 13.95. Found: C, 59.79; H, 5.04; N, 13.92.

B.—The previous reaction was repeated using the acetamido **2b** in place of the amino compound **2a**. The product was identical with that obtained (part A above) by acetylation of **2a**, as shown by comparison of the infrared spectra and by mixture melting point determinations.

3-Methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one (6).—To a suspension of 2-acetyl-4-nitro-1,3-indandione[3] (5 g, 0.02 mol) in 250 ml of ethanol was added 10 g (0.02 mol) of a hydrazine solution, prepared by dissolving 13 g of 85% hydrazine hydrate in 87 g of ethanol. After stirring under reflux for 48 hr the reaction mixture was filtered hot to remove 2 g of suspended yellowish-yellow solid and the filtrate was refrigerated for 18 hr to yield 2.2 g (50%) of golden yellow crystals. Sublimation at 220° (1.5 mm), followed by recrystallization from ethanol gave **6** as light yellow crystals of orange fluorescence, mp 251.5–252°.

Anal. Calcd for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.06; N, 18.34. Found: C, 57.97; H, 3.07; N, 18.27.

5-Amino-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (3). A. From indandione 1b (Wolff–Kishner Reduction Conditions).—In an open flask 2.0 g (0.01 mol) of amine **1b**[3] and 2.0 g (0.04 mol) of 100% hydrazine hydrate were added to 30 ml of diethylene glycol; the solution was heated to 150° over a 1-hr period. Then 1 g of pulverized potassium hydroxide was added and the temperature quickly raised to 180°, held there for 1 hr and then raised to 200° for 15 min. To the reaction mixture 200 ml of water was added at room temperature and a small amount of a brown resinous substance filtered off and discarded. The filtrate was extracted with seven 100-ml portions of ether. The combined extracts were washed with 50 ml of water and dried over $MgSO_4$. Removal of the solvent left 1.1 g of yellow solid, which chromatographed on an alumina-packed column with tetrahydrofuran as the eluent gave 1.0 g (51%) of **3** as crystals of bright yellow fluorescence, mp 280–283°.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.33; H, 4.52; N, 21.10. Found: C, 66.24; H, 4.85; N, 20.81.

B. From Hydrazone 2a.—A suspension of compound **2a** (5 g, 0.025 mol) in anhydrous ethanol (300 ml) was heated to reflux and a few drops of concentrated hydrochloric acid were added. Within 2 min a clear solution was obtained. Refluxing was continued for an additional hour, and then the solvent was evaporated *in vacuo* leaving 5 g of crude orange material. Sublimation at 200° (1 mm) gave 4.2 g (85%) of **3** as pale yellow crystals, mp 280–283°, identical (melting point and ir) with **3** obtained by procedure A.

5-Acetamido-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (4).—A mixture of **2b** (4.5 g, 0.017 mol) and 200 ml of anhydrous ethanol was refluxed with stirring for 48 hr during which time most of the solid gradually dissolved. The reaction mixture was filtered while hot to remove 1.0 g of insoluble nonfluorescent material. Concentration of the filtrate gave 2.5 g (60%) of **4** as pale yellow crystals of yellow fluorescence, which upon sublimation at 200° (1 mm) and recrystallization from ethanol melted above 300°.

Anal. Calcd for $C_{13}H_{11}N_3O_2$: C, 64.73; H, 4.56; N, 17.42. Found: C, 64.78; H, 4.64; N, 17.39.

Compound **4** when refluxed in a small portion of ethanol containing a few drops of concentrated hydrochloric acid gave the amine **3** in quantitative yield.

5-Acetamido-1-acetyl-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one (9). A. From the Aminoindenopyrazolone 3.—To 1.0 g (0.0041 mol) of **3** in a test tube was added 2 ml (0.01 mol) of acetic anhydride. The mixture was heated slowly until the solid went into solution and then was refluxed for 5 min, and upon cooling to room temperature 1.0 g (77%) of bright yellow needles of diacetylated product was obtained, which upon sublimation at 170° (1 mm) and recrystallization from acetic anhydride gave **9** as yellow needles of bright yellow fluorescence and mp 206–208°.

Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.59; N, 14.84. Found: C, 63.55; H, 4.70; N, 14.66.

B. From the Acetamidoindenopyrazolone 4.—A mixture of 1.0 g of **4** and 2 ml of acetic anhydride was refluxed for several minutes then cooled to room temperature. The precipitate was collected by filtration, washed, and purified to give yellow needles. A mixture melting point with a sample of **9** prepared by acetylation of **3** (part A above) showed no depression.

3-Methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one Hydrazone (7a).—A mixture of 2-acetyl-4-nitro-1,3-indandione[3] (3.0 g, 0.013 mol) and 95% hydrazine (2.5 g, 0.078 mol) in absolute ethanol (200 ml) was stirred and refluxed for 48 hr. Complete solution was never attained, but the color of the solid material in the flask changed from yellow to orange. The hot reaction mixture was filtered to give 2.6 g (82.5%) of **7a** as orange crystals, slightly soluble in most solvents. Soxhlet extraction with toluene or xylene for 24 hr gave orange-yellow needles, mp 270–273°.

Anal. Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.70; N, 28.81. Found: C, 54.03; H, 3.91; N, 29.45.

To a refluxing mixture of hydrazone **7a** (0.5 g), dioxane (10 ml), and acetone (5 ml) were added 2 drops of concentrated hydrochloric acid and the refluxing continued for 0.5 hr. The solid was collected by filtration and crystallized from xylene to give a quantitative yield of 3-methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one *azine with acetone* as pale yellow, nonfluorescent needles, mp 297–299°.

Anal. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.59; N, 24.73. Found: C, 59.48; H, 5.00; N, 24.57.

Hydrazone **7a** and 2-nonanone, when refluxed as described above, gave 3-methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one *azine with 2-nonanone* as yellow, nonfluorescent crystals, mp 133–134° (ethanol).

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(5) Melting points were determined with a Fisher–Johns melting point apparatus and are uncorrected. The melting points of the hydrazones were taken by preheating the apparatus to a few degrees below the melting point of the samples. Then the samples were placed on the hot stage and the temperature was raised rapidly to the melting point. Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer Model 137 using sodium chloride plates.

Samples used in H-bonding studies were dissolved in chloroform and the infrared spectra were taken on a Perkin-Elmer spectrophotometer Model 421. Elemental analyses were performed by Dr. A. Bernhardt Microanalytisch Laboratorium in Max Planck Institut für Kohlenforschung, Mülhein (Ruhr), West Germany.

Anal. Calcd for $C_{20}H_{25}N_5O_2$: C, 65.39; H, 6.81. Found: C, 64.83; H, 6.87.

5-Acetamido-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one Hydrazone (7b).—A mixture of 4-acetamido-2-acetyl-1,3-indandione[3] (5 g, 0.020 mol), anhyrous ethanol (400 ml), and 95+% hydrazine (6 ml, 0.19 mol) was stirred and refluxed for 48 hr. An orange solution was rapidly formed, and then a yellow solid precipitated which gradually redissolved. The reaction mixture was filtered hot to remove a small amount of grayish powder. The filtrate was cooled in a refrigerator for 12 hr and the precipitate was collected by filtration, washed with water, and dried to give 4.5 g (88%) of **7b** as pale yellow needles, mp 264.5–265° (ethanol).

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.18; H, 5.10. Found: C, 61.21; H, 5.14.

Hydrazone **7b**, when treated with hydrazine and potassium hydroxide following the procedure described for compound **3** from **1b**, gave 5-amino-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one, identical with an authentic sample prepared as described above.

5- (or 8-) Hydroxy-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one Hydrazone (7c).—By the method used for the preparation of **7b**, a mixture of 2-acetyl-4-hydroxy-1,3-indandione[3] (3.0 g, 0.015 mol) in anhydrous ethanol (400 ml) was reacted with 95+% hydrazine (4 ml, 0.12 mol). A 15% yield (0.5 g) of **7c** was obtained as pale yellow crystals, mp 298–300° (ethanol) with darkening and sublimation.

Hydrazone **7c**, when refluxed in acetone for 5–10 min, gave 5- (or 8-) hydroxy-3-methylindeno[1,2-*c*]pyrazol-4(1*H*)-one *azine with acetone* as pale yellow needles, mp 299–300°.

Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.14; H, 5.51; N, 22.05. Found: C, 66.30; H, 5.57; N, 21.96.

3-Methyl-6- (or -7-) nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one Hydrazone (13).—To a stirred and refluxing mixture of 2-acetyl-5-nitro-1,3-indandione[3] (1.0 g, 0.004 mol) and absolute ethanol (100 ml), 95+% hydrazine (1.0 ml, 0.03 mol) was added. The indandione dissolved rapidly to give an orange-red solution from which a precipitate of yellow crystals began to form after approximately 2 hr. An additional 0.5 ml of 95% hydrazine was added and refluxing was continued for 22 hr. The precipitate was collected by filtration, washed with ethanol, and dried to give 0.84 g (89%) of **13** as yellow platelets, decomposing at about 300° (dimethylformamide–water).

Anal. Calcd for $C_{11}H_9N_5O_2$: N, 28.81. Found: N, 28.74.

5-Amino-1,4-dihydro-3-methylindeno[1,2-*c*]pyrazole (10).—A mixture of 10 g of zinc amalgam (prepared from mossy zinc, mercuric chloride, and concentrated hydrochloric acid[6]), 7.5 ml of water, 17.5 ml of concentrated hydrochloric acid, and 1 g (0.005 mol) of **3** was heated on a steam bath for 10 hr. The colorless solution still hot was then decanted from any unchanged zinc amalgam. The residue in the flask was extracted by boiling with 10 ml of water and the clear solution decanted. The combined decanted solutions were cooled and 1.2 g of colorless needles was collected by filtration. These crystals were dissolved in 100 ml of water, and the solution was made basic with 1 *N* NaOH and extracted with five 100-ml portions of ether. The combined ether extracts were dried over KOH pellets, filtered, and treated with excess dry hydrogen chloride. The precipitate was removed by filtration and dissolved in a small amount of water and the solution treated with enough 1 *N* KOH to precipitate the free amine. Filtration and washing of the precipitated amine with a small portion of cold water gave 0.52 g (56%) of **10**, as colorless needles, mp 224–226° (water).

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.35; H, 5.95; N, 22.70. Found: C, 71.40; H, 5.92; N, 22.65.

5-Acetamido-1-acetyl-1,4-dihydro-3-methylindeno[1,2-c]pyrazole (11).—Amine **10** (0.2 g) was added to acetic anhydride (1 ml) and the mixture heated to reflux for several minutes. The precipitate formed upon cooling was collected by filtration, washed with ether, and dried to give a quantitative yield of **11**. Sublimation at 220° (1 mm), followed by crystallization from acetic anhydride, gave **11** as needles of mp 260–262°.

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.58. Found: C, 66.82; H, 5.69.

8-Amino-1,4-dihydro-3-methylindeno[1,2-*c*]pyrazole (8).—A solution of 10 ml of 95+% hydrazine in 50 ml of ethanol was added dropwise over a 2.5-hr period to a stirred and refluxing mixture of **7a** (2.6 g, 1.1 mol) and 10% Pd–C (0.7 g) in ethanol (200 ml). The mixture was refluxed for additional 72 hr and then was filtered still hot, and the filtrate evaporated to dryness to give 1.2 g (60%) of crude **8**. Recrystallization from ethanol–water (Darco) gave **8** as pale yellow needles, mp 205.5–208°. The mixture melting point of this compound and the amine **10** (mp 224–226°) showed a significant depression (mmp 171–182°) and the ir spectra showed differences in the "fingerprint" region.

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.35; H, 5.95; N, 22.70. Found: C, 71.35; H, 6.21; N, 22.92.

Registry No.—**2a**, 25906-41-6; **2b**, 25906-42-7; **2c**, 25906-43-8; **3**, 25906-44-9; **4**, 25906-45-0; **5**, 25957-52-2; **6**, 25906-46-1; **7a**, 25906-47-2; **7b**, 25906-48-3; **7c**, 25898-66-2; **8**, 25906-49-4; **9**, 25906-50-7; **10**, 25906-51-8; **11**, 25906-52-9; **13**, 25898-67-3; 3-methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one azine with acetone, 25906-53-0; 3-methyl-8-nitroindeno[1,2-*c*]pyrazol-4-(1*H*)-one azine with nonanone, 25906-54-1; 5- or 8-hydroxy-3-methylindeno[1,2-*c*]pyrazol-4-(1*H*)-one azine with acetone, 25898-68-4.

Acknowledgment.—We gratefully acknowledge the valuable assistance of Dr. Mario F. Sartori in connection with this research.

(6) R. Adams, "Organic Reactions," Vol. 1, Wiley, New York, N. Y., 1942, p 163.

The Configuration of 1,3-Dioximinoacetone and 1-Oximinoacetone

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The configuration of 1,3-dioximinoacetone prepared by the nitrosation of acetone dicarboxylic acid has been determined by spectral and acidity studies to be syn–syn. 1-Oximinoacetone prepared by the nitrosation of acetone has been determined to be anti.

1,3-Dioximinoacetone (1,3-diisonitrosoacetone, mesoxaldehyde dioxime, DIA) was first described by Pechmann and Wehsarg[1] in 1886 and studied more recently by Geissman, Schlatter, and Webb.[2] Because of the important use of this substance as a colorimetric reagent,[3] we have undertaken to determine the geometry of this compound and, because of its relationship to the above compound, we have also studied 1-oximinoacetone.

Three forms of DIA are possible—syn–syn, syn–anti, and anti–anti—and all possibilities may be present depending upon energy and spatial relationships. It is known from nmr studies that the C–H resonance frequencies differ for syn and anti forms of propionaldoxime with the syn form having the lower field signal.[4] Thin layer chromatography studies indicate that DIA prepared according to the method of Geissman[2] is over 95% one isomer; indication of trace amount of two other substances are present and these might be other isomers but they do not give the characteristic color reactions of DIA.[3] The same spectral characteristics are shown by a number of different preparations, fractions, crude products, as well as the "heat and ultraviolet light stable isomer" of Pechmann.[1] The nmr spectrum for DIA in 20% solution in dimethyl sulfoxide gives only two signals, equal area peaks: a sharp singlet at 8.13 ppm assigned to the aldehydic proton and a broad singlet at 11.8–12.8 ppm assigned to the hydroxyl proton. The simple spectra with only one type of carbon-bound proton serves to exclude the possibility of the syn–anti isomer but does not permit a decision between the other two isomers although the anti–anti might be favored because of the possibility of very strong hydrogen bonding, and the broad band for the oxygen-bound proton would tend to support this. The nmr spectrum of the monoanion of DIA in D_2O gives a sharp singlet for C–H resonance at 7.92 which would support rapid exchange in a charged anti–anti form but the same spectrum would be expected from the syn–syn if exchange with solvent water were rapid enough which is entirely possible

The ultraviolet spectrum of recrystallized DIA in carbon dioxide–water shows only one broad peak centered at 250 mμ, ϵ 19,200; the dianion (pH 11.10, NaOH) shows a peak at 217 mμ, ϵ 5500, and a more intense broad peak at 322 mμ, ϵ 32,200. The infrared spectrum was studied in potassium bromide disk because of the insolubility of DIA in carbon tetrachloride or chloroform; the spectrum of DIA-d_2 was also studied. The differences of these two spectra are at 7.0 μ, between 9 and 11 μ, and 13 and 15.25 μ with the most striking differences being in the 9–11 region. The position of the broad band due to hydrogen-bonded hydroxyl is close to the 3250 cm^{-1} reported by Palm and Werbin[5] for α oximes but the C=N stretching band appears some 50 cm^{-1} to lower frequencies than reported by these authors for α oximes and some 40 cm^{-1} reported for β oximes. This latter effect is probably due to conjugation between the C=N linkages and the carbonyl group. This would also explain the low frequency of the C=O stretching mode although intramolecular hydrogen bonding would also produce a shift to lower frequencies. The spectral data are consistent with either syn–syn or anti–anti. Dilution infrared studies should permit a decision, but, as mentioned, solubility problems make this type of study impracticable with DIA.

Since intramolecular hydrogen bonding in monoanions markedly alters the K_1 to K_2 ratio for dibasic acids[6] (*e.g.*, maleic acid *vs.* fumaric acid), the ionization constants for DIA were determined by titration with 0.1 *N* sodium hydroxide in carbon dioxide free water. The neutralization equivalent determined to be 58.13 against 58.04 for theory indicates that the keto oxime did not hydrolyze appreciably during the 2 hr required for the determination. A titration curve showed no sharp breaks indicating that the two pK_a values lie close together: pK_1 was found to be 7.58 and pK_2, 8.85. The ratio between the two ionization constants ($K_1 = 18.2K_2$) is very close to that reported for fumaric acid[6] ($K_1 = 22K_2$) and considerably different from that for maleic[6] acid ($K_1 = 49140K_2$) indicating that the negative charge on the monoanion exerts very little effect in reducing ionization of the second proton. This would favor the syn–syn structure.

To obtain definite spectral confirmation, model compounds were studied so that appropriate assignments might be made. The syn–syn isomer of DIA should, in dilute solution, show only intermolecular hydrogen bonding while the anti–anti form should show only intramolecular hydrogen bonding. 1-Oximinoacetone can exist in syn and anti forms with the anti, in high dilution, expected to show only intramolecular hydrogen bonding. However, to make meaningful assignments in this compound it was also necessary to study the spectrum of ethyl oximinoacetoacetate; regardless of isomer, this compound involves the possibility of intramolecular bonding between the hydroxyl hydrogen and a carbonyl oxygen. Both of these compounds have sufficient solubilities in chlorinated solvents to make dilution studies convenient.

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(1) H. Pechmann and K. Wehsarg, *Ber.*, **19**, 2465 (1886).

(2) T. A. Geissman, M. J. Schlatter, and I. D. Webb, *J. Org. Chem.*, **11**, 736 (1946).

(3) S. Sass, W. D. Ludemann, B. Witten, V. Fischer, A. J. Sisti, and J. I. Miller, *Anal. Chem.*, **29**, 1346 (1957). B. J. Jandorf, *J. Amer. Chem. Soc.*, **78**, 3686 (1956).

(4) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958). See J. A. Pople, W. G. Schenider, and H. J. Berstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 374.

(5) A. Palm and H. Werbin, *Can. J. Chem.*, **31**, 1004 (1953).

(6) P. Sykes, "A Guidebook to Mechanism in Organic Chemistry," Wiley, New York, N. Y., 1961, p 47.

At relative high concentrations of ethyl oximinoacetoacetate in carbon tetrachloride, two OH absorption peaks are observed: 3380 cm^{-1} (broad) and 3560 cm^{-1} (sharp). On dilution, the intensity of the 3380 band decreased and could be made to disappear while the 3560 band changed only slightly on dilution. In carbon tetrachloride solution, 1-oximinoacetone showed the same characteristics: a concentration dependent band at 3380 cm^{-1} and a concentration independent band at 3560 cm^{-1}. The 1-oximinoacetone, prepared by the nitrosation of acetone by butyl nitrite, is the anti isomer.

A comparison of the 1600–1800 cm^{-1} region of the spectra of *anti*-1-oximinoacetone and ethyl oximinoacetoacetate, Table I, indicates that the best configuration for the latter involves hydrogen bonding between the OH and the acetyl carbonyl group. This configuration had been assigned by Jovitschitsch[7] to this compound prepared by a different procedure in 1898.

TABLE I

COMPARISON OF IR SPECTRA 1600–1800 cm^{-1} REGION ACETONITRILE SOLUTION

Functional group	*anti*-1-Oximinoacetone	Ethyl oximinoacetoacetate	DIA
C=O ester		1730	
C=O nonbonded keto	1700	1700	1695
C=O bonded keto	1675, strong	1675, strong	1650, very weak
C=N	1620, weak	1619, weak	1620,[a] very strong

[a] Concentration dependent.

anti-1-Oximinoacetone showed equal intensities at 1700 and 1675 cm^{-1} for the free and bonded carbonyl groups. A weak band in DIA at 1650 cm^{-1} might be assigned to an intramolecularly bonded carbonyl but the intensity of this band is much less than for the bonded carbonyl of *anti*-1-oximinoacetone. In addition, the C=N band in DIA is much more intense than the 1650 band while the opposite is true for the oximinoacetone. This would argue against assigning a bonded carbonyl in DIA and would support the syn–syn conformation.

Additional support for the syn–syn structure is obtained from further nmr studies. *anti*-1-Oximinoacetone in deuteriochloroform shows three bands: three protons at 2.45 (methyl group), one proton at 7.50 (aldehydic), and one proton at 9.70 ppm (hydroxyl). The aldehydic proton in DIA appears at 8.13 ppm, a much lower position. Since the oximino groups in DIA are not conjugated, the downfield position of the aldehydic proton would not be expected to arise solely from the influence of an additional oximino group on each aldehydic proton. The additional deshielding observed for the aldehydic protons of DIA relative to the oximinoacetone must arise from the deshielding influence of the oxygen atoms of the two oximino groups in DIA. Since the configuration of the oximinoacetone is known to be anti, the oximino groups in DIA must be syn. The difference in the chemical shifts of the aldehydic protons of syn and anti propionaldoxime has been shown to be 42 cps while the difference in chemical shifts of the aldehydic protons in oximinoacetone and DIA is 36 cps.[4] The similarity of these shifts indicate that DIA must have a configuration opposite to *anti*-1-oximinoacetone. The nmr spectra for the *syn*-oximinoacetophenone shows a chemical shift for the aldehydic proton of 8.13 ppm[8] which is identical with that in DIA. The syn–syn structure of DIA would appear to be certain.

(7) M. Jovitschitsch, *Ber.*, **28**, 2683 (1898).

Experimental Section

Preparations of Materials.—1,3-Dioximinoacetone (DIA) was prepared according to the process of Geissman, *et al.*,[2] in about 60% yield. The acetonedicarboxylic acid used was prepared according to Adams, Chiles, and Rassweiler.[9] The crude DIA was recrystallized from water at 60°, with considerable loss, dried *in vacuo* over phosphoric anhydride, and stored under refrigeration in brown bottles. It is quite stable under these conditions. Melting point is a poor criterion of purity; recrystallized material showing only one spot on tlc silica gel G, unactivated, developed with chloroform–methanol (80:20) does not give a sharp phase transition but changes from transparent birefringent flakes at 125–140 into an opaque white solid which decomposes with darkening and gas evolution at 206–212°. The so-called "heat and ultraviolet stable isomer"[1] shows the same changes except that the original material is not birefringent.

Anal. Calcd for $C_3H_4N_2O_3$: C, 31.10; H, 4.30; N, 24.10. O, 41.30. Found: C, 31.21; H, 3.43; N, 23.98; O, 41.21.

DIA-1,3-d_2 was prepared by the Geissman method[2] using 85% D_2O as solvent in the nitrosation; recrystallization was from water.

Anal. Calcd for $C_3H_2D_2N_2O_3$: C, 30.51; H and D, 5.12; O, 40.63.

Anal. Calcd for 83% DIA-d_2–17% DIA: C, 30.58; H, 4.84; O, 40.77. Found: C, 30.85; H, 3.56; O, 40.68.

Deuterium content was determined by nmr analysis comparing the integrated area under the C–H peak at 7.42 ppm with the OH peak at 11.14 ppm using acetone-d_6 as solvent. The ratio was 85:7 indicating 91.7%. This is probably slightly high due to adventitious water. The C–H peak of the DIA-d_2, at 7.42 while in DIA it is at 8.13, is very small indicating high deuterium incorporation.

1-Oximinoacetone was prepared by the butyl nitrite nitrosation of acetone by the method of Slater.[10] Ethyl oximinoacetoacetate was prepared by the method of Adkins and Reeves.[11]

Nmr Studies.—All nmr spectra were recorded on a Varian Associates A-60A spectrometer, generally in dimethyl sulfoxide, with tetramethylsilane as internal standard.

Infrared and Ultraviolet Studies.—These were carried out on a Perkin-Elmer Model 221 and Model 202.

Ionization Constants.[12]—Recrystallized DIA was dissolved in CO_2-free water and titrated with 0.1 *N* sodium hydroxide with a Leeds and Northrup pH meter to follow changes. Some 60 points were recorded between pH 4.1 and 11.63. There were no sharp breaks. The pK_a values were calculated in such a way as to minimize interference from the additional ionization mode. $K_1 = [H^+][HP^-]/[H_2P]$ {where $[H^+]$ = hydrogen ion concentration (mol/l.), $[HP^-]$ = concentration of DIA monoanion (mol/l.) and $[H_2P]$ = concentration of undissociated DIA (mol/l.)} which gave $K_1 = 2.61 \times 10^{-8}$ for the first ionization and $^pJ_1 = 7.58$ Hz. The second ionization was calculated from the relationship $K_A = K_W/K_H$, where $K_W = 1.0 \times 10^{-14}$ and K_H = hydrolysis constant for DIA. To calculate K_H, it was necessary to determine the equivalence point by a plot of pH (ml *vs.* ml). Concentration of appropriate species at the pH defined by the equivalence point were then calculated and substituted into $K_H = [OH^-][HP^-]/(P^{2-})$ to give $K_H = 7.00 \times 10^{-6}$, from which K_A, which equals $K_2 = 1.43 \times 10^{-9}$, and p$K_2 = 8.85$.

(8) N. S. Bacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, p 501.

(9) R. Adams, H. M. Chiles, and C. F. Rassweiler, "Organic Syntheses," Coll. Vol. I, Wiley, 1941, p 10.

(10) W. K. Slater, *J. Chem. Soc.*, 587 (1920).

(11) H. Adkins and E. W. Reeves, *J. Amer. Chem. Soc.*, **60**, 1327 (1938).

(12) G. H. Brown and E. M. Sallee, "Quantitative Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1963, p 168–181.

Appropriate corrections were made for increase in reactant volume due to added titrant.

Registry No.—*syn-syn*-DIA, 26309-06-8; *anti*-1-oximinoacetone, 17280-41-0.

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α-Methoxy-α-trifluoromethylphenylacetic Acid. Configuration by Asymmetric Synthesis[1]

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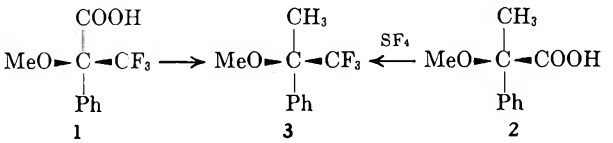
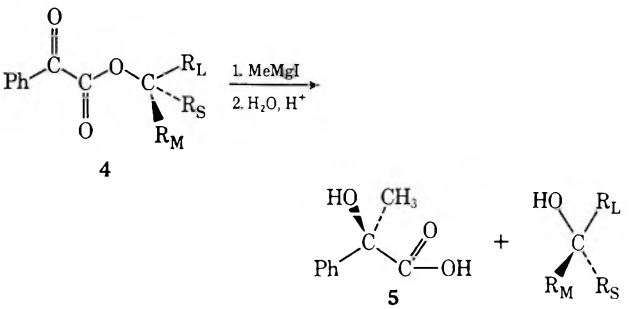
(−)-α-Hydroxy-α-trifluoromethylphenylacetic acid (**13**) has been prepared by asymmetric synthesis involving the reaction of phenylmagnesium bromide with (−)-menthyl trifluoropyruvate [**10**, CF_3COCOO-(−)-menthyl]; 22% asymmetric induction was observed. Application of Prelog's generalization to this system is unambiguous and leads to the assignment of the *S* configuration to this product and to the corresponding methyl ether **1** and methyl ether–methyl ester **14**, in accord with previous work. (−)-Menthyl glyoxylate [$HCOCOO$-(−)-menthyl] gave 19% asymmetric synthesis of the (*S*)-mandelic ester; this indicates that the nature of the achiral group (CF_3 *vs.* H) has only a minor effect upon the *extent* of asymmetric induction in this system.

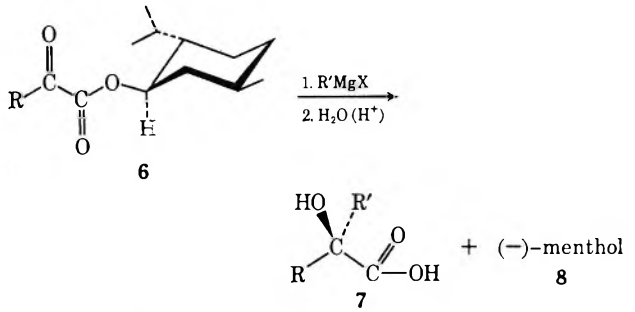
α-Methoxy-α-trifluoromethylphenylacetic acid (**1**, MTPA)[3] is a valuable reagent for the determination of enantiomeric purity of alcohols and amines. Circumstantial evidence for the *S* configuration for (−)-MTPA has been obtained by correlation of the nmr chemical shift of (−)-methyl α-methoxy-α-trifluoromethylphenylacetate in a chiral solvent with that of (*R*)-(−)-methyl mandelate.[4] More recently an extensive study of the circular dichroism of a series of α-substituted phenylacetic acids[5] has convincingly supported this assignment. We had hoped to establish the absolute configuration of MTPA by the conversion of *O*-methylatrolactic acid (**2**) of known configuration into the methyl ether of methylphenyltrifluoromethylcarbinol (**3**) by treatment with sulfur tetrafluoride. This intermediate, **3**, should be readily accessible from MTPA **1**. This approach is similar to that which we have



used to establish the configuration of phenyltrifluoromethylcarbinol and methyltrifluoromethylcarbinol.[6] However repeated attempts to achieve the conversion of **2** to **3** have failed to produce a detectable amount of the trifluoromethyl product **3**; therefore this direct approach has been reluctantly abandoned in favor of the following alternative.

According to the Prelog generalization,[7] when the small, medium, and large groups (R_S, R_M, R_L) in the alcohol moiety of a chiral benzoylformate ester are as represented in **4**, *R*-(−)-atrolactic acid (**5**) will be produced in excess upon treatment with methylmagnesium iodide. This empirical correlation has been exceedingly reliable for predicting the configuration of secondary carbinols; less use has been made of this generalization for the determination of configuration of α-hydroxy acids, even though the correlation here should be on even firmer ground. For example, the (−)-menthyl group in the keto ester **6** is responsible for the different rates of attack of the reagent on one *vs.* the other diastereotopic faces of the prochiral keto group to give **7** in excess. If R is varied while the chiral "inducing"





(−)-menthyl group is retained, stereoisomers of corresponding configuration should predominate regardless of the nature of the achiral R group. In such comparable reactions the asymmetric reaction is brought about by the same chiral moiety while R, which is achiral, is separated by at least three atoms from the inducing chiral centers. The proximity of R to the

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(2) On leave from the Institute of Chemical Technology, Prague, Czechoslovakia.

(3) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

(4) W. H. Pirkle and S. D. Beare, *Tetrahedron Lett.*, 2579 (1968).

(5) G. Barth, W. Voelter, H. S. Mosher, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **92**, 875 (1970).

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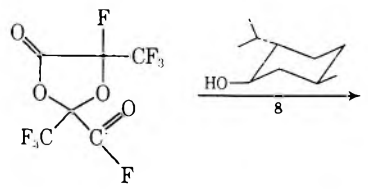
emerging chiral α-hydroxy center may have an effect upon the *extent* of asymmetric synthesis but it certainly should not alter the *sense* of asymmetric synthesis. The same should apply to variations in the R′ group of the reagent. A survey of the available literature confirms that this is so as far as it has been studied.[7,8] For instance, when (−)-menthyl benzoylformate (**6**, R = Ph) is treated with methylmagnesium iodide, (*R*)-(−)-atrolactic acid (**7**, R = Ph; R′ = CH_3) is formed[8b] in 25% excess over the racemate [25% e e (enantiomeric excess)]; when (−)-menthyl pyruvate (**6**, R = CH_3) is treated with phenylmagnesium iodide, (*S*)-(+)-atrolactic acid (**7**, R = CH_3; R′ = Ph) is formed[8g] as predicted (18% e e). Thus by studying the asymmetric reaction of (−)-menthyl trifluoropyruvate (**6**, R = CF_3) with phenylmagnesium bromide (R′ = Ph), additional evidence concerning the configuration of MTPA (**1**) can be obtained. This approach is singularly free of complications from the standpoint of stereochemical interpretation.

Trifluoropyruvyl fluoride and its dimer have been described recently.[9,10] (−)-Menthyl trifluoropyruvate (**10**) was prepared from the dimer of trifluoropyruvyl fluoride [**9**, 4-oxo-2,5-di(trifluoromethyl)-5-fluoro-2-fluorocarbonyl-1,3-dioxolane]. The dioxolane **9** decomposes to trifluoropyruvic acid in the presence of base.[9] The dimer was treated directly with (−)-menthol in the presence of sodium fluoride and a mixture of the desired (−)-menthyl trifluoropyruvate **10** and the menthyl ester, of the dimer (**11**) was obtained. These were separable by gas chromatography. Treatment of



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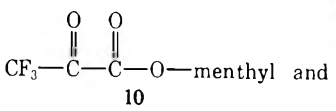

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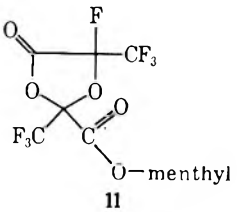
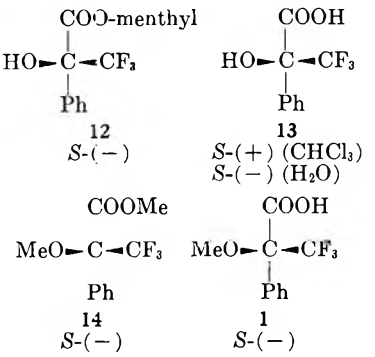
and



11

(−)-menthyl pyruvate (**10**) with phenylmagnesium bromide gave (−)-menthyl α-trifluoromethyl-α-hydroxyphenylacetate (**7**, R = CF_3; R′ = Ph). Based on the Prelog generalization, this must have the *S* configuration at the position α to the carboxyl group as shown in **12**. The acid **13**, formed on hydrolysis, must



likewise have the *S* configuration. This acid [**13**, (+) in chloroform, (−) in water] was conveniently purified by conversion to the methyl ether–methyl ester (**14**) and preparatively gas chromatographed. The rotation of the methyl α-methoxy-α-trifluoromethylphenylacetate was $[\alpha]^{24}D$ −21.3° (*c* 4.74, acetone) which corresponds to 22% excess of the *S*-(−) enantiomer. It has been shown[3,11] that (−)-**14** gives (−)-**1**, thereby establishing the *S* configuration for (−)-MTPA as previously assigned.[4,5] It is of interest that this per cent asymmetric synthesis is rather close to the 25% found[8b] for (−)-menthyl pyruvate in the comparable asymmetric synthesis.

To obtain further evidence concerning the assumption that the nature of the R group in **6** does not change the stereochemical course of the reaction, we have studied (−)-menthyl glyoxylate (**6**, R = H). Treatment of this with phenylmagnesium bromide gave (−)-menthyl mandelate which was proven to have the *S* configuration by reduction to the known (*S*)-(+)-phenylethylene glycol (19% e e). This not only substantiates the predicted stereochemical course of the reaction but also the prediction that reasonable changes in the R group should have minor influence upon only the *extent* of asymmetric synthesis.

Experimental Section

(−)-Menthyl Trifluoropyruvate (10).—(−)-Menthol (15 g, 96 mmol) was dissolved in glyme (1,2-dimethoxyethane, 100 ml, distilled from lithium aluminum hydride) and sodium fluoride (30 g, 1.25 mol) was added. 4-Oxo-2,5-di(trifluoromethyl)-5-fluoro-2-fluorocarbonyl-1,3-dioxolane[9,10] (**9**, 18 g, 6.25 mmol, crude, bp 57–70°) was slowly added to the well-stirred suspension. After the exothermic reaction subsided, the mixture was stirred overnight. Sodium fluoride was removed by filtration; the solvent was evaporated at reduced pressure and the resulting oil distilled to give 23 g of product, bp 85–87° (1 mm). Preparative gas chromatography (silicone gum rubber SE-60 column, 0.25 in. × 20 ft, 175°, helium flow rate 150 ml/min) showed the presence in approximately equal amounts of two substances, retention times of 24 and 30 min, respectively. The first fraction was menthyl trifluoropyruvate: bp 63–65° (0.7 mm); $[\alpha]^{24}D$ −66.8° (*c* 4.07, CH_3OH); ir spectrum (film) 2950, 1775, 1735, 1455, 1320, 1260, 1170, and 1010 cm^{-1}. The pmr spectrum showed only signals for the menthyl group.

Anal. Calcd for $C_{13}H_{19}O_3F_3$: C, 55.70; H, 6.83; F, 20.33. Found: C, 55.51, 55.61; H, 6.89, 6.85; F, 19.64.

The second fraction was menthyl 4-oxo-2,5-di(trifluoromethyl)-5-fluoro-1,3-dioxolane-5-carboxylate (**11**): bp 65–68° (0.5 mm); $[\alpha]^{24}D$ −45.0° (*c* 10.8, CH_3OH); ir spectrum (film) 2960, 1860, 1770, 1460, 1285, 1225, 1170, 1110, 1070, and 1025 cm^{-1}. The ^{19}F nmr indicated that all four possible stereoisomers, differing in configuration at carbon atoms 2 and 5 of the dioxolane ring, were present in approximately equal amounts.

Anal. Calcd for $C_{16}H_{19}O_5F_7$: C, 45.29; H, 4.51; F, 31.34. Found: C, 45.44; H, 4.50; F, 31.06.

(8) (a) V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954). (b) V. Prelog and H. L. Meier, *ibid.*, **36**, 320 (1953). (c) R. H. Cornforth, J. W. Cornforth, and V. Prelog, *Justus Liebigs Ann. Chem.*, **634**, 197 (1960). (d) R. J. D. Evans and S. R. Landor, *Proc. Chem. Soc.*, 182 (1962). (e) G. Vavon, G. Quesnel, and Y. Runavat, *C. R. Acad. Sci., Ser. C*, **237**, 617 (1953). (f) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 168 (1961). (g) J. A. Reid and E. E. Turner, *ibid.*, 3219 (1951). (h) I. Iwai and Y. Yura, *Yakugaku Zasshi*, **80**, 1193 (1969); *Chem. Abstr.*, **55**, 3656 (1961). (i) S. Mitsui and A. Kanai, *Nippon Kagaku Zasshi*, **87**, 179 (1966); *Chem. Abstr.*, **65**, 17006 (1966).

(9) S. Selman, U. S. Patent 3,321,517 (1967).

(10) We are most grateful to Dr. Roy Plunkett and Dr. Harold L. Jackson of the Du Pont Company for a sample of the dimer of trifluoropyruvyl fluoride used in the present study.

(11) D. L. Dull and H. S. Mosher, *J. Amer. Chem. Soc.*, **89**, 4230 (1967).

(−)-Menthyl trifluoropyruvate forms a hydrate when exposed to air: mp 129–135.5°; ir spectrum ($CHCl_3$ solution) 3450, 2960, 1725, 1450, 1250, 1185, 1140, 1105, 940, and 900 cm^{-1}; $[\alpha]^{24}D$ −116.0° (*c* 2.3, $CHCl_3$). The optical rotation in absolute methanol changes from $[\alpha]^{24}D$ −97° (*c* 6.07, CH_3OH) immediately after solution to an equilibrium value of $[\alpha]^{24}D$ −67.1° (*c* 6.07, CH_3OH) after 3 hr.

Anal. Calcd for $C_{13}H_{19}O_3F_3 \cdot H_2O$: C, 52.34; H, 7.10; F, 19.11. Found: C, 53.24; H, 6.95; F, 18.70.

(*S*)-(−)-Methyl α-Methoxy-α-trifluoromethylphenylacetate (14).—To the cooled ethereal solution of the Grignard reagent from bromobenzene (2.2 g, 14 mmol in ether) and sublimed magnesium (0.5 g, 20 mmol) was added a solution of (−)-menthyl trifluoropyruvate (3 g, 10.7 mmol) in anhydrous ether. After the reaction mixture was refluxed for 30 min, it was decomposed with dilute sulfuric acid and extracted with ether. The combined ethereal extracts were successively washed with water, sodium bicarbonate solution, and water. The ether was evaporated to give a slightly yellow oil which was saponified with 50% aqueous ethanolic sodium hydroxide by refluxing for 3 hr. The ethanol was removed by vacuum evaporation and the residue taken up in water and the solution extracted several times with ether to remove menthol. The water layer was acidified and extracted with ether to give 1.35 g (57% yield) of α-trifluoromethyl-α-hydroxyphenylacetic acid (**13**) as a slightly brown solid which was methylated without purification by dissolving in glyme (20 ml), adding a suspension of sodium hydride (0.3 g, 12.5 mmol) in glyme and treating with dimethyl sulfate (1.8 g, 14.3 mmol) at room temperature for 4 hr. Unreacted dimethyl sulfate and sodium hydride were decomposed in the cold with 10 ml of ammonium hydroxide; the mixture was acidified with cold, dilute sulfuric acid followed by extraction with ether. Evaporation of the ethereal solution after washing with sodium bicarbonate and drying (Na_2SO_4) gave an oil which yielded upon distillation 0.9 g (62% yield) of (−)-methyl α-methoxy-α-trifluoromethylphenylacetate (**14**), bp 72–75° (0.5 mm). Traces of impurities were removed by preparative gas chromatography (silicone QFl column, 0.25 in. × 20 ft, 200°) to give purified **14**, $[\alpha]^{24}D$ −21.8° (*c* 6.48, acetone), which corresponds to 22.7% excess of the (*S*)-(−) enantiomer. The nmr and ir spectra were identical with those from an authentic sample.[3,11]

This experiment was repeated under the same conditions to give methyl α-methoxy-α-trifluoromethylphenylacetate, $[\alpha]^{24}D$ −21.3° (*c* 4.74, acetone), corresponding to 22.2% enantiomeric excess, in an overall yield of 70%.

(−)-Menthyl Glyoxylate.—A solution of 1 equiv of (−)-menthol in chloroform was slowly added to a chloroform solution of oxalyl chloride. The mixture was heated at 60° for 3 hr, the solvent evaporated under vacuum, and the residue distilled to give menthyl oxalyl chloride, bp 80° (0.3 mm), 80% yield [lit.[12] bp 123–125° (8–9 mm)].

(−)-Menthyl oxalyl chloride (30 g) in 150 ml of benzene under nitrogen was refluxed while 10% excess of tri-*n*-butyltin hydride [39 g, bp 85–95° (1 mm), prepared[13] by reduction of tri-*n*-butyltin chloride with lithium aluminum hydride] dissolved in 50 ml of benzene was slowly added. After 2 hr at reflux, the solvent was removed under reduced pressure and the residue distilled. The first fraction, (−)-menthyl glyoxylate, 14.9 g (58%), bp 102–103° (1.5 mm), $[\alpha]^{24}D$ −65.0° (*c* 9.02, CH_3OH), showed only trace impurities by glc [bis-(2-ethylhexyl)tetrachlorophthalate column, 0.25 in. × 10 ft, 135°]. The second fraction, 10.5 g, bp 103–115° (1 mm), was mostly (−)-menthyl glyoxylate but was contaminated with tri-*n*-butyltin chloride. The addition of 2 ml of water to this fraction caused the formation of a white solid which was recrystallized from petroleum ether (bp 60–68°) to give 6.9 g (24%) of (−)-menthyl glyoxylate hydrate, mp 79–80°, $[\alpha]^{22}D$ −84.9° (*c* 3.44, $CHCl_3$).

Anal. Calcd for $C_{12}H_{20}O_3 \cdot H_2O$: C, 62.58; H, 9.63. Found: C, 62.85; H, 9.66.

The third fraction, bp 115–120° (1 mm), was primarily tri-*n*-butyltin chloride.

(−)-Menthyl glyoxylate gave the following: ir spectrum (film) 2950, 2920, 2860, 1800 (w), 1750, 1720 (s), 1450, 1290, 1220, and 975 cm^{-1}; nmr spectrum (neat, 60 MHz) δ 9.35 (s, 1 H), 4.8 (sextet, 1 H), 0.7–2.3 (broad, menthyl group). The nmr spectrum of the hydrate ($CDCl_3$) showed δ 5.27 (s, 1 H), 4.6 (broad, 3 H, reduced to a singlet, 1 H by washing with D_2O), and the characteristic menthyl group signals. The 2,4-dinitrophenylhydrazone, mp 145–146°, $[\alpha]^{24}D$ −105° (*c* 2.77, $CHCl_3$), was prepared in the usual way.

Anal. Calcd for $C_{18}H_{24}N_4O_6$: C, 55.09; H, 6.17; N, 14.25. Found: C, 55.33; H, 6.14; N, 14.05.

Reaction of (−)-Menthyl Glyoxylate with Methylmagnesium Iodide.—An ethereal solution of the Grignard reagent from 3.5 g of methyl iodide was added to an ether solution of 4.25 g of (−)-menthyl glyoxylate at 0°. The reaction was refluxed for 10 hr and hydrolyzed with a saturated ammonium chloride solution. The washed (H_2O, $NaHCO_3$, H_2O) and dried (Na_2SO_4) ether extracts were evaporated; the residue was distilled to give 3.1 g of menthyl lactate, bp 80–85° (1 mm). The per cent asymmetric synthesis was determined as follows by conversion to 1,1-diphenylpropane-1,2-diol (whose absolute configuration and enantiomeric purity are known[14]). An ether solution of the total menthyl lactate from the above experiment was added to an ethereal phenyl Grignard solution made from 13 g of phenyl bromide and 3.4 g of sublimed magnesium. The reaction mixture was refluxed for 12 hr and hydrolyzed with cold saturated ammonium chloride solution. The washed (H_2O) and dried (Na_2SO_4) ether layer was evaporated and the residue was steam distilled to remove menthol and biphenyl. The nonvolatile oil was taken into ether solution which was dried (Na_2SO_4) and evaporated to give an oil, 1.25 g, 41%, which was purified by silica gel column chromatography using benzene solvent; 1.08 g of pure diol, mp 88–92°, $[\alpha]^{24}D$ −24.3° (*c* 3.54, benzene), which corresponds to 16% of the rotation of the pure isomer [lit.[14] mp 92–93°, $[\alpha]^{20}D$ +149.8° (*c* 2.43, benzene)], was obtained. The spectra were as follows: ir (benzene) 3570 (s), 2980, 2930 (w), 1490, 1450 (s), 1100, 890, and 690 cm^{-1}; nmr (60 MHz, acetone-d_6) δ 7.8–70 (aromatic protons, 10 H), 4.85 (q, 1 H, J = 6 Hz), 1.03 (d, 3 H, J = 6 Hz), 4.5 (s, 1 H), and 3.0–3.8 (broad, 2 H). These last two signals disappeared upon D_2O exchange.

The asymmetric synthesis was first carried out as above but with hydrolysis of the Grignard reactions using dilute sulfuric acid, instead of saturated ammonium chloride solution, to give a 45% overall yield of 1,1-diphenylpropane-1,2-diol, mp 86–90°, $[\alpha]^{24}D$ −19.3° (*c* 2.02, benzene), corresponding to 13% asymmetric synthesis.

Reaction of Phenylmagnesium Bromide with (−)-Menthyl Glyoxylate.—The ethereal phenyl Grignard solution prepared from 5.3 g of bromobenzene was added to a cold, ether solution containing 6 g of (−)-menthyl glyoxylate. After refluxing overnight, the reaction mixture was hydrolyzed with saturated ammonium chloride solution and the water layer extracted with ether. The combined ether extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to give a residue of menthyl mandelate, 8.3 g. One-half of this residue was reduced with lithium aluminum hydride, 0.7 g, in ether. The reaction mixture was decomposed with water and 15% sodium hydroxide. The precipitated hydroxides were removed by filtration, and the residue, after evaporating with ether was purified by silica gel column chromatography. Menthol was removed by chloroform elution and the phenylethylene glycol with methanol elution to give 0.6 g, 35% yield, which was further purified by sublimation: mp 58–62°; $[\alpha]^{24}D$ +12.4° (*c* 9.07, $CHCl_3$). This corresponds to 19.4% asymmetric synthesis based on the reported value[8a,15] for (*S*)-(+)-phenylethylene glycol of $[\alpha]^{23}D$ +63.8° (*c* 9.5, $CHCl_3$), mp 66–67°. The racemic diol has a melting point of 69–70°.[16] It has been reported[17] that the maximum rotation of phenylethylene glycol should be 30% higher than this; however, we have confirmed Bakshi and Turner's value by means of nmr studies of the MTPA derivative.[18]

The second half of the reaction product from phenylmagnesium bromide and (−)-menthyl glyoxylate was treated with excess phenylmagnesium bromide. However the triphenylethane-1,2-diol obtained (2.7 g, mp 150–155°, $[\alpha]^{22}D$ −5.2° (*c* 2.68, acetone), corresponded to 2.4% enantiomeric purity based on the rotation of $[\alpha]D$ +218.9° (*c* 2, acetone).[19] It was concluded that extensive racemization of this glycol had occurred.

DL-Methylphenyltrifluoromethylcarbinyl Methyl Ether (3).—

(12) G. von Frank and W. Caro, *Ber.*, **63**, 1534 (1930).

(13) H. G. Kuivila and O. T. Beumel, *J. Amer. Chem. Soc.*, **83**, 1296 (1961).

(14) R. Roger, *Biochem. Z.*, **230**, 320 (1931).

(15) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 168 (1961).

(16) J. D. D'Ianni and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 1675 (1939).

(17) G. Berson and M. Greenbaum, *ibid.*, **81**, 6456 (1959).

(18) J. Dale, Ph.D. Thesis, Stanford University, 1970.

(19) R. Roger and W. B. McKay, *J. Chem. Soc.*, 2229 (1931).

DL-Methylphenyltrifluoromethylcarbinol[20,21] (5.7 g), bp 95–100° (20 mm), prepared in 89% yield by the action of phenylmagnesium bromide on methyl trifluoromethyl ketone and in 90% yield by the action of methylmagnesium iodide on phenyl trifluoromethyl ketone) was treated in ether solution (30 ml) with sodium hydride (4.0 g, 50% mineral oil dispersion) followed by refluxing (1 hr) with dimethyl sulfate (4 g) to give the methyl ether **3** (6.1 g). This product showed no unreacted carbinol by vpc analysis (UCON LB 1715, 5 ft × 0.25 in., 150°, helium flow rate 30 ml/min, retention time 4 min): nmr ($CDCl_3$) δ 1.78 (q, 3 H, J = 0.8 Hz, long range CF_3 coupling), 3.22 (s, 3 H), 7.2 ppm (broad, 5 H, aromatic).

Anal. Calcd for $C_{10}H_{11}F_3O$: C, 58.81; H, 5.43. Found: C, 58.98; H, 5.51.

This material was used as a calibration standard for vpc and thin layer chromatography (tlc) studies in connection with the following sulfur tetrafluoride reactions.

Reactions of Sulfur Tetrafluoride with DL-*O*-Methylatrolactic Acid 2.—A stainless steel hydrogenation-type autoclave, 150-ml capacity, was charged with *O*-methylatrolactic acid[22] (2.0 g) and cooled to −60°. Sulfur tetrafluoride (25 g) was condensed in the autoclave followed by hydrogen fluoride (29 g) and the mixture was shaken at 20–25° for 24 hr. The reaction mixture was processed as indicated previously.[23] No starting material was recovered but no methylphenyltrifluoromethylcarbinyl methyl ether could be detected by tlc. Essentially the same procedure was conducted at 50° for 22 hr and at 90° for 3 days. In these runs a spot was observed on tlc with the same R_f value as the desired ether, but preparative silica gel chromatography failed to isolate any of the desired ether. Further experiments in which SF_4 was added to the acid sample **2** in water to generate the HF *in situ* were likewise unsuccessful, leading in some cases to block residues and in others to mixtures like the above which contained no starting acid but in which the ether could not be detected.

Registry No.—**3**, 26315-60-6; **6** (R = H), 26315-61-7; **6** 2,4-DNP, 26315-62-8; **10**, 26315-63-9; **11**, 26315-64-0; **14**, 26164-19-2.

(20) G. V. Kazennikova, T. V. Talalaeva, A. V. Zimin, A. P. Simonov, and K. A. Kocheskov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1066 (1961); *Chem. Abstr.*, **55**, 271546 (1961).

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The Peroxide-Initiated Decarbonylation of 9-Carbazolylacetaldehyde. A Possible Free-Radical Displacement[1a]

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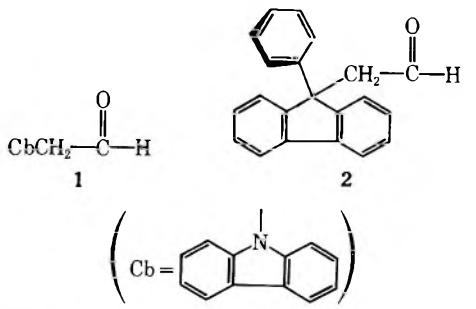
The peroxide initiated decarbonylation of 9-carbazolylacetaldehyde was studied in *o*-dichlorobenzene at 140 and 170° in an effort to observe a free radical N → C migration. No migration was detected. A reaction did occur, however, with the formation of 9-methylcarbazole, 1,2-dicarbazol-9-ylethene, and dicarbazol-9-ylmethane. Evidence is presented to support the structures of these compounds and the mechanism of their formation.

As part of a study on free-radical migration reactions,[2,3] we were prompted to investigate the peroxide-initiated decarbonylation of 9-carbazolylacetaldehyde (**1**). It was hoped that the stabilizing forces in this molecule would contribute to the first example of a nitrogen to carbon free-radical migration.[4]

This system was chosen because of its similarity to 9-phenyl-9-fluorenylacetaldehyde (**2**) which on decarbonylation was found to give a smooth conversion to 9-phenylphenanthrene.[5] Similar rearrangement in **1** would reduce ring strain with the simultaneous formation of the strongly stabilized free radical of the type R—CH_2—N—Ar.



The desired rearrangement would be expected to occur irreversibly[6] and most probably lead to the formation of the stable aromatic compound, phenanthridine, in a manner similar to the reaction of **2**. Radical stabilization and relief of ring strain, which are not necessary for carbon-to-carbon migration,[7] could provide the necessary driving force for nitrogen-to-carbon homolytic phenyl migration.

The aldehyde, **1**, was synthesized by an alkaline permanganate oxidation of 9-allylcarbazole[8] to yield 1-carbazol-9-yl-2,3-dihydroxypropane. This glycol was further oxidized with periodic acid to yield **1** the structure of which was verified by infrared, nmr and elemental analyses.

The di-*t*-butyl peroxide (DTBP) initiated decarbonylation was carried out both in the presence of oxygen and in deoxygenated systems. The results appear in Table I. When the decarbonylation was carried out in the presence of excess oxygen under the various conditions described in Table I (runs 1, 2, and 3), the only product

(1) (a) Based on the Ph.D. Thesis of M. L. Herz, University of Rhode Island, 1969. U.S. Army Natick Laboratory, Natick, Mass. (b) American Hoeshst Fellow, 1967–1968.

(2) For a review, see C. Walling, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 409 ff.

(3) (a) J. W. Wilt and M. Stumpf, *J. Org. Chem.*, **30**, 1256 (1965); (b) J. W. Wilt and O. Koluve, *J. Amer. Chem. Soc.*, **87**, 2071 (1965); (c) J. W. Wilt, O. Koluve, and J. F. Kraemer, *ibid.*, **91**, 2624 (1969).

(4) A possible 1,3-N → C migration has recently been described by R. W. Binkley, *Tetrahedron Lett.*, 1893 (1969).

(5) B. M. Vittimberga, *ibid.*, 2383 (1965).

(6) W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963).

(7) (a) W. H. Urry and N. Nicholaides, *J. Amer. Chem. Soc.*, **74**, 5163 (1952). (b) F. H. Seubold, *ibid.*, **75**, 2532 (1953); (c) L. H. Slaugh, *ibid.*, **81**, 2262 (1959).

(8) This compound was prepared using a modification of the procedure of B. Levy, *Monatsh. Chem.*, **33**, 182 (1912).

TABLE I
DECARBONYLATION OF CARBAZOLYLACETALDEHYDE

Run	Concn,[a] M	% CO[b]	% Cb–CH₃[c]	% Cb₂CH₂[c]	% Cb—CH=CH–Cb[c]
1[d,e]	Neat	35			12.8
2[e]	6				2.4
3[d,f]	6				0.8
4	1	58	8.6	4.3	
5	3	60[h]	9.3	4.7	
6	6	58	6.5	7.2	
7	6[i]	40	7.2	3.7	
8[g]	6	50	30.6	0.4[j]	

[a] The solvent used was *o*-dichlorobenzene. Unless otherwise noted the reaction temperature was 140° using two 20 mol % portions of DTBP added 2 hr apart. [b] Carbon monoxide was based on the theoretical amount of gas that would be produced in a complete reaction and was detected by vpc; however, the per cent of gas evolved is uncorrected for other possible volatile products making these values approximations. [c] Based on the total amount of recovered solids. [d] DTBP (90 mol %) was employed at 170°. [e] Oxygen was present in the reaction system. [f] Solution saturated with oxygen. [g] Thiophenol (35 mol %) was present. [h] DTBP (one 40 mol % portion) was used. [i] Not degassed, but in a closed system with very limited oxygen. [j] Recovered 0.500 g of the disulfide.

that could be isolated from the reaction mixture was 1,2-dicarbazol-9-ylethene (**4**). The structure of **4** was

Cb—CH=CH—Cb
4

assigned on the basis of its elemental, infrared, and mass spectrographic analysis and by its synthesis from 1,2-dicarbazol-9-ylethane (*vide infra*).

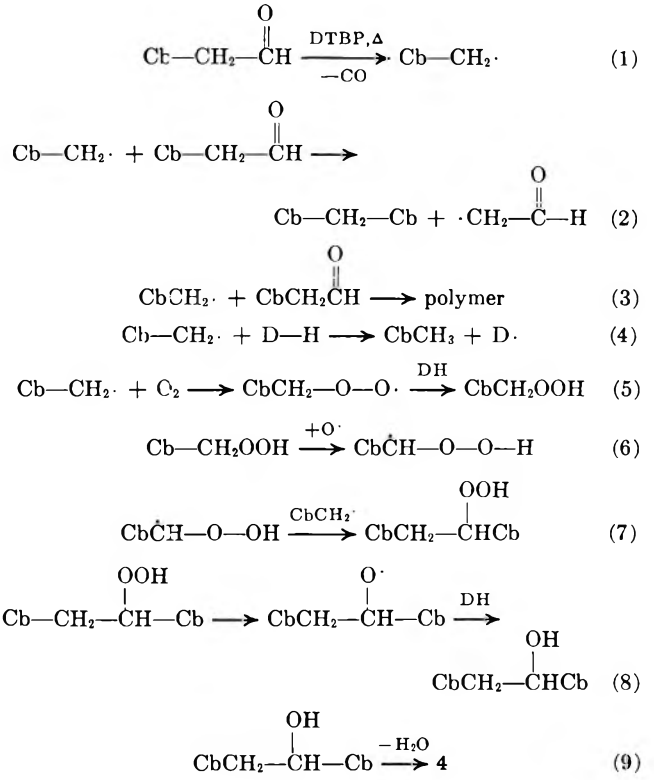
The yields of **4** were low and varied. In the case where none of this olefin was formed, the products were the same as those formed in deoxygenated systems (*vide infra*) The presence of oxygen in sufficient amounts appeared necessary for the formation of this product. This was evident from the fact that only those reactions in which a large amount of oxygen was present in the system (runs 1, 2, and 3) gave **4**. Presumably, when oxygen was present in limited quantities it could be flushed from the reaction mixture by the volatile products formed in the reaction.

When the solutions were deoxygenated prior to reaction, two different products were isolated along with polymeric material and unreacted aldehyde. The compounds were identified as 9-methylcarbazole (**5**) and the novel dicarbazol-9-ylmethane (**6**), the structure of which was assigned on the basis of its elemental, ir, nmr and mass spectrographic analyses [*m/e* (rel intensity) 346 (16, M^+), 180 (100)]. Further support for structure **6** was obtained by treating this compound with 47% hydriodic acid which produced carbazole in 83% yield. The decarbonylation data indicate that the 9-carbazolylmethyl radical is rather stable and does not propagate the reaction.

Contrary to results found in other systems (*i.e.*, the neophyl radical[9]), dilution did not change the nature of the products formed. This indicates that if any rearrangement were possible, it would occur at a much slower rate than the other processes which consume the radical, such as coupling, hydrogen abstraction, etc.

At first it was felt that dicarbazolylethene **4** was formed by coupling of the unrearranged radical followed by oxidation. To test this hypothesis the coupling product, 1,2-dicarbazole-9-ylethane (**7**) was synthesized by a carbazole anion displacement on the ditosylate of ethylene glycol. Surprisingly, this compound was found to be very stable at temperatures up to 170° even in the presence of oxygen and was recovered unchanged when added to decarbonylation reactions of **1**. It could, however, be dehydrogenated at 170°, in the presence of both oxygen and large amounts of DTBP, to the olefin **4** and amorphous material. The conversion of **7** to **4** most likely occurs by way of the hydroperoxide which then reacts according to eq 8 in the scheme below.

The following mechanism is proposed to explain the observations.



When oxygen is present in the reaction of **1** it acts to prevent the formation of **5** and **6** and reaction 5 becomes the major path for the production of monomeric products. The 9-carbazolylmethyl radical is trapped by oxygen and consequently is prevented from undergoing reactions 2, 3, and 4, thereby allowing the formation of **4**. Although it is probable that dicarbazolylethane **7** once formed would be converted to the olefin, the absence of this compound among the products of any of these reactions, particularly those carried out in the absence of oxygen, makes it highly doubtful that coupling is a reaction of any importance in this system. Moreover, at temperatures above 100° it would be expected that formation and decomposition of hydroperoxides would become increasingly competitive especially at the higher temperatures.[10] Besides the normal peroxide induced reactions, oxidation of the starting material, intermediates, and products can occur thereby reducing the amount of monomeric material obtained.

In deoxygenated solutions the carbazolylmethyl radical is sufficiently reactive to undergo reactions 2–4. Although this radical is present in large concentrations

(9) S. Winstein and F. H. Seubold, *J. Amer. Chem. Soc.*, **69**, 2916 (1947).

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 710.

in these solutions, it does not undergo coupling to any observable extent with thiyl, *t*-butoxy, or methyl radicals (the latter produced by the decomposition of the *t*-butoxy radicals). For the most part it undergoes nonchain reactions with the starting aldehyde, **1**, such as attack on the carbonyl group or aromatic substitution on the very active carbazole nucleus.[11] These reactions are the most likely source of the polymeric material which makes up the remainder of the reaction products.

The 9-carbazolylmethyl radicals which are not consumed by polymer formation react by two possible routes to form discrete products. They can either abstract hydrogen to form 9-methylcarbazole (reaction 4) or undergo a reaction with **1** that appears to be a free radical displacement (reaction 2). Acetaldehyde radicals which would also form through this mechanism would be expected to undergo decomposition under the conditions of the reaction.[12]

In order to test the possibility that dicarbazolylmethane might arise from the coupling of 9-carbozolyl and 9-methylcarbazolyl radicals, the decarbonylation was carried out in the presence of thiophenol as a radical trap. No detectable carbazole, which is stable under the conditions used, was formed in the reaction thus precluding this coupling mechanism as a possibility.

The polymeric material which was obtained was not examined extensively since it could not be purified by chromatography, sublimation, or recrystallization. Infrared and nmr analysis of this material show it to be an amorphous, polymeric substance very similar to that obtained by the acid catalyzed condensation of **1**.[13]

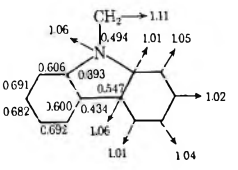
It is very doubtful that any rearrangement occurred, since phenanthridine was found to be stable to the reaction conditions. The results obtained with the addition of a hydrogen donor show the 9-carbazolylmethyl radical to be the major radical produced by the decarbonylation which has its origin in **1**. The failure of this radical to undergo rearrangement could be due, in part, to a stabilizing influence of the nitrogen atom as well as the possible delocalization over the π system of carbazole. Its poor hydrogen abstracting ability and simple HMO calculations carried out on this system support such possibilities.[14] The large bond order associated with the 9,10 bond would further increase the activation energy to prevent the rearrangement. Further efforts are being made to obtain information which might allow greater insight into the mechanism of this and other related reactions.

(11) W. A. Waters and J. E. White, *J. Chem. Soc. C*, 740 (1968).

(12) The two most likely products to be formed from reactions of the acetaldehyde radical, $\cdot CH_2C(=O)H$, are ketene and acetaldehyde. Under the conditions of the reaction the latter would undergo decarbonylation to yield carbon monoxide and methyl radical. R. K. Brinton and D. H. Volmen [*J. Chem. Phys.*, **20**, 1053 (1952)] found that in the gas phase DTBP did, in fact, cause this decarbonylation at temperatures of 124 to 156°. For another example of a free-radical displacement, see H. M. Frey and R. Walsh, *Chem. Commun.*, 159 (1969).

(13) M. L. Herz and B. M. Vittimberga, Abstracts, First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1969, No. 226. The ir spectrum of the product obtained from the acid-catalyzed condensation of **1** had bands at 3410, 2990, 2940, 1750, 1205, 1120, 720, and 745 cm^{-1}. The intractable material from the decarbonylation reaction showed similar absorption except for the fact that its bands were broadened and differed in intensity at 1740 (C=O) and 3410 cm^{-1} (OH). The nmr (acetone-d_6) spectrum showed typical, intense but undefined carbazole resonance (δ 8.3–6.8) and broad unresolved peaks of varying (between samples) intensities between δ 5.9 and 1.1.

(14) For a discussion of the possible stabilizing effect of nitrogen, see R. S. Davidson and P. F. Lambeth, *Chem. Commun.*, 1265 (1967). Bond orders and free-valence indices were determined for this system on an IBM 360 Model 50 computer using a coulomb integral of 1.5 and a resonance integral of 1.0: see A. Streitwieser, Jr., "Molecular Orbital Theory," Wiley, New York, N. Y., 1961, p 123. These values are shown below in the usual manner.



Experimental Section

All melting points are corrected and were determined on a Thomas–Hoover melting point apparatus. The nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer at 60 MHz using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide on either a Beckman IR-8 or a Perkin-Elmer Model 521 spectrophotometer. All the ultraviolet spectra were measured on a Cary Model 15 spectrophotometer in absolute ethanol. The microanalyses were performed by Micro-Analysis, Inc., Wilmington, Del.

Preparation of 9-Allylcarbazole.—The potassium salt of carbazole, prepared from the fusion at 260° of 100 g (0.582 mol) of carbazole and 34.0 g (0.606 mol) of potassium hydroxide, was mixed with 50.0 ml (70.0 g, 0.538 mol) of allyl bromide, 80 ml of dry benzene, and 0.2 g of potassium iodide in a 500 ml erlenmeyer flask carrying a condenser capped with a drying tube. After 30 min of very moderate reaction, the flask was placed in an ice bath and 5 ml of dry DMF was added to produce a highly exothermic reaction. When the reaction had subsided, a further portion of 15 ml (21.0 g, 0.162 mol) of allyl bromide was added, the ice bath was removed, and the reaction was stirred overnight using a magnetic stirrer. The resulting slurry was filtered, the inorganic salts washed with acetone and the filtrate evaporated. The product (red crystals) was recrystallized from denatured ethanol (89.7 g, 0.434 mol, 74.5%): mp 55–56° (lit.[8] mp 56°); ir 3060, 2990, 2945, 1625, 1420, 997, and 933 cm^{-1}; nmr ($CDCl_3$) δ 7.9–6.8 (m, 8), 5.73 (m, 1, –CH=), 4.90 (m, 2, CH_2=), and 4.60 (m, 2, CH_2).

1-Carbazol-9-yl-2,3-dihydroxypropane.—A solution of 100 g (0.483 mol) of 9-allylcarbazole, 2.0 g (0.356 mol) of potassium hydroxide, and 700 ml of acetone was cooled, with stirring, to ~10°. A solution of 80 g (0.595 mol) of potassium permanganate dissolved in 61% aqueous acetone was then added with vigorous stirring over a period of 1.5 hr at such a rate that the solution temperature remained constant. The mixture produced was stirred with 3 g of activated charcoal for 6 hr and the manganese dioxide was removed by suction filtration to give a light red solution. After evaporation of the acetone a solid remained which was purified by recrystallization, first from 50% aqueous methanol and then from denatured ethanol, to yield the desired product (76.7 g, 0.318 mol, 65.8%): mp 134.5–136°; ir 3240 (O–H), 1030, and 1050 cm^{-1} (C–O); nmr (acetone-d_6) δ 7.5 (m, aromatic), 4.41 (m, CH_2–Cb), 4.11 (s, 2, O–H), 3.82 (m, CH–OH), and 3.62 (m, CH_2–OH).

Anal. Calcd for $C_{15}H_{15}NO_2$ (241.3): C, 74.67; H, 6.27; N, 5.81. Found: C, 74.72; H, 6.34; N, 5.90.

9-Carbazolylacetaldehyde (1).—To a solution of 20.0 g (0.083 mol) of the diol and 850 ml of 76% aqueous methanol was added with stirring 20.0 g (0.088 mol) of periodic acid in 250 ml of water. This produced a gold colored solution which immediately gave a white precipitate. After 1.5 hr, 600 ml of water was added and the precipitate was collected on a filter, washed well with water, and dried over anhydrous calcium chloride. Crystallization of this product from carbon tetrachloride gave the pure aldehyde (16.2 g, 0.078 mol, 93.5%): mp 140.5–141.5°; ir 2850 (aldehyde C–H), and 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 9.63 (t, 1, J = 4.0 Hz), 7.5 (m, 8), 4.76 (d, 2, J = 4.0 Hz).

Anal. Calcd for $C_{14}H_{11}NO$ (209.25): C, 80.36; H, 5.30; N, 6.70. Found: C, 80.46; H, 5.23; N, 6.66.

The 2,4-dinitrophenylhydrazone of **1** melted 125–126°.

Materials and Equipment Used in the Free-Radical Decarbonylations.—Matheson, Coleman, and Bell 1,2-dichlorobenzene was purified by shaking successively with (1) small portions of concentrated sulfuric acid until the acid layer remained colorless,

(2) water, (3) 10% aqueous sodium carbonate until carbon dioxide evolution ceased, (4) water, and then dried over calcium chloride and distilled (bp 178.5–179.0°). The di-*t*-butyl peroxide (DTBP) was distilled under vacuum [bp 55–56° (120 mm)]. Matheson, Coleman, and Bell benzenethiol [bp 53–54° (10 mm)] was used without further purification.

The vpc analysis of the gases produced by the decarbonylation was carried out using a Perkin-Elmer Model 154 vapor fractometer equipped with a 20 × 0.25 in. column containing molecular sieve 5A. The analysis was carried out at room temperature with a helium carrier gas flow rate of 3 cc/min in order to confirm the evolution of carbon monoxide as a reaction product.

Thermal Stability of 1.—The 9-carbazolylacetaldehyde (0.50 g, 0.24 mmol) and 2.5 ml of *o*-dichlorobenzene were placed in a 18 × 150 mm test tube. After the tube was flushed with nitrogen gas, which was bubbled through the solvent for 30 min, it was sealed with a rubber stopper, equipped with a rubber policemen which had been slit to act as a gas bleed, and then heated at 140° for 8 hr. At the end of this time the light tan solution was cooled yielding crystals of 1 with a brownish tint (mp 138–140°).

Thermal Stability of 1 in the Presence of Thiophenol.—The thermal stability experiment described above was repeated using 0.50 g (0.24 mmol) of aldehyde, 0.25 ml (0.209 g, 0.244 mmol) of thiophenol and 2.5 ml of *o*-dichlorobenzene. A temperature of 140–145° was used for a period of 7 hr. The solvent was removed on a rotary evaporator (90°) and the crystalline residue was recrystallized from carbon tetrachloride. The recovered material melted at 141–142° (0.46 g, 92%) and had an infrared spectrum which was superimposable on that of the starting aldehyde.

Carbazole Stability under the Reaction Conditions.—Carbazole 0.50 (2.00 mmol), was placed in a 50 ml three-necked flask equipped with a gas inlet tube, condenser, and serum cap. To this was added 5 ml of *o*-dichlorobenzene and the temperature raised to 144–145°. Nitrogen was bubbled into the mixture as the temperature was raised and throughout the entire reaction period. After 1 hr at this temperature 0.175 g (0.22 ml, 1.20 mmol, 40 mol %) of DTBP was injected through the serum cap causing the solution to darken slightly. Heating was continued for 4 hr at this temperature. Then on cooling, a crystalline mass formed, wt 0.66 g. The solid was recrystallized from ethanol giving white crystalline plates melting at 243.5–244.5°. This was shown to be carbazole by infrared spectroscopy and mixture melting point determination, wt 0.47 g (95%).

Phenanthridine Stability under the Reaction Conditions.—The experiment described above for carbazole was repeated with phenanthridine. The quantities used were 0.50 g (2.79 mmol) of phenanthridine, 0.162 g (0.204 ml, 1.11 mmol) of DTBP and 5 ml of *o*-dichlorobenzene. At the end of the 4 hr reaction time the solvent was removed under vacuum giving 0.58 g of white solid as a residue. Recrystallization from ethanol gave 0.46 g (92%) of white crystals which melted at 106–107° and which had an infrared spectrum identical with that of a known sample of phenanthridine. Mixture melting point determination with the starting material showed no depression.

Preparation of 9-Methylcarbazole.—Carbazole (15 g, 0.090 mol), methyl sulfate (15.0 ml, 20.0 g, 0.159 mol) and 75 ml of acetone were stirred with a magnetic stirrer for 10 min. To this rapidly stirred mixture was added 15.0 g (0.376 mol) of sodium hydroxide in 10 ml of water. After 15 min the carbazole had gone into solution with the formation of precipitate of sodium sulfate. The mixture was then poured into 600 ml of water containing 25 ml of concentrated ammonium hydroxide to precipitate the desired product. The reaction gave an almost quantitative yield of 9-methylcarbazole which was recrystallized from 95% ethanol: mp 86–89° (lit.[15] 88°); ir 3045, 2920, 1462, and 1350 cm^{-1}; nmr ($CDCl_3$) δ 8.2–2.0 (m, 8, aromatic), 3.66 (s, 3).

Preparation of the Ditosylate of Ethylene Glycol.—To a cooled solution of 10.0 g (9 ml, 0.161 mol) of ethylene glycol and 150 ml of pyridine in a 250 ml erylenmeyer flask was added 120 g (0.630 mol) of tosyl chloride with vigorous stirring. After a solution had formed the flask was left in the refrigerator for 8 hr. The crystalline mass which formed was poured into 600 ml of cold water and the mixture stirred for 15 min. The product was separated by filtration and dried in a vacuum desiccator (57.0 g, 0.154 mol, 96%), mp 117–119° (lit.[16] 126–127°).

Preparation of 1,2-Dicarbazol-9-ylethane.—The ditosylate of ethylene glycol (30.0 g, 0.081 mol) was placed in a 500 ml round-bottomed flask. A solution of 16.0 g (0.097 mol) of carbazole, 20 g (0.50 mol) of sodium hydroxide, 13 ml of water, and 150 ml of acetone was added to the flask and the mixture stirred for 30 min. The solution was then heated at reflux on a steam bath for 6 hr. The resulting solution was evaporated to one-half volume and poured with stirring into 350 ml of water to produce a brown precipitate which was isolated on a filter and washed with water to give a pasty mass. After drying in a vacuum desiccator over calcium chloride the crude product was extracted with hot ligroin (bp 60–90°). The residue was recrystallized from benzene to give the desired product, **7** (2.1 g, 5.85 mmol, 7.2%): mp 304–305°; ir 3050, 2950, and 2890 cm^{-1} (C–H).

Anal. Calcd for $C_{26}H_{20}N_2$ (360.5): C, 86.63; H, 5.59; N, 7.77. Found: C, 86.72; H, 5.57; N, 7.65.

Stability of 1,2-Dicarbazol-9-ylethane. A. At 140°.—In a 25 ml flask equipped with a condenser 0.50 g (1.39 mmol) of **7** was dissolved in 5 ml of *o*-dichlorobenzene at 140°. To this solution was added 0.26 ml (0.206 g, 1.41 mmol) of DTBP and the reaction vessel was shaken for 4 hr while open to the atmosphere. The contents of the flask, allowed to cool, formed a crystalline mass (0.424 g), which was found to be starting material by ir and melting point, and tars which were not examined extensively. Infrared spectra showed that no conversion to dicarbazolylethene (4) had been effected.

Similarly, 0.20 g (0.555 mmol) of **7** was heated at 140 with 2 ml of *o*-dichlorobenzene and 0.050 ml (0.054 g, 0.488 mmol, 88 mol %) of thiophenol for 5 hr. All the starting material in this case was recovered unchanged.

B. At 170°.—In a 18 × 150 mm test tube 200 mg of **7** was heated at 170° for 17 hr while oxygen was bubbled through the solution. Upon cooling 0.194 g of the starting material (identified by mp and infrared spectrum) was recovered unchanged.

In a 10 ml pear-shaped flask equipped with a gas-inlet tube and a condenser, 0.200 g of **7** in 1 ml of *o*-dichlorobenzene was flushed for 1 hr with nitrogen at 170° (bath temperature). Then over a period of 2 hr 0.0804 ml (0.666 g, 4.56 mmol, 800 mol %) of DTBP was added. Heating was continued with nitrogen flushing for 15 hr after which, upon cooling, 0.184 g of slightly impure starting material was recovered (mp 289–293°). The filtrate contained ~60 mg of a red amorphous material which contained no olefin (4) as determined by ir spectral analysis, but some small amount of carbazole substituted material that could not be isolated in amounts large enough to identify.

Using similar apparatus 0.200 g of **7**, 1.22 ml (1.23 g, 1.12 mmol) of thiophenol, and 1 ml of *o*-dichlorobenzene was heated at 167° (bath temperature) for 16 hr with an oxygen flow. The solution was then poured into 10 ml of 95% ethanol to precipitate unchange **7**, 0.180 g (mp 301–303°; ir identical with that of an authentic sample). Further manipulation resulted in the isolation of 0.430 g of phenyl disulfide [mp 59–60 (lit.[17] 61°) which did not depress the melting point of an authentic sample upon admixture and which had an ir spectrum identical with that of a standard spectrum (*vide ante*)].

A mixture of 1.00 g (2.78 mmol) of 1,2-dicarbazol-9-ylethane, 2.0 ml (1.59 g, 10.9 mmol) of DTBP, and 4 ml of *o*-dichlorobenzene was heated in an 18 × 150 mm test tube open to the atmosphere at 165–170° (bath temperature) for eight hr. At the end of this time a second 2 ml portion of DTBP was added and the heating continued for a total of 20 hr to produce a deeply colored solution from which crystals (0.220 g) were separated. The remainder of the material was separated on 50 g of Woelm neutral alumina (activity grade I) in an 18 × 300 mm column. The elution of this material with hexane, hexane–benzene (3:1), and hexane–benzene (2:1) produced a clear oil (0.068 g) which appeared by ir and nmr spectroscopy to be predominantly aliphatic material and was evidently produced by the peroxide decomposition.[18] Further elution with hexane–benzene (1:1), hexane–benzene (1:2), and benzene gave 0.063 g of crystalline material. Finally, elution with polar solvents produced amorphous materials which contained small amounts of carbazole (~0.050 g estimated by ir spectra). The crystalline material was composed of a mixture of the 1,2-dicarbazol-9-ylethene and lesser amounts of starting material. Comparison

(15) T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, **123**, 2140 (1923).

(16) W. F. Edgell and L. Parta, *J. Amer. Chem. Soc.*, **77**, 4899 (1955).

(17) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. 1, Oxford University Press, New York, N. Y., 1934, p 653.

(18) The ir spectrum shows weak absorption at 3045, 750, and 720 cm^{-1} characteristic of the carbazole ring system. The nmr spectrum had extremely weak bands at about δ 7.5 with broad complex bands at δ 4.0–0.8. On this basis it was assumed that this fraction is principally aliphatic in nature and was probably derived from reactions of the initiator.

of the ir spectrum of the mixture with the spectra of prepared mixtures of the authentic materials provides an estimated 70%, 1,2-dicarbazol-9-ylethene (*vide infra*). Careful recrystallizations of the material from benzene gave 0.135 g: mp 333–336°; ir spectrum and mixture melting point determination further confirmed the identity of the compound. Thus the dehydrogenation produced 0.202 g (0.566 mmol, 20.4%) of **4** and large quantities of intractable decomposition product leaving 0.086 g (9%) of recoverable starting material.

Decarbonylation of 9-Carbazolylacetaldehyde. A. In the Presence of Oxygen with 90 mol % of Peroxide at 170° (Table I, Run 1).—In a 50 ml flask maintained at 170 ± 5° and equipped with an addition funnel and a condenser, followed by an inverted graduated cylinder to collect gases, was placed 7.0 g (0.033 mol) of **1**. DTBP (4.40 g, 0.030 mol, 90 mol %) was then added over a period of 3.5 hr and the mixture was heated for another 15.5 hr during which time ~260 ml (35% of the theoretical amount) of gases was evolved. The solution which resulted was placed in acetone to separate a refractory crystalline material and a soluble amorphous material. The crystalline material upon recrystallization from benzene gave 0.71 g (2.03 mmol, 12%) of 1,2-dicarbazol-9-ylethene (**4**): mp 340–342° dec; ir 3080, 3045, 930, 915, and 890 cm^{-1}; mass spectrum (70 eV at 240°) *m/e* (rel intensity) 359 (37), 358 (100, M^+), 192 (16), 191 (18), 190 (6), 180 (10), 179 (26), 178 (16), 176 (10, M^{2+}), 167 (7), 166 (6), 165 (9), 152 (5), 140 (5).

Anal. Calcd for $C_{26}H_{18}N_2$ (385.4): C, 87.12; H, 5.06; N, 7.82. Found: C, 86.93; H, 4.67; N, 7.88; mol wt (by mass spectroscopy), 358.

The remainder of the material could be separated into two portions both with a reddish brown color; one was an ether soluble glass and the other an ether insoluble amorphous solid. These materials had identical spectra, which were very similar to that of other amorphous solids obtained in the condensations and other decarbonylation experiments (*vide infra*) and which proved to be intractable.[13]

B. In the Presence of Oxygen with 60 mol % Peroxide at 140° (Run 2).—In a flask maintained at 140 ± 1° connected to a shaker apparatus and open to the atmosphere was placed 5.0 g (2.39 mmol) of **1** and 5.0 ml of *o*-dichlorobenzene forming a light yellow solution. To this, 2.10 g (1.43 mmol, 60 mol %), of DTBP was added in three portions over a period of 6.5 hr. The oil with a reddish-brown color produced by the reacton was dissolved in a minimum of carbon tetrachloride and this concentrated solution placed on a 22 × 350 mm column of 60 g of Mallinckrodt silicic acid (100 mesh). Elution with hexane gave only *o*-dichlorobenzene (~4.5 ml) and with hexane–benzene (1:1) gave 0.10 g of a crystalline material which was identified by ir spectrum and mp as **4**. Further elution with this solvent mixture followed by hexane–benzene (1:3) gave a red tar, from which starting material could be separated by crystallization from carbon tetrachloride, and an amorphous solid. Further elution with ether and acetone gave a second band of the amorphous solid. Finally, methanol was used to strip the column of any remaining organic matter. It was estimated from the characteristic carbonyl absorption (1730 cm^{-1}) that ~1.6 g of the aldehyde (32%) was still present in a mixture with the amorphous solids. These solids (~3.1 g) gave infrared spectra like that obtained for the amorphous materials in the preceding experiment.

C. In Deoxygenated Solutions with 40 mol % Peroxide at 140° (Runs 4–7).—In a flask maintained at 140 ± 1° connected to a shaker apparatus and to an inverted gas buret was placed 2.50 g (0.012 mol) of **1** and 2.0 ml of *o*-dichlorobenzene (6 *M*). To the solution which formed after 5 min, 0.584 g (0.0048 mol, 40 mol %) of DTBP was added over a period of 4 hr. The reaction solution was allowed to cool and was then chromatogrammed on a 22 × 350 mm column of Mallinckrodt silicic acid (100 mesh). Elution with solvent mixtures of increasing polarity yielded **1**, **5**, **6**, and carbazole mixed with colored amorphous material.

Since **6** is insoluble in ether and acetone, it could be separated easily by washing with ether or ether–acetone mixtures in which **5** or carbazole are soluble. The identification of these components of the reaction mixture was made by comparison of their melting points and ir spectra with those of authentic samples.

Decarbonylations were carried out employing this procedure for product separation of 1 *M* (run 4) and 3 *M* (run 5) concentrations of aldehyde. With these low concentrations of **1** it was necessary to remove most of the *o*-dichlorobenzene by flash evaporation at 90° before chromatography. The various reaction conditions and results are listed in Table I.

D. With Mercaptan Using 40 mol % Peroxide at 140° (Run 8).—To a deoxygenated solution of 5.0 g (2.39 × 10^{-2} mol) of **1**, 0.845 ml (0.911 g, 34.6 mol %) of thiophenol, and 4.0 ml of *o*-dichlorobenzene (6 *M*)—in a flask connected to a shaker apparatus and an inverted gas buret, and maintained at 140 ± 1°—was injected 1.76 ml (1.40 g, 40 mol %) of DTBP over a period of 4 hr. The solvent was removed by flash evaporation at 90° and replaced with carbon tetrachloride (~25 ml). From the solution crystallized 0.537 g of **1** (mp 140–142°) which was isolated on a filter. The remaining material which was dissolved in a minimum amount of carbon tetrachloride was separated as usual by column chromatography on silicic acid to yield, in order of elution from the column, phenyl disulfide,[19] **5**, a mixture of **5**, **6**, and carbazole,[20] and mixtures of colored glasses.

The product yields are given in Table I (run 8).

The 9-methylcarbazole was identified by comparison of ir and nmr spectra and mp (87–89°) with those of an authentic sample (*vide ante*). In addition its structure was confirmed by its mass spectrum (70 eV) *m/e* (rel intensity) 181 (57, M^+), 166 (100, $M^+ - CH_3$), 165 (43), 152 (13, $M^+ - :N{-}CH_3$), 140 (10), 139 (34).

The structure of **6** was based upon the following data: mp 307° dec; ir 3045, 2960, 2920 (C–H), and 1060 cm^{-1}; nmr ($CDCl_3$)[21] δ 8.2–7.1 (m, 8) and 6.7 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 347 (4.2), 346 (16, M^+), 181 (22), 180 (100), 167 (14), 152 (14), 140 (10).

Anal. Calcd for $C_{25}H_{18}N_2$ (346.4): C, 86.88; H, 5.24; N, 8.09. Found: C, 86.45; H, 5.51; N, 8.26; mol wt (by mass spectroscopy), 346.

E. In the Presence of 1,2-Dicarbazol-9-ylethane Using 40 mol % Peroxide at 140°.—In a 30 × 150 mm test tube were placed 0.625 g (2.99 mmol) of 9-carbazolylacetaldehyde, 0.625 g (1.74 mmol) of 1,2-dicarbazol-9-ylethane, and 6 ml of *o*-dichlorobenzene and the mixture heated to 140° in an oil bath. The solution which formed was degassed by bubbling in nitrogen gas for 15 min after which the tube was connected to a gas measuring system and the entire system flushed with nitrogen for an additional 15 min. Then 0.146 g (0.184 ml, 0.0012 mol, 40 mol % relative to aldehyde) of DTBP was injected and the gas evolution was measured for a period of 4 hr. When the red reaction mixture was cooled, crystals formed which were separated by filtration and recrystallized from benzene (0.263 g, mp 300–302°). This material was shown to be dicarbazolylethane by infrared and mixture melting point determination. The combined filtrates were then subjected to chromatographic separation on silicic acid. The total amount of solid isolated from the reaction was 1.195 g composed of 74.3 mg (6.7%) of 9-methylcarbazole, 13.4 mg (1.1%) of 1,2-dicarbazol-9-ylethene, 552.2 mg (46.3%) of 1,2-dicarbazol-9-ylathane, 33.0 mg (2.8%) of aldehyde (**1**), and 521.6 mg (43.6%) of amorphous solid. Identifications were made by melting point and infrared spectroscopy. Approximately 90% of the added dicarbazolylethane was recovered in this reaction.

Degradative Reactions of 6. A. Oxidation.—Using the method of Rieveschl and Ray,[22] 1.0 g (3.2 mmol) of dicarbazol-9-ylmethane was dissolved in 25 ml of glacial acetic acid and treated with 5.0 g (17 mmol) of sodium dichromate and 2.15 ml (2.37 g, 22.7 mmol) of acetic anhydride to give 0.1 g of carbazole (mp 242–247° and ir spectrum identical with that of an authentic sample) and water soluble oils which were not examined.

B. Reduction with Hydriodic Acid.—A mixture of 0.174 g (0.502 mmol) of **6** and 5.0 ml (2.85 g, 18.4 mmol) of 47% hydriodic acid in an 18 × 150 mm test tube was frozen at liquid

(19) The phenyl disulfide recovered from the column (0.230 g) was recrystallized once from 95% ethanol: mp 59–60° (lit.[17] 60–61°); ir 3090, 1590, 1480, 1440, 740, and 690 cm^{-1}; nmr ($CDCl_3$) δ 7.6–7.0 (m).

(20) The infrared spectrum of the material separated from **6** by extraction with ether indicates a very small band which could be attributed to the N–H stretching of carbazole. An estimate of the maximum quantity of carbazole present using the low intensity peak at 3420 cm^{-1} gives a value of 10 mg. If this band were carbazole, this amount is certainly much too small to lead to the large amount of dicarbazol-9-ylmethane obtained by this reaction without hydrogen donor present.

(21) This nmr spectrum was measured on a Varian HA-100 spectrometer using tetramethylsilane as an internal standard.

(22) G. Rieveschl, Jr., and F. E. Ray, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 420.

nitrogen temperature and the tube sealed. After heating the tube at 150° for 58 hr the contents were poured into water and the brown precipitate that was produced was isolated by filtration and dried. Recrystallization from 95% ethanol gave carbazole (0.140 g, 0.837 mmol, 83%) which was identified by its melting point and infrared characteristics.

Registry No.—**1**, 25557-77-1; 2,4-dinitrophenylhydrazone of **1**, 25557-78-2; **4**, 25557-80-6; **6**, 6510-63-0; **7**, 25557-82-8; 1-carbazol-9-yl-2,3-dihydroxypropane, 25557-79-3.

Acknowledgment.—The authors gratefully acknowledge the American Hoechst Corporation for supporting this research. We are also indebted to Mr. Donald L. Travis of Varian Associates for the HA-100 nmr spectra.

The Hydrolysis of Bis(4-Nitrophenyl) Carbonate and the General Base Catalyzed Hydrolysis of *o*-(4-Nitrophenylene) Carbonate

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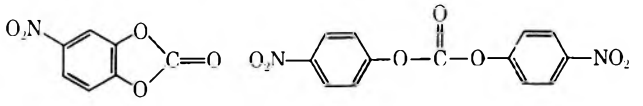
The rates of hydrolysis of *o*-(4-nitrophenylene) carbonate have been measured in H_2O at 30°. The values of k_{obsd} for spontaneous hydrolysis are independent of pH from pH 1 to pH 7. In this pH region a water-catalyzed reaction is occurring with a D_2O solvent isotope effect (k_{H_2O}/k_{D_2O}) of 2.35. As acid concentration is increased from 1.0 *M* to 5.29 *M*, the rate of hydrolysis decreases. This behavior is similar to that observed previously for bis(4-nitrophenyl) carbonate. Hydrolysis is catalyzed by a series of general base catalysts. A linear plot of log k_B *vs.* the pK_a of the catalyzing base is obtained with a slope of 0.30. The point for imidazole fits well on this line with catalysts of much lower basicity including H_2O. The value of $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 3.49, indicating proton transfer in the transition state. In contrast, nucleophilic catalysis takes place in the imidazole-catalyzed hydrolysis of bis(4-nitrophenyl) carbonate. Formation and decomposition of an intermediate could be observed in that reaction. Reasons for the mechanism change with the cyclic ester are discussed.

The imidazole-catalyzed hydrolysis of esters having a leaving group of low basicity, such as *p*-nitrophenyl acetate, has been shown to take place with nucleophilic attack by imidazole at the carbonyl of the ester.[1,2] It was thought that it would be of considerable interest to determine the effect on rate and mechanism of constraining an ester with a good leaving group in a cyclic cis configuration since constraint of this type could take place in an enzymatic reaction, and indeed has been suggested for α-chymotrypsin.[3] As part of a general investigation of steric effects on the mechanisms of hydrolysis of esters and amides, both enzymatic and nonenzymatic,[4] we have therefore studied the hydrolysis of the cyclic ester *o*-(4-nitrophenylene) carbonate (I) and, for comparison purposes, the analogous noncyclic bis(4-nitrophenyl) carbonate (II). The hydrolysis of



I II

bis(4-nitrophenyl) carbonate in various acid solutions where the reaction involves water catalysis has been studied,[5] but kinetic studies of carbonate ester hydrolysis in buffer solutions have not been previously reported.

Experimental Section

Materials.—*o*-(4-Nitrophenylene) carbonate was prepared from 4-nitrocatechol and phosgene by the same procedure previously utilized for the preparation of bis(4-nitrophenyl) carbonate.[5] The pale yellow crystals melted at 99–100°. *Anal.* Calcd for $C_7H_3NO_5$: C, 46.42; H, 1.67; N, 7.72. Found: C, 46.47; H, 1.71; N, 7.67. The infrared spectrum was consistent with structure I. There was no absorption band present due to phenolic OH. Complete hydrolysis in HCl or in buffered solutions gave 1 equiv of 4-nitrocatechol per equiv of ester, as determined spectrophotometrically.

N-(*p*-Nitrophenoxycarbonyl)imidazole was prepared by adding dropwise 5.0 g (0.025 mol) of *p*-nitrophenyl chloroformate in dry benzene to 3.4 g (0.05 mol) of imidazole in refluxing dry benzene. The mixture was stirred for 2 hr, cooled, and filtered. Upon evaporation of the benzene a solid residue was obtained which was recrystallized from benzene. The material melted at 128–129°. *Anal.* Calcd for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found: C, 51.62; H, 3.01; N, 17.94.

p-Nitrophenyl chloroformate was obtained from K and K Laboratories. Acetonitrile was Eastman Kodak Spectrograde and was further purified by distillation from P_2O_5 and K_2CO_3. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories. Hydrochloric acid was Baker Reagent grade. The concentration of HCl solutions was determined by titration of standard base. Imidazole was obtained from Eastman Kodak and was recrystallized from benzene. All other chemicals were reagent grade.

Kinetic Measurements.—The rates of hydrolysis of *o*-(4-nitrophenylene) carbonate at 30° in H_2O were followed by measuring the appearance of 4-nitrocatechol at 335 mμ or the monoanion at 410 mμ with a Gilford 2000 recording spectrophotometer. The hydrolysis of bis(4-nitrophenyl) carbonate was followed by measuring the appearance of *p*-nitrophenol at 330 mμ or *p*-nitrophenoxide ion at 400 mμ. The spectrum of the solution upon completion of the reaction was identical with that of *p*-nitrophenol or 4-nitrocatechol in the appropriate buffer solution.

In spectrophotometric determinations the ester was dissolved in acetonitrile and 50 μl of this solution was added with a Hamilton syringe to 3 ml of solution in the cuvette with stirring. The reactions were followed to completion, and infinity points were stable. Constant temperature (±0.1°) was maintained by circulating water from a Precision Scientific Lo-Temptrol 154 circulating water bath around the cell compartment. The temperature inside the cell compartment was determined with a probe supplied with the Gilford instrument. Pseudo-first-

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(1) M. L. Bender and B. W. Turnquest, *J. Amer. Chem. Soc.*, **79**, 1652, 1656 (1957).

(2) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

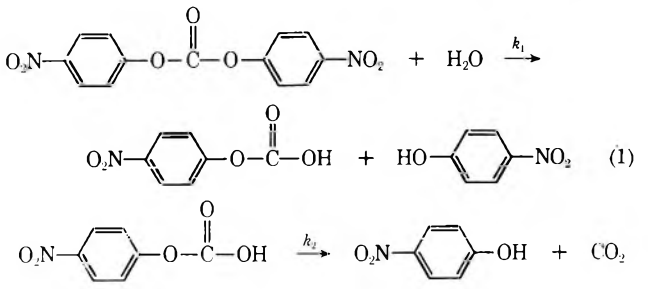
(3) T. C. Bruice, *J. Polym. Sci.*, **49**, 101 (1961).

(4) For previous papers, see (a) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 4597 (1965); (b) J. A. Fee and T. H. Fife, *J. Org. Chem.*, **31**, 2343 (1966); (c) J. A. Fee and T. H. Fife, *J. Phys. Chem.*, **70**, 3268 (1966); (d) T. H. Fife and J. B. Milstien, *Biochemistry*, **6**, 2901 (1967); (e) J. B. Milstien and T. H. Fife, *J. Amer. Chem. Soc.*, **90**, 2164 (1968).

(5) T. H. Fife and D. M. McMahon, *ibid.*, **91**, 7481 (1969).

order rate constants (k_{obsd}) were calculated with an Olivetti-Underwood Programma 101 programmed to calculate a least squares evaluation of the slope and intercept of a plot of ln $[(OD_\infty - OD_0)/(OD_\infty - OD_t)]$ *vs.* time. Correlation coefficients were invariably in the range 0.9990 to 0.9999. A twofold variation in substrate concentration produced no change in the observed rate constants.

The most probable reaction scheme in acidic solution is that illustrated in eq 1 for hydrolysis of bis(4-nitrophenyl) carbonate. Formation of the monoester, the step governed by k_1, must be



(1)

rate determining for spontaneous hydrolysis, considering the reaction to be irreversible, since excellent first-order kinetics were always observed and an initial rapid release of *p*-nitrophenol was not detected.[5] Complete hydrolysis of II invariably gave 2 equiv of *p*-nitrophenol per equiv of diester. Identical rate constants were obtained in the presence or absence of 10^{-4} *M* *p*-nitrophenol. Good first-order kinetics would not be observed if decomposition of monoester was rate determining unless the first step in the sequence was exceedingly rapid. In that case, however, there would be a burst of 1 equiv of *p*-nitrophenol which was not observed.

Further evidence for k_1 being rate determining is provided by the very rapid spontaneous hydrolysis of *p*-nitrophenyl chloroformate (see Results). In that reaction mono(4-nitrophenyl) carbonate can reasonably be assumed to be formed as an intermediate. The chloroformate hydrolyzes to *p*-nitrophenol at a much faster rate than observed for either I or II at all acid concentrations.

The excellent first-order kinetics and stable infinity points observed in the hydrolysis of *o*-(4-nitrophenylene) carbonate indicate that ring opening is very probably rate determining. A monoester intermediate would, of course, have an appreciable extinction coefficient at the wavelengths employed, but as with II, a rapid reaction followed by a slower change in absorbance was not observed. A fast initial release of product followed by a slower reaction was not observed in any case in acid or buffer solutions, except for II in imidazole buffers.

The pH measurements were made with a Radiometer Model 22 pH meter. To determine pD, the glass electrode correction equation of Fife and Bruice was employed.[6]

Results

In Table I rate constants are given for hydrolysis of *p*-nitrophenyl chloroformate in various acidic solutions at 30°. These rate constants are much greater than observed for either I or II at the same acid concentrations. The hydrolysis of *p*-nitrophenyl chloroformate was too fast to measure at 30° in 0.125 *M* formate or acetate buffers. The rate constants for hydrolysis of *p*-nitrophenyl chloroformate in imidazole buffers are much smaller than for spontaneous hydrolysis. An intermediate is therefore being formed which hydrolyzes relatively slowly.

The hydrolysis of bis(4-nitrophenyl) carbonate is subject to marked buffer catalysis. In Table II the second-order rate constants at 50° and μ = 0.5 are presented. In Figure 1 is shown a plot of k_{obsd} *vs.* total formate buffer concentration at constant pH and ionic strength. The slope increases as the pH is increased. Thus, formate ion is the active species. Formate

(6) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

TABLE I

RATE CONSTANTS (k_{obsd}, MIN^{-1}) FOR HYDROLYSIS AT 30° OF *p*-NITROPHENYL CHLOROFORMATE, *N*-(4-NITROPHENOXYCARBONYL)IMIDAZOLE, AND THE INTERMEDIATE PRODUCED IN THE IMIDAZOLE-CATALYZED HYDROLYSIS OF BIS(4-NITROPHENYL) CARBONATE

	p-Nitrophenyl chloroformate	*N*-(4-Nitrophenoxycarbonyl)-imidazole	Intermediate
5.29 *M* HCl	0.438		
3.53 *M* HCl	1.165		
2.03 *M* HCl	2.75		
1.36 *M* HCl	3.31		
0.1 *M* HCl	6.17		
0.001 *M* HCl	6.22	2.64	
0.001 *M* Imidazole[a]			0.0292
0.002 *M* Imidazole[a]			0.0415
0.004 *M* Imidazole[a]		0.055	0.054
0.006 *M* Imidazole[a]		0.06	0.0589
0.01 *M* Imidazole[a]	0.147	0.149	0.151
0.02 *M* Imidazole[a]	0.378	0.362	0.392
0.04 *M* Imidazole[a]	1.18	1.09	1.08
0.064 *M* Imidazole[a]	2.30	2.26	2.35
0.08 *M* Imidazole[a]	3.32	3.35	3.56

[a] Total imidazole concentration at pH 7.17, μ = 0.5 *M* with KCl.

TABLE II

RATE CONSTANTS FOR CATALYSIS OF THE HYDROLYSIS OF BIS(4-NITROPHENYL) CARBONATE AT 50°, μ = 0.5 *M* WITH KCl

Catalyst	pK_a, 50°	Solvent	k_B l. mol^{-1} min^{-1}
H_2O	−1.74	H_2O	0.00305[a]
$H_2PO_4^-$	2.10	H_2O	0.163[b]
$HCOO^-$	3.60	H_2O	0.182
$HCOO^-$	4.04	D_2O	0.112
CH_3COO^-	4.60	H_2O	0.304
Pyridine	4.99	H_2O	16.4
HPO_4^{2-}	6.70	H_2O	11.34[c]
Imidazole	7.10[d]	H_2O	1450[e]
Imidazole	7.54[d]	D_2O	1500[e]
sym-Collidine	7.10	H_2O	0.783

[a] $k_0/55.5$. [b] Determined in H_3PO_4–$H_2PO_4^-$ buffers. [c] Corrected for catalysis by $H_2PO_4^-$. [d] Measured at 30°. [e] Rate constant for intermediate formation at 30°.

buffer catalysis is reduced in D_2O, ($k_{HCOO^-}{}^{H_2O}/k_{HCOO^-}{}^{D_2O}$ = 1.63). The intercept in Figure 1 is also considerably less in D_2O than in H_2O ($k_0{}^{H_2O}/k_0{}^{D_2O}$ = 2.65). It was previously shown[5] that spontaneous hydrolysis is a pH-independent reaction with k_{H_2O}/k_{D_2O} = 2.88 for hydrolysis in 0.1 *M* HCl and 0.1 *M* DCl. In a plot of log k_B *vs.* the pK_a of the catalyzing base, differing types of bases do not fit well on a single straight line.

Imidazole is undoubtedly acting as a nucleophile in the hydrolysis of bis(4-nitrophenyl) carbonate since an intermediate can be detected in the reaction. At 50° there is a very rapid initial release of *p*-nitrophenoxide ion although the extent of this reaction could not be determined quantitatively because of the subsequent hydrolysis of the intermediate. However, by working at lower temperature and low total imidazole concentration (0.001 *M*–0.01 *M*), the initial burst of *p*-nitrophenoxide ion can be measured. At 30°, pH 7.17 and 6.74, and a substrate concentration of 2×10^{-5} *M*, approximately 1 equiv of *p*-nitrophenoxide per equiv of

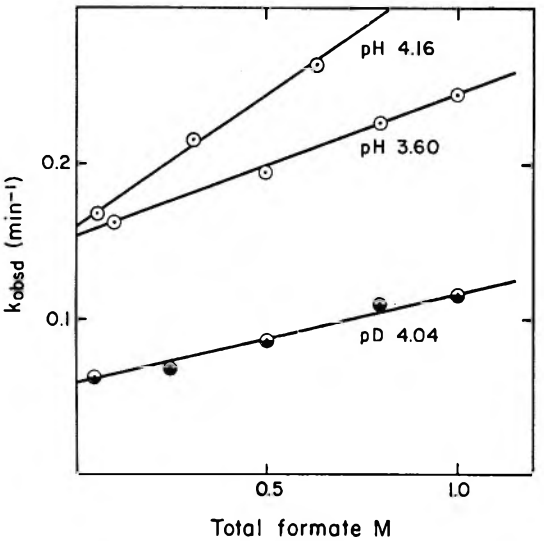
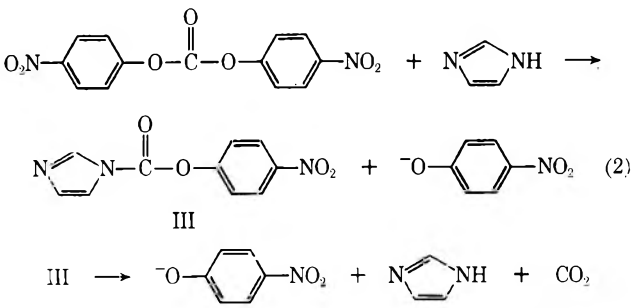


Figure 1.—Plot of k_{obsd} for hydrolysis of bis(4-nitrophenyl) carbonate at 50° and μ = 0.5 *vs.* total formate concentration ($HCOO^-$ + HCOOH) in H_2O ⊙ and D_2O ◒.

substrate was rapidly released. This reaction was then followed by a much slower release of *p*-nitrophenoxide ion. The observed rate constants for both steps were pseudo-first-order. Thus, the reaction scheme being followed is that of eq 2. Identical first-order rate



constants were obtained in the presence of 1.04×10^{-4} *M* *p*-nitrophenol showing that there is little reversibility under the conditions of the experiments. Plots of k_{obsd} for formation of the intermediate III *vs.* imidazole concentration at two pH values in H_2O and one pD value in D_2O were linear. The ratio $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 0.97.

Plots of k_{obsd} for hydrolysis of the intermediate *vs.* imidazole concentration at 2 pH values show a definite upward curvature. A plot of $(k_{obsd} - k_0)/Im_B$ *vs.* Im_B in Figure 2 is linear following eq 3, where Im_B is the

$$k_{obsd} = k_0 + k'_{Im}(Im_B) + k''_{Im}(Im_B)^2 \quad (3)$$

concentration of imidazole in the free base form. An intercept is observed. Thus, hydrolysis of the intermediate acyl imidazole displays both a first-order and a second-order dependence on imidazole concentration. The value of k'_{Im} is 12 l. mol^{-1} min^{-1}, and k''_{Im} has the value 1610 $l.^2$ mol^{-2} min^{-1}. It will be noted in Table I that the rate constants in imidazole buffers for hydrolysis of the intermediate from II and for *p*-nitrophenyl chloroformate are nearly identical, as would be expected if the same intermediate is being formed in the two reactions. This was supported by synthesis of III and the study of its hydrolysis in imidazole buffers. As seen in Table I, the rate constants obtained are nearly

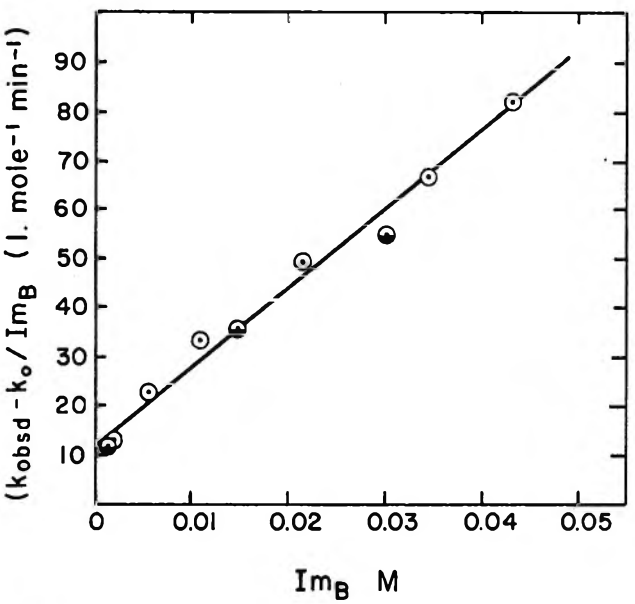


Figure 2.—Plot of $(k_{obsd} - k_0)/Im_B$ for hydrolysis of the intermediate formed in the hydrolysis of bis(4-nitrophenyl) carbonate at 30° *vs.* Im_B, the concentration of imidazole in the free base form at pH 7.17 ○ and pH 6.74 ◒.

identical with those for hydrolysis of the intermediate from II and *p*-nitrophenyl chloroformate.

The values of k_{obsd} for hydrolysis of *o*-(4-nitrophenylene) carbonate at 30° and at various HCl concentrations are presented in Table III. Also given in Table III are

TABLE III

RATE CONSTANTS FOR HYDROLYSIS OF *o*-(4-NITROPHENYLENE) CARBONATE IN VARIOUS AQUEOUS SOLUTIONS AT 30°

HCl, *M*	pH	$k_{obsd} \times 10^2$ min^{-1}
5.29		5.24
3.53		11.69
2.03		25.26
1.36		39.48
1.01		44.28
0.10		66.0
0.10[a]		63.22
0.10[b] (D_2O)		28.1
0.01		66.31
0.01[a]		60.69
0.001	3.02	70.9
0.001[a]	3.02	66.20
	3.60[c]	62.3[d]
	4.62[e]	58.5[d]
	5.34[f]	66.8[d]
	6.74[g]	77.0[d]
	6.74[h]	75.2[d]
	7.17[g]	93.0[d]
	7.64[g]	135.0[d]

[a] μ = 0.5 with KCl. [b] DCl in D_2O. [c] Formate buffer, μ = 0.5 with KCl. [d] Rate constants were obtained by extrapolation to zero buffer concentration. [e] Acetate buffer, μ = 0.5 with KCl. [f] Pyridine buffer, μ = 0.5 with KCl. [g] Imidazole buffer, μ = 0.5 with KCl. [h] Phosphate buffer, μ = 0.5 with KCl.

values of k_{obsd} for spontaneous hydrolysis at various pH values. When buffer solutions (μ = 0.5) were employed these rate constants were obtained by extrapolation to zero buffer concentration. The rate constants decrease significantly as HCl concentration is increased

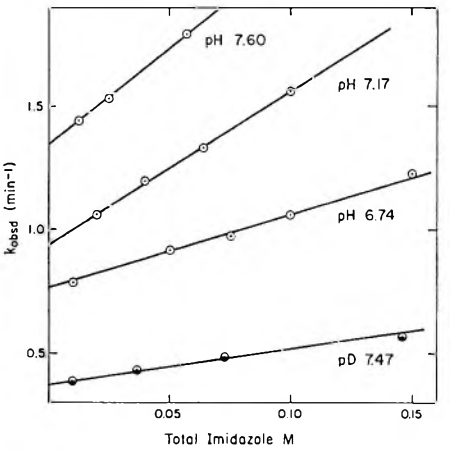


Figure 3.—Plot of k_{obsd} for hydrolysis of *o*-(4-nitrophenylene) carbonate at 30° *vs.* total imidazole concentration (Im + ImH^+) in H_2O ⊙ or D_2O ◒.

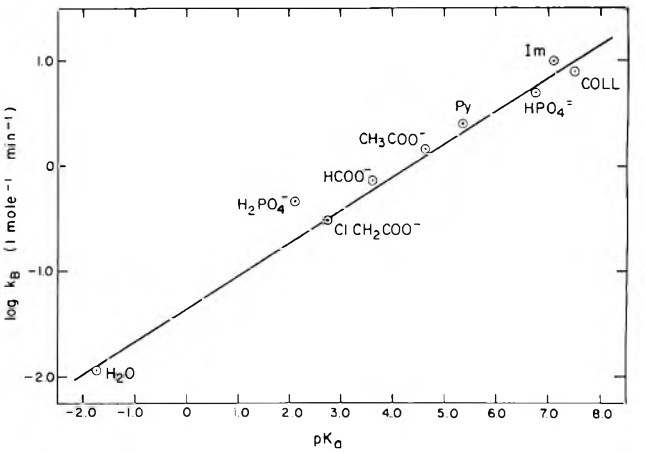


Figure 4.—Plot of log k_B for catalysis of the hydrolysis of *o*-(4-nitrophenylene) carbonate by various bases at 30° *vs.* the pK_a of the catalyzing base.

from 1.0 *M* to 5.29 *M*. When ionic molarity was held constant at 4.80 *M* with LiCl however, the decrease in k_{obsd} was smaller as HCl concentration was increased, k_{obsd} being 0.101 min^{-1} at 1.08 *M* HCl and 0.066 min^{-1} at 3.82 *M* HCl. At pH values from 1–7 spontaneous hydrolysis is independent of pH. Hydroxide ion catalysis occurs at pH values greater than 7. Increasing the ionic strength with KCl has a small rate retarding effect on the spontaneous reaction. For example, k_{obsd} is 0.663 min^{-1} in 0.01 *M* HCl and 0.607 min^{-1} in 0.01 *M* HCl with 0.5 *M* KCl added. Addition of 0.5 *M* $NaClO_4$ produced only a slightly larger effect, k_{obsd} being 0.523 min^{-1}. The pH-independent reaction is much slower in D_2O than H_2O, the ratio k_{H_2O}/k_{D_2O} being 2.35 for hydrolysis in 0.1 *M* HCl and 0.1 *M* DCl in D_2O.

A pronounced buffer catalysis is observed in the hydrolysis of *o*-(4-nitrophenylene) carbonate. In Figure 3 a plot is shown of k_{obsd} *vs.* total imidazole concentration at 3 pH values in H_2O and 1 pD value in D_2O. The plots are linear, and the slope increases as pH increases showing the base form of imidazole to be catalytically active. There is a large D_2O solvent isotope effect for both the imidazole-catalyzed reaction and the spontaneous reaction. The ratio $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 3.49. The second-order rate constants for general base catalysis are given in Table IV. A plot of log k_B *vs.* pK_a of the acid of the catalyzing base is shown in Figure 4. The plot is linear with all bases, including water, fitting well on a line with a slope of 0.30 (r = 0.989). Statistical corrections had essentially no effect on the slope. With statistical corrections[7] the slope was 0.32 and the correlation coefficient was 0.983.

TABLE IV

SECOND-ORDER RATE CONSTANTS FOR GENERAL BASE CATALYZED HYDROLYSIS OF *o*-(4-NITROPHENYLENE) CARBONATE AT 30°, μ = 0.5 WITH KCl

Catalyst	pK_a	k_B, l. mol^{-1} min^{-1}
H_2O	−1.74	0.012[a]
$H_2PO_4^-$	2.10	0.468[b]
$ClCH_2COO^-$	2.70	0.305
$HCOO^-$	3.60	0.736
CH_3COO^-	4.62	1.48
Pyridine	5.34	2.55
HPO_4^{2-}	6.74	5.02[c]
Imidazole (pH 6.74)		9.55
Imidazole (pH 7.17		10.92
Imidazole (pH 7.64)		9.73
Imidazole (average)	7.10	10.06
Imidazole (D_2O)	7.54	2.88
sym-Collidine	7.50	8.04

[a] k_0/55.5. [b] Determined in H_3PO_4–$H_2PO_4^-$ buffers. [c] Corrected for catalysis by $H_2PO_4^-$.

Discussion

The lack of acid catalysis in the hydrolysis of *o*-(4-nitrophenylene) carbonate is similar to what was observed previously for bis(4-nitrophenyl) carbonate and esters of dichloracetic acid[5] and can be explained in the same manner. Strong electron withdrawal from the carbonyl group will greatly reduce the equilibrium concentration of protonated ester so that acid catalysis cannot compete with the rapid pH-independent reaction. Thus, kinetically significant protonation is not taking place. The large rate decreases produced by increasing acid concentration with these compounds are similar to those observed in reactions where acid has no further catalytic effect because protonation of the substrate is complete.[4c,8–10] This behavior occurs when water is involved in the critical transition state. The observed rate decreases in those cases have been explained by the decrease in water activity as acid concentration is increased,[11] or by a change in rate-determining step.[10] Fedor and Bruice[12] have observed a similar dependence on acidity of the rate constants for spontaneous hydrolysis of ethyl trifluorothiolacetate. A plot of log k_{obsd} for *o*-(4-nitrophenylene)carbonate *vs.* the logarithms of the activity of water in the acid solutions had distinct curvature, but when ionic molarity and the activity of H_2O was maintained constant with LiCl the decrease in k_{obsd} with increasing acidity was relatively small. This was also observed in the case of *p*-nitrophenyl dichloroacetate.[5]

The pH-independent hydrolysis of both bis(4-nitrophenyl) carbonate[5] and *o*-(4-nitrophenylene) carbonate

(7) R. P. Bell and P. G. Evans, *Proc. Roy. Soc., Ser. A.*, **291**, 297 (1966).

(8) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000, 2009 (1957); J. A. Leisten, *ibid.*, 765 (1959).

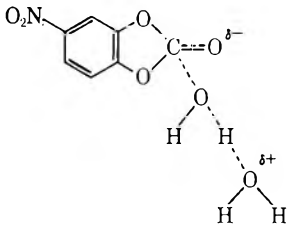
(9) S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.*, **84**, 232 (1962).

(10) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962).

(11) J. F. Bunnett, *ibid.*, **88**, 4956, 4968, 4973 (1961).

(12) L. R. Fedor and T. C. Bruice, *ibid.*, **87**, 4138 (1965).

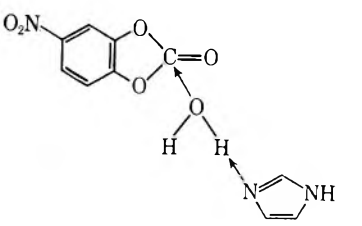
undoubtedly involves a water-catalyzed reaction. Proton transfer is taking place in the transition state as in IV or a kinetic equivalent as indicated by the much slower reactions in D_2O than in H_2O.



Imidazole-catalyzed hydrolysis of bis(4-nitrophenyl) carbonate proceeds with imidazole functioning as a nucleophile. Detection of an intermediate in the reaction shows this conclusively. Accordingly, the second-order rate constant for intermediate formation is approximately the same in D_2O as in H_2O ($k_{Im}^{H_2O}/k_{Im}^{D_2O}$ = 0.97). Nucleophilic catalysis does not lead to a D_2O solvent isotope effect appreciably greater than unity,[13] whereas general base catalysis of ester hydrolysis by imidazole, involving proton transfer in the transition state, generally gives rise to a D_2O solvent isotope effect of 2–3.

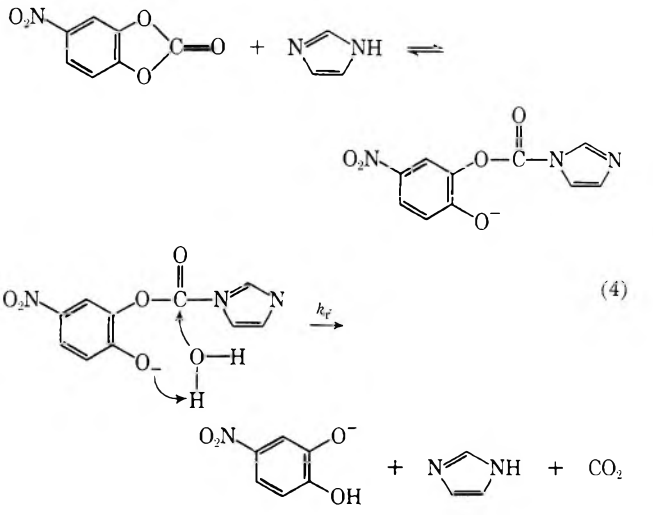
The second-order rate constant for imidazole catalysis of the hydrolysis of II (intermediate formation) is much greater than might be expected on the basis of its pK_a in comparison with the other bases studied. As seen in Table II, the rate constant for imidazole catalysis at 30° is 128 times as large as that for HPO_4^{2-} at 50°, even though these bases have closely similar pK_a values, in accord with the fact that imidazole is participating as a nucleophile in this reaction. Water is very likely acting as a general base since k_{H_2O}/k_{D_2O} = 2.88.[5] It is probable that the formate ion catalysis is also, to a large extent, general base catalysis in view of the low pK_a of formate in comparison to the leaving group, and the D_2O solvent isotope effect significantly greater than unity (1.63). Acetate ion catalyzed hydrolysis of *p*-nitrophenyl acetate has been found previously to be largely general base.[14] A line with a slope of 0.3 can be drawn through the points for water, formate, and acetate in a plot of log k_B *vs.* pK_a, but, with the exception of *sym*-collidine, there is marked positive deviation of the points for the other bases. A change in mechanism to nucleophilic as the pK_a of the catalyst base becomes comparable to that for the leaving group (7.1) should result in a positive deviation from the Brønsted plot. It has previously been observed that, in nucleophile-catalyzed hydrolysis of *p*-nitrophenyl acetate, bases of different type lie on different lines in a Brønsted plot,[15] whereas, in the general base catalyzed hydrolysis of ethyl dichloroacetate,[16] bases of divergent type fit a single plot (β = 0.47).

In the case of the cyclic carbonate ester *o*-(4-nitrophenylene) carbonate, the evidence strongly indicates that a mechanism change has taken place, with imidazole catalysis most likely proceeding by a general base mechanism. Thus, the ratio $k_{Im}^{H_2O}/k_{Im}^{D_2O}$ is 3.49. A linear plot of log k_B *vs.* pK_a is now obtained (Figure 4)



with all points, including those for H_2O and imidazole, fitting well on a line with a slope of 0.30. It will be noted that now imidazole and HPO_4^{2-} have approximately the same rate constant, as might be expected for catalysts with nearly the same pK_a in a general base catalyzed reaction.[16] The kinetically equivalent general-acid, specific-base catalysis can also be considered as a possibility.

An alternative possibility is the mechanism shown in eq 4. Such a reaction, although involving nucleophilic

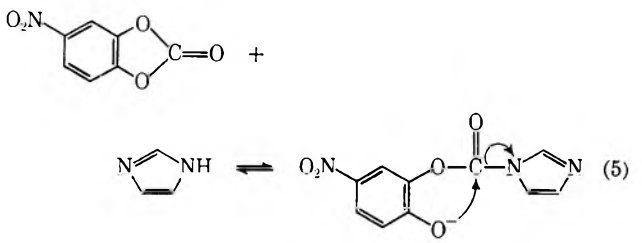


(4)

attack by imidazole, would still give rise to a large solvent isotope effect since proton transfer takes place in the rate-determining step. In ester hydrolysis reactions general base catalysis by a neighboring phenoxy anion has been suggested for hydrolysis of *p*-nitrophenyl 5-nitrosalicylate.[17] However, the mechanism of eq 4 is very unlikely for imidazole-catalyzed hydrolysis of the cyclic carbonate since imidazole lies on the same line in the plot of log k_B *vs.* pK_a with all of the other catalysts, including H_2O, chloroacetate, and formate which certainly are not acting solely as nucleophiles in view of their low pK_a. The point for imidazole should deviate from the plot if a different mechanism was occurring. The point for *sym*-collidine (2,4,6-trimethylpyridine) also fits well on the same line with imidazole and the other bases. *sym*-Collidine cannot effectively participate as a nucleophile because of the methyl groups at the 2 and 6 positions of the pyridine ring which sterically inhibit nucleophilic attack by nitrogen at carbon.[18] In general base catalyzed reactions the effects of the 2,6-methyl group substitution are small compared with those in nucleophilic reactions.[19] Thus, all of the compounds in the series, including imidazole, are most likely catalyzing ring opening by a general base mechanism.

(13) M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Amer. Chem. Soc.*, **84**, 595 (1962).
(14) A. R. Butler and V. Gold, *J. Chem. Soc.*, 1334 (1962).
(15) T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, **80**, 2265 (1958).
(16) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).
(17) M. L. Bender, F. J. Kezdy, and B. Zerner, *ibid.*, **85**, 3017 (1963).
(18) J. G. Pritchard and F. A. Long, *ibid.*, **79**, 2365 (1957).
(19) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).

There would appear to be no reason why imidazole could not attack the cyclic ester as a nucleophile. The reason for a general base or kinetic equivalent mechanism must then be that the reaction cannot readily go forward to products when imidazole attacks as a nucleophile. This could be due to a rapid reclosure of the ring as in eq 5 to regenerate starting material.



The mechanism might therefore change to the normally less favorable general base pathway since the reaction would then go directly to products. This argument assumes that there is no great energy barrier for ring formation. Reversibility was not detected in the imidazole reaction with II at low concentrations of *p*-nitrophenol, but in an intramolecular reaction the effective concentration of the attacking group is greatly increased.[20]

The second-order rate constant for attack of imidazole on bis(4-nitrophenyl) carbonate at 30° is 144 times as large as k_{Im} for the cyclic carbonate at 30°, whereas the rate constant for water catalysis is 4 times as large at 30° for the cyclic ester as that for the noncyclic ester at 50°. Thus, the cyclic compound, while more reactive in the water-catalyzed reaction is much less susceptible to imidazole catalysis, in accord with the fact that a normally less favorable mechanism is involved.

Five- and six-membered ring lactones having a cis configuration are hydrolyzed with hydroxide ion catalysis much more rapidly than are lactones having a trans configuration or noncyclic esters.[21,22] Facile imidazole catalysis was observed in the hydrolysis of the cis lactones, γ-butyrolactone and δ-valerolactone,[23] but imidazole catalysis of the hydrolysis of aliphatic esters without acyl group activation can be detected as occurring at only an extremely slow rate.[24] Thus, the reactive cis configuration is enhancing imidazole catalysis of lactone hydrolysis. In the case of carbonate ester hydrolysis, however, as indicated in the present study, when reversibility of ring opening is likely on steric grounds imidazole catalysis will be less effective for esters in the cis configuration than for analogous noncyclic esters.

Registry No.—I, 25859-54-5; II, 5070-13-3; III, 25859-56-7; *p*-nitrophenyl chloroformate, 7693-46-1.

Acknowledgment.—This work was supported by The National Institutes of Health Research Grant GM-14357.

(20) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 10–13.

(21) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).

(22) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, p 22.

(23) T. C. Bruice and J. J. Bruno, *J. Amer. Chem. Soc.*, **83**, 3493 (1961).

(24) J. F. Kirsch and W. P. Jencks, *ibid.*, **86**, 833, 837 (1964).

Acid-Catalyzed Reactions of Certain δ-Hydroxyamides Having γ Hydrogen. Mechanisms[1a]

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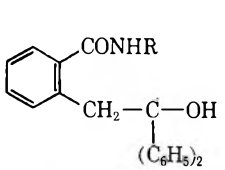
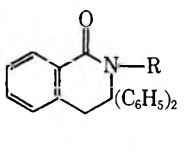
Received October 14, 1969

Certain δ hydroxyamides having γ hydrogen undergo three types of acid-catalyzed reactions; these involve cyclodeamination, linear dehydration, and cyclodehydration to form a δ lactone, an olefin–amide, and a δ lactam, respectively. The predominant course of reaction is dependent on the acidic medium, the temperature, and the structure of the hydroxyamide. The olefin–amide is evidently an intermediate in the conversion of certain hydroxyamides into lactams, but not in that of certain others. Mechanisms are suggested and the usefulness of the methods in synthesis are indicated.

Recently,[2] δ-hydroxyamides such as **1a** were shown to undergo cyclodehydration with cold concentrated sulfuric acid to furnish a useful method of synthesis of corresponding δ lactams, which are substituted 3,4-dihydroisocarbostyrils. Thus, **1a** afforded lactam **2a**. The hydroxyamides **1a** and **1b** are readily prepared by dilithiation of the appropriate N-substituted *o*-toluamide with *n*-butyllithium followed by condensation of the resulting dilithioamide with benzophenone.[3]



1a, R = CH_3
b, R = C_6H_5



2a, R = CH_3

In the present investigation, a study was made of the reactions and mechanisms of hydroxyamides such as **1a** with various acidic reagents. This study promised to be of interest because of the possibility of effecting two new types of acid-catalyzed reactions and of determining the mechanisms of all three types of reactions. Both new types of reaction were realized. Thus, hydroxyamides **1a** and **1b** underwent linear dehydration and cyclodeamination with appropriate acidic reagents to give olefin–amides **3a** and **3b** and lactone **4**, respectively. Also, olefin–amide **3a** under-

(1) (a) Supported by the National Science Foundation. (b) Deceased.

(2) C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 83 (1969).

(3) R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964).

TABLE I

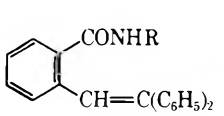
ACID-CATALYZED REACTIONS OF δ-HYDROXYAMIDES 1a AND 1b OR OLEFIN–AMIDES 3a AND 3b

Expt no.	Hydroxyamide or olefin–amide	Acid reagent	Reaction temp, °C	Reaction time, hr	Product	Yield, %
1	1a	HOAc	20–30	240	Lactone 4	[a]
2	1a	HOAc	Reflux	4–12	Lactone 4	80–88
3	1a	HCl–HOAc[b]	20–30	4	Olefin 3a	89
4	1a	HOAc–H_2SO_4[c]	20–30	4	Olefin 3a	63
5	1a	HOAc–H_2SO_4[c]	20–30	1344	3a + 2a	75[d]
6	1a	HOAc–H_2SO_4[c]	Reflux	0.4	Lactam 2a	85
7	1a	BTDA[e]	20–30	4	Olefin 3a	41
					Lactam 2a	16
8	1a	BTDA[e]	Reflux	1	Lactam 2a	62
9	1a	H_2SO_4	0	2	Lactam 2a	54[f]
10	1a	H_2SO_4	20–30	2	Lactam 2a	58
11	3a	HCl–HOAc[b]	Reflux	0.5	Lactam 2a	78
12	3a	HOAc–H_2SO_4[c]	20–30	168	Lactam 2a	[g]
13	3a	HOAc–H_2SO_4[c]	Reflux	0.5	Lactam 2a	96
14	3a	H_2SO_4	0	2	Lactam 2a	75
15	1b	HOAc	Reflux	12	Lactone 4	91
16	1b	HCl–HOAc[b]	20–30	4	Olefin 3b	88
17	1b	HOAc–H_2SO_4[c]	20–30	4	Olefin 3b	73

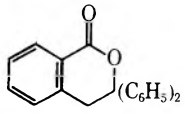
[a] Lactone 4 was obtained mixed with much recovered 1a; the ratio was 15:85 (by nmr). [b] Acetic acid saturated with hydrogen chloride gas. [c] Acetic acid containing a few drops of concentrated sulfuric acid. [d] Ratio of 3a to 2a was 41 to 59 (by nmr). [e] Boron trifluoride–diacetic acid complex. [f] Reference 2. [g] Lactam was obtained mixed with recovered olefin 3a; the ratio of 2a:3a was 57:43 (by nmr).

went acid-catalyzed cyclization to afford δ lactam 2a. The results are summarized in Table I.

Table I shows that hydroxyamide 1a afforded exclusively lactone 4 with acetic acid (expt 1 and 2), but produced the olefin–amide 3a and/or lactam 2a with



3a, R = CH_3
b, R = C_6H_5

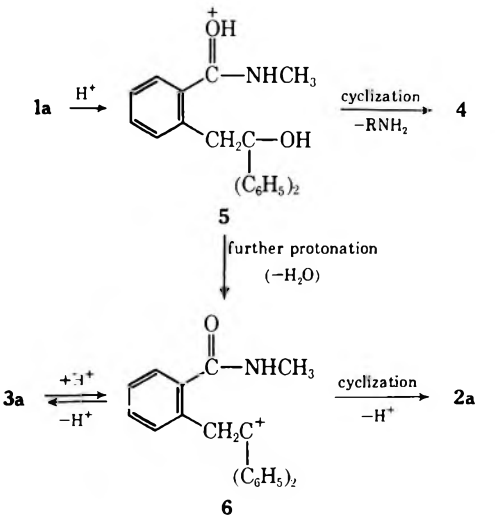


4

the stronger acids, hydrogen chloride gas or a little sulfuric acid in acetic acid (expt 4–6), boron trifluoride–diacetic acid complex (BTDA) (expt 7 and 8), and concentrated sulfuric acid (expt 9 and 10). The effective acid with the hydrogen chloride or sulfuric acid in acetic acid would presumably be $CH_3COOH_2^+$, and that in BTDA might be $CH_3COO \rightarrow BF_3H^+$, $H^+{-}BF_3OCOCH_3$, or BF_3. Consequently, olefin–amide 3a must be an intermediate in the conversion of hydroxyamide 1a into lactam 2a by $CH_3COOH_2^+$ and BTDA; the formation of olefin–amide 3a is evidently kinetically controlled, and that of lactam 2a thermodynamically controlled. Although olefin–amide 3a was not isolated in the reaction with sulfuric acid, it was shown to be converted into lactam 2a by this acid (expt 14); therefore 3a may also be an intermediate when this acid is employed. Insofar as studied, the results obtained with hydroxyamide 1b are similar to those with 1a (see expt 15–17, Table I).

On the basis of these results, the mechanisms represented in Scheme I are suggested. The mechanism of cyclodeamination to form lactone 4 presumably involved protonation of the oxygen at the amide group to form cation 5,[4] which undergoes cyclization accompanied by elimination of methylamine.[5] That the present cyclodeamination is not merely a thermal reaction as observed previously at 180–190°[3] was indicated by almost quantitative recovery of hydroxyamide 1a after refluxing it in *n*-amyl alcohol, which boils 20° higher than acetic acid.

SCHEME I



The mechanisms of the linear dehydration and the cyclodehydration of hydroxyamide 1a presumably involve protonation of the hydroxyl oxygen to form carbonium ion 6 which may be a common intermediate in the formations of olefin–amide 3a and lactam 2a. Thus, carbonium ion 6 may lose a linear proton to produce 3a or undergo cyclization accompanied by loss of the proton on nitrogen to give 2a (see Scheme I).

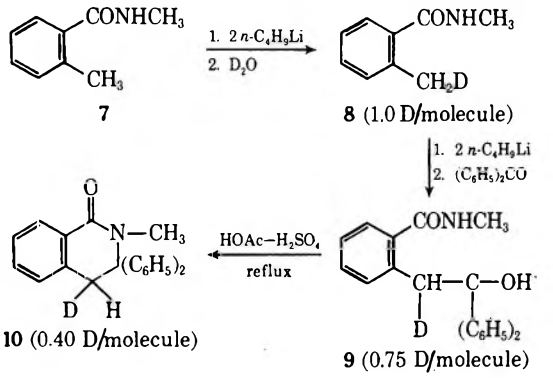
That at least some of lactam 2a arises through olefin–amide 3a was supported by loss of some deuterium on acid-catalyzed cyclodehydration of deuteriohydroxyamide 9. For example, deuteriohydroxyamide 9,

(4) Although protonation at either the amide nitrogen or oxygen should catalyze lactone formation, only the latter protonation is shown in Scheme I; see A. R. Katritzky, and R. A. Y. Jones, *Chem. Ind.*, (London), 722 (1961).

(5) See C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, 6, 475 (1969).

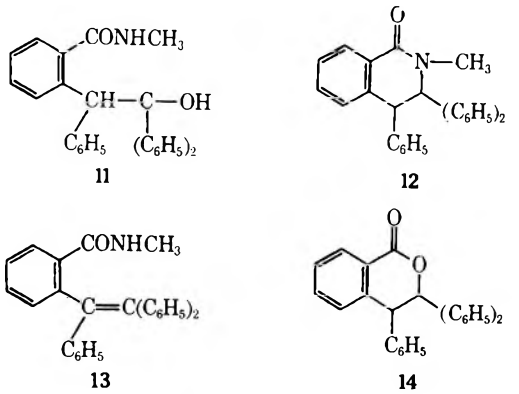
prepared from **7** through **8**, underwent cyclodehydration with a little sulfuric acid in acetic acid (HOAc–H_2SO_4) to form lactam **10**, containing less deuterium (Scheme II). Lactam **10** was shown to retain all of its

SCHEME II



deuterium under such conditions. Similar results were obtained from deuteriohydroxyamide **9** containing 1.0 D/molecule and concentrated sulfuric acid (see Experimental Section).

Similarly, δ-hydroxyamide **11**, which has recently been shown to undergo cyclodehydration with cold sulfuric acid to form lactam **12**,[2] underwent linear dehydration with a little sulfuric acid in acetic acid (HOAc–H_2SO_4) and cyclodeamination with acetic acid to give olefin–amide **13** and lactone **14**, respectively. However, in contrast to olefin–amide **3a**, olefin–amide **13** failed to undergo cyclization with either HOAc–H_2SO_4 or concentrated sulfuric acid. Also, hydroxyamide **11** afforded only olefin–amide **13**, not lactam **12**, with refluxing HOAc–H_2SO_4, which readily produced the lactam from hydroxyamide **1a** (see Table I).

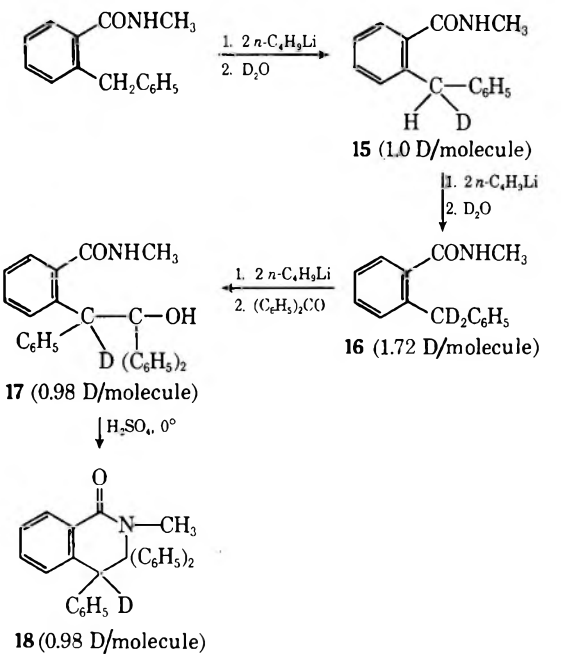


Interestingly, in contrast to deuteriohydroxyamide **9**, deuteriohydroxyamide **17** underwent cyclodehydration with cold concentrated sulfuric acid to form deuteriolactam **18** without loss of deuterium. This result and the preparation of deuteriohydroxyamide **17** through deuteriohydroxyamides **15** and **16** are shown in Scheme III. The reaction of deuteriohydroxyamide **17** with HOAc–H_2SO_4 was not studied since only the olefin–amide would have resulted (see above).

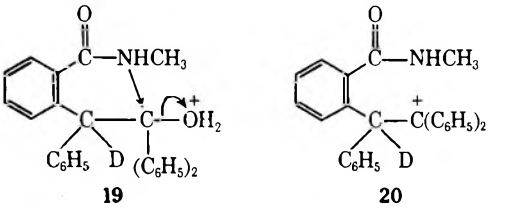
Two explanations for this result seem possible. One would involve the concerted mechanism represented in **19**,[6] and the other the irreversible conversions of

(6) This mechanism was suggested recently in a preliminary report, see C. L. Mao, F. E. Henoch, and C. R. Hauser, *Chem. Commun.*, 1595 (1968).

SCHEME III



carbonium ion **20** to deuteriolactam **18** and olefin–amide **13**.



Incidentally, carbinol **21**, which is related to hydroxyamide **11**, but has no amide group, has been reported to undergo acid-catalyzed linear dehydration by a concerted mechanism to form olefin **22**.[7]

Discussion

The present realization of three different types of acid-catalyzed reactions of a single compound, a δ-hydroxyamide, seems rather remarkable. Although two of the three courses of reaction, those involving linear dehydration and cyclodehydration, are both initiated by protonation of the hydroxyl oxygen leading to formation of a common carbonium ion, **6** and **20**, the subsequent courses of the two reactions are different. Moreover, the linear loss of a proton from carbonium ion **6** is reversible (see Scheme I) whereas that from carbonium ion **20** is apparently not.

The predominant course of reaction observed with a hydroxyamide is dependent on the acidic reagent and temperature employed (see Table I). Although the structure of the hydroxyamide also may be important (compare **1a** and **1b** with **11**), the present results indicate that, at least for hydroxyamides **1a** and **1b** and **11**, the acetic acid method is more convenient than the earlier thermal procedure for cyclodeamination, and

(7) A. Gandini and P. H. Plesch, *J. Chem. Soc.*, 6019 (1965).

that the HOAc–H_2SO_4 reagent is preferable to the previous concentrated sulfuric acid method for cyclodehydration (see Table I). Also, the HOAc–H_2SO_4 or HCl–HOAc reagent is the reagent of choice for linear dehydration. Besides these synthetic methods, those involved in preparations of the deuterio derivatives should be useful.

Experimental Section[8]

The results of acid-catalyzed reactions of δ-hydroxyamides **1a** and **1b**[3] or olefin-amides **3a** and **3b** are summarized in Table I. In each case, the reaction mixture was poured into ice–water and the crude product was removed by filtration and recrystallized from an appropriate solvent. The experimental details are described below.

Cyclodeamination of δ-Hydroxyamides 1a and 1b.—Solutions of 0.5–1.0-g samples of **1a** in 10 ml of acetic acid (HOAc) were refluxed for 4 and 12 hr to give lactone **4**, mp and mmp 145–146° (EtOH–H_2O) (lit.[3] mp 144–144.5°), in yields of 80 and 88%, respectively.

To show that this was not a thermal cyclodeamination,[3] a 1.0-g sample of hydroxyamide **1a** was refluxed in *n*-amyl alcohol for 12 hr. There was recovered 0.95 g (95%) of the original hydroxyamide **1a**.

Similarly, treatment of **1b** (1.0 g) in 15 ml of HOAc gave 0.7 g (91%) of lactone **4**, mmp 144–146°.

Linear Dehydration of δ-Hydroxyamides 1a and 1b. A.—With Hydrogen Chloride in Acetic Acid (HCl–HOAc).—A 0.5-g sample of **1a** in 20 ml of HOAc saturated with dry HCl gas was stirred at room temperature for 4 hr. The yellow solution was worked up to give, after one recrystallization from CH_3CN, 0.42 g (89%) of olefin-amide **3a**: mp 202–204°; ir 3300 (NH) and 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.85 (s, 3, CH_3N) and 7.25 (m, 15, ArH).

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.29; H, 6.05; N, 4.54.

Likewise, treatment of a 1.0-g sample of **1b** with HCl–HOAc at room temperature afforded 0.84 g (88%) of olefin-amide **3b**, mp 151–153°, ir 3310 (NH) and 1635 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{21}NO$: C, 86.37; H, 5.64; N, 3.73. Found: C, 86.17; H, 5.90; N, 3.79.

B. With Acetic Acid Containing Sulfuric Acid (HOAc–H_2SO_4).—A 1.0-g sample of **1a** or **1b** in 20 ml of acetic acid containing a few drops of concentrated sulfuric acid (HOAc–H_2SO_4) was stirred at room tempersture for 4 hr. The yellow solution was worked up as usual to afford 0.6 g (63%) of olefin-amide **3a**, mp 201–203°, or 0.7 g (73%) of olefin-amide **3b**, mp 151–153°, respectively.

C. With Boron Trifluoride–Diacetic Acid Complex (BTDA).—A 2.0-g sample of **1a** was treated with 20 ml of BTDA at room temperature for 4 hr. The amber-colored solution was poured into ice water and the aqueous mixture was neutralized with solid $NaHCO_3$. The crude product was removed by filtration to give 1.5 g of yellowish solid, mp 160–180°. Trituration of the crude product with 20 ml of hot CH_3CN left 0.8 g (41%) of insoluble olefin-amide **3a**, mp 202–204°. The hot CH_3CN solution was cooled in an ice bath to give 0.31 g (16%) of lactam **2a**, mp and mmp 196–198° (lit.[2] mp 196–198°).

Cyclodehydration of δ-Hydroxyamide 1a. A. With HOAc–H_2SO_4.—A 1.0-g sample of **1a** in 20 ml of HOAc–H_2SO_4 was refluxed for 25 min. The crude product was recrystallized from CH_3CN to give 0.81 g (85%) of lactam **2a**.

B. With BTDA.—A 2.0-g sample of **1a** in 20 ml of BTDA was heated at reflux for 1 hr to give 1.2 g (62%) of lactam **2a**, mp 196–198°.

C. With Concentrated Sulfuric Acid (H_2SO_4).—A 1.0-g sample of **1a** was slowly dissolved in 10 ml of H_2SO_4 at room temperature. After 2 hr the orange-red solution was worked up to give 0.52 g (85%) of lactam **2a**, mp and mmp 196–198°.

Similarly, treatment of **1a** with H_2SO_4 at 0° gave lactam **2a** in 52% yield.

Cyclization of Olefin-Amide 3a to Form Lactam 2a. A. With HCl–HOAc.—A 0.5-g sample of **3a** in 20 ml of HCl–HOAc was refluxed for 1 hr to give 0.39 g (78%) of lactam **4a**, mp 196–198° (CH_3CN).

In another experiment, the reaction mixture was refluxed for 30 min to give a mixture of lactam **2a** and the starting olefin-amide **3a** (detected by ir).

B. With HOAc–H_2SO_4.—A 0.3-g sample of olefin-amide **3a** in 10 ml of HOAc–H_2SO_4 was refluxed for 30 min. There was isolated 0.29 g (96%) of lactam **2a**, mp 196–198°.

C. With Concentrated Sulfuric Acid (H_2SO_4).—A 0.2-g sample of **3a** was slowly dissolved in 10 ml of H_2SO_4 at 0° for 2 hr. After recrystallization from CH_3CN, there was obtained 0.15 g (75%) of lactam **2a**, mmp 196–198°.

A similar result was obtained when olefin-amide **3a** was treated with H_2SO_4 at room temperature.

Preparation of Deuterio Derivatives of δ-Hydroxyamides 1a.—To 0.02 mol of dilithioamide, prepared from 0.02 mol of N-methyl-*o*-toluamide and 0.04 mol of *n*-butyllithium in THF–hexane[2] at 0°, was added 3 ml of deuterium oxide. After 20 min of stirring, 100 ml of cold water was added. The layers were separated and the crude product was recrystallized from hexane–benzene to give deuterio compound **8** in 75% yield; the compound contained 1.0 D/molecule by nmr.

To 0.005 mol of deuterioamide **8** in 20 ml of THF at 0°, was added 0.011 mol of *n*-butyllithium in hexane and the mixture was treated, after 30 min, with 0.005 mol of benzophenone in 10 ml of THF. The reaction mixture was worked up to give deuteriocarbinolamide **9** in 60% yield, containing 0.75 D/molecule.

In another experiment, deuterioamide **9**, containing 1.0 D/molecule was obtained by repeated deuteration of amide **7** followed by condensation with benzophenone.

Cyclization of 9 to Form 10. A. With HOAc–H_2SO_4.—A 1.0-g sample of **9** was dissolved in 20 ml of HOAc–H_2SO_4 and the mixture refluxed for 20 min. The orange solution was worked up to afford 0.56 g (60%) of lactam **10**, containing 0.4 D/molecule.

B. With H_2SO_4.—The treatment of 0.5 g of amide **9** (1.0 D/molecule) with 10 ml of H_2SO_4 acid at 0° for 2 hr and at 20–30° for 0.5 hr afforded of lactam **10**, (0.3–0.4 g), which contained 0.77 D/molecule and 0.50 D/molecule.

Linear Dehydration of δ-Hydroxyamide 11.—A 0.4-g sample of amide **11** was stirred with 20 ml of HOAc–H_2SO_4 at room temperature for 5 hr. The yellow mixture was worked up giving 0.3 g of crude product, mp 270–274°. After one recrystallization from CH_3CN–DMF, there was obtained 0.21 g (55%) of pure olefin-amide **13**: mp 274–275°; ir 3320 (NH) and 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.96; N, 3.60. Found: C, 86.25; H, 6.03; N, 3.53.

In another experiment, a 0.5-g sample of amide **11** in 20 ml of HOAc–H_2SO_4 was refluxed for 4 hr. The reaction mixture was worked up to give 0.4 g (83%) of olefin-amide **13**, mmp 273–275°. No lactam **12** was isolated.

Attempted Cyclization of Olefin-Amide 13 to Form Lactam 12. A. With HOAc–H_2SO_4.—A 0.5-g sample of olefin-amide **13** was refluxed with 20 ml of HOAc–H_2SO_4 for 4 hr. The resulting yellow solution was worked up to afford 0.45 g (90%) of the starting olefin-amide **13**, mmp 274–275°. None of the lactam **12** was detected (by nmr).

B. With H_2SO_4.—A 0.5-g sample of olefin-amide **13** was slowly dissolved in 10 ml of H_2SO_4 at 0° during 1 hr. The yellow solution was poured onto ice water and the clear aqueous solution was carefully neutralized with solid $NaHCO_3$. The aqueous solution was then extracted with ether. Evaporation of the ethereal extract gave no residue. Neither the lactam **12** nor the starting olefin-amide **13** was isolated. Apparently, water soluble material was formed.

Preparation of Deuterio Derivatives.—To 0.02 mol of the dilithio derivative of δ-hydroxyamide **11** in THF–hexane was added 3 ml of deuterium oxide. After 20 min of stirring, 100 ml of water was added to it. The layers were separated and the crude product was recrystallized from aqueous ethanol to give deuterio compound **15** in 80% yield. The nmr determination showed that this compound contained 1.0 D/molecule.

A 0.01-mol portion of deuterioamide **15** was again treated with with *n*-butyllithium and followed by deuterium oxide to give

(8) Melting points were taken on Thomas–Hoover capillary melting point apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer Infracord Model 137 or 237 in KBr disks. Nmr spectra were obtained with a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. Analyses were preformed by M-H-W Laboratories, Garden City, Mich. *n*-Butyllithium was obtained from Foote Mineral Company, Exton Pa. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride.

deuterioamide **16** in 75% yield. The nmr spectrum of this compound was shown to consist of 1.72 D/molecule.

To 0.005 mol of deuterioamide **16** in 20 ml of THF at 0° was added 0.011 mol of *n*-butyllithium in hexane and the mixture was treated, after 30 min, with 0.005 mol of benzophenone in 10 ml of THF. The reaction mixture was worked up to give deuteriocarbinolamide **17** in 60% yield. This amide was shown to contain 0.98 D/molecule.

Cyclization of 17 to Form 18.—A sample of deuteriocarbinolamide **17** (1.0 g) was dissolved in 5 g of H_2SO_4 at 0° for 20 min. The reaction mixture was poured onto ice and the solution was made basic with NaOH. The crude product was collected and recrystallized from CH_3CN to give 0.56 g (58%) of **18**, mp 190–192°, containing 0.98 D/molecule (by nmr). A similar result was obtained after repeating the experiment.

Cyclodeamination of γ-Hydroxyamide 11.—As in the case of cyclodeamination of **1a**, a 1.0-g sample of **11** was refluxed with 50 ml of acetic acid overnight (*ca.* 12 hr). The product was worked up and recrystallized from aqueous DMF to give 0.62 g (65%) of 3,3,4-triphenyl-3,4-dihydroisocoumarin (**14**), mp 265–267°, ir 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{20}O_2$: C, 86.14; H, 5.35. Found: C, 85.93; H, 5.17.

Registry No.—**1a**, 2594-59-4; **1b**, 21868-83-7; **2a**, 20141-85-9; **3a**, 24097-53-8; **3b**, 24097-54-9; **13**, 24097-55-0; **14**, 24097-56-1.

Pyrolysis of Alkenylidenecyclopropane and Biscyclopropylidene Systems[1a]

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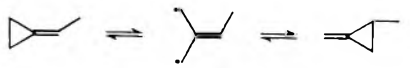
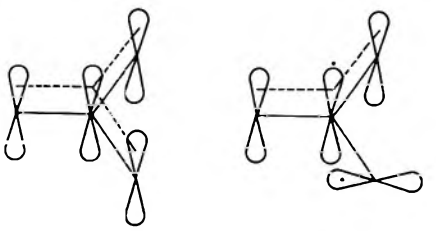
Received March 27, 1970

Pyrolysis of 1-(2-methylpropenylidene)-2,2,3,3-tetramethylcyclopropane (**3**) gives, in good yield, 1,2-(bis-isopropylidene)-3,3-dimethylcyclopropane (**4**). The synthesis of 1,1,2,2,5,5-hexamethylbiscyclopropylidene (**15**) was accomplished by the reaction of **3** with excess methylene iodide/zinc–copper couple. Pyrolysis of **15** at 400° in a flow pyrolysis system produces 1-isopropylidene-2,2,4,4-tetramethylspiropentane (**20**) while at higher temperatures **15** leads to 2,4,5-trimethyl-3-isopropylidenehexa-1,4-diene (**21**) as well as *o*- and *p*-xylene. Pyrolysis of 1-methylene-2-isopropylidene-3,3,4,4-tetramethylcyclobutane (**29**) at 460° leads cleanly to triene **21**. At 620° **4** gives enyne **13** as well as *p*-xylene and toluene. The mechanistic details of these transformations are discussed in terms of diradical intermediates.

The thermal rearrangement of methylenecyclopropanes has been known for a number of years. One of the first examples was the thermolysis of Feist's ester which has been studied by Ettlinger.[2] A number of examples have since been reported which indicate that the rearrangement proceeds *via* a trimethylenemethane diradical.[3] This is illustrated below for a simple case. Gajewski[4] has recently looked at optically active methylenecyclopropanes and concluded that, in substituted



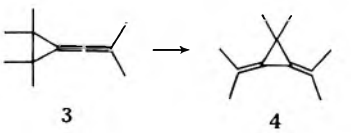
methylenecyclopropanes, the intermediate is not the planar delocalized diradical **1** but rather an orthogonal diradical represented as **2**. Consideration of these



1 **2**

results suggests that a similar rearrangement may obtain in more complicated methylenecyclopropyl systems. This report concerns itself with alkenylidenecyclopropane and biscyclopropylidene thermal chemistry.

A simple entry into the alkenylidenenecyclopropane system can be effected through reaction of allenic[5] or propargylic[6] halides with *tert*-butoxide in the presence of olefins. Synthesis of **3** was achieved in good yield by reaction of 1-bromo-3-methylbuta-1,2-diene with tetramethylethylene. Pyrolysis of **3**, carried out in a flow system at 360° (0.1 mm), results in an almost quantitative conversion to dimethylenecyclopropane **4**. A



3 **4**

similar and more instructive conversion was effected by thermolysis of alkenylidenecyclopropane **5**. Three isomeric hydrocarbons, **6**, **7**, and **8** were produced. The ratio of these products varies with temperature; the **6**:**7**:**8** ratio is 10:2:3 at 360° and 2:3:6 at 410°. Furthermore, pyrolysis of either **6** or **7** at 380° yields a mixture of the three isomeric compounds. On the other hand, **8** is recovered essentially unchanged at this temperature. Raising the temperature to 460°, however, causes partial transformation of **8** to **6** and **7**. The structural assignments of **6**, **7**, and **8** have been discussed previously.[7]

(1) (a) Supported by a research grant from the National Science Foundation. (b) Public Health Service Predoctoral Fellow, 1966–1968. (c) Author to whom correspondence should be addressed. Alfred P. Sloan Research Fellow, 1968–1970. (d) Indiana University Foundation and National Science Foundation Undergraduate Research Participant, 1968–1969.

(2) M. G. Ettlinger, *J. Amer. Chem. Soc.*, **74**, 5805 (1952).

(3) J. P. Chesick, *ibid.*, **85**, 2720 (1963); E. F. Ullman, *ibid.*, **81**, 5386 (1959); **82**, 505 (1960); E. F. Ullman and W. J. Fanshawe, *ibid.*, **83**, 2379 (1961); T. C. Shields, B. A. Shoulders, J. F. Krause, D. L. Osborn, and P. D. Gardner, *ibid.*, **87**, 3026 (1965); H. M. Frey, *Trans. Faraday Soc.*, **57**, 951 (1961).

(4) J. J. Gajewski, *J. Amer. Chem. Soc.*, **90**, 7178 (1968).

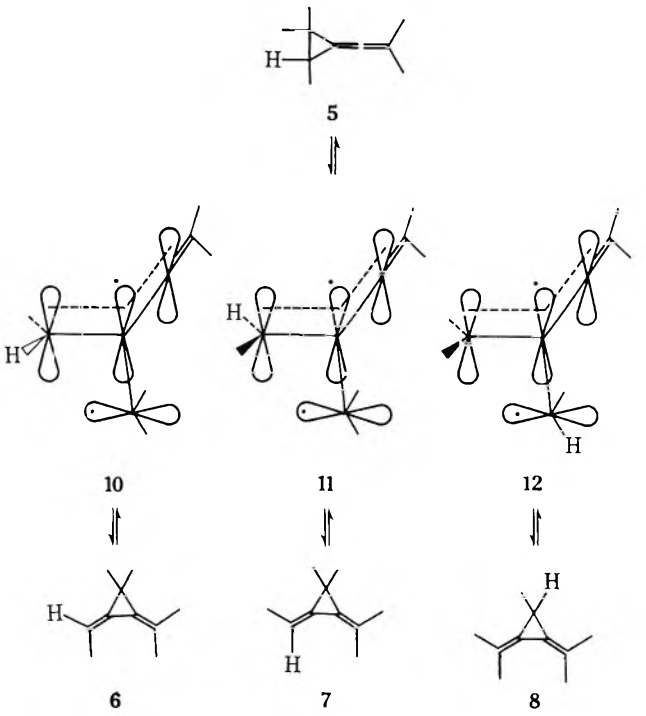
(5) S. R. Landor, A. N. Patel, P. F. Whiter, and P. M. Greaves, *J. Chem. Soc. C*, 1223 (1966); S. R. Landor and P. F. Whiter, *J. Chem. Soc.*, 5625 (1965).

(6) H. D. Hartzler, *J. Amer. Chem. Soc.*, **83**, 4990 (1961).

(7) J. K. Crandall and D. R. Paulson, *ibid.*, **88**, 4302 (1966).

The mechanistic details of these thermal interconversions are very likely analogous to methylenecyclopropanes themselves. A similar set of orthogonal diradicals[4] can be invoked to describe this reaction. These intermediates differ from the parent system in that one of the peripheral carbon atoms is sp hybridized.[8] Scheme I depicts a rational scheme in terms

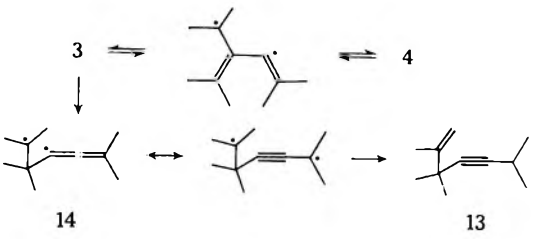
SCHEME I



of these intermediates. A number of orthogonal trimethylenemethane intermediates are possible. However, **10**, **11**, and **12** are the only ones which do not contain an unfavorable localized vinyl radical. If the rate constants for formation of products from **10**, **11**, and **12** are assumed to be nearly identical, then the kinetic preference for formation of **6** can be explained by a destabilizing half-filled *p*-orbital–methyl interaction.[4] This interaction would result in **10** being more stable than **11** or **12** and as a result the favored intermediate from **5**. At higher temperatures interconversion among the biradical intermediates and the dimethylenecyclopropanes becomes more facile and the product distribution approaches the thermodynamic equilibrium value. Each of the products can in theory be reconverted to the biradical intermediates by the reversal of its formative process and thus be repartitioned among the original three products. Compounds **6** and **7** undergo this redistribution easily but more drastic conditions are required for **8**. This is easily explained since **8** with a single stabilizing methyl on the saturated center requires a greater activation energy for bond homolysis than either **6** or **7** which give tertiary radicals at this sight.

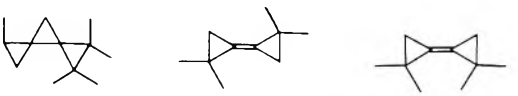
Pyrolysis of dimethylenecyclopropane **4** (or its precursor **3**) at 520° gives a mixture of **4** (39%) and enyne **13** (48%). The structure of **13** was clearly defined by its spectroscopic properties: the infrared spectrum of **13** shows a terminal double bond (6.08 and 11.1 μ), while the ultraviolet spectrum is characteristic of a nonconjugated acetylene.[9] This transformation is visualized in Scheme II. The formation of enyne **13**

SCHEME II



appears to require funneling through a small equilibrium concentration of **3** to diradical **14**. A 1,6 hydrogen transfer mechanism then leads directly to **13**.[10]

A second type of methylenecyclopropane, in which the double bond is exocyclic to two cyclopropyl rings (*i.e.*, a biscyclopropylidene) can be envisioned to undergo a simple methylenecyclopropane rearrangement to produce a methylenespiropentane. This type of rearrangement has been realized in the case of **15**. A surprisingly simple and convenient synthesis of **15** was effected by treatment of alkenylidenecyclopropane **3** with a large excess of the Simmons–Smith reagent.[11] This reaction produced predominantly biscyclopropylidene **15** in good yield. Under different experimental conditions it was possible to isolate the other monoadduct **16** and the diadduct **17**. An alternate



synthesis was realized using the diethyl zinc–methylene iodide[12] modification of the Simmons–Smith to give **15** exclusively in 40% yield. Biscyclopropylidene **15** displays spectral data consistent with the assigned structure and similar to model compounds **18** and **19**.[13] Predominate formation of **15** over **16** can be predicted on the basis of both steric and electronic factors.[14]

Pyrolysis of **15** in a flow system at 400° (0.1 mm) proceeds smoothly to give starting material (4%), methylenespiropentane **20** (87%), and its structural isomer **16** (9%). The ir spectrum of **20** shows a weak methylenecyclopropane band[15] at 5.55 μ and its nmr displays a two-proton AB quartet[16] centered at τ 9.38 ($\Delta\nu$ = 10.3 Hz, J = 4.0 Hz), four methyls on saturated carbon and two olefinic methyls. An independent

(8) This argument makes the reasonable assumption that the destablizing interaction of a methyl group and a p orbital would be greater for a half-filled p orbital than for a p orbital involved in double bond formation.

(9) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, pp 54–55.

(10) Although not usually a favored process, a similar 1,6 hydrogen shift has apparently been detected: R. F. Bleiholder, *Diss. Abstr. B*, **27**, 1080 (1966).

(11) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(12) J. Furulsowa, N. Kawabata, and J. Nishimura, *Tetrahedron Lett.*, 3353 (1966); *Tetrahedron*, **24**, 53 (1968).

(13) B. du Laurens. A. Bezaguet, G. Davidovics, M. Bertrand, and J. Chouteau, *Bull. Chim. Soc. Fr.*, 799 (1967).

(14) J. K. Crandall, D. R. Paulson, and C. A. Bunnell, *Tetrahedron Lett.*, 5063 (1968).

(15) W. Rahman and H. G. Kuivilla, *J. Org. Chem.*, **31**, 722 (1966).

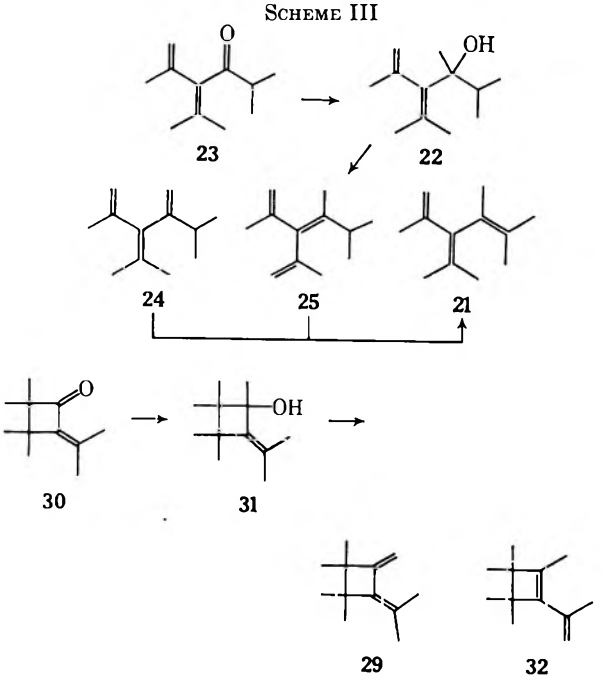
(16) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 102.

synthesis of **20** was realized by treatment of dimethylenecyclopropane **4** with Simmons–Smith reagent.[11]

Thermolysis of methylenespiropentane **20** under the above conditions did not result in reversal to **15**, but at higher temperature (510°) this material was connected to a mixture of 37% **20**, 31% triene **21**, and quite unexpectedly *p*-xylene (13%) and *o*-xylene (5%). Even more surprising was the extent of xylene formation at higher temperatures; for instance, at 610° the *p*- and *o*-xylene were isolated in 50 and 33%, respectively. Pyrolysis of isomer **16** gave similar results. At 520° triene **21** and *p*-xylene were obtained in the ratio of 7:1 while at 610° a mixture of triene **21**, *p*-xylene, and *o*-xylene were formed in the ratio of 1:21:14.

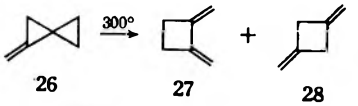
The structure of triene **21** was readily verified by its straightforward synthesis as shown in Scheme III.

SCHEME III



Alcohol **22** was obtained in 87% by methyllithium addition to ketone **23**.[17] Dehydration of **22** in sulfuric acid–acetic acid gave a mixture of 25% **24**, 51% **25**, and 24% of the desired triene **21**. Pyrolysis of this mixture of triene at 490° cleanly transformed **24** and **25** into the more stable isomer **21**. These transformations are readily interpreted in terms of 1,5 hydrogen shifts.

While this work was in progress, Dolbier reported on the thermolysis of the parent methylenespiropentane **26**.[18] At temperatures above 300° compound **26** isomerizes to a 7:1 mixture of **27** and **28**. This observa-

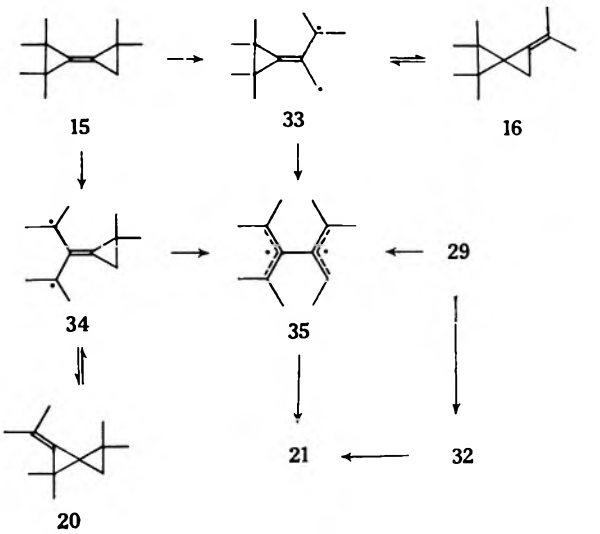


tion prompted an investigation of the thermolysis of the analogous 1,2-dimethylenecyclobutane **29** which would be expected in the present system. Its synthesis is also outlined in Scheme III. Treatment of ketone **30**[17] with methyllithium gave alcohol **31** in almost quantitative yield. Dehydration of **31** in phosphorus oxychloride–pyridine produced a mixture of **29** (52%) and **32** (48%). A convenient isolation of **29** from this mixture was effected by pyrolysis of the reaction product at 360° which gives 52% **21**, 2% **32**, and 46% unchanged **29**. This procedure proved convenient since a mixture of triene **21** and diene **29** can easily be separated by preparative glpc while the same is not true of the original mixture. The pyrolytic conversion of **32** to **21** is readily interpreted as a simple cyclobutene to butadiene thermal isomerization. Kiefer and Tanna[19] have recently studied several very similar pyrolytic conversions.

Pyrolysis of diene **29** at 460° afforded 72% triene **21**, 4% starting material, and a number of minor products. This experiment clearly demonstrates why diene **29** is absent from the thermolysis products of **15**, **16**, or **20**, since this material would not have accumulated in the 460° pyrolysate even if it were an important product. At 460° very little, if any, isomerization of **20** occurs.

A reasonable mechanism for the thermal rearrangements of **15**, **16**, and **20** is shown in Scheme IV. Doe-

SCHEME IV



ring and Gilbert[20] have summarized strong evidence that the thermal rearrangement of spiropentane systems involve diradical intermediates rather than concerted processes. The rearrangements undergone by **15**, **16**, and **20** are also best described in terms of such diradical intermediates. The biscyclopropylidene **15** is converted to isomers **16** and **20** *via* the respective trimethylenemethane intermediates **33** and **34**. Pyrolysis of **16** or **20** does not result in any back reaction to form **15** in agreement with the predicted lower thermal stability of **15**. The preference for products derived from **34** rather than **33** is a reflection of the stabilization of alkyl groups on the radical centers and relief of nonbonded interaction in the transition state leading to **34**. There is no evidence for appreciable interconversion of **15** and **16** in support of this kinetic argument. At more elevated temperatures the cyclopropyl ring in the reversibly formed intermediates **33** and **34** is cleaved leading to the interesting bisallyl diradical **35**. This process is postulated to involve collapse of the cyclopropyl radical moiety of the trimethylenemethane in-

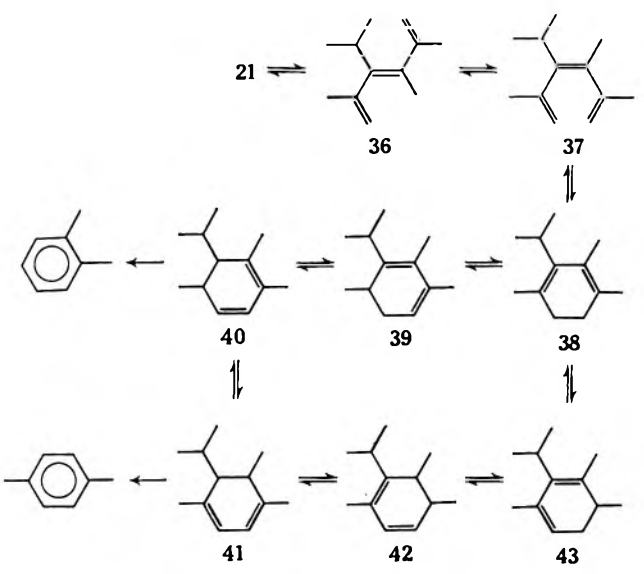
(17) J. K. Crandall and D. R. Paulson, *J. Org. Chem.*, **33**, 991 (1968).
(18) W. R. Dolbier, Jr., *Tetrahedron Lett.*, 393 (1968).
(19) E. F. Kiefer and C. H. Tanna, *J. Amer. Chem. Soc.*, **91**, 4478 (1969).
(20) W. E. Doering and J. C. Gilbert, *Tetrahedron, Suppl.*, **7**, 397 (1966).

termediates **33** and **34**. Cyclopropyl radicals are known to rearrange thermally to allylic radicals with an activation energy of less than 18 kcal/mol,[21] although they appear to maintain their structural integrity at lower temperatures.[22] The presence of an appreciable energy barrier for the cyclopropyl radical to allyl radical interconversion is also apparent in the present rearrangement. Other modes of bond breakage in **15**, **16**, or **20** would lead to intermediates of much higher energy and, in addition, not provide a straightforward pathway to triene **21**. Diradical **35** leads readily to triene **21** by disproportionation through a favorable six-center hydrogen transfer. Gajewski[23] has recently observed similar 1,5 hydrogen transfers *via* bisallyl biradicals.

At least two paths can be recognized for the conversion of dimethylenecyclobutane **29** into triene **21**. The first of these is initiated by homolytic cleavage of **29** to bisallyl diradical **35**, an intermediate in the main sequence described above. The second pathway proceeds *via* a concerted 1,5 hydrogen shift to yield cyclobutene **32** followed by the experimentally demonstrated isomerization of **32** to **21**.

One of the most interesting problems connected with this study involves the mode of formation of *o*- and *p*-xylene. Since pyrolysis of triene **21** at 580° gives 50% *p*-xylene and 30% *o*-xylene, it is likely that **21** is an intermediate in the formation of the xylenes from **15**, **16**, and **20**. A plausible mechanism for these novel transformations is shown in Scheme V. Concerted

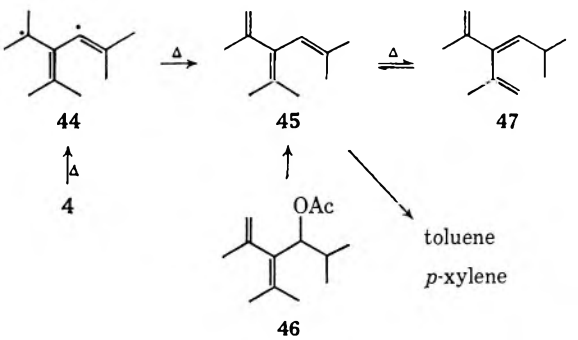
SCHEME V



1,5 hydrogen shifts interconvert the trienes **21** and **36**. This general type of rearrangement has been carefully studied by several groups.[24] The well-precedented cyclization pictured for triene **37** can take place only from the cis olefin.[25] Presumably trans olefin **36** provides this configuration by thermal isomerization. The cyclohexadienes **38** through **43** are also proposed to equilibrate by 1,5 hydrogen shifts. Similar hydrogen transfers have been observed before in cyclohexadienes.[25] Loss of the elements of butane from the key intermediates **40** and **41** would lead to *o*-xylene and *p*-xylene directly. There are several reports concerning the loss of the elements of hydrogen or low-molecular-weight hydrocarbons to form aromatic products during the pyrolysis of cyclohexadienes.[26] It was originally suspected that an intact molecule of isobutane might be formed in this elimination. However, the major gaseous hydrocarbons from the pyrolysis of triene **21** at 620° were propylene and ethylene. The exact process by which the elements of butane are lost appears to be a rather complex one, and is probably free radical in nature.

A similar series of transformations occurs when dimethylenecyclopropane **4** is pyrolyzed at high temperature. At 620° compound **4** gives 50% enyne **13**, 30% *p*-xylene 8% toluene along with at least six unidentified minor products. It was independently shown that enyne **13** is not an intermediate in the formation of the aromatic compounds. A mechanism analogous to that shown in Scheme V is proposed. Trimethylenemethane diradical **44** undergoes 1,4 hydrogen abstraction[27] to form triene **45** which yields the aromatic hydrocarbons by a process similar to that elaborated in Scheme V for triene **21**. Pyrolysis transformation of an authentic sample of triene **45** to the observed aromatics demonstrates the viability of this proposal.

Triene **45** was prepared by hydride reduction of ketone **23** followed by acylation to give acetate **46**. Pyrolysis of **46** in a flow system at 420° gave a 1:1 mixture of trienes **45** and **47**; at 460° the ratio was 3:1. The presence of both **45** and **47** in the pyrolysis of acetate **46** is accounted for by equilibration of acetate **46** and its allylic isomer prior to elimination of acetic acid[28] and/or by thermal interconversion of **45** and **47** by 1,5 hydrogen migration.



Experimental Section

General.—Infrared spectra (ir) were obtained with Perkin-Elmer Model 137 and 137G infrared spectrophotometers in carbon tetrachloride solution unless otherwise specified. Nuclear magnetic resonance (nmr) spectra were obtained with Varian

(21) A. S. Gordon, *Pure Appl. Chem.*, **5**, 441 (1962).
(22) D. I. Schuster and J. D. Roberts, *J. Org. Chem.*, **27**, 51 (1963).
(23) J. J. Gajewski and C. N. Shih, *J. Amer. Chem. Soc.*, **91**, 5900 (1969).
(24) J. Wolinski, B. Chollar, and M. D. Baird, *ibid.*, *Soc.*, **84**, 2775 (1962); H. M. Frey and R. J. Ellis, *J. Chem. Soc.*, 4770 (1965).
(25) E. N. Morrell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965).
(26) H. Pines and R. H. Kozlowski, *J. Amer. Chem. Soc.*, **78**, 3776 (1956); H. Pines and C. T. Chen, *ibid.*, **81**, 928 (1959); G. Dupont and R. Dulou, *Bull. Chim. Soc. Fr.*, C-29 (1951).
(27) At least one example of a 1,4 hydrogen migration to a vinyl radical has been documented: J. A. G. Dominguez and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 940 (1962); S. W. Benson and W. B. DeMore, *Ann. Rev. Phys. Chem.*, **16**, 397 (1965).
(28) W. J. Bailey and R. Barclay, Jr., *J. Org. Chem.*, **21**, 328 (1956).

A-60 and HR-100 spectrometers in carbon tetrachloride solution. Ultraviolet spectra (uv) were recorded on a Cary 14 spectrophotometer. Raman spectra were taken on a Cary 81 spectrophotometer. Mass spectra were obtained with an AEI MS-9 mass spectrometer at 70 eV. Gas chromatography (glpc) was performed on Aerograph Model 600 and Model 1200 chromatographs. The analytical column was 10 ft × 1/8 in. 15% Carbowax 20M on 60–80 Chromosorb W; preparative columns were 10 ft × 3/8 in. or 20 ft × 3/8 in. 30% Carbowax 20 Mon 60–80 Chromosorb W or 10 ft × 3/8 in. 30% Ucon polar 2000 on 60–80 Chromosorb W. Percentage composition data were estimated by peak areas.

1-(2-Methylpropenylidene)-2,2,3,3-tetramethylcyclopropane (3). A.—A mixture of 30 g of tetramethylethylene and 10 g of potassium *tert*-butoxide was stirred under a nitrogen atmosphere for 10 min, after which 11.7 g of freshly distilled 1-bromo-3-methyl-1,2-butadiene was added over a 30-min period. The mixture was stirred at room temperature for 3 hr and 100 ml of pentane was added. The reaction mixture was suction filtered through a sintered-glass Büchner funnel containing Hyflow-Supercel filter aid. The pentane was distilled from the reaction mixture and the residue was eluted with hexane through a short column of Florisil. Removal of the hexane by flash evaporation gave 7.0 g (60%) of **3**. A recrystallized sample has mp 48–48.5°, (lit.[6] mp 48.6–49.3°).

B.—Using the procedure of Hartzler,[6] yields of **3** on the order of 25–30% were obtained.

1,2-Bis(isopropylidene)-3,3-dimethylcyclopropane (4).—A 137-mg sample of **3** was pyrolyzed at 360° and 0.25 mm. The pyrolysis was carried out on a vacuum pyrolysis system consisting of a glass-helices packed Pyrex column, 10 mm × 130 mm, passing through an E. H. Sargent and Co. tube furnace. The sample was placed in a 5-ml flask attached at one end of the tube and a Dry Ice trap, 20 mm × 150 mm, was attached to the other end of the tube. Vacuum was applied at the trap and the pyrolysis product collected in the trap. The pyrolysis gave 131 mg (96%) of 1,2-bis(isopropylidene)-3,3-dimethylcyclopropane (**4**). The spectral properties of this product agree in detail with those reported by Schecter.[29]

1-(2-Methylpropenylidene)-2,2,3-trimethylcyclopropane (5).—Using the procedure of Hartzler,[6] 23.2 g of potassium *tert*-butoxide, 60 g of 2-methyl-2-butene and 18.5 g of 3-chloro-3-methylbutyne gave 5.5 g (24%) of **5**.

Pyrolysis of 5.—A 1.0-g sample of **5** was pyrolyzed on the vacuum pyrolysis system at 360° to give 0.90 g of crude product. Glpc analysis showed 26% **5** and three products as 11, 48, and 15% of the reaction product. The 11% product was identified as *anti*-1-ethylidene-2-isopropylidene-3,3-dimethylcyclopropane (**7**): ir 5.56 and 6.03 μ; nmr τ 8.76 (s, 6), 8.2 (m, 9), and 4.42 (quartet, 1, J = 7.0 Hz); uv max (hexane) 244 mμ (ε 18,700) and 254 mμ (15,700); mass spectrum with a strong molecular ion at m/e 136.

The 48% product was shown to be *syn*-1-ethylidene-2-isopropylidene-3,3-dimethylcyclopropane (**6**): ir 5.56 and 6.06 μ; nmr τ 8.84 (s, 6), singlets at 8.19 and 8.09 overlapping a doublet in the same region (9 protons total), 4.60 (quartet, 1, J = 7.0 Hz); uv max (hexane) 245 mμ (ε 20,000) and 253 (17,500); mass spectrum with a strong molecular ion at m/e 136.

The 15% product was identified as 1,2-bisisopropylidene-3-methylcyclopropane (**8**): ir 5.53 and 6.05 μ; nmr τ 8.89 (distorted doublet, 3, J = ~6 Hz) and 8.1 (m, 13); uv max (hexane) 251 mμ (ε 19,700) and 262 (18,560); mass spectrum with a strong molecular ion at m/e 136.123 (Calcd for $C_{10}H_{16}$: 136.125).

Pyrolysis of a 1.0-g sample of **33** at 410° on the vacuum pyrolysis system gave 0.95 g of crude product. Glpc analysis showed **7**, **6**, and **8** in the ratio of 2:3:6.

Pyrolysis of 7, 6, and 8.—A 5 mg sample of **7** was pyrolyzed on the vacuum pyrolysis system at 380°. Glpc analysis of the crude product showed **7**, **6**, and **8** in the ratio of 5:2:1. Using the same procedure on 5 mg of **6** gave **7**, **6**, and **8** in the ratio of 2:2:1. Compound **8** remained essentially unchanged by these conditions. However at 460° **8** gives **7**, **6**, and **8** in the ratio of 3:2:5.

High Temperature Pyrolysis of 3 and 4.—The following products (Table I) were obtained from pyrolysis of **3** and **4** on the vacuum pyrolysis system at 0.25 mm. The products were purified by preparative glpc.

TABLE I

Reactant (mg)	Temp, °C	4, %	13, %	a	b	c	Yield, mg
3 (320)	500	63	33			1	290
3 (440)	560	39	48			4	310
3 (490)	600	3	51	17	5	5	390
3 (312)	620		50	30	8	6	280
4 (70)	520	48	47			3	62

[a] % of *p*-xylene. [b] % of toluene. [c] Number of other products.

Pyrolysis of 13 at 620°.—A 40-mg sample of **13** was pyrolyzed on the vacuum pyrolysis system at 620° and 0.20 mm. Glpc and nmr analysis of the crude product showed **13** as 50% of the sample along with a large number of products. None of these minor products account for more than 5% of the mixture.

Pyrolysis of 45.—A 5-mg sample of **45** was pyrolyzed on the vacuum pyrolysis system at 620° and 0.20 mm. Glpc analysis of the crude product showed 66% *p*-xylene and 12% toluene. A 0.12-g sample of 65% **47** and 35% **45** was pyrolyzed under the same condition to give 0.08 g of crude product. Glpc analysis showed 65% *p*-xylene and 15% toluene. No other product accounted for more than about 2% of the crude product. The presence of *p*-xyelne and toluene was clearly demonstrated by nmr and ir spectral data.

2,5-Dimethyl-3-isopropylidene-4-acetoxyhex-1-ene (46).—A solution of 25 ml of pyridine, 1.35 g of acetic anhydride, and 0.92 g of 2,5-dimethyl-4-isopropylidenehex-5-en-3-ol was heated at 85° for 12 hr and cooled to room temperature, and three drops of water were added. The resulting mixture was stirred for 15 min, poured into 100 ml of water, and extracted with four 50-ml portions of pentane. The combined pentane extracts were washed with 5% hydrochloric acid solution and dried. Removal of the solvent gave 0.98 g of crude product. Glpc analysis showed the sample to be 87% **46**: ir 5.78 (OAc), 6.14 (C=C), 8.91, 9.8, and 11.1 μ (C=CH_2, strong); 100 MHz nmr τ 9.10 (d, 3, J = 8.0 Hz), 9.16 (d, 3, J = 8.0 Hz), 8.31 (s, 3), 8.21 (s, 3), 8.19 (s, 3), 8.02 (s, 3), 5.45 (m, 1), 4.97 (m, 1), and 4.66 (d, 1, J = 10.0 Hz).

Pyrolysis of 46.—A 218-mg sample of **46** was pyrolyzed on the vacuum pyrolysis system at 420° and 0.25 mm. The crude product was dissolved in 25 ml of pentane, washed with 10 ml of saturated sodium bicarbonate solution, and dried. Removal of the pentane by flash evaporation gave 162 mg of crude product. Glpc analysis showed two major products as 50 and 47% of the volatile reaction product. Preparative glpc collection showed the 50% product to be 2,5-dimethyl-3-isopropenylhexa-1,3-diene (**47**): ir 6.1 (C=C), 6.2 (C=C), 7.3, 10.4, and 11.2 μ (C=CH_2, strong); 100 MHz nmr τ 9.04 (d, 6, J = 7.0 Hz), 8.19 (m, 3), 8.13 (m, 3), 7.4 (m, 1), 5.34 (m, 1), 5.12 (m, 1), 5.07 (m, 1), and 4.82 (m, 1); uv max (hexane) 233 mμ (ε 20,000); mass spectrum with a molecular ion at m/e 150.1410 (Calcd for $C_{11}H_{18}$: 150.1408).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.52; H, 11.85.

The 47% product was shown to be 2,5-dimethyl-3-isopropylidenehexa-1,4-diene (**45**): ir 6.2 (C=C), 7.3, and 11.2 μ (C=CH_2); 100 MHz nmr τ 8.45 (s, 3), 8.41 (s, 3), 8.25 (m, 9), 5.40 (m, 1), 5.13 (m, 1), and 4.45 (m, 1), uv max (hexane) 220 mμ (ε 9600).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.92; H, 12.00.

1,1,2,2,5,5-Hexamethylbiscyclopropylidene (15).—To predried flask was added 100 ml of anhydrous ether, 72.3 g of methylene iodide, 17.55 g of zinc–copper couple, and a crystal of iodine. The ethereal solution was heated to reflux until the iodine color disappeared and 2.76 g of 1-(2-methylpropenylidene)-2,2,3,3-tetramethylcyclopropane (**3**) in 50 ml of ether was added dropwise. After 12 hr of reflux, the mixture was filtered and washed with two 50-ml portions of saturated ammonium chloride solution, three 50-ml portions of saturated sodium bicarbonate solution, and three 50-ml portions of saturated sodium chloride solution. The ether was removed by flash evaporation and the product (insoluble in methylene iodide) was purified by trap to trap distillation at 25° and 0.3 mm to give 2.2 g (75%) of 1,1,2,2,5,5-hexamethylbiscyclopropylidene (**15**): ir 7.3, 8.9, 9.4, and 10.5 μ; 100 MHz nmr τ 9.08 (s, 2), 8.87 (s, 6), 8.86 (s, 6), and 8.84 (s, 6).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.60; H, 12.19.

(29) R. F. Bleiholder and H. Shechter, *J. Amer. Chem. Soc.*, **86**, 5032 (1964).

Under conditions of longer reaction time, more concentrated solutions and larger excesses of the Simmons–Smith reagent, crude yields ranging from 70–90% were obtained. Glpc analysis showed three major products formed in nonreproducible ratios ranging 6–12:2–24:1. The products were separated by column chromatography from a silver nitrate–silica gel column prepared from 160 g of silica gel and 21 g of silver nitrate. The products were further purified by preparative glpc.

The first product was identified as **15**. The second product was identified as 1,1,2,2,5,5-hexamethyldispiro[2.0.2.1]heptane (**17**): ir (neat) 7.3, 8.9, 9.0, and 9.1 μ; 60 MHz nmr τ 9.50 (m, 2), 9.32 (m, 2), 9.01 (s, 3), 8.96 (s, 6), 8.93 (s, 6), and 8.86 (s, 3).

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.54; H, 12.41.

The third product was identified as 1-isopropylidene-4,4,5,5-tetramethylspiro[2.2]pentane (**16**): ir 7.3, 8.2, 9.0, 9.2, 9.7, 10.4, and 11.0 μ; 60 MHz nmr τ 9.15 (m, 2), 8.91 (s, 6), 8.85 (s, 6), and 8.21 (m, 6). Mass spectral analysis of the molecular ion gave *m/e* 164.1572 (Calcd for $C_{12}H_{20}$: 164.1565).

Reaction of Diethylzinc with 3.—To a predried flask was added 8 g (54 mmol) of **3** and 150 ml of anhydrous ether. The ethereal solution and a sample of diethylzinc, prepared by Noller's method,[30] were degassed, and 12.5 ml (120 mmol) of diethylzinc was vacuum transferred to the reaction flask at 0.01 mm and −180°. The system was flushed with nitrogen and the reaction flask was transferred to an oil bath. Care was taken to keep oxygen and water from the reaction mixture. As a solution of 2.8 g ether was added dropwise, the reaction mixture was refluxed under a nitrogen atmosphere. The solution was refluxed for 18 hr, cooled, and 100 ml of saturated ammonium chloride was very cautiously added. The ether layer was separated, washed with a 100-ml portion of saturated sodium bicarbonate solution, two 100-ml portions of saturated sodium chloride solution, and dried. The solvent was removed by flash evaporation and the residue vacuum distilled at 0.25 mm and 25°. A crude yield of 4.42 g was obtained. Glpc analysis showed **15** to be the exclusive product. Spectral data confirmed the results.

Pyrolysis of 15.—A 335-mg sample of **15** was pyrolyzed in the flow system at 0.25 mm and 400°. Glpc analysis showd **15** (4%), **20** (87%), and **16** (9%). Compounds **20** and **16** were purified by preparative glpc and identified by spectral data.

Pyrolysis of 16.—A 10-μl sample of **16** was pyrolyzed in the flow system at 520° and 0.25 mm. Glpc retention time comparison on a 250 ft × 1/100 in. UCON polar capillary column showed that **21** and *p*-xylene were obtained in the ratio 6.5:1.

A 10-μl sample of **16** was pyrolysed in the flow system through a quartz-chip packed quartz tube at 610° and 0.25 mm. Glpc retention time comparison on the capillary column showed **21** and *p*- and *o*-xylene in the ratio 1:21:14.

1-Isopropylidene-2,2,4,4-tetramethylspiro[2.2]pentane (20).—To a predried flask was added 150 ml of ether, 27.0 g of methylene iodide, 6.6 g of zinc–copper couple, and a crystal of iodine. The resulting mixture was stirred under reflux until the iodine color disappeared and 0.5 g of 1,2-bisisopropylidene-3,3-dimethylcyclopropane (**4**) in 25 ml of ether was added dropwise. After 5 days of reflux the reaction mixture was cooled and filtered, and the solid residue washed well with ether. The combined ethereal portions were washed with two 100-ml portions of saturated ammonium chloride solution, two 100-ml portions of saturated sodium bicarbonate solution, 100 ml of saturated sodium chloride solution, and dried. The ether was removed by distillation through a 6-in. glass helices packed column to give 0.52 g of crude product. Glpc analysis of the crude product showed 50% of **4** and 50% of 1-isopropylidene-2,2,4,4-tetramethylspiro[2.2]-pentane (**20**): ir 5.55 (very weak), 7.15, 7.35, 9.0, 9.2, 9.5, 9.9, and 10.5 μ; 100 MHz nmr AB pattern centered at τ 9.38 (2, $\Delta\nu$ = 10.3 Hz, J = 4.0 Hz), 9.01 (s, 3), 8.95 (s, 3), 8.93 (s, 3), 8.91 (s, 3), 8.44 (s, 3), and 8.34 (s, 3).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.55; H, 12.34.

2,3,5-Trimethyl-4-isopropylidenehex-5-en-3-ol (22).—To a predried flask containing a solution of methyl lithium (prepared from 0.14 g of lithium wire and 1.42 g of methyl iodide in 20 ml of ether) under a nitrogen atmosphere was added dropwise a solution of 0.40 g of 2,5-dimethyl-4-isopropylidenehex-5-en-3-one (**23**) in 20 ml of ether. After stirring at room temperature for 2 hr, 10 ml of water was added dropwise with cooling, the resulting mixture was poured into 50 ml of water and extracted with three 50-ml portions of ether. The combined ethereal fractions were dried and the ether removed on the flash evaporator to give 0.40 g of crude product. Glpc analysis showed the sample to be 87% **22** and 13% **23**. Glpc collection gave pure **22**: ir 2.77 (OH), 3.23 (=CH), 6.0 (C=C), 6.1 (C=C), 10.8, and 11.5 μ (C=CH_2); 100 MHz nmr τ 9.10 (m, 6), 8.68 (d, 3), 8.34 (m, 3), 8.22 (s, 3), 8.16 (m, 3), 7.82 (m, 1), 5.42 (m, 1), and 5.00 (m, 1).

Dehydration of 22.—A 0.22-g sample of **22** was dissolved in 25 ml of glacial acetic acid containing 8 drops of concentrated sulfuric acid. After stirring for 30 min, the reaction was poured into 100 ml of water and extracted with five 50-ml portions of pentane. The combined pentane extracts were washed with 50 ml of saturated sodium bicarbonate solution and dried, and the pentane removed by flash evaporation to give 0.19 g of crude product. Glpc analysis showed three major products as 25, 51 and 24% of the reaction product.

The 25% product was identified as 2,5-dimethyl-3-isopropylidene-4-methylenehex-1-ene (**24**): ir 3.2 (=CH), 6.15 (C=C), 7.35, 9.2, and 11.15 μ (C=CH_2, strong); 100 MHz nmr τ 9.04 (d, 6, J = 7.0 Hz), 8.43 (s, 3), 8.26 (s, broad, 6), 7.10 (septet, 1, J = 7.0 Hz), 5.35 (m, 2), and 5.07 (m, 2).

The 51% product was shown to be 2,4,5-trimethyl-3-isopropenylidenehexa-1,3-diene (**25**): ir 3.2 (=CH), 6.12 (C=C), 7.3, and 11.12 μ (C=CH_2, strong); 100 MHz nmr τ 9.03 (d, 6, J = 6.5 Hz), 8.32 (s, 6), 8.26 (s, 3), 7.65 (septet, 1, J = 6.5 Hz), 5.36 (m, 2), and 5.06 (m, 2); uv max (hexane) 225 mμ (ϵ 10,000); mass spectrum with a molecular ion at *m/e* 164.1575 (Calcd for $C_{12}H_{20}$: 164.1565).

The 24% product was identified as 2,4,5-trimethyl-3-isopropylidenehexa-1,4-diene (**21**): ir 3.20 (=CH), 6.12 (C=C), 7.3, 9.2, and 11.2 μ (C=CH_2, strong); 100 MHz nmr τ 8.51 (s, 3), 8.44 (s, 3), 8.36 (m, 9), 8.31 (s, 3), 5.37(m, 1), and 5.07 (m, 1); uv max (hexane) 216 mμ (ϵ 12,500).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.47; H, 12.19.

Pyrolysis of 15 and 20.—The following pyrolysis products were obtained upon pyrolysis of **15** and **20** in a vacuum pyrolysis system at 0.25 mm. On each run there were a number of relatively minor products present. The major products were obtained by washing the pyrolysis system trap with ether and collecting each product by preparative glpc. These products were then compared directly with authentic samples. The pecentages listed are percentages of total volatile material (Table II).

TABLE II

Reactant (mg)	Temp, °C	**20**, %	**21**, %	A, %[a]	B, %[b]	Crude yield, mg
15 (108)	500	47.0	22.6	12.5	2.4	78
15 (60)	520	7.7	51.5	12.9	2.9	46
15 (48)	540		36.1	27.6	15.1	32
15 (114)	560		20.7	33.0	21.8	98
20 (24)	510	36.7	30.5	13	4.4	18
20 (19)	600			50	32.7	15

[a] A, % *p*-xylene. [b] B, % *o*-xylene.

1,3,3,4,4-Pentamethyl-2-isopropylidenecyclobutan-1-ol (31).—To a predried flask containing a solution of methyllithium (prepared from 0.50 g of lithium wire, 50 ml of anhydrous ether, and 5.1 g of methyl iodide) under a nitrogen atmosphere was added dropwise a solution of 3.0 g of 2-isopropylidene-3,3,4,4-tetramethylcyclobutanone (**30**) in 25 ml of ether. After stirring at room temperature for 45 min, 25 ml of water was added dropwise with cooling. The resulting mixture was poured into 100 ml of water and extracted with four 100-ml portions of ether. The combined ethereal portions were dried and the solvent removed by flash evaporation to give 3.15 g of crude product. Glpc analysis showed 97% of **31** and 3% of **30**. Glpc collection gave **31**: mp 64.5–65.5°; ir 2.72 (OH), 2.84 (OH), 5.88, 7.3, 7.6, 9.1, 9.2, 9.4, 10.5, and 11.4 μ; 100 MHz nmr τ 9.09 (s, 3), 9.03 (s, 3), 8.89 (s, 6), 8.68 (s, 3), 8.40 (s, 3), 8.26 (s, 3), and 8.10 (s, 1, OH).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.07; H, 11.99.

Dehydration of 31. A.—To a solution of 0.31 g of **31** in 20 ml of glacial acetic acid was added 10 drops of concentrated sulfuric acid. After stirring for 1 hr, the resulting solution was poured

(30) C. R. Noller, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 184.

into 50 ml of water and extracted with four 50-ml portions of pentane. The combined pentane extracts were dried and the pentane removed by flask evaporation to give 0.23 g of crude product. Glpc analysis showed 42% **21**, 8% of an unidentified compound and 35% of 1-methylene-2-isopropylidene-3,3,4,4-tetramethylcyclobutane (**29**): ir 3.21 (C=CH), 6.0 (C=C), 6.12 (C=C), and 11.6 μ (C=CH_2, strong); 100 MHz nmr τ 8.98 (s, 6), 8.87 (s, 6), 8.29 (s, 3), 8.25 (s, 3), 5.36 (m, 1), and 5.19 (m, 1); uv max (hexane) 248 mμ (ϵ 14,300).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.40; H, 12.11.

B.—To a solution of 3.5 g of **31** in 30 ml of pyridine was added dropwise a solution of 4.0 g of phosphorous oxychloride in 20 ml of pyridine. After stirring for 4 hr, the reaction mixture was poured into 100 ml of water and extracted with four 100-ml portions of pentane. The combine pentane extracts were washed with two 100-ml portions of 5% hydrochloric acid solution, 100 ml of saturated sodium bicarbonate solution and 100 ml of saturated sodium chloride solution and dried. Removal of the pentane by flash evaporation gave 1.7 g of crude product. Glpc analysis showed 52% **29** and 48% of 1-isopropenyl-2,3,3,4,4-pentamethylcyclobut-1-ene (**32**): ir 3.20 (=CH), 6.06 (C=C), 6.22 (C=C) and 11.4 μ (C=CH_2, strong); 100 MHz nmr τ 9.02 (s, 6), 8.87 (s, 6), 8.30 (s, 3), 8.13 (s, 3), 5.31 (m, 1), and 5.26 (m, 1); uv max (hexane) 243 mμ (ϵ 19,000); mass spectrum with a molecular ion at *m/e* 164.1562 (Calcd for $C_{12}H_{20}$: 164.1565).

Pyrolysis of 32.—A 1.0-g sample of **32** was pyrolyzed on the vacuum pyrolysis system at 360° and 0.25 mm to give 0.91 g of crude product. Glpc analysis and preparative collection showed sample to be 96% **21** and 4% **32**.

Pyrolysis of 29.—A 168-mg sample of **29** was pyrolyzed on the vacuum pyrolysis system at 460° and 0.25 mm to give 160 mg of crude product. Glpc analysis showed 72% **21**, 4% **29**, and five other minor unidentified components.

Pyrolysis of 21.—A 66-mg sample of **21** was pyrolyzed on the vacuum pyrolysis system at 580° and 0.25 mm to give 55 mg of crude product. Glpc analysis showed 17% **21**, 50% *p*-xylene, 33% o-xylene, and four other unidentified minor products.

An apparatus consisting of a vacuum pyrolysis system followed by a Dry Ice trap and liquid nitrogen trap connected together in series was used to analyze the low-molecular-weight gaseous products. A 71-mg sample of **21** was pyrolyzed at 620° and 0.15 mm using the above system. Glpc analysis of the product in the Dry Ice trap showed **21**, *p*-xylene, and o-xylene in the ratio of 1:6:4 along with a number of minor products. Analysis of the products in the liquid nitrogen trap by infrared and mass spectral analysis showed propylene as the major product along with a substantial amount of ethylene.

Registry No.—**6**, 13831-98-6; **7**, 13303-33-8; **8**, 13303-32-7; **15**, 24730-83-4; **16**, 25914-01-6; **17**, 25914-02-7; **20**, 24730-82-3; **21**, 24730-81-2; **22**, 25914-05-0; **24**, 25914-06-1; **25**, 25914-07-2; **29**, 24730-80-1; **31**, 25914-09-4; **32**, 25914-10-7; **45**, 25914-11-8; **46**, 25914-12-9; **47**, 25914-13-0.

Quinone Methide Chemistry. The Benzylic Oxidative Methoxylation of 2,6-Di-*tert*-butyl-*p*-cresol

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Oxidation of 2,6-di-*tert*-butyl-*p*-cresol (**1**) with excess *active* manganese dioxide and lead dioxide in methanol followed by hydrolysis affords 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**5**, 72%) and methyl 3,5-di-*tert*-butyl-4-hydroxybenzoate (**7**, 47%), respectively. Evidence for the intermediacy of quinone methides in these reactions has been obtained by the isolation and characterization of the methanol addition products **3**, **4**, and **6**. A mechanism for metal oxide oxidations of **1** in methanol is presented.

A major subject of investigation of the chemistry of 2,6-di-*tert*-butyl-*p*-cresol (**1**) has been the mechanism of oxidation.[1,2] A substantial understanding of the oxidation of **1** in aprotic solvents has been achieved.[1b,c] However, the oxidations of **1** in protic media have not been as intensively studied. We have now undertaken a product study of the oxidations of **1** in methanol with two commonly used inorganic phenol oxidants, lead dioxide and *active* manganese dioxide.[1b]

Results

A. Manganese Dioxide.[3]—The reaction of **1** with manganese dioxide in a 1:10 weight ratio[4] in methanol at 25° for 72 hr gave, after hydrolysis, a 72% yield of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**5**). A minor product of this reaction, detected to be present to about 5% by vpc, was methyl 3,5-di-*tert*-butyl-4-hydroxybenzoate (**7**). The oxidation of **1** (see Table I) with an equal weight of oxidant was found to give a moderate yield of 2,6-di-*tert*-butyl-α-methoxy-*p*-cresol (**3**). Subsequent reaction of **3** with an equal weight of the oxidant in methanol led to 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde dimethyl acetal **4** in 37% yield. The acetal displayed moderate stability and could be purified by recrystallization from hexane. However, upon standing at room temperature for extended periods, the acetal slowly hydrolyzed to the corresponding aldehyde **5**. Further complete oxidation of **4** in methanol with this oxidant in a 1:5 weight ratio finally gave trimethyl 3,5-di-*tert*-butyl-4-hydroxyorthobenzoate (**6**) in 13% yield. An independent synthesis of **6** by the classical method of Pinner[5] employing 3,5-di-*tert*-butyl-4-hydroxybenzonitrile was not successful since the intermediate methyl 3,5-di-*tert*-butyl-4-hydroxybenzimidate was stable to further methanolysis.

B. Lead Dioxide.—Whereas the oxidation of **1** with

(1) (a) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957), and references cited therein. (b) H. Musso, *Angew. Chem. Int. Ed. Engl.*, **2**, 723 (1963), and references cited therein. (c) E. R. Altwicker, *Chem. Rev.*, **67**, 475 (1967), and references cited therein. (d) L. V. Gorbunova, N. S. Valileiskaya, M. L. Khidekel, and B. A. Razuvaev, *J. Org. Chem. USSR*, **2**, 1227 (1966). (e) J. Sugita, *Nippon Kagaku Zasshi*, **87**, 1082 (1966); *Chem. Abstr.*, **66**, 9477w (1967). (f) L. R. Mahoney and M. A. DaRooge, *J. Amer. Chem. Soc.*, **89**, 5619 (1967). (g) C. M. Orlando, Jr., *J. Org. Chem.*, **33**, 2516 (1968). (h) H.-D. Becker, *ibid.*, **34**, 1203 (1969).

(2) H.-D. Becker, *ibid.*, **30**, 982 (1965).

(3) Hereafter, manganese dioxide will be used in the text to represent *active* manganese dioxide.

(4) In manganese dioxide oxidations, the quantity of oxidant employed is generally in considerable excess of the substrate since only part of the oxygen in this metal oxide is available for oxidation.[5]

(5) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, 3032 (1957).

(6) Examples of the application of the Pinner method in synthesis of orthobenzoates have been described: H. Kwart and M. B. Price, *J. Amer. Chem. Soc.*, **82**, 5123 (1960).

TABLE I

LEAD DIOXIDE (A) AND MANGANESE DIOXIDE (B) OXIDATIONS IN METHANOL AT 25°

Entry No.	Reactant (mol)	Oxidant	Ratio[a]	Methanol, ml	Time, hr	Product	% yield	Mp, °C	Ir (CCl_4), cm^{-1}	Nmr (CCl_4), τ
1	1 (0.022)	A	1:3	100	20	7[b]	47	157–159[c]	2610, 2950, 1710, 1590, 1420, 1295, 1225, 1148, 1125, 993, 690	8.58 (18), 6.21 (3), 4.46 (1), 2.24 (2)
2	1 (0.01)	A	1:1	50	17	3	47	98–99[d]	3625, 2950, 1425, 1370, 1310, 1228, 1150, 1093, 870	8.60 (18), 6.76 (3), 5.79 (2), 5.0 (1), 3.0 (2)
3	1 (0.022)	A	1:3	100	5	6[e]	22	135–136	3630, 2950, 2830, 1430, 1295, 1230, 1155, 1118, 1090, 1040, 895	8.54 (18), 6.95 (9), 4.88 (1), 2.74 (2)
						4[f]	13	82–84	3630, 2950, 2830, 1430, 1355, 1230, 1205, 1190, 1155, 1110, 1050, 990, 880, 700	8.58 (18), 6.8 (6), 4.89 (1), 4.74 (1), 2.85 (1)
4	3 (0.015)	A	1:1	50	7	4	52	82–84	[g]	[g]
5	3 (0.02)	A	1:2	60	7	6	23	134–136	[g]	[g]
6	4 (0.0075)	A	1:1	50	7	6	27	133–135	[g]	[g]
7	1 (0.01)	B	1:10	100	72	5[b]	72	185–187[h]	3605, 2945, 1680, 1580, 1420, 1233, 1188, 1150, 885, 680	8.55 (18),[i] 4.17 (1), 2.3 (2), 0.14 (1)
						7[b,j]	5	157–159	[k]	[k]
8	1 (0.01)	B	1:1.2	60	72	3	27	100–101	[l]	[l]
9	1 (0.01)	B	1:10	100	72	4	17	82–84	[g]	[g]
10	3 (0.02)	B	1:1	35	48	4	34	82–84	[g]	[g]
11	4 (0.0035)	B	1:5	25	13.5	6	13	133–135	[g]	[g]

[a] Ratio = reactant:oxidant (oxidant A, mole ratio; oxidant B, weight ratio). [b] The reaction mixture was filtered and the filtrate stirred with 50 ml of 1% aqueous HCl for 3 hr before product isolation. [c] Mp 159–161°: E. Muller, A. Rieker, R. Mayer, and K. Scheffler, *Justus Liebigs Ann. Chem.*, **645**, 36 (1961). [d] Mp 99.5°: M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435 (1957). [e] *Anal.* Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.60; H, 9.52. [f] *Anal.* Calcd for $C_{17}H_{28}O_3$: C, 72.80; H, 10.00. Found: C, 72.50; H, 10.17. [g] Same as entry 3. [h] Mp 189°: G. M. Coppinger and T. W. Campbell, *J. Amer. Chem. Soc.*, **75**, 734 (1953). [i] Identified by vpc using a 4-ft 10% UCW98 column; T = 100–300° and 12°/min. [j] Spectrum taken in $CDCl_3$. [k] Same as entry 1. [l] Same as entry 2.

excess manganese dioxide in methanol gave the aldehyde **5** as a major product after hydrolysis, the reaction of **1** with excess lead dioxide resulted in the formation of methyl 3,5-di-*tert*-butyl-4-hydroxybenzoate (**7**) in 47% yield. With only 3 mol equiv of oxidant, the oxidation in methanol, when interrupted after 5 hr, gave a mixture of 13% of the dimethyl acetal **4** and 22% of the trimethyl orthobenzoate **6** (see Table I). The main product of the oxidation of **1** with 1 equiv of oxidant was the α-methoxy-*p*-cresol **3**. Further oxidation of **3** with 1 equiv of oxidant gave the dimethyl acetal **4** which could be further oxidized with another equivalent of oxidant to the trimethyl orthobenzoate **6**.

Finally, when a concentrated solution of **1** in methanol was oxidized with only 0.5 equiv of lead dioxide under nitrogen, 4-(2,6-di-*tert*-butyl-4-methylphenoxy)-2,6-di-*tert*-butyl-4-methyl-2-cyclohexadien-1-one (**2**) was obtained in 19% yield. This product was identical in all respects with a sample prepared by the oxidation of **1** with dichlorodicyano-*p*-benzoquinone (DDQ) in methanol.[2] The attempted isolation of **2** from the corresponding oxidation of **1** with manganese dioxide in methanol was unsuccessful.

Discussion

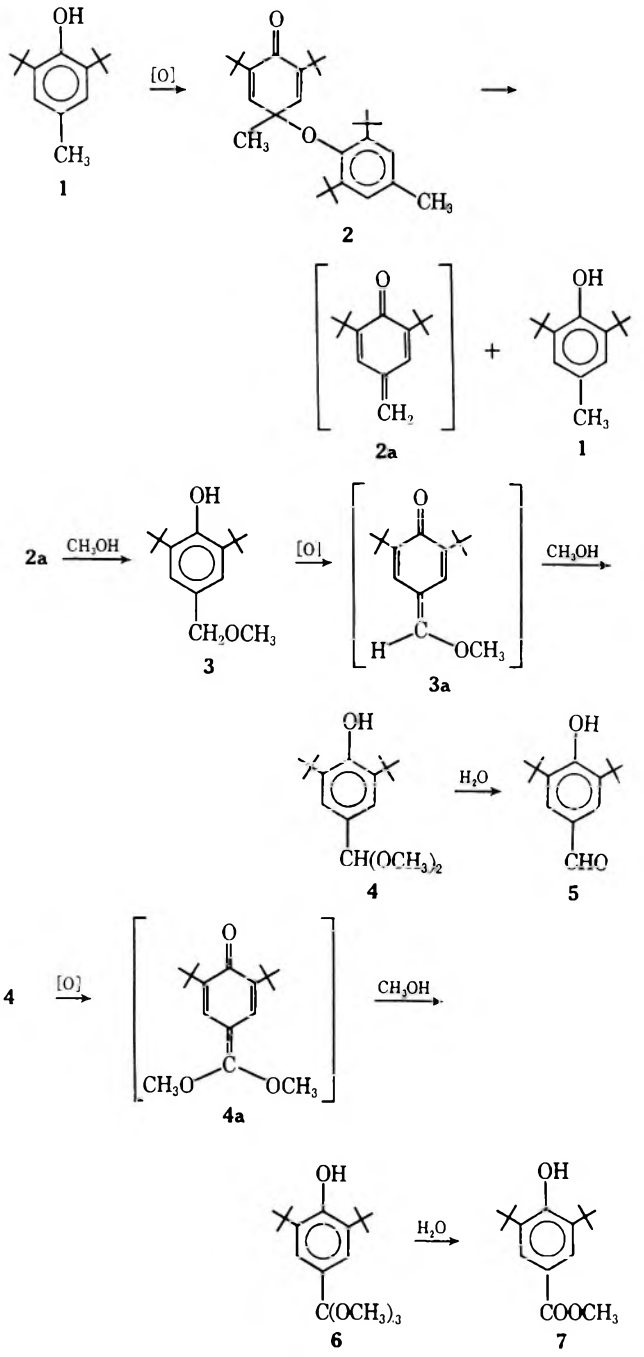
Addition reactions of methanol to quinone methides are well known.[7] The oxidations of **1** with DDQ[2] and 2,6-di-*tert*-butyl-4-cyanophenoxy radical[8] in methanol give 2,6-di-*tert*-butyl-α-methoxy-*p*-cresol (**3**) through the intermediacy of the quinone methide **2a**. Recently, it has been established that **2a** results from an irreversible disproportionation of the quinol ether **2**, a dimer of the 2,6-di-*tert*-butyl-4-methylphenoxy radical.[2] Both the α-methoxyquinone methide **3a** and the dimethyl acetal **4** have been postulated as intermediates in the oxidation of α-methoxy-*p*-cresol **3** to 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**5**)[2,8] (Scheme I).

The manganese dioxide and lead dioxide oxidations of **1** in methanol have now been demonstrated to proceed by stepwise benzylic methoxylation to α-methoxy-*p*-cresol **3**, dimethyl acetal **4**, and the trimethyl

(7) (a) E. Adler and B. Stenemur, *Ber.*, **89**, 291 (1956); (b) C. D. Cook and B. E. Norcross, *J. Amer. Chem. Soc.*, **78**, 3797 (1956); (c) K. Freudenberg and H.-K. Werner, *Ber.*, **97**, 579 (1964); (d) L. Filar and S. Winstein, *Tetrahedron Lett.*, **25**, 9 (1960).

(8) E. Muller, A. Rieker, K. Ley, R. Mayer, and K. Scheffler, *Ber.*, **92**, 2278 (1959).

SCHEME I



orthobenzoate **7**. The formation of the aldehyde **5** and the methyl benzoate **7** in these oxidations under certain conditions (see Table I) involves respective methoxylation to acetal **4** and ortho ester **6** followed by hydrolysis. The intermediacy of the α-methoxyquinone methide **3a** in the oxidation of **3** to the acetal **4** is clearly indicated by the fact that a methanolic solution of the α-methoxyquinone methide, prepared by an alternative method, gave a quantitative yield of the acetal. The conversion of the acetal **4** to the ortho ester **6** presumably involves the intermediacy of the dimethoxyquinone methide **4a**.

In a preliminary examination of the metal oxide oxidations of 4,6-di-*tert*-butyl-*o*-cresol in methanol, a mixture of the 4,6-di-*tert*-butyl-α-methoxy-*o*-cresol and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde dimethyl acetal was obtained with manganese dioxide. However, the lead dioxide oxidation of the *o*-cresol gave only the acetal. Attempts to prepare trimethyl 3,5-di-*tert*-butyl-2-hydroxyorthobenzoate using either oxidant was not successful. The formation of methoxy-4,-6-di-*tert*-butyl-*o*-cresol derivatives in these oxidations presumably involves *o*-quinone methide intermediates in analogy with the chemistry of the para isomer described above. An alternate method of trapping *o*-quinone methides using dienophiles has been described by Bolon.[9]

Experimental Section

Melting points were determined using a Thomas–Hoover apparatus and are corrected. Infrared and nmr spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer and a Varian A-60 spectrometer, respectively. Elemental analyses were done by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Reagents.—4,6-Di-*tert*-butyl-*o*-cresol and 2,6-di-*tert*-butyl-*p*-cresol were purchased from City Chemical Corporation, New York, N. Y., and Eastman Kodak Company, Rochester, N. Y., respectively, and were recrystallized before use. "Active" manganese dioxide was prepared by Dr. J. R. Ladd according to the literature description.[10] The lead dioxide (96.3%) was certified ACS grade material purchased from Fisher Scientific Company, Fairlawn, N. J. Anhydrous reagent grade methanol was used as solvent.

General Oxidation Procedure for the Isolation of Methanol Addition Products.—A suspension of manganese dioxide (1–10 times the weight of cresol derivative) or lead dioxide (1, 2, or 3 mol equiv) in a solution of 1 mol equiv of the cresol (**1**), α-methoxy cresol (**3**), or dimethyl acetal (**4**) in absolute methanol was stirred at 25°. The period of reaction varied over a range of 5.0–72 hr depending upon the oxidant and the cresol derivative. The reaction mixture was filtered and the filtrate was evaporated to a residue which was further purified by recrystallization. The results of these experiments are listed in Table I.

Oxidation of 1 with 0.5 Mol Equiv of Lead Dioxide.—Lead dioxide (0.66 g, 0.0027 mol) was rapidly added to a solution of 1.0 g (0.0045 mol) of **1** in 20 ml of methanol and the mixture was agitated with a stream of nitrogen. Within 2 min the suspended lead dioxide coagulated and fell to the bottom of the flask while a fine white solid deposited from solution. Decantation and filtration of the reaction mixture gave 4-(2,6-di-*tert*-4-methylphenoxy)-2,6-di-*tert*-butyl-4-methyl-2-cyclohexadien-1-one (**2**), 0.185 g (19%), mp 85–90° (lit.[2] mp 85–90°).

Oxidation of 4,6-Di-*tert*-butyl-*o*-cresol with Manganese Dioxide in Methanol.—A mixture of 1.0 g (0.0045 mol) of the *o*-cresol and 2.4 g of the oxidant was stirred at 25° in 35 ml of methanol for 216 hr. The mixture was filtered and the filtrate evaporated to an oil (0.558 g). This product was shown to be a 2:1 mixture of 4,6-di-*tert*-butyl-α-methoxy-*o*-cresol and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde dimethyl acetal by the following nmr data (CCl_4): τ 5.42 (s, 4, $ArCH_2OCH_3$), 4.53 [s, 1, $CH(OCH_3)_2$].

Oxidation of 4,6-Di-*tert*-butyl-*o*-cresol with Lead Dioxide in Methanol.—A mixture of 0.72 g (0.0032 mol) of the *o*-cresol and 2.38 g (0.0096 mol) of lead dioxide in 50 ml of methanol was stirred at 25° for 46 hr. The reaction mixture was filtered and the filtrate evaporated to an oil which was dissolved in hexane and treated with charcoal. Filtration and evaporation of the hexane solution gave the pure 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde dimethyl acetal: 0.193 g (21%); $\nu_{cm^{-1}}^{neat}$ 3350, 1600, 1235, 1105, 1055, 1040; nmr (CCl_4) τ 8.72 (s, 9, *tert*-Bu), 8.62 (s, 9, *tert*-Bu), 6.68 (s, 6, $-OCH_3$), 4.52 [s, 1, $CH(OCH_3)_2$], 3.2 and 2.8 (AB system, 2), 2.15 (s, 1, –OH).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.81; H, 10.06. Found: C, 72.99; H, 10.23.

Preparation of Dimethyl Acetals. A. Of 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (4).—A mixture of 11.7 g (0.05 mol) of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde, 41 g (0.38 mol) of trimethyl orthoformate, 30 ml of absolute methanol, and 0.5 g of

(9) D. A. Bolon, *J. Org. Chem.*, **35**, 3666 (1970).

(10) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. N. Evans, B. A. Heins, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

ammonium chloride was refluxed for 3.5 hr. The reaction mixture was cooled and filtered, and the filtrate evaporated to a solid. The solid was recrystallized from hexane (5°) to give white needles of the acetal 4, 7.0 g (57%), mp 84–86°. The ir and nmr spectra of this product were identical with corresponding spectra of the acetal isolated in the oxidation reactions.

B. Of 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde.—A mixture of 0.39 g (0.0016 mol) of 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, 5 g (0.04 mol) of trimethyl orthoformate, 3 ml of absolute methanol, and 0.05 g of ammonium chloride was refluxed for 36 hr. The reaction mixture was cooled and filtered, and the filtrate evaporated to the liquid acetal, 0.436 g (97%). The ir and nmr spectra of this product were identical with the corresponding spectra of the acetal isolated from the oxidation of 4,6-di-*tert*-butyl-*o*-cresol.

Preparation of 2,6-Di-*tert*-butyl-4-methoxymethylidene Quinone Methide (3a).—A mixture of 11.7 g (0.05 mol) of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**5**), 30 ml of trimethyl orthoformate, 30 ml of absolute methanol, 30 ml of xylene, and 0.5 g of ammonium chloride was refluxed 1 hr. Approximately 0.5 the total volume of the reaction mixture was removed by distillation. The residual solution was refluxed for an additional 2 hr. Filtration of the cooled reaction mixture and evaporation of the filtrate in vacuum gave an orange solid. Crystallization of the product from petroleum ether (bp 60–110°) gave orange needles of the quinone methide (**3a**), 7.5 g (60%), mp 136–138° (lit.[11] mp 136–138°).

Reaction of 3a with Methanol.—A solution of 0.86 g (0.0034 mol) of **3a** in 15 ml of absolute methanol was stirred at 25° for 1 hr. The characteristic orange color of this quinone methide was instantaneously discharged upon dissolving in methanol and a colorless solution resulted. Evaporation of the solvent gave a quantitative yield of the dimethyl acetal **4**, mp 81–83°.

Registry No.—**1**, 128-37-0; **4**, 23093-16-5; manganese dioxide, 1313-13-9; lead dioxide, 1309-60-0.

(11) E. Muller, R. Mayer, U. Heilmann, and K. Scheffler, *Justus Liebigs Ann. Chem.*, **645**, 66 (1961).

New Friedel–Crafts Chemistry. XXIII. The Mechanism of the Aluminum Chloride Catalyzed Rearrangement of *tert*-Pentylbenzene to 2-Methyl-3-phenylbutane

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Transalkylations between *tert*-pentylbenzene (**1a**) and toluene and between *p*-*tert*-pentyltoluene (**1b**) and benzene have been effected by $AlCl_3$–CH_3NO_2 without significant isomerization of the *tert*-pentyl group. When transalkylations between 1a and toluene were repeated, but with the addition of a molar equivalent of isopropyl chloride, extensive isomerization of the *tert*-pentyl group occurred. Treatment of 2-chloro-3-methyl-3-phenylbutane (**10a**) with $AlCl_3$–CH_3NO_2 and methylcyclohexane produced a mixture of 1a and 2-methyl-3-phenylbutane (**2a**). Reaction of 1,2-dibromo-2-methylpropane (**13**, X = Br) with benzene and $AlCl_3$–CH_3NO_2 yields a mixture of two diphenylbutanes, whereas 1,3-dichloro-3-methylbutane, under similar conditions, gives no diphenylpentane. Treatment of 1-chloro-2-methyl-2-phenylpropane (**14**, X = Cl) with $AlCl_3$–CH_3NO_2 and methylcyclopentane gave isobutylbenzene but no *sec*-butylbenzene. On the basis of the transalkylation results and of the behavior of **10a**, **13**, and **14**, we conclude that the rearrangement of **1a** to **2a** takes place by a hydride abstraction process concerted with phenyl participation, producing a phenonium ion intermediate, followed by a second hydride transfer to the phenonium ion from the side chain of another arene molecule.

Alkylations of benzene with *tert*-pentyl chloride,[2–4] isopentyl bromide,[3] 1-chloro-2-methylbutane,[5] and 2-chloro-3-methylbutane[5] have been found to give mixtures of *tert*-pentylbenzene (**1a**) and 2-methyl-3-phenylbutane (**2a**). When aluminum chloride was used as catalyst, the pentylbenzene isomers were produced in an apparent equilibrium proportion of 15–18% **1a** and 85–82% **2a**. However, when the reactions were catalyzed by only trace amounts of aluminum chloride[4] or by weaker alkylation catalysts such as BF_3,[3] $ZrCl_4$,[3] $AlCl_3$–CH_3NO_2,[2,5] or $FeCl_3$,[2] *tert*-pentylbenzene was the sole or major product. These results have been explained in terms of initial alkylation by *tert*-pentyl cation (which is produced by rapid ionization and/or isomerization of the isomeric pentyl halides) to give *tert*-pentylbenzene (**1a**), followed by a slower rearrangement of **1a** to 2-methyl-3-phenylbutane (**2a**) brought about by the stronger catalysts.[3,5,6] In a recent paper,[5] we described two plausible mechanisms for the subsequent isomerization of **1a** to **2a**, but we concluded that the data available at that time did not allow a choice between the two possibilities.

The alternative mechanisms for rearrangement of **1a** to **2a** may be presented as shown in Scheme I. The first, which may be referred to as an *intermolecular* mechanism, involves the dealkylation–rearrangement–realkylation sequence **1a** → **3** → **4** → **2a**.[7–9] The second, which may be referred to as an *intramolecular* mechanism (since the rearranging side chain never becomes separated from the aromatic ring) involves a hydride abstraction, which may or may not be concerted with phenyl participation *via* a phenonium ion, **5a**,[5] or with methyl participation *via* a methyl-bridged cation, **6a**. If the hydride abstraction is not a concerted process, the classical ions **7a**, **8a**, and **9a** may be involved. We have now obtained additional experimental data which we believe constitute definitive evidence for the most probable pathway for the rearrangement of **1a** to **2a**.

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(1) Robert A. Welch Postdoctoral Fellow, on leave from Assiut University, Assiut, U. A. R.

(2) M. Inatome, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **74**, 292 (1952).

(3) L. Schmerling and J. P. West, *ibid.*, **76**, 1917 (1954).

(4) B. S. Friedman and F. L. Morritz, *ibid.*, **78**, 2000 (1956).

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

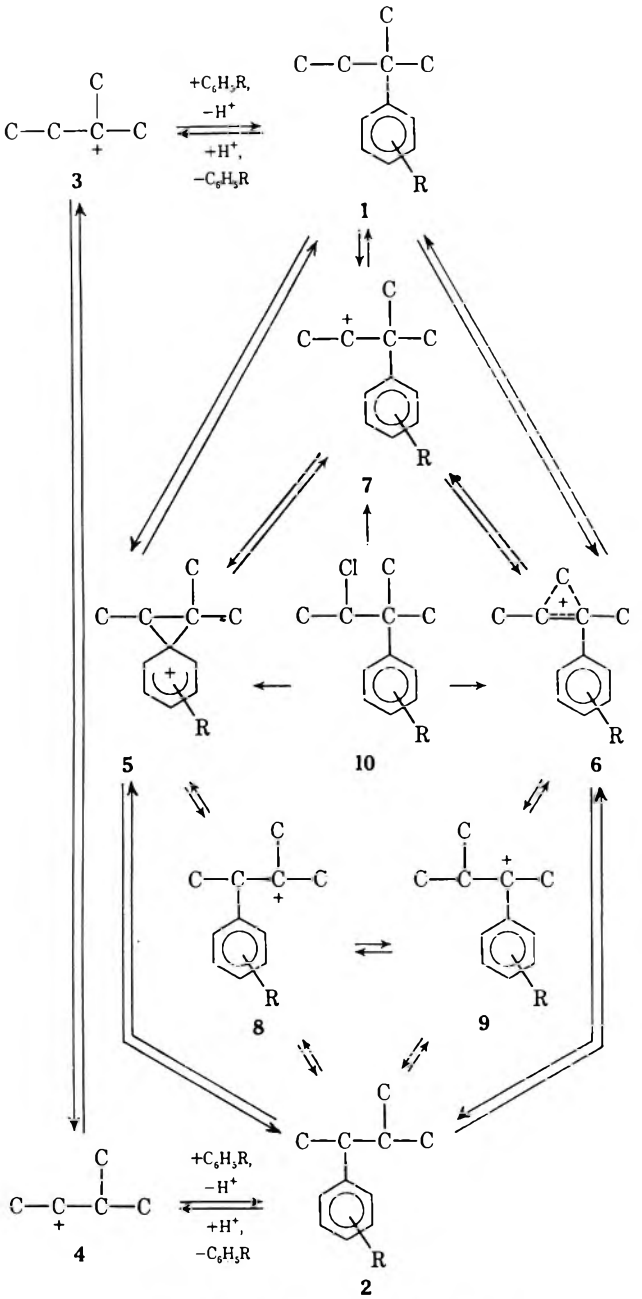
(6) L. Schmerling, J. P. Luvisi, and R. J. Welch, *J. Amer. Chem. Soc.*, **81**, 2718 (1959).

(7) B. S. Friedman, F. L. Morritz, C. J. Morrisey, and R. Koncos, *ibid.*, **80**, 5867 (1958).

(8) G. Baddeley, *Quart. Rev. (London)*, **8**, 355 (1954).

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 450.

SCHEME I



1a, R = H; **1b**, R = *p*-CH_3; **1c**, R = *m*-CH_3; etc.

Transalkylations of sec- and *tert*-alkylarenes are known to take place readily in the presence of mild catalysts such as $FeCl_3$[10] and $AlCl_3$–CH_3NO_2,[11-14] but processes involving hydride abstraction require a stronger catalyst and/or more strenuous conditions.[3-7] Thus, one logical explanation for the rearrangement of **1a** to **2a** by $AlCl_3$ but not by $AlCl_3$–CH_3NO_2 is that the modified catalyst is not capable of the hydride abstraction which is required for the intramolecular rearrangement mechanism. An alternative explanation in terms of the intermolecular mechanism is that the rate of dealkylation (**1a** → **3**) is so slow with $AlCl_3$–CH_3NO_2 catalyst that only **1a** is found as the product of kinetic control of alkylation, whereas with $AlCl_3$ catalyst the rate of dealkylation becomes significant, and **2a** is found as the product of equilibrium control.[15] Thus, if it could be demonstrated that dealkylation of **1a** takes place readily, even when the modified catalyst is used, the second explanation would be discredited and the intramolecular mechanism for rearrangement catalyzed by the unmodified $AlCl_3$ would be supported.

Results and Discussion

We have now demonstrated that dealkylation of **1a** takes place readily in the presence of $AlCl_3$–CH_3NO_2, by carrying out transalkylations between **1a** and toluene. The *tert*-pentyl group was also transferred from *p-tert*-pentyltoluene (**1b**) to benzene. The conditions and results of these transalkylations are summarized in Tables I and II.

It is evident from the results of experiments 1, 2, and 3 that the *tert*-pentyl group was transferred without significant internal rearrangement. The pentyltoluenes present in the reaction mixtures after 24 hr (experiments 2 and 3) apparently represent an equilibrium composition of 67–70% *m*- and 30–33% *p-tert*-pentyltoluene. This equilibrium proportion was verified by allowing *p-tert*-pentyltoluene to react with $AlCl_3$–CH_3NO_2, whereby the same proportion of isomers was produced (see Experimental Section). An equilibrium mixture of the related isomeric *tert*-butyltoluenes was shown to contain about 64% *m*- and 36% *p-tert*-butyltoluene.[12]

A transalkylation between 2-methyl-3-*p*-tolylbutane (**2b**) and benzene was also carried out (experiment 4, Table I). The reaction was much slower, and extensive internal rearrangement of the alkyl group accompanied its transfer. This result is not surprising, since secondary alkyl groups are known to undergo dealkylation much more slowly than tertiary alkyl groups,[16] and the 3-methyl-2-butyl cation (**4**) so produced would be expected to rearrange partially to the more stable *tert*-pentyl cation (**3**) before alkylating benzene. It is interesting to note that the 2-methyl-3-*p*-tolylbutane underwent no reorientation to the meta isomer in this experiment, indicating that the reorientation of the secondary alkyl group is still slower than the transalkylation.

Since the transalkylation experiments have demonstrated that dealkylation of *tert*-pentylbenzene may take place readily in the presence of $AlCl_3$–CH_3NO_2, the failure to find rearrangement to 2-methyl-3-phenylbutane when this catalyst is used must be attributed to the relative rates of the alkylation of benzene by the tertiary carbonium ion, **3**, and of its rearrangement to the secondary carbonium ion, **4**. The first process (alkylation) must be extremely fast compared to the rearrangement. When *p*-xylene is alkylated with *tert*-pentyl chloride, the secondary pentyl xylene corresponding to **2** is produced because competition from alkylation of *p*-xylene by the *tert*-pentyl cation is vir-

(10) V. N. Ipatieff and B. B. Corson, *J. Amer. Chem. Soc.*, **59**, 1417 (1937).

(11) R. H. Allen, *ibid.*, **82**, 4856 (1960).

(12) G. A. Olah, M. W. Meyer, and N. A. Overchuk, *J. Org. Chem.*, **29**, 2310 (1964).

(13) R. L. Burwell, Jr., and A. D. Shields, *J. Amer. Chem. Soc.*, **77**, 2766 (1955), and references given there.

(14) G. A. Olah, S. H. Flood, and M. E. Moffatt, *ibid.*, **86**, 1060 (1964).

(15) The rates of isomerization of **3** to **4** and of the alkylation step **4** → **2** are presumably fast enough, since alkylation of *p*-xylene with *tert*-pentyl chloride and $AlCl_3$–CH_3NO_2 gives 2-methyl-3-*p*-xylylbutane (**2b**).[7]

(16) R. M. Roberts, E. K. Baylis, and G. J. Fonken, *J. Amer. Chem. Soc.*, **85**, 3454 (1963).

TABLE I

TRANSALKYLATIONS BETWEEN *tert*-PENTYLBENZENE AND TOLUENE AND BETWEEN *tert*-PENTYLTOLUENE AND BENZENE WITH $AlCl_3$–CH_3NO_2 CATALYST AT 25°

Expt no.	Reactants, mole ratios	Time, hr	Products, %[a] *tert*-Pentylbenzene	2-Methyl-3-phenylbutane	*p-tert*-Pentyltoluene	*m-tert*-Pentyltoluene	2-Methyl-3-*p*-tolylbutane
1[b]	*tert*-Pentylbenzene–toluene–$AlCl_3$–CH_3NO_2, 1:2:0.06:0.6; mixture was saturated with dry HCl gas.	1	99	0	1	Trace	0
		24	88	1	7	4	0
2	*tert*-Pentylbenzene–toluene–$AlCl_3$–CH_3NO_2, 1:3:1:6	1	93	0	5	2	0
		24	37	4	18	41	0
3	*p-tert*-Pentyltoluene–benzene–$AlCl_3$–CH_3NO_2, 1:3:1:6	0.25	50	0	35	15	0
		24	83	1	5	11	0
		48	82	2	4	12	0
4	2-Methyl-3-*p*-tolylbutane–benzene–$AlCl_3$–CH_3NO_2, 1:3:1:6	24	5.5	0.5	0	0	94
		48	10	2	0	0	88

[a] Benzene (expt 1 and 2) or toluene (expt 3) and products with retention times higher than monopentylarenes were produced in roughly the same amounts and never exceeded 2–3% of the total aromatics. [b] The conditions of this experiment are comparable to the alkylation conditions used by Roberts and McGuire. (See ref 5.)

TABLE II

TRANSALKYLATION BETWEEN *tert*-PENTYLBENZENE AND TOLUENE AT 25°

Expt no.	Reactants, mol ratios	Time, hr	Products, %[a] *tert*-Pentylbenzene	2-Methyl-3-phenylbutane	*p-tert*-Pentyltoluene	*m-tert*-Pentyltoluene + 2-methyl-3-*p*-tolylbutane	2-Methyl-3-*m*-tolylbutane
5	*tert*-Pentylbenzene–toluene–$AlCl_3$, 1:1:0.1	1 min	54	3	16	26	1
		10 min	37	8	16	34	5
		2	20	29	8	23	20
		24	11	44	3	15	27
6	*tert*-Pentylbenzene–toluene–isopropyl chloride–$AlCl_3$–CH_3NO_2, 1:4:1:0.1:1	1	80	14	5	1	
		24	32	32	11	25	
7	*tert*-Pentylbenzene–toluene–isopropyl chloride–$AlCl_3$–CH_3NO_2, 1:4:1:1:5	0.25	51	20	12	17	
		1	26	25	16	33	
		24	20	25	8	37	10

[a] Products with retention times higher and lower than monopentylarenes were also produced but were not identified.

tually eliminated by steric hindrance.[7] The transalkylations of experiments 1–3 take place readily without appreciable incursion of the rearrangement of **3** to **4** because there is no such steric hindrance in alkylation of benzene and toluene by the *tert*-pentyl cation.

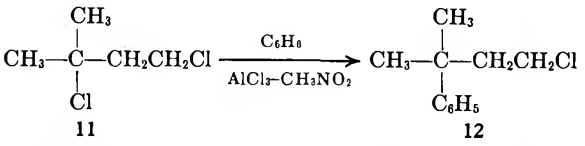
The demonstration of facile transfers of *tert*-pentyl groups between benzene and toluene molecules in the presence of $AlCl_3$–CH_3NO_2 with little or no isomerization of the pentyl group makes it appear unlikely that the effect of unmodified $AlCl_3$ in producing rearrangement of **1** to **2** is simply to increase the rate of dealkylation of **1**. More probably, the effect is to open up another mechanistic route from **1** to **2** by virtue of the hydride abstracting capability of $AlCl_3$. The results of experiment 5 (Table II) show that, although equilibrium is reached in transfer of pentyl groups between benzene and toluene in about 1 min, only 3% of rearrangement of **1** to **2** has occurred; the rearrangement of the *tert*-pentyl groups attached to both benzene and toluene then occurs progressively.

We have demonstrated previously[17] that the addition of an alkyl halide to $AlCl_3$ augments its hydride abstracting capability. When the transalkylations between *tert*-pentylbenzene and toluene were repeated, using $AlCl_3$–CH_3NO_2, but with the addition of 1 mol equiv of isopropyl chloride, extensive rearrangement of the pentyl side chain was observed (experiments 6 and 7, Table II). It is noteworthy that 14% of rearrangement of **1** to **2** occurred before significant para–meta equilibration of the *tert*-pentyltoluenes took place (experiment 6), in contrast to the results of experiments 2 and 5. Apparently the carbonium ion source provided by the isopropyl chloride, in conjunction with even the moderated catalyst, produces a medium capable of initiating and sustaining the hydride exchanges required for the intramolecular mechanism,[7] so that **1** → **2** rearrangement becomes faster than transalkylation and reorientation.

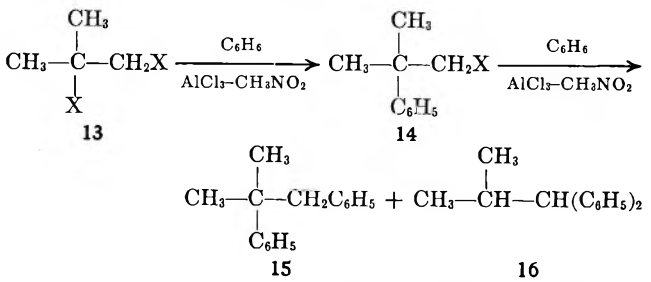
(17) R. M. Roberts, A. A. Khalaf, and R. N. Greene, *J. Amer. Chem. Soc.*, **86**, 2846 (1964).

Consistent with this theory is the finding that 2-chloro-3-methyl-3-phenylbutane (**10a**) produced a mixture of *tert*-pentylbenzene (**1a**) and 2-methyl-3-phenylbutane (**2a**) upon treatment with $AlCl_3$–CH_3NO_2 and methylcyclohexane, which serves as a hydride donor. The proportion of **1a**:**2a** changes from an initial (5 min) value of 56:44 to 33:67 after 48 hr. Referring to Scheme I, one may rationalize the formation of these products in terms of the same intermediates (**5a**–**9a**) postulated for the intramolecular mechanism for rearrangement of **1a** to **2a**.

Turning now to the problem of deciding which of these intermediates constitute the most probable pathway for the intramolecular mechanism, we had on hand information pointing up the importance of phenyl participation in such reactions. 1,3-Dichloro-3-methylbutane (**11**) reacts with benzene in the presence of $AlCl_3$–CH_3NO_2 to produce 1-chloro-3-methyl-3-phenylbutane (**12**), and no diphenylpentane.[18] On the other



hand, treatment of either 1,2-dibromo-2-methylpropane (**13**, X = Br) or 1-chloro-2-methyl-2-phenylpropane (neophyl chloride, **14**, X = Cl) with $AlCl_3$–CH_3NO_2 yields a mixture of the two isomeric diphenylbutanes, **15** and **16**.[19] The failure of alkylation to occur at the



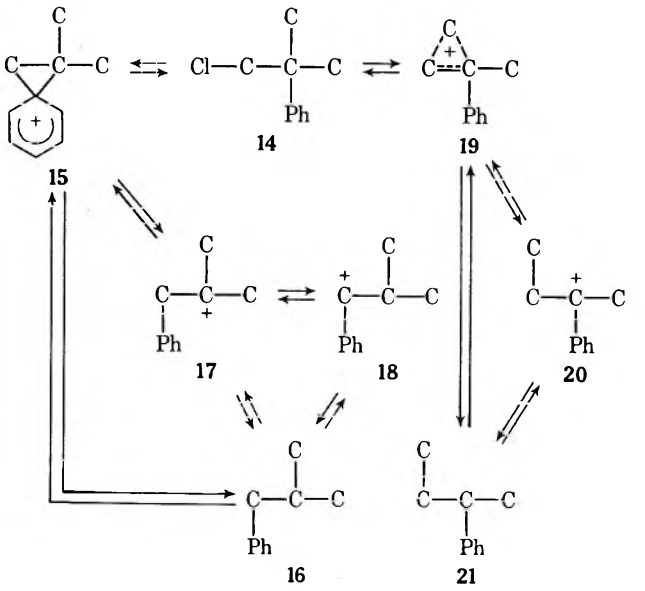
primary carbon atom in **12**, whereas it occurs readily in the reaction of **14** under the same experimental conditions, strongly suggests phenyl participation as a driving force in the latter case.

Additional evidence bearing on the probability of phenyl participation, to produce a phenonium ion intermediate (**5**), rather than methyl participation, to produce a bridged methyl intermediate (**6**), was obtained from a study of the reaction of **14** (X = Cl) with $AlCl_3$–CH_3NO_2 and methylcyclopentane, which may serve as a hydride donor. This system is similar to that containing **10a** in that both phenyl and methyl may participate in the hydride abstraction, but it is different in that different products should be formed after hydride donation, as shown in Scheme II. Phenyl participation should produce isobutylbenzene (**16**), whereas methyl participation should yield *sec*-butylbenzene (**21**). When this experiment was performed and the butylbenzene fraction of the reaction mixture was examined by gas chromatography and infrared spectrometry, it was found to consist of isobutylbenzene exclusively. Unmodified $AlCl_3$ was found to give the same result.

(18) L. Schmerling, R. W. Welch, and J. P. West, *J. Amer. Chem. Soc.*, **78**, 5406 (1956).

(19) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 926 (1966).

SCHEME II



In summary, on the basis of the results of the transalkylation reactions in which *tert*-pentyl groups were transferred between benzene and toluene, and the hydride exchange reactions of **10a** and **14**, we conclude that the rearrangement of **1a** to **2a**, induced by $AlCl_3$ (or by $AlCl_3$–CH_3NO_2 plus isopropyl chloride), takes place by a hydride abstraction process concerted with phenyl participation, producing a phenonium ion intermediate (**5a**).[20] The rearrangement is completed by a second hydride abstraction by the phenonium ion from the side chain of another molecule of hydrocarbon, so that a chain process is set up. Thus, we may now state that the formation of 2-methyl-3-phenylbutane in the aluminum chloride catalyzed reaction of benzene with *tert*-pentyl halides is the result of an initial rapid alkylation, followed by a slower rearrangement of *tert*-pentylbenzene to its isomer by a chain mechanism in which hydride exchange is concerted with phenyl participation.

Experimental Section[21]

Authentic Hydrocarbons.—*tert*-Pentylbenzene, 2-methyl-3-phenylbutane, 2-methyl-3-*p*-tolybutane, and 2-methyl-3-*m*-tolylbutane were available from previous work.[5] *p*-*tert*-Pentyltoluene was obtained by alkylating toluene with *tert*-pentyl alcohol in the presence of concentrated sulfuric acid, bp 212–215°, $n^{24}D$ 1.4885 [lit.[22] bp 86° (12 mm), $n^{20}D$ 1.4965]. Glpc

(20) Although the classical carbonium ions **7**, **8**, and **9** cannot be entirely ruled out as intermediates, there is no experimental evidence supporting them. It is interesting to note that, if one assumed **7a** to be an intermediate produced by hydride abstraction from **1a**, one might logically predict a 1,2-methyl shift to be more probable than a 1,2-phenyl shift on the basis that a tertiary benzyl cation (**9a**) would result from the former and only a tertiary alkyl cation (**8a**) from the latter process. The experimental results from the reaction of **14** indicate that phenyl participation represents a stronger driving force than the small difference in stability of cations such as **9a** (or **20**) and **8a** (or **17**), and indeed it appears that the formation of **7a** by a hydride abstraction that does not involve phenyl participation is unlikely.

(21) Microanalysis were performed by Chemalytics, Inc., Tempe, Ariz. The nmr spectra were determined on a Varian A-60 unless specified otherwise. A Beckman IR-5A spectrophotometer was used to record the ir spectra. The glpc analysis was carried out using a Varian Aerograph Hy-Fi Model 600-D instrument; the columns employed were either a 50 × 0.125 in. silicone oil DC 550 Hypak column operated at 150–160° with nitrogen carrier gas at 60 psi or a 16 ft × 0.125 in. DEGA (25%) column operated at 120–130° with nitrogen carrier gas at 22 psi. The identity and purity of starting materials and products were determined by glpc, ir, and nmr analysis.

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

analysis of the product indicated the presence of not more than 3% of the meta isomer.

Synthesis of 2-Chloro-3-methyl-3-phenylbutane. 3-Methyl-3-phenyl-2-butanone.—Phenyl-2-propanone (26.8 g, 0.2 mol) dissolved in 50 ml of dry dimethyl sulfoxide was added under nitrogen at room temperature over a period of 30 min to a stirred slurry of 50% sodium hydride (19.2 g, 0.4 mol) in 100 ml of dry dimethyl sulfoxide. After the addition, the reaction mixture was stirred for another hour at room temperature. Methyl iodide (56.8 g, 0.4 mol) was added dropwise at such a rate that the temperature was kept below 30°. The reaction mixture was then stirred at room temperature for 4 hr after which it was poured into 1000 ml of water and extracted with ether. The ether solution was washed several times with water and dried over anhydrous magnesium sulfate, and ether was removed using a rotatory evaporator. Distillation of the residue gave 21 g (70%) of 3-methyl-3-phenyl-2-butanone: bp 66–67° (0.7 mm), n^{25}D 1.5072 [lit.[23] bp 76–77° (15 mm), n^{25}D 1.5078]; nmr (CCl_4) δ 7.21 (s, 5, aromatic), 1.82 (s, 3, CH_3CO), and 1.42 ppm (s, 6, gem methyls).

3-Methyl-3-phenyl-2-butanol.—Reduction of 3-methyl-3-phenyl-2-butanone with sodium borohydride in refluxing methanol following standard procedures gave 3-methyl-3-phenyl-2-butanol in 94% yield: bp 80–81° (0.9 mm), n^{25}D 1.5195; nmr (CCl_4) δ 7.2 (m, 5, aromatic), 3.73 (quartet, 1, sec-CH, J = 6.5 Hz), 2.16 (s, 1, –OH), 1.26 and 1.25 (two overlapping singlets, 6, gem diastereomeric methyls), and 0.91 ppm (d, 3, CH_3, J = 6.5 Hz). *Anal.* Calcd for $C_{11}H_{16}O$: C, 80.42; H, 9.82. Found: C, 80.23; H, 10.08.

2-Chloro-3-methyl-3-phenylbutane.—A solution of thionyl chloride (13 g, 0.11 mol) in pyridine (8.69 g, 0.11 mol) was added to a stirred, cooled solution of 3-methyl-3-phenyl-2-butanol (16 g, 0.1 mol) at such a rate that the temperature did not exceed 5°. After addition was complete, the mixture was heated at 40° for 2 hr. The reaction mixture was diluted with water and extracted with ether, and the ether layer was washed with water, dilute sodium bicarbonate, and finally with water, and then dried over anhydrous magnesium sulfate. Careful vacuum distillation gave 12 g (66%) of the title compound: bp 80° (1.2 mm); nmr (CCl_4) δ 7.17 (s, 5, aromatic), 2.99 (quartet, 1, CHCl, J = 7 Hz), 1.51 (s, 3, first diastereomeric gem CH_3), 1.43 (s, 3, second diastereomeric gem CH_3), and 1.47 ppm (doublet with lower field signal overlapping the first diastereomeric gem methyl, 3, CH_3, J = 7 Hz). These overlapping signals were resolved when the sample was analyzed on the HA-100. *Anal.* Calcd for $C_{11}H_{15}Cl$: Cl, 19.41. Found: Cl, 19.31.

General Transalkylation Procedure.—Reactions were carried out in stoppered flasks with magnetic stirring. The hydrocarbons were placed into the flask and the catalyst ($AlCl_3$ or $AlCl_3$–CH_3NO_2) was added in one portion to the stirred solution. Samples were withdrawn at intervals and quenched with water, and the organic material was extracted with ether. The dried ether extracts were analyzed by glpc. All reactions were carried out at room temperature (~25°). Other reaction conditions are summarized in Tables I and II.

The isomer distributions were established using glpc. Results in Tables Iand II are given in normalized mole % of total monopentylarenes.

Reaction of Neophyl Chloride (1-Chloro-2-methyl-2-phenylpropane) with $AlCl_3$ in Methylcyclopentane.—Neophenyl chloride (1.68 g, 0.01 mol) was added all at once to a stirred slurry of $AlCl_3$ (0.133 g, 0.001 mol) in 10 ml of methylcyclopentane. The reaction m xture was stirred for 0.5 hr and then decomposed with water, and the products extracted with ether. The ether layer was washed, dried, and distilled. Among other fractions, this gave 0.1 g of a cut, bp 57–58° (2.15 mm). This was found by vpc and ir to contain isobutylbenzene with no detectable amounts of *sec*-butylbenzene.

Reaction of Neophyl Chloride with $AlCl_3$–CH_3NO_2 in Methylcyclopentane.—The same procedure and amounts of reagents s described above were used except that the catalyst was $AlCl_3$ dissolved in 1.5 g of CH_3NO_2 and the reaction time was extended to 1.5 hr. After processing and distillation of the product, a fraction with bp 55–56° (2.0 mm) was found by glpc and ir to contain isobutylbenzene with no detectable amounts of the secondary isomer.

Reaction of 2-Chloro-3-methyl-3-phenylbutane with $AlCl_3$–CH_3NO_2 in Methylcyclohexane.—2-Chloro-3-methyl-3-phenylbutane (1.82 g, 0.01 mol) was added all at once to a rapidly stirred solution of $AlCl_3$ (0.133 g, 0.001 mol) and CH_3NO_2 (0.61 g, 0.01 mol) in methylcyclohexane (3.92 g, 0.04 mol). Samples were withdrawn after various time intervals, decomposed, and analyzed by glpc for monopentylbenzenes. The following proportions of *tert*-pentylbenzene to 2-methyl-3-phenylbutane were found after the times given: 5 min, 56:44; 15 min, 40:60; 2 hr, 40:60; 6 hr, 41:59; 26 hr, 35:65; 48 hr, 33:67.

Treatment of *p-tert*-Pentyltoluene and 2-Methyl-3-*p*-tolylbutane with $AlCl_3$–CH_3NO_2.—The reaction procedure was similar to that described above for transalkylation; a molar ratio of hydrocarbon–$AlCl_3$–CH_3NO_2 of 3.3:1:6 was used.

Starting with *p-tert*-pentyltoluene, the following proportions of *p*- to *m-tert*-pentyltoluene were found after the times given: 1 hr, 94:6; 2 hr, 78:22; 5 hr, 54:46; 24 hr, 30:70. Toluene, as well as two other products with higher retention times than monopentyltoluenes, were also produced and amounted to about 20% of the total aromatics after 24 hr.

Similar treatment of 2-methyl-3-*p*-tolylbutane resulted in no change even after 24 hr.

Registry No—**1a**, 2049-95-8; **1b**, 4237-70-1; **2a**, 4481-30-5; 3-methyl-3-phenyl-2-butanol, 2977-31-3; **10a**, 25975-92-2.

Acknowledgment—We thank the Robert A. Welch Foundation for generous support of this work.

(23) W. D. Kumler, L. A. Strait, and E. L. Alpen, *J. Amer. Chem. Soc.*, **72**, 1463 (1950).

Acetolysis Studies of Pinacolyl-Type Tosylates. Rapid Solvolysis Rates of Possible Steric Origin

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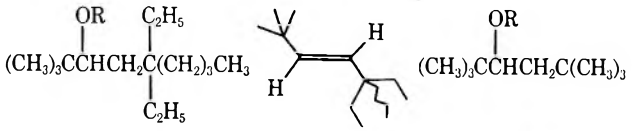
The acetolysis rates of a series of pinacolyl-type tosylates have been studied. The acetolysis of 5,5-diethyl-2,2-dimethyl-3-nonyl tosylate (**1**, R = Ts) has been found to yield 58% of olefin **2** of unrearranged carbon skeleton. Tosylate **1** (R = Ts) and 2,2,5,5-tetramethyl-3-hexyl tosylate (**3**, R = Ts) undergo acetolysis 119 and 71.5 times faster, respectively, than 2,2-dimethyl-3-nonyl tosylate (**4**). It is suggested that these rate enhancements are steric in origin.

It recently has been reported that 5,5-diethyl-2,2-dimethyl-3-nonanol (**1**, R = H) yields a single olefin **2** on dehydration with potassium hydrogen sulfate.[2] This dehydration, without rearrangement, of a pinacolyl-type alcohol is of considerable interest in that systems of this general type are prone to undergo rearrangement on dehydration. While the mechanism of the dehydration of **1** (R = H) with potassium hydrogen sulfate is uncertain (probably of some ionic character), the related 2,2,5,5-tetramethyl-3-hexanol (**3**, R = H) has been shown to lead to a mixture of olefins on dehydration under the same conditions utilized for **1** (R = H).[2] It has been suggested that the carbonium ion from **1** (R = H) is more crowded than the corresponding cation from **3** (R = H). Steric factors were



1 **2** **3**

proposed as controlling the formation of the single olefin **2** from **1** (R = H) since any rearrangement of the carbonium ion from **1** (R = H) would lead to a more sterically crowded ion.

It was therefore of considerable interest to study the solvolysis of the tosylates **1** (R = Ts) and **3** (R = Ts) in order to make rate and product comparisons to other pinacolyl-type systems.

Results

The acetolysis data and the activation parameters for the tosylates **1** (R = Ts) and **3** (R = Ts) along with those for several model compounds are tabulated in Table I. In order to make rate comparisons with the tosylates studied here and other related systems, comparative rate data are presented in Table II.

The products obtained from **1** (R = Ts) are of interest in that 87% olefinic material and 13% acetate were produced (nmr area ratios). Of the olefinic material, 67% was the unrearranged olefin of, readily identified by its characteristic AB quartet at δ 4.2.[2] The other olefinic product was that of rearranged carbon skeleton and exhibited in the nmr a pattern at δ 4.6 representative of a terminal methylene group. The acetate product was also that of a rearranged carbon skeleton since the acetate protons appeared at δ 1.9, while the nmr signal for the unrearranged acetate appeared at δ 1.6 [prepared from **1** (R = H) *via* acetic anhydride in pyridine]. It should be noted that 58% of the acetolysis product from **1** (R = Ts) is the olefin of unrearranged carbon skeleton. In contrast, the acetolysis products from 2,2-dimethyl-3-nonyl tosylate (**4**) were predominantly of rearranged skeletons (85%). The products consisted of 15% unrearranged olefin, 17% rearranged acetate, and 68% an olefin mixture resulting from methyl transposition (1-ene to 2-ene ratio, 1.4:1).

As can be seen from the data presented in Table II, the tosylates **1** (R = Ts) and **3** (R = Ts) undergo acetolysis considerably faster than the model *tert*-butyl *n*-alkylcarbinyl tosylates **4** and **5**. The acetolysis rate of **1** (R = Ts) is the fastest one in the series despite the formation of a substantial amount of olefin of unrearranged carbon skeleton (58%).

Discussion

The interpretation of the data presented herein raises the question of whether the solvolysis of these pinacolyl-related esters proceeds *via* a concerted or a stepwise pathway. The same question has also been asked regarding neopentyl arenesulfonates.[3] The solvolysis rates of pinacolyl brosylate have been compared to those of isopropyl brosylate[4] in several solvents and methyl participation has been discussed. However, the use of isopropyl brosylate as a comparative standard is open to question.[5] If isopropyl arenesulfonates solvolyze with considerable nucleophilic solvent assistance at the transition state (k_s) with no contribution from k_Δ, this would be a poor model for comparison with pinacolyl esters since the large steric hindrance to backside solvent approach in the latter would make the k_s contribution unimportant and the solvolysis would proceed either through a k_Δ or a k_c pathway (nucleophilic solvent and neighboring group unassisted).

Deno and Newman have reported that *d*-pinacolyl hydrogen sulfate racemizes faster than it rearranges in

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(1) Department of Chemistry, University of Missouri, Columbia, Mo. 65201.

(2) N. Rabjohn and C. A. Drake, *J. Amer. Chem. Soc.*, **88**, 3154 (1966).

(3) (a) I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969). (b) A. Diaz, I. L. Reich, and S. Winstein, *ibid.*, **91**, 5637 (1969). (c) P. C. Myhre and K. S. Brown, *ibid.*, **91**, 5639 (1969). (d) S. H. Liggero, R. Sustmann, and P. von R. Schleyer, *ibid.*, **91**, 4571 (1969). (e) V. J. Shiner, Jr., and W. Dowd, *ibid.*, **91**, 6528 (1969).

(4) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952).

(5) (a) P. von R. Schleyer and C. J. Lancelot, *ibid.*, **91**, 4297 (1969), and papers cited therein. (b) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. von R. Schleyer, *ibid.*, **92**, 2538 (1970). (c) J. L. Fry, J. M. Harris, R. C. Bingham, and P. von R. Schleyer, *ibid.*, **92**, 2540 (1970). (d) P. von R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *ibid.*, **92**, 2542 (1970). (e) A. Streitwieser, Jr., and C. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969).

TABLE I

ACETOLYSIS RATES OF PINACOLYL-TYPE TOSYLATES

Tosylate[a]	Temp, °C[b]	$k_t \times 10^4$ sec^{-1}[c]	ΔH^*, kcal	ΔS^*, eu
1 (R = Ts)	15.0	0.45 ± 0.10	22.6 ± 1	+0.3 ± 3
	25.0	1.75 ± 0.14		
3 (R = Ts)	25.0	1.05 ± 0.03		
4, $(CH_3)_3CCH(CH_2)_5CH_3$ (OTs)	40.0	0.128 ± 0.006	26.0 ± 1	+2.1 ± 3
	60.0	1.66 ± 0.08		
5, $(CH_3)_3CCH(CH_2)_7CH_3$ (OTs)	40.0	0.120 ± .004	26.4 ± 1	+3.1 ± 3
	60.0	1.63 ± 0.08		

[a] Performed in acetic acid in solutions 0.04–0.07 *M* in ester and 0.1 *M* in sodium acetate. [b] Temperature deviation of ±0.05°. [c] Average of two kinetic runs using the least squares rate constants; the error is the average standard deviation.

TABLE II

RELATIVE RATE COMPARISONS FOR PINACOLYL-TYPE TOSYLATES

Tosylate	k_t (sec^{-1})[a]	Relative k (25°)
1 (R = Ts)	1.75×10^{-4}[b]	119
3 (R = Ts)	1.05×10^{-4}[b]	71.5
4	1.47×10^{-6}[d]	1.0
5	1.36×10^{-6}[d]	0.93
6, $(CH_3)_3CCHCH_3$ (OTs)	1.92×10^{-7}[c]	0.13
7, $(CH_3)_3CCHCH_2CH_3$ (OTs)	1.37×10^{-6}[c]	0.93
8, $(CH_3)_3CCH(CH_2)_2CH_3$ (OTs)	2.10×10^{-6}[c]	1.4

[a] All rate constants are tabulated at 25°. [b] Experimentally determined at 25°. [c] Calculated at 25° from data at other temperatures (data taken from the thesis of J. J. Harper, Princeton University, 1968). Performed in unbuffered acetic acid. [d] Calculated from data at other temperatures. Performed in buffered acetic acid.

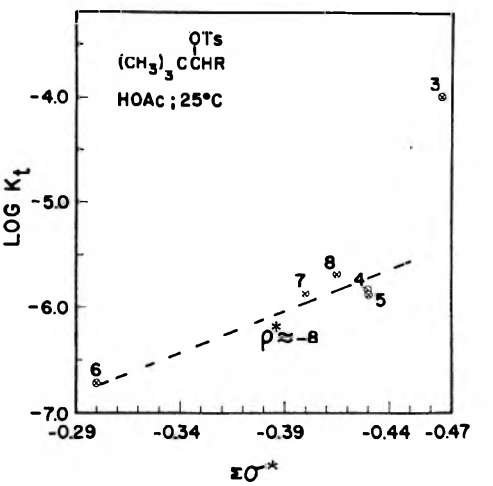


Figure 1.—Acetolysis rates (25°) of the alkyl-substituted *tert*-butylcarbinyl tosylates listed in Table II *vs.* the $\Sigma\sigma^*$ constants.

sulfuric acid solutions.[6] It was proposed that the ionization proceeds to carbonium and bisulfate ions followed by reassociation to racemic pinacolyl hydrogen sulfate. The trifluoroacetolysis of pinacolyl brosylate has been interpreted as proceeding through rate-determining formation of a tight ion pair while the trifluoroacetolysis of isopropyl brosylate is thought to proceed through rate-determining dissociation of a tight ion pair.[7] Pinacolyl brosylate has been proposed as a useful reference compound for estimating unassisted ionization rates of secondary substrates in the absence of ion pair return.

In the series of alkyl-substituted *tert*-butylcarbinyl arenesulfonates, it is of interest to look at the response of the solvolysis rate as a function of the alkyl substituent. In these systems the solvolysis should proceed through a k_Δ or a k_c pathway (k_s contribution expected to be unimportant). The appropriate data for the Taft[8] correlation (log k_t *vs.* $\Sigma\sigma^*$) is graphically illustrated in Figure 1.

Since the substrates **4**, **5**, **6**, **7**, and **8** listed in Table II have no branching in the alkyl side chain (all have a common *tert*-butyl grouping), the steric influence of this group can probably be neglected. Although only five compounds have been utilized to determine the line, and the linearity is questionable, the estimated ρ^* of −8 (acetic acid, 25°) is of considerable speculative interest. The ρ^* value of −2.6 (acetic acid, 70 and 100°)[9] found for simple secondary systems with no β-alkyl branching is to be contrasted with this value. The increased negative ρ^* value for the *tert*-butyl-*n*-alkylcarbinyl esters is consistent with a diminished backside solvent stabilization effect at the transition state, in comparison to the simple secondary esters which probably solvolyze with considerable nucleophilic solvent assistance.[5]

In the absence of complicating steric effects, the $\Delta\rho^*$ of about −5 may perhaps be taken as a measure of the difference in the degree or amount of positive charge at the reaction site in the transition state in the two series. A k_c route would be expected to exhibit a pronounced response to the inductive contribution of an alkyl group. However, it might be noted that partial methyl bridging (k_Δ route) at the transition state might also exhibit a high group response dependent on the degree of participation at the transition state (both routes k_c and k_Δ would proceed without backside nucleophilic solvent stabilization of the transition state).

The simple Taft treatment is clearly not sufficient to rationalize the rate enhancements found in **1** (R = Ts)

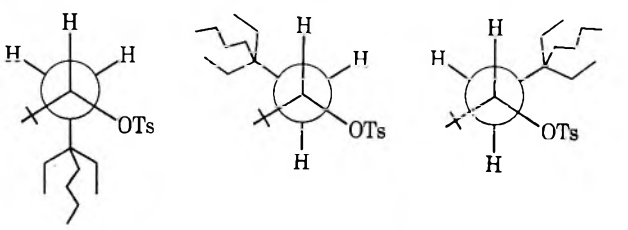
(6) N. C. Deno and M. S. Newman, *J. Amer. Chem. Soc.*, **73**, 1920 (1951).
(7) V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *ibid.*, **91**, 7748 (1969).
(8) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556 ff.
(9) (a) P. E. Peterson, R. E. Kelley, Jr., R. Belloli, and K. A. Sipp, *J. Amer. Chem. Soc.*, **87**, 5169 (1965). (b) P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *ibid.*, **89**, 5902 (1967). (c) W. Pritzkon and K. H. Schoppler, *Chem. Ber.* **95**, 834 (1962). (d) C. J. Lancelot, J. J. Harper, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4294 (1969).

and **3** (R = Ts) as is illustrated for **3** (R = Ts) in Figure 1. No apparent rate correlation exists based solely on the Foote–Schleyer[10] "angle-effect," since the ν_{CO} for the ketone corresponding to **1** is 1705 cm^{-1}, while that for pinacolone is 1709 cm^{-1}.

In the comparison of **1** (R = Ts) to the model system **4** (R = Ts) one sees a rate enhancement of 119 (Table I). If methyl participation is the major solvolytic pathway in **4** (R = Ts), then the magnitude of this participation effect should be comparable to that of compound **1** (R = Ts), and, indeed, the bridging at the transition state **1** (R = Ts) may be sterically less favorable than the comparable bridged transition state in **4** (R = Ts). This comparison might lead to predicting a lower rate for **1** (R = Ts) than for **4** (R = Ts) if k_Δ is the major solvolytic pathway. One can then conclude in the case of system **1** (R = Ts) that the major rate *increase* over the model pinacolyl system is *steric* in origin.

In the solvolyses of several highly branched tertiary carbinyl esters such as 2-chloro-2,3,3,4,4-pentamethylpentane, the products were predominantly of unrearranged carbon skeletons and it was proposed that alkyl participation did not occur.[11] A Taft plot of $\Sigma\sigma^*$ *vs.* log relative *k* for tertiary carbinyl halides (80% aqueous ethanol) seems to indicate that polar effects may account for the solvolysis rates of simple tertiary halides, and even for di-*tert*-butylmethyl carbinyl chloride, but that neopentyl groups introduce marked rate accelerations ascribed to ground-state steric congestion.[12]

In **1** (R = Ts) the bulky alkyl group interacts sterically with the *tert*-butyl group of the neopentyl system in two conformations **1a** and **1b**, and with the tosylate group in two conformations **1a** and **1c**. Conformation **1c** might be expected to be the predominant conformation due to the lesser steric repulsions between groups. However, steric bumping is indicated in conformation **1c** as the bulky side chain interacts with the oxygen atom of the tosylate group. The increased rate of **1** (R = Ts), relative to the model systems in Table I, could be readily rationalized by release of ground-state strain (F strain) at the transition state.[13] The relative decrease in rate of **3** (R = Ts) in comparison to **1** (R = Ts) might simply reflect a greater steric strain release in **1** (R = Ts) than in **3** (R = Ts) due to the greater bulk of the groups in the former compound.



1a **1b** **1c**

It is possible that the solvolysis of **1** (R = Ts) proceeds *via* a k_c route. In this route proton loss at the ion pair stage or the carbonium ion stage would lead to **2** and competitive methyl transposition would lead to products of rearranged carbon skeleton. If an ion pair mechanism is assumed, less internal return (steric assistance to anion departure) might be expected in the comparison of **1** (R = Ts) to **4** (R = Ts) and a rate enhancement for **1** would result.[7] Steric factors would seem to control the formation of the trans olefin **2** as this would be formed from the lower energy trans-like transition state from conformation **1c**. The products from **1** (R = Ts) could also arise *via* a bridged species. A steric bias for methyl migration could produce **2** as the major product *via* proton loss from a bridged ion and partial competitive methyl migration to a tertiary cation followed by reaction of this cation with solvent or proton loss could lead to rearranged acetate and terminal olefin, respectively. The products from the acetolysis of **3** (R = Ts) have not been determined.

In conclusion, the fast rates of acetolysis of **1** (R = Ts) and **3** (R = Ts) are steric in origin even if the exact mechanism of solvolysis can be questioned. No definite conclusion can be reached from the present data as to whether these compounds or the other model systems solvolyze *via* the k_Δ or k_c routes (k_s sterically inhibited) although we favor the k_c route. Further investigations will be necessary to establish these points.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 21 infrared spectrophotometer. All infrared spectra of solids were taken from a CCl_4 solution and all liquids were taken in the neat phase. The nuclear magnetic resonance spectra were determined on a Varian A-60 nuclear magnetic resonance spectrophotometer. Both solids and liquids were examined in CCl_4 solutions with an internal tetramethylsilane standard. Boiling and melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by the Microanalytical Laboratory at the University of Massachusetts, Amherst, Mass.

Synthesis of the Alcohols. A. 2,2,5,5-Tetramethyl-3-hexanol (3, R = H).—This sample was prepared by the procedure of Drake (Ph.D. Thesis, University of Missouri, 1967).[2]

B. 5,5-Dimethyl-2,2-dimethyl-3-nonanol 1 (R = H).—This sample was prepared by the procedure of Drake (Ph.D. Thesis, University of Missouri, 1967).[2]

C. 2,2-Dimethyl-3-nonanol.—Magnesium turnings (2.4 g, 0.1 g-atom) were placed in a 100-ml flask fitted with a condenser, a nitrogen inlet tube, and an addition funnel. The vessel was flushed with nitrogen, and a solution of *n*-hexyl bromide (16.5 g, 0.1 mol) in 50 ml of dry ether was added slowly, to maintain a slow reflux rate. The mixture was allowed to reflux an additional 15 min, and a solution of freshly distilled 2,2-dimethylpropanal (7.74 g, 0.09 mol) in 30 ml of dry ether was added slowly, with cooling. After addition was complete, the reaction mixture was stirred for an additional 10 min, poured into ice water, and extracted with ether. The extract was washed with saturated aqueous sodium bicarbonate and aqueous sodium chloride, dried over anhydrous magnesium sulfate, and the ether was removed on an aspirator. The residue was distilled at reduced pressure to yield 7.35 g (48%) of *tert*-butyl-*n*-hexylcarbinol, bp 45° (0.2 mm).

Anal. Calcd for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 76.99; H, 13.90.

The nmr spectrum showed absorption at δ 3.12 (m, 1 H, –CHOH), 1.92 (s, 1 H, –CHOH), 1.31 (m, 10 H, $-CH_2-$), and 0.85 (s, 12 H, $-CH_3$).

D. 2,2-Dimethyl-3-undecanol.—The procedure above was used to convert *n*-octyl bromide (19.3 g, 0.1 mol) to 9.4 g (52%) of *tert*-butyl-*n*-octylcarbinol. The product distilled at 71° (0.2 mm).

Anal. Calcd for $C_{13}H_{28}O$: C, 77.93; H, 14.08. Found: C, 77.95; H, 14.34.

(10) (a) C. S. Foote, *J. Amer. Chem. Soc.*, **86**, 1853 (1964); (b) P. von R. Schleyer, *ibid.*, **86**, 1854, 1856 (1964).

(11) (a) V. J. Shiner, Jr., and G. F. Meier, *J. Org. Chem.*, **31**, 137 (1966). (b) P. D. Bartlett and T. T. Tidwell, *J. Amer. Chem. Soc.*, **90**, 4421 (1968), and papers cited therein.

(12) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 124–125. The point scatter is significant and the correlation is poor.

(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 323.

Table III

	-CH=CH-	Rearranged CH_3CO_2–	$CH_2{=}C<$		$CH_3{-}\overset{\|\|}{C}{-}$		$(CH_3)_2C{=}C(CH_3){-}$
Chemical shift, δ	5.38	1.88	4.67			1.62	
Protons	2	3	2		3		9
Nmr area ratios	50	86	131			624	
	50	86	131		196.5		427.5
Mole ratios	25	28		66			47
Product %	15	17		40			28

Synthesis of the Tosylates. General Procedure.[14]—In a three-necked flask fitted with an addition funnel, a rubber septum and a reflux condenser was placed up to 3 g of alcohol dissolved in absolute ether. By means of a syringe, a 10% mol excess (with respect to the alcohol) of methyllithium in ether was added with stirring to the solution of the alcohol. After allowing the resulting solution to stir for approximately 5 min, an ethereal solution of tosyl chloride was added dropwise with stirring. A nitrogen atmosphere was maintained throughout the course of the reaction. After stirring from 2 to 24 hr, depending on the particular alcohol, the lithium chloride was filtered through a sintered glass funnel. The filtrate was concentrated by means of a rotary evaporator and placed in a freezer to induce crystallization. Recrystallization was from pentane or a pentane–ether mixture.

A. **5,5-Diethyl-2,2-dimethyl-3-nonyl Tosylate (1, R = Ts).**—The general procedure was employed to convert 5,5-diethyl-2,2-dimethyl-3-nonanol (2.9 g, 0.013 mol), using tosyl chloride (2.65 g, 0.014 mol), and 8.5 ml of 1.6 *M* methyllithium to 1.7 g (37% yield) of 5,5-diethyl-2,2-dimethyl-3-nonyl tosylate, mp 50–52°. The analytical sample was crystallized from pentane, mp 51–52°.

Anal. Calcd for $C_{22}H_{38}O_3S$: C, 69.08; H, 10.02. Found: C, 69.00; H, 10.01.

The infrared spectrum showed strong bands characteristic of the tosylate at 1355 and 1175 cm^{-1}. The nmr spectrum showed signals at δ 7.50 (A_2B_2 quartet, 4 H, J = 8 Hz, aromatic protons), 4.7 (m, 1 H, -CHOTs), 2.44 (s, 3 H, aromatic CH_3), 0.92 (s, 9 H, protons of *tert*-butyl), and 0.5–1.7 (complex multiplets, 21 H).

B. **2,2,5,5-Tetramethyl-3-hexyl Tosylate (3, R = Ts).**—The general procedure described above was employed to convert 2,2,-5,5-tetramethyl-3-hexanol (0.50 g, 0.0022 mol), using tosyl chloride (0.62 g, 0.0022 mol), and 2.0 ml of 1.6 *M* methyllithium, to 2,2,5,5-tetramethyl-3-hexyl tosylate (0.362 g, 38% yield), mp 62–64°. The analytical sample was recrystallized from pentane, mp 63–64°.

Anal. Calcd for $C_{17}H_{28}O_3S$: C, 65.31; H, 9.02. Found: C, 65.20; H, 8.99.

The infrared spectrum showed strong bands characteristic of the tosylate at 1350 and 1175 cm^{-1}. The nmr spectrum showed signals at δ 7.50 (A_2B_2 quartet, 4 H, aromatic protons, J = 8 Hz), 4.7 (m, 1 H, -CHOTs), 2.45 (s, 3 H, aromatic CH_3), 1.6 (d, 2 H, $-CH_2-$), and 0.9 (s, 18 H, $-CH_3$).

C. **2,2-Dimethyl-3-nonyl Tosylate (4).**—The general procedure was used to convert 3.0 g (0.0174 mol) of the parent alcohol to 2,2-dimethyl-3-nonyl tosylate in a 69% yield (3.94 g). The product was an oil at room temperature.

Anal. Calcd for $C_{18}H_{30}O_3S$: C, 66.22; H, 9.26. Found: C, 66.24; H, 9.14.

The nmr spectrum showed absorption at δ 7.50 (A_2B_2 quartet, 4 H, aromatic protons), 4.34 (m, 1 H, -CHOTs), 2.37 (s, 3 H, aromatic CH_3), 1.18 (broad pattern, 10 H, $-CH_2-$), and 0.88 (broad s, 12 H, CH_3).

D. **2,2-Dimethyl-3-undecyl Tosylate (5).**—The general procedure was utilized to convert the parent alcohol (3.58 g, 0.0174 mol) to the tosylate **5** in a 57% yield (3.53 g). The product was an oil at room temperature and was not further purified. The nmr spectrum showed absorption at δ 7.50 (A_2B_2 quartet, 4 H, J = 8 Hz, aromatic protons), 4.36 (m, 1 H, -CHOTs), 2.42 (s, 3 H, aromatic CH_3), 1.23 (broad split peak, 14 H, $-CH_2-$) and 0.87 (broad s, 12 H, CH_3).

(14) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *J. Amer. Chem. Soc.*, **89**, 370 (1967).

Acetolysis Kinetics.—The acetolysis procedures were the same as those used by previous investigators.[15] The infinity titer technique was utilized in which aliquots were taken at appropriate intervals from approximately 0.05 *M* solutions of the sulfonate ester in buffered acetic acid (approximately 0.1 *M* in sodium acetate) in the thermostated bath. Each aliquot was titrated with a standardized perchloric acid solution in acetic acid using a 1% solution of crystal violet in acetic acid as the indicator. The sample was taken as zero time and the infinity titer was taken after at least 12 half-lives had elapsed.

Treatment of Experimental Data.—The first-order rate constants were calculated according to the standard procedures.[16] The calculations were performed on an IBM 1130 computer and the least squares average rate constant was calculated along with the standard deviation and the correlation coefficient for each run. The activation parameters and rates at different temperatures were calculated on the IBM 1130 computer.[17]

Product Studies. Acetolysis of 2,2-Dimethyl-3-nonyl Tosylate (4).—The tosylate **4** (0.52 g) was dissolved in 20 ml of 0.1 *N* sodium acetate in acetic acid and kept at 60° for 12 half-lives. The cooled solution was poured into ice water and the products extracted with pentane. The combined pentane extracts were washed with a saturated solution of aqueous sodium bicarbonate, a saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The pentane was carefully removed and the remaining oil (0.32 g) was identified by nmr analysis. The product data is tabulated in Table III. The vinyl methyl absorption was separated into the two fractions on the basis of the exocyclic methylene protons. Unrearranged acetate was shown not to be present by the absence of the tertiary acetate proton, and by the acetate absorption at δ 1.88; secondary acetates absorb at δ 1.95.

Acetolysis Products of 5,5-Diethyl-2,2-dimethyl-3-nonyl Tosylate (1).—In a round-bottom flask fitted with a reflux condenser was placed a mixture of 0.300 g of 5,5-diethyl-2,2-dimethyl-3-nonyl tosylate and 20 ml of 0.0998 *M* sodium acetate in acetic acid and the solution was stirred at room temperature for 3 days. The mixture was then poured into an equal volume of cold water, extracted with pentane, and washed with water, 5% sodium bicarbonate, and again with water. The pentane solution was dried over potassium carbonate and then concentrated on a rotary evaporator to give 0.150 g of product. The neat infrared spectrum of the product mixture showed strong absorption at 1730 cm^{-1} characteristic of acetates. The nuclear magnetic resonance spectrum showed signals at δ 5.2 (AB quartet, characteristic of olefin **2**), 4.6 (broad d, for $=CH_2$ of rearranged olefin) and 1.90 (s, $CH_3{-}\overset{|}{C}{=}O$).

From the relative peak area ratios at 5.2 (unrearranged olefin **2**) and 4.6 ($H_2C{=}\overset{|}{C}{-}$ of rearranged olefin), it can be ascertained that of the total olefin formed 67% of **2** is present and 33% is rearranged olefin.

From the relative peak areas the molar composition of the acetolysis product is 58% unrearranged olefin **2**, 29% of the rearranged olefin with a $CH_2{=}C$– grouping, and 13% of rearranged acetate.

(15) (a) S. Winstein, C. Hanson, and E. Grunwald, *ibid.*, **70**, 812 (1948). (b) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951). (c) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960).

(16) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

(17) R. G. Johanson, Ph.D. Thesis, University of Vermont, 1969, lists the program utilized.

Reference Samples. 5,5-Diethyl-2,2-dimethyl-3-nonene (2).—In a flask fitted with a reflux condenser was placed a mixture of 5,5-diethyl-2,2-dimethyl-3-nonanol (1, R = H) (0.85 g, 0.0037 mol) and 3.0 g of potassium hydrogen sulfate. The mixture was then heated at 170–180° for 20 hr. After allowing the mixture to cool, it was distilled at reduced pressure to give 0.70 g (89% yield) of 5,5-diethyl-2,2-dimethyl-3-nonene (2), bp 63–65° (1.0 mm) [lit.[2] bp 120–121° (40 mm)]. The nmr showed signals at δ 5.2 (AB quartet, 2 H, J = 16 Hz), 1.0 (s, 9 H, *tert*-butyl group), and 0.5–1.8 (m, 19 H).

5,5-Diethyl-2,2-dimethyl-3-nonyl Acetate.—The acetate was prepared by refluxing 5,5-diethyl-2,2-dimethyl-3-nonanol (0.5 g, 0.0022 mol) with acetic anhydride (2.0 g, 0.019 mol) in 5.0 ml of dry pyridine for 2 hr. The mixture was cooled, poured onto ice water, and extracted with pentane. The pentane layer was washed with 10% hydrochloric acid, 5% sodium bicarbonate, and finally with water. The pentane solution was dried over magnesium sulfate and then distilled to give 0.3 g (50% yield) of 5,5-diethyl-2,2-dimethyl-3-nonyl acetate, bp 80–82° (0.5 mm). The infrared spectrum showed evidence of slight alcohol impurity, but the characteristic strong acetate absorption was present at 1735 cm^{-1}. The nmr spectrum showed signals at δ 4.8 (q, 1 H, –CHOH), 1.95 (s, 3 H, $CH_3C{=}O$), 0.9 (s, 9 H, *tert*-butyl group), and 0.7–1.5 (m, 21 H).

Registry No.—**1** (R = Ts), 25966-57-8; **3** (R = Ts), 25966-58-9; **4**, 25966-59-0; **5**, 25966-60-3; **6**, 25966-61-4; **7**, 25966-62-5; **8**, 25966-63-6; 2,2-dimethyl-3-nonanol, 25966-64-7; 2,2-dimethyl-3-undecanol, 25966-65-8; 2,2-dimethyl-3-nonyl acetate, 25966-66-9; 5,5-diethyl-2,2-dimethyl-3-nonyl acetate, 25966-67-0.

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The Decarboxylation and Rearrangement of 3,3-Dialkyl-2-oxocarboxylic Acids[1]

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The thermal decomposition of 3,3-dialkyl-2-oxocarboxylic acids (1) has been shown to lead to decarboxylation and rearrangement. Although 3,3-dimethyl-2-oxobutyric acid (**1e**) undergoes decarbonylation, 2-oxo acids with larger groups in the 3 position, **1a–d**, afforded mixtures of ketones by 1,2 shifts. Ethyl, butyl, and heptyl groups migrated with similar ease, **1b**, while phenyl was found to have essentially the same migratory aptitude as pentyl in 2-oxo-3-pentyl-3-phenyloctanoic acid (**1c**). However, the phenyl group shifted almost exclusively, in preference to ring expansion, in 1-phenylcyclohexaneglyoxylic acid (**1d**). These results are ascribed to the bulk and conformational effects of the groups in the 3 position of **1**. It is suggested that either a zwitterionic or a concerted process (Scheme 1) best explains the experimental observations.

In a related investigation,[3] it was observed that a small amount of a low-boiling material was obtained on distillation of the product from the base-catalyzed autoxidation of ethyl 2-cyano-3,3-dipentyloctanoate. Since vpc analysis of the crude mixture showed that the only volatile products were unchanged cyano ester and the corresponding 2-keto ester, and these are known to be stable at distillation temperatures, it appeared that the pyrolysis of some nonvolatile species in the reaction mixture was responsible for the low-boiling unknown. The latter was present when either DMF or DMSO–*tert*-BuOH was used as the reaction medium, which eliminated condensation products of dimethyl sulfoxide[4] as possible precursors.

The ir spectrum of the crude autoxidation mixture had broad absorptions at 3200–3600 and 2550–2700 cm^{-1} which suggested the presence of a carboxylic acid. This was confirmed by the preparation of 3,3-dipentyl-2-oxooctanoic acid (**1a**) which on attempted distillation gave a 77% yield of the unknown pyrolysate. It was identified as 7-pentyl-6-dodecanone (**2a**) by comparison of its spectral properties with those of an authentic sample of this ketone.

Although the decarbonylation of 2-oxo esters is well known,[5] the decarboxylation of the corresponding acids has received relatively little attention. In those cases which have been studied,[6] aldehydes have been obtained as the common products. The present paper describes the investigation of the thermal decarboxylation and accompanying rearrangement of a number of 3,3-dialkyl-2-oxocarboxylic acids, **1**, to ketones **2**, **3**, and **4**. In addition, exploratory experiments were carried out in an attempt to elucidate the mechanism of the reaction.

$$\underset{\mathbf{1}}{R_1R_2R_3CCOCO_2H} \xrightarrow{\Delta} \underset{\mathbf{2}}{R_2R_3CHCOR_1} + \underset{\mathbf{3}}{R_1R_3CHCOR_2} + \underset{\mathbf{4}}{R_1R_2CHCOR_3} + CO_2$$

1a, $R_1 = R_2 = R_3 = C_5H_{11}$
b, $R_1 = C_2H_5$; $R_2 = C_4H_9$; $R_3 = C_7H_{15}$
c, $R_1 = R_2 = C_5H_{11}$; $R_3 = C_6H_5$
d, $R_1, R_2 = (CH_2)_5$; $R_3 = C_6H_5$
e, $R_1 = R_2 = R_3 = CH_3$
f, $R_1, R_2 = (CH_2)_5$; $R_3 = H$

The pyrolysis of **1a–d** on attempted distillation afforded the corresponding **2**, **3**, and **4**, whereas **1e** was decarbonylated to pivalic acid; the less highly substituted acid, **1f**, produced a mixture of four components.

Attempts to analyze and separate the mixture of ketones from **1b** by vpc on several different columns were not successful, but nmr analysis suggested that **2**, **3**, and **4** were present in the approximate ratio of 40:30:30, respectively. Compound **1c** gave 7-phenyl-6-dodecanone (**2c**, pentyl migration) and 2-pentylheptanophenone (**4c**, phenyl migration) in the ratio of 66:34. The migratory abilities of the phenyl and pentyl groups then are approximately equal in this case since pentyl migration is favored statistically by a factor of 2:1.

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(1) Taken from the Ph.D. Thesis of C. A. Harbert, 1967, and presented in part at the 3rd Midwest Regional American Chemical Society Meeting, Columbia, Mo., Nov 2–3, 1967.

(2) NDEA Fellow, 1963–1966.

(3) N. Rabjohn and C. A. Harbert, *J. Org. Chem.*, **35**, 3240 (1970).

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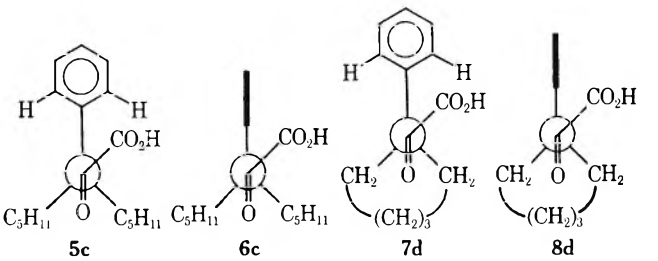
(5) A. C. Cope, H. L. Holmes, and H. O. House, in R. Adams, "Organic Reactions," Vol. 9, Wiley, New York, N. Y., 1957, p 147.

(6) G. Darzens and A. Levy, *C. R. Acad. Sci., Ser. C*, **204**, 272 (1937); G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938); J. Cymerman-Craig, J. W. Loder, and B. Moore, *Aust. J. Chem.*, **9**, 222 (1965).

Acid **1d**, which offers the possibility of ring expansion, required a temperature of 200–220° (5 mm) for decomposition, and the product consisted of cyclohexyl phenyl ketone, **4d** (phenyl migration), and trace amounts of 2-phenylcycloheptanone (alkyl migration) and 1-phenylcyclohexanecarboxaldehyde (decarboxylation), as indicated by nmr.

The above limited data are to be compared with the diversity of migratory aptitudes reported for other systems. Although aryl and other unsaturated groups generally migrate more readily than alkyl groups in 1,2-cationic rearrangements,[7] Parham and Czuba[8] have found the ratio of phenyl to cyclohexyl migration to be 0.2–0.9:1 in the ring expansion of a hexahydrofluorenone with diazomethane and the related Tiffeneau–Demjanov type of ring expansion of an ether of an aminomethylhexahydrofluorenone with nitrous acid. They ascribed these results to the geometric requirements of phenyl migration. Recent studies by Miller and coworkers[9] on the thermal sigmatropic rearrangement of substituted indenes indicate an order of H > C_6H_5 > CH_3 which contrasts with those of 1,2-cationic,[7] anionic,[10] and free-radical rearrangements.[11] Dubois and Bauer[12] have investigated bis-*tert*-alkyl ketone rearrangements in sulfuric acid and have shown that the migrating tendency of an ethyl group relative to methyl varies from 1.2 to 5.0 depending on the structure of the ketone. The widely varying data for different rearrangements suggest that the migratory aptitudes of groups are greatly dependent upon the system involved and the structural environment of the origin and terminus of the migration.

The steric bulk at the 3 position of **1** seems to be an important factor which influences the course of the thermal decomposition of these compounds. This is demonstrated by the failure of **1e** and **1f** to rearrange under conditions in which **1a–d** afforded ketones **2–4**. Also, the phenyl to pentyl migration ratio for **1c** is lower than normal for a carbonium ion process; however, as indicated previously other such examples are known[8] including the acid-catalyzed rearrangement of trisubstituted acetaldehydes to ketones.[13] The origin of this effect in the present case seems to be largely steric in nature. If it is assumed that a migrating phenyl group must be perpendicular to the plane described by the migrating carbon, the migration origin and the migration terminus,[14] then it follows that the preferred conformation for phenyl group migration in **1c** is that depicted by the Newman projection **5c** in which the phenyl group lies in the plane of the paper as viewed from atoms C_2–C_3. Since this conformation should be of higher energy than **6c**, in which the phenyl ring is twisted to avoid interaction with the pentyl groups, it follows that the activation energy for phenyl migration would be increased by the difference in energy between conformations **5c** and **6c**. This could explain the nearly statistical phenyl to pentyl migration ratio observed on pyrolysis of **1c**.



5c **6c** **7d** **8d**

The pyrolysis of **1d** might be considered in a similar manner. The interacting methylene groups in **7d** are held rigid by the ring, thereby lowering the energy of this conformation relative to that of **8d**. However, additional driving force for phenyl migration in this case should arise from the loss of 1,3-diaxial interactions in **1d**. The fact that higher temperatures were required to rearrange **1d** than **1c** suggests that the former is a more strain-free system and the driving force of relief of strain is less in this compound.

The information available concerning relative migration tendencies of alkyl groups is quite limited.[15] Ethyl migrates better than methyl in the pinacol rearrangement and in the acetolysis of neopentyl-type brosylates; however, the opposite order has been reported for the solvolysis of 3,4-dimethyl-4-phenyl-3-hexyl *p*-bromobenzoate, and the acetolysis of some alkyl-substituted neopentyl brosylates.[16] In the latter study it was shown that lengthening an alkyl group without branching (C_2H_5, *n*-C_3H_7, and *n*-C_4H_9) has no effect on the relative rate of acetolysis of molecules of this type. A similar situation might be expected to obtain in **1b**, and this was borne out by the results obtained on thermolysis of **1b**, where essentially equal amounts of the expected rearranged ketones, **2–4**, were formed.

A detailed mechanistic study of the thermal decomposition of **1** was not carried out. Such an investigation would be complicated by the pyrolysis conditions which are not amenable to the trapping or identification of possible intermediates. At least four possible mechanisms can be considered for the pyrolysis and rearrangement of **1**: (1) a free-radical process, (2) an initial decarboxylation to aldehydes which subsequently rearrange to ketonic products, (3) a zwitterionic mechanism, and (4) a concerted decarboxylation rearrangement. Free-radical processes seem unlikely since homolytic decarboxylations usually require radical initiators and/or metal catalysts.[17] This is supported by the observation that no noticeable increase in ketone formation, as compared to an uncatalyzed reaction, was observed when the pyrolysis of **1a** was conducted in the presence of di-*tert*-butyl peroxide. Furthermore, it might be expected that an acyl free radical $R_1R_2R_3\dot{C}{=}O$, formed either by decarboxylation of a carboxylate radical, $R_1R_2R_3CO\text{-}CO_2\cdot$, or by direct homolysis, would decarbonylate rather than rearrange. This was confirmed by heating

(7) For leading references, see (a) G. W. Wheland, "Advanced Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1960, pp 573–597; (b) Y. Pocker, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 22–24; (c) C. F. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 724–744; (d) N. F. Phelan, H. H. Jaffé, and M. Orchin, *J. Chem. Educ.*, **44**, 626 (1967).

(8) W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

(9) L. L. Miller, R. Greisinger, and R. F. Boyer, *ibid.*, **91**, 1578 (1969).

(10) H. E. Zimmerman, in ref 7b, pp 391–399; ref 7c, pp 787–792.

(11) C. Walling, in ref 7b, pp 409–423.

(12) J. E. Dubois and P. Bauer, *J. Amer. Chem. Soc.*, **90**, 4511 (1968).

(13) Reference 7a, pp 549, 580, 592; C. J. Collins, *Quart. Rev. (London)*, **14**, 357 (1960).

(14) For a discussion, see ref 7d and 8.

(15) For leading references, see R. L. Heidke and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **88**, 5816 (1966).

(16) E. N. McElrath, R. M. Fritz, C. Brown, C. Y. LeGall, and R. B. Duke, *J. Org. Chem.*, **25**, 2195 (1960).

(17) W. H. Starnes, Jr., *ibid.*, **31**, 1436 (1966).

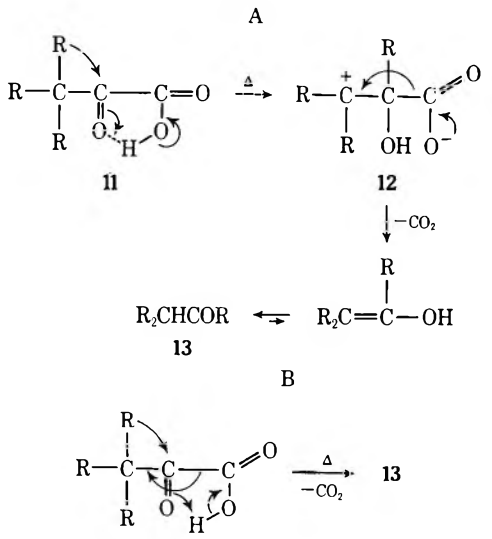
2,2-dipentylheptanal (**9**) with di-*tert*-butyl peroxide. Only the expected **10** was obtained (75%), and carbonyl products could not be detected.

$$(C_5H_{11})_3CCHO \xrightarrow{DTBP} [(C_5H_{11})_3C\dot{C}{=}O] \xrightarrow{-CO} \xrightarrow{IH} (C_5H_{11})_3CH$$
9 **10**

The intermediacy of trisubstituted acetaldehydes was tested by pyrolyzing **1a** in the presence of the corresponding aldehyde, **9**. Approximately 80% of the latter was recovered which suggests that this species is not an intermediate in the pyrolysis of **1a**. It should be noted, however, that this does not rule out the possibility of a vibrationally excited aldehyde intermediate.

The related zwitterionic and concerted pathways, Scheme I, appear to offer reasonable explanations for

SCHEME I



the decarboxylation of **1** and the accompanying rearrangement to ketones. The combination of hydrogen bonding[18] and steric compression in **11** should facilitate thermally induced rearrangement. The migration of R in a stepwise process (Scheme I, A) would be expected to produce zwitterion **12**, which upon loss of carbon dioxide would lead to the enol form of ketone **13**. If rearrangement and loss of carbon dioxide were to occur simultaneously, the mechanism can be depicted by the concerted process as shown in Scheme I, B. Similar mechanisms have been suggested for the decarboxylation of glycidic acids[19] and β-keto acids.[20] It is not possible to distinguish between mechanisms A and B on the basis of the present investigation; however, it seems that the true mechanism lies somewhere between these extremes, and probably closer to the concerted process.

Experimental Section[21]

Materials.—The 3,3-disubstituted 2-oxocarboxylates used in this study were prepared by the autoxidation of the corresponding ethyl 2-cyano-3,3-disubstituted anions,[3] with the exception of ethyl 3,3-dimethyl-2-oxobutyrate which was obtained from the reaction of *tert*-butylmagnesium chloride with diethyl oxalate.

Saponification of Ethyl 3,3-Dipentyl-2-oxooctanoate and Pyrolysis of the Resulting Acid, 1a.—A solution of 16.3 g (0.05 mol) of ethyl 3,3-dipentyl-2-oxooctanoate, 14 g (0.21 mol) of 85% KOH pellets, 15 ml of H_2O, and 90 ml of C_2H_5OH was heated at reflux for 4 hr. The C_2H_5OH was removed by distillation, the residue was treated with 100 ml of 10% HCl, and the mixture was extracted with three 30-ml portions of ether. The combined extracts were worked up to give a pale yellow oil: $n^{25}D$ 1.4528; nmr (CCl_4) δ 10.82 (s, 1, CO_2H), 1.6 (m, 6, CH_2), and 0.6–1.5 (m, 27, CH_2, CH_3); ir (neat) 3100–3450 (m, CO_2H), 2500–2700 (m, bonded OH), and 1710–1750 cm^{-1} (s, C=O).

Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.43; H, 11.48. Found: C, 72.53; H, 11.68.

The attempted distillation of 7.5 g of crude **1a** through a spinning-band column resulted in considerable foaming and gave 4.9 g (77%) of a product: bp 70–75° (0.05 mm); $n^{25}D$ 1.4389; nmr (neat) δ 2.38 (t, 3, $CHCOCH_2$) and 0.6–1.8 (m, 31, CH_2, CH_3); ir (neat) 1715 cm^{-1} (s, C=O). These spectra are identical with those of an authentic sample of 7-pentyl-6-dodecanone (**2a**), which was synthesized by the condensation of pentylmagnesium bromide with 2-pentylheptanenitrile: bp 135–138° (3 mm); $n^{25}D$ 1.4388.

Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.40; H, 13.20.

The 2-pentylheptanenitrile was prepared by the dialkylation of acetonitrile with pentyl bromide and sodium amide according to the method of Newberry and Webster:[22] bp 83–84° (1.5 mm); $n^{25}D$ 1.4308.

Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79. Found: C, 79.66; H, 12.58.

Pyrolysis of 3-Butyl-3-ethyl-2-oxodecanoic Acid (1b).—The saponification of 11.9 g of ethyl 3-butyl-3-ethyl-2-oxodecanoate according to the method in the preceding experiment afforded 11 g of crude **1b**. Attempted distillation of this material caused pronounced foaming and gave 6.4 g (72%) of product: bp 83–85° (0.1 mm); $n^{25}D$ 1.4359.

Anal. Calcd for $C_{15}H_{30}O$: C, 79.57; H, 13.36. Found: C, 79.55; H, 13.16.

The ir of the pyrolysate had an absorption at 1715 cm^{-1} (C=O) and nmr (neat) δ 2.38 (m, 3, $CHCOCH_2$) and 0.6–1.8 (m, 27, CH_2, CH_3). The assignment for the downfield multiplet was based on the ability of these protons to exchange with D_2O under basic conditions. The nmr (CCl_4) of a synthetic mixture of **2b**, **3b**, and **4b** in the ratio of 40:30:30, respectively, was identical with the spectrum (CCl_4) of the pyrolysate.

The reaction of a benzene solution of heptyl bromide with hexanenitrile in the presence of sodium amide[22] afforded 2-butylnonanenitrile (72%): bp 115–117° (2.5 mm); $n^{25}D$ 1.4337.

Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90. Found: C, 80.21; H, 12.65.

This nitrile was caused to react with ethylmagnesium bromide to give **2b** (44%): bp 146–147° (40 mm); $n^{25}D$ 1.4360.

Anal. Calcd for $C_{15}H_{30}O$: C, 79.57; H, 13.36. Found: C, 79.74; H, 13.18.

The ketone, **3b**, bp 148–150° (20 mm), $n^{25}D$ 1.4360 (*Anal.* Calcd for $C_{15}H_{30}O$: C, 79.57; H, 13.36. Found: C, 79.36; H, 13.12), was obtained (48%) in a similar fashion from *n*-butylmagnesium bromide and 2-ethylnonanenitrile. The latter, bp 113–114° (10 mm), $n^{25}D$ 1.4279, was prepared (59%) from butyronitrile, heptyl bromide, and sodium amide by the previously described procedure.[22]

Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65. Found: C, 79.06; H, 12.91.

Ketone **4b**, bp 111–112° (4 mm), $n^{25}D$ 1.4358, was prepared (35%) by the reaction of heptylmagnesium bromide with 2-ethylhexanenitrile: bp 115–117° (135 mm), $n^{25}D$ 1.4142 [lit.[23] bp 98–100° (50 mm), $n^{25}D$ 1.4148].

(18) Intramolecular hydrogen bonding has been well demonstrated for 2-oxo acids, although the bonding decreases as the steric bulk increases at the 3 position: *cf.* M. Hirota and F. Shinozaki, *Bull. Chem. Soc. Jap.*, **42**, 2614 (1969); G. Oehme, G. Fischer, and A. Schellenberger, *Chem. Ber.*, **100**, 425 (1967); A. Schellenberger and G. Oehme, *Z. Phys. Chem. (Leipzig)*, **227**, 112 (1964).

(19) V. J. Shiner, Jr., and B. Martin, *J. Amer. Chem. Soc.*, **84**, 4824 (1962).

(20) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, pp 303–309.

(21) The infrared spectra were recorded on a Perkin-Elmer Model 237-B spectrophotometer and the nmr spectra were run on a Varian A-60 spectrometer employing tetramethylsilane as an internal standard. Elemental microanalyses were performed by Drs. Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical vpc was done on a Wilkens Aerograph A90-P3 and a Microtek 2000-R gas chromatograph. All boiling points are uncorrected.

(22) G. Newberry and W. Webster, *J. Chem. Soc.*, 738 (1937).

(23) P. A. Levene and M. Kuna, *J. Biol. Chem.*, **140**, 263 (1941).

Anal. Calcd for $C_{15}H_{30}O$: C, 79.57; H, 13.36. Found: C, 79.38; H, 13.24.

Decarboxylation and Rearrangement of Other 3,3-Disubstituted 2-Oxocarboxylic Acids, 1.—The acids were prepared by the saponification of the corresponding ethyl esters in the manner described for 1a and heated under a spinning-band column until distillation occurred.

A. 2-Oxo-3-pentyl-3-phenyloctanoic Acid (1c).—Distillation of the crude acid (from 15.5 g of the ester) gave 81% of a product, bp 110–115° (0.5 mm), which consisted of two components. The spectra of the low-boiling fraction [$n^{25}D$ 1.4869; nmr (CCl_4) δ 7.18 (s, 5, aromatic), 3.56 (t, 1, CH), 2.28 (t, 2, CH_2CO), and 0.6–1.5 (m, 20, CH_2, CH_3); ir (neat) 1715 cm^{-1} (C=O)] are identical with those of authentic 7-phenyl-6-dodecanone. The latter was synthesized by the reaction of 2-phenylheptanenitrile, bp 141–143° (4 mm), $n^{25}D$ 1.4970 [lit.[24] bp 165–168° (22.5 mm), $n^{25}D$ 1.4996], with pentylmagnesium bromide, bp 119–120° (0.5 mm), $n^{25}D$ 1.4877.

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.15; H, 10.60.

The higher boiling fraction, $n^{25}D$ 1.4928, was approximately 85% pure: nmr (CCl_4) δ 7.3–7.5 and 7.8–8.1 (m, 5, aromatic), 3.1–3.6 (s, 1, CH), and 0.6–1.9 (m, 22, CH_2, CH_3). Small signals at δ 7.18 and 2.28 were attributed to the presence of the lower boiling compound. The nmr and ir (neat), 1685 (s) and 1715 (m) cm^{-1} carbonyl absorptions, spectra were essentially identical with those of authentic 2-pentylheptanophenone, when allowance was made for the absorptions arising from the 7-phenyl-6-dodecanone.

The 2-pentylheptanophenone was prepared (88%) by condensing 2-pentylheptanenitrile with phenylmagnesium bromide, bp 116–119° (0.4 mm), $n^{25}D$ 1.4940.

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.29; H, 10.86.

B. 1-Phenylcyclohexaneglyoxylic Acid (1d).—An 8-g portion of the crude acid was distilled through a spinning-band column to give 3.7 g of product [bp 97–99° (0.2 mm); $n^{25}D$ 1.5435; nmr (CCl_4) δ 10.60 (s, 1, CO_2H), 7.17 (m, 5, aromatic), and 1.0–2.7 (m, 10, CH_2), ir (neat) 3000–3400 (s), 2500–2700 (m), and 1700–1750 cm^{-1} (s)] and a tarry residue.

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.49; H, 7.17.

Distillation of 7 g of the crude acid at a pot temperature of 200–220° produced 2.7 g (48%) of material: bp 135–139° (5 mm); $n^{25}D$ 1.5490; nmr (CCl_4) δ 7.0–8.0 (m, 5, aromatic), 3.0–3.5 (m, 1, CHCO), and 1.0–2.0 (m, 10, CH_2). The absorptions are consistent with those of cyclohexyl phenyl ketone.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.79; H, 8.56.

Weak signals in the nmr at δ 9.25 and 5.5–6.5 were attributed to impurities which presumably included 1-phenylcyclohexanecarboxaldehyde and 2-phenylcycloheptanone, respectively.

C. 3,3-Dimethyl-2-oxobutyric Acid (1e).—A 6-g sample of freshly distilled 1e, bp 74–76° (15 mm), $n^{25}D$ 1.4222 [lit.[25] bp 80° (15 mm)], was distilled through a spinning-band column with a pot temperature of 220–240°. Considerable foaming occurred and there was obtained 1.9 g of a liquid, bp 120–130°, $n^{26}D$ 1.3982 (lit.[26] $n^{36.5}D$ 1.3931), for pivalic acid. This material also had the same retention time as does pivalic acid on a silicone rubber vpc column. Approximately 3 g of a brown oil remained in the distillation flask, and vpc analysis indicated that the volatile material was mainly pivalic acid. No ketonic products were detected.

D. Cyclohexaneglyoxylic Acid (1f).—The attempted distillation of the crude acid from 5.2 g of ethyl cyclohexylglyoxylate produced a mixture of at least four products and a considerable amount of a tarry residue. No cycloheptanone could be detected by vpc comparison with an authentic sample, and no effort was made to identify the components of the mixture.

Ethyl 3,3-Dimethyl-2-oxobutyrate.—A Grignard reagent, prepared from 49.5 g (0.54 mol) of *tert*-butyl chloride, 13.2 g (0.54 g-atom) of Mg, and 300 ml of dry ether was added to a solution of 197 g (1.35 mol) of diethyl oxalate in 200 ml of dry ether while the temperature was maintained at −50 to −60°. The mixture was allowed to warm to 0° and was decomposed by pouring it onto iced, dilute HCl. It was worked up in the usual manner and distilled through a Podbielniak column to give 48 g (56%) of product, bp 156–158°, $n^{25}D$ 1.4070 [lit.[27] bp 65–66° (15 mm), $n^{25}D$ 1.4096].

Pyrolysis of 3,3-Dipentyl-2-oxooctanoic Acid (1a) in the Presence of Di-*tert*-butyl Peroxide.—A mixture of 3 g (0.01 mol) of crude 1a and 0.22 g (0.0015 mol) of di-*tert*-butyl peroxide was heated at 140° for 3.5 hr and an aliquot was analyzed by vpc using a 25% silicone rubber SE-30 on Chromosorb W column. The chromatogram was identical with that of a control sample of 1a which had been heated under the same conditions without catalyst. An additional 0.8 g (0.008 mol) of peroxide was added to the reaction mixture and heating was continued for 5.5 hr at 160°. Only a slight change in the relative peak areas of 7-pentyl-6-dodecanone (2a) was observed for the heated samples, with and without peroxide, as compared to a chromatogram of crude 1a which had not been heated.

2,2-Dipentylheptanal (9).—A mixture of 75 g (0.28 mol) of 2,2-dipentylheptanoic acid, bp 149–152° (0.75 mm), $n^{25}D$ 1.4485 [lit.[28] bp 167–168° (2 mm)], and 119 g (1 mol) of thionyl chloride afforded 65 g (82%) of the acid chloride, bp 137–139° (0.5 mm), $n^{26}D$ 1.4530.

Anal. Calcd for $C_{17}H_{33}ClO$: C, 70.66; H, 11.43. Found: C, 70.56; H, 11.26.

A mixture of 60 g (0.21 mol) of 2,2-dipentylheptanoyl chloride, 150 ml of dry xylene, 8.4 g of Pd–$BaSO_4$ catalyst, and 0.9 g of quinoline–sulfur poison was heated at 150° while H_2 was passed through it for 30 hr according to the procedure of Hershberg and Cason.[29] It was worked up in the usual way to give 39 g (75%) of aldehyde, bp 105–108° (1 mm), $n^{25}D$ 1.4435.

Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.40; H, 13.36.

Reaction of 2,2-Dipentylheptanal (9) with Di-*tert*-butyl Peroxide.—A modification of the method of Wilt and Philip[30] was adopted. A mixture of 10.2 g (0.04 mol) of 9 and 0.58 g (0.004 mol) of di-*tert*-butyl peroxide was heated at 140° for 9 hr, allowed to cool, and distilled. There was obtained 7.1 g (78%) of 6-pentylundecane (10), bp 136–138° (15 mm), $n^{25}D$ 1.4332.

Anal. Calcd for $C_{16}H_{34}$: C, 84.86; H, 15.14. Found: C, 85.06; H, 14.98.

Pyrolysis of 3,3-Dipentyl-2-oxooctanoic Acid (1a) in the Presence of 3,3-Dipentylheptanal (9).—A mixture of 7 g of crude 1a and 1.25 g of 9 was distilled through a spinning-band column to give a mixture of unchanged 9 and 7-pentyl-6-dodecanone (2a). The relative amounts of aldehyde and ketone were determined by the nmr integration ratios of the aldehyde absorption at δ 9.33 and the ketone absorption at δ 2.38. It was determined that 0.95 g (76%) of the aldehyde, 9, had been recovered.

Registry No.—1a, 26269-42-1; 1b, 26269-43-2; 1c, 26269-44-3; 1d, 26269-45-4; 1e, 815-17-8; 1f, 4354-49-8; 2a, 26269-48-7; 2b, 26322-43-0; 3b, 26269-49-8; 2-butylnonanenitrile, 19480-27-4; 2-pentylheptanophenone, 26269-51-2; cyclohexyl phenyl ketone, 712-50-5; 2,2-dipentylheptanoic acid chloride, 26269-53-4; 9, 26269-54-5; 10, 7249-32-3.

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Perhaloalkyl Hypochlorites and Pentafluorosulfur Hypochlorite. IV. Reactions with Olefins

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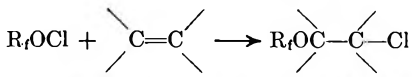
Polyfluoroalkyl hypochlorites add readily and, in most cases, nearly quantitatively to both unsubstituted and halogen-substituted terminal olefins. The direction of addition is such that when the hypochlorites are added to unsymmetrical olefins the principal product is an ether in which the chlorine atom of the hypochlorite has become bonded to the olefinic carbon bearing the greatest electron density.

We have recently described the preparation of several members of a new class of compounds, the polyfluoroalkyl hypochlorites,[1-3] and have shown that they undergo facile and nearly quantitative insertion of carbon monoxide or sulfur dioxide into the oxygen–chlorine bond to produce chloroformates and chlorosulfates, respectively.[3,4] Schack and coworkers have also prepared some of these compounds[5,6] and have briefly described the addition of trifluoromethyl hypochlorite and pentafluorosulfur hypochlorite to two fluorinated olefins, tetrafluoroethylene and chlorotrifluoroethylene.[7]

We have investigated a more extensive series of reactions between the polyfluoroalkyl hypochlorites and selected olefins and have shown that the reaction is quite general for terminal olefins and that, in most cases, the addition is nearly quantitative and predominantly unidirectional. The generalized equation below represents the reactions and products described in this work.



R_f = CF_3–; olefin = C_2F_4, C_2H_4, C_2F_3Cl, C_2H_3Cl, CF_2CH_2, $CF_3OCH{=}CH_2$
R_f = i-C_3F_7–; olefin = C_2F_4
R_f = $(CF_3)_3C$–; olefin = C_2F_4, C_2H_4
R_f = SF_5–; olefin = C_2F_4, C_2H_4

In appropriately substituted cases, the polyhaloethers were dehydrohalogenated to yield perfluoroalkyl vinyl ethers, $R_fOC{=}C<$, providing a simple route to the synthesis of such materials.

Experimental Section

The polyfluoroalkyl hypochlorites and pentafluorosulfur hypochlorite were prepared by methods previously described.[1-3] Ethylene was obtained from the Matheson Company and chlorotrifluoroethylene from Peninsular ChemResearch. Vinyl chloride and tetrafluoroethylene were obtained from the Allied Chemical Corporation's Plastics and Specialty Chemicals Divisions, respectively.

Infrared spectra were obtained using a Perkin-Elmer Model 137B spectrophotometer. Nuclear magnetic resonance spectra were obtained with a JEOLCO C60H or Varian 56–60 spectrometer.

All the ethers were prepared in the same general manner: A small amount (~3–15 mmol) of the desired hypochlorite (R_fOCl) was condensed into a 30-ml stainless steel cylinder using standard vacuum techniques and a nickel–Monel vacuum system. The temperature of the reaction cylinder was then brought to a temperature at which the hypochlorite was liquid but had a rather small vapor pressure. Incremental portions of the olefin were then added to the reaction cylinder through pressurization, and, when a stoichiometric amount of the olefin had been added, the temperature was allowed to warm to room temperature. Trap-to-trap fractionation followed (in some instances) by gas–liquid chromatography using a 0.25 in. × 12 ft column packed with Kel-F No. 10 oil on Teflon (20% by weight) usually produced a pure product.

The experimental conditions for preparing these compounds are given in Table I. Spectroscopic values are provided in Table II. The dehydrochlorination of $CF_3OCH_2CH_2Cl$ was performed by condensing approximately 3 mmol of $CF_3OCH_2CH_2Cl$ into a 75-ml stainless steel cylinder containing about 5 g of KOH pellets. The mixture was then heated to 100° and maintained at this temperature for about 16 hr. The resultant $CF_3OCH{=}CH_2$ was purified by trapping it at −158°. The impurities, which were more volatile, passed to a −196° trap.

Discussion

The high-yield (>90%) additions of polyfluoroalkyl hypochlorites, R_fOCl, to olefins under even the most stringent conditions (*i.e.*, direct combination of undiluted reactants in substantial amounts) is in marked contrast to the behavior of R_fOF analogs with the same olefins. Cady, for example, has shown that CF_3OF reacts violently with tetrafluoroethylene, $CF_2{=}CF_2$, over a wide range of conditions and in almost all concentrations to yield polytetrafluoroethylene and degradation products rather than the adduct $CF_3OCF_2CF_3$.[8] In the case of ethylene, addition of CF_3OF was only possible under conditions of gas-phase mixing at very high dilution with inert gas.[9] Additions of the bifunctional fluoroxy compound $CF_2(OF)_2$ to fluoro olefins were only possible when the gas-phase reactions were greatly moderated by an inert diluent, and even then explosions were common.[10]

Because of the great difficulty in moderating the additions of R_fOF compounds to olefins, the direction of addition to unsymmetrically substituted double bonds has only been established in one case. Williamson[11,12] has shown that the carefully moderated addition of

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TABLE I

PREPARATION OF THE ETHERS[a]

Ether	Reactants	Reaction temp, °C	Bp, °C	Fractionation temp,[b] °C	% C Calcd	% C Found	% F Calcd	% F Found	% Cl Calcd	% Cl Found
$CF_3OCF_2CF_2Cl$	CF_3OCl $CF_2=CF_2$	−80	10.6[c]	−111	16.34	16.34	60.32	60.10		
$CF_3OCH_2CH_2Cl$	CF_3OCl $CH_2=CH_2$	−80	63	−63					23.91	25.39
$CF_3OCHClCH_2Cl$	CF_3OCl $ClCH=CH_2$	−111		−45	19.7	19.04	31.15	30.50	38.8	37.71
$CF_3OCF_2CH_2Cl$	CF_3OCl $CF_2=CH_2$	−80	40	−80	19.51	19.47	51.49	51.00		
$(CF_3O)_2CHCH_2Cl$ + $CF_3OCHClCH_2OCF_3$	CF_3OCl $CF_3OCCl=CH_2$	−111		−45	17.98	17.62	42.70	41.39		
$CF_3OCF_2CFCl_2$ + $CF_3OCFClCF_2Cl$	CF_3OCl $CF_2=CFCl$	−80		−80					29.93	29.29
$(CF_3)_2CFOCF_2CF_2Cl$	i-C_3F_7OCl $CF_2=CF_2$	−20	54	−111	18.72	18.58	65.21	64.82		
$(CF_3)_2CHOCF_2CF_2Cl$	$(CF_3)_2CHOCl$ $CF_2=CF_2$	∼−80		−80	19.83	19.50	62.80	62.56		
$(CF_3)_3COCH_2CH_2Cl$	$(CF_3)_3COCl$ $CH_2=CH_2$	−45		−45	24.12	24.08	57.29	57.00	11.89	11.85
$(CF_3)_3COCF_2CF_2Cl$	$(CF_3)_3COCl$ $CF_2=CF_2$	−45	80	−80	19.43	19.31	66.67	66.10	9.57	9.95
$SF_5OCH_2CH_2Cl$	SF_5OCl $CH_2=CH_2$	−80		−63			46.00	46.93	(15.49)	(% S = 14.85)
$SF_5OCF_2CF_2Cl$	SF_5OCl $CF_2=CF_2$	−80		−100	8.63	8.25			12.74 (11.50)	12.67 (% S = 11.01)

[a] Several of the ethers described here have been previously prepared by others, some by alternate methods ($CF_3OCF_2CF_2Cl$,[d] $CF_3OCH_2CH_2Cl$,[e] and i-$C_3F_7OCF_2CF_2Cl$[f]) and others by essentially the same method ($CF_3OCF_2CF_2Cl$, $SF_5OCF_2CF_2Cl$, and the mixture of $CF_3OCFClCF_2Cl$ + $CF_3OCF_2CFCl_2$[f]). [b] The fractionation temperature is the higher temperature trap for a trap-to-trap fractionation. The second trap was invariably set at −196°. [c] See ref 7. [d] A. V. Tumanova, V. A. Gukanov, and I. M. Dolgopol'sk, *Zh. Obshch. Khim.*, **35**, 587 (1965). [e] P. E. Aldrich and W. A. Sheppard, *J. Org. Chem.*, **29**, 11 (1964). [f] H. R. Nychka and R. E. Eibeck, private communication.

SF_5OF to unsymmetrical olefins produces $SF_5O\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}F$ adducts in which the fluorine atom of the OF group adds to the carbon with the *least* electron density.

For the cases investigated here, the polyfluoroalkyl hypochlorites, R_fOCl, behave toward olefins in a manner more closely resembling that of alkyl hypochlorites, ROCl, than of the fluoroxy compounds, R_fOF (*i.e.*, they add nearly quantitatively and predominantly unidirectionally across the double bond). The direction of addition for both R_fOCl and ROCl is the same, with the result that a bond between the most electron-rich carbon of the alkene with the chlorine atom from the hypochlorite is formed. For instance, in the reaction of CF_3OCl with $CF_2=CH_2$, it was shown by ^{19}F and ^1H nmr studies that the $CF_3OCF_2CH_2Cl$ isomer comprised 96% of the ether product. The resonance signal of the $-CF_2-$ fluorines was observed as a 1:5:10:10:5:1 sextet, the multiplicity being attributed to near equivalence of the magnitude of J_{FH} and J_{FF}. Furthermore, the direction of addition in the reaction of CF_3OCl and vinyl chloride provided $CF_3OCHClCH_2Cl$ and not $CF_3OCH_2CHCl_2$. The configuration of the ether was indicated by the proton nmr spectrum of its dehydrochlorination product. The latter, a vinyl ether which was recovered as the sole product of the dehydrochlorination in near-quantitative yield, was found to contain a terminal $=CH_2$ group. Such a group would not result from the dehydrochlorination of $CF_3OCH_2CHCl_2$ but would be expected from $CF_3OCHClCH_2Cl$.

The predominance of the favored isomer is, expectedly, related to the degree of difference in electron density between the two carbon atoms of the olefin, and in cases where this is small ($CF_2=CFCl$, $CF_3CF=CF_2$) significant amounts of both isomers are formed.

The very highly fluorinated ethers, $R_fOCF_2CF_2Cl$, formed when tetrafluoroethylene is the substrate for hypochlorite addition, are exceptionally stable compounds. They undergo little or no change when held at temperatures in excess of 400° for over 1 week and may be held over KOH pellets at room temperature without harm (higher temperatures were not studied).

The less highly fluorinated ethers, such as $CF_3OCH_2CH_2Cl$, which have chlorine and hydrogen bonded to adjacent carbon atoms, readily undergo dehydrohalogenation as mentioned above. The resultant fluoro olefin can then be reacted again with the same or an alternate hypochlorite. In this way a number of interesting polyfluoroethers can be prepared. A simple example of this buildup is represented by the equations below.

$$CF_3OCl + CH_2CH_2 \longrightarrow CF_3OCH_2CH_2Cl$$

$$CF_3OCH_2CH_2Cl \xrightarrow{KOH} CF_3OCH=CH_2$$

$$CF_3OCH=CH_2 + CF_3OCl \longrightarrow (CF_3O)_2CHCH_2Cl + \text{trace of } CF_3OCHClCH_2OCF_3$$

Although our studies of this area have not been sufficiently extensive to define the limits of its applicability, even the most cursory examination of the rather large number of fluorinated hypochlorites and olefins available suggests that quite large numbers of fluorine-containing polyethers may be possible by this method.

Table II

Characterization of the Ethers

Compd	Registry no.	^{19}F, ppm[a]	^1H, ppm[b]	J, Hz	Infrared, cm^{-1}
$CF_3OCF_2CF_2Cl$ a b c	1561-50-8	ϕ_a = +55.8 (triplet) ϕ_b = +89.1 (quartet of triplets) ϕ_c = +73.9 (unresolved)	X X X	J_{ab} = 9.25 J_{bc} = 1.8	1369 (m), 1297 (vs), 1270 (vs), 1212 (vs), 1181 (vs), 1143 (m, shoulder), 1072 (w), 990 (m), 927 (vw), 894 (w), 862 (w), 827 (w), 695 (vw), 665 (w)
			A_2B_2		
$CF_3OCH_2CH_2Cl$ a b c	1645-95-0	ϕ_a = +61.6 (singlet)	$\delta_b \cong -4.18$ $\delta_c \cong -3.66$	J_{bc} = 6.0	3030 (w), 1470 (vw), 1408 (mw), 1280 (vs), 1258 (vs, (shoulder), 1170 (vs), 1078 (w), 1050 (w), 780 (mw), 725 (w), 694 (w)
$CF_3OCHClCH_2Cl$ a b c	25957-32-8		δ_b = −5.92 (triplet) δ_c = −3.78 (dectet of triplets)	J_{bc} = 5.5	3000 (w), 1440 (w), 1285 (vs), 1220 (s), 1200 (s), 1110 (m), 1042 (m), 944 (w), 885 (vw), 287 (w, shoulder), 795 (m), 745 (s)
$CF_3OCF_2CH_2Cl$ a b c	25957-33-9	ϕ_a = +56.2 (triplet) ϕ_b = +77.5 (sextet)	δ_c = 3.75	J_{ab} = 9.4 J_{bc} = 9.3	3000 (vw), 1430 (m), 1333 (s), 1300 (s) 1235 (s), 1190 (s), 1118 (s), 1110 (s, shoulder), 958 (m), 925 (m), 880 (m), 837 (m), 807 (m)
$(CF_3O)_2CHCH_2Cl$ + $CF_3OCHClCH_2OCF_3$		Mixture which was not separated			
$CF_3OCF_2CFCl_2$ + $CF_3OCFClCF_2Cl$		Mixture which was not separated			
$(CF_3)_2CFOCF_2CF_2Cl$ a b c d	25957-34-0	ϕ_a = 80.3 (triplet of doublets) ϕ_b = 143.1 (complex triplet) ϕ_c = 83.8 (complex doublet) ϕ_d = 73.2 (complex)	X X X X	J_{ab} = 1.8 J_{bc} = 21.8 J_{cd} = 2.1 J_{ac} = 6.3	1322 (m), 1308 (m), 1250 (s), 1198 (s), 1147 (s), 1125 (s), 1111 (m), 990 (m), 970 (s), 725 (m), 710 (m), shoulder)
$(CF_3)_2CHOCF_2CF_2Cl$ a b c d	25957-35-1	ϕ_a = 73.5 (dectet of triplets) ϕ_c = 88.1 (triplet) ϕ_d = 72.8 (unresolved)	ϕ_b = −4.85 (septet)		1356 (m), 1320 (w), 1205 (m), 1255 (s), 1220 (s), 1190 (s), 1155 (m), 1138 (m), 1120 (m), 1100 (w), 1072 (w), 972 (m), 903 (m), 805 (m), 730 (m), 690 (m)
$(CF_3)_3COCH_2CH_2Cl$ a b c	25957-36-2	ϕ_a = +74.4 (singlet)	δ_c = −4.26 ϕ_d = −3.61	J_{ab} = 0.7 J_{bc} = 6.0	3035 (mw), 1470 (mw), 1410 (mw), 1312 (s, shoulder), 1280 (vs), 1235 (m), 1190 (ms), 1170 (vs), 1090 (mw), 1030 (ms), 1015 (ms), 980 (s), 794 (mw), 735 (s), 693 (mw)
$(CF_3)_3COCF_2CF_2Cl$ a b c	25957-37-3	ϕ_a = +70.3 (triplet) ϕ_b = +84.0 (dectet of triplets) ϕ_c = +73.3 (unresolved)	X X X	J_{ab} = 9.5 J_{bc} =2.0	1290 (vvs), 1232 (m), 1193 (s), 1185 (s, shoulder), 1137 (s), 1111 (m), 1098 (m), 998 (s), 981 (s), 972 (s, shoulder), 807 (mw), 796 (mw), shoulder), 769 (w), 733 (s), 671 (w)
		AB_4[c]	A_2B_2		
$FSF_4OCH_2CH_2Cl$ a b c d	26039-34-9	ϕ_a = −74.9 ϕ_b = −59.8	δ_c = −74.9 δ_d = −3.62	J_{ab} = 146 J_{cd} = 6.2	3005 (w), 1470 (w), 1312 (w), 1175 (ms), 1042 (s), 911 (vs), 894 (vs), 856 (ms), 785 (w), 725 (w), 695 (w)
$FSF_4OCF_2CF_2Cl$ a b c d	25353-14-4	ϕ_a = −60.2[c] ϕ_b = −71.0 ϕ_c = +87.1 ϕ_d = +72.5	X X X X	J_{ab} = 153.6[c] J_{ac} = 2.6 J_{bc} = 12.6 J_{cd} = 1.95	1315 (m), 1202 (vs), 1126 (s), 995 (s, shoulder), 990 (s), 944 (s), 929 (s), 899 (ms), 820 (s), 744 (w), 675 (w)

[a] Relative to CF_3Cl internal standard. [b] Relative to TMS internal standard. [c] The calculations of the nmr spectra for the AB_4 models were accomplished by the use of a generalized seven-spin program written for the IBM 360/50 computer. An excellent fit of the theoretical and experimental plots indicated that the calculated parameters were accurate.

One surprising aspect of this study is that attempts to add trifluoromethyl hypochlorite to either perfluoro-2-butene or perfluoro-2-butyne were unsuccessful, though in each case the reaction mixture was heated to the decomposition point of the hypochlorite (~150°).

The mechanism for the reactions described here remains uncertain. The direction of addition to unsymmetrical olefins, *i.e.*, $CF_2{=}CH_2$, argues for a "Cl^+" type mechanism rather than a radical process, but the definitive experiments with radical inhibitors and with certain specialized olefins have not been performed.

Registry No.—Pentafluorosulfur hypochlorite, 22675-70-3.

Halogenated Ketenes. XV. Studies on Aldohalo- and Aldoalkylketene Cycloadditions[1]

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The dehydrohalogenation of haloacetyl halides in the presence of cyclopentadiene produces the corresponding 1,2 cycloadducts of fluoro-, chloro-, and bromoketenes. These unsymmetrical aldohaloketenes undergo cycloaddition stereospecifically to produce only the *endo*-halo isomer. Methyl-, ethyl-, and isopropylketenes were prepared in an analogous manner and the cycloadditions with cyclopentadiene were also stereospecific to yield only the *endo*-alkyl isomers. The results are discussed in terms of the principle of orbital symmetry conservation.

The cycloaddition of ketoketenes and olefins has received a lot of attention in the literature in the past few years. However, there have been essentially no reports on cycloadditions involving aldoketenes, presumably because of the instability of these ketenes and the necessity of performing *in situ* reactions. Since aldoketenes are unsymmetrical, the possibility exists for the formation of two stereomers in the (2 + 2) cycloaddition reaction as illustrated with cyclopentadiene. Unsymmetrical ketoketenes are, of course, also possible but the stereochemistry of these cycloadditions has apparently gone unnoticed. Hasek and Martin have reported the preparation of the cycloadduct of butylethylketene with cyclopentadiene but only mentioned that two isomers were apparently formed as evidenced by vpc.[2] Jaz and Denis have recorded in a communication the preparation of adducts of methyl-, ethyl-, *n*-propyl-, isopropyl- and *n*-butylketenes with cyclopentadiene but no mention was made about the stereochemistry.[3] We have recently reported on the stereochemistry of alkylhaloketene (unsymmetrical ketoketenes) and cyclopentadiene cycloadditions.[4-6]

Continuing our efforts in studies involving the preparation and cycloaddition of halogenated ketenes, we have investigated the aldohaloketenes. There has been only one report on this type of ketene and this was simply the mention of chloroketene by Opitz and coworkers on the cycloaddition with an enamine.[7] Consequently, the purpose of this paper is to describe the preparation of fluoro-, chloro-, and bromoketenes and relate the stereochemistry of the cycloadditions with cyclopentadiene and also the stereochemistry of some aldoalkylketene cycloadditions. Two preliminary reports of this work have appeared.[5,9]

Results

Fluoro-, chloro-, and bromoketenes were prepared by the dehydrohalogenation of the appropriately substituted acetyl halide with triethylamine at −78°. The ketenes could not be isolated but could be trapped by performing the cycloadditions in the presence of cyclopentadiene. The ketenes appeared to be quite stable in the reaction mixture at −78° but upon warming to room temperature polymerized to a black tar. The cycloaddition with cyclopentadiene does not occur at −78° as warming to room temperature is necessary to produce the bicyclo[3.2.0]hept-2-en-6-ones.

Fluoroketene was also trapped with diisopropylcarbodiimide to form the 1,2 cycloadduct, 3-fluoro-1-isopro-

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(1) Paper XIV: W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **92**, 4618 (1970).

(2) J. C. Martin, G. P. Gott, V. M. Goodlett, and R. H. Hasek, *J. Org. Chem.*, **30**, 4175 (1965).

(3) E. Jaz and E. Denis, *Bull. Soc. Chim. Belges*, **75**, 845 (1966).

(4) W. T. Brady and B. M. Holifield, *Tetrahedron Lett.*, 5511 (1966).

(5) W. T. Brady and B. M. Holifield, *Tetrahedron*, **23**, 4251 (1967).

(6) W. T. Brady, R. Roe, Jr., E. F. Hoff, Jr., and F. H. Parry, III, *J. Amer. Chem. Soc.*, **92**, 146 (1970).

(7) G. Opitz, M. Kleemann, and F. Zimmermann, *Angew. Chem.*, **74**, 32 (1962).

(8) W. T. Brady and E. F. Hoff, Jr., *J. Amer. Chem. Soc.*, **90**, 6256 (1968).

(9) W. T. Brady, E. F. Hoff, Jr., R. Roe, Jr., and F. H. Parry, III, *ibid.*, **91**, 5679 (1969).

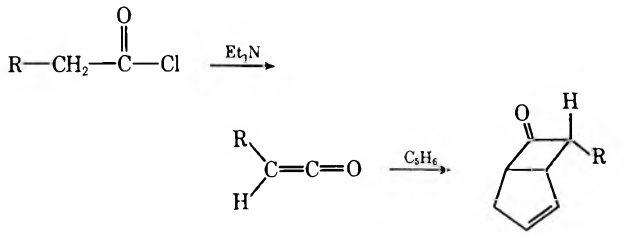
pyl-4-isopropyliminoazetidin-2-one which has been reported elsewhere.[10]

Both the *endo*- and *exo*-halo isomers were expected from each of the systems since the cyclopentadiene adducts from methylchloro- and methylbromoketenes were a mixture of isomers.[4,5] However, distillation of the reaction products yielded only one fraction which contained cycloadduct. An extensive vpc analysis indicated only one isomer was present. A check of the reaction mixture prior to distillation also revealed only one isomer.

In an effort to make a structural assignment of the single isomer produced in each system, the *endo*-chloro adduct (II) was synthesized by an independent method. The cycloadduct of dichloroketene and cyclopentadiene, 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one, was stereoselectively reduced with tri-*n*-butyltin hydride[11] to produce only the *endo*-chloro isomer.[12] The pmr spectrum

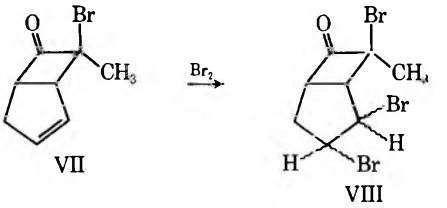
of this compound was compared to the pmr spectrum of the chloroketene–cyclopentadiene adduct and the two were identical.[12] The pmr spectra of the fluoro- and bromoketene cycloadducts with cyclopentadiene were found to be consistent with assignment as the endo isomers.

Molecular models reveal that the endo halogen is right over the residual π system of the diene. Therefore, in an effort to determine if the halogen was causing the endo specificity, the investigation of some aldoalkylketene systems was undertaken. The dehydrochlorination of propionyl chloride, butyryl chloride, and isovaleryl chloride with triethylamine in the presence of cyclopentadiene produced the corresponding 1,2 cycloadducts of methyl-, ethyl-, and isopropylketenes. Only one isomer was produced in each system.

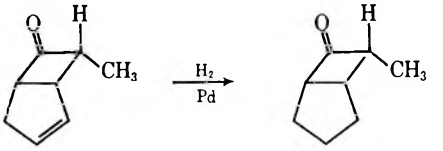


IV, R = Me
V, R = Et
VI, R = *i*-Pr

The pmr spectrum of IV clearly revealed that only the *endo*-methyl isomer had been produced. Also, the pmr spectrum of a brominated IV revealed that the product of bromination was the same as that obtained by the bromination of VII.[5]



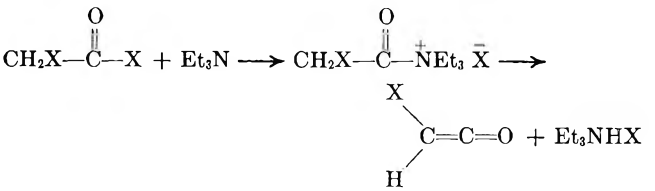
Also, the pmr spectrum of the hydrogenated IV revealed a shift (~2 cps) in the methyl resonance.



Compounds V and VI were also found to be the *endo*-alkyl isomers by pmr analysis of the brominated adducts.

Discussion

In the preparation of the aldohaloketene–cyclopentadiene adducts, the addition of the acid halide to the reaction solution at −78° results in the immediate formation of an insoluble salt. However, the cycloadduct is not produced at this temperature, not even after 48 hr, but upon warming to room temperature the cycloadduct is readily formed. The exothermic nature of the dehydrohalogenation and decreased yields are detrimental to effecting the dehydrohalogenation at room temperature or higher. It is very likely that the salt initially formed is the acyl ammonium salt which upon



warming decomposes to the ketene. Such an acylammonium salt is known and has been characterized.[13]

Integration of the pmr spectrum of I revealed that the area for the vinyl resonance was too large and the area for the proton geminal to fluorine was too small. This was due to the large coupling constant (55 cps) of fluorine which caused half of the resonance for this proton to occur downfield under the vinyl resonance. This was demonstrated by bromination which eliminated the vinyl resonance and revealed a multiplet of equal area, 55 cycles downfield from the resonance assigned to the proton geminal to fluorine. The brominated product could not be distilled nor chromatographed; thus further characterization was not achieved.

A more convincing proof of structure resulted from hydrogenation of I and complete characterization of the product. The pmr spectrum of the hydrogenated product revealed a multiplet (area equivalent to one-half proton) which was 55 cycles downfield from the reso-

(10) W. T. Brady, E. D. Dorsey, and F. H. Parry, III, *J. Org. Chem.*, **34**, 2846 (1969).

(11) H. G. Kuivila, *Accounts Chem. Res.*, 299 (1968).

(12) This same *endo*-chloro isomer was prepared by the zinc–acetic acid stereoselective reduction of the dichloroketene–cyclopentadiene adduct by Professor Andre' Dreiding of the University of Zurich [M. Rey, U. A. Huber, and A. S. Dreiding, *Tetrahedron Lett.*, 3583 (1968)]. The pmr spectrum of this compound was also identical with that of the chloroketene–cyclopentadiene adduct.

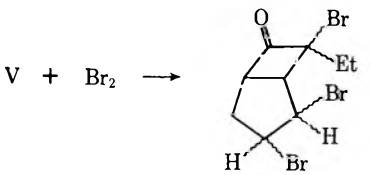
(13) (a) H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949). (b) G. B. Payne, *J. Org. Chem.*, **31**, 718 (1966).

nance assigned to the proton geminal to fluorine (area one-half proton).

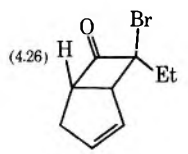
Bromoketene underwent cycloaddition to produce only about a 5% yield of the cycloadduct compared to 40% for the fluoroketene adduct and 60% for the chloroketene adduct. All of the preparations are accompanied by the formation of a black tarry substance which is the result of a competing polymerization reaction of the ketene. Apparently, bromoketene is more susceptible to this undesirable polymerization or less reactive toward cycloaddition.

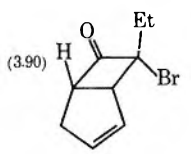
The methylketene adduct with cyclopentadiene was prepared utilizing the procedure and conditions which were so successful for the chloroketene system. This resulted in a very low yield (~10%), but the reaction conditions and solvents were varied to increase the yield to about 35%. The pmr spectrum of IV revealed a methyl doublet at δ 0.99. Martin and coworkers have reported that the pmr spectrum of the dimethylketene–cyclopentadiene adduct showed the methyl resonance at δ 1.28 and 0.93.[2] We have recently demonstrated in two methylhaloketene–cyclopentadiene systems that the upfield resonance was *endo*-methyl and the downfield resonance the *exo*-methyl. Thus, the methyl resonance at δ 0.99 observed in this system must be due to *endo*-methyl.

The cycloaddition of ethylketene to cyclopentadiene results in the isolation of only one isomer of 7-ethylbicyclo[3.2.0]hept-2-en-6-one as evidenced by vpc. The pmr spectrum did not indicate which isomer was produced. Bromination resulted in the replacement of the proton geminal to the ethyl group by bromine.



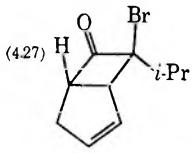
Both endo and exo isomers have been reported for a number of alkylhaloketene–cyclopentadiene cycloadducts. The pmr spectra of these compounds have been thoroughly investigated and a pattern observed for endo and exo isomers. The isomers of the ethylbromoketene cycloadduct are easily distinguished by a consideration of the chemical shift of the proton on carbon atom number five.[1] This resonance occurs at δ 4.26 when the ethyl group is endo and δ 3.90 when exo. Bromination of the ethylketene adduct produced a spectrum like

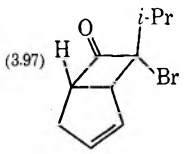




that of the ethylbromoketene cycloadduct with a resonance at δ 4.3 and no resonance at 3.90.[14]

Also, only one isomer was produced in the isopropylketene–cyclopentadiene system and this was the endo isomer as evidenced by bromination and subsequent pmr analysis. The pmr spectrum of the *endo*-isopropyl isomer of the isopropylbromoketene–cyclopentadiene adduct had a resonance at δ 4.27 for the proton on carbon atom number five. The *exo*-isopropyl isomer

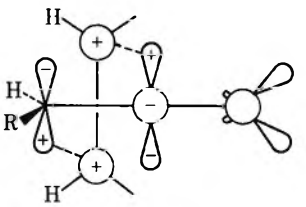




showed a resonance at δ 3.97 for this same hydrogen.[1] Bromination of the isopropylketene–cyclopentadiene adduct resulted in the appearance of a characteristic resonance at δ 4.25 and no resonance at δ 3.97.[14]

In summary, all of the aldoketenes investigated in this work were observed to undergo stereospecific cycloaddition with cyclopentadiene under the conditions described.

Woodward and Hoffmann have recently reported that in order for a (2 + 2) cycloaddition to be symmetry allowed as a thermal, concerted process, the reacting molecules must approach one another in an orthogonal manner. Ketenes are considered to play an antarafacial role ($\pi 2_s + \pi 2_a$) in the cycloaddition as illustrated.[15] Steric repulsion prevents the approach of the

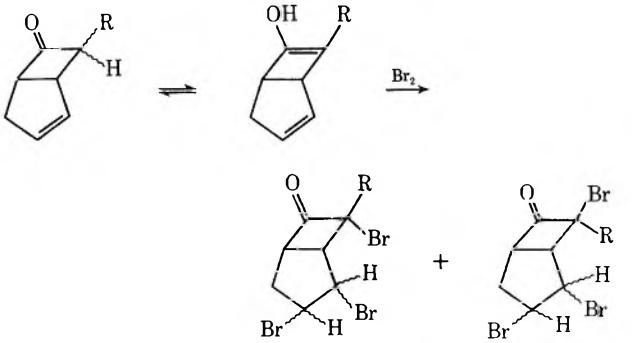


olefin on the side of the much larger R group. Also, in the sterically preferred approach, the bulky substituent on the olefin is away from the ketene hydrogen. These steric considerations in the orthogonal transition state lead to the prediction of a strong preference for the endo isomer. Since this is exactly what we have observed, this represents an excellent correlation with the recent theoretical developments in this area.

Experimental Section

Vpc separations were accomplished with an Aerograph AP-49 or Varian Model 1525-B instrument, using thermal conductivity detectors. Separations were achieved employing a 10 ft × 1/4 in. column packed with 15% Ucon 50 HB 2000 Polar and 2% Oronite NIW on Chromosorb W (DNSC) 60–80 mesh, or a 10 ft × 1/4 in. column packed with 10% QF-1 on Chromosorb W (acid washed) 60–80 mesh.

(14) It was expected that the bromination of IV, V, and VI would proceed through the enol form of the cycloadduct and produce both *endo*- and *exo*-bromo isomers. Since both isomers were not produced, another pathway



was indicated whereby a retention of configuration occurred at C_7. This is supported by the fact that IV was established to be *endo*-methyl isomer by pmr; yet bromination afforded only the *endo*-methyl isomr.

(15) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

Pmr spectra were obtained with a Varian A-60 nuclear magnetic resonance spectrometer, employing tetramethylsilane as the internal standard at 25°.

All solvents were dried and purified by distillation from calcium hydride or lithium aluminum hydride and subsequently stored over calcium hydride or molecular sieves 4A.

Fluoroacetyl chloride was prepared from sodium fluoroacetate and phosphorous pentachloride according to the procedure of Truce.[16] All of the other acid halides were prepared from commercially available acids by standard procedures. Cyclopentadiene was obtained by thermally cracking commercially available dicyclopentadiene at about 140°. Tri-*n*-butyltin hydride was prepared from commercially available tri-*n*-butyltin chloride and lithium aluminum hydride.[17] The dichloroketene–cyclopentadiene adduct was prepared by the dehydrochlorination of dichloroacetyl chloride in the presence of cyclopentadiene.[18]

7-Fluorobicyclo[3.2.0]hept-2-en-6-one (I).—A solution containing 40 g (0.395 mol) of triethylamine and 120 g (1.87 mol) of cyclopentadiene in 125 ml of ether was cooled to −78°. A 34.5-g (0.35 mol) portion of fluoroacetyl chloride was added to the cold solution dropwise and with stirring over a period of about 30 min. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to warm to room temperature overnight. The originally white colored salt turned brown as the temperature rose. The salt was removed by filtration and the filtrate concentrated on a rotatory evaporator. The concentrate was distilled at 73.5° (4.5 mm) to yield 17.5 g (40%) of the adduct: ir 1800 (C=O) and 1605 cm^{-1} (C=C); pmr (CCl_4) δ 2.6 (m, 2 H), 3.45 (m, 1 H), 3.85 (m, 1 H), 5.52 (m, 1 H), and 5.87 (m, 2 H); the pmr employing a fluorine decoupler demonstrated the presence of fluorine.

Anal. Calcd for C_7H_7FO: C, 66.65; H, 5.59. Found: C, 66.50; H, 5.55.

Bromination of 7-Fluorobicyclo[3.2.0]hept-2-en-6-one.—A 0.16-g (1.3 mmol) portion of I in 0.25 ml of CCl_4 in an nmr tube was treated with a solution of 0.20 g (1.27 mmol) of bromine in 0.25 ml of CCl_4 with intermittent agitation. The pmr spectrum revealed that saturation of the vinyl region had occurred because the vinyl resonance disappeared and upfield resonances were more complicated. However, elimination of the vinyl resonance revealed the other half of the resonance for the proton geminal to fluorine.

Hydrogenation of 7-Fluorobicyclo[3.2.0]hept-2-en-6-one.—A mixture of 0.1 g of palladium black and 50 ml of absolute ethanol was stirred at 27° under a hydrogen atmosphere. A 1.4 g (0.01 mol) portion of I was injected into the system and hydrogen absorbed continuously for 1.5 hr and more slowly for another 3 hr. A total of 252 ml (0.01 mol) of hydrogen was absorbed. The alcohol was removed by distillation and the hydrogenated product purified by vpc at 150° on a 10 ft × 1/4 in. XF-1150 column: ir 1795 cm^{-1} (C=O) and no C=C; pmr (CCl_4) δ 1.86 (m, 6 H), 3.38 (m, 2 H), and a pair of multiplets separated by 55 cps centered at 5.52 (1 H).

7-Chlorobicyclo[3.2.0]hept-2-en-6-one (II). **Method A.**—To a solution containing 11.6 g (0.115 mol) of triethylamine and 84.4 g (1.3 mol) of cyclopentadiene in 250 ml of hexane was added, dropwise at −78°, 17 g (0.108 m) of chloroacetyl bromide with stirring. Upon warming overnight, the salt was removed and the filtrate yielded 9.2 g (60%) of II at 64° (0.6 mm): ir 1795 (C=O) and 1605 cm^{-1} (C=C); pmr (CCl_4) δ 2.6 (m, 2 H), 3.84 (m, 2 H), 5.08 (m, 1 H), and 5.81 (m, 2 H).

Anal. Calcd for C_7H_7ClO: C, 58.8; H, 4.91. Found: C, 58.55; H, 4.93.

Method B.—A solution of 8.85 g (0.05 mol) of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one in 15 ml of toluene was rapidly added to 16.3 g (0.056 mol) of tri-*n*-butyltin hydride in 5 ml of toluene. The resulting solution is allowed to stand for 1 hr and distilled to yield 6 g (84%) of II at 40–45° (0.2–0.3 mm). The ir and pmr spectra were identical with those recorded above.

7-Bromobicyclo[3.2.0]hept-2-en-6-one (III).—A 60-ml portion of ether, 50 g (0.5 mmol) of triethylamine, and 80 g (1.41 mol) of cyclopentadiene were stirred at −78° while 50.5 g (0.25 mol) of bromoacetyl bromide was added dropwise. After warming to room temperature, the amine salt was removed and the solvent evaporated on a rotorary evaporator. Such a small amount of liquid remained that distillation was not attempted. Purification was accomplished by vpc and estimations indicated the yield was approximately 5%: ir 1795 (C=O) and 1617 cm^{-1} (C=C); pmr (CCl_4) δ 2.6 (m, 2 H), 3.87 (m, 2 H), 5.14 (m, 1 H), and 5.8 (m, 2 H).

Anal. Calcd for C_7H_7BrO: C, 44.8; H, 3.74. Found: C, 45.1; H, 3.96.

7-Methylbicyclo[3.2.0]hept-2-en-6-one (IV).—To a refluxing solution of 50 g (0.5 mol) of triethylamine, 165 g (2.5 mol) of cyclopentadiene, and 100 ml of hexane was added dropwise 46 g (0.5 mol) of propionyl chloride. After the addition was complete, refluxing was continued 1.5 hr and then the reaction mixture was allowed to cool to room temperature overnight. The amine salt was removed by filtration, the solvent evaporated, and the residue distilled at 60–65° (4.7 mm) to yield 57 g of a mixture of IV and dicyclopentadiene. Vpc was necessary to accomplish a separation and revealed that approximately 20 g (33%) was produced. The ir and pmr data were consistent with those already in the literature.[3]

Hydrogenation of 7-Methylbicyclo[3.2.0]hept-2-en-6-one.—A mixture of 0.1 g of palladium black and 50 ml of absolute ethanol was stirred for about 1 hr at 27° under a hydrogen atmosphere and then 1.6 g (0.013 mol) of IV was injected into the system. When hydrogen was no longer absorbed, the solution was concentrated by distillation of the alcohol and the product purified by vpc at 125° using the Ucon–Oronite column: ir 1744 cm^{-1} (C=O), no C=C; pmr (CCl_4) δ 0.95 (d, 3 H), 1.72 (m, 6 H), 2.95 (m, 2 H), and 3.5 (m, 1 H).

Bromination of 7-Methylbicyclo[3.2.0]hept-2-en-6-one.—Bromine was slowly and cautiously added dropwise to a 30% solution of IV in CCl_4 in an nmr tube. The addition was done intermittently and continuously until the pmr spectrum revealed no resonance for vinyl protons. However, this spectrum also showed the proton geminal to the methyl group had been displaced by bromine; this was obvious because the methyl doublet (δ 0.99) disappeared and a singlet appeared downfield at δ 1.9. Attempts to purify the brominated product resulted in decomposition.

7-Ethylbicyclo[3.2.0]hept-2-en-6-one (V).—A gently refluxing solution of 34 g (0.336 mol) of triethylamine, 66 g (1 mol) of cyclopentadiene, and 100 ml of CCl_4 was treated with a 32-g (0.30 mol) portion of butyryl chloride dropwise over a 15-min period. Refluxing was continued for 1.5 hr and the solution was allowed to cool overnight. Removal of salt, concentration of the filtrate, and distillation resulted in 14 g (34%) of V at 70–71.5° (4.7 mm): ir 1773 (C=O) and 1613 cm^{-1} (C=C); pmr (CCl_4) δ 1.02 (m, 3 H), 1.90 (m, 2 H), 2.45 (m, 2 H), 3.2–4.1 (m, 3 H), and 5.8 (m, 2 H).

The 2,4-dinitrophenylhydrazone derivative was prepared by a standard procedure.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.06; N, 17.72. Found: C, 57.22; H, 5.14; H, 17.96.

Partial bromination of the cycloadduct with a 10% solution of bromine in CCl_4 resulted in displacement of the proton geminal to the ethyl group by bromine. This was evident from the pmr spectrum because part of the multiplet at δ 3.2–4.1 was eliminated and a pattern appeared at δ 4.3 which was easily recognized as part of the *endo*-ethyl isomer of ethylbromoketene–cyclopentadiene cycloadduct.

7-(2-Propyl)bicyclo[3.2.0]hept-2-en-6-one (VI).—To a refluxing solution of 66 g (1 mol) of cyclopentadiene and 25 g (0.25 mol) of triethylamine in 120 ml of $CHCl_3$ was added 24 g (0.2 mol) of isovaleryl chloride dropwise over a 15-min period. Refluxing was continued 1.5 hr and the solution cooled while standing overnight. Filtration, concentration, and distillation afforded 11 g (37%) of VI at 79–80° (4.7 mm): ir 1770 (C=O) and 1607 cm^{-1} (C=C); pmr (CCl_4) δ 0.94 (m, 6 H), 1.6 (m, 1 H), 2.4 (m, 2 H), 3.0–3.9 (m, 3 H), and 5.8 (m, 2 H).

Anal. Calcd for $C_{10}H_{14}O$: C, 80.0; H, 9.34. Found: C, 80.3; H 9.59.

Partial bromination of VI with a 10% solution of bromine in CCl_4 resulted in displacement of the proton geminal to the isopropyl group by bromine. This was apparent from the pmr spectrum because part of the resonance at δ 3.0–3.9 was eliminated and a new resonance appeared at δ 4.25 which was recognized as part of the *endo*-isopropyl isomer of the isopropylbromoketene–cyclopentadiene cycloadduct.

(16) W. E. Truce, *J. Amer. Chem. Soc.*, **70**, 2828 (1948).

(17) G. J. M. Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 366 (1957).

(18) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. F. Gaughan, *J. Amer. Chem. Soc.*, **87**, 5257 (1965).

Registry No.—I, 25975-83-1; II, 25169-61-3; III, 25975-85-3; IV, 25169-69-1; V, 25975-87-5; VI, 25975-88-6.

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Stereochemistry of Solvolytic Cyclization of the 5-Hexenyl System. Acetolysis of Methyl-5-hexenyl *p*-Bromobenzenesulfonates[1a]

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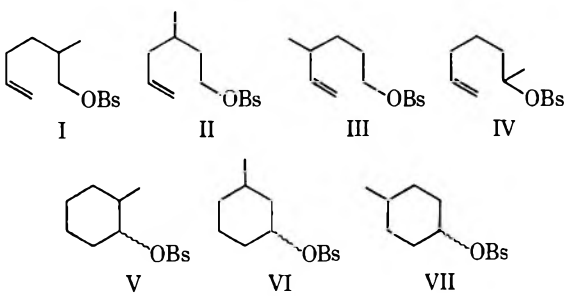
The rates and products of acetolysis of 2-, 3-, and 4-methyl-5-hexenyl *p*-bromobenzenesulfonates are reported, as well as the products of acetolysis of *cis*- and *trans*-2-, 3-, and 4-methylcyclohexyl and 6-hepten-2-yl *p*-bromobenzenesulfonates, thus furnishing data for comparison of π- and σ-route products for the three secondary methylcyclohexyl cations. As found in most previous instances for secondary carbonium ions, the π route yields less than half as much elimination product as the σ route. The stereochemistry of the substitution products from the π-route reactions strongly implies cyclization through a chairlike conformation and very rapid reaction of the resulting chair cyclohexyl cation with solvent.

Solvolytic cyclization of 5-hexenyl systems to cyclohexyl cations, the so-called π route[2] to these cations, has received considerable study,[3,4] and even synthetic use.[5] It is usually assumed that the cyclohexyl cation produced in these cyclizations is in a chair conformation, and Johnson and Harding have presented rather compelling evidence that this is the case for the mechanistically similar acid-catalyzed cyclization of 4-(3-butenyl)-3-cyclohexenol systems.[6] However, it was not at all clear that simpler, more flexible, 5-hexenyl systems should necessarily yield only the chair form of the cation in reactions involving intramolecular displacement of the leaving group by the π bond. It was therefore felt important to examine a simple system, employing a relatively innocuous marker, a methyl group, for detection of the preferred conformation of cyclization. At the same time it was hoped that presence of such a marker might help show other differences in product formation from π- and σ-route cyclohexyl cations. To this end, the rates and products of acetolysis of 2-, 3-, and 4-methyl-5-hexenyl *p*-bromobenzenesulfonates (I, II, and III) were determined, as well as the acetolysis products of 6-hepten-2-yl *p*-bromobenzenesulfonate (IV) and cis and trans isomers of 2-, 3-, and 4-methylcyclohexyl *p*-bromobenzenesulfonates (V, VI, and VII).



a, cis

b, trans

Results and Discussion

The products of acetolysis of all the brosylates are given in Table I. Because of the many components present in the product mixtures a rather elaborate method of analysis was necessary. Three separate analyses were performed on each product mixture. First, the initial pentane extract (see Experimental Section) was subject to gc analysis using a silver nitrate–ethylene glycol column which effectively separated 1-methylcyclohexene from 3- and 4-methylcyclohexene as well as "baseline" separating all the other hydrocarbons. (The separation of 3- and 4-methylcyclohexene could not be completely achieved and their yields are lumped together in Table I.) Secondly, a suitable internal standard was added to the pentane extract and the solution analyzed on a "UC-W98" (silicone rubber) column. This column separated all acetates (except certain of the cyclic ones from each other) and acyclic olefins (dienes) from cyclic ones. Finally, the product mixtures were subjected to lithium aluminum hydride reduction to convert acetates to alcohols and the resulting product mixture analyzed either with a glycerol column or a combination column composed of a forecolumn of THEED (tetrahydroxyethylethylenediamine) preceding a diglycerol column. Certain pairs of alcohols could not be separated on any columns tried. These were *trans*-3- and *cis*-4-methylcyclohexanol and *cis*-3- and *trans*-4-methylcyclohexanol. This is unfortunate, but in several instances the peak in question was collected, its ir spectrum being measured, and shown to be at least predominantly the expected isomer and not that resulting from hydride shift. All results shown in Table I are the average of at least two separate experiments. As mentioned previously,[7] the reproducibility in measurement of peak areas was no worse than $\pm 10\%$ for small peaks

(1) (a) Supported in part by the National Science Foundation (Grant GP-5658); (b) Alfred P. Sloan Research Fellow, 1968–1970. Author to whom correspondence should be addressed.

(2) S. Winstein and P. Carter, *J. Amer. Chem. Soc.*, **83**, 4485 (1961).

(3) P. D. Bartlett, W. D. Closson, and T. J. Cogdell, *ibid.*, **87**, 1308 (1965).

(4) (a) P. D. Bartlett, E. M. Nicholson, and R. Owyang, *Tetrahedron Suppl.*, **8**, 399 (1966). (b) W. S. Trahanovsky and M. P. Doyle, *J. Amer. Chem. Soc.*, **89**, 4867 (1967); W. S. Trahanovsky and M. P. Doyle, *Chem. Commun.*, 1021 (1967).

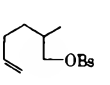
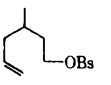
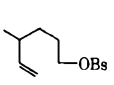
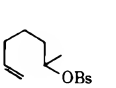
(5) W. S. Johnson, *Accounts Chem. Res.*, **1**, 1 (1968).

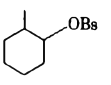
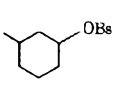
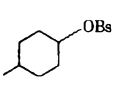
(6) W. S. Johnson and J. E. Harding, *J. Org. Chem.*, **32**, 478 (1967).

(7) S. A. Roman and W. D. Closson, *J. Amer. Chem. Soc.*, **91**, 1701 (1969).

TABLE I

ACETOLYSIS PRODUCTS OF METHYL-5-HEXENYL AND METHYLCYCLOHEXYL BROSYLATES[a]

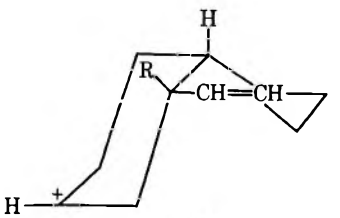
	Methyl-5-hexenyl Brosylates			
	% yield of			
				
trans-2-Methylcyclohexyl acetate		0.6	20.9	
cis-2-Methylcyclohexyl acetate		0.5	4.2	
trans-3-Methylcyclohexyl acetate		5.8	0.8	3.1
cis-3-Methylcyclohexyl acetate		38.5	1.4	6.3
trans-4-Methylcyclohexyl acetate	3.5			
cis-4-Methylcyclohexyl acetate	17.0			
1-Methylcyclohexyl acetate			1.1	
3- and 4-methylcyclohexene	11.4[b]	20.8[b]	5.4[c]	5.3[b]
1-Methylcyclohexene	1.9	1.8	6.7	
Cyclopentylmethylcarbinyl acetate			2.1	
Alkenes related to above			1.4	
Unrearranged acetate	21.2	32.2	56.0	38.2
Acyclic dienes	38.3			43.8
Other	5.7[d]	(5.3)[e]		3.1[f]
Total cyclic alkenes	13.3	22.6	13.5	5.3
Total cyclic acetates	20.5	45.4	30.5	9.4
% cyclization	34	68	44	15
% recovery	99	93	90	99.5

	Methylcyclohexyl Brosylates					
	% yield of					
						
	cis	trans	cis	trans	cis	trans
trans-2-Methylcyclohexyl acetate	0.5	7.6	0.3	0.3		
cis-2-Methylcyclohexyl acetate	0.2	12.0	0.1	0.8		
trans-3-Methylcyclohexyl acetate	0.4	0.6	22.3	6.1		
cis-3-Methylcyclohexyl acetate	0.1	1.2	2.8	15.9		
trans-4-Methylcyclohexyl acetate					12.0	2.3
cis-4-Methylcyclohexyl acetate					9.4	19.6
1-Methylcyclohexyl acetate	11.0	2.9	0.5	0.9		
3- and 4-methylcyclohexene	3.1[c]	26.1[c]	71.0[b]	71.7[b]	76.1[b]	78.1[b]
1-Methylcyclohexene	84.7	44.7	3.0	4.3	2.5	
Cyclopentylmethylcarbinyl acetate		1.8				
Alkenes related to above		3.1				
Total alkenes	88	74	74	75	79	78
Total acetates	12	26	26	24	21	22
% recovery	89	99	98	90	98	98

[a] Reactions carried out at 100°; [ROBs] = 0.1 *M*; [NaOAc] = 0.15 *M*. [b] Major component is 4-methylcyclohexene. [c] Major component is 3-methylcyclohexene. [d] 2-Methyl-5-hexen-2-yl acetate. [e] 3-Methyl-5-hexenyl chloride; not included in calculation of total yield. [f] Two or more unidentified components eluting near unrearranged acetate.

(less than 10% of total peak area in gc spectrum) and about ±2% for larger peaks.

Johnson and Harding concluded that the carbonium ion VIII reacts with solvent formic acid in the conformation shown, and reacts faster than the octalin ring system can undergo inversion.[6] Whiting has also suggested that carbonium ions in hydroxylic solvents react considerably faster than rotation about carbon–carbon



VIII

single bonds.[8] Berson and coworkers have noted in several publications that certain bicyclic carbonium ions must react by internal bond migration while still retaining a "memory" of the conformation of the starting material.[9] Thus, one can conclude that the products from a carbonium ion reaction in hydroxylic media may reveal the conformation of the cation. If we assume, after Johnson and Harding,[6] that solvent attack occurs mostly from the direction of least steric hindrance and if we make the reasonable assumption that the methyl group will tend to be located in the least hindered position during cyclization of the 5-hexenyl system and thus in the newly formed cyclohexyl cation,

(8) M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966).

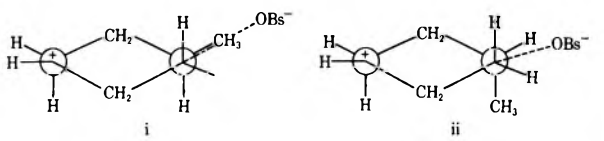
(9) See J. A. Berson, R. G. Bergman, G. M. Clarke, and D. Wege, *J. Amer. Chem. Soc.*, **91**, 5601 (1969), and previous papers in this series.

ther. one should be able to predict the configuration of the principle substitution product for each methyl-5-hexenyl system for any given conformation during cyclization. For a chair conformation, the predictions would be *cis*-4-methylcyclohexyl acetate from I,[10] *cis*-3-methylcyclohexyl acetate from II, *trans*-2-methylcyclohexyl acetate from III, and *cis*-3-methylcyclohexyl acetate from IV. The data from Table I show that these *are* the major cyclic substitution products in each case by rather sizable factors: 83% *cis* for I, 87% *cis* for II, 83% *trans* for III, and ~67% *cis* for IV. Thus, if we wish to assume a common conformation for cyclization of these minimally substituted 5-hexenyl derivatives, it must be chairlike. The minor product, in each case, can arise from axial attack of solvent on the preferred chair conformer of the cation, from reaction of small amounts of higher energy conformers, or both. The near identity in yields of the major isomeric substitution products from I, II, and III (~84%) makes our original assumption[10] that the eclipsing interaction in I would force the methyl predominantly axial look very good. In fact, the methyl group in the cation from I appears to be as predominantly axial as those in the cations from II and III are equatorial. This would be expected if the eclipsing interaction in I is as large (3.9 kcal/mol) as claimed in III[10] and if the free energy difference between "axial" and "equatorial" methyl during cyclization of the methyl-5-hexenyl derivatives is approximately the same as for cyclohexane (~1.7 kcal/mol).[12] The similarity in yields of product apparently derived from equatorial solvent attack on the more stable chair conformer in these systems to that observed by Johnson and Harding for equatorial attack (83%) of formic acid on ion VIII (R = H)[6] is interesting, but may be only coincidental.[13]

One troublesome aspect of interpreting π-route product mixtures is the question of internal return, which could result in formation of σ-route type products from π-route reactions. Since the methylcyclohexyl brosylates all react at least an order of magnitude faster than the primary 5-hexenyl derivatives, their formation during acetolysis of I, II, and III would be difficult to detect. Since one does see internal return in π-route reactions in kinetically favorable situations[14] one must consider it for these. Using the yield of one or more of the olefins (predominant products from σ-route reaction) as the limiting factor, one may estimate upper-limits for internal return for each of the methyl-5-hexenyl system for both cyclic systems related to it. In most cases the upper limit on internal return is quite high, 40–50%. This may be at least partly due to the necessity of lumping 3- and 4-methylcyclohexene together as one product, the one used as the limiting factor in all but one case. The situation for 4-methyl-5-hexenyl brosylate (III) is more meaningful, since here 1-methylcyclohexene could be reliably used as the limiting factor. The upper limits on internal return for III turn out to be only 18% for *cis*-2-methylcyclohexyl brosylate (Ia) and 34% for *trans*-Vb. After "correction" for maximum possible internal return to Va and Vb, the only striking change in the product mixture from III is the lack of 1-methylcyclohexene and its effect on the acetate–olefin ratio. This, of course, may be only an artifact of "correction." In fact, since everything else seems to be produced in the π-route reaction of III, even after "correction," it would seem reasonable that some 1-methylcyclohexene should be produced. Making the simple assumption that the amount of 1-methylcyclohexene from π-route reaction should be about half the amount of 3-methylcyclohexene (proportional to the number of β hydrogens) lowers the upper limits on internal return to Va and Vb to 11% and 21%, respectively. If we assume that this is typical for π-route reactions of 5-hexenyl systems, then internal return does not represent a major reaction pathway for the π-route cations (say, 25% at most) and does not have a serious effect on the composition of the observed product mixture, or the conclusions drawn from them.

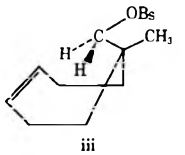
In Table II are given the overall rates of acetolysis for I, II, and III, as well as for the unsubstituted system, 5-hexenyl brosylate. Also included are estimated

(10) In cyclization of 2-methyl-5-hexenyl brosylate (I) through a chair conformation the methyl group must either eclipse the brosylate as in i, or be oriented axially as in ii. Felkin and coworkers[11] have concluded that a



i ii

similar eclipsing interaction during solvolytic cyclization of 1-methyl-Δ^4-cycloheptenylmethyl brosylate (iii) raises the activation energy for the



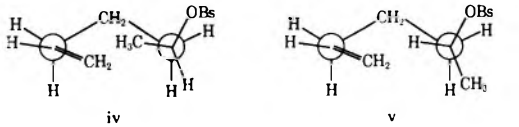
iii

process by 3.9 kcal/mol. While the 5-hexenyl cyclization may differ somewhat from that of iii, we feel that the eclipsing interaction should be large enough in i to make ii preferred and thus lead to formation of *cis*-4-methylcyclohexyl acetate if I cyclizes through a chair conformation.

(11) C. Chuit, F. Colard, and H. Felkin, *Chem. Commun.*, 118 (1966).

(12) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 44.

(13) The one instance where the observations do not fit so well is that of the 3-methylcyclohexyl cation derived from IV. Rather than a 5:1 ratio in favor of the predicted cis acetate, only a 2:1 ratio was observed. The yield of cyclic acetate is only 9% in this case, and the identification of both acetate products rests only on gc retention times and peak enrichment techniques. However, assuming the identifications and ratio measurements are correct, the cation from IV seems clearly less selective either in production of the two possible chair conformations or in the subsequent substitution reactions. There would seem little reason for diminished selectivity in the substitution process, but there are some serious steric interactions for IV in conformations leading to a chair cation. If, after Chuit, Colard, and Felkin,[11] we assume colinearity of incoming and leaving groups is necessary during the displacement, the two conformations of IV necessary to produce a chair cation would be iv and v. In iv the methyl must nearly eclipse the adjacent



iv v

methylene; in v it must be oriented pseudo-axially. It seems rather plausible that IV may cyclize at least partly through some nonchair conformation where the 1-methyl substituent can avoid some of the steric interactions apparent in iv and v.

(14) (a) H. L. Goering and R. F. Myers, *J. Amer. Chem. Soc.*, **91**, 3386 (1969); H. L. Goering and W. D. Closson, *ibid.*, **83**, 3511 (1961). (b) W. D. Closson and G. T. Kwiatkowski, *Tetrahedron Lett.*, 6435 (1966). (c) P. E. Peterson and R. J. Kamat, *J. Amer. Chem. Soc.*, **91**, 4521 (1969).

TABLE II
EFFECTS OF METHYL GROUPS ON RATES OF ACETOLYSIS OF 5-HEXENYL BROSYLATES[a]

Brosylate	10^5k, sec^{-1}	Approximate rate of cyclization, 10^5k, sec^{-1}[b]
5-Hexenyl	4.29 ± 0.04	1.1[c]
2-Methyl-5-hexenyl	2.55 ± 0.01[d]	0.87
3-Methyl-5-hexenyl	10.2 ± 0.1[e]	6.95
4-Methyl-5-hexenyl	5.65 ± 0.03[f]	2.5

[a] At 100°; [ROBs] = 0.03 *M*, [NaOAc] = 0.035 *M*. [b] Estimated using per cent cyclizations from Table I. See also ref 15. [c] Estimated using data from ref 14. [d] $\Delta H^* = 24.4$ kcal/mol; $\Delta S^* = -14.5$ eu. [e] $\Delta H^* = 24.9$ kcal/mol; $\Delta S^* = -10.1$ eu. [f] $\Delta H^* = 24.9$ kcal/mol; $\Delta S^* = -11.0$ eu.

rates of cyclization for each case.[15] The effects of the methyl groups on these rates of cyclization are fairly large and quite instructive. The increased ease of cyclization caused by a substituent on the chain is a well-known phenomenon (sometimes referred to as the "*gem*-dimethyl effect") and should not depend much on its positioning on the chain.[17] Here we find almost an order of magnitude variation. The difference in effect between II and III is probably due to the difference in ground state torsional interactions and rotational energy barriers between a methyl group adjacent to sp^2 carbon and to sp^3 carbon.[18] The 8.7-fold difference in k for I and II corresponds to a $\Delta\Delta F^*$ (at 100°) of about 1.5 kcal, remarkably close to the free energy difference between axial and equatorial methyl (1.7 kcal).[12] This kinetic effect provides rather pleasing confirmation of our postulation that I should be the only one of the systems to cyclize to a cyclohexyl cation with a predominantly axial methyl group.

The pattern of products from the σ-route reactions (Table I) agree quite well with those observed from *tert*-butyl substituted cyclohexyl systems by Whiting, Sicher, and coworkers,[19] a general pattern of greater amount of substitution for equatorial brosylates, predominant inversion of configuration during substitution, and considerable hydride-shift product (with predominant retention of configuration at the new site when substitution occurs) being observed. The large amount of inverted substitution product obtained from the predominantly equatorial brosylate (always more predominantly inverted than the corresponding axial brosylate products) supports the postulation of a non-chair transition state for solvolysis of "rigid" equatorial cyclohexyl brosylates.[19,20] As in most comparisons of π- and σ-route product mixtures, there is an almost complete reversal of elimination–substitution ratios between the two pathways to the "same" cyclohexyl cation. While this difference does not show up in the case of the more rigid bicyclic carbonium ions (where elimination is difficult in any case)[2,9,21] or apparently in the more stable benzylic cations,[7] this pattern seems almost characteristic for the simpler secondary monocyclic cations.[3,4,14b]

Experimental Section[22]

Materials.—The compounds used in this study were either obtained from commercial sources or prepared by standard techniques. Their physical properties, derivatives, or sources are listed below.

3-Methyl-5-hexen-1-ol had bp 73–74° (12 mm): n^{20}D 1.4407; nmr (CCl_4) δ 0.95 (dubulet, 3 H), 1.0–2.1 (multiplet, 5 H), 3.6 (triplet, 2 H), 4.1 (singlet, 1 H), 4.8–6.1 (multiplet, 3 H).

The α-naphthylurethan had mp 45–46° (petroleum ether).

Anal. Calcd for $C_{19}H_{21}O_2N$: C, 76.30; H, 7.47. Found: C, 76.60; H, 7.49.

2-Methyl-5-hexen-1-ol had bp 68° (12 mm), n^{20}D 1.4399 [lit.[23] bp 166–168° (736 mm), n^{22}D 1.4382]: nmr (CCl_4) δ 0.9 (doublet, 3 H), 1.0–2.3 (multiplet, 5 H), 3.4 (doublet, 2 H), 4.0 (singlet, 1 H), 4.7–6.2 (multiplet, 3 H).

The α-naphthylurethan had mp 45.6–47.5° (petroleum ether).

Anal. Calcd for $C_{18}H_{21}O_2N$: C, 76.30; H, 7.47. Found: C, 76.52; H, 7.47.

4-Methyl-5-hexen-1-ol had bp 68° (12 mm), n^{22}D 1.4375: nmr (CCl_4) δ 1.0 (doublet, 3 H), 1.1–2.4 (multiplet, 5 H), 3.5 (triplet, 2 H), 4.6 (singlet, 1 H), 4.7–6.1 (multiplet, 3 H).

The α-naphthylurethan melted at 55.5–56° (petroleum ether).

Anal. Calcd for $C_{18}H_{21}O_2N$: C, 76.30; H, 7.47. Found: C, 76.29; H, 7.60.

6-Hepten-2-ol had bp 84–86° (60 mm), n^{20}D 1.4371 [lit.[24] bp 64–65° (13 mm), n^{18}D 1,4387): nmr (CCl_4) δ 1.1 (doublet, 3 H), 1.3–1.7 (multiplet, 4 H), 2.1 (multiplet, 2 H), 3.7 (multiplet, 1 H), 3.9 (singlet, 1 H), 4.8–6.1 (multiplet ,3 H).

Anal. Calcd for $C_7H_{14}O$: C, 73.76; H, 12.65. Found: C, 73.63; H, 12.36.

3-Methylhexan-1-ol had bp 135–140° (600 mm) [lit.[25] bp 168–169° (754 mm). The α-naphthylurethan melted at 44–46° (lit.[25] 45–47°).

2-Methyl-5-hexen-2-ol had bp 142–143° (760 mm) [lit.[26] bp 143–144° (760 mm)].

1-Methylcyclohexanol and **cyclopentylmethylcarbinol** were prepared on small scales by appropriate Grignard reactions, purified by small scale sublimative distillations and had ir and nmr spectra in complete agreement with structure.

***cis*-3-Methylcyclohexanol** had bp 72–74° (15 mm), and its *p*-nitro benzoate melted at 45–46° (aqueous methanol) (lit.[27] mp 45.5–46.5°).

***trans*-3-Methylcyclohexanol** was obtained from a mixture of the epimers by preparative gc. Its *p*-nitrobenzoate melted at 60–61° (lit.[28] mp 61.5–62.5°).

***trans*-2-Methylcyclohexanol** had bp 82° (21 mm) [lit.[28] bp 75° (14 mm)]. The *p*-nitrobenzoate melted at 64–65° (aqueous methanol), (lit.[28] mp 64.5–65°).

(15) A referee has suggested that our product studies should have been carried out in acetic acid buffered with urea in the manner suggested by Trahanovsky, *et al.*,[16] in order to eliminate that fraction of acyclic product that arises from SN2 displacement by acetate ion. Unfortunately, urea does not completely inhibit further acid-catalyzed reactions of the acetolysis products, even cyclohexene being partly converted to cyclohexyl acetate under typical reaction conditions.[16] Since the stereochemistry of the substitution products were of prime concern in this study, a more effective buffering agent was necessary. However, since the bulk of the SN2 product must still come from attack by acetic acid at the concentration of acetate ion used in our product studies,[16] and since the acetate ion concentration was the same (0.15 *M*) in each case, the rates of cyclization stated in Table II and derived from the expression $k_{cyc} = k_{obs} \times$ fraction of cycl are at least proportional to the true cyclization rates in pure acetic acid and at best only slightly underestimated.

(16) W. S. Trahanovsky, M. P. Doyle, and P. D. Bartlett, *J. Org. Chem.*, **32**, 150 (1967).

(17) N. L. Allinger and V. Zalkow, *ibid.*, **25**, 701 (1960).

(18) (a) See ref 11, pp 19–21. (b) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 133–134.

(19) (a) 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). (b) M. Pánková, J. Sicher, M. Tichý, and M. C. Whiting, *ibid.*, 365 (1968). (c) M. Tichý, J. Hapala, and J. Sicher, *Tetrahedron Lett.*, 3739 (1969).

(20) V. J. Shiner and J. G. Jewett, *J. Amer. Chem. Soc.*, **87**, 1382 (1965).

(21) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *ibid.*, **87**, 1288 (1965), and subsequent papers in this series.

(22) Melting and boiling points are uncorrected. Nuclear magnetic resonance spectra (nmr) were measured at 60 MHz, using tetramethylsilane as internal standard. Preparative gas chromatography was carried out on an Aerograph A-90 gas chromatograph; analytical gas chromatography was performed using a Hewlett–Packard 5750 research chromatograph.

(23) R. Brettle and F. S. Holland, *J. Chem. Soc.*, 4836 (1962).

(24) P. Gaubert, R. P. Linstead, and H. N. Rydon, *ibid.*, 1971 (1937).

(25) A. Dewael and A. Weckering, *Bull. Soc. Chim. Belges*, **33**, 495 (1924).

(26) J. K. Kochi, *J. Amer. Chem. Soc.*, **85**, 1958 (1963).

(27) W. Hückel and J. Kurz, *Chem. Ber.*, **91**, 1290 (1958).

(28) E. L. Eliel and C. A. Lukack, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).

cis-2-**Methylcyclohexanol** was separated from a mixture of the epimeric alcohols by preparative gc and had spectroscopic properties in keeping with its structure. Its brosylate is described in Table III.

TABLE III

YIELDS, PROPERTIES, AND ACETOLYSIS EQUIVALENTS OF BROSYLATES

Brosylate	Yield, %	Mp, °C	Acetolysis equivalent—Calcd	Found
2-Methyl-5-hexenyl (I)	70	Oil	333	343
3-Methyl-5-hexenyl (II)	60	Oil	333	342
4-Methyl-5-hexenyl (III)	70	Oil	333	335
5-Hepten-2-yl (IV)	58	Oil	333	338
3-Methylhexyl	74	Oil	335	341
5-Hexenyl	50	Oil	319	327
cis-2-Methylcyclohexyl (Va)	67	56–56.5	333	334
trans-2-Methylcyclohexyl (Vb)	80	48.5–49.5	333	334
cis-3-Methylcyclohexyl (VIa)	69	41.5–42.5	333	335
trans-3-Methylcyclohexyl (VIb)	87	54–54.5	333	335
cis-4-Methylcyclohexyl (VIIa)	72	86.5–87	333	333
trans-4-Methylcyclohexyl (VIIb)	82	48.5–49	333	334

4-Methylcyclohexanols.—Both cis and trans isomers were obtained in pure form from Aldrich Chemical Co.

p-**Bromobenzenesulfonates** were prepared in the usual manner. Solid *p*-bromobenzenesulfonates (brosylates) were purified by recrystallization from pentane at 0°; brosylates that were liquid at room temperature were purified by recrystallization from pentane at −50 to −80°. The yields, properties, and acetolysis equivalents are given in Table III.

Acetates of the alcohols were prepared on a small scale from the pure alcohols and acetic anhydride in pyridine. Pure samples were obtained by preparative gc in most cases, and all had ir and nmr spectra in agreement with assumed structure.

Product Analysis.—Solvolyses were carried out by heating a 0.10 *M* solution of brosylate in 0.15 *M* sodium acetate (in acetic acid) in a sealed ampule for at least ten half-lives at 100°. The reaction mixture was cooled, diluted with water, and continuously extracted with pentane for 24 hr. The pentane extract was carefully washed with water, dilute sodium bicarbonate solution, and saturated brine, and dried with anhydrous magnesium sulfate. Concentration was not necessary since the volume of pentane used was kept small, 30–40 ml. Products were analyzed directly from the dried pentane solution by gc on the following columns: (1) a 12 ft × 1/8 in. silver nitrate-ethylene glycol Chromosorb W acid washed 60–80 mesh column, for olefin determination; (2) a 6 ft × 1/8 in. 10% UC W-98 80–100 mesh column, for quantitative determination of olefin and acetate; (3) a 6 ft × 1/8 in. 15% diglycerol Anachrom 90–100 mesh with a 2 ft × 1/8 in. 20% THEED Chromosorb P 60–80 mesh fore column, or a 5 ft × 1/8 in. 25% glycerol Chromosorb P 60–80 mesh column, for alcohols from reduced acetate.

For all product analyses three general procedures were used.

1. **Olefin Determination.**—A small sample (0.5 λ) from the pentane extract was analyzed on the silver nitrate column operated at 30°. This column was effective in separating the isomeric methylcyclohexenes. 1-Methyl-cyclohexene eluted first followed by 4-methylcyclohexene and 3-methylcyclohexene. This was the same order observed by Gil-Av.[29] However, on several silver nitrate columns prepared according to his procedure, 4-methylcyclohexene and 3-methylcyclohexene could not be completely resolved. The 3 isomer always shouldered on the 4 isomer.

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

2. **Quantitative Determination of Olefin and Acetate.**—A measured amount of internal standard, chlorobenzene, was added to the pentane extract. Analysis was carried out on the UC-W-98 column programmed from 75 to 120° at 20°/min, the program was initiated 7 min after injection of the sample, and the upper temperature was maintained for 8 min after it had been reached. Molar response factors for standard solutions containing weighed amounts of olefin, acetate, and internal standard were determined in exactly the same way. In general the UC-W-98 column used in this was was effective in separating tertiary, secondary, and acyclic acetates. In addition 1-methylcyclohexene separated from its isomers and dienes separated from the cyclic olefins.

3. **Analysis of Alcohols.**—The pentane extract was treated with 0.5 g of lithium aluminum hydride and stirred for 1 hr. Reduction product was carefully worked up (in the usual way) and analyzed on the glycol columns operated at 95–100°. Secondary alcohols separated from tertiary alcohols and mixtures of epimeric methylcyclohexanols (except for the 3 and 4 systems) were completely resolved. Coupling the information gained from the three analyses enabled quantitative determination of olefin and acetate products.

All products were identified by comparing their gc retention times with authentic material and by collecting products, when feasible, and comparing their spectral properties with authentic samples. Product percentages (given in Table I) are the average of two or more analyses. A typical product analysis, that of the acetolysis products from III, is given below.

Products from the Acetolysis of 4-Methyl-5-hexenyl *p*-**Bromobenzenesulfonate.**—From 0.663 g (1.99 mmol) of the *p*-bromobenzenesulfonate in 20 ml of 0.15 *M* sodium acetate in acetic acid was obtained 1.72 mmol (90.6%) of product shown by gc analysis to consist of 6.8% 1-methylcyclohexene, 5.4% a mixture of 3- and 4-methylcyclohexene (predominantly the 3 isomer), 1.3% olefin which eluted before the methylcyclohexene isomers (thought to be a mixture of vinylcyclopentane, 1-ethylcyclopentene, and ethylidenecyclopentane), 1.0% 1-methylcyclohexyl acetate, 4.2% *cis*-2-methylcyclohexyl acetate, 20.9% *trans*-2-methylcyclohexyl acetate, 2.1% methylcyclopentylcarbinyl acetate, 0.9% *trans*-3-methylcyclohexyl acetate, 1.4% *cis*-3-methylcyclohexyl acetate, and 56.0% 4-methyl-5-hexenyl acetate.

Stabilities of acetolysis products to acetolysis conditions were tested by heating solutions of the compounds in question in acetic acid, containing sodium acetate and sodium brosylate in concentrations corresponding to those present at the end of the acetolysis product study, for a period corresponding to ten half-lives for the acyclic precursor, then isolation and analysis as described above. Most compounds showed no change, but methylenecyclohexane was partially converted to 1-methylcyclohexene (18.5%) and 1-methylcyclohexyl acetate (7.5%), 1-methylcyclohexyl acetate was partially converted to 1-methylcyclohexene (51%) and methylenecyclohexane (4%), and 1-methylcyclohexene yielded a small amount (3%) of 1-methylcyclohexyl acetate.

Kinetic experiments were performed using the ampoule technique as described previously.[7]

Registry No.—3-Methyl-5-hexen-1-ol, 25913-87-5; 3-methyl-5-hexen-1-ol (α-naphthylurethan), 25957-53-3; 2-methyl-5-hexen-1-ol, 25913-88-6; 2-methyl-5-hexen-1-ol (α-naphthylurethan), 25906-55-2; 4-methyl-5-hexen-1-ol, 25906-56-3; 4-methyl-5-hexen-1-ol (α-naphthylurethan), 25906-57-4; 6-hepten-2-ol, 24395-10-6; 3-methylhexan-1-ol, 13231-81-7; *cis*-3-methylcyclohexanol, 5454-79-5; I, 25906-60-9; II, 25906-61-0; III, 25906-62-1; IV, 25906-78-9; 3-methylhexyl brosylate, 25906-79-0; 5-hexenyl brosylate, 25906-80-3; Va, 25903-10-0; Vb, 10300-00-2; VIa, 25902-72-1; VIb, 25902-73-2; VIIa, 25902-74-3; VIIb, 25902-75-4.

Primary Isotope Effects in Hydrogen Atom Transfer Reactions from α-Hydroxyalkyl and Monohydropyridyl Radicals[1]

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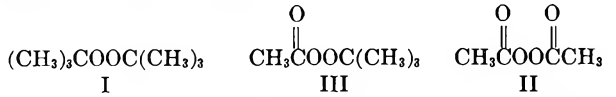
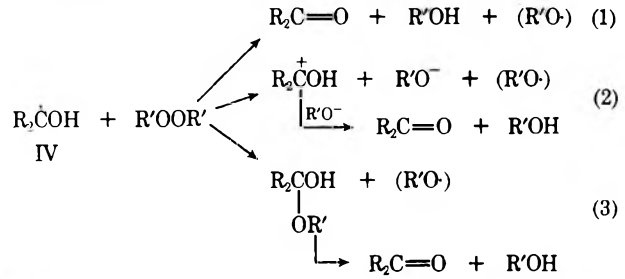
The rates of oxidation of *O-d*-2-butanol and *N-d*-3,5-dicarbethoxy-1,4-dihydro-2,6-lutidine by *tert*-butyl peroxide are slower than those of nondeuterated samples of these compounds. This isotope effect is ascribed to hydrogen atom transfer reactions of radicals derived from these species to the oxygen–oxygen linkage of the peroxide. No isotope effect was observed in the reactions of either acetyl peroxide or *tert*-butyl peracetate with the secondary alcohol or oxidation of the dihydropyridine with acetyl peroxide. A route other than hydrogen atom transfer, possibly a direct displacement or an electron transfer process, likely is operative in the reduction of the peroxide by the radicals derived from these compounds.

The enhanced decomposition rates of *tert*-butyl peroxide (I),[3] acetyl peroxide (II),[4] and *tert*-butyl peracetate (III),[5] in primary and secondary alcohols has been attributed to participation of the peroxides in a chain



I III II

reaction with the α-hydroxyalkyl radical (IV) derived from the alcohol. Three modes of interaction of the alcohol-derived radical with the peroxide linkage that appear feasible are a hydrogen atom transfer reaction (eq 1), an electron transfer (eq 2), and a direct displacement (eq 3). In this study we have sought support for the hydrogen atom transfer reaction (eq 1) by determining the deuterium isotope effect (if any) in the interaction of the radical derived from *O-d*-2-butanol (V) with these peroxides. The rates of reaction of *tert*-butyl peroxide and acetyl peroxide in the presence of 3,5-dicarbethoxy-1,4-dihydro-2,6-lutidine (VI) and its N-deuterated derivative (VII) were also measured to determine if the hydrogen atom transfer is operative in the interaction of the monohydropyridyl radical (VIII) with these peroxide linkages.[6]



(1)

(2)

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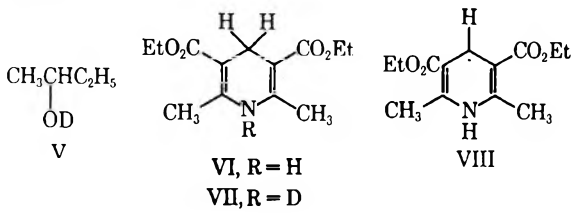
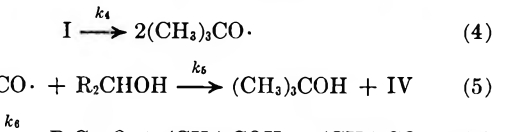


V VI, R = H VII, R = D VIII

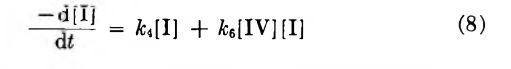
Discussion and Results

The oxidation of a secondary alcohol with *tert*-butyl peroxide (I) proceeds by the mechanism shown in eq 4–7. The decomposition rate of the peroxide is the



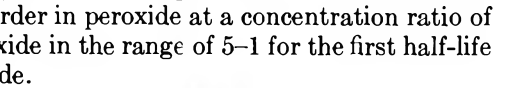
(4) (5) (6) (7)

sum of the rates of reaction 4 and 6 shown in eq 8. The



(8)

derived steady state rate law for the decomposition of the peroxide as given in eq 9 is applicable if the cross-termination process 7 is operative. The reaction is indeed first order in peroxide at a concentration ratio of alcohol–peroxide in the range of 5–1 for the first half-life of the peroxide.



(9)

The decomposition rate of *tert*-butyl peroxide in 2-butanol containing varying amounts of the oxygen-deuterated alcohol (V) (Table I) is slower in the deuterated alcohol. The reaction rates were followed through about one half-life of the peroxide minimizing

TABLE I

RATE DATA FOR DECOMPOSITION OF *tert*-BUTYL PEROXIDE IN 2-BUTANOL AND *O-d*-2-BUTANOL

Initial molar ratio of alcohol–peroxide	% *O-d*-2-Butanol	k' × 10^4 sec^{-1}	Standard deviation
4.84	0	0.454	0.009
5.07	0	0.453	0.005
5.13	0	0.458	0.014
5.26	80	0.322	0.004
4.96	80	0.313	0.002
5.01	80	0.343	0.009
5.00	90	0.297	0.006
4.87	90	0.287	0.002
5.06	90	0.288	0.002
5.01	99	0.276	0.004
5.10	99	0.277	0.007
5.07	99	0.285	0.008

* To whom correspondence should be addressed.

(1) Preliminary report: E. S. Huyser and A. A. Kahl, *Chem. Commun.*, 1238 (1969).

(2) NASA Fellow, 1966–1969. Taken in part from the thesis submitted by A. A. K. in partial fulfillment of the requirements for the M.S. degree from the University of Kansas, 1969.

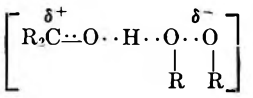
(3) E. S. Huyser and C. J. Bredeweg, *J. Amer. Chem. Soc.*, **86**, 2401 (1964).

(4) M. S. Kharasch, H. N. Friedlander, and W. H. Urry, *J. Org. Chem.*, **14**, 91 (1949).

(5) C. Walling and J. C. Azar, *ibid.*, **33**, 3888 (1968).

(6) E. S. Huyser, C. J. Bredeweg, and R. M. Van Scoy, *J. Amer. Chem. Soc.*, **86**, 4148, (1964).

the amount of exchange between the deuterated alcohol and *tert*-butyl alcohol produced in the reaction. The pseudo-first-order rate constants in Table I include all of the terms in the brackets of the rate law 9. Retardation of reactions 4, 5, or 6 or enhancement of reaction 7 by the deuterated alcohol would be required to account for the observed effect. The magnitude of the isotope effect (k'_H/k'_D) in the 99% deuterated alcohol is 1.63 and indicative of a primary isotope effect. Oxygen–hydrogen bond rupture occurs only in eq 6 and 7. A sizable inverse isotope effect would be required to explain the observed results in terms of the termination reaction. Retardation of the reaction of the α-hydroxyalkyl radical with a peroxide linkage (reaction 6) is a more likely explanation for the observed effect. Since the reaction rate constant k_6 is a square root term in k', a closer approximation of the minimum isotope effect, assuming all other terms in the bracket are the same for both alcohols, is 1.63[2] or 2.66. Although the reduction of the peroxide linkage by the α-hydroxyalkyl radical is significantly exothermic (approximately 35–40 kcal/mol), the isotope effect is indicative of extensive bond breaking of the oxygen–hydrogen bond in the transition state as would be the case if the hydrogen atom transfer (reaction 1) were operative.



The lack of an isotope effect in the reaction of *O-d*-2-butanol with both acetyl peroxide and *tert*-butyl peracetate (Table II) indicates that the interactions of the

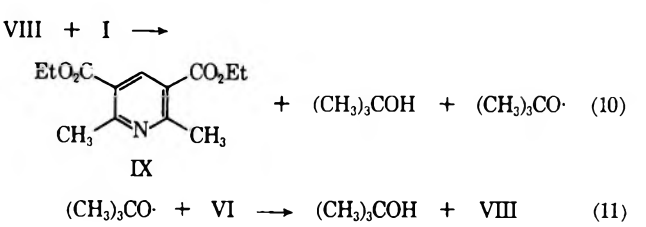
TABLE II

RATE DATA FOR DECOMPOSITION OF ACETYL PEROXIDE (II) AND *tert*-BUTYL PERACETATE (III) IN 2-BUTANOL AND *O-d*-2-BUTANOL (V)

Alcohol	Mole ratio	$k' \times 10^4$, sec^{-1}	Standard deviation
	Acetyl Peroxide (70°)		
2-Butanol	4.91	0.578	0.002
	4.84	0.580	0.005
	4.99	0.568	0.006
O-d-2-Butanol	4.91	0.584	0.004
	4.89	0.562	0.006
	5.00	0.578	0.007
	tert-Butyl Peracetate (90°)		
2-Butanol	5.03	0.980	0.002
	5.02	0.959	0.002
	5.00	0.944	0.002
O-d-2-Butanol	4.96	0.953	0.001
	4.99	0.959	0.002
	5.00	0.950	0.002

α-hydroxyalkyl radical with these peroxide linkages are not hydrogen atom transfer reactions. The direct displacement by the alcohol-derived radical on the peroxide was originally proposed to account for the reactions of alcohols with acetyl peroxide.[4] This suggestion finds support in the reaction of ether-derived α-alkoxyalkyl radicals with acyl peroxides which yield isolable acylals as reaction products.[7]

α-Aminoalkyl radicals having at least one nitrogen-bonded hydrogen react with *tert*-butyl peroxide as evidenced by the induced decomposition of the peroxide in primary and secondary amines.[6] A particularly marked enhancement of the decomposition rate of *tert*-butyl peroxide was observed in the reactions with 3,5-dicarbethoxy-1,4-dihydro-2,6-lutidine (VI) which is oxidized to the corresponding pyridine derivative IX in the chain process shown in eq 10 and 11. An isotope effect is ob-



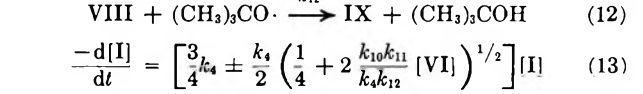
served (Table III) when the rate of reaction of the per-

TABLE III

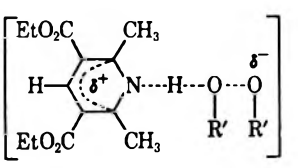
DECOMPOSITION RATES OF *tert*-BUTYL PEROXIDE IN TETRAHYDROFURAN SOLUTION OF DIHYDROPYRIDINES VI AND VII AT 125° (MOLE RATIO OF THF–DIHYDROPYRIDINE–*tert*-BUTYL PEROXIDE 36:2:1)

Compd	$k' \times 10^4$ sec^{-1}	Standard deviation
3,5-Dicarbethoxy-1,4-dihydro-2,6-lutidine (VI)	0.636	0.028
	0.666	0.015
	0.620	0.019
1-Deuterio-3,5-dicarbethoxy-1,4-dihydro-2,6-lutidine (VII)	0.407	0.006
	0.409	0.006
	0.402	0.006

oxide with VI is compared with that of 1-deuterio-3,5-dicarbethoxy-1,4-dihydro-2,6-lutidine (VII). Although both steps in the chain sequence are rapid, a considerable amount of reaction of the peroxide still occurs by the unimolecular decomposition (eq 4). Reaction with both VI and VII are first order in peroxide through the first half-life of the peroxide indicating cross termination of the chain sequence (eq 12). The derived rate law is



essentially the same as that given in eq 9, namely eq 13. The isotope effect on the observed rates of reaction of VI and VII with I is 1.58 and k_H/k_D for reaction 10 is approximately 2.5 indicating appreciable breaking of the nitrogen–hydrogen bond in the transition state of the reaction.



The pseudo-first-order rate constants found for the acetyl peroxide oxidations of VI and VII are given in Table IV. No isotope effect was observed in this reaction which is spontaneous at room temperature but likely proceeds by a free-radical chain mechanism involving interaction of the monohydropyridyl radical VIII with peroxide.[8] The reduction of the peroxide by

(7) W. E. Cass, *J. Amer. Chem. Soc.*, **69**, 500 (1947).

(8) A more complete description of this reaction will be reported in a later publication.

TABLE IV
RATE DATA FOR OXIDATION OF VI AND VII WITH ACETYL PEROXIDE IN ACETONITRILE AT 30°

Amine	Initial concentrations [Peroxide] $\times 10^{-2}$	[Amine] $\times 10^{-4}$	$k' \times 10^4$ sec^{-1}	Standard deviation
VI	2.48	1.57	0.220	0.008
	2.48	1.57	0.217	0.012
	2.48	1.57	0.218	0.012
VII	2.48	1.52	0.208	0.014
	2.48	1.52	0.214	0.017
	2.48	1.52	0.209	0.016

VIII probably does not involve breaking of the nitrogen–hydrogen bond in the transition state of the reaction and may likely be an electron-transfer process.

Experimental Section

Materials.—*tert*-Butyl peroxide (Wallace and Tiernan, Inc.) and a 25% solution of acetyl peroxide in dimethyl phthalate (Wallace and Tiernan, Inc.) were used without further purification. *tert*-Butyl peracetate (Wallace and Tiernan, Inc.) (75% perester in benzene) was purified by vacuum distillation. The following commercial reagents were distilled twice before using: 2-butanol (from sodium), tetrahydrofuran (from sodium), and acetonitrile (from phosphorous pentoxide).

3,5-Dicarbethoxy-1,4-dihydro-2,6-lutidine (VI) was prepared from acetoacetic ester, formaldehyde, and ammonia by the method of Singer and McElvain[9] (mp 183–185°).

1-Deuterio-3,5-dicarbethoxy-1,4-dihydro-2,6-lutidine (VII) was prepared by allowing a mixture of 5 g of VI to reflux for 2 hr with 10 ml of deuterium oxide in 100 ml of dimethoxyethane. The compound was isolated and recrystallized from ethanol and the process repeated twice with fresh deuterium oxide. After the final exchange, no nitrogen–hydrogen bond could be observed in either the infrared or the nmr spectra of the material.

***O-d*-2-Butanol (V)** was prepared by reaction of the sodium alkoxide with deuterium oxide in the following manner. Freshly distilled 2-butanol (500 ml) and sodium (20 g) cut in small pieces were placed in a 1-l. round-bottomed flask equipped with a reflux condenser. After the initial rapid reaction the mixture was heated at reflux for an additional 16 hr during which period all of the sodium reacted. Excess 2-butanol was removed under a vacuum leaving a white solid which was heated under vacuum for an additional 24 hr. Deuterium oxide (20 ml) was added to the dry solid producing a reddish brown mixture. The organic layer was distilled twice yielding *O-d*-2-butanol that by nmr analysis was 99% deuterated (30.2 g, 47% theory).

Peroxide Decomposition Rates.—The rates of reaction of *tert*-butyl peroxide in 2-butanol and *O*-D-2-butanol were determined by the gas chromatographic method described previously.[3] The decomposition rate of *tert*-butyl peroxide in the tetrahydrofuran solutions of VI and VII were also made by the gas chromatographic analysis of the unreacted peroxide as previously described.[4]

The decomposition rates of acetyl peroxide and *tert*-butyl peracetate in the presence of 2-butanol and *O-d*-2-butanol were determined by the method described by Silbert and Swern;[10] 1-ml samples of the reaction mixture were pipeted into a flask through which nitrogen had been passed for 20 sec. A saturated sodium iodide solution (about 2 ml) and 15 ml of freshly distilled glacial acetic acid containing 0.002% ferric chloride were added to the contents in the flask. The flask was stoppered and permitted to stand in the dark for 10–15 min. About 50 ml of distilled water was added to the solution which was titrated to a starch–iodine end point with 0.2 *N* thiosulfate to determine the amount of molecular iodine produced. A blank determination was run on all of the reagents.

Spectrophotometric Determination of Oxidation of Dihydrolutidines with Acetyl Peroxide.—Stock solutions of VI and VII in acetonitrile and of the acetyl peroxide–dimethyl phthalate solution in the same solvent were prepared. Samples of these solutions were thermostated at 30° before mixing. Immediately after mixing, the solutions were placed in a thermostatically controlled cell compartment of a Beckman DU spectrophotometer. The rates of reaction of the dihydropyridine derivatives were followed by measuring their absorption at 363 mμ as a function of time.

Registry No.—I, 110-05-4; II, 110-22-5; III, 107-71-1; 2-butanol, 78-92-2; V, 4712-39-4; VI, 1149-23-1; VII, 25894-44-4.

(9) A. Singer and S. M. McElvain, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 214.

(10) L. S. Silbert and D. Swern, *Anal. Chem.*, **30**, 385 (1958).

Substituent Effects in Alkali Metal–Ketyl Ion Pairs. An Infrared Scrutiny

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The carbonyl stretching frequency (ir) of alkali metal–4,4′-disubstituted ketyl ion pairs shows a startling deviation from the expected influence of five para substituents. Measurements indicate that the ketyl C–O bond is strengthened, rather than loosened, by electron-donating substituents. Plots of σ_R^+ *vs.* ketyl frequency are given. A possible explanation lies in the consideration of ion pairing by the counterion M^+ with increased electron density at the ketyl site. Such ion pairing might be able to reduce the antibonding influence of the added electron, thus allowing bonding π electrons to exert a stronger bonding force between the carbon and the oxygen atoms.

The utility of the carbon–oxygen stretching frequency of ketones as a sensitive indicator of electron density changes has long been recognized. Shifts in the carbonyl frequency are subject to both inductive and mesomeric effects which change the electron density at the carbon–oxygen bond.[2] Correlation of Hammett σ values with the carbonyl stretching frequencies in five 4,4′-disubstituted benzophenones has been shown to be nearly linear.[3] In essence, the studies all show that the greater the electron density at the C=O site, the lower the frequency (in cm^{-1}).

A one-electron reduction of a ketone results in a ketyl with the commonly given valence bond structure of >C—$\dot{O}$. Such a structure does not reflect the fact that only one of the π electrons of the C=O bond has been essentially "cancelled" by the introduction of the new electron into the lowest antibonding orbital of the

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(2) (a) R. E. Kagarise, *J. Amer. Chem. Soc.*, **77**, 1377 (1955); (b) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 241 ff.

(3) N. Fuson, M.-L. Jósien, and E. M. Shelton, *J. Amer. Chem. Soc.*, **76**, 2526 (1954).

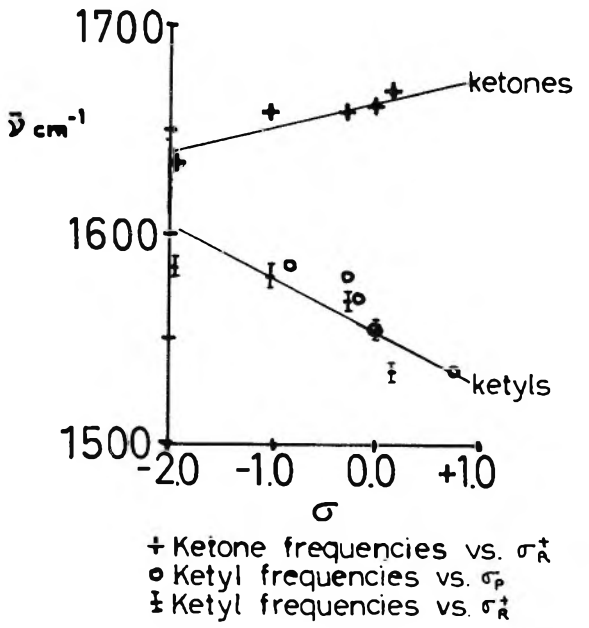


Figure 1.

carbonyl system. Thus the actual result is the "loosening" of the C=O stretching frequency by an amount equivalent to one-half of a π bond. Only a two-electron reduction would result in frequencies which might be considered to be comparable to C–O (zero π-bond order) stretching frequencies. The attachment of an aromatic group to the ketyl (*e.g.*, benzophenone anion radical) results in the delocalization of the odd electron from the ketyl group, significantly reducing the effect of the added electron upon the carbonyl stretching frequency.[4] For instance, the electron density of benzophenone as studied by epr results in a total electron density on the carbonyl ketyl of only 0.415.[5]

Experimental Section

Previous work definitely indicates the feasibility of producing anion radicals for study by infrared spectroscopy, and some measurements have been made on the frequency shifts of several types of aromatic compounds.[4,6] We realize that stretching frequency is not an absolute measure of electron density; however, it is proportional to the force constant, and thus should reflect changes in electron density at the carbonyl site.

In this work we have used standard alkali metal reduction techniques in dimethoxyethane (used previously for epr studies) in conjunction with NaCl cavity cells of 0.05-mm width. In all cases measurements were made using matched cells. Concentrations usually were in the range of 5 ($\pm$5) $\times$ 10^{-2} M. Occasionally it was necessary to use diluted samples around 10^{-4} M, but this required opened slits and increased source intensities on the instrument in order to obtain useful information.

The lithium reductions were performed with lithium amalgam; Na and K were distilled into the sample tube. Observations of the ketyls have been carried out at room temperature and measurements were made on Beckman IR-5 and Perkin-Elmer 21 and 521 instruments. Table I indicates the frequencies of the unreduced species, the observed frequencies of ketyls, the Hammett σ values (see discussion below), and the frequency difference between unreduced and reduced species. Figure 1 indicates a plot of σ_R^+ *vs.* $\bar{\nu}$ (ketyl) values. Figure 2 shows the

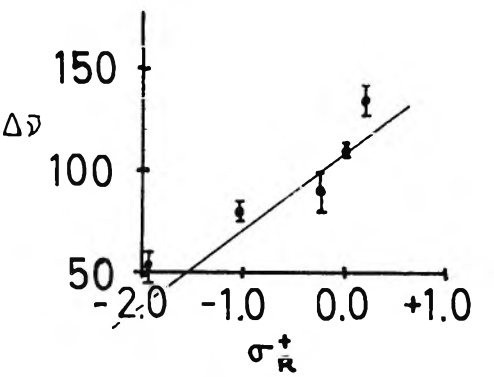


Figure 2.

plot of σ_R^+ *vs.* $\Delta\bar{\nu}$ (the difference between the parent ketone and the ketyl).

Choice of σ Values.—Only those ketones which would not tend to decompose upon metal reduction at room temperature were chosen for study; of these, only two of the five aromatic compounds studied are not susceptible to resonance interaction. In view of the fact that ketyls are essentially anion radicals, we found it desirable to use the σ_R^+ values determined for the cation radicals of *N*,*N*-dimethylaniline as determined by Latta and Taft.[7] As these authors mention, their results for σ are similar to those used for anion radicals by Strom.[8] Strom, however, used σ_P parameters from Brown and Okamoto[9] which do not reflect problems in resonance interaction between the para substituent and the measuring site. We have plotted the σ_P values also (circles, in Figure 1). A linear relationship is obtained with these values; nevertheless, we feel that the σ_R^+ parameters ($\sigma_R^+ = \sigma_P - \sigma_I$) of Latta and Taft are more applicable in our case. We are using single σ values, although to be more exact it might be more appropriate to double the σ values, since there are two substituents affecting the measuring site.

An interesting comparison of hyperfine splittings (hfs) with three 4,4′ substituents can be seen in Table II. Here we see that the spin density (as reflected by hfs) upon the aryl rings is increasing with increasing electron donation. Epr results are not available for $-N(CH_3)_2$ and $-NO_2$ substituents. Since a significant portion of the spin density in the $-NO_2$ substituted ketyl probably resides in that substituent, comparison of hfs for that ketyl would not be realistic, heeding Janzen's *caveat* for that situation.[10] This means, of course, that the spin density at the carbonyl site must be *decreasing*. This observation is in line with the results plotted in Figure 2; *i.e.*, the more negative σ values result in less perturbation of the carbonyl stretching frequency.

It has been suggested to us that inclusion of ir data from 4,4′-disubstituted phenyl nitroxides might be instructive. This has not been included for two reasons. At present there exist no such data, although we are attempting to secure it. Further, nitroxides represent a class of compounds in which the odd electron is in a nonbonding situation, and thus cannot reasonably be compared with a charge species which bears the odd electron in an antibonding orbital and which also has a closely associated positively charged metal ion. Some correlations of the N–O stretching frequency of substituted pyridine *N*-oxides with Hammett σ values have been made,[11] but, again, *N*-oxides of tertiary amines do not represent a bonding situation comparable to that of ketyls. We would like, in addition, to emphasize that Figures 1 and 2 do not represent an attempted strict Hammett-type correlation of free energy values, but rather do demonstrate a definite trend toward lowered frequencies upon increasing electron withdrawal at the ketyl site by whatever means, inductive, resonant, or both.

(4) D. H. Eargle, Jr., and E. W. Cox, "The Alkali Metals," Special Publication No. 22, The Chemical Society, London, 1967, pp 116–124. (Typical spectra are published here.)

(5) P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, **37**, 2811 (1962).

(6) D. H. Eargle, Jr., Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., 1967, pp 55–60; *J. Chem. Soc.*, in press.

(7) B. M. Latta and R. W. Taft, *J. Amer. Chem. Soc.*, **89**, 5172 (1967).

(8) E. T. Strom, *ibid.*, **88**, 2065 (1966).

(9) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).

(10) E. G. Janzen, *Accounts Chem. Res.*, **2**, 282 (1969). "When a large fraction of the total spin density is localized on any substituent, Hammett relationships break down."

(11) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, pp 122–126.

TABLE I

4,4′-DISUBSTITUTED BENZOPHENONE KETYL FREQUENCIES

Substituent	Registry no.	$\bar{\nu}_{ketone}$, cm^{-1}	$\bar{\nu}_{ketyl}$, cm^{-1} [a]	$\Delta\nu$	σ_R^+ [b]	σ_P [c]
$N(CH_3)_2$	90-94-8	1650 ± 2	1585 ± 5	65 ± 7	−1.97	−0.83
OCH_3	90-96-0	1660 ± 5	1580 ± 5	80 ± 6	−1.03	−0.27
CH_3	611-97-2	1660 ± 2	1568 ± 5 (K^+)	92 ± 7	−0.26	−0.17
			1572 ± 1 (Na^+)			
			1575 ± 2 (Li^+)			
			concd and dilute			
H	119-61-9	1664 ± 1	1554 ± 2 (K^+, Na^+)	110 ± 3	0.00	0.00
			1563 ± 2 (Li^+)			
			concd (dimer)			
			1617 ± 3 (Li^+)			
			dilute (monomer)			
NO_2	1033-26-7	1670 ± 2	1535 ± 5	135 ± 7	+0.18	+0.78
Di-*tert*-butyl ketone	15796-82-4	1689 ± 2	1558 ± 2	131 ± 4		

[a] Several of our values in dimethoxyethane differ somewhat from those determined in CCl_4 by Fuson, *et al.* (ref 3). [b] See ref 7. [c] See ref 9.

TABLE II

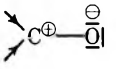
4,4′-DISUBSTITUTED BENZOPHENONE Hfs[a]

Substituent	Position			σ_R^+ (ref)	ρ(aryl) Q = −23.5 G
	ortho	meta	para		
OCH_3	2.78	−0.99	0.27(OCH_3)	−1.03 (7)	
CH_3	2.73	−0.91	3.64(CH_3)	−0.26 (7)	0.62
H	2.52	−0.82	3.50	0.00 (7)	0.59
Cl	2.5	−0.84		0.08 (9)	

[a] P. L. Nordio, G. Giacometti, and P. Favero, *Ric. Sci. Parte 2 Rend. Sez. A*, **3**, 107 (1963).

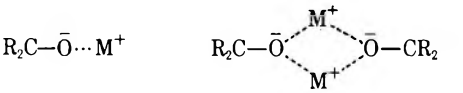
Discussion

Regardless of the set of σ values used, the most startling feature of the results is the *decrease* in ketyl stretching frequency corresponding to an increase in the electron-withdrawing power of the substituent. The carbonyl stretching frequencies of the unreduced benzophenones reflect fairly well the expected variations with substituent electron donation[11] weakening the C–O bond by stabilizing the structure



In Figure 2 is plotted the *difference* in the ketone and the ketyl stretching frequencies ($\Delta\nu$) *vs.* the σ_R^+ values. These differences become progressively larger with the greater electron-withdrawing power of the para substituent. Thus, both the results of Figures 1 and 2 are disquieting in that neither reflects what might have been predicted, that is, that the ketyl C–O bond should become tighter with an increase in the value of σ as in the ketones. The results appear to say that electron-donating groups, instead of further loosening the C–O bond, actually strengthen it.

At this point it should be noted that we are probably observing the stretching frequency of a metal–ketyl dimeric ion pair II, studied originally by Hirota,[12–14] rather than the monomer I. Hirota's work shows that at lower concentrations ($\sim 10^{-5}$ *M*) the metal ion is



I II

R = aryl or *tert*-butyl

highly solvated and causes only weak, if any, epr hyperfine splittings. However, at concentrations near 10^{-2} *M* the metal hyperfine splittings are quite pronounced and the epr studies show unequivocally that form II predominates (in dimethoxyethane) and that the metal–oxygen nuclear distance is only about 2 Å.[13b] Since our concentrations range from about 10^{-1} to 5×10^{-2} *M*, we are no doubt observing phenomena due to these dimeric ion pairs. It is not likely, either that we are observing pinacolate-type dimers; Hirota and Weissman[14] have shown spectrophotometrically that at 10^{-2} *M* concentrations in DME this dimer is present in negligibly small concentrations. With one exception we have found no observable change in the frequency of the ketyl upon dilution from concentrations of $\sim 10^{-2}$ *M* to $\sim 10^{-4}$ *M*. Were the species under observation to markedly change its degree of solvation, we should expect a change towards a different frequency upon progressive dilution. Only in the case of benzophenone do we observe an abrupt change of frequency upon extreme ($>10^{-4}$ *M*) dilution; however, the color of the material also changes, indicating that we are observing a change from the dimer (purple) to the monomer (blue), as reported by Hirota's study of the visible spectra.[13a] Therefore, we must conclude that the lack of frequency (and color) changes in the higher concentration ranges indicates that either we are observing the same species throughout the dilution process, or the ir spectrometer is too insensitive to detect a change.

The effect of the nature of the alkali metal also bears upon this point. There is little or no difference (within experimental error) of the ketyl absorptions of the K^+ and Na^+ counterions (see Table I), a fact which again strongly implies, as does Hirota's epr study, that there is little difference in structure between Na^+ and K^+ ketyls. Yet, when we go to the Li^+ counterion we should expect a more tightly held ion pair. If our hypothesis of counterion assistance is correct, a more

(12) Several of our values in dimethoxyethane differ somewhat from those determined in CCl_4 by Fusion, *et al.* (ref 3).

(13) (a) N. Hirota, Ph.D. Thesis, Washington University, 1963. University Microfilms, Inc., Ann Arbor, Mich., No. 64-2316; T. Kaiser and L. Kevan, "Radical Ions," Interscience, New York, N. Y., 1968, Chapter 2. (b) Reference 13, p 68.

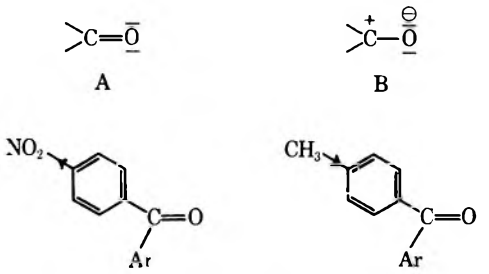
(14) N. Hirota and S. I. Weissman, *J. Amer. Chem. Soc.*, **86**, 2538 (1964).

tightly held ion should serve to increase the C–O bond strength, as indeed Li^+ does, to the extent of 7–9 cm^{-1} in benzophenone and ditolyl ketone.

The ketyl of di-*tert*-butyl ketone (lifetime ~30 min) has been included in Table I for reference purposes. This ketyl represents one in which the odd electron is almost totally confined to the C–O site (Hirota reports little solvent or temperature dependence and a quite large metal hfs, resulting in a "tight" ion pair of structure II). Comparison of its frequency shift to those of its aromatic cousins demonstrates its similarity to the 4,4′-dinitro species.

The problem of describing these effects at the ketyl site is, simply stated, to devise a mechanism wherein the antibonding character of the odd electron may be increased, as reflected by a lower observed C–O frequency, or decreased, in the case of a higher one.

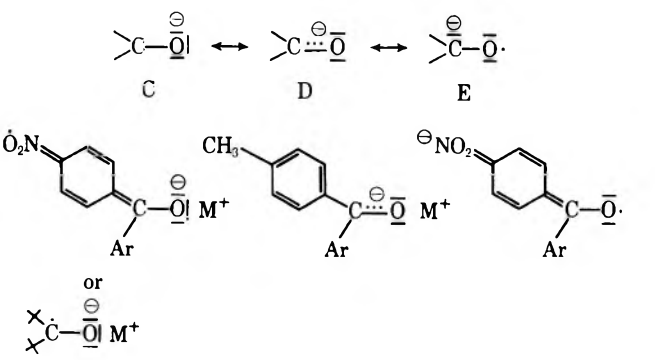
Valence bond structures may be invoked to describe the observed effects, but prove to be rather awkward in depicting all situations. The conventional resonance structures of the ketone (A, B) are adequate to describe the substituent effects of the unreduced ketone.



ketone structures with examples

In order to approach a depiction of the ketyl, Pauling's three-electron bond concept (his subterfuge for antibonds) must be summoned. Three contributing resonance structures of the ketyl may be shown by models C, D, and E. Electron-donating substituents can be seen to increase the probability of structure D, in which the resident electron density on the ketyl is greater than that of either C or E. In structure D we should expect some influence of metal counterion and also an increased C–O bond strength with increased electron donation, as borne out by experiment (see *p*-tolyl, Table I).

Since *p*-tolyl benzophenone ketyl possesses a higher frequency than benzophenone ketyl (and neither has large substituent resonance effects), it must be assumed that the counterion effect is stronger in the former and, at the same time, allows more delocalization of the odd electron (see Table II). This is reasonable, since electron-donating groups would certainly increase the entire electron density at the ketyl site.

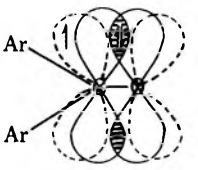


ketyl structures with examples

Electron-withdrawing substituents such as NO_2 cause structure C or E to predominate. The similarity in stretching frequency of 4,4′-dinitrobenzophenone ketyl and di-*tert*-butyl ketyl can be rationalized by involving only structure C, in which very little delocalization of either charge or spin can occur and in which counterion influence must be large, giving the known "tight" ion pair.

A partial MO description (F), while possessing some defects, can perhaps characterize the situation in MO terms in which the bonding π orbitals between C and O are occupied as well as the nonbonding orbitlas of oxygen (not shown). The antibonding orbitals between C and O are also occupied, by the odd electron, which upon the influence of electron donation by Ar is more likely to be found on the central carbon atom, while the charge density is increased on the oxygen. Electron withdrawal by Ar results in a greater influence in antibonding by the odd electron and at the same time possibly allows enhanced bonding of the metal–oxygen pairs.

bonding π orbitals (solid lines)



antibonding π orbitals (dotted lines)

F

Acknowledgments—Many thanks to the Illinois Research Board of the University of Illinois (for support while the authors were at the University of Illinois at Chicago Circle) and the Gulbenkian Foundation of Portugal for supporting grants, and to Dr. Robert N. Schwartz for helpful repartee.

The Reaction of Potassium Hexacyanodinickelate(I) with Organic Halides

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Reaction of potassium hexacyanodinickelate(I) (1) with various organic halides in aqueous solutions were examined. Three types of reactions were observed to occur rather selectively depending on the halides used: hydrogenolysis in the case of *p*-cyanobenzyl bromide and phenacyl bromide; coupling in the case of benzyl, *p*-methylbenzyl, and *p*-methoxybenzyl bromide and *trans*-β-bromostyrene; cyanation in the case of cinnamyl bromide. When the same reaction was carried out in the presence of carbon monoxide, carbonylation reaction occurred easily under mild conditions to give symmetrical ketone or ester. In the presence of acrylonitrile or ethyl acrylate, the reaction of 1 with benzyl bromide gave 4-phenylbutyronitrile and ethyl 4-phenylbutyrate, respectively. Unstable organonickel(II) complexes containing a carbon–nickel σ bond were postulated as intermediates in these reactions.

In recent years, a variety of anionic organometallic complexes have been shown to be excellent nucleophilic reagents in various synthetic reactions: *e.g.*, lithium acylmetal carbonylate in the synthesis of unsymmetrical ketones[1] or 1,4-dicarbonyl compounds,[2] reagents from nickel carbonyl and alkali metal alkoxides for alkoxycarbonylation of alkenyl or alkyl halides,[3] potassium hexacyanodinickelate(I)[3] and sodium dicyanocuprate(I)[4] for cyanation of alkenyl halides, and lithium dialkylcuprate[5] in the reaction with organic halides or α,β-unsaturated ketones.

In a preliminary communication[6] the present authors have reported a reagent useful for the formation of new carbon–carbon bonds. Potassium hexacyanodinickelate(I) (1) in an aqueous solution reacted smoothly with benzyl bromide at room temperature to give bibenzyl (89.0%), and, in the presence of carbon monoxide (CO), the same reaction gave dibenzyl ketone in a high yield. In this report we wish to propose the formation of organonickel(II) complexes as precursors to the products resulted from the following reactions; *i.e.*, hydrogenolysis, coupling, cyanation, carbonylation (in the presence of CO), and benzylation of olefins (in the presence of olefins).

Results

Reaction of Potassium Hexacyanodinickelate(I) (1) with Organic Halides.—To the blood-red aqueous acetone solutions of 1 were added dropwise organic halides (molar ratio, 1:R−X = 1:1 ∼ 2) at 0° or at room temperature under a nitrogen atmosphere. The results of analyses of organic compounds formed are summarized in Table I.

When an aqueous acetone solution of 1 was treated with an equimolar amount of benzyl bromide at 0°, the color of the solution changed to pale yellow within 30 min. The pale yellow color remained unchanged even after the solution was stirred at 0° for 6 hr, but when the reaction temperature was raised up to 20°, a rapid decomposition took place to give a yellow-green suspension. Glpc analysis of the products showed the presence of the following compounds: bibenzyl (89.0%), benzaldehyde (0.6%), and benzyl alcohol (2.0%). When 2 mol of benzyl bromide was used per mol of 1, just 1 mol of halide was consumed to give bibenzyl (96.4% based on 1 used) and the excess of the halide was recovered (eq 1).

$$\underset{\mathbf{1}}{K_2Ni_2(CN)_6} + C_6H_5CH_2Br \longrightarrow {}^1/_2C_6H_5CH_2CH_2C_6H_5 \quad (1)$$

p-Methyl- and *p*-methoxybenzyl bromide gave exclusively the corresponding bibenzyl derivatives and in these reactions only a trace amount of hydrogenolysis product (*p*-xylene, *p*-methoxytoluene, respectively) was detected by glpc.[7] The reaction of 1 with *p*-cyanobenzyl bromide is interesting and, in this case, the yield of hydrogenolysis product, *p*-cyanotoluene, increased remarkably (50.0%) at the expense of coupling product, *p,p'*-dicyanobibenzyl.

It should be noted that the reactivity of 1 to organic halides and the product distribution depend greatly on the halides used. Although the cyanonickelate reagent 1 was quite inactive towards simple alkyl bromides and aryl halides, it showed a high reactivity towards alkenyl or allyl bromides; *i.e.*, *trans*-β-bromostyrene and cinnamyl bromide reacted smoothly with 1 to give *trans,trans*-1,4-diphenyl-1,3-butadiene and cinnamyl cyanide, respectively, in high yields. When an equimolar amount of phenacyl bromide in *N,N*-dimethylformamide (DMF) was added dropwise to a solution of 1 in aqueous DMF at 0°, a rapid reaction occurred to give acetophenone (47.5%), 1,2-dibenzoylethane (9.4%), and a significant amount of black polymeric materials. The yield of coupling product, 1,2-dibenzoylethane, increased to 46.8% when the same reaction was carried out in anhydrous DMF.

Reaction of Potassium Hexacyanodinickelate(I) (1) with Organic Halides in the Presence of CO.—It was reported that 1 is coordinatively unsaturated and its aqueous solution easily absorbs two molecules of CO according to eq 2a to give the yellow carbonyl–cyanonickel(I) complex.[8a,b] But, very recently, the carbonylation of 1 has been found, actually, to form an equi-

* To whom correspondence should be addressed.

(1) Y. Sawa, M. Ryang, and S. Tsutsumi, *Tetrahedron Lett.*, 5189 (1969).

(2) (a) Y. Sawa, I. Hashimoto, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2159 (1968); (b) E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 4926 (1969).

(3) E. J. Corey and L. S. Hegedus, *ibid.*, **91**, 1233 (1969).

(4) H. O. House and W. F. Fischer, *J. Org. Chem.*, **34**, 3626 (1969).

(5) (a) G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969); (b) J. Klein and R. M. Turkel, *ibid.*, **91**, 6186 (1969).

(6) I. Hashimoto, M. Ryang, and S. Tsutsumi, *Tetrahedron Lett.*, 3291 (1969).

(7) The result in the case of *p*-methoxybenzyl bromide is not satisfactory in respect to the yield because the halide was easily hydrolyzed by water to the alcohol, but the ratio of coupling product to hydrogenated product would represent the reactivity of the halide toward 1 [A. Lapworth and J. B. Shoesmith, *J. Chem. Soc.*, **121**, 1391 (1922)].

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TABLE I

REACTION OF POTASSIUM HEXACYANODINICKELATE(I) (1) WITH ORGANIC HALIDES

R–X	Solvent	Ratio, 1:RX	Temp, °C	Time, hr	Product, %[a] R—H	R—R	R—CN
$C_6H_5CH_2Br$	Water–acetone	1:1	0–20	8	*d*	89.0	
$C_6H_5CH_2Br$	Water–acetone	1:2	0–60	3	*d*	96.4	
p-$CH_3C_6H_4CH_2Br$	Water–acetone	1:1	15	6	Trace	92.5	
p-$CH_3OC_6H_4CH_2Br$	Water–acetone	1:1.4	20	4	Trace	21.5	
p-$NCC_6H_4CH_2Br$	Water–acetone	1:1	20	10	50.0	11.5	
$C_6H_5CH_2CH_2Br$	Water–acetone	1:1	20–50	12			
C_6H_5I	Water–acetone	1:1	15–45	12			
trans-$C_6H_5CH{=}CHBr$	Water–acetone	1:1	18–23	1		72.9	6.6
trans-$C_6H_5CH{=}CHCH_2Br$	Water–acetone	1:2	5–20	10		6.7	83.0
$C_6H_5C(=O)CH_2Br$	Water–DMF[b]	1:1	5	0.5	47.5	9.4	
$C_6H_5C(=O)CH_2Br$	Methanol[c]	1:1	40–50	10	38.1	14.0	
$C_6H_5C(=O)CH_2Br$	DMF[b]	1:1	0–10	10	12.0	46.8	
p-$BrC_6H_4C(=O)CH_2Br$	Methanol[c]	1:1	30	15	13.7[e]	32.6[f]	

[a] Yields are based on 1 used. [b] *N*,*N*-Dimethylformamide. [c] Suspension. [d] No effort was made to detect it. [e] *p*-Bromoacetophenone. [f] *p*,*p*′-Dibromo-1,2-dibenzoylethane.

TABLE II

REACTION OF POTASSIUM HEXACYANODINICKELATE(I) (1) WITH ORGANIC HALIDES IN THE PRESENCE OF CO

R–X	Solvent	Ratio, 1:RX	Temp, °C	Time, hr	Product, %[a]
$C_6H_5CH_2Br$	Water–acetone	1:2	4–22	14	Dibenzyl ketone, 90.4
$C_6H_5CH_2Br$	Water–acetone	1:1.7	0–15	2	Dibenzyl ketone, 61.0
p-$CH_3C_6H_4CH_2Br$	Water–acetone	1:1.1	10–45	21	*p*,*p*′-Dimethyldibenzyl ketone, 67.0
n-C_4H_9I	Water–methanol	1:2	0–30	4	Di-*n*-butyl ketone, 4
trans-$C_6H_5CH{=}CHBr$	Water–methanol	1:1.4	10–35	17	Methyl *trans*-cinnamate, 57.0 Cinnamaldehyde, 10.2

[a] Yields are based on 1 used.

molar amount of $K_2[Ni^{II}(CN)_4]$ and $K_2[Ni^0(CO)_2(CN)_2]$ (2) as shown in eq 2b.[8c]

$$1 + 2CO \longrightarrow K_4[(CN)_3(CO)Ni{-}Ni(CO)(CN)_3] \quad (2a)$$

$$1 + 2CO \longrightarrow \underset{2}{K_2[Ni(CN)_4]} + K_2[Ni(CO)_2(CN)_2] \quad (2b)$$

An excess of organic halides (molar ratio, $1:1.1 \sim 2$) was introduced to an aqueous solution of **2** and gentle bubbling of CO was continued with vigorous stirring for several hours. The results are summarized in Table II.

Benzyl and *p*-methylbenzyl bromide gave dibenzyl ketone and *p*,*p*′-dimethyldibenzyl ketone, respectively, in high yields in water–acetone solution. Formation of any methyl ester was not observed even if the same reaction was carried out in water–methanol solution. The carbonylating reagent **2** was also much less reactive towards alkyl halides, and *n*-butyl iodide gave di-*n*-butyl ketone only in a low yield. Contrary to the results from benzyl bromide, methyl *trans*-cinnamate (57.0%) and cinnamaldehyde (10.2%) were obtained from *trans*-β-bromostyrene in water–methanol.

Reaction of Potassium Hexacyanodinickelate(I) (1) with Benzyl Bromide in the Presence of Olefin.—When an excess of acrylonitrile was added to the aqueous solution of **1** at room temperature, a yellow color resulted instantly, presumably owing to the formation of a weak π complex between **1** and olefin. Benzyl bromide was then added dropwise at −7° with stirring. Upon work-up, a 23.0% yield of 4-phenylbutyronitrile and 57.4% bibenzyl was obtained. A similar reaction of **1** with benzyl bromide in the presence of ethyl acrylate gave ethyl 4-phenylbutylate in a lower yield (8.0%) and bibenzyl (20.0%). A definite color change from red to yellow was observed when an excess of butadiene was added to an aqueous solution of **1**, but an attempt at benzylation was unsuccessful and almost all of the benzyl bromide was recovered. It seems likely that a strong coordination of butadiene to **1** led to the prevention of the attack of benzyl bromide on **1**.

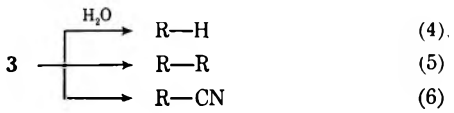
Discussion

It is reasonable to consider the formation of unstable organonickel(II) σ complexes (**3**) as intermediates in the reaction of **1** with organic halides. In the reaction of **1**

$$1 + R\text{-}X \longrightarrow \underset{3}{K_2[R\text{-}Ni^{II}(CN)_3]} + K_2[Ni^{II}(CN)_3X] \quad (3)$$

with benzyl bromide, the assumption of formation of tricyanobenzylnickelate(II) (**3**, R = $C_6H_5CH_2$) was supported by the following chemical proofs, although our previous attempts to isolate it were unsuccessful and spectral study has not yet been done because of its thermal instability: (1) treatment of **1** with an equimolar amount of benzyl bromide in water–acetone at 0° gives a pale yellow solution which is stable at the temperature for several hours but decomposes near room temperature to afford bibenzyl almost quantitatively: (2) bubbling of CO into the yellow solution gives dibenzyl ketone (34%) as well as bibenzyl (50%); (3) treatment of the yellow solution with $HgCl_2$ gives benzylmercuric chloride (17%) and bibenzyl (60%); and (4) benzylation of olefins occurs when an appropriate olefin is present in the reaction system.

Decomposition of **3** in aqueous solutions gave the three types of products by hydrogenolysis (eq 4), coupling (eq 5), or cyanation (eq 6).

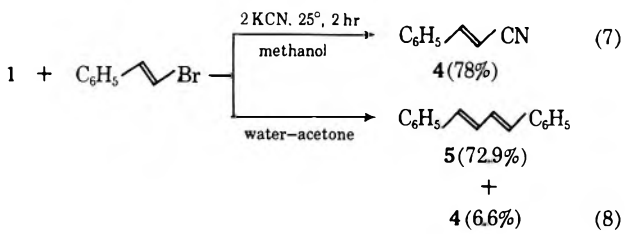


(4)
(5)
(6)

In some cases, competition between the former two or the latter two types occurred. Phenacyl bromide in aqueous solution underwent hydrogenolysis to yield acetophenone as a main product but, when anhydrous DMF was used as a solvent, the coupling product, 1,2-dibenzoylethane, was mainly formed. *trans*-β-Bromostyrene gave the coupling product in a high yield, whereas the nitrile was produced from cinnamyl bromide. It should be noted that the course of decomposition depends largely on the structural type of the organic moiety. Especially in a series of *para*-substituted benzyl bromides, a definite substitution effect on the product distribution was observed; benzyl, *p*-methylbenzyl, and *p*-methoxybenzyl bromide gave the corresponding coupling products almost exclusively, but *p*-cyanobenzyl bromide gave *p*-cyanotoluene as a main product.

Tricyanobenzylnickelate(II) (**3**, R = $C_6H_5CH_2$), as well as pentacyanobenzylcobaltate(III),[9] is classified as hydrolytically inert in contrast to benzylchromium(III) species[10] which is easily hydrolyzed by water to give mainly toluene.

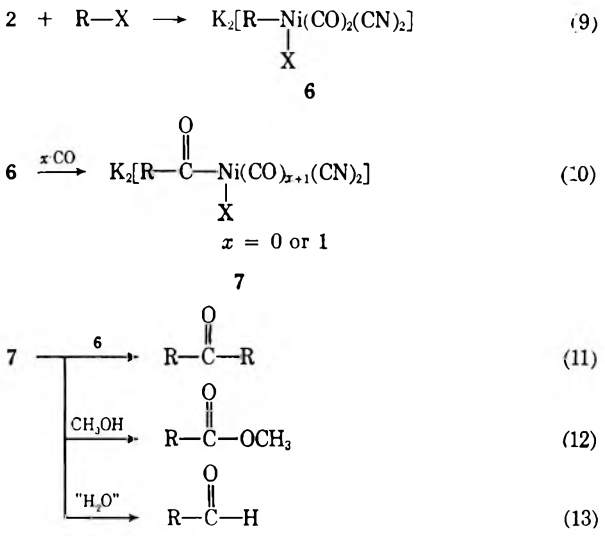
Reaction of **1** with *trans*-β-bromostyrene is interesting. Recently, Corey and Hegedus[3] reported that 78% of *trans*-β-cyanostyrene **4** was obtained from this reaction in methanol in the presence of 2 mol equiv of KCN (eq 7). However, when the same reaction was



(7)
(8)

carried out in the absence of KCN in water–acetone, the coupling product was obtained in a good yield and the yield of the nitrile **4** drastically decreased. Contrary to the formation of cinnamyl cyanide from **1** and cinnamyl bromide in a high yield, the presence of free cyano ion is necessary for the cyanation of *trans*-β-bromostyrene.

Carbon monoxide insertion reactions into the carbon–metal σ bond of alkyl (or aryl) transition metal complexes are well known and their mechanistic considerations have been done by several workers.[11] Carbonylation reaction of organic halides by the carbonyl cyanonickelate(I) reagent **2** seems to proceed *via* the formation of organonickel(II) σ complexes (**6**) as intermediates, according to eq 9–13.

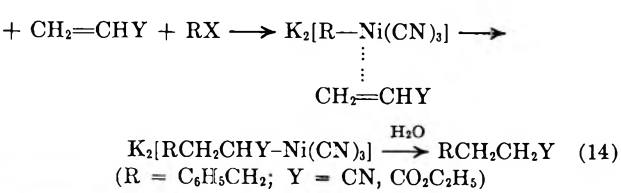


(9)
(10)
(11)
(12)
(13)

Comparison of the reactivity of **2** and nickel carbonyl (**8**) toward various organic halides is of particular interest. In the present reaction using **2**, symmetrical ketones were obtained in a high yield from benzyl or *p*-methylbenzyl bromide and, in a much lower yield, from *n*-butyl iodide, but any ester or carboxylic acid was not obtained from these halides when water–methanol or water–acetone was used as a solvent. It has, however, been reported that the reaction of **8** with benzyl bromide gave dibenzyl ketone in DMF solution and ethyl phenylacetate in ethanol in high yields.[12] On the other hand, alkyl or alkenyl halides are known to be inert to **8** and can be converted to esters only by a more powerful carboxylating reagent (alkali metal alkoxide–**8**–alcohol system),[3] and therefore the high reactivity of **2** (and **1**) toward *trans*-β-bromostyrene is attractive.

The formation of cinnamaldehyde (10.2%) as a by-product in the reaction of **2** and *trans*-β-bromostyrene is intriguing because, in general, acyl transition metal complexes are known to afford carboxylic acids instead of aldehydes by hydrolysis,[11a] but the mechanism leading to the aldehyde (eq 13) is still open to question.

The fact that an aqueous solution of **1** easily absorbs CO makes it possible to expect the coordination of other unsaturated compounds, which has, indeed, been postulated in the reaction of cyclization of a certain acetylenic compound[13] or of hydrogenation of olefins.[14] Olefin insertion reactions into alkyl transition metal σ bonds are also reported.[15] From the analogy of previously observed reactions, the benzylation reaction of olefins using **1** is explicable by eq 14.



(14)

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A similar benzylation reaction using chromium(II) was reported by Kochi and Davis.[16]

Experimental Section

General.—Benzyl bromide, β-bromostyrene (trans 92.5%, cis 7.5%), *n*-butyl iodide, phenacyl bromide, *p*-bromophenacyl bromide, acrylonitrile, and ethyl acrylate were of reagent grade and purified by distillation or recrystallization from ethanol. *p*-Methylbenzyl bromide, mp 40° (lit.[17] mp 39°), *p*-methoxybenzyl bromide, bp 128–130° (15 mm) [lit.[18] bp 124–126° (12 mm)], and cinnamyl bromide, bp 90–91° (2 mm) [lit.[19] bp 84–85° (0.8 mm)], were prepared from the corresponding alcohols by the action of phosphorous tribromide in carbon tetrachloride in the presence of pyridine. *p*-Cyanobenzyl bromide was prepared by the reported method[20] and purified by sublimation *in vacuo*, mp 115–115.5°. Commercially available $K_2Ni(CN)_4 \cdot H_2O$ was dried *in vacuo* at 100°. *N,N*-Dimethylformamide (DMF) was fractionated and dried over molecular sieves. All solvents were saturated with nitrogen before use and all the reactions were carried out under a nitrogen atmosphere. Gas–liquid partition chromatographic analyses were performed on a Yanagimoto GCG-5DH instrument using 2.5 m × 3 mm columns packed with 20% SE-30 or 20% PEG-20M. Yields were based on potassium hexacyanodinickelate(I) used.

Preparation of Potassium Hexacyanodinickelate(I) (1).—The cyanonickelate(I) reagent 1 was prepared by the reported method[21] with a slight modification. To a solution containing 24.1 g (0.100 mol) of anhydrous potassium tetracyanonickelate-(II), $K_2Ni(CN)_4$, in *ca.* 300 ml of liquid ammonia was added 2.80 g (0.070 g-atom) of potassium in the form of small pieces. Ammonia was then evaporated slowly with stirring at atmospheric pressure and later *in vacuo*. Residual red powder was washed with five successive 60-ml portions of methanol in order to remove the remaining ammonia and resulting KCN and dried *in vacuo*.[22]

Reaction of Potassium Hexacyanodinickelate(I) (1). A. With *p*-Methylbenzyl Bromide in Water–Acetone.—Potassium hexacyanodinickelate(I) (1) (0.0267 mol) in 160 ml of water was charged into a 400-ml five-necked flask equipped with a dropping funnel, gas-inlet and -outlet tubes, a thermometer, and a mechanical stirrer, and 100 ml of acetone was added. *p*-Methylbenzyl bromide (4.95 g, 0.0267 mol) in 30 ml of acetone was added *via* the dropping funnel, slowly with efficient stirring, over a period of 90 min at room temperature. The initially blood-red solution turned to dark red during the addition, and a dark green suspension was finally obtained. The reaction mixture was stirred at room temperature for 2 hr. After filtration of inorganic materials, the yellow filtrate was concentrated to *ca.* 100 ml at reduced pressure, followed by extraction with 200 ml of ether. The colorless ether extract was washed with aqueous NaCl and was dried over anhydrous $MgSO_4$. After removal of the ether, the residual oil was distilled under reduced pressure to give the following fractions: (1) bp 58–60° (15 mm), 0.79 g of diacetone alcohol containing a trace amount of *p*-xylene (detected by glpc); (2) bp 90–120° (1.1 mm), 0.16 g of colorless oil; (3) bp 121–126° (1.1 mm), 2.49 g of colorless oil. Fraction 3 crystallized on standing to give colorless needles which were found to be *p,p'*-dimethylbibenzyl, mp 82° (lit.[23] 82–83°). Glpc analysis (column, 20% PEG-20M; 120–240°, 4°/min program; carrier gas, He, 10 ml/min) indicated that fraction 2 contained 0.03 g (0.9%) of *p*-methylbenzyl alcohol and 0.10 g (total yield 2.59 g, 92.5%) of *p,p'*-dimethylbibenzyl.

B. With *p*-Cyanobenzyl Bromide in Water–Acetone.—To a solution containing 0.030 mol of 1 in 90 ml of water and 100 ml of acetone was added dropwise 5.9 g (0.030 mol) of *p*-cyanobenzyl bromide in 40 ml of acetone with vigorous stirring at room temperature over a period of 30 min. The color of the solution changed from red to yellow, and near the end of addition, to light green. After the same treatment as above, the organic layer was distilled under reduced pressure to give the following fractions: (1) bp 92–98° (14 mm), 1.95 g of *p*-cyanotoluene (50.0 %); (2) bp 100–110° (0.3 mm), 1.25 g of recovered *p*-cyanobenzyl bromide. The residue (*ca.* 1 g) was chromatographed on silica gel. From the ether eluate, colorless needles of *p,p'*-dicyanobibenzyl were obtained: mp 200–201° (recrystallized from ethanol) (lit.[24] mp 198°); yield 0.40 g (11.5%); ir (KBr) 2220 cm^{-1} (C≡N).

C. With *trans*-β-Bromostyrene in Water–Acetone.—To a solution containing 0.035 mol of 1 in 120 ml of water and 70 ml of acetone was added dropwise 6.4 g (0.035 mol) of *trans*-β-bromostyrene in 30 ml of acetone with stirring at room temperature over period of 30 min. The reaction proceeded exothermically and the temperature of the reaction mixture rose from 18 to 23°. The color of the solution changed from blood-red to transient black, and at the end of addition, to dark green. Stirring was continued for a further 30 min. After the same treatment, the filtrate was extracted with 100 ml of ether and 150 ml of benzene. Removal of solvent gave a pale yellow oil which crystallized on cooling to 0°. Filtration of the resulting crystals and washing with 30 ml of cold methanol gave 1.74 g of colorless leaflets, mp 151–152.5°. A sample of *trans,trans*-1,4-diphenyl-1,3-butadiene (5), prepared by another method,[25] showed the same behavior and the melting point was undepressed when mixed with the above sample. Their ir spectra were also identical in all respects. Distillation of the mother liquor under reduced pressure gave 0.30 g (6.6%) of *trans*-β-cyanostyrene (4) and another 0.89 g of 5 (total yield 2.63 g, 72.9%).

D. With Cinnamyl Bromide in Water–Acetone.—To a solution containing 0.035 mol of 1 in 120 ml of water and 110 ml of acetone was added 13.8 g (0.070 mol) of cinnamyl bromide in 50 ml of acetone with stirring at 5° during 1 hr. Stirring was continued for a further 9 hr at room temperature until the reaction mixture gave a yellowish green suspension. After similar treatment, the organic layer was distilled under reduced pressure. A fraction of bp 93–96° (0.8 mm) gave 4.19 g (83.0%) of cinnamyl cyanide: mp 61–61.5° (recrystallized from ethanol) (lit.[26] 59–60°); ir 2270 (C≡N) and 1655 cm^{-1} (C=C). The residue was chromatographed on a 2.5 × 15 cm silica gel column. From the petroleum ether–benzene (4:1) eluate, 0.55 g of colorless leaflets was obtained, mp 80.5–81.5°, which was found to be *trans,trans*-1,6-diphenyl-1,5-hexadiene (lit.[27] mp 80.5–81°) (yield 6.7%).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.19; H, 7.85.

E. With Phenacyl Bromide in DMF.—A mixture of 0.035 mol of 1 and 7.0 g (0.035 mol) of phenacyl bromide in 200 ml of DMF was stirred at 0–10° for 10 hr. The color of the solution changed from red to dark reddish brown. The reaction mixture was poured into 700 ml of water and was extracted with ether. After similar treatment, 0.51 g (20.0%) of acetophenone (identified by ir and glpc) and 1.87 g (46.8%) of 1,2-dibenzoylethane (melting point and mixture melting point with authentic sample,[28] 145–146°) were obtained.

F. With *p*-Bromophenacyl Bromide in Methanol.—When *p*-bromophenacyl bromide instead of phenacyl bromide was reacted with an equimolar amount of 1 in absolute methanol in the usual manner, the following two compounds were isolated: *p*-bromoacetophenone (13.7%) and *p,p'*-dibromo-1,2-dibenzoylethane (32.6%), mp 180–181° (purified by sublimation *in vacuo*). Melting point of the latter compound was not depressed by admixture with authentic sample.[28]

Reaction of Potassium Hexacyanodinickelate(I) (1) in the Presence of CO. A. With *p*-Methylbenzyl Bromide in Water–Acetone.—Into a red solution containing 0.035 mol of 1 in 120 ml of water and 100 ml of acetone, CO was bubbled at 10° with vigorous stirring. The color of the solution changed to yellow within 10 min. *p*-Methylbenzyl bromide (7.0 g, 0.038 mol) in 30 ml of acetone was added at 10°. Stirring and gentle bubbling of CO were continued for 21 hr at 10–45°. A small amount of

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(22) It was confirmed that the presence of the excess of the cyanonickelate(II) does not effect on the present reactions; *i.e.*, when a mixture of benzyl bromide (7.0 g, 0.0400 mol) and $K_2Ni^{II}(CN)_4$ (9.6 g, 0.0400 mol) in 100 ml of water was stirred at 40–70° for 5 hr, almost all of the bromide was recovered unchanged or partly as benzyl alcohol (16%) but bibenzyl was not detected.
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greenish-white solid precipitated in the course of the reaction. After similar treatment, the organic part was distilled under reduced pressure to give the following fractions: (1) bp 78–85° (1.0 mm), 0.93 g of *p*-methylbenzyl alcohol; (2) bp 135–160° (1.0 mm), 2.70 g of colorless needles. Fraction 2 was recrystallized from ethanol to give colorless crystals, mp 54–55°, which were identified as *p,p'*-dimethyldibenzyl ketone: ir (KBr) 1703 cm^{-1} (C=O); nmr (CCl_4) τ 7.70 (s, 6, CH_3), 6.55 (s, 4, CH_2), and 3.10 (s, 8, C_6H_4).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.55; H, 7.39.

Glpc analysis (column, 20% SE-30; 200–280°, 4°/min program; carrier gas, He, 10 ml/min) of fraction 2 showed the presence of a trace amount of *p,p'*-dimethylbibenzyl as a sole impurity.

B. With *trans*-β-Bromostyrene in Water–Methanol.—Carbon monoxide was bubbled into a solution containing 0.035 ml of 1 in 120 ml of water and 100 ml of methanol. *trans*-β-Bromostyrene (9.2 g, 0.050 mol) in 20 ml of methanol was added, and stirring and gentle bubbling of CO were continued for 17 hr at 10–35°. After similar treatment, the organic part was distilled under reduced pressure. A fraction of bp 80–87° (2 mm) was collected to give 4.50 g of pale yellow liquid. The ir spectrum and quantitative glpc analysis (column 20% PEG-20M; 120–280°, 4°/min program; carrier gas, He, 10 ml/min) of the fraction showed the presence of the following compounds: 3.23 g (57.0%) of methyl *trans*-cinnamate, 0.47 g (10.2%) of cinnamaldehyde, 0.10 g (2.2%) of *trans*-β-cyanostyrene, and 0.59 g of recovered *trans*-β-bromostyrene.

Reaction of Potassium Hexacyanodinickelate(I) (1) with Benzyl Bromide in the Presence of Acrylonitrile or Ethyl Acrylate.—To a solution containing 0.035 mol of 1 in 120 ml of water and 40 ml of acetone was added 5.3 g (0.10 mol) of acrylonitrile with stirring. The color of the solution changed immediately to transparent yellow. Benzyl bromide (6.0 g, 0.035 mol) in 20 ml of acetone was added dropwise with stirring at −7° in a period of 1 hr. The reaction mixture was gradually warmed to room temperature during 12 hr with efficient stirring. After similar treatment described above, the organic layer was distilled to give 3.00 g of distillate, bp 89–91° (0.7 mm), which was subjected to quantitative glpc analysis (column, 20% PEG-20M; 130–240°, 4°/min program; carrier gas, He, 12 ml/min) and was found to consist of the following two compounds: 1.17 g (23.0%) of 4-phenylbutyronitrile and 1.83 g (57.4%) of bibenzyl.

When a reaction similar to the preceding example was carried out using ethyl acrylate instead of acrylonitrile, ethyl 4-phenylbutyrate and bibenzyl were obtained in 8.0 and 20.0% yield, respectively (analyzed by ir spectra and glpc). Authentic samples of 4-phenylbutyronitrile and ethyl 4-phenylbutyrate were prepared by the reported methods.[15a]

Isolation of Benzylmercuric Chloride.—To a solution containing 0.035 mol of 1 in 140 ml of water and 40 ml of acetone was added 6.0 g (0.035 mol) of benzyl bromide in 30 ml of acetone at 0° with stirring. The red color of the solution turned pale yellow within 30 min. Mercuric chloride (9.50 g, 0.035 mol) in 30 ml of acetone was added dropwise at 0° over a period of 1 hr. After usual treatment, 1.88 g (17.0%) of benzylmercuric chloride, mp 104–106° (recrystallized from ethanol) (lit.[29] 104°), and 1.91 g (60.0%) of bibenzyl were isolated.

Registry No.—**1**, 123-87-132; benzyl bromide, 100-39-0; *p*-methylbenzyl bromide, 104-81-4; *p*-methoxybenzyl bromide, 2746-25-0; *p*-cyanobenzyl bromide, 17201-43-3; *trans*-β-bromostyrene, 588-72-7; *trans*-cinnamyl bromide, 26146-77-0; phenacyl bromide, 70-11-1; *p*-bromophenacyl bromide, 99-73-0; *n*-butyl iodide, 542-69-8; *p,p'*-dimethyldibenzyl ketone, 26146-78-1.

(29) K. C. Bass, *J. Organometal. Chem.*, **4**, 92 (1965).

Synthesis, Spectra, and Reactions of *N*-Triphenylmethylpyridinium Salts. Reaction of Triphenylmethyl Chloride with Pyridine under High Pressure

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N-Triphenylmethyl- (trityl-) pyridinium chloride (I) was synthesized from trityl chloride and pyridine by means of high pressure (4000–5000 atm) in dioxane or pyridine solution at 60–70°. Compound I was found to react rapidly with methanol and water to produce trityl methyl ether and triphenylcarbinol, respectively. With moisture, it was converted into the molecular complex (II) of triphenylcarbinol and pyridinium chloride in the solid state. The ir, uv, visible, and nmr spectra of I were compared to those of *N*-tritylpyridinium perchlorate and fluoroborate. The deshielding of pyridine ring protons of these *N*-tritylpyridinium compounds is much smaller than that of other *N*-alkylpyridinium compounds. Explanation of this phenomenon is suggested. *N*-tritylpyridinium bromide (III) was synthesized from trityl bromide and pyridine without applying high pressure. The differences between trityl chloride and bromide in the formation of *N*-tritylpyridinium compounds are also discussed.

It has long been known that the yellow color of the trityl ion in nitromethane solutions of trityl chloride discharged immediately upon addition of pyridine. This phenomenon was attributed to the formation of tritylpyridinium chloride (I).[1] The solids "tritylpyridinium chloride" reported in the literature[2] were shown to be a complex (II) of triphenylcarbinol and pyridinium chloride associated through a weak hydrogen bond in the solid state.[3]

Generally, in nucleophilic reactions the stronger nucleophilic reagent, pyridine, would be expected to react faster with alkyl halides than methanol.[4] However, the synthesis of *N*-tritylpyridinium chloride from trityl chloride and pyridine by conventional procedures was unsuccessful, although under similar conditions methanol reacted readily with trityl chloride to form trityl methyl ether.[3] Failure to synthesize *N*-tritylpyridinium chloride may be attributed to its unfavorable

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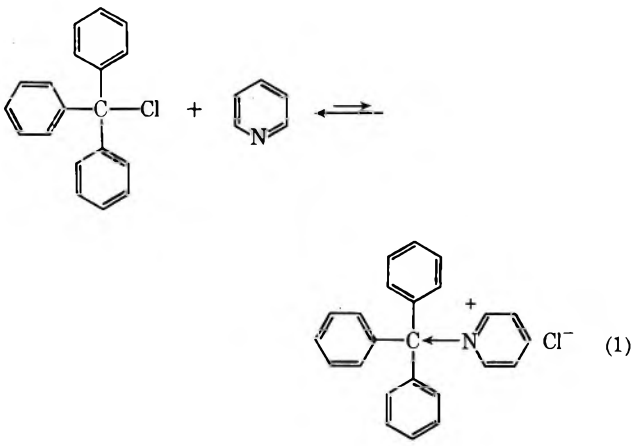
(1) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 82.

(2) Prepared from trityl chloride and pyridine by J. F. Norris and L. R. Culver, *Amer. Chem. J.*, **29**, 134 (1903), by E. V. Meyer and P. Fischer, *J. Prakt. Chem.*, [2], **82**, 523 (1910), by C. A. Kraus and R. Rosen, *J. Amer. Chem. Soc.*, **47**, 2744 (1925). It was also obtained from a pyridine solution of triphenylcarbinol and hydrogen chloride by B. Helferich and H. Dehe, *Ber.*, **58**, 1605 (1925); this product was shown to contain the elements of one molecule of water by B. Helferich and H. Sieber, *ibid.*, **59**, 600 (1926), and Helferich's conclusions were later confirmed by E. D. Hughes, *J. Chem. Soc.*, 75 (1933).

(3) C. G. Swain and Y. Okamoto, *J. Amer. Chem. Soc.*, **92**, 3409 (1970).

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 356.

equilibrium or slow rate relative to methanol captive, shown in eq 1.



(1)

Reactions of alkyl halides with amines to give a quaternary ammonium salt have been extensively studied with respect to steric effect between reactants and the effects of pressure on rate and equilibrium. The rate generally increases with increasing applied pressure. The equilibrium of eq 1 would be expected to shift from left to right with increasing applied pressure on the system, due to decrease in volume on the reaction.[5]

The present investigation was initially undertaken to attempt the synthesis of I from trityl chloride and pyridine by means of high pressure. The properties of I successfully obtained are described.

Results and Discussion

Synthesis of *N*-Tritylpyridinium Chloride (I).—A dioxane solution of trityl chloride and pyridine or a mixture of both components (the latter in large excess ratio) was heated at 60–70°, for 10–15 hr under 4000–5000 atm pressure. The white solid I obtained was separated by filtration and washed three times with dried benzene. The crystals were dried in a desiccator under vacuum. The microanalysis of the compound fitted the molecular formula $C_{24}H_{20}NCl$. The melting point was 90–95° with some decomposition. However, when the solid was exposed to the atmosphere, the melting point gradually rose and finally reached 176°. The mixture melting point of the 176° compound with the complex II of triphenylcarbinol and pyridinium chloride did not show any depression. Furthermore, the 176° compound was identified by ir spectrum as II.

The ir spectrum of alkyl chloride shows a C–Cl bending absorption band at 280–360 cm^{-1} as well as its symmetrical stretching absorption in the region 500–600 cm^{-1} and an asymmetric absorption peak in the region 600–700 cm^{-1}.[6] The stretching absorption bands are usually difficult to distinguish from phenyl ring absorptions, whereas the bending absorption band is more reliable for identification. The C–Cl bending absorption band at 345 cm^{-1} of trityl chloride was not in the spectrum of I in the solid state (Nujol mull). However, the spectrum of an equimolar mixture of trityl chloride and pyridine in Nujol mull shows the C–Cl bending absorption band. When I was treated with an excess of methanol at room temperature, trityl methyl ether and pyridinium chloride were obtained. With water, I was readily converted into triphenylcarbinol and pyridinium chloride.

Properties of I in Solution.—Compound I was insoluble in benzene or carbon tetrachloride, but soluble in chloroform, acetonitrile, and dimethyl sulfoxide. The ultraviolet absorption peaks of I in dichloromethane appeared at 234 mμ (ε 5400) and 257 (2500). The latter peak is due to pyridinium ion. *N*-Tritylpyridinium perchlorate and fluoroborate were prepared from the reactions of trityl perchlorate and fluoroborate with pyridine without applying pressure. The visible absorption spectrum of I as well as of tritylpyridinium perchlorate and fluoroborate in dichloromethane was recorded. However, adsorption in the region 400–450 mμ for the trityl ion was not observed.

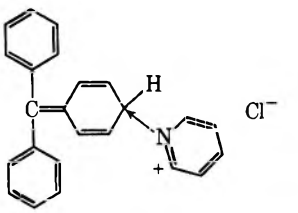
The nmr spectrum of I was almost identical with those of *N*-tritylpyridinium perchloride and fluoroborate. The phenyl proton spectrum appeared at τ 2.70 as a singlet.[7]

For comparison, the chemical shifts of the α-, β-, and γ-pyridine ring protons for other pyridinium compounds are summarized in Table I.[9] The substantial deshielding of the pyridine ring protons in the pyridinium compounds are due to the decrease in electron charge density at the individual carbon nuclei as a result of the formation of the positively charged nitrogen.[10] The

(5) S. D. Hamann, "High Pressure Physics and Chemistry," Vol. 2, R. S. Bradly, Ed. Academic Press, New York, N. Y., 1963.

(6) N. B. Colthup, N. H. Daly, and F. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964.

(7) Recently, the recharacterization of "hexaphenylethane" produced by the dimerization of triphenylmethyl radical was reported by Lankamp, Nauta, and MacLean.[8] The 1-diphenylmethylene-4-trityl-2,5-cyclohexadiene structure was proposed for the dimerization product. Accordingly, the question might arise for the structure of I; instead of I, the pyridine may attack at the para position of phenyl and form 1-diphenylmethylene-2,5-



IV

cyclohexadiene 4-pyridinium chloride (IV). However, the nmr spectra of I shows that the phenyl protons were a singlet (τ 2.70). The absorptions corresponding to the olefinic protons (τ 3.6–4.2) and aliphatic proton (τ ~5) were not observed. Moreover, the proton ratio of phenyls and pyridine were approximately 3:1.

(8) H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968).

(9) The chemical shifts of the pyridine ring protons in pyridinium salts were examined in various concentrations of $CDCl_3$. The concentrations

	Concentration (w/v%) value					
	5%			10%		
	α	β	γ	α	β	γ
Pyridinium chloride	0.96	1.88	1.42	0.93	1.83	1.39
Pyridinium bromide	0.87	1.75	1.37	0.81	1.71	1.27
	15%			20%		
	α	β	γ	α	β	γ
Pyridinium chloride	0.89	1.75	1.30	0.89	1.74	1.29
Pyridinium bromide	0.79	1.69	1.21	0.80	1.69	1.22

dependent on the shifts are about within τ ±0.1 over these concentration ranges. The nmr in Table I, II, and III were measured in 0.1~0.5 *M* solution.

(10) I. C. Smith and W. G. Schneider, *Can. J. Chem.*, **39**, 1158 (1961).

TABLE I

CHEMICAL SHIFTS OF PYRIDINE RING PROTONS OF THE PYRIDINIUM DERIVATIVES (τ VALUES)[a]

Compd	$CDCl_3$ solution						CH_3CN solution						DMSO-d_6 solution					
	α	$\Delta\alpha$[b]	β	$\Delta\beta$	γ	$\Delta\gamma$	α	$\Delta\alpha$	β	$\Delta\beta$	γ	$\Delta\gamma$	α	$\Delta\alpha$	β	$\Delta\beta$	γ	$\Delta\gamma$
Pyridine	1.56	(0)	2.90	(0)	2.50	(0)	1.44	(0)	2.66	(0)	2.34	(0)	1.34	(0)	2.65	(0)	2.28	(0)
Pyridinium chloride	0.98	(0.58)	1.88	(1.02)	1.44	(1.06)	1.16	(0.28)	1.94	(0.72)	1.44	(0.90)	0.90	(0.44)	1.75	(0.90)	1.25	(1.03)
N-Methylpyridinium iodide	1.08	(0.48)	1.80	(1.10)	1.40	(1.10)												
N-Benzylpyridinium chloride	0	(1.56)	1.80	(1.10)	1.50	(1.00)	0.24	(1.20)	1.88	(0.78)	1.54	(0.80)						
N-Benzhydrylpyridinium chloride	0.56	(1.00)	1.84	(1.06)	1.40	(1.10)							0.88	(0.46)	1.72	(0.93)	1.25	(1.03)
N-Tritylpyridinium chloride (I)	1.36	(0.20)	2.44	(0.46)	2.04	(0.46)	1.40	(0.04)	2.50	(0.11)[c]	2.18	(0.16)	1.30	(0.04)	2.42	(0.23)	2.08	(0.20)
N-Tritylpyridinium bromide (III)	1.32	(0.24)	2.46	(0.44)[c]	2.24	(0.26)												
N-Tritylpyridinium perchlorate							1.30	(0.14)	2.44	(0.22)[c]	2.06	(0.28)	1.30	(0.04)	2.38	(0.27)	2.00	(0.28)
N-Tritylpyridinium fluoroborate													1.25	(0.09)	2.35	(0.30)	1.92	(0.36)

[a] All chemical shifts referred to tetramethylsilane as internal standard. [b] These values indicate applied shifts from the corresponding pyridine ring protons. [c] Peaks are partially overlapped with the phenyl proton absorption.

deshielding of the β- and γ-pyridine ring protons in benzyl and benzhydryl pyridinium chlorides is similar to that of *N*-methylpyridinium iodide and pyridinium chloride. On the other hand, the deshielding of the α-pyridine ring protons is quite varied. This may be due to the effect of counterions[11] (ion pair formation) or to the shielding by the adjacent phenyl group.[12] From Table I, it is clear that the deshielding of the β- and γ-pyridine ring protons of *N*-tritylpyridinium compounds is much smaller as compared to that in other pyridinium compounds. A similar trend is also observed in the chemical shifts of the methyl protons of the γ-picolinium compounds; *i.e.*, the chemical shift of the methyl group of *N*-trityl-γ-picolinium perchlorate appears in between those of γ-picoline and γ-picolinium chloride (Table II). The exact explanation of this

TABLE II

CHEMICAL SHIFTS OF γ-PICOLINE RING PROTONS AND γ-METHYL PROTONS OF THE *N*-γ-PICOLINIUM (τ VALUES)

Compd	DMSO-D_6 solution					
	α	$\Delta\alpha$[a]	β	$\Delta\beta$	γ-CH_3	Δ[b]
γ-Picoline	1.50	(0)	2.80	(0)	7.70	(0)
N-γ-Picolinium chloride	1.00	(0.50)	1.90	(0.90)	7.28	(0.42)
N-Trityl-γ-picolinium perchlorate	1.40	(0.10)	2.55	(0.25)	7.56	(0.14)

[a] These values indicate applied shifts from the corresponding pyridine ring protons. [b] These values indicate shifts from the methyl protons of γ-picoline.

phenomenon is not clear. However, this may be attributed to the following: The coordination bond between the carbon and nitrogen in *N*-tritylpyridinium compounds is stretched in order to minimize the steric strain between phenyl groups and pyridine. This may also be enhanced by a gain in resonance energy of three phenyls in the partially developed trityl ion. Thus, the resulting electron charge density on the nitrogen atom is not as low as those of *N*-benzyl and *N*-benzylhydryl pyridinium chlorides. Consequently, the deshielding effect of the pyridine ring protons in I is not as pronounced as those in the other pyridinium compounds.

It can also be attributed to ion-pair formation. The pyridinium ion pairs with counterions such as chloride or iodide in acetonitrile or nitrobenzene. The counterion is most probably situated close to the positively charged nitrogen,[13] and thus reduces considerably the π-electron polarization calculated for an isolated pyridinium ion.[14] Thus, when the bulky group is bonded to the α position or on the nitrogen atom of pyridine, the counterion may not be as close to the positive nitrogen and may be situated near the electron deficient and less sterically hindered β and γ positions of the pyridine. As a result, the low field shifts of the β and γ protons in *N*-tritylpyridinium compounds are found to be smaller than those of other pyridinium compounds cited in Table I.[15]

A similar phenomenon was observed in the chemical shift of α-substituted pyridinium compounds (Table III). The magnitude of the low field chemical shift ($\sim$1 ppm) of the β- and γ-pyridine ring protons of 2,6-lutidinium compounds is similar to those in pyridinium or *N*-methylpyridinium halides. However, the low field chemical shifts of the β- and γ-pyridine ring protons in 2,6-di-*tert*-butyl-*N*-pyridinium iodide are not as large as those of less sterically hindered pyridinium compounds. This may also be attributed to the counterion association close to the electron deficient β and γ positions of the pyridinium and to the reduced polarity of C–H bonds.

The nmr spectrum of I did not change after the chloroform solution was allowed to stand for 10 days at room temperature. However, when I was dissolved in chloroform at room temperature and then the solvent was removed under vacuum, trityl chloride was isolated instead of I. These results indicate that, as the solvent is removed, the chloride ion reacts with the trityl moiety to form trityl chloride and pyridine.

Recently, syntheses of *N*-tritylpyridinium bromide (III) from trityl bromide and pyridine in acetonitrile[17]

(11) G. Kotowycz, T. Shaffer, and E. Bock, *Can. J. Chem.*, **42**, 2541 (1964).

(12) D. G. Farnum, *J. Amer. Chem. Soc.*, **86**, 934 (1964).

(13) C. Rerat, *Acta Crystallogr.*, **15**, 427 (1962).

(14) G. Kotowycz, T. Shaefer, and E. Bock, *Can. J. Chem.*, **42**, 2541 (1964).

(15) The structure of tritylpyridinium may be similar to that of tetraphenylmethane of which phenyl groups are twisted to each other (55° angle between the ring and the vertical planes).[16] This unique configuration may be effected to shield ($\sim$0.5 ppm) the β- and γ-pyridine ring protons by the adjacent phenyl ring current. However, the phenyl ring protons of tetraphenylmethane are absorbed at τ 2.76 (as a singlet) which is not different from the phenyl ring proton absorption (τ 2.70) of trityl chloride in $CDCl_3$.

(16) A. I. Kitaigorodskii "Organic Chemical Crystallography," Consultants Bureau, New York, N. Y., 1961, p 404.

(17) R. Damico and C. D. Broadlus, *J. Org. Chem.*, **31**, 1607 (1966). Damico and Broadlus report the chemical shifts of the α-, β-, and γ-pyridine ring protons of III in chloroform, and 0.9–1.9 which are similar to those of pyridinium salt. However, we could not reproduce these data and obtained the values cited in Table I.

Table III

Chemical Shifts of β- and γ-Ring Protons of α-Substituted Pyridine Derivatives (τ Values)

Compd	Registry no.	DMSO-d_6 solution β	(Δβ)[a]	γ	(Δγ)[a]
2,6-Dimethylpyridine	708-48-5	3.00	0)	2.44	(0)
2,6-Dimethyl-*N*-pyridinium iodide	24994-62-5	2.18	(0.82)	1.66	(0.78)
2,6-Dimethyl-*N*-methylpyridinium iodide	2525-19-1	2.06	(0.94)	1.60	(0.84)
2,6-Di-*tert*-butylpyridine	585-48-8	2.85	(0)	2.38	(0)
2,6-Di-*tert*-butyl-*N*-pyridinium iodide	26154-14-3	2.40	(0.45)	2.00	(0.38)

[a] These values indicate shifts from the corresponding pyridine ring protons.

and in acetone–dimethyl sulfoxide[18,19] were reported. III was readily synthesized at room temperature, whereas under similar conditions or under more drastic conditions, the preparation of I was not successful without applying high pressure. The ir spectrum of III in Nujol mull was almost identical with that of I. Furthermore, the pyridine ring protons of III have similar deshielding effects to those observed in other tritylpyridinium salts (Table I). These results show that trityl bromide and pyridine react in the solvents such as acetonitrile to form III. When the solvent was removed, III was recovered, unlike the case of I, which dissociated into trityl chloride and pyridine. These remarkably different results may be due to the differences of reactivity of Br^- and Cl^-. In general, Br^- is a stronger nucleophilic reagent than Cl^-. However in aprotic solvents, Cl^- is more reactive than Br^-.[20,21] Thus, the above result may be accounted for by the sequence of (i) nucleophilicity and (ii) the size of ions. The larger and less reactive ion, Br^-, does not react with the trityl moiety of III, upon solvent removal. As a result, III was synthesized by evaporation of solvents from the mixture of trityl bromide and pyridine in polar solvents. This explanation is further supported by the following result: When III was mixed with pyridinium chloride in acetonitrile at room temperature and the solvent removed to dryness, the solid obtained was treated with petroleum ether. After the petroleum ether was evaporated, trityl chloride was obtained in good yield (80%). This result shows that, as solvent was evaporated, Cl^- readily reacts with the trityl moiety of III to form trityl chloride and pyridine.

The reactions of trityl chloride with 2,6-lutidine were attempted under high pressure (up to 6000 atm). However, no reaction was detected and trityl chloride was recovered quantitatively.

Experimental Section

Solvents and Reagents.—All solvents were dried over Drierite and distilled. Pyridine, γ-picoline, and 2,6-lutidine (Eastman Kodak Co.) were dried over calcium hydride and distilled. Trityl chloride (K and K Laboratories, Inc.) was twice recrystallized from benzene–petroleum ether with acetyl chloride, mp 111–112°.[22] Triphenylcarbinol (Eastman Kodak Co.) was recrystallized from ethanol, mp 161°.

Instrumental Analyses.—Nmr spectra were obtained on a Varian A60 instrument. A Perkin-Elmer Model 237 infrared spectrophotometer equipped with sodium chloride optics was used for ir measurements in the wavelength region 4000–700 cm^{-1}. For the far-infrared region, a Perkin-Elmer Model 621 grating spectrophotometer with cesium iodide cell was used. Ultraviolet and visible spectra were measured with a Perkin-Elmer Model 202 spectrophotometer.

Trityl Fluoroborate and Perchlorate.—These compounds were prepared by the method previously reported.[23] Trityl fluoroborate and perchlorate melted at 198° dec and 142°, respectively.

***N*-Benzyl- and *N*-Benzhydrylpyridinium Chloride.**—These pyridinium compounds were prepared from benzyl chloride and benzhydryl chloride with excess pyridine by refluxing. The products were recrystallized from chloroform–benzene solution. Benzylpyridinium chloride (hygroscopic)[24] and benzhydrylpyridinium chloride[25] melted at 125 and 207°, respectively.

Reaction of Trityl Chloride with Pyridine by High Pressure.—The reactions of trityl chloride with pyridine under high pressure were carried out in either dioxane or pyridine as solvent. Trityl chloride (1.15 g) and pyridine (2.20 g) were dissolved in 5 ml of dioxane in a drybox. The high pressure technique described earlier was followed.[26]

***N*-Tritylpyridinium Chloride (I).**—A dioxane solution of trityl chloride and pyridine was heated at 60–70° for 10–15 hr under 5500–6000 atm. After the die had cooled, the pressure was released to 1 atm. The capsule was opened in a drybox. The white crystals obtained (60–70% yield) were separated by filtration from the dark red solution and washed three times with dry benzene. The crystals were dried in a desiccator under vacuum, mp 90–95° dec.

Anal. Calcd for $C_{24}H_{20}NC$: C, 80.55; H, 5.58; N, 3.92; Cl, 10.00. Found: C, 80.40; H, 5.80; N, 3.85; Cl, 9.71.

The melting point of I was determined in an open-ended Pyrex capillary tube. After 4 hr from the first measurement, the melting point of the compound had risen to 160–169° and it reached 175–176° a few days later. When I was exposed to the atmosphere, it was converted rapidly into the high melting compound.

Reactions of *N*-Tritylpyridinium Chloride with Water and Methanol.—I (0.1 g) was dissolved in chloroform and the solution was treated with water at room temperature for 10 min. The chloroform solution was separated and dried over Drierite. Upon evaporating the chloroform, white crystals (0.07 g) were obtained and recrystallized from ethanol, mp 160°, undepressed by admixture with triphenylcarbinol.

I (0.1 g) was treated with 2 ml of methanol for 5 min at room temperature. The solid material was isolated and washed with methanol, mp 82°, no depression on mixing with pure trityl methyl ether, mp 84°, prepared from a methanol solution of trityl chloride and pyridine. The triphenylcarbinol and trityl methyl ether isolated were also identified by infrared spectroscopic study.

***N*-Tritylpyridinium Perchlorate and Tetrafluoroborate.** Trityl perchlorate (2.0 g) was dissolved in 10 ml of acetonitrile (yellow solution). Pyridine (1 ml) was added to the acetonitrile solution to give a colorless solution. After the solution was allowed to stand at room temperature for 10 min, the solvent was removed *in vacuo* to give the yellow solid. The solid was washed with benzene three times and dried under vacuum. There was obtained an 82% yield of *N*-tritylpyridinium perchlorate, mp 209–212° dec.

N-Tritylpyridinium tetrafluoroborate was prepared from a mixture of solution of trityl tetrafluoroborate and pyridine in acetonitrile in the same way as the perchlorate, mp 155–157°.

(18) G. Briegleb, *Angew. Chem., Int. Ed. Engl.*, **2**, 545 (1963).
(19) Personal communication with Professor G. Briegleb.
(20) S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, **9**, 24 (1964).
(21) W. M. Weaver and J. D. Hutchison, *J. Amer. Chem. Soc.*, **86**, 261 (1964).
(22) C. G. Swain and E. E. Pegues, *ibid.*, **80**, 812 (1958).
(23) H. J. Dauben, Jr., L. R. Honner, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).
(24) A. G. Anderson, Jr., and G. Berkelhammer, *ibid.*, **23**, 1109 (1958).
(25) G. D. Sichev, *J. Russ. Phys. Chem.*, **60**, 325 (1928); *Chem. Abstr.*, **23**, 1330 (1929).
(26) Y. Okamoto and H. Shimizu, *J. Amer. Chem. Soc.*, **90**, 6145 (1968).

Trityl Bromide.—Trityl bromide was prepared by the method previously reported.[27] The colorless solid melted at 145–147°.

***N*-Tritylpyridinium Bromide.** The solution of 5.2 g (0.016 mol) of trityl bromide and 7.1 g (0.09 mol) of pyridine in 50 ml of acetonitrile was stirred for 24 hr and then the solvent and excess pyridine were removed under vacuum. After washing with pentane, a slightly tan solid was recovered in 40% yield, mp 137–139° dec (lit.[27] mp 139° dec).

Reaction of *N*-Tritylpyridinium Bromide with Pyridinium Chloride.—The mixture of solution of 2.00 g (0.005 mol) of *N*-tritylpyridinium bromide and 1.50 g (0.013 mol) of pyridinium chloride in 50 ml of dry acetonitrile was stirred at room temperature for 10 min and the solvent was evaporated under reduced pressure. The residue was extracted with 50 ml of dry petroleum ether and then the solvent was removed under reduced pressure. The white solid, recovered in 80% yield, melted at 111–112° and proved to be trityl chloride by mixture melting point measurement and infrared spectroscopy.

α-Substituted Pyridinium Compounds.—2,6-Dimethyl-*N*-pyridinium iodide was obtained by passing dry hydrogen iodide into the benzene solution of 2,6-dimethylpyridine, mp 185°. 2,6-Dimethyl-*N*-methylpyridinium iodide was synthesized from 2,6-dimethylpyridine with methyl iodide by refluxing. The product was recrystallized from ethanol, mp 239–240°.

Anal. Calcd for $C_8H_{12}NI$: C, 38.6; H, 4.82; N, 5.63; I, 51.0. Found: C, 38.4; H, 4.83; N, 5.77; I, 51.1.

2,6-Di-*tert*-butylpyridine was prepared by the method of Brown and Kanner,[28] bp 61–62° (1 mm), the chloroaurate, mp 188° (lit.[28] 184.5°).

Anal. Calcd for $C_{13}H_{22}NAuCl_4$: C, 29.4; H, 4.15; Cl, 26.7; N, 2.64. Found: C, 29.9; H, 4.29; Cl, 26.4; N, 3.08.

2,6-Di-*tert*-butyl-*N*-pyridinium iodide was synthesized by passing dry hydrogen iodide into the benzene solution of 2,6-di-*tert*-butylpyridine, mp 196–197°.

Registry No.—Triphenylmethyl chloride, 76-83-5; pyridine, 110-86-1; I, 26156-82-1; I perchlorate, 26156-83-2; I fluoroborate, 26156-84-3; pyridinium chloride, 628-13-7; *N*-methylpyridinium iodide, 930-73-4; *N*-benzylpyridinium chloride, 2876-13-3; *N*-benzhydrylpyridinium chloride, 26156-88-7; III, 7206-97-5; γ-picoline, 108-89-4; *N*-γ-picolinium chloride, 14401-93-5; *N*-trityl-γ-picolinium perchlorate, 26154-09-6.

Acknowledgment.—The authors gratefully acknowledge numerous stimulating discussions with Professor C. G. Swain.

(27) W. E. Backmann, "Organic Syntheses," Coll. Vol. 3, Wiley, New York, N. Y., p 841.

(28) H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, **88**, 986 (1966).

Bromine–Lithium Exchange of *p*-Bromo-*N*,*N*-dimethylaniline with *n*-Butyllithium

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A product study of the reaction between *p*-bromo-*N*,*N*-dimethylaniline (1) and *n*-butyllithium (2) was made. Yields as high as 91% of *p*-(*N*,*N*-dimethylamino)phenyllithium (3) were obtained at 25° with a contact time of 30 hr. Several amines arising from nitrogen, ring, and chain alkylation were found at all temperatures. A dimeric amine, *N*,*N*,*N*′,*N*′-tetramethyl-*p*-benzidine (9), was isolated from runs at high temperature. *N*-Methyl alkylation of 3 with 2 and 1-iodobutane failed. Ring carbon alkylation with 1-iodobutane gave the expected product, *p*-(*n*-butyl)-*N*,*N*-dimethylaniline (8).

The halogen–lithium exchange reaction between organolithium compounds and organic halides, mainly bromides and iodides, first discovered by the schools of Gilman[1b] and Wittig[2] has received wide synthetic application. Mechanistic studies have also been carried out in order to unveil the details of the reaction.[3]

Our interest in halogen–lithium exchange reactions and in the chemistry of tertiary amines has led us to reinvestigate the reaction between *p*-bromo-*N*,*N*-dimethylaniline (1) and *n*-butyllithium (2) in the inert solvent *n*-hexane. The reaction is known to yield *p*-(*N*,*N*-dimethylamino)phenyllithium (3), which was derivatized with carbon dioxide and eventually identified as the methyl ether.[4] Since 1 is also used for a color test of aliphatic organolithium compounds,[5] it was of interest to know the spectrum of products arising from the exchange reaction as well as their dependence on reaction conditions.

Results and Discussion

Glc quantitative determination[6] showed that *N*,*N*-dimethylaniline was obtained in 91% yield by quenching with water the reaction mixture from the interaction of 1 with a 60% excess of 2 at 0°. Quenching with D_2O (Table II, run 6) gave *p*-deuterio-*N*,*N*-dimethylaniline (5),[7] whose mass spectrum (M^+ 122, Table I) was consistent with nuclear deuteration (*m*/*e* at 78), but was not distinct from that of *o*-deuterio-*N*,*N*-dimethylaniline, which was prepared by direct metalation of *N*,*N*-dimethylaniline with *n*-butyllithium,[8] followed by quenching with deuterium oxide. The pmr spectrum of 5, however, besides revealing no significant *m*-deuteration and an isotopic purity of ~80%, showed a distinct A_2B_2 quartet in the aromatic region and the ir spectrum confirmed the position of deuteration with the characteristic *o*-*o*-*p* bending absorption of aromatic hydrogen at 12.15 μ as well as the expected pattern[9] at 5–6 μ. Table II shows all the

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(1) (a) This work is taken in part from the doctorate thesis of G. L., 1969–1970. (b) H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1939).

(2) G. Wittig, U. Pockels, and H. Dröge, *Chem. Ber.*, **71**, 1903 (1938).

(3) (a) D. E. Applequist and D. F. O'Brien, *J. Amer. Chem. Soc.*, **85**, 743 (1963). (b) H. J. S. Winkler and H. Winkler, *ibid.*, **88**, 964, 969 (1966). (c) A. R. Lepley, *Chem. Commun.*, 64 (1969).

(4) H. Gilman and I. Banner, *J. Amer. Chem. Soc.*, **62**, 344 (1940).

(5) H. Gilman and J. Swiss, *ibid.*, **62**, 1847 (1940).

(6) Essential glc data are collected in Table I and conditions are reported in the Experimental Section.

(7) G. Fraenkel and J. P. Kim, *J. Amer. Chem. Soc.*, **88**, 4203 (1966).

(8) A. R. Lepley, W. A. Khan, A. B. Giumanini, and A. G. Giumanini, *J. Org. Chem.*, **31**, 2047 (1966).

(9) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 118.

Table I

Mass Spectrometry[a] and Glc Retention Time Ratios (ρ) at 150° of Tertiary Amines Related with the Exchange Reaction of *p*-Bromo-*N*,*N*-dimethylaniline (1) with *n*-Butyllithium (2)

Compd	Molecular formula	Ten highest ions (*m/e*)[c] (relative abundance)										ρ[d]
N,*N*-Dimethylaniline (4)[b]	$C_8H_{11}N$	120	121	77	51	42	105	39	104	50	91	
		100	68	33		17	17	14	14	11	8	0.40
p-*d*-*N*,*N*-Dimethylaniline (5)	$C_8H_{10}DN$	121	122	78	120	106	105	52	51	42	123	
		100	80	28	18	17	16	15	14	14	14	0.40
o-*d*-*N*,*N*-Dimethylaniline[e]	$C_8H_{10}DN$	121	122	123	120	78	106	42	52	51	105	
		100	94	32	29	27	19	17	17	16	16	0.40
N-(*n*-Butyl)-*N*-methylaniline (6)[b]	$C_{11}H_{17}N$	120	77	104	51	42	39	105	121	163	91	
		100	34	17	16	13	12	12	10	7	7	0.73
N-(*n*-Pentyl)-*N*-methylaniline (7)[b]	$C_{12}H_{19}N$	120	77	104	51	105	39	121	42	41	91	177
		100	41	19	18	16	12	11	11	9	9	6	1.000
p-(*n*-Butyl)-*N*,*N*-dimethylaniline (8)	$C_{12}H_{19}N$	134	118	177	135	91	77	39	65	146	51	
		100	33	28	23	15	13	8	8	7	6	1.17
p-Bromo-*N*,*N*-dimethylaniline (1)[b]	$C_8H_{10}BrN$	200	199	198	201	118	77	50	75	63	51	
		100	94	93	91	33	25	25	18	18	18	1.92
p-(*n*-Butyl)-*N*-(*n*-butyl)-*N*-methylaniline (11)	$C_{15}H_{25}N$	176	118	41	42	120	91	34	177	133	77	219
		100	86	53	45	42	36	30	29	27	26	12	2.25
p-(*n*-Butyl)-*N*-(*n*-pentyl)-*N*-methylaniline (12)	$C_{16}H_{27}N$	176	118	41	43	120	39	133	190	132	146	233
		100	58	39	38	37	28	26	22	22	22	20	3.15
p-Bromo-*N*-(*n*-pentyl)-*N*-methylaniline (14)	$C_{12}H_{18}BrN$	198	200	119	118	256	42	258	41	185	39	
		100	100	18	17	13	12	12	12	9	8	
N,*N*,*N*′,*N*′-Tetramethyl-*p*-benzidine (9)[b]	$C_{16}H_{20}N_2$	240	225	241	119	224	152	239	120	119	209	
		100	44	20	18	16	11	10	10	8	7	1.52[f]

[a] For experimental conditions see Experimental Section. [b] Spectra of the compound from an independent synthesis. The spectrum of the actual compound from the reaction corresponded to this fragmentation pattern. [c] Parent peaks are underlined. [d] See Experimental Section for glc conditions. [e] Spectrum of the iterative metalation–deuteration mixture described in the Experimental Section. [f] At 250°, using diphenylamine as standard.

Table II

Reaction of *p*-Bromo-*N*,*N*-dimethylaniline (1) with *n*-Butyllithium (2). Product Distribution[a]

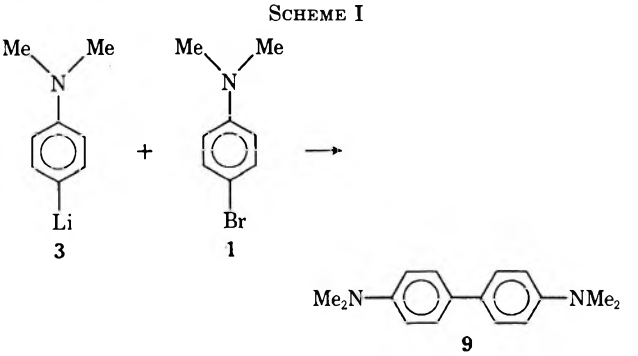
Run	1, mmol	2, mmol	Ratio, 2:1	Temp, °C	Reaction time, hr	Products (% yield)[b] *p*-Bromo-*N*,*N*-dimethylaniline 1	*N*,*N*-Dimethylaniline 4	*N*-(*n*-Butyl)-*N*-methanylaniline 6	7	8
1[c]	25	50	2.0	48	27	...[d]	>47.0	...[d]	...[d]	...[d]
2	25	100	4.0	62 ± 2	3	0.0	53.0	...[d]	6.2	12.0
3[e]	5	16	3.2	75 ± 2	3	0.0	76.0	...[d]	10.9	8.8
4[e]	5	16	3.2	2 ± 1	3	...[d]	35.7	...[d]	...[d]	...[d]
5	5	16	3.2	25 ± 1	30	0.0	91.0	1.2	4.2	3.3
6[e,f]	25	55	2.2	32	15	0.0	38.5	1.5	4.6	6.2

[a] Runs were carried out in nitrogen atmosphere unless stated otherwise. Butyllithium concentration in hexane was between 1.4 and 1.6 *N*. [b] Yields were determined by glc using 1 as internal standard. [c] Dropwise addition of 2 during 15 min. In all other runs 2 was added in one lot at room temperature. [d] The product was present in undetermined yield. [e] Not in nitrogen atmosphere. [f] Quenching with deuterium oxide. Upon distillation, *p*-deuterio-*N*,*N*-dimethylaniline was obtained in 36% yield.

pertinent results relative to the reaction of **1** with **2**. Glc at higher temperature[6] of the water-quenched exchange mixture revealed the presence of at least three other products, adequately separated to obtain their mass spectra and allow their quantitative evaluation by means of an added standard. The new amines were *N*-(*n*-butyl)-*N*-methylaniline (**6**), *N*-(*n*-pentyl)-*N*-methylaniline (**7**), and *p*-(*n*-butyl)-*N*,*N*-dimethylaniline (**8**), as initially revealed by their retention time ratios and enhancing with authentic materials and definitively ascertained on the basis of the recorded mass spectra (Table I). Vacuum distillation of the more volatile products (runs 2 and 3) left a dark oil from which was isolated *N*,*N*,*N*′*N*′-tetramethyl-*p*-benzidine (**9**).

It is likely that **9** was formed by direct substitution (Scheme I); aryl bromides are known to undergo such reaction with aryllithiums under similar conditions.[10]

Scheme I



Indeed, gas chromatography–mass spectrometry of the higher boiling amines which were formed in small amounts in the exchange reactions at higher tempera-

(10) L. Friedman and J. F. Chlebowski, *J. Amer. Chem. Soc.*, **91**, 4864 (1969).

TABLE III

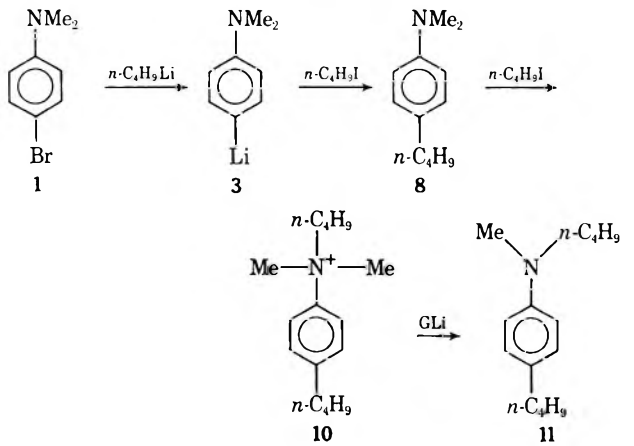
REACTIONS OF p-(N,N-DIMETHYLAMINO)PHENYLLITHIUM (3) AND RELATED EXPERIMENTS[a]

Run	Reactants exchange system[c] 1, mmol	2, mmol	Temp, °C	Time, hr	Coreactant[c] (mmol)	Temp, °C	Time, hr	Products, % yield[b] 1	4	6	7	8
1[e]	25	55	24	24	1-Iodobutane (30)	24	100	0.0	25.0	...[d]	1.7	15.7
2	25	52	15	27	1-Iodobutane (26)	Reflux	24	...[d]	...[d]	...[d]	...[d]	30.0[f]
3	25	48	70	4	1-Iodobutane (30)	Reflux	5.5	0.0	6.5	...[d]	0.4	32.5
4	25	50	65	4.5	1-Iodobutane (51) 2 (25)	−15 up to +15	4.5	0.0	37.0	...[d]	6.05	11.0
5	5	22.5	25	24	1-Iodobutane (12.5) Et_2O (5 ml)	0	3	0.0	40.0	...[d]	4.5	4.4
6[g]		1 (5)			1-Iodobutane (10) 2 (20)	−8 up to +18	24	14.9	23.0	Trace	2.5	1.2
7[h]	Final unquenched reaction mixture from run 6				2 (80)	20	24	0.0	...[d]	...[d]	...[d]	...[d]

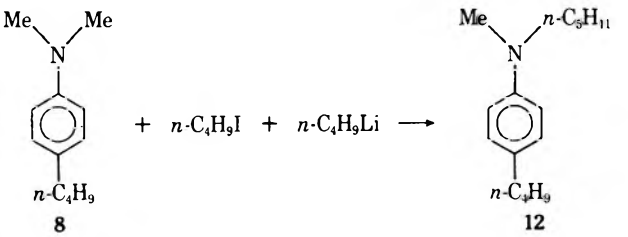
[a,b] See footnotes *a* and *b* of Table II. [c] Butyllithium and coreactant were added in one lot. [d,e] See footnotes *d* and *e* of Table II. [f] Yield in distilled product corrected for impurities. [g] Also ~6% of *p*-bromo-*N*-(*n*-pentyl)-*N*-methylaniline (**14**). [h] The final reaction mixture showed an increased ratio 7:8 and the disappearance of **14**.

tures did not reveal any *N,N,N′,N′*-tetramethyl-3,4′-diaminobiphenyl in the complex mixture, suggesting that a benzyne reaction is not a major pathway, although the substituent effect on the addition of a carbanion to a 1-dimethylamino-3,4-benzyne is not known.[11] Oxidation of **3** could perhaps lead to **9**,[12] but there was no difference between reactions in air and in a pure nitrogen atmosphere.

When **3** was treated with 1-iodobutane, the major product was the *para*-substituted amine **8**, whose structure was confirmed by pmr spectroscopy (A_2B_2 quartet for 4 H, singlet for 6 H, triplet for 2 H and the *n*-propyl characteristic pattern all in the expected locations). The reaction was best effected at reflux temperature and the most important side product was *p*-(*n*-butyl)-*N*-(*n*-butyl)-*N*-methylaniline (**11**), identified by mass spectroscopy and most probably arising from quaternarization of **8** by 1-iodobutane, followed by methyl displacement.



Another amine, well separated under the glc conditions used, was identified as *p*-(*n*-butyl)-*N*-(*n*-pentyl)-*N*-methylaniline (**12**) on the basis of its mass spectrum, showing a molecular ion at *m/e* 233 and ions from both propyl and butyl cleavage. Since *N*-(*n*-pentyl)-*N*-methylaniline (**7**) does not exhibit propyl elimination, this amine cannot be *N,N*-di(*n*-pentyl)aniline, a product which would arise from double lateral alkylation of *N,N*-dimethylaniline: it was formed most likely by the action of 1-iodobutane and leftover *n*-butyllithium on *p*-(*n*-butyl)-*N,N*-dimethylaniline (**8**). A pathway similar to that outlined above for **11** should hypothetically also be operative for **6**. The exchange reaction produces 1-bromobutane which can react either with any organometallic species (*i.e.*, with *n*-butyllithium to give *n*-octane or **3** to yield **8**) or with the nitrogen of **3** (or **1**) to give a quaternary ion which is eventually transformed to **6** by *n*-butyllithium.



N-(*n*-Pentyl)-*N*-methylaniline (**7**) is a product of lateral alkylation[13] of *N,N*-dimethylaniline. But it is quite unlikely that large amounts of the latter compound are formed under these conditions. It was therefore anticipated that **3** could undergo lateral alkylation. To test this hypothesis, **3** was treated with excess *n*-butyllithium and 1-iodobutane under the conditions for lateral alkylation. Since the amount of **7** did not increase (Table III, run 4), **3** did not undergo lateral alkylation. Also, the reaction of 1-iodobutane with *n*-butyllithium mainly to yield *n*-octane in these conditions is faster than any other. This could be due to the insolubility[14] of **3** in the reaction mixture; the necessary[15] amine–organolithium complex could not be formed, thus preventing further reaction. In this line of thought, we solubilized **3** by the addition of ether, but, again, lateral butylation did not occur to a larger extent (Table III, run 5). Evidently **3** is unable to coordinate *n*-butyllithium, perhaps because of de-

(11) R. W. Hoffman, "Dehydrobenzene and Cycloalkenes," Academic Press, New York, N. Y., 1967, pp 106–150.

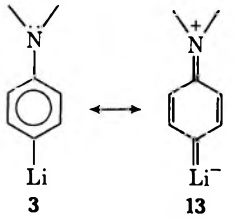
(12) G. A. Razuvayev, E. V. Mitrofanova, and G. G. Petukhov, *Zh. Obshch. Khim.*, **31**, 2343 (1961); A. R. Lepley, V. C. Dohm, and A. G. Giumanini, *J. Org. Chem.*, **34**, 3042 (1969).

(13) A. R. Lepley and A. G. Giumanini, *Chem. Ind. (London)*, 1035 (1965).

(14) A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **31**, 2055 (1966).

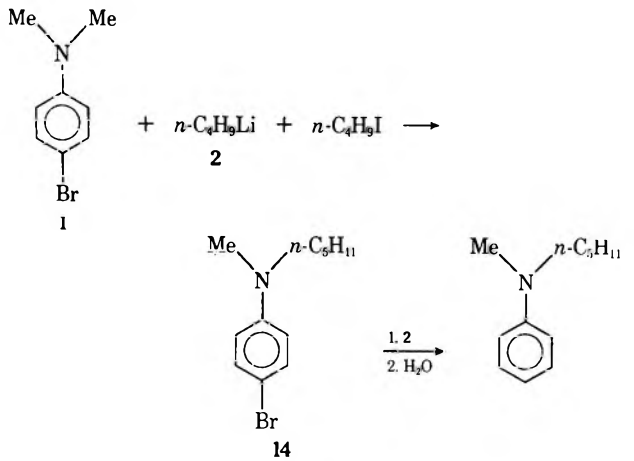
(15) A. G. Giumanini, W. A. Khan, and A. R. Lepley, *Chim. Ind. (Milan)*, **49**, 1340 (1967).

creased basicity of the nitrogen lone pair, which may be delocalized according to "structure" **13** in what amounts



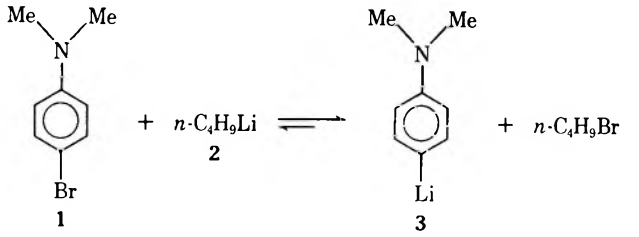
3 **13**

to internal solvation. But **1** was found to dissolve in *n*-hexane containing *n*-butyllithium (it is insoluble in *n*-hexane alone) and the complex formed to react smoothly with 1-iodobutane to yield **14** (Table III, run 6): it appears that it is the complex **1**–**2** which is laterally alkylated to **14** by the 1-bromobutane formed in the exchange. Indeed, **14** was completely converted to **7** by subsequent treatment with *n*-butyllithium (Table III, run 7).



Conclusions

The exchange equilibrium of the reaction lies largely to the right in agreement with the relative group basic-



ities of *p*-(*N*,*N*-dimethylamino)phenyl and *n*-butyl "anions."[3a] Possibly, it is further drawn into the preferred direction by the rapid reaction of 1-bromobutane with *n*-butyllithium to give octane for the most part. Lower temperatures favor high yields of **3**, but side reactions take place at any temperature to give alkylated amines in significant amounts especially at high temperatures, which also cause the formation of dimeric products.[16]

Some *o*-metalated *N*,*N*-dimethylaniline, evidenced by the pmr spectrum of a distilled sample of the exchange reaction mixture quenched with deuterium oxide, has probably to be related to direct metalation of small amounts of **4** formed from **3** and any potential proton donor (*e.g.*, 1-bromobutane) followed by direct *o*-metalation by *n*-butyllithium.

This work has therefore pointed out that the apparently simple[4] halogen–metal interchange studied may be accompanied by a number of side reactions, which depend on experimental conditions and become very important at high temperatures.

Experimental Section

Materials.—*p*-Bromo-*N*,*N*-dimethylaniline (**1**) was obtained from BDH and used without further purification. *n*-Butyllithium (**2**) was prepared in *n*-hexane from 1-chlorobutane (Carlo Erba) as previously described[17] (1.4–1.6 *N*). 1-Iodobutane was obtained from Fluka. Amines **6** and **7** were available from previous work.[11,12]

Mass Spectra.—Mass spectra were recorded with a Perkin-Elmer 270 gas chromatograph–mass spectrometer at 70 eV and a chamber temperature of 220–260°. Table I contains all essential data on compounds of interest to this work.

Gas Chromatography.—A Perkin-Elmer 900 gas chromatograph using a flame ionization detector was used. Best results were obtained with a 2-m column packed with 5% FFAP supported on 80–100 mesh Chromosorb W. Compound **1** was used as internal standard for quantitative determinations; calibration factors were determined with authentic materials. Convenient temperatures were in the range 120–250°. Table I contains all glc data of compounds related to this work. Neutral compounds formed in the exchange reactions did not interfere with the quantitative determination of the resulting amines or the starting material.

Pmr and ir spectra were recorded respectively with a Varian DP 60 in carbon tetrachloride and with a Beckman IR 5 (neat or KBr pellet for solid materials) spectrometer.

Melting points were determined by a Kofler apparatus and are not corrected.

Reaction of *p*-Bromo-*N*,*N*-dimethylaniline (1) with *n*-Butyllithium (2). General Procedure.[18]—The amine (25 mmol) and *n*-butyllithium (**2**) (50 mmol) were stirred during 27 hr under nitrogen atmosphere in a tightly sealed erlenmeyer flask at 48°. The mixture was cooled to room temperature and carefully quenched with water (10 ml). The amines may be extracted with hydrochloric acid and liberated with sodium hydroxide and then distilled. It was found that there was no interference from neutral materials to the quantitative and qualitative determination of amines; therefore this determination was often carried out directly on the quenched hexane solution. The exclusion of air from the reaction was also found not necessary to obtain yields as good as 91% of *N*,*N*-dimethylaniline (**4**). Exchange reaction results are collected in Table III. *N*,*N*,*N*′,*N*′-Tetramethyl-*p*-benzidine (**9**) was separated from high temperature reactions as follows: the amine fraction from acid–base separation of the reaction mixture was distilled at ~13 Torr up to a temperature of 200° (external oil bath). The residue[16] partially solidified at room temperature to a slightly brown crystalline solid, which had the same glc retention time of authentic **9** (see infrared data and Table I). Two recrystallizations from ethanol gave an ochre compound, mp 190–194° (lit.[7] 198°); mixture melting point gave no depression.

***p*-(*n*-Butyl)-*N*,*N*-dimethylaniline (8).**—**1** (25 mmol) was stirred with *n*-butyllithium (52 mmol) during 27 hr at 15°. The mixture was taken to reflux temperature and 1-iodobutane (25 mmol) was added during 5 min and reflux then continued for 24 hr. Work-up of the mixture gave 5.73 g of amines, which were distilled under vacuum to yield 33% of **8**, bp 84°, 0.8 Torr.[19] Another preparation in which the lithium–bromine interchange was performed at 60° during 3 hr and at 75° for an additional hour, followed by 5.5 hour reflux with 1-iodobutane, gave 32.5% yield (glc). When the exchange was performed in optimal conditions (91% yield) but followed by 100 hr stirring

(16) Very small amounts of "dimeric" amines are contained in the higher boiling fractions from exchange runs at elevated temperatures. These compounds may derive from benzyne and free-radical coupling reactions.

(17) A. G. Giumanini and A. R. Lepley, *Bull. Soc. Chim. Jap.*, **42**, 2359 (1969).

(18) In addition to the papers of Gilman's group (ref 4 and 5), another recent paper appeared describing the preparation of **3**: G. Hallas and D. R. Waring, *Chem. Ind. (London)*, 620 (1969).

(19) Lit.[6] 185° at 2 Torr. This value seems to be in error.

at 24° with 1-iodobutane, only 15.7% (glc) of the new amine was obtained. Small impurities of *N*-(*n*-butyl)-*N*-methylaniline (6), *N*-(*n*-pentyl)-*N*-methylaniline (7), and *p*-(*n*-butyl)-*N*-(*n*-butyl)-*N*-methylaniline (11) were detected in the reaction mixture by glc: ir 3.44 s, 3.52 s, 3.60 m, 6.20 s, 6.61 s, 6.80 m, 7.45 m, 8.18 w, 8.41 w, 8.62 m, 8.85 w, 9.45 w, 10.57 w, and 12.42 μ m; pmr δ 0.92 (3 H), 1.61 (4 H), 2.48 (2 H), 2.80 (6 H), and 6.78 (4 H, A_2B_2, q).

Attempted Lateral Alkylation of 3.—(1) In two parallel experiments, **3** was prepared. In one the reaction mixture from the exchange and hydrolysis was analyzed (**4**, 53%; **7**, 6.2%; **8**, 12%); the other was treated with 25 mmol **2** and 51.5 mmol 1-iodobutane at −15° and the mixture stirred during 4 hr, allowing it to warm up to 15°. Glc analysis gave **4** (37.0%), **7** (6.05%), and **8** (11.0%). No lateral alkylation of **3** was achieved by the standard alkyllithium–alkyl iodide technique. (2) To **3** from 5 mmol of 1 and 22.5 mmol of **2** (24 hr, 25°) was added 5 ml of anhydrous ether and, at 0°, 12.5 mmol of 1-iodobutane. The temperature was allowed to go up to 20° during 3 hr. The quenched reaction mixture was analyzed (glc): **3** (40%), **7** (4.5%), and **8** (4.4%). No lateral alkylation was therefore achieved by the addition of 1-iodobutane.

Lateral Alkylation of *p*-Bromo-*N*,*N*-dimethylaniline (1). Lithium–Bromine Exchange of *p*-Bromo-*N*-(*n*-pentyl)-*N*-methylaniline (14) with *n*-Butyllithium (12).—*p*-Bromo-*N*,*N*-dimethylaniline (1) (5 mmol) and *n*-butyllithium (2) (20 mmol) were mixed at −10° and, as soon as a homogeneous solution formed, 1-iodobutane (10 mmol) was added. After stirring for 1 hr at −8°, the solution was gradually warmed up to 18° in 23 hr. The quenched reaction mixture contained (glc) **4** (23%), **7** (2.55%), **8** (1.2%), 1 (14.9%) and **14** (6%). The dry hexane mixture was then stirred 24 hr with excess *n*-butyllithium at room temperature and quenched as usual. Both brominated amines disappeared completely while the **7** to **8** ratio increased from 2.13 to 3.1.

***p*-Deuterio-*N*,*N*-dimethylaniline (5).**—This compound could be easily obtained by adding deuterium oxide to the exchange mixture and distilling the product:[20] ir 3.27 m, 3.33 m, 3.50 s, 3.60 s, 4.44 w, 4.84 w, 5.33 w, 5.70 w, 5.86 vw, 6.29 s, 6.70 s, 6.97 s, 7.45 s, 8.22 s, 8.42 s, 8.86 m, 9.45 s, 9.78 m, 10.23 s, 10.62 s, 11.61 w, 12.19 s, 13.37 w, 13.63 m, 13.94 m, and 14.52 μ w; pmr (neat) δ 2.65 (6 H, s), 6.85 (4.28 H, A_2B_2, q). This spectrum is in agreement with that reported in the literature.[6]

***o*-Deuterio-*N*,*N*-dimethylaniline.**—This compound, with possible traces[17] of *m*-deuterio substitution, and in admixture with *o*,*o*′-dideuterioaniline and unreacted *N*,*N*-dimethylaniline (4) may be obtained by repetitive metalation with refluxing *n*-butyllithium (2) followed by quenching with deuterium oxide. A sample in our hands contained (4 iterations) 18% unreacted material, 53% monodeuterioaniline and 29% dideuterioaniline, as was determined by mass spectrometry.

***N*,*N*,*N*′,*N*′-Tetramethyl-*p*-benzidine (9).**—This compound was prepared according to a method described in the literature,[21] by adding 20 mmol of potassium permanganate in 100 ml of 2 *N* sulfuric acid to a well-stirred solution of 0.1 mol of *N*,*N*-dimethylaniline in 60 ml of 2 *N* sulfuric acid at room temperature during 15 min. Work-up as indicated,[21] followed by treatment with base, extraction with ether–alcohol, evaporation of the solvent, and recrystallization from ethanol, gave slightly ochre needles: mp 194–198° (lit.[21] 198°); ir (KBr) 3.42 w, 6.17 s, 6.63 s, 6.92 m, 7.37 s, 8.13 m, 8.33 s, 8.50 m, 9.48 w, 10.54 w, and 12.36 μ s; pmr (CS_2–CCl_4) δ 6.77 (8 H, A_2B_2, q) and 2.94 (12 H, s); mass spectrum (vaporized from the solid inlet system at ∼90°) mol wt, 240. The same compound was obtained in low yield from the interaction of *p*-benzidine with dimethyl sulfate (3 hr at 100°).

Registry No.—**1**, 586-77-6; **2**, 109-72-8; **4**, 121-69-7; **5**, 19125-73-6; **6**, 3416-49-7; **7**, 3299-39-6; **8**, 13330-29-5; **9**, 366-29-0; **11**, 25906-38-1; **12**, 25906-36-9; **14**, 25906-39-2; *o*-*d*-*N*,*N*-dimethylaniline, 24214-95-7.

Acknowledgments.—We wish to express our gratitude to Mrs. Armida B. Giumanini for recording the mass and pmr spectra and to Professor U. Pallotta of the Institute of Industrial Agriculture of this University for kindly allowing us to use some of his laboratory facilities.

(20) The isotopic purity of the separated dimethylaniline is ∼80%. The deviation from the theoretical value may be due to some protolysis (see above) during the exchange reaction and, only partially, to the proton content of heavy water.

(21) R. Willstaetter and R. Pummerer, *Chem. Ber.*, **37**, 3733 (1904).

Schmidt Reaction of 2,4,6-Cyclooctatrien-1-one

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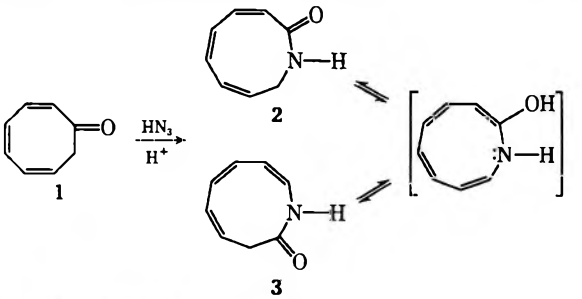
The Schmidt reaction of 2,4,6-cyclooctatrien-1-one in concentrated sulfuric acid produced 8,9-dihydrophthalimidine (4), which could have formed only from the migration of the methylene group. The other isomeric product, 3a,9a-dihydroindolone, which would have required the migration of the vinyl group, was not observed. On the other hand, the same reaction in trifluoroacetic acid produced 5*H*-tetrazolo[1,5-*a*]azonine (5) and its valence isomer 5a,9a-dihydro-5*H*-tetrazolo[5,1-*a*]isoindole (6) as the main products, with a small amount of **4**.

The Schmidt reaction of 2,4,6-cyclooctatrien-1-one (1) is expected to produce 2,9-dihydro-2-oxoazonine (2) and 2,3-dihydro-2-oxoazonine (3) from the migration of alkyl and vinyl groups, respectively. Both **2** and **3** are tautomers of 2-hydroxyazonine, a 10-π electron system which could show aromatic properties. Azonine and its analogs, oxonin and thionin, are of theoretical interest due to the possibility of their being 10-π aromatic systems isoelectronic with cyclooctatetraene dianion[1b] and cyclononatetraene anion,[2] both of which are 10-π aromatic systems. 4,5:6,7-Dibenzoxonin and 4,5:6,7-dibenzothionin have been prepared and shown to exist in nonaromatic buckled conformations.[3] The urethan



(1) (a) This is publication number 23-69 from Colorado State University. (b) T. J. Katz, *J. Amer. Chem. Soc.*, **82**, 3784 (1960).

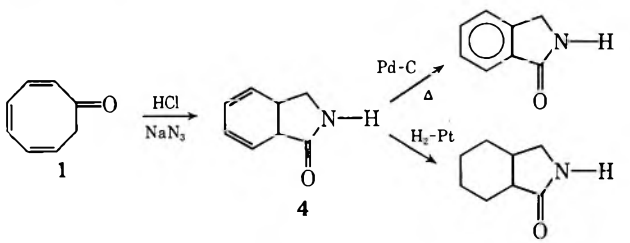
(2) (a) E. A. LaLancette and R. E. Benson, *ibid.*, **85**, 2853 (1963); **87**, 1941 (1965). (b) T. J. Katz and P. J. Garratt, *ibid.*, **85**, 2852 (1963); **86**, 5194 (1964).

(3) A. P. Bindra, J. A. Elix, P. J. Garratt, and R. H. Mitchell, *ibid.*, **90**, 7372 (1968).

of the parent azonine, namely *N*-carbethoxyazonine,[4b] and the parent oxonin[4a] have been recently prepared; neither compound shows aromatic stability.

Results

Reaction in Hydrochloric Acid.—The reaction of **1** with an equimolar quantity of sodium azide in concentrated HCl produced only 8,9-dihydrophthalimidine (**4**) in 66% yield, due to the migration of the methylene group. The other isomeric product, 3a,7a-dihydroindolone, which would result from the migration of the vinyl group, was not found. Also no evidence was found for the formation of either **2** or **3**. The structure of **4** was assigned on the basis of its spectral data (ir, uv, nmr, mass spectral) and its catalytic dehydrogenation to phthalimidine, a known compound. Furthermore, catalytic hydrogenation of **4** gave a product whose

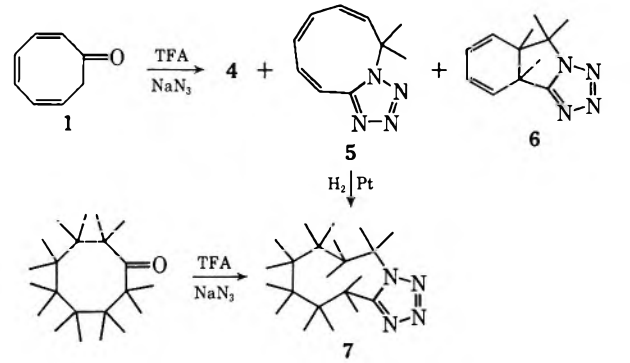


melting point agrees with the known *cis*-hexahydrophthalimidine, indicating that **4** probably has a cis-ring fused geometry.

Kroner[5] isolated **4** as a minor product from the Beckmann rearrangement of *anti*-2,4,6-cyclooctatrienone oxime benzenesulfonate (anti relative to CH_2).

Reaction in Sulfuric Acid.—The reaction of **1** with an equimolar quantity of sodium azide in concentrated sulfuric acid at 0° gave a 10% yield of **4** and recovered ketone **1**. Again, there was no evidence for **2**, **3**, or 3a,7a-dihydroindolone.

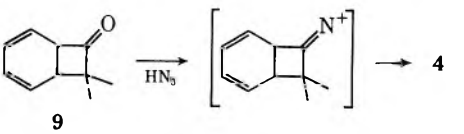
Reaction in Trifluoroacetic Acid (TFA).—Treatment of **1** with an excess of sodium azide in trifluoroacetic acid at 0° gave a small amount of **4**, unreacted ketone, and two new products, 5*H*-tetrazolo[1,5-*a*]azonine (**5**) and 5a,9a-dihydro-5*H*-tetrazolo[5,1-*a*]isoindole (**6**).



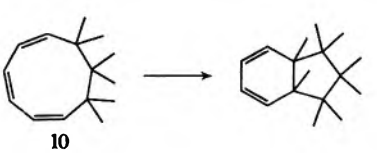
Compounds **5** and **6** were obtained in lower yields with more recovered ketone when an equimolar quantity of sodium azide was used. The structure of **5** is compatible with the spectral data. Its nmr spectrum showed a multiplet between δ 6.8 and 5.9 for the six olefinic protons and a doublet at δ 5.36 (J = 7.5 Hz) for the two methylene protons. Proof for the structure of **5** comes from quantitative hydrogenation to azacyclonona[1,2-*d*]tetrazole (**7**). This hydrogenation required 3 mol of hydrogen for each mole of **5**, ruling out a tricyclic structure with two double bonds such as an isomer of **6**. In addition, **7** was independently synthesized by the Schmidt reaction on cyclooctanone in TFA. The spectral properties (nmr, ir) of the tetrazole obtained from reduction of **5** were identical with those of the tetrazole obtained from the Schmidt reaction with cyclooctanone. The structure of **6** was assigned on the basis of the close resemblance of its nmr spectrum to that of **4** and the facile thermal conversion of **5** to **6**. Thus, heating a solution of **5** in diphenyl ether furnished cleanly and exclusively a crystalline product which has identical nmr and ir spectra with those of **6** obtained from the Schmidt reaction.

Discussion

The isolation of 8,9-dihydrophthalimidine (**4**) from the Schmidt reaction of **1** could be indicative of the formation of **2** as a reactive intermediate in this reaction. It is possible that **4** could also arise from treatment of bicyclo[4.2.0]octa-2,4-dien-7-one (**9**), the valence



bond isomer of **1** to Schmidt reaction conditions. Huisgen and coworkers[6] have reported that at 60° cyclooctatrienone (**1**) contains 6.6% of **9** at equilibrium. Although we do not know the equilibrium concentration of **9**, under our conditions it is undoubtedly sufficiently high to be the precursor of **4**. However, the isolation of **5** as a major product from the reaction in TFA is difficult to explain in terms of **9** as the starting component of the reaction sequence. The possibility that **5** would arise from an equilibrium between it and its valence isomer **6** is not ruled out, but it is very unlikely that **5** would be the major product of such an equilibrium in view of its facile and apparently complete isomerization to **6**. Comparison of such an equilibrium reaction to the equilibrium of *cis,cis,cis*-1,3,5-cyclononatriene (**10**) and *cis*-2,3,3a,7a-tetrahydroindene which contains less than 0.2% of the monocyclic isomer[7] indicates the validity of this assumption. On the other hand, our inability to isolate **2** casts doubt on its formation. Should **2** form, its isomerization to **4** would be analogous to the isomerization of **10**. This



latter reaction was observed by Glass, Watthey, and Winstein[7] to have an activation energy of 23.0 kcal/mol, sufficiently high to allow rather easy isolation of **10**. From a comparison of the models of **2** and **10** and

(4) (a) A. G. Anastassiou and R. P. Cellura, *Chem. Commun.*, 903 (1969); (b) A. G. Anastassiou and J. H. Gebrian, *J. Amer. Chem. Soc.*, **91**, 4011 (1969).

(5) M. Kroner, *Chem. Ber.*, **100**, 3162 (1967).

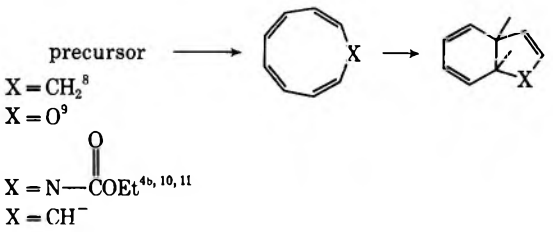
(6) R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, *Tetrahedron Lett.*, 5215 (1968).

(7) D. S. Glass, J. W. H. Watthey, and S. Winstein, *ibid.*, 377 (1965).

(b) A. G. Anastassiou and J. H. Gebrian, *J. Amer. Chem. Soc.*, 91, 4011 (1969).

(6) R. Huisgen, G. Boche, A. Dahmen, and W. Hechtl, *Tetrahedron Lett.*,

neglecting electronic contributions from the amide group, a fair approximation considering the high degree of puckering in the ring (the amide π system is orthogonal to the olefinic π systems), one would expect approximately the same resistance to ring closure in each case and therefore isolation of 2 should also be relatively easy. Our failure to isolate the monocyclic amide, 2, would indicate that either it is not as stable towards transannular ring closing as might be thought or it is formed in a very small yield and is not an intermediate in the formation of 4. Evidence bearing on this point is provided by the stabilities of known unsubstituted cyclononatetraene systems. Katz[2b] has reported that when water is added to cyclononatetraene anion, the resulting neutral compound rapidly goes through a transannular ring closing reaction to form 8,9-dihydroindene. The isolation of cyclononatetraene (X = CH_2) and its thermal isomerization to *cis*-8,9-

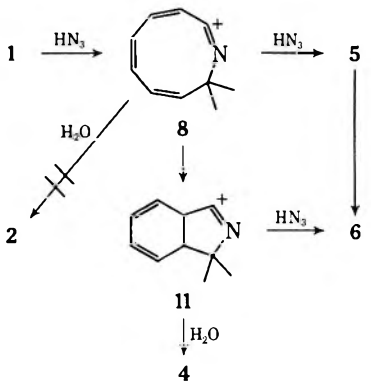


dihydroindene has been reported independently by Radlick[8a] and Masamune.[8b] Oxonin (X = O) was shown to undergo thermal rearrangement into *cis*-8,9-dihydrobenzofuran[9] in accordance with the conservation of orbital symmetry. Anastassiou[4b,10] has recently reported that *N*-carbethoxy-1-azacyclonona-2,4,6,8-tetraene (X = N-C(O)OEt) is not stable at room temperature but readily undergoes thermal isomerization to *N*-carbethoxy-*cis*-8,9-dihydroindole through transannular ring closing. The same result was obtained by other workers.[11] In fact, up to this date, the cyclononatetraene anion (X-CH$^-$) is the only species that is thermally stable at room temperature. Vogel[12] has suggested that this instability is the result of ring strain in the puckered tetraene due to the fourth double bond in the ring.

The instability of 8 is analogous to that observed for the above systems and suggests that 2 is not an intermediate in the formation of 4, but rather that 4 arises from the reaction of water with 3a,7a-dihydroisoindolium ion (11), which is the ring closed isomer of 8.

The ring strain in 8 can be relieved by either transannular ring closing or by reacting with a nucleophile capable of forming a double bond to carbon thus destroying the iminocarbonium ions which are causing the strain.

If ring closing is competitive with nucleophilic attacks, then it is not surprising that the relatively weak nucleophile, water, is unable to compete to form 2, while the much better nucleophile, HN_3, competes readily and forms 5 as the major product. A scheme showing the relationship of the various products is shown below.



It is interesting to note that no evidence was found for vinyl migration although it occurs readily in the corresponding Beckmann rearrangement.[5,13] Apparently the products are controlled completely by migratory aptitude.

Experimental Section[14]

Cyclooctatetraene Oxide.—This compound was prepared by oxidation of cyclooctatetraene following the procedure of Cope and Tiffany.[15] The oxide was obtained in 27% yield as a light yellow liquid: bp 74–75° (12 mm); n^{25}D 1.5389 [lit.[15] bp 74–75° (12 mm), n^{25}D 1.5383].

2,4,6-Cyclooctatrien-1-one (1).—This ketone was prepared by the base-catalyzed ring opening reaction of cyclooctatetraene oxide according to the procedure of Cope and Tiffany.[15] The yellow ketone was obtained in 90% yield: bp 75–101° (13 mm); n^{25}D 1.5749 [lit.[15] bp 75–105° (13 mm), n^{25}D 1.5750]. Semicarbazone had mp 193–194° dec (lit.[15] mp 192–194° dec).

Schmidt Reaction of 2,4,6-Cyclooctatrien-1-one.—A solution of 2.3 g (19 mmol) of 2,4,6-cyclooctatrien-1-one (1) in 12 ml of concentrated hydrochloric acid was cooled in an ice bath while 1.87 g (28.7 mmol) of sodium azide was added slowly over a period of 1 hr. The solution darkened and a large quantity of gas evolved. After 4 hr at room temperature, during which the mixture was occasionaly stirred, significant gas evolution ceased. The reaction mixture was poured into 50 ml of cold water and exhaustively extracted with chloroform. The chloroform extracts were combined and washed with 25 ml of 10% sodium bicarbonate solution and two 50-ml portions of water. After drying over anhydrous potassium carbonate, the solvent was evaporated. There was obtained 1.7 g (66%) of the crude product as a brown solid. The nmr spectrum showed peaks attributable only to 8,9-dihydrophthalimide. It was purified by chromatographing on alumina (neutral activity grade I). Chloroform (fourteen 50-ml fractions) was collected from the column. The solvent was stripped from each fraction and the melting point of the residue was determined. The melting points ranged between 97 and 101°, thus indicating the similarities of the residues which were then combined in one fraction. Recrystallization from hexane provided an analytical sample of 8,9-dihydrophthalimidine (4) as colorless plates: mp 98.5–101°; uv λ_{max} (hexane) 258 mμ (ϵ 4.04 × 10^3), 266 (3.85 × 10^3), and 276 (shoulder, 2.25 × 10^3); ir (KBr) 3.1 (lactam NH), 5.93 and 6.02 (lactam C=O), 7.54, 7.97, 9.39, 13.98, and 14.66 μ; nmr ($CDCl_3$) δ 7.7 (s, 1 H), 5.86 (m, 4 H), 3.66 (m, 1 H), and 3.26 ppm (m, 3 H).

Schmidt Reaction of 2,4,6-Cyclooctatrien-1-one in Concentrated Sulfuric Acid.—To the dark mixture of 1.8 g (0.015 mol) of 2,4,6-cyclooctatrien-1-one (1) in 1.5 ml of concentrated sul-

(8) (a) P. Radlick and G. Alford, *J. Amer. Chem. Soc.*, **91**, 6529 (1969); (b) S. Masamune, P. M. Baker, and K. Hojo, *Chem. Commun.*, 1203 (1969).

(9) (a) A. G. Anastassiou and R. P. Cellura, *ibid.*, 1521 (1969); (b) J. M. Holouka, R. P. Grabbe, P. D. Gardner, C. B. Strow, M. L. Hill, and T. V. Van Auken, *ibid.*, 1522 (1969); (c) S. Masumune, S. Takada, and R. T. Seidner, *J. Amer. Chem. Soc.*, **91**, 7769 (1969).

(10) A. G. Anastassiou and J. H. Gebrian, *Chem. Eng. News*, **47**, 48 (1969).

(11) S. Masamune, K. Hojo, and S. Takada, *Chem. Commun.*, 1204 (1969).

(12) E. Vogel, *Angew. Chem.*, **74**, 838 (1962).

(13) A. H. Khuthier, Ph.D. Thesis, Colorado State University, Fort Collins, Colo., 1969.

(14) The following instruments were used in this work: ir, Perkin-Elmer Models 337 and 457; nmr, Varian A-60A; mass spectra, AEI Model MS-12 spectrometer; uv, Bausch and Lomb Spectronic 500. Microanalysis was performed by Galbraith Laboratories, Knoxville, Tenn. Quantitative hydrogenation was performed by Huffman Laboratories, Wheatridge, Colo.

(15) A. C. Cope and E. D. Tiffany, *J. Amer. Chem. Soc.*, **73**, 4158 (1951).

furic acid at 0° was added 0.98 g (0.015 mol) of sodium azide over a period of 0.5 hr. The brown thick paste was allowed to stand at room temperature for 3 hr with occasional stirring. The reaction mixture was poured into water containing some crushed ice. The brown oil that separated was extracted several times with chloroform. The chloroform extracts were washed with 10% sodium bicarbonate solution, followed by water, and dried over anhydrous potassium carbonate. Evaporation of the solvent produced a dark oil whose nmr spectrum showed unreacted ketone with a small amount of 8,9-dihydrophthalimidine (**4**). The mixture was placed onto alumina (neutral activity grade I) and the unreacted ketone was eluted with Skellysolve H. The lactam was collected with several fractions of chloroform which were combined and the solvent was evaporated. There was obtained 0.2 g (10%) of a yellow solid. Recrystallization from hexane produced an analytical sample of 8,9-dihydrophthalimidine (**4**) as colorless plates, mp 99–101°.

Schmidt Reaction of 2,4,6-Cyclooctatrien-1-one in Trifluoroacetic Acid.—To a mixture of 2.0 g (16.6 mmol) of 2,4,6-cyclooctatrien-1-one (**1**) in 10 ml of trifluoroacetic acid at 0° was added 2.7 g (42 mmol) of sodium azide over a period of 1 hr. The solution darkened a little and an exothermic reaction took place with evolution of a large quantity of gas. After 3 hr during which the mixture was occasionally stirred, 3 ml more of trifluoroacetic acid was added. The mixture was allowed to stand at room temperature for 3 hr more and then poured into 50 ml of cold water. The oil that separated was extracted with three 40-ml portions of chloroform. The chloroform extracts were combined and washed with 50 ml of 10% sodium bicarbonate solution and 50 ml of water. After drying over anhydrous sodium carbonate, the solvent was evaporated. The resulting dark oil was chromatographed on alumina (neutral activity grade I) with Skellysolve H containing an increasing proportion of chloroform. Elution with pure Skellysolve H produced 0.13 g of unreacted ketone. Skellysolve H–chloroform (10:1) fractions yielded 0.51 g of a colorless crystalline product which was identified as 5*H*-tetrazolo[1,5-*a*]azonine (**5**). Recrystallization of this material from benzene–hexane produced an analytical sample of **5** as colorless sharp needles: mp 85–86°; uv λ_{max} (MeOH) 215 mμ (ε 9.0 × 10^3), 252 (2.68 × 10^3); ir (KBr) 6.1, 6.67, 7.3, 8.0, 9.13, 9.48, 11.6, 12.37, 13.47, and 15.29 μ; nmr ($CDCl_3$) δ 6.8–5.9 (m, 6 H), 5.36 (d, 2 H, J = 7.5 Hz); mass spectrum m/e (rel intensity) 160 (2) 131 (9), 103 (17), 78 (100), 77 (35), 52 (46).

Anal. Calcd for $C_8H_8N_4$: C, 60.00; H, 5.00; N, 35.00. Found: C, 60.18; H, 4.95; N, 35.10.

Skellysolve H–chloroform (10:2) gave a second product (0.17 g) as light yellow crystals which was identified as 5a,9a-dihydro-5*H*-tetrazolo[5,1-*a*]isoindole (**6**). Recrystallization from benzene–hexane provided an analytical sample of **6** as colorless needles: mp 100–100.5°; uv λ_{max} (MeOH) 205 mμ (ε 2.44 × 10^3), 255 (4.4 × 10^3), 246 (shoulder), 264 (4.05 × 10^3), 275 (shoulder); ir (KBr) 6.6, 6.76, 7.6, 8.7, 9.2 (w), 9.3, 10.4, 11.76, 13.3, 14.0, and 14.3 μ; nmr ($CDCl_3$) δ 5.96 (m, 4 H), 4.66 (m, 1 H), 4.2 (m, 3 H); mass spectrum m/e (rel intensity) 160 (2), 105 (9), 78 (100), 77 (16), 52 (22).

Anal. Calcd for $C_8H_8N_4$: C, 60.00; H, 5.00; N, 35.00. Found: C, 59.88; H, 5.23; N, 34.86.

Later Skellysolve H–chloroform (1:1) elutions gave 0.1 g of colorless solid which was identified as 8,9-dihydrophthalimidine (**4**).

Reduction of 8,9-Dihydrophthalimidine (4).—A solution of 0.172 g (1.27 mmol) of **4** in 5 ml of *p*-dioxane containing a catalytic amount of platinum black was subjected to hydrogenation at 90° and 30 psi for 12 hr. After removal of the catalyst and solvent, 0.2 g of the crude product was obtained as a yellow solid. It was purified by sublimination at 70–80° and 0.3 mm followed by two recrystallizations from hexane. The product, *cis*-hexahydrophthalimidine, was obtained as colorless crystals: mp 95.5–97° (lit.[16] mp 98°); ir (KBr) 3.1 (lactam NH), 5.95 (lactam C=O), 6.92, 7.03, 7.7, 9.88, and 13.3 μ; nmr ($CDCl_3$) δ 7.1 (s, 1 H), 3.43 (m, 1 H), 3.0 (m, 1 H), 2.43 (m, 2 H), 2.06–1.0 ppm (m, 8 H).

Schmidt Reaction of Cyclooctanone in Trifluoroacetic Acid.—To a mixture of 4.2 g (0.033 mol) of cyclooctanone in 10 ml of trifluoroacetic acid at 0° was added 6.5 g (0.1 mol) of sodium azide over a period of 1 hr. After 4 hr 5 ml more of trifluoroacetic acid was added. A large quantity of nitrogen gas was evolved. The reaction mixture was allowed to stand overnight at room temperature with occasional stirring, then was poured into 50 ml of water. The oil that separated was extracted with four 30-ml portions of chloroform. The chloroform extracts were combined and washed with a 10% solution of sodium carbonate followed by water. Evaporation of the solvent, after drying over anhydrous potassium carbonate, yielded 5 g of a colorless oil which was shown by nmr to contain a mixture of products. The desired tetrazole was separated, as a colorless oil, either by chromatographing on alumina (neutral activity grade I) with Skellysolve H–chloroform (10:1) as the eluent or by distillation under reduced pressure: bp 144° (0.1 mm) [lit.[17] 145–146° (0.1 mm)]; ir (neat) 3.4, 3.5, 6.6, 6.8, 6.9, 7.0, 8.06, 8.9, 9.16, 9.48, 9.85, 10.1, 12.3, and 13.2 μ; nmr (CCl_4) δ 4.55 (t, 2 H, J = 6 Hz), 3.06 (t, 2 H, J = 6 Hz), 1.93 (m), and 1.38 ppm (m). The last two poorly resolved multiplets integrate for 10 H.

Reduction of 5*H*-Tetrazolo[1,5-*a*]azonine (5).—A solution of 50 mg of **5** in 10 ml of glacial acetic acid containing a catalytic amount of Adams catalyst was subjected to hydrogenation of 30 psi and room temperature for 20 hr. After removal of the catalyst the reaction mixture was poured into 40 ml of water. The oil that separated was extracted with four 30-ml portions of chloroform. The chloroform extracts were combined and washed with 30 ml of 10% solution of sodium carbonate followed by 30 ml of water. Evaporation of the solvent, after drying over anhydrous potassium carbonate, produced 45 mg (87%) of the product as a colorless oil. The nmr and ir spectra of this material were identical with those of the tetrazole prepared by the Schmidt reaction of cyclooctanone: ir (neat) 3.4, 3.5, 6.6, 6.8, 6.9, 7.0, 8.06, 8.9, 9.16, 9.48, 9.85, 10.1, 12.3, and 13.2 μ; nmr (CCl_4) δ 4.5 (t, 2 H, J = 6 Hz), 3.05 (t, 2 H, J = 6 Hz), 1.93 (m), and 1.38 ppm (m). The last two poorly resolved multiplets integrate for 10 H.

Dehydrogenation of 8,9-Dihydrophthalimidine (4).—A mixture of 110 mg of 8,9-dihydrophthalimidine (**4**) (obtained from the Schmidt reaction of 2,4,6-cyclooctatrien-1-one in concentrated HCl) and a small amount of 10% palladium-on-carbon catalyst in 5 ml of toluene was refluxed for 2 hr. Removal of the catalyst and solvent produced 100 mg (92%) of colorless crystals. Recrystallization from benzene yielded analytical sample of phthalimidine as fine white felted needles: mp 152–152.5° (lit.[18] 152.5–152.8°); uv λ_{max} (methanol) 227 mμ (ε 1.0 × 10^4), 263 (shoulder), 271 (1.75 × 10^3), and 278 (1.7 × 10^3); ir (KBr) 3.1 (lactam NH), 6.0 (lactam C=O), 6.8, 6.9, 7.6, 8.8, 10.6, and 13.75 μ; nmr ($CDCl_3$) δ 7.6 (s, 1 H), 7.1 (m, 1 H), 6.7 (m, 3 H), and 3.5 ppm (s, 2 H).

Registry No.—**1**, 4011-22-7; **4**, 16327-30-3; **5**, 276-65-3; **6**, 25902-76-5; **7**, 7140-70-7.

Acknowledgment.—We wish to thank the Chemistry Department of Colorado State University for the support of this work. Also, we are indebted to the Badische Anilin- and Soda-Fabrik AG., Ludwigshaven am Rhein, for a generous gift of cyclooctatetraene.

(16) H. Cristol, A. Donche, and F. Plenat, *Bull. Soc. Chim. Fr.*, 2535 (1966); *Chem. Abstr.*, **66**, 2250n (1967).

(17) L. Ruzicka, M. W. Goldberg, and M. Hurbin, *Helv. Chim. Acta*, **16**, 1335 (1933).

(18) (a) J. Bornstein, S. F. Bedell, P. E. Drummond, and C. L. Kosloski, *J. Amer. Chem. Soc.*, **78**, 83 (1956); (b) A. Oppe, *Ber.*, **46**, 1099 (1913).

The Reverse Mannich Reaction of Some 5-Hydroxyindoles[1]

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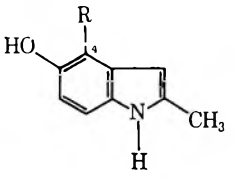
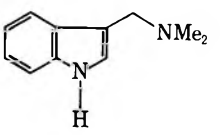
The C_4-dimethylaminomethyl Mannich adducts of 3-substituted 5-hydroxyindoles undergo a facile, amine catalyzed carbon–carbon bond cleavage to yield the corresponding C_4-hydrogen indole derivatives. Reverse Mannich condensation occurs most readily in C_3-carbethoxy substrates, then in C_3-ethyl derivatives; no reverse reaction was observed for C_3-hydrogen derivatives. An indole N–H group is not required for reverse reaction. This transformation is catalyzed by primary (most efficient), secondary, and tertiary amines. The role of the C_3 substituent is discussed in terms of both steric and electronic effects. It is concluded that a steric C_3–C_4 peri interaction is responsible for the observed difference in behavior between the C_3-carbethoxy and C_3-hydrogen derivatives.

Formation of a new carbon–carbon bond resulting in addition of a one carbon substituent to an existing skeleton by means of the Mannich reaction is a well-documented synthetic tool.[3] Recently it has been established[4] that Mannich condensation of 5-hydroxyindoles (*e.g.*, **1**) results in selective introduction of an



1, R = H
1a, R = CH_2NMe_2



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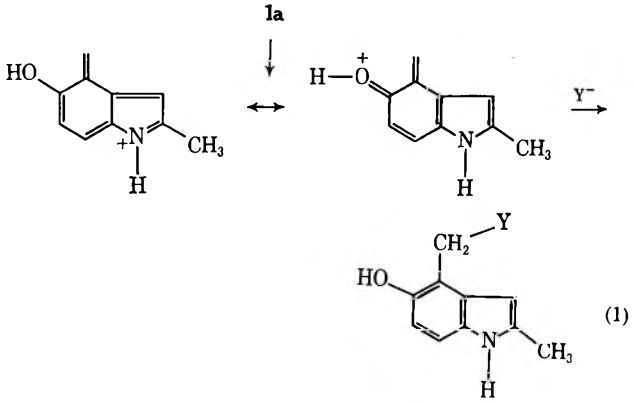
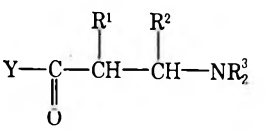


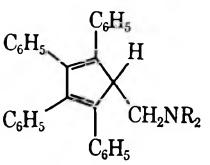
(1)

aminomethyl substituent at the C_4 position (*e.g.*, **1a**). It was anticipated that these C_4 indole adducts (*e.g.*, **1a**) would undergo net substitution *via* an elimination–addition mechanism (eq 1) analogous to that proposed[3,5] for gramine (**2**), the Mannich adduct of indole. In support of this hypothesis Mannich adducts of this general type have been used as synthetic intermediates in the construction of more complex hydroxyindole derivatives.[6]

An alternative, although less common, reaction course of Mannich adducts is a *reverse* Mannich condensation resulting in rupture of the previously formed carbon–carbon bond to regenerate the starting substrates.[7,8] The most common examples of reverse condensation involve cleavage of an sp^3–sp^3 carbon–carbon bond to yield a resonance stabilized anion. For example, acid- and/or base-catalyzed reverse Mannich condensations have been reported for aryl[7,8] and vinyl[9] ketone adducts (**3**), for aminomethyl fulvene derivatives[10] (**4**), and for the diphenylacetonitrile adduct **5**.[11,12]



3, Y = aryl or vinyl



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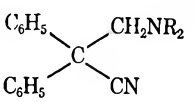


5

By way of comparison, examples of reverse Mannich condensation involving formal cleavage of an sp^2–sp^3 carbon–carbon bond are much less common. Treatment of the β-naphthol adduct **6** with piperidine (sealed tube, 180°) or with refluxing morpholine resulted in 30–35% reverse reaction.[9] Formation of the diarylmethane derivative **8** from the primary amine adduct **7** was postulated to involve a reverse Mannich condensation of **7**, followed by addition of β-naphthol to a second molecule of **7** *via* the normal elimination–addition sequence.[13] The same product (**8**), however, could arise

(1) Financial support of this research by the National Institutes of Mental Health (MH15544) is gratefully acknowledged.

(2) A training stipend from the Food and Drug Administration, Public Health Service, DHEW, is gratefully acknowledged.

(3) (a) B. Reichert, "Die Mannich-Reaktion," Springer Verlag, Berlin, 1959; (b) H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, GMBH, Weinheim, 1960.

(4) (a) S. A. Monti, W. O. Johnson, and D. H. White, *Tetrahedron Lett.*, 4459 (1966), and references therein; (b) S. A. Monti and W. O. Johnson, *Tetrahedron*, in press.

(5) J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953).

(6) (a) F. Troxler, *Helv. Chim. Acta*, **51**, 1214 (1968); (b) M. Julia and J. Y. Lallemand, *C. R. Acad. Sci., Ser. C*, **267**, 1506 (1968); (c) G. D. Castillo, unpublished results, this laboratory.

(7) H. Rivière, *Ann. Chim. (Paris)*, **5**, 1273 (1960).

(8) H. Larramona and B. Tchoubar, *Bull. Soc. Chim. Fr., C*, 53 (1953).

(9) B. V. Unkovskii, F. I. Psal'ti, and E. P. Badosov, *Zh. Org. Khim.*, **4**, 1546 (1968); *J. Org. Chem. (USSR)*, **4**, 1485 (1968).

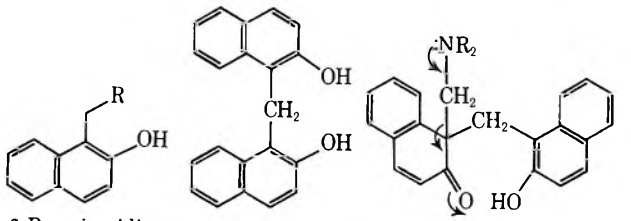
(10) D. Taber, E. I. Becker, and P. E. Spoerri, *J. Amer. Chem. Soc.*, **76**, 776 (1954); K. A. Kun and P. E. Spoerri, *ibid.*, **77**, 4676 (1955).

(11) H. E. Zaugg, B. W. Harrom, and M. R. Vernsten, *ibid.*, **75**, 288 (1953).

(12) For other examples of reverse Mannich reactions, see (a) H. R. Snyder and J. H. Brewster, *ibid.*, **71**, 1061 (1949); (b) M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943); (c) H. R. Snyder, C. Y. Meyers, and D. B. Kellom, *J. Amer. Chem. Soc.*, **75**, 4672 (1953); (d) W. Kutscher and O. Klamerth, *Chem. Ber.*, **86**, 352 (1952); (e) R. Jacquier, M. Mousseron, and S. Boyer, *Bull. Soc. Chim. Fr.*, 1653 (1956); (f) D. R. Howton and D. R. V. Golding, *J. Org. Chem.*, **15**, 1 (1950); (g) W. E. Bachmann and L. B. Wick, *J. Amer. Chem. Soc.*, **72**, 3388 (1950); (h) W. Reid and G. Keil, *Justus Liebigs Ann. Chem.*, **616**, 96 (1958).

(13) W. J. Burke, W. A. Nasutavicus, and C. Weatherbee, *J. Org. Chem.*, **29**, 407 (1964).

via intermediate **9**, thus negating the requirement for a reverse Mannich reaction.[14]



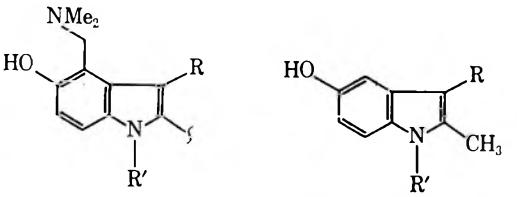
6, R = piperidino
7, R = NHR′

8 **9**

We now wish to report that this second reaction is available to the C_4 Mannich adducts of 5-hydroxyindoles. As discussed in detail below, Mannich adducts of general structure **10** readily undergo reverse Mannich condensation to yield the parent hydroxyindole precursor.

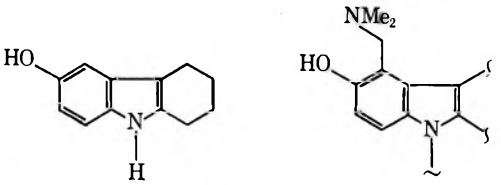
Results and Discussion

The C_4-dimethylaminomethyl Mannich adducts of the following 5-hydroxyindoles were used as substrates in this study: 2-methyl-5-hydroxyindole (**1**), 2-methyl-3-carbethoxy-5-hydroxyindole (**11**), 1,2-dimethyl-3-carbethoxy-5-hydroxyindole (**12**), 2-methyl-3-ethyl-5-hydroxyindole (**13**), and 6-hydroxytetrahydrocarbazole (**14**). In each case the Mannich adduct (part structure **15**) was heated under reflux with excess amine in ethanol.



10, R ≠ H
R′ = H or alkyl

11, R = CO_2Et; R′ = H
12, R = CO_2Et; R′ = CH_3
13, R = CH_2CH_3; R′ = H



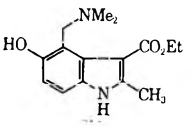
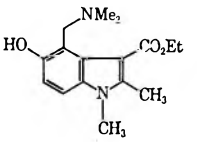
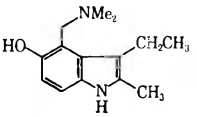
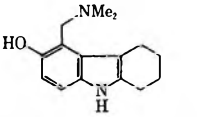
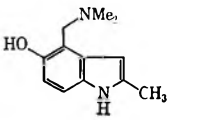
14 **15**

Reaction progress was monitored by tlc, and final product compositions were established by isolation and comparison to authentic samples, nmr spectroscopy, and tlc analysis. These results are summarized in Table I.

Consideration of the data in Table I delineates two structural features of the indole substrates that undergo reverse Mannich condensation. Most significantly, a C_3 substituent is a requirement; reverse reaction occurs most readily in C_3-carbethoxy substrates (**11a**), then in those with a C_3-ethyl group (**13a**). Under the conditions employed, the C_3-hydrogen substituted adduct (**1a**) did *not* undergo detectable reverse condensation. Secondly, the presence of an indole N–H group is not necessary for reverse reaction as seen by the behavior of the *N*-methyl derivative **12a**. In order to compare our results with those previously reported for formal

(14) A. Merijan and P. D. Gardner, *J. Org. Chem.*, **30**, 3965 (1965).

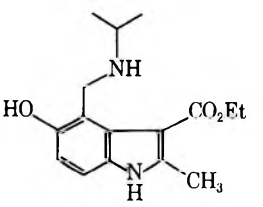
TABLE I
REVERSE MANNICH CONDENSATION OF SOME 4-DIMETHYLAMINOMETHYL-5-HYDROXYINDOLES

Substrate	Amine	Time, hr	Results
 **11a**	Cyclohexylamine	5	*ca.* 50% reverse
	Isopropylamine	6	*ca.* 50% reverse
	Isopropylamine	32	100% reverse
	Dimethylamine	50	84% reverse
	Triethylamine	50	*ca.* 40% reverse
	Ethanol	50	Trace reverse
 **12a**	Isopropylamine	6	35% reverse, 55% exchange
 **13a**	Isopropylamine	6	10% reverse, 65% exchange
	Isopropylamine	52	100% reverse
 **14a**	Isopropylamine	6	75% exchange, trace reverse
	Isopropylamine	52	*ca.* 100% exchange, trace reverse
 **1a**	Isopropylamine	28	100% exchange, no reverse
	Piperidine	6	*ca.* 90% exchange, no reverse

cleavage of sp^2–sp^3 carbon–carbon bonds,[9] the dimethylaminomethyl adduct of β-naphthol (**6**, R = NMe_2) was treated with isopropylamine in ethanol. The major product isolated was the diarylmethane **8**; no evidence for the formation of β-naphthol was found. As discussed above, the formation of **8** does not necessarily involve reverse Mannich condensation.[14]

With respect to the amine component, reverse reaction takes place most readily in the presence of primary amines but it does occur with secondary and tertiary amines.

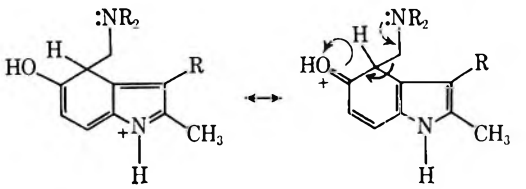
In the reactions involving primary amines, amine exchange most probably precedes reverse condensation to yield the primary amine adducts (*e.g.*, **16**) which rapidly



16

undergo reverse reaction. In support of this hypothesis, the unstable but spectrally characterized isopropylamine adduct **16** readily reversed to **11** during attempted recrystallization from acetonitrile or when heated to its melting point. The corresponding dimethylamine adduct **11a** is stable to these conditions. The piperidine adducts of these hydroxyindoles were stable to both amine exchange and reverse condensation reactions.

In general mechanistic terms, reverse Mannich condensation of these hydroxyindole adducts **10** involves (1) protonation at C_4 to yield the resonance stabilized intermediate **17**, followed by (2) carbon–carbon bond

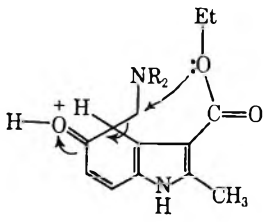


17

fragmentation to give the products. Theoretically three factors could account for the pronounced difference in behavior between the C_3-carbethoxy derivative **11a** and the C_3-hydrogen substrate **1a**: an electronic effect, a neighboring group effect, or a steric effect attributable to the C_3-ester function. If one assumes that protonation at C_4 (step 1 above) is the rate-determining step, then preferential protonation of **11a**, due to any of the three factors enumerated above, offers an attractive explanation for the observed difference. To test this postulate, both the C_3-hydrogen (**1**) and the C_3-carbethoxy (**11**) 5-hydroxyindoles were treated with isopropylamine in the presence of methanol-*O-d*. After 6 hr *complete* exchange[15] of the C_4 hydrogen by deuterium (nmr analysis) had occurred for *both* indoles, **1** and **11**.[16] Thus it seems reasonable to assume that both Mannich adducts, **1a** and **11a**, undergo facile C_4 protonation under the conditions of reverse condensation, thereby excluding step 1 as the rate-determining one.

The observed difference in behavior, therefore, must be explicable in terms of the carbon–carbon fragmentation step. In terms of electron logistics, rupture of the carbon–carbon bond in **17** results in reverse reaction while cleavage of the carbon–hydrogen bond simply reverses the protonation step to give back **10**. Clearly there is no conceivable mechanism by which a C_3-ester group could electronically distinguish between the electron pair in the C–H bond and that in the C–C bond. Thus an electronic effect can be excluded from further consideration.

Neighboring group participation of one of the ester oxygen atom lone electron pairs to assist carbon–carbon bond fragmentation *via* a six-centered process (see arrows in **18** for one possible mode) could explain the



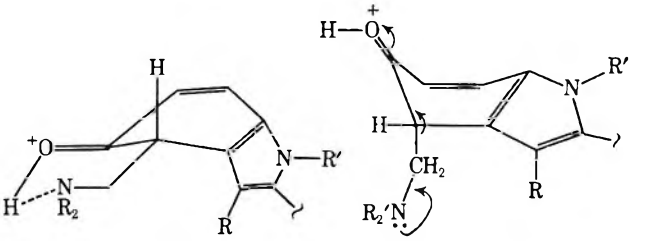
18

observed difference. The behavior of the C_3-ethyl adduct **13a**, however, clearly indicates that neighboring group participation of a heteroatom is not necessary for reverse condensation. Thus one is left with a steric effect.

(15) J. W. Daly and B. Witkop, *J. Amer. Chem. Soc.*, **89**, 1032 (1967).

(16) Under these conditions, no exchange of the other aromatic protons of **1** or **11** or of the C_3-H of **1** was observed.

The stereoelectronic requirements for maximum overlap during bond formation[17] require that initial protonation of **10** occur along an axis perpendicular to the plane of the ring carbons. This yields intermediate **19** with the C_4-hydrogen atom in a pseudoaxial position and the C_4-aminomethyl group in a pseudoequatorial orientation. For analogous reasons, rupture of the C–H bond (deprotonation) is the most favored process in this conformation. For reverse Mannich condensation to occur, a conformational "flip" to **20** is necessary.



19 **20**

Now continuous overlap with the existing π system can be maintained during cleavage of the pseudoaxial carbon–carbon bond. The observation that adduct **16** is stable in acid solution suggests that participation of the nitrogen atom lone electron pair (as shown in **20**) is necessary for bond cleavage.[18]

When the C_3 substituent R is small, conformer **19** with the large aminomethyl group in a pseudoequatorial position should be most stable. Intramolecular hydrogen bonding (see **19**) further stabilizes this conformer with respect to **20**. As the effective size of the C_3-R group increases, the resulting peri interaction between the C_4 pseudoequatorial substituent and the C_3-R function will destabilize **19** with respect to **20**.[19] In a qualitative sense, the observed behavior of the Mannich adducts summarized in Table I is consistent with such a steric effect. The infrared carbonyl absorption of the C_3-ester adduct **11a** (1650 cm^{-1}, vinylogous carbamate) indicates extensive delocalization between the indole nucleus and the carbonyl function. This restricted rotation maximizes the peri interaction in conformer **19**. Similarly, the freely rotating C_3-ethyl group of **13a** destabilizes **19** with respect to **20**, although the effective size of the ethyl group is less than that of the carbethoxy subtituent.

An examination of molecular models of the tetrahydrocarbazole adduct **14a** indicates that the C_3–C_4 peri interaction is diminished considerably due to the rigid nature of the cyclohexene ring. In the C_3-H adduct **1a** this peri effect is minimal.

The facile reverse reaction of the isopropylamine adduct **16** compared to the dimethylamine adduct **11a**, is consistent with the observation that the neutral imine leaving group **21** can be lost from **16** while the charged species **22** must be lost from **11a**.

21 **22**

(17) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 56–57.

(18) The practical consequence of this observation is that acid catalyzed Mannich condensations of C_3-ester derivatives **11** give optimum yields.[4]

(19) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966); F. Johnson, *ibid.*, **68**, 375 (1968).

Experimental Section

Melting points are uncorrected and were obtained on a Mel-Temp apparatus. Nmr spectra were obtained on a Varian Associates Model A-60 spectrometer; ir spectra were run on a Perkin-Elmer Model 237B grating spectrophotometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

General Procedure for Reverse Mannich Reactions.—A solution of the Mannich adduct (*ca.* 100 mg) and the appropriate amine (3 ml) in ethanol (5 ml) was heated at reflux under a nitrogen atmosphere for the time indicated in Table I. Reaction progress was monitored conveniently by tlc (silica gel, 20% ethanol–benzene). The crude product(s) were isolated by evaporation of solvent *in vacuo*. In those cases where appreciable reverse reaction occurred (>30%) the relatively insoluble parent hydroxyindole (**11**, **12**, and **13**) was purified by crystallization and was characterized by melting point and mixture melting point and/or nmr and ir. The extent of amine exchange in all systems and the amount of reverse reaction in those cases involving <10% reverse reaction were estimated by nmr of the product mixture using characteristic peaks for each component. For adduct **1a** the amine exchange products were identified by nmr and/or comparison to authentic[4] samples; no evidence for the presence of the reverse reaction product **1** was observed by tlc and nmr analysis of the crude reaction mixtures. Nmr data for the isopropylamine exchange product from **1a** are (acetone-d_6) δ 1.10 [d, 6, J = 6.0 Hz, $CH(CH_3)_2$], 2.35 (s, 3, C_2-CH_3), 2.86 (heptet, 1, J = 6.0 Hz, $CHMe_2$), 4.12 (broad s, 1, $CH_2N<$), 6.03 (broad s, 1, C_3-H), 6.53 (d, 1, J = 8.0 Hz, C_6-H), and 7.03 (d, 1, J = 8.0 Hz, C_7-H).

The Mannich adducts **1a**,[4] **11a**,[4] **12a**,[20] and **14a**[4] were prepared as previously described.

2-Methyl-3-ethyl-5-hydroxyindole (13).[21]—A tetrahydrofuran solution of diborane (25 ml, 1.05 *M*, 26 mmol) was added slowly to a stirred suspension of 2-methyl-3-acetyl-5-hydroxyindole[22] (1.0 g, 5.3 mmol) in tetrahydrofuran (10 ml) under a nitrogen atmosphere. After hydrogen evolution was complete, the mixture was heated under reflux for 1 hr, cooled, and then added to acetone (75 ml). The resulting mixture was heated to boiling and then evaporated *in vacuo*. The residue was heated with methanol (50 ml) for 20 min, the solution was concentrated, and then hydrochloric acid (3 *N*, 40 ml) was added. This mixture was extracted with ether; the combined ether extracts were dried ($MgSO_4$) and evaporated to yield a yellow oil. Sublimation (90°, 0.05 mm) or recrystallization ($CHCl_3$–hexane) yielded pure product **13**: mp 108–108.5°; yield 0.76 g (82%), nmr (acetone-d_6) δ 1.14 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.28 (s, 3, C_2-CH_3), 2.6 (q, 2, J = 7.5 Hz, $-CH_2CH_3$), 6.64 (dd, 1, J = 9 and 2.5 Hz, C_6-H), 6.91 (d, 1, J = 2.5 Hz, C_4-H), and 7.05 (d, 1, J = 9 Hz, C_7-H).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.38; H, 7.48; N, 8.00. Found: C, 74.99; H, 7.69; N, 8.38.

2-Methyl-3-ethyl-4-(dimethylamino)methyl-5-hydroxyindole (13a).—A mixture of paraformaldehyde (0.13 g, 4.32 mmol) and dimethylamine (0.5 ml, 40% aqueous solution, 4.44 mmol) in ethanol (30 ml) was warmed to dissolve the paraformaldehyde. This solution was cooled and indole **13** (0.75 g, 4.29 mmol) and glacial acetic acid (3 ml) were added. The resulting mixture was stirred under nitrogen at room temperature for 12 hr. After evaporation of the ethanol, the residue was made basic (pH *ca.* 9) with Na_2CO_3 solution and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to yield a dark oil. Filtration through a silica gel column (10 g, benzene eluent) yielded a yellow oil which still contained a small amount of **13** (tlc). Purification of **13a** was accomplished by conversion to the water soluble oxalic acid salt, removal of starting indole **13** by ether extraction and liberation of **13a** by sodium carbonate neutralization to give pure **13a** as a homogeneous oil (tlc): yield 0.51 g (52%); nmr ($CDCl_3$) δ 1.11 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.18 (s, 3, C_2-CH_3), 2.30 [s, 6, $N(CH_3)_2$], 2.67 (q, 3, J = 7.0 Hz, CH_2CH_3), 3.92 (s, 2, CH_2NR_2), 6.43 (d, 1, J = 8.5 Hz, C_6-H), and 6.77 (d, 1, J = 8.5 Hz, C_7-H).

2-Methyl-3-carbethoxy-4-(isopropylamino)methyl-5-hydroxyindole (16).—A mixture of paraformaldehyde (0.08 g, 2.8 mmol) and isopropylamine (0.16 g, 2.7 mmol) in ethanol (15 ml) was warmed to dissolve the paraformaldehyde. The solution was cooled and indole **11** (0.58 g, 2.65 mmol) and glacial acetic acid (3 ml) were added. The mixture was stirred under nitrogen at 65° for 4.5 hr. Tlc indicated appreciable conversion to product at this point. After evaporation of the ethanol the residue was made basic (pH *ca.* 9) with Na_2CO_3 solution and extracted with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated to yield the crude product. Attempted purification by crystallization resulted in reverse condensation to give indole **11** (tlc, nmr). Chromatography on alumina(III) furnished a fairly homogeneous sample (tlc) of **16**, mp 130–132°, in low yield. Tlc analysis of the sample after melting indicated only **11** was present. The nmr ($CDCl_3$) of **16** showed δ 1.15 [d, 6, J = 6.5 Hz, $CH(CH_3)_2$], 1.38 (t, 3, J = 7.0 Hz, CH_2CH_3), 2.50 (s, 3, C_2-CH_3), 2.96 [m, 1, J = *ca.* 6 Hz, $CH(CH_3)_2$], 4.33 (q, 2, J = 7 Hz, CH_2CH_3), 6.69 (d, 1, J = 8.5 Hz, C_6-H), 7.01 (d, 1, J = 8.5 Hz, C_7-H), and 7.8 (broad, 2, OH, NH).

1-(Dimethylamino)methyl-2-naphthol (6, R = NMe_2).—A solution of 2-naphthol (1.44 g, 10.0 mmol), paraformaldehyde (0.30 g, 10.0 mmol), and dimethylamine (1.2 ml, 40% aqueous solution, 10.6 mmol) in ethanol (40 ml) was stirred under nitrogen at room temperature for 12 hr. The solvent was evaporated *in vacuo* to yield a mixture (tlc) which was purified by conversion *via* the hydrochloride salt to yield pure **6** (R = NMe_2): yield 1.3 g (65%); mp (hexane) 73–74° (lit.[24] 74–75°); nmr (CCl_4) δ 2.30 [s, 6, $N(CH_3)_2$], 3.95 (s, 2, CH_2NR_2), 6.9–7.8 (m, 6, aromatic H's), and 11.52 (s, 1, OH).

Treatment of 1-(Dimethylamino)methyl-2-naphthol with Isopropylamine.—Dimethylaminomethyl Mannich adduct **6**[23] (R = NMe_2) (0.82 g, 4.06 mmol) was refluxed in a mixture of isopropylamine (15 ml) and ethanol (20 ml) under nitrogen for 10 hr. Evaporation of the solvent yielded a solid which on repeated recrystallization from cyclohexane yielded pure product **8**: mp 191–193° (lit.[14] 193–196°); yield 0.47 g (39%); nmr (acetone-d_6) δ 4.92 (s, 2, $-CH_2-$), 7.1–7.4 (m, 8, aromatic H's), 7.5–7.8 (m, 4, aromatic H's), and 6.25–6.48 (m, 2, –OH). Nmr of the residue indicated *ca.* 30% amine exchange and *ca.* 30% unreacted **6**.

Deuterium Exchange Reactions.—The 3-carbethoxyindole **11** (0.105 g, 4.83 mmol) and the 3-H indole **1** (0.102 g, 6.98 mmol) were separately refluxed in a mixture of isopropylamine (6 drops), methanol-*O*-*d* (1 ml), and deuterium oxide (0.2 ml) under nitrogen for 6 hr. Nmr spectra obtained on the residues after evaporation of the solvent showed complete disappearance of the C_4-H doublet in both cases; the C_6-H now appeared as a doublet. The C_3-H of **1** was not exchanged for deuterium under these conditions.

Registry No.—**1a**, 25913-93-3; **11a**, 13098-13-0; **12a**, 25913-94-4; **13**, 25913-95-5; **13a**, 25913-96-6; **14a**, 25913-97-7; **16**, 25913-98-8.

(20) E. A. Steck, U. S. Patent 2,852,527; *Chem. Abstr.*, **53**, P8163*h* (1959).

(21) Experiment performed by R. Schmidt of these laboratories.

(22) A. N. Grinev, V. I. Shvedov, and A. P. Terent'ev, *Zh. Obsch. Khim.*, **26**, 1629 (1956); *Chem. Abstr.*, **51**, 6996*a* (1957).

(23) N. A. Dzhanovskiĭ, S. V. Marochko, and A. N. Kost, *Sb. Statei Obshch. Khim.*, **1**, 607 (1953); *Chem. Abstr.*, **49**, 986*f* (1955).

Acid-Catalyzed Cyclization Reactions. IX. The Formation of Oxazolinium and Thiazolinium Cations from *N*-Allyl and Substituted *N*-Allylamides, -urethans, -ureas, and -thioureas[1]

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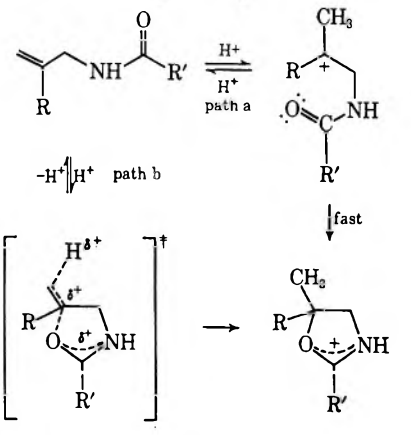
N-Allyl and substituted *N*-allylamides, -urethans, -ureas, and -thioureas have been cyclized in 60–96% sulfuric acid to their corresponding oxazolinium and thiazolinium cations. By drowning certain of these acid solutions into base, a useful synthetic route to 2-oxazolines and 2-thiazolines has been demonstrated. The formation of oxazolinium (**2a–o**) and thiazolinium (**2p–r**) cations was studied by nmr techniques. In general, the simple *N*-allyl derivatives were only protonated at carbonyl oxygen or thiocarbonyl sulfur when introduced into the acid media at room temperature. The cyclic ions (**2**) formed upon heating. The formation of *N*-acylpolyethyleneimines competed with cyclization in some of these examples. *N*-2-Methylallyl and *N*-2-phenylallyl derivatives cyclized immediately at room temperature. The remarkable stability of oxazolinium and thiazolinium cations was indicated by their stability towards heating in acid media and their marked resistance to H–D exchange. Oxazolinium and thiazolinium ions are more resistant to H–D exchange than are oxoniacyclopent-1-enyl and 1,3-dioxoniacyclopent-1-enyl cations. The nmr spectra of these heterocyclic ions are tabulated and discussed. The mechanism of the cyclization process is discussed in light of these findings.

Intramolecular neighboring-group participation by nonbonding and π-bonding electrons in carbonium ion reactions has received considerable attention. Examples include participation by halogen,[4] olefinic bonds,[5] and carbonyl oxygen[6] in solvolytic reactions of trialkyl oxonium ions, halides, and sulfonates. Evidence for participation commonly includes enhanced solvolysis rates in compounds where this participation occurs compared to solvolysis rates of model compounds. In some cases intermediates have been isolated.[6a,7] The ready cyclization of *N*-allylbenzamides to 5-(bromomethyl)-2-phenyl-2-oxazolines upon bromination[8] and to fluorine-containing oxazolines on direct fluorination[9] in polar solvents also represents examples of neighboring-group participation of amide groups.

Heteronuclear stabilized carbonium ions, which are intermediates in the above reactions, have been prepared in many ways[10] and are exceptionally stable if the neighboring heteroatom is oxygen or nitrogen. Few of the reports[10] allow one to judge the relative stability of the ions reported. A recent paper[11] detailing physical studies of triphenylcarbonium ions with multiple neighboring group treats relative stabilities to a limited degree.

In view of the possibility for two discrete pathways for cyclization of allylic amides upon olefinic carbon protonation (see Scheme I), the study of some of these

Scheme I



reactions using nmr techniques to follow the reaction attracted our attention. In addition basic studies of thiazolinium and oxazolinium ions seemed appropriate because of some mention that has been given them with regard to some chemical processes. For example, thiazolinium cations play a role in the reaction mechanism of intramolecular *S*- to *N*-acetyl transfer of *S*-acetylmercaptoethylamine.[12] Oxazolinium cations are intermediate in the preparation of *N*-acyl-substituted polyethylenimines[13] and in the rearrangement of *N*-

(1) (a) For other papers in this series, see S. P. McManus, and J. T. Carroll, *Org. Prep. Proced.*, **2**, 71 (1970), and C. U. Pittman and S. P. McManus, *J. Org. Chem.*, **35**, 1187 (1970). (b) This work was supported in Huntsville in part by the Petroleum Research Fund, administered by the American Chemical Society, and in Tuscaloosa in part by the University of Alabama Research Committee, project 562. (c) A preliminary account of portions of this work was presented: Abstracts, 20th Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 4, 1968, pp 69–70.

(2) Coprincipal investigator; inquiries should be addressed to S. P. M.

(3) American Chemical Society Petroleum Research Fund Scholar, 1968–1969.

(4) P. E. Peterson and F. J. Slama, *J. Amer. Chem. Soc.*, **90**, 6515 (1968).

(5) For leading references, see (a) T. L. Jacobs and R. S. Macomber, *ibid.*, **91**, 4824 (1969); (b) P. E. Peterson and R. J. Kamat, *ibid.*, **91**, 4521 (1969); and (c) J. W. Wilson, *ibid.*, **91**, 3238 (1969).

(6) (a) H. R. Ward and P. D. Sherman, *ibid.*, **90**, 3812 (1968); (b) S. Oae, *ibid.*, **78**, 4030 (1956); (c) D. J. Pasto and M. P. Serve, *ibid.*, **87**, 1515 (1965); and (d) O. K. J. Kovacs, G. Schneider, L. D. Lang, and J. Apjok, *Tetrahedron Lett.*, 4186 (1967).

(7) S. Winstein, L. Goodman, and R. Boschan, *J. Amer. Chem. Soc.*, **72**, 2311 (1950).

(8) L. Goodman and S. Winstein, *ibid.*, **79**, 4788 (1957).

(9) R. F. Merritt, private communication.

(10) See (a) C. U. Pittman and S. P. McManus, *J. Amer. Chem. Soc.*, **91**, 5915 (1969); (b) G. Olah and P. v R. Schleyer, Ed., "Carbonium Ions," Vol. II and IV, Interscience, New York, N. Y., in press.

(11) R. Breslow, L. Kaplan, and D. LaFollette, *J. Amer. Chem. Soc.*, **90**, 4056 (1968).

(12) R. Barnett and W. P. Jencks, *ibid.*, **90**, 4199 (1968).

(13) (a) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Their, and H. Hellmann, *Agnew. Chem. Int. Ed. Engl.*, **5**, 875 (1966); (b) T. G. Basseri, A. Levy, and M. Litt, *J. Polym. Sci., Part B*, **5**, 871 (1967); (c) A. Levy and M. Litt, *ibid., Part A*, **6**, 57, 63 (1968); (d) D. A. Tomalia and D. P. Sheetz, *ibid.*, **4**, 2253 (1966).

TABLE I

NMR SPECTRAL DATA FOR PROTONATED *N*-ALLYLAMIDES, -UREAS, -URETHANS, AND -THIOUREAS (3)[a,b]

Ion	X	CH_2=	=CH-	-CH_2-	-NH-	R′
3a	O	5.65–5.91, m	6.22, m	4.59, b	9.5, b	-H, 8.80, s
3b	O	5.71–5.98, m	6.32, m	4.60, t, J = 5	9.16, b	-CH_3, 3.00, s
3c	O	5.72–5.97, m	6.34, m	4.74, t, J = 5.3	9.25, t but b	-C_6H_6, 6.91–7.39, m
3e	O	5.66–5.90, m	6.22, m	4.67, b	9.20, b	p-$CH_3C_6H_4$, 2.82, s (CH_3), A_2B_2 centered at 7.93
3f	O	5.26–5.55, m	5.86, m	4.35, b	9.10, b	p-FC_6H_4 7.10–7.47, m, 7.70–8.02, m
3g	O	5.60–5.90, m	6.20, m	4.34, d, J = 5–6	Not observed	-NH_2, not observed
3h	O	5.65–5.90, m	6.20, m	4.48, d, J = 6	Not observed	-OCH_3, 4.64, s
3i	O	5.56–5.82, m	6.26, m	4.27, d, J = 5	Not observed	-OCH_2CH_3, 4.72, q, J = 7 1.80, t, J = 7
3p	S	5.70–6.01, m	6.41, m	4.48, b	7.65, b	-NH_2, 8.16, b
3q	S	5.64–5.88, m	6.15, m	4.43, b	8.8–9.2, b (area 2)	-NHC_6H_5, 7.6–7.98, m

[a] Nmr positions are in ppm downfield from TMS present in internal capillary; the areas of the assigned bands were in the correct ratio with the numbered protons represented by that band in each case. [b] m multiplet, s singlet, d doublet, t triplet, q quartet, b broadened band; resolution of hyperfine splitting not clear; coupling constants (J) given in Hz.

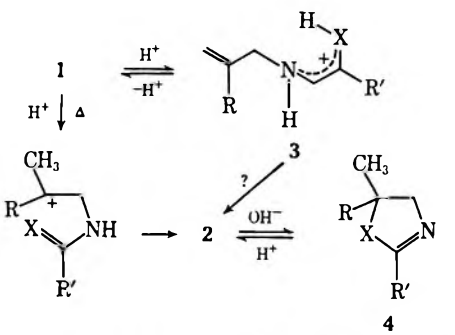
acylaziridines.[14] Thus, we have investigated the acid-catalyzed cyclization of a series of *N*-allyl and substituted *N*-allylamides, -urethans, -ureas, and -thioureas to their corresponding heterocyclic cations and present the results of these studies here.

Results and Discussions

Cyclization Studies in H_2SO_4 and Structure Proof of the Heterocyclic Cations.—When allylacetamide (**1b**) is dissolved into 96% H_2SO_4 at room temperature, an nmr spectrum consistent with O protonation of the amide[15] is obtained. Upon heating at 70–85°, the protonated amide (**3b**) undergoes a change as evidenced from the development of a more complex nmr spectrum. The lines assigned to **3b** begin to decrease in intensity as new lines belonging to the 2,5-dimethyloxazolinium cation (**2b**) slowly increase in intensity. After heating for about 10 min, the lines due to protonated amide have disappeared entirely, and the spectrum is consistent with the quantitative formation of the 2,5-dimethyloxazolinium cation (**2b**). During the heating interval, no lines other than those assigned to **2b** and **3b** were observed. The reaction sequence is depicted in Scheme II. All the other *N*-allylamides, -ureas, -thioureas, and -urethans studied were only O or S protonated in 60–90% H_2SO_4 at room temperature. The nmr spectral data of these protonated compounds are summarized in Table I. With the exception of resolution and a charge-induced downfield shift, the spectra are similar in appearance to the amides in CCl_4. All the *N*-allyl derivatives cyclized when heated to 60–100° in the H_2SO_4 solutions.

In a few cases, polymerization of the oxazolinium

SCHEME II



1–4, a–o, X = O; p–r, X = T
1–4, a–i, p, q, R = H; j–m, r, R = CH_3; n, o, R = C_6H_5
1–4, for R′, see Table II

cations to *N*-acyl-substituted polyethylenimines competes favorably with the initial cyclization. For instance, heating a 96% H_2SO_4 solution of protonated *N*-allylformamide (**3a**) for 3 hr resulted in a very viscous solution of the polymer. By using 82% H_2SO_4 as the solvent, a complex spectrum is obtained on heating which can be attributed to a mixture of the 5-methyloxazolinium cation and protonated polymer.[13] However, only a maximum of a 25% of the cation could be obtained, and further heating led to complete conversion to polymer. Depending on the acidity and the temperature used for the cyclization, polymerization can compete with cyclization during the preparation of **2f** and **2g**.

When *N*-(2-methylallyl)- or *N*-(2-phenylallyl)amides (**1j–o**) were dissolved into 96% H_2SO_4 at 10–15°, their room temperature nmr spectra (determined within 1 min of mixing) indicated the presence of the oxazolinium cations (**2j–o**) without any trace of the protonated amides. Even at −20° in FSO_3H, protonated *N*-(2-methylallyl)acetamide cannot be observed due to quantitative formation of the cyclic ion (**2k**). Apparently, because formation of a tertiary carbonium ion is favorable, these cyclizations compete favorably with O

(14) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Amer. Chem. Soc.*, **81**, 2202 (1959).

(15) Presence of the characteristic pattern of a monosubstituted vinyl group precludes the formation of the sulfate ester or of the carbonium ion. Protonation of amides at the oxygen function rather than at nitrogen is expected: *cf.* G. A. Olah, J. A. Olah, and R. H. Schlosberg, *J. Org. Chem.*, **35**, 328 (1970).

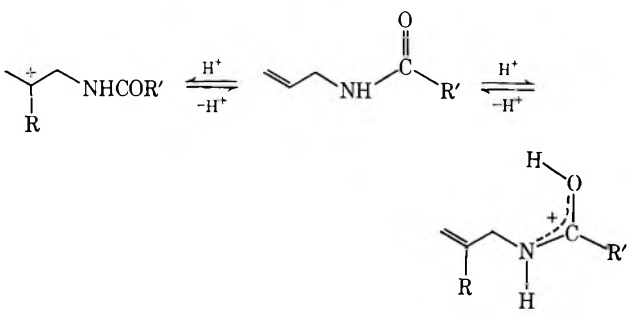
Table II

Nmr Spectra of Oxazolinium and Thiazolinium Cations in H_2SO_4

Cation no.	R′	C-4 hydrogens	C-5 hydrogens	C-5 methyl(s)	NH
2a	H, 8.87, s	4.47, m		2.14, d, J = 6	
2b	CH_3, 2.95, s	4.41, m	5.56, m	2.02, d, J = 6.8	9.44, b
2c	C_6H_5, 7.75–8.35, m	4.20, t, J = 10, 4.72, t, J = 10	5.91, m	2.03, d, J = 6	9.98, b
2d	p-$NO_2C_6H_4$, A_2B_2 centered at 8.88	4.64, t 5.05, t	6.30, m	2.32, d, J = 6	9.80, b
2e	p-$CH_3C_6H_4$, 2.86, s, (CH_3), A_2B_2 centered at 8.04	4.45, b	5.58, m	2.03, d, J = 5.7	9.48, b
2f	p-FC_6H_4, 7.08–7.49, m, 7.73–8.20, m	4.50, b	5.61, m	1.79, d, J = 6	9.63
2g	NH_2, not observed	4.19, b	5.50, m	2.07, d, J = 6	Not observed
2h	OCH_3, 4.14, s	3.66, m	4.86, m	1.63, d, J = 5.8	Not observed
2i	OC_2H_5, α 4.30, q, J = 7, β 1.75, t, J = 7	3.64, m	4.79, m	1.84, J = 6.4	Not observed
2j	H, 8.81, s	4.37, s, b		2.17, s	10.22, s (b)
2k	CH_3, 2.90, s	4.34		2.16, s	9.75, s
2l	C_6H_5, 7.75–8.35, m	4.30, s		2.08, s	9.72
2m	p-$NO_2C_6H_5$, A_2B_2 pattern, 8.81	4.59, s		2.29, s	10.68, b
2n	CH_3, 3.01, s	4.67, s		2.40, s, 7.83 (C_6H_5)	9.75
2p	NH_2, 8.3, b	4.20,[a] m	5.43,[a] m	2.05, d, J = 6	Not observed
2q	NHC_6H_5, N–H at 9.37, phenyl at 7.6–8.05, m	4.19, b[a] 5.40, b	5.40, b[a]	1.95, d, J = 6	Not observed
2r	NHC_6H_5, N–H at 9.50, 7.47–7.95 m changes to A_2B_2 quartet at 8.33, J_{AB} = 8.2, in 2 weeks	4.17, s		1.98, s	Not observed

[a] Exact assignments of the C-4 and C-5 hydrogens in these compounds is more difficult than in the case of the oxazolines. Studies on the picrate of 2q indicate the assignment made for that ion; see the Experimental Section for those studies.

protonation. When compared to the necessity of heating in order to generate ions **2a–i**, the ease of formation of oxazolinium ions **2j–o** supports the intermediacy of discrete acyclic carbonium ions as opposed to the direct formation of **2** by neighboring-group participation during C protonation[16] (see Scheme I). One could argue that both paths a and b would be favored by substitution of the vinylic position due to stabilization of the transition state in C protonation. However, the oxazolinium ions possess such remarkable stability that one could not expect any substantial differences in stability in the transition states of the allyl verses methallyl derivatives (due to an extra methyl substituent at the vinyl position) if strong neighboring-group participation is occurring.[17]



This generalization may be extended to the cyclization of thioamides (**1p–r**) to their corresponding 2-amino (or 2-anilino) thiazolinium cations (**2p–r**). The S-protonated *N*-allylthioureas (**1p** and **q**) are only cyclized upon heating several hours at >85°, whereas 1-(2-methylallyl)-3-phenyl-2-thiourea (**1r**) is instantaneously cyclized at 15°.

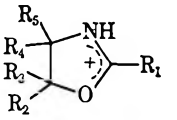
Definitive identification of the oxazolinium and thiazolinium cations **2a–r** was straightforward. Their formation was accompanied by loss, in the nmr spectra of each ion, of vinylic absorption and the appearance of new bands due to a methyl group(s). In the case of *N*-allyl derivatives **1** (R = H), this new band was a doublet. Whenever R was methyl or phenyl (**1j–o, r**), a new singlet was observed. The nmr spectral data of these ions are summarized in Table II. These particular bands, when combined with the rest of the spectrum, identified the cations. This identification was confirmed in several ways. First, several 2-oxazoline derivatives, which were either commercially available or readily prepared, were treated with cold 96% H_2SO_4 and the nmr spectra of the resulting authentic oxazolinium cations were obtained. These authentic models exhibit nmr spectra which could be compared directly to the spectra of the ions formed by cyclization. Table III summarizes the spectra of these model cations, which to our knowledge have not been previously reported. For proof that these ions were identical with those obtained by cyclization, the 2,5,5-trimethyl-2-oxazolinium cation was prepared by adding an equimolar mixture of methallylacetamide and the parent oxazoline to 96% H_2SO_4; the nmr spectrum revealed a

(16) S. P. McManus, *Chem. Commun.*, 235 (1969).

(17) Stated another way: The R group in the transition state shown in path b, Scheme I, would not be expected to contribute much to its stability if neighboring-group participation is well developed in that transition state. The stabilizing effect of the developing oxazolinium ion should swamp out the effect of the methyl group.

TABLE III

NMR SPECTRAL DATA OF MODEL OXAZOLINIUM AND THIAZOLINIUM CATIONS IN 90% H_2SO_4. BAND POSITIONS OF THE CATION



Parent compd	Registry no.	R_1	R_2, R_3	R_4, R_5	NH
2-Methyl-2-oxazoline	23704-69-0	2.9, s	5.53, t, J = 9.9	4.62, t, J = 9.9	9.94, b
2-Propyl-2-oxazoline	25898-55-9	α 3.20, t, J = 7 β 1.59, h, J = 7 γ 1.54, t, J = 7	5.56, t, J = 9.8	4.64, t, J = 9.8	9.68, b
2,4,4-Trimethyl-2-oxazoline	25898-56-0	2.90, s	5.17, s	2.03, s	10.01, b
Benzoxazole	25898-57-1	10.16, s	7.9–8.34, m		13.81, b
2,5-Dimethylbenzoxazole	25898-58-2	3.48, s	5-CH_3, 2.86, s, phenyl protons, multiplet centered at 7.69		13.42, s
2-Methylthiazoline	25898-59-3	3.14, s	4.28, t, J = 9.1	4.91, t, J = 9.1	Not observed
2-Methylbenzothiazole	25898-60-6	3.59, s	7.98–8.72, m		4.64, s
Benzothiazole	25898-61-7	10.19, d, J = 5.8	7.81–7.99, m		12.55, b
2,5-Dimethylbenzothiazole	25898-62-8	3.50, s	5-CH_3, 2.79, s, phenyl protons, 7.71–8.18, m		12.49, b
2-Aminothiazoline	25898-63-9	NH_2, not observed	4.17, t, J = 8.0	4.59, t, J = 8.0	Not observed
2-Mercaptothiazoline	25898-64-0	sh, not observed	4.42, t, J = 8	4.93, t, J = 8	9.95

single cation.[18] The nmr spectrum of cation **2k**, which is representative of the spectra obtained for the oxazolinium cations, is recorded in Figure 1.

The identification of the cyclic cations was further strengthened by the isolation of the corresponding oxazolines upon drowning the acid solutions into a well-stirred solution of cold, dilute, excess base with continuous ether extraction. The oxazolines, thus isolated, were identified by ir, nmr, elemental analysis, and studies of their physical properties.[19] Furthermore, when the isolated oxazolines were redissolved into cold 96% H_2SO_4, the same oxazolinium cations (as determined by their nmr spectra) were obtained as had been obtained in the amide cyclizations. As expected, the protonated amides, ureas, and urethans **3** and the cyclic ions **2** exhibited the anticipated downfield nmr chemical shifts relative to their corresponding oxazolines and thiazolines **4**. The magnitude of this charge-induced deshielding is that expected from applying the previous studies of dioxolinium ions[20] and a variety of other protonated compounds.[10b] For similar cations,

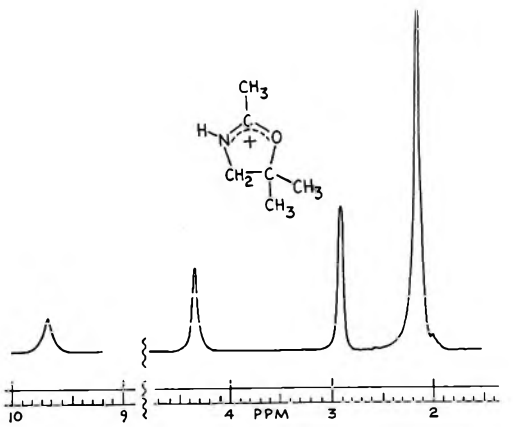


Figure 1.—Nmr spectrum of the 2,5,5-trimethyl-2-oxazolinium cation (**2k**).

Tomalia[21] has correlated $\Delta\delta$ values for different solvents.

The nmr spectra of oxazolines and thiazolines, **4**, where R′ is an alkyl group, exhibit long-range coupling between the α protons or R′ and the C-4 ring protons.[22] The coupling constant generally varies between 1.0 and 2.0 Hz. For instance, in 2-methyloxazoline (**5**) the

(18) The same ion is formed by the rearrangement of 1-acetyl-2,2-dimethylaziridine. In that case, an identified nmr spectrum is obtained; *cf.* Pittman and McManus, ref 1a.

(19) S. P. McManus, J. T. Carroll, P. M. Grohse, and C. U. Pittman, *Org. Prep. Proced.*, **1**, 183, 235 (1969). These references describe a useful and convenient synthetic method for preparing certain substituted oxazolines.

(20) (a) C. U. Pittman, Jr., and S. P. McManus, *Tetrahedron Lett.*, 339 (1969). (b) H. Hart and D. Tomalia, *ibid.*, 3383, 3389 (1966); 1347 (1967).

(21) D. A. Tomalia, N. D. Ojha, and B. P. Thill, *J. Org. Chem.*, **34**, 1400 (1969).

(22) M. A. Weinberger and R. Greenbalgh, *Can. J. Chem.*, **41**, 1038 (1963).

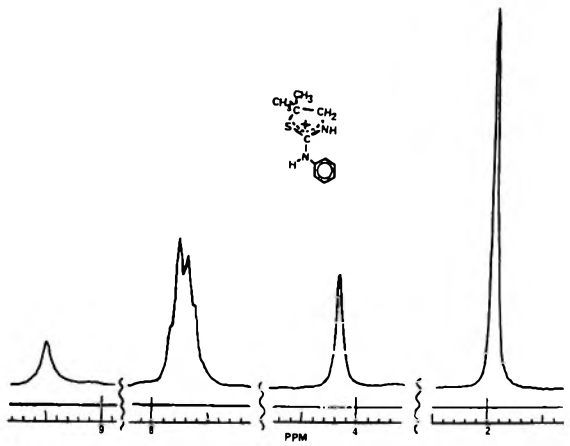
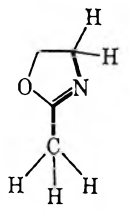


Figure 2.—Nmr spectrum of the 2-anilino-5,5-dimethyl-2-thiazolinium cation (**2r**).

methyl appears as a triplet (J = 1.4 Hz), while the methyl resonance in the corresponding oxazolinium cation **6** is a singlet. Long-range coupling is also



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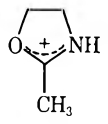

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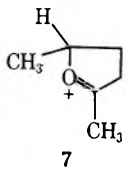
lacking in oxonia- and 1,3-dioxoniacyclopentene cations (**7** and **8**).[10a,20,23] Since each of these ions has a π bond



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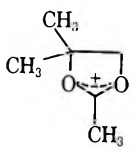

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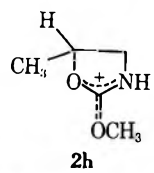
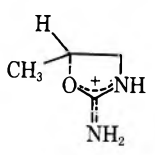
in one resonance structure, the absence of long-range coupling might indicate that σ–π electron interactions, which are thought[24] to be responsible for this type of coupling, are substantially reduced in the ions. An alternate explanation is that the fine structure in the spectra of the ions does not appear because of solvent effects. The latter possibility is currently being investigated.

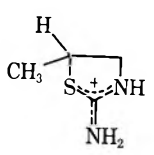
N-Allylurea (**1g**), *N*-carbomethoxyallylamine (**1h**) and its homolog **1i**, *N*-allylthiourea (**1p**), and *N*-allyl-*N'*-phenylthiourea (**1q**) were each protonated in cold 96% H_2SO_4 (see Table I). Heating each acid solution resulted in conversion to the highly resonance stabilized cations **3g–i, p, q**, respectively. The nmr spectra of the



2h



2g



2p

(23) C. U. Pittman and S. P. McManus, *Chem. Commun.*, 1479 (1968).

(24) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., pp 176–180.

cations (Table II) were straightforward. While conversion of **1h** to cation **2h** was nearly quantitative, attempts to isolate 2-methoxy-5-methyl-2-oxazoline (**4h**) by drowning into excess base in the normal manner[19] failed.

The cyclization of S-protonated allylthiourea (**3p**) in 70–96% H_2SO_4 was much slower than cyclizations of *N*-allylamides, *N*-allylureas, or *N*-allyurethans. About 24 hr at 70° was required to complete the cyclization of **1p** to the 2-amino-5-methyl-2-thiazolinium cation (**2p**) (*vs.* 2 hr for the conversion of **1g** to **2g**). The lack of N–H resonances in the nmr spectra of **2g** and **2o** indicates rapid exchange of these protons in the concentrated acid solution.

1-(2-Methylallyl)-3-phenyl-2-thiourea (**1r**) behaves in a manner analogous to amides **1j–n**. Upon mixing it with 96% H_2SO_4, immediate quantitative conversion to the 2-(anilino)-5,5-dimethyl-2-thiazolinium cation (**2r**) occurs. The nmr spectrum of **2r** is shown in Figure 2. Upon drowning the acid solution of **2r** into a cold dilute base solution, 2-anilino-5,5-dimethyl-2-thiazoline[25] (**4r**) was isolated in 50% yield. Redissolving the isolated thiazoline in 96% H_2SO_4 allowed for quantitative regeneration of cation **2r** as evidenced by the reproduction of an nmr spectrum identical with that in Figure 2.

Cyclization Studies in D_2SO_4 and H–D Exchange Experiments —When allylic amides were cyclized in 96% D_2SO_4, a single deuterium was incorporated in the C-5 methyl group(s) determined by peak intergration. The N–H disappeared, as expected, due to exchange with solvent. *No further* incorporation of deuterium into the ions occurred. The 2-propyl-2-oxazolimum ion, prepared by dissolving the parent oxazoline in acid, showed no H–D exchange, other than N–H, after 14 hr at 120° in 96% D_2SO_4 or after 10 min at 122° in 65% D_2SO_4. Allen and Ginos[26] reported that H–D exchange occurs at the 2-methyl group of 2,3,4,4-trimethyl-2-oxazolinium iodide in 0.005 and 0.1 *M* HI solutions in D_2O. Under their more basic conditions, however, H–D exchange is much more likely than in the present case.

The resistance to H–D exchange is also exhibited by the thiazolinium ions. The 2-methyl-2-thiazolinium cation exhibits no H–D exchange after 1.3 hr at 120° in 96% D_2SO_4 or after 13 min at 122° in 65% D_2SO_4.

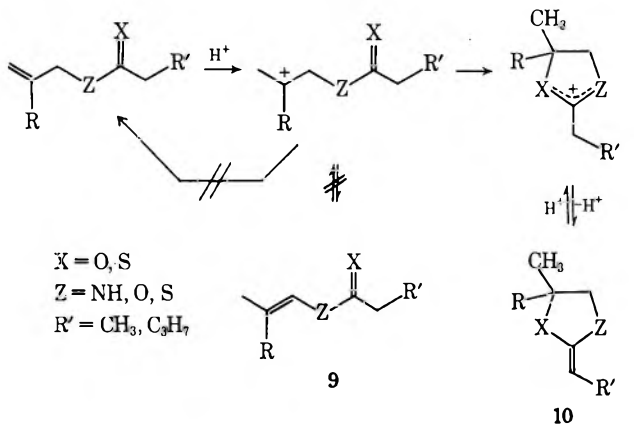
When compared to other heteroatom-stabilized cyclic ions, certain trends are evident. Five-membered ring cyclic carbonium ions with a single adjacent heteroatom (O, N, S) incur H–D exchange among both the C-2 methyl hydrogens and the C-3 methylene hydrogens. For example in **7**, the C-2 methyl hydrogens are 34% exchanged during 68 hr at 24° and 65% exchanged during 7 min at 120° in 96% D_2SO_4. The C-3 methylene hydrogens of **7** were 43 and 78% exchanged under those conditions.[23] The C-4 and C-5 hydrogens are not exchanged in 96% D_2SO_4 even after heating overnight at 120°.[10a] Five-membered ring cyclic carbonium ions with two heteroatoms are stabilized sufficiently that H–D exchange does not occur in concentrated acid solutions.[20a]

(25) The endocyclic structure rather than the tautomeric exocyclic structure is assigned in line with the implicit evidence obtained from the study of the analogous 2-anilino-2-oxazoline systems: *cf* J. R. Carson, G. I. Poos, and H. R. Almond, *J. Org. Chem.*, **30**, 2225 (1965).

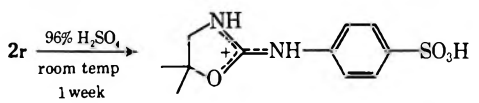
(26) P. Allen and J. Ginos, *ibid.*, **28**, 2759 (1963).

As shown in Scheme III, the intermediate acyclic carbonium ion is not in equilibrium with the starting allyl derivative or vinyl derivative **9**, but must be captured by O (or S) before proton loss occurs. Also, oxazolinium (thiazolinium) cations are not in equilibrium with their *exo*-2-methylene derivatives **10**.

SCHEME III



Stability of Oxazolinium and Thiazolinium Cations.—Oxazolinium and thiazolinium cations are thermally stable in addition to being relatively resistant to H–D exchange. After 72 hr in 96% H_2SO_4, the 2-phenyl-5-methyl-2-oxazolinium cation remains unchanged. 2,5,-5-Trisubstituted oxazolinium cations were unchanged after several days at 90° in 96% H_2SO_4 or 70% H_2SO_4. The 2-amino-2-thiazolinium cation, **2p**, is unchanged after being heated to 80° in 70% H_2SO_4 for 64 hr. The remarkable ability of the heteroatoms to stabilize a positive charge, within the heterocyclic ring, is illustrated by the para sulfonation of the phenyl ring of the 2-anilino-5,5-dimethyl-2-thiazolinium cation (**2r**) after a week at 22° in 96% H_2SO_4. During this period the nmr spectrum of the phenyl proton changes to an A_2B_2 quartet with an area of 4. Thus, the amino nitrogen is able to support para attack of the phenyl ring in spite of its attachment to the 2 position of a thiazolinium ion!



Oxazolinium and thiazolinium ions do not cleave on heating in strong acid media. This behavior is in contrast to that of the analogous dioxolinium and oxathiolinium cations which readily undergo $A_{AL}1$ cleavage at elevated temperatures.[20a] This suggests that oxazolinium (thiazolinium) ions are more stable (*i.e.*, **2k** > **8**).

Characteristics of Cation Nmr Spectra —The chemical shifts of the protons of **2** are shifted downfield with respect to their corresponding 2-oxazolines[21] and 2-thiazolines. The protons at C-5 (adjacent to oxygen) are found more than 0.7 ppm downfield from the protons at C-4 in oxazolinium ions. In thiazolinium ions, the order is reversed and the separation of the C-4 and C-5 protons is more variable.[27] The proton on nitrogen in both sets of ions appears as a broadened singlet due to the nitrogen quadrapole[28] which shortens the spin–lattice relaxation time to a value comparable with the reciprocal of the J_{H-N} coupling constant. This broadening due mainly to asymmetric fields near N, indicates the hybridization at nitrogen is still sp^2 in the cations. When sp^2 hybridized, the electric field symmetry is far lower than in sp^3-hybridized cases such as ammonium ions.[29] It should be noted that the proton at the ring nitrogen is not observed in the spectra of both oxazolinium and thiazolinium ions when amino, anilino, mercapto, or alkoxy substituents are attached at C-2 (*i.e.*, R′). Since these substituents would disperse the charge to a greater degree than with aryl or alkyl substituents (where the proton at nitrogen is observed), the results appear to be contradictory to predictions: at constant acid concentrations, as the basicity of the ring nitrogen increases, the rate of N–H exchange with solvent increases! The expected result occurs in those systems where the N–H is observed: as the acid concentration is decreased, the exchange rate of the N–H with solvent increases. Thus, in 60% H_2SO_4 the nitrogen is not observed in any systems.

The cis and trans vicinal couplings between ring protons at C-4 and C-5 are equal, within experimental error, in the 2-methyl and the 2-propyl oxazolinium ions. This accounts for the clean triplets observed. This is also true of the 2-methyl, the 2-amino, and the 2-mercapto-2-thiazolinium ions. While this is an exception to predictions of the Karplus equation, this phenomenon has been previously observed in dihydrofuran ring systems,[30] five-membered ring oxonium ions[20a,23] as well as being observed in the corresponding oxazolines and thiazolines. The size of these couplings is large, being from 9–10 Hz in 2-alkyl or 2-aryl[1a] oxazolinium and thiazolinium ions. In these cases, the coupling constant increases from 1.0 to 1.5 Hz going from the parent heterocycle to the cation. When a mercapto or amino group is present at the 2 position in the ions, the size of the coupling constant is about 8 Hz and shows no increase when compared with its parent compounds.

Currently, studies are being extended to the formation of six-membered and larger rings in strong acid media. Since the six-membered rings are not expected to be as stable thermodynamically,[31] systems may be designed which will allow an equilibrium between the open-chain carbonium ion and the cyclic ion. Also, the possible similarity between these cyclizations and acid-catalyzed rearrangements of acylaziridines[1a] and acylcyclopropanes[10a] is being studied.

Experimental Section[32]

Materials.—The following were purchased and used without further purification: all compounds in Table II (Aldrich) except 2,4,4-trimethyl-2-oxazoline, which was prepared as previously described,[33] and compounds **1g** and **1p** (Eastman "White Label").

(27) In 2-thiazolines the C-4 protons appear downfield of the C-5 protons rather than the reverse which is true for 2-oxazolines; *cf.* ref 22.

(28) J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 4495 (1956).

(29) G. V. D. Tiers and F. A. Bovey, *J. Phys. Chem.*, **63**, 302 (1959).

(30) L. M Jackman, "Applications of NMR Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 87.

(31) Based on comparison with the isoelectronic carbocyclic derivatives; *cf.* T. S. Sorensen, *J. Amer. Chem. Soc.*, **91**, 6398 (1969).

(32) Unless otherwise noted all nmr spectra were recorded using a Varian HA-100 spectrometer with a variable temperature probe. The chemical shifts are relative to tetramethylsilane as an internal standard (internal capillary in acid solutions). Neutral samples, unless otherwise noted, were run in carbon tetrachloride solutions. Ir spectra were recorded using an IR-10 spectrophotometer. Microanalyses were performed by Gailbraith Laboratories, Inc., Knoxville, Tenn. Melting points (capillary tube) and boiling points are uncorrected.

(33) H. Wenker, *J. Amer. Chem. Soc.*, **57**, 1079 (1935).

Table IV

Data for Isolated Oxazolines and Thiazolines

Compd	Registry no.	Yield, %	Mp °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2,5-Dimethyl-5-phenyl-2-oxazoline	25913-84-2	70	Picrate 152–153			13.86			13.68
2,5-Diphenyl-5-methyl-2-oxazoline	24913-85-3	60	Picrate 153–154			12.01			11.76
2-Anilino-5,5-dimethyl-2-thiazoline	24913-86-4	40	153	64.04	6.84	13.58	63.95	6.76	13.48

Compounds 1l and 1m were kindly provided by Dr. R. F. Merritt of the Rohm and Haas Company. The preparation of compounds 1b–f and 1k has been described elsewhere.[19]

Allylformamide (1a).—Allylamine (11.4 g, 0.2 mol) was slowly added to 14.8 g (0.2 mol) of ethyl formate in a 50-ml round-bottomed flask equipped with a magnetic stirrer and condenser. After about 5 min heat from the reaction caused the mixture to reflux. The reaction was complete in about 30 min, but stirring was continued overnight. The solution was vacuum distilled to yield 14.0 g (83%) of 1a, bp 104–107 (14 mm) [lit.[32] 109° (15 mm)], d^{20}_4 1.004 (lit.[34] 1.008).

Methallylformamide (1j).—In the same manner as for the preparation of 1a above, 10 g (0.141 mol) of methallylamine and 10.8 g (0.141 mol) of ethyl formate produced 10.4 g (70%) of 1j, bp 78° (1.5 mm), n^{25}_0 1.4641. The nmr spectrum of 1j contained singlets at δ 148.5 (3 protons) and 337.5 ppm (2 protons), and a multiplet centered at 717 ppm.

Anal. Calcd for C_5H_9NO: N, 14.13. Found: N, 13.89.

***N*-Carbomethoxyallylamine (1h).**—Allyl isocyanate (16.6 g, 0.2 mol, Aldrich) was added dropwise to 50 ml of methanol in a round-bottomed flask fitted with a condenser and magnetic stirrer. Heat produced from the reaction caused gentle refluxing to occur. The mixture was stirred overnight and distilled to yield 17.2 g (75%) of 1h, bp 92–94° (30 mm) [lit.[35] 179.5–183.5 (748 mm)].

***N*-Carbethoxyallylamine (1i).**—In the same manner as for the preparation of 1h above, 16.6 g (0.2 mol) of allyl isocyanate reacted with 50 ml of absolute ethanol to yield 20.2 g (78%) of 1i, bp 92–93° (15 mm) [lit.[36] 92° (15 mm)].

***N*-2-Phenylallylacetamide (1n).**—Potassium phthalimide (10 g, 54 mmol) and 8.2 g (54 mmol) of 2-phenylallyl chloride were added to 100 ml of dimethyl sulfoxide and the resulting solution was heated on a steam bath while being stirred mechanically. After two hr the clear solution was cooled and poured into 300 ml of water containing about 100 g of ice. The phthalimide precipitated and was collected and dried overnight. The crude product weighed 12.9 g (91%) and melted at 116–118°. The phthalimide (10 g) was refluxed for 1 hr with 4.6 ml of hydrazine hydrate in 190 ml of methanol. The solution was cooled, treated with 30 ml of 10 *N* hydrochloric acid, and filtered. The phthalhydrazide was collected triturated with 100 ml of water and filtered, and the combined extracts were evaporated to dryness under reduced pressure. The residue was treated with 30 ml of 20% aqueons potassium hydroxide solution and extracted with three 20-ml portions of ether. The combined extracts were dried (Na_2SO_4) and treated with ketene[13] (about 70 mmol). Removal of the ether under reduced pressure gave 4.1 g (70%) of 1n, mp 78–79° (from ethanol–water).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.28; H, 7.43; N, 7.80.

The ir spectrum of 1n was consistant with the assigned structure: 3290 (s), 3080 (m), 2930 (m), 1640 (s), 1533 (s), 1282 (s), 900 (m), and 700 cm^{-1} (m). The nmr spectrum of 1n confirmed the structure assignment.

***N*-2-Phenylallylbenzamide (1o).**—The amine was prepared in the same manner as for the preparation of 1n above. In a typical run, the ethereal solution of the amine, prepared from 10 g (33.4 mmol) of the phthalimide, was concentrated at reduced pressure and to the residue was added 20 ml of dry benzene and 5 ml of triethylamine. While maintaining the flask in a bath at 0–5°, 5 g (35.5 mmol) of benzoyl chloride in 20 ml of dry benzene was slowly added with stirring. The solution was allowed to slowly warm to room temperature and after 2 hr the triethylamine hydrochloride salt was filtered and the filtrate was concentrated at reduced pressure. The solid residue was crystallized from ethanol–water to yield 5.3 g (67%) of 1o, mp 122–123°.

Anal. Calcd for $C_{16}H_{15}NO$: N, 5.90. Found: N, 5.71.

1-(2-Methylallyl)-3-phenyl-2-thiourea (1r).—To a stirred solution of 7.1 g (0.1 mol) methallylamine in 75 ml of absolute ethanol, phenyl isothiocyanate (13.6 g, 0.1 mol) was added with gentle reflux. Ten minutes after the addition was complete, the solution was cooled and to it was added 75 ml of ice water. After standing in the freezer for 0.5 hr, the white crystals were collected, dried, and recrystallized from ethanol–water to yield 21.3 g (81%) of 1r, mp 79–80° (lit.[37] 80–81°). The ir spectrum of 1r had major peaks at 3376 (s), 2210 (s), 1596 (m), 1540 (s), 1520 (s), 1315 (m), 1225 (m), 880 (m), and 740 cm^{-1} (m). The nmr spectrum ($CDCl_3$) was consistant with the structure: δ 142 (s, 3 protons), 413 (d, J = 5.5 Hz, 2 protons), 475 (m, 2 protons), 636 (b, 1 proton), 723 (m, 5 protons), and 902 ppm (b, 1 proton).

1-Allyl-3-phenyl-2-thiourea (1q).—This derivative was prepared precisely in the manner described for 1r, mp 98–99° (lit.[38] 98°).

Isolation of Oxazolines and Thiazolines.—Previously described methods[19] were used to isolate some of the 2-oxazoline and 2-thiazoline derivatives. All isolated compounds were fully characterized. Data on new compounds isolated are compiled in Table IV.

Decoupling Experiments with the Picrate of 1q.—The picrate of 1q, mp 152–153° (lit.[39] 153°), was prepared from the isolated thiazoline. The nmr spectrum, obtained in acetone-d_6 with a Bruker HFX-90 spectrometer, contained the following: δ 1.58 (d, J = 6 Hz, 3 protons), 3.91 (m, 1 proton), 4.35 (m, 2 protons), 7.47 (s, 5 protons), and 8.81 ppm (s, 2 protons). The N–H protons were not observed. Decoupling experiments between the C-5 methyl group (δ 1.58) and the C-4 and C-5 protons indicated that the C-5 proton is centered at 4.44 ppm. One C-4 proton is then in the multiplet centered at 4.35 ppm and the other is the multiplet at 3.91 ppm.

Registry No.—**1j**, 25913-66-0; **1n**, 25957-50-0; **1o**, 25913-67-1; **1r**, 25913-68-2; **2a**, 25898-39-9; **2b**, 23704-70-3; **2c**, 23704-73-6; **2d**, 25898-42-4; **2e**, 25898-43-5; **2f**, 25898-44-6; **2g**, 25898-45-7; **2h**, 25898-46-8; **2i**, 25898-47-9; **2j**, 25898-48-0; **2k**, 23704-71-4; **2l**, 25898-50-4; **2m**, 25898-51-5; **2n**, 25898-52-6; **2p**, 25898-53-7; **2q**, 25898-54-8; **2r**, 25950-25-8; **3a**, 25913-69-3; **3b**, 25913-70-6; **3c**, 25913-71-7; **3e**, 25913-72-8; **3f**, 25913-73-9; **3g**, 25913-74-0; **3h**, 25913-75-1; **3i**, 25913-76-2; **3p**, 25913-77-3; **3q**, 25913-78-4; 2,5,5-trimethyl-2-oxazolinium cation, 25913-83-1.

Acknowledgments.—The authors acknowledge samples from Dr. R. F. Merritt and discussions with Professors M. T. Emerson and L. D. Kispert.

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1,3-Bridged Aromatic Systems. VII. Quinolines[1,2]

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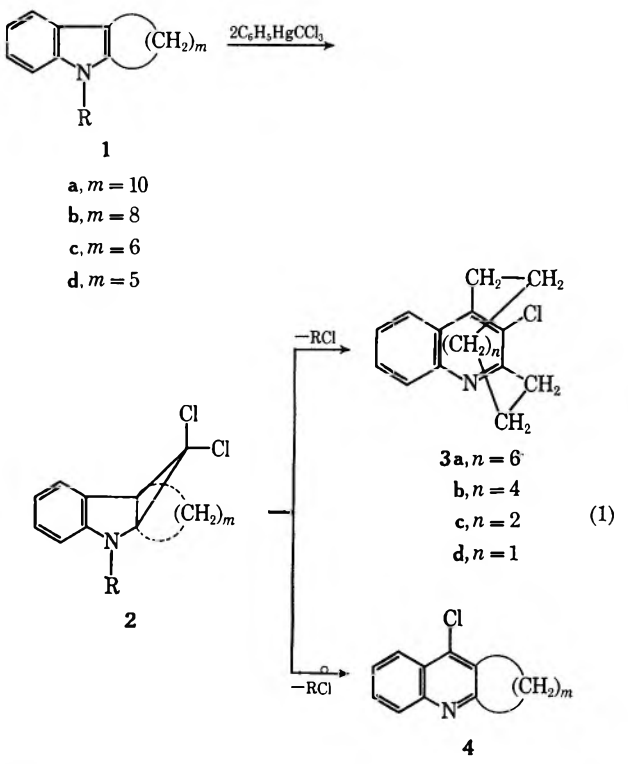
The preparation of 1,3-bridged quinolines of type **3** are described. As the value of n in these pyridinophanes is reduced, the methylene bridge is more constrained and the pyridine ring is strained; such strain is reflected by changes in spectral and chemical behavior. The asymmetry of the quinolines **3** was established by conversion of **3a** to the epimeric alcohols **6a** and **6b** in which the hydroxyl functions are at carbon-1 of the bridge. The pK_a of representative examples of **3** are compared with that of the model 3-chloro-2,4-dimethylquinoline. The pyridinophane **3a** undergoes only monobromination with *N*-bromosuccinimide to give **15**; by contrast the dechloro derivative **8a** readily gives the dibromide **17**. These reactions, and the lack of reactivity of **17**, are discussed in terms of steric requirements for reaction.

In a preliminary communication[4] we described the preparation of the 1,3-bridged quinolines **3a–c** (48–76% yield) by addition of dichlorocarbene to the indoles **1** (R = H or R = C(O)CH$_3$), as summarized in eq 1.



1

a, $m = 10$
b, $m = 8$
c, $m = 6$
d, $m = 5$

3a, $n = 6$
b, $n = 4$
c, $n = 2$
d, $n = 1$

(1)

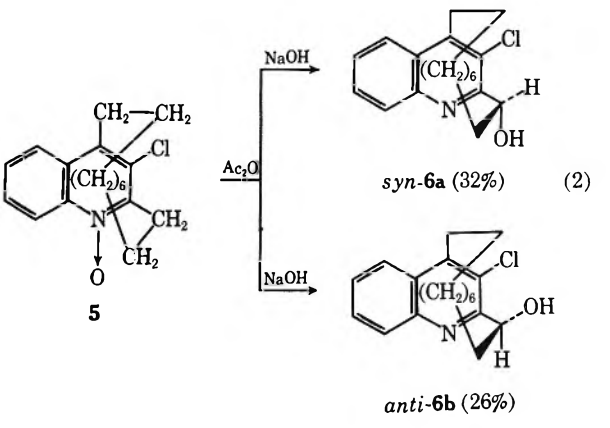
2

4

The limiting value of m for the preparation of **3** was found to be 6; when $m = 6$ the quinoline **4** ($m = 6$) was formed as a minor compound (2.7% yield) together with **3c**, and, when $m = 5$, the quinoline **4** ($m = 5$) was the only product characterized (11.6% yield).[5,6]

In this paper we describe experimental procedures for these syntheses, and report additional studies bearing on the physical and chemical properties of these heterocyclic metacyclophanes.

Reaction of 12,13-Benzo-16-chloro[10](2,4)pyridinophane *N*-Oxide (5) with Acetic Anhydride.—Comparision of the nmr spectra of the cyclophanes **3a–b** with the dechlorinated analogs **8** suggested that in the former the methylene bridge cannot pass over the halogen to the other face of the aromatic ring; thus, molecules **3a–c** are asymmetric and exist as *dl* pairs. This conclusion was confirmed by a study of the reaction of the *N*-oxide **5**, derived from **3a** (96% yield) by oxidation with hydrogen peroxide, with acetic anhydride (eq 2). The products,



5

syn-**6a** (32%) (2)

anti-**6b** (26%)

obtained subsequent to hydrolysis of the intermediate acetates, were the *syn*-alcohol **6a** (32%) and the *anti*-alcohol **6b** (26%). The conversion of 2-alkylpyridine *N*-oxide to the corresponding pyridinemethanols is well known;[7] the nonequivalence of the α-benzyl hydrogen atoms leading to the diastereomeric alcohols **6a** and **6b** confirms the asymmetry of the metacyclophane structure. This reaction is also attractive as a route for derivatives of **3** with functionality in the methylene side chain.

Both isomers of **6** are oxidized to the same ketone **7** with chromium trioxide in pyridine, which confirms the diastereomeric relationship of the isomeric alcohols. The hydroxyl group of the syn isomer (**6a**) was found to be completely intramolecular hydrogen bonded to nitrogen (ν_{OH} 3440 cm^{-1}), while the anti isomer exists entirely as free hydroxyl (ν_{OH} 3615 cm^{-1}). A model compound, *o*-chlorobenzyl alcohol, displayed no significant intramolecular hydrogen bonding.

Reduction of **7** with sodium borohydride gave predominantly the syn isomer (79% **6a**, 4.4% **6b**). The

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(1) Supported by the National Science Foundation, Grants GP-6169X and GP-11918.

(2) For the preceding article in this series, see W. E. Parham and R. W. Davenport, *J. Org. Chem.*, **35**, 0000 (1970).

(3) In part from the thesis of R. W. Davenport, The University of Minnesota, 1969.

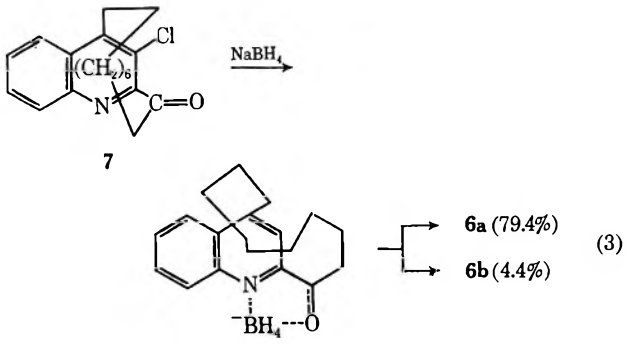
(4) W. E. Parham, R. W. Davenport and J. B. Biasotti, *Tetrahedron Lett.*, **7**, 557 (1969).

(5) W. E. Parham, D. R. Johnson, C. T. Hughes, M. K. Meilahn, and J. K. Reinhart, *J. Org. Chem.*, **35**, 1048 (1970).

(6) The mechanism for the conversion of **2** to **4** is thought to occur by phenyl migration in the intermediate carbonium ion prior to disrotatory ring opening, as discussed in ref 5 for cyclopropanes derived from related indenes.

(7) (a) V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954); (b) K. Biemann, G. Büchi, and B. H. Walker, *ibid.*, **79**, 5558 (1957).

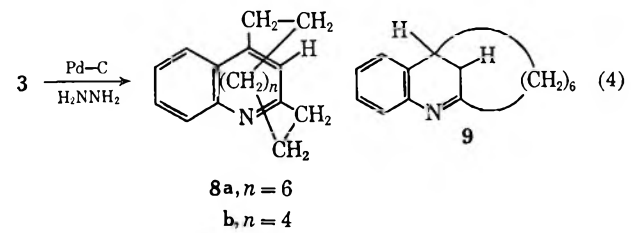
most probable transition state is shown in eq 3, in which the boron is partially bonded to both oxygen and nitrogen to become part of a five-membered ring. In order to obtain such a transition state, the carbonyl group must orient itself in the plane of the aromatic ring, and hydride attack is from the side opposite to the methylene chain.



(3)

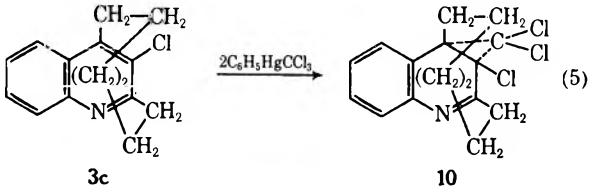
Reduction.—As the value of n in **3** is reduced progressively from 6 to 4 to 2, the nitrogen-containing aromatic ring becomes more strained and distorted from its normal planar configuration by the methylene bridge.[8] Chemical evidence for this conclusion was obtained by studies of the reduction of **3a–c**.

Both **3a** and **3b** were reduced (eq 4) with hydrazine on charcoal to the corresponding dechlorinated pyridinophanes **8a** and **8b** in 88 and 96% yield, respectively. Removal of the chlorine atom from **3a** and **3b** permits the methylene bridge to invert to either face of the aromatic ring.[9,10] The nitrogen containing ring in **3c** is evidently more strained and reactive, for, under identical conditions used for **3a** and **3b**, the nitrogen ring is reduced to give **9** (~100%). The structure of **9** was assigned on the basis of the composition of the derived picrate, and by its spectra (see Experimental Section, $\nu_{C=N}$ at 1622 cm^{-1}).



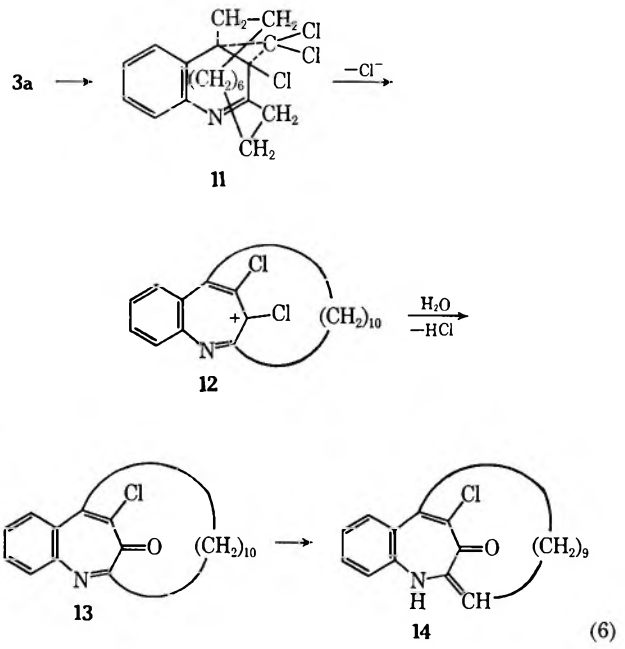
(4)

Reaction of 3 with Phenyl(trichloromethyl)mercury.—Deformation and increased reactivity of the aromatic ring in **3c** was also evidenced by comparison of the reaction of **3c** and **3a** with phenyl(trichloromethyl)-mercury as shown in eq 5 and 6. The cyclopropane **10** was first isolated as a minor product from the reaction of **1c** with phenyl(trichloromethyl)mercury, and its structure was assigned on the basis of the composition and spectra, and by its facile preparation (46%) by reaction of **3c** with phenyl(trichloromethyl)mercury. The cyclopropane **10** was quite stable in polar solvents and showed no tendency to undergo ring expansion, a conclusion consistent with the high degree of strain in products projected by normal ring expansion of the cyclopropane ring in **10**.



(5)

The only product isolated (8% yield by liquid chromatography) from a similar reaction of **3a** with phenyl(trichloromethyl)mercury, other than unchanged **3a** (31%), was assigned structure **14** on the basis of its composition and spectra, coupled with the logic of its formation as shown in eq 6. The derivative **13** is assumed to be formed from the adduct **11**, which is analogous to **10** formed from **3c**. In this case, however, the system is less strained by the larger methylene bridge; normal ring expansion with hydrolysis of the derived ion **12** would be expected to produce the ketone **13**. It is assumed that the initial product **13** undergoes prototropic isomerization to **14**, since **14**, but not **13**, is consistent with the observed spectral data.



(6)

Effect of Ring Strain on the Basicity of 3.—Although factors determining the basicity of amines have been thoroughly investigated,[11] there have been no studies which correlate base strength of aromatic heterocyclic amines with deformation of the nitrogen-containing ring.

The acid dissociation constants (pK_a) of **3a**, **3c**, and 3-chloro-2,4-dimethylquinoline were determined by potentiometric titration in 70% ethanol and are listed in Table I. The results suggest that deformation of the ring has no appreciable effect on basicity. As the process involved is one of equilibrium, these results suggest

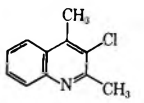
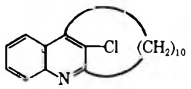
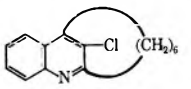
(8) This conclusion is supported by comparisons of nmr spectra and ultraviolet spectra as discussed in ref 4.

(9) This conclusion is supported by the nmr spectra of **3a–b** and **8a–b**; see Experimental Section.

(10) Similar results are described in ref 5 for the corresponding naphthalene analogs.

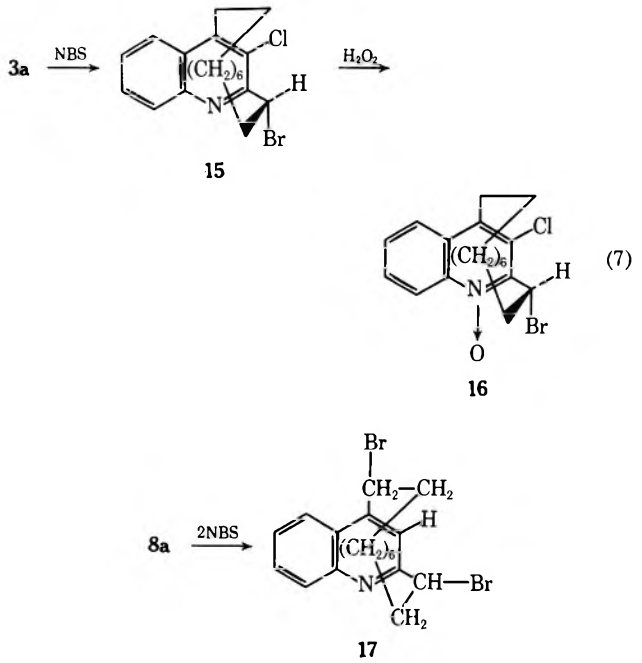
(11) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, Chapter 7.

TABLE I

Compd	pK_a
 3-Chloro-2,4-dimethylquinoline	3.04 ± 0.03
 3a	2.88 ± 0.03
 3c	3.03 ± 0.03

that the energy difference between the protonated and unprotonated forms of these three amines is small.[12]

Reaction of 3a and 8a with *N*-Bromosuccinimide.—The reaction **3a** with 1 equiv of *N*-bromosuccinimide gave a monobromo derivative (23% yield) which was assigned structure **15** (eq 7). Assignment of structure



15 as the syn isomer shown was made partially on the basis of steric considerations. Models showed that the alternate methylene position (C-10) to be hindered by the peri hydrogen and the chlorine atoms, respectively, and the epimeric anti position by the bridge and by the chlorine atom. Support for this conclusion was obtained by failure to detect a dibromo derivative when **3a** was treated with 2 equiv of *N*-bromosuccinimide; the yield of **15** was increased slightly to 30% in this case. Similarly, **15** was recovered unchanged (>69%) subsequent to attempted reaction with *N*-bromosuccinimide. Further support for structure **15** was the observation that the *N*-oxide **16**, derived from **15**, was recovered unchanged when heated with hot acetic anhydride under conditions identical with those used for the conversion of **5** to **6**. Lack of reactivity of the *N*-oxide is reasonable for **16**, but unlikely if the bromine atom was at the alternate methylene position (C-10).

One would expect that removal of the chlorine atom from **15** would sufficiently reduce the steric constraint of the pyridinophane to permit dibromination, and this was shown to be the case; **8a** reacted readily with 2 equiv of *N*-bromosuccinimide to give the dibromo derivative **17**, which was isolated in 47% yield. The bromine atoms in **15** and **17** are unreactive; **17** was recovered (88%) after 10 hr in hot acetic acid containing 5 mol equiv of potassium acetate.[13] The properties of halides of type **15** and **17** will be the subject of a subsequent report; however, these preliminary studies suggest that they can be compared qualitatively with bridgehead halides. Thus, there is steric interference to SN2 attack, and ionization of halogen is inhibited by the additional steric demands imposed when the ring methylene carbon changes from sp^3 to sp^2 hybridization.

Experimental Section

All nmr spectra, unless otherwise stated, were determined at 20% concentration (wt/v) on a Varian A-60 spectrophotometer; ultraviolet spectra were determined in 95% ethanol.

General Procedure for the Preparation of 3. 12,13-Benzo-16-chloro[10](2,4)pyridinophane (3a). A.—Phenyl(trichloromethyl)mercury (17.1 g, 43.2 mmol) and 2,3-cyclododecenoindole[14] (1a, 5.03 g, 19.7 mmol) were heated under a nitrogen atmosphere in refluxing anhydrous benzene (200 ml) for 44 hr. The mixture was cooled, filtered to remove phenylmercuric chloride (12.2 g, 90.2%), and concentrated to a dark brown oil (7.63 g). The residue was shaken with petroleum ether, filtered to remove additional phenylmercuric chloride, and chromatographed on alumina (200 g) using petroleum ether as initial eluent. Elution of the column with petroleum ether–ether (10%) gave the pyridinophane **3a** as a yellow oil (4.11 g, 69.1% yield) which solidified (mp 75.0–78.0°). The material was purified by conversion to the hydrochloride (3.83 g, 57.5%), white needles (mp 187–197°). The hydrochloride was suspended in water and ether and aqueous sodium hydroxide was added dropwise until the solution was alkaline. The ether layer was dried ($MgSO_4$) and concentrated to give nearly pure **3a** (3.29 g, 55.2% yield, mp 77–81.5°). Pure **3a** showed mp 81.5–82.5° (from methanol); uv max 235 mμ (ε 44,100), 285 (4250), 296 (4160), 309 (3980), and 323 (4200); ir (Nujol) 1579 (m), 1501, 1030 (m), and 771 cm^{-1} (s); nmr (CCl_4) τ 1.90–2.76 (m, 4.1, aromatic **H**) and 6.04–10.40 (very complex, 19.9, CH_2).

Anal. Calcd for $C_{19}H_{24}ClN$: C, 75.60; H, 8.01; Cl, 11.75; N, 4.64. Found: C, 75.87; H, 7.93; Cl, 11.95; N 4.59.

Picrate of 3a had mp 177–178° (from methanol).

Anal. Calcd for $C_{25}H_{27}ClN_4O_7$: C, 56.55; H, 5.13; Cl, 6.68; N, 10.55. Found: C, 56.57; H, 5.19; Cl, 6.84; N, 10.36.

Hydrochloride of 3a had mp 194–221° (from anhydrous ether–ethanol).

Anal. Calcd for $C_{19}H_{25}Cl_2N$: C, 67.45; H, 7.45; Cl, 20.96; N, 4.14. Found: C, 67.19; H, 7.58; Cl, 21.14; N, 3.99.

This procedure was employed to prepare **3a–3c**[4] and the properties of these pyridinophanes have been reported.

B.—1-Acetyl-2,3-cyclododecenoindole (1a, R = CH_3CO) was prepared by a modification of the procedure[15] by Atkinson, *et al.* The crude product (65% yield, mp 82–92°) was difficult to purify by recrystallization (petroleum ether at −78°, then petroleum ether and finally methanol) and considerable loss was encountered. Pure 1a (R = CH_3CO) (4.6 g, 15.8%, mp 113–

(12) The basicity of the amines is determined by the availability of the lone pair on nitrogen. Either the ring deformation is not enough to overcome other factors such as inductive effects of the alkyl groups, or there are compensating effects in base and conjugate acid. One would not expect *a priori* that these effects would be the same. Another possibility suggested by a referee, that has not been explored, is that the solvent may be introducing compensating errors.

(13) This is a general procedure for converting benzyl bromides to benzyl acetates: *cf.* W. Wenner, *J. Org. Chem.*, **17**, 523 (1952).

(14) Ng. Ph. Buu-Hoï, *J. Chem. Soc.*, 2882 (1949); L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, 7, 313 (1964); Ng. Ph. Buu-Hoï, P. Jacquignon, and T. B. Loc, *J. Chem. Soc.*, 738 (1958).

(15) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *ibid.*, 165 (1954).

114°) showed uv max 246 mμ (ε 15,900), 266 (sh) (11,100), 291 (sh) (5630), and 302 (5460); ir (Nujol) 1702 cm^{-1} (C=O); nmr (CDCl$_3$) τ 2.08–2.80 (m, 4.1, aromatic H), 6.76–7.39 (2 t and s, 6.8, allylic CH$_2$ and COCH$_3$), and 7.88–8.90 (m, 6.1, CH$_2$).

Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.91; H 9.06; N, 4.68.

The acetyl derivative **1a** (13.5 mmol) was reacted with phenyl(trichloromethyl)mercury (29.6 mmol) essentially as described above. The pyridinophane was eluted essentially pure (mp 81.0–81.5°, 75.8% yield) with petroleum ether–ether (10%).

When 1-acetyl-2,3-dimethylindole was employed, the crude 3-chloro-2,4-dimethylquinoline (55%, mp 64–68°) was easily purified (35.3%, mp 70–72.8°); when 2,3-dimethylindole was used, as in procedure A, the yield of pure 3-chloro-2,4-dimethylquinoline, mp 71–72.5°, was 35% (lit.[16] mp 73°).

C. Isolation of 10 and 4 (m = 6).—The dark brown residue obtained from 2,3-cyclooctenoindole[14] (**1c**, 20.0 g, 0.10 mol, procedure A) was chromatographed on alumina (800 g).

The adduct **10** was eluted from the column with petroleum ether–ether (5–8%) as a light brown solid (2.17 g, 6.6%) which melted at 125–126° (from petroleum ether, bp 30–60°): uv max 230 mμ (ε 23,100), 236 (sh) (20,300), 294 (5140), and 305 (sh) (3910); ir (Nujol) 1625 (s) (C=N), 1591 (m), 1565 (m), 1121 (m), 1050 (m), 1035 (m), 981 (s), 855 (m), 821 (m), 738 (m), and 755 cm^{-1} (s); nmr (CDCl$_3$) τ 2.64 (unresolved m, 3.9, aromatic H), 7.03–7.57 (m, 1.8, allylic CH$_2$), and 7.91–9.27 (m, 10.2, CH$_2$); mass spectrum m/e 327 (calcd mol wt, 327).

Anal. Calcd for $C_{16}H_{16}Cl_3N$: C, 58.47; H, 4.91; Cl, 32.36; N, 4.26. Found: C, 58.30; H, 5.00; Cl, 32.20; N, 4.19.

Elution of the column with petroleum ether–ether (15%) gave a mixture of **3c** and **4** (m = 6). The crude product was dissolved in petroleum ether, bp 30–60°, treated with charcoal, filtered through Celite, and crystallized at −78°. The pyridinophane **3c** melted at 60–65° (6.40 g, 26%) and at 67–68° after additional recrystallization. The mother liquor was recrystallized (petroleum ether at −78°) to give additional **3c** (1.48 g, 6.0% yield, mp 61–64°). The mother liquor was reprocessed to give 4-chloro-2,3-cyclooctenoquinoline (**4**) as yellow crystals (0.66 g, 2.7% yield, mp 73–77.5°). Pure **4** (m = 6) showed mp 82.5–83.0°; uv max 233 mμ (ε 53,500), 283 (5040), 288 (4980), 294 (4960), 299 (4230), 307 (5170), 311 (sh) (3320), 316 (sh) (3010), and 320 (6340); ir (Nujol) 1590, 1560, and 770 cm^{-1}; nmr (CDCl$_3$) τ 1.75–2.70 (m, 4.1, aromatic H), 6.67–7.10 (m, 3.6, benzylic CH$_2$), and 7.90–8.93 (m, 8.3, CH$_2$).

Anal. Calcd for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; Cl, 14.43; N, 5.70. Found: C, 73.35; H, 6.57; Cl, 14.39; N, 5.57.

12,13-Benzo-16-chloro[10](2,4)pyridinophane *N*-oxide (5) was obtained in 96% yield (mp 103–110°) by oxidation of **3a** with hydrogen peroxide[7] and showed mp 125–127° [chromatography (25–55% petroleum ether–ether) and recrystallization (petroleum ether)]; uv max 349 mμ (log ε 3.88), 334 (3.95), 250 (4.61), 241 (sh) (4.47), 234 (sh) (4.40), and 224 (4.32); nmr (25% CDCl$_3$) τ 0.74–0.99 (m, 1, aromatic H), 1.99–2.71 (m, 3, aromatic H), and 6.07–7.01 (m, 4, benzylic CH$_2$), and 7.45–10.03 (m, 16 CH$_2$).

Anal. Calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41; Cl, 11.15. Found: C, 72.05; H, 7.46; N, 4.15; Cl, 11.25.

12,13-Benzo-16-chloro[10](2,4)pyridinophan-1-ol (6).—The reaction of **5** (5.00 g) with acetic anhydride (20 ml) was effected for 15 hr at 100° by a procedure similar to that described by Biemann, Büchi, and Walker.[7b] The crude acetate was heated (reflux) in methanol (100 ml) containing aqueous (20%) potassium hydroxide and the crude alcohols (4.6 g, 92% yield, mp 139–158°) were chromatographed on neutral alumina (500 g) using petroleum ether–ether (15%) as initial eluent.

syn-**6a** (1.54 g, 30.8% yield, mp 154–158°) eluted first and showed mp 160–162° (petroleum ether–chloroform); uv max 323 mμ (log ε 3.82), 308 (3.78), 296 (3.81), 286 (3.83), 241 (sh) (4.80), 236 (4.84), and 216 (4.71); nmr (10% CDCl$_3$) τ 1.82–2.63 (m, 4, aromatic H), 4.40–5.05 (broad s, 2, CHOH, 4 lines when D$_2$O used as solvent), 6.22–6.92 (m, 2, benzylic CH$_2$), and 7.12–10.41 (m, 16, CH$_2$).

Anal. Calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41; Cl, 11.15. Found: C, 72.01; H, 7.76; N, 4.32; Cl, 10.91.

anti-**6b** (1.21 g, 24.2% yield, mp 202–204.5°) showed mp 205.5–207° (from petroleum ether–chloroform); uv max 326 mμ (log ε 3.62), 311 (3.58), 297 (sh) (3.62), 283 (3.68), 236 (4.73), and 218 (sh) (4.55); nmr (7% CDCl$_3$) τ 1.80–2.50 (m, 4, aromatic H), 4.67–5.20 (broad s, 2, CHOH, 4 lines when D$_2$O used as solvent), and 6.0–10.33 (m, 18, CH$_2$).

Anal. Found: C, 71.59; H, 7.60; N, 4.24; Cl, 10.95.

12,13-Benzo-16-chloro[10](2,4)pyridinophan-1-one (7).—Oxidation of **6a** or **6b** (500 mg) was effected with chromium trioxide in pyridine as described for related compounds.[7] The crude ketone was purified by chromatography on alumina (PF$_{254}$, eluent ether) and the ketone was purified (38.5 and 50% yield, respectively) from petroleum ether (bp 30–60°) to give pure **7**: mp 136–137.5; ir $\nu_{C=O}$ 1712 cm^{-1}; uv max 324 mμ (log ε 3.56), 310 (sh) (3.62), 291 (3.72), 236 (4.71), and 212 (4.54); nmr (10% DCCl$_3$) τ 1.75–2.67 (m, 4, aromatic H) and 6.45–10.30 (m, 18, CH$_2$).

Anal. Calcd for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; Cl, 11.22; N, 4.43. Found: C, 72.15; H, 6.93; Cl, 11.43; N, 4.19.

Preparation of 8. General Procedure.—The pyridinophane **3a** (0.579 g, 1.91 mmol) was reduced with hydrazine (5 ml) and palladium on charcoal (0.200 g, 10%) in absolute ethanol (50 ml) for 35 min according to the procedure of Mosby.[17] The crude product obtained from the ethanol showed one spot on tlc [R_f 0.29, silica gel HF254, petroleum ether–ether (10%)] and was chromatographed on alumina (50 g) using petroleum ether–ether (10%) as eluent to give **8a** (mp 60–61°) in 88% yield. Pure **8a** showed mp 62–63°; hydrochloride mp 230–234°; uv max 229 mμ (ε 45,100), 232 (sh) (41,100), 279 (4930), 289 (sh) (4660), 302 (3950), and 316 (4370); nmr (CCl$_4$) τ 1.87–2.88 (m, 4.0, aromatic H), 2.98 (s, 1.0, 16-H), 6.87–7.22 (m, 4.1, benzylic CH$_2$), and 7.88–9.40 (m, 15.9, CH$_2$).

Anal. Calcd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.24. Found: C, 85.36; H, 9.64; N, 5.20.

Anal. Calcd for $C_{19}H_{26}ClN$ (hydrochloride): C, 75.09; H, 8.63; Cl, 11.67; N, 4.61. Found: C, 75.05; H, 8.53; Cl, 11.44; N, 4.57.

The yield of **8b** was 96%; the properties of **8b** have been reported.[4]

4,5,6,7,8,9-Hexahydro-2,9-methano-3*H*-1-benzazacycloundecine (9).—Reduction of **3c** (0.500 g, 2.04 mmol) with hydrazine as described above for **3a** gave a yellow oil (0.422 g, 98.0% yield) of essentially pure **9**. The ir spectrum of the product was essentially identical with that of a sample further purified by preparative tlc [alumina PF254, petroleum ether–ether (10%) as eluent] and showed ir $\nu_{C=N}$ 1622 cm^{-1}; nmr (CCl$_4$) τ 2.67–3.15 (m, 3.8, aromatic H) and 7.00–9.00 (m, 15.2, CH and CH$_2$).

The amine **9** was unstable and was converted into the corresponding picrate: mp 167–169° (from methanol); mass spectrum m/e (relative intensity) 213 (30), 229 (10) (calcd mol wt of **12**, 213; of picric acid, 229). The mass spectrum of picric acid showed m/e 213 (1), 229 (10).

Anal. Calcd for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01; N, 12.66. Found: C, 56.74; H, 5.09; N, 12.69.

Preparation of 10.—The pyridinophane **3c** (0.500 g, 2.04 mmol) was treated with phenyl(trichloromethyl)mercury (0.806 g, 2.04 mmol) in dry benzene (80 ml) for 39 hr as described for the preparation of **3a**. The residue was extracted with chloroform and filtered to remove additional phenyl mercuric chloride; preparative tlc [silica gel PF254, petroleum ether–ether (5%) as eluent] gave crude **10** (0.305 g, 45.7% yield, brown oil), recovered **3c** (0.140 g, 28%) and four other minor products. The amine **10** was obtained with considerable loss of product by recrystallization from petroleum ether, bp 30–60° (mp 126–127°, mmp (with **10** from **1c**) 126–127°).

Reaction of 3a with Phenyl(trichloromethyl)mercury.—Chromatography [preparative tlc, silica gel PF254, petroleum ether–ether (10%)] of the crude product obtained by reaction of **3a** (0.400 g, 1.32 mmol) with phenyl(trichloromethyl)mercury (0.528 g, 1.33 mmol) as described above showed at least nine products. The major components were removed with chloroform–methanol (10%) and were A, recovered **3a** (30.8%) and B, a solid (mp 184–186°, 8% yield, from petroleum ether) which was assigned **14**: uv max 236 mμ (ε 19,400), 240 (19,700), 254 (17,200), 298 (6290), 312 (5740), and 325 (5200); ir (Nujol) ν_{NH} 3325 (broad), $\nu_{C=O}$ 1681 cm^{-1}; nmr (CDCl$_3$) τ 1.52–3.10 (m, 4.7, NH and aromatic H), 4.52–5.09 (m, 0.8, C=C—H), and 6.30–9.80 (m, 18.4, CH$_2$).

Anal. Calcd for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.34. Found: C, 72.90; H, 7.61.

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Basicity Studies.—Carefully purified samples of 3-chloro-2,4-dimethyl quinoline, **3a** and **3c**, were weighed into 50-ml volumetric flasks and dissolved in 35.00 ml of 95% USP ethanol. Water (carbonate free) was added to the mark and the solution was thermostated at 25° and titrated with 0.1 *N* ethanolic hydrochloric acid using a Radiometer automatic titration apparatus (type TTT1c), glass and calomel electrodes. The pK_a values were calculated from eq 8,[18] where C = initial concentration of

$$pK_a = pH + \log \frac{C/2 + [H^+]}{C/2 - [H^+]} \quad (8)$$

base; the values of pH and $[H^+]$ are those measured at the calculated half-neutralization point. No correction was made for the presence of ethanol in the solutions.

12,13-Benzo-1-bromo-16-chloro[10](2,4)pyridinophane (15).—A mixture of **3a** (2.0 g, 6.64 mmol), *N*-bromosuccinimide (1.18 g, 6.64 mmol), and carbon tetrachloride (30 ml) was heated at the reflux temperature and benzoyl peroxide (80 mg) was added in portions every 0.5 hr for 1.5 hr, and the mixture was heated at the reflux temperature under nitrogen for an additional 4 hr. The solid obtained by removal of solvent was chromatographed [neutral alumina, 250 g, petroleum ether–ether (10%) as eluent] to give **15** (23.5%): mp 149.5–151° (from petroleum ether, bp 30–60°); uv max 330 mμ (log ε 3.58), 316 (3.68), 303 (3.72), 295 (sh) (3.71), 240 (4.70), and 217 (4.58); nmr (15% in $CDCl_3$) τ 1.70–2.54 (m, 4, aromatic **H**), 3.78–4.10 (q, 1, CHBr), 6.30–6.70 (m, 2, benzylic CH_2), 7.03–10.42 (m, 16, CH_2).

Anal. Calcd for $C_{19}H_{23}ClBrN$: C, 59.93; H, 6.09; N, 3.68. Found: C, 60.19; H, 6.10; N, 3.64.

The yield of **15** was 30.5% when 2 equiv of *N*-bromosuccinimide was employed. Attempt to further brominate **15** with *N*-bromosuccinimide gave only **15** (69.3% recovered, mp and mmp 149–150°).

The *N*-oxide **16** was prepared from **15** (2.5 g, 6.6 mmol) and hydrogen peroxide as described above for **5**. The crude product (1.9 g) was chromatographed on neutral alumina (220 g) using petroleum ether–ether as eluent. There was obtained 1.3 g (52%) of recovered **15** and the *N*-oxide **16** (412 mg, 15.8%): mp 186–188° (from petroleum ether–chloroform); uv max 364 mμ (sh) (log ε 3.64), 345 (sh) (3.74), 333 (3.77), 258 (4.38), 244 (sh) (4.33), and 226 (sh) (4.23); nmr ($CDCl_3$) τ 1.09–1.30 (m, 1, aromatic H), 1.86–2.42 (m, 3, aromatic **H**), 3.77–4.09 (q, 1, CHBr), 6.30–7.00 (m, 2, benzylic CH_2), and 7.44–10.00 (m, 16, CH_2).

Anal. Calcd for $C_{19}H_{23}BrClNO$: C, 57.52; H, 5.84; N, 3.53. Found: C, 57.62; H, 5.94; N, 3.28.

12,13-Benzo-1,10-dibromo[10](2,4)pyridinophane (17).—Reaction of **8a** (6.70 g, 0.025 mol) with *N*-bromosuccinimide (8.9 g, 0.050 mol) was carried out as described for the preparation of **15**. The crude product was chromatographed on neutral alumina (750 g) using petroleum ether and petroleum ether–ether as eluent. There was obtained 5.0 g (47.1%) of the dibromo derivative (**17**): white crystals, mp 133.5–135° (from petroleum ether); uv max 322 mμ (log ε 3.51), 310 (3.61), 298 (3.64), 210 (sh) (3.54), 239 (4.51), and 213 (4.41); nmr ($CDCl_3$) τ 1.75–2.47 (m, 5, aromatic **H**), 4.06–4.33 (q, 1, CHBr), 4.62–4.90 (q, 1, CHBr), and 6.87–9.78 (m, 16, CH_2); picrate mp 183.5–185°.

Anal. Calcd for $C_{19}H_{23}Br_2N$: C, 53.67; H, 5.45; Br, 37.58; N, 3.29. Found: C, 53.70; H, 5.46; Br, 37.26; N, 3.12.

Anal. Calcd for $C_{25}H_{26}Br_2N_4O_7$ (picrate): C, 45.87; H, 3.98; N, 8.56. Found: C, 46.10; H, 3.85; N, 8.18.

Reduction of 7.—The pyridinophane **12** (1.0 g, 3.17 mmol) was treated with sodium borohydride (0.121 g, 3.17 mmol) in absolute ethanol (50 ml). The solution was heated (reflux) for 18 hr. Removal of solvent gave the crude product (0.92 g, 92.3%, mp 150–157°) of which 0.800 g was chromatographed [silica gel, 80 g, petroleum ether–ether (0–30%)] to give **6a** (0.635 g, 79.4% yield, mp and mmp 160.5–162.5°). Eluted second was **6b** (0.035 g, 4.4% yield, mp and mmp 205.5–207°).

Registry No.—**1a**, 25907-80-6; **3a**, 22200-39-1; **3a** picrate, 25866-33-5; **3a** HCl, 25866-34-6; **4**, 25866-35-7; **5**, 25907-81-7; **6a** *syn*, 25866-36-8; **6b** *anti*, 25907-82-0; **7**, 25859-31-8; **8a**, 22200-42-6; **8a** HCl, 25830-79-7; **9**, 25859-33-0; **9** picrate, 25859-34-1; **10**, 25859-35-2; **14**, 25859-36-3; **15**, 25859-37-4; **16**, 25859-38-5; **17**, 25859-39-6; **17** picrate, 25859-40-9.

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Stereochemistry of the Isomerization of *N*-Acyl-2,3-Disubstituted Aziridines to Δ²-Oxazolines

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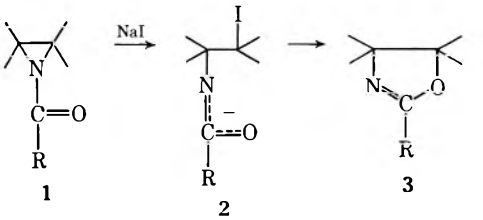
The iodide ion catalyzed isomerization of *cis*- and *trans*-1-acetyl and 1-aroyl-2,3-disubstituted aziridines to Δ²-oxazolines has been studied. The rearrangement is stereoselective, the selectivity being greater with *trans*-aziridines than with *cis*-aziridines. The former yield 90–95% *trans*- and 10–5% *cis*-Δ²-oxazolines while the latter give 40–90% *cis* and 60–10% *trans*. The selectivity of isomerization for *cis*-1-aroylaziridines was found to vary with the iodide ion concentration and the solvent system employed while the ratio of Δ²-oxazolines formed from the corresponding *trans*-aziridines was unaffected. Using tetrabutylammonium iodide as the isomerization catalyst also affected the Δ²-oxazoline isomer distribution. The stereochemical outcome of this reaction was found to be insensitive to the size of the 2,3-dialkyl substituents and to resonance effects. The ratio of isomers formed was determined by glpc, while stereochemical configurations were elucidated by means of nmr spectroscopy.

The rearrangement of *N*-acylaziridines (**1**) to the isomeric 2-aryl- or 2-alkyl-Δ²-oxazoline ring system (**3**) by nucleophiles such as iodide ion and thiocyanate ion has been the subject of a number of studies.[2–6] The mechanism of the iodide-catalyzed isomerization has been postulated as occurring by attack of the nucleophile on a carbon atom of the aziridine ring to produce



1 2 3

R = aryl or alkyl

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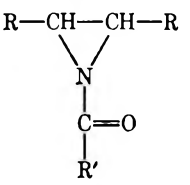
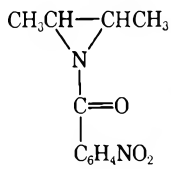
TABLE I

N-ACYLAZIRIDINES

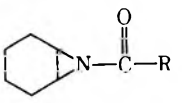


Compd	Stereochemistry	R	R′	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7a	cis	C_2H_5	C_6H_5	76.81	8.43	6.89	76.77	8.51	6.88
8a	trans	C_2H_5	C_6H_5	76.81	8.43	6.89	76.97	8 41	6.81
7b	cis	C_8H_{17}	C_6H_5	80.80	11.12	3.77	80.72	11.11	3.76
8b	trans	C_8H_{17}	C_6H_5	80.80	11.12	3.77	80.60	11.07	3.70
7c	cis	C_2H_5	CH_3	68.04	10.71	9.92	68.17	10.63	9.82
8c	trans	C_2H_5	CH_3	68.04	10.71	9.92	68.12	10.73	9.83
7d	cis	C_2H_5	p-$NO_2C_6H_4$–	62.89	6.50	11.28	62.87	6.53	11.42
7e	cis	C_8H_{17}	p-NO_2-C_6H_4–	72.08	9.68	6.72	71.93	9.52	6.66
7f	cis	C_8H_{17}	CH_3	77.61	12.70	4.53	77.65	12.77	4.50

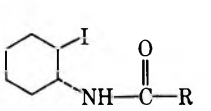
an intermediate *N*-2-iodoalkyl amido ion (2) which subsequently cyclizes to the oxazoline.[2,7] Such a mechanism predicts that rearrangement of *N*-acyl-2,3-disubstituted aziridines to 4,5-disubstituted Δ^2-oxazolines should be a stereospecific process.[7] Indeed, a stereospecific rearrangement has been observed for the iodide-catalyzed isomerization of *N*-*p*-nitrobenzoyl-2,3-dimethylaziridine[7] (4) and *N*-*p*-nitrobenzoylcyclohexylimine (5a).[8] In contrast, *N*-benzoylcyclohexylimine (5b) did not give the expected Δ^2-oxazoline isomer but *trans*-2-iodocyclohexylbenzamide (6) as the sole reaction product.[6,8]



4



5a, R = $C_6H_4NO_2$
b, R = C_6H_5



6 R = C_6H_5

In view of the limited number of examples of stereospecific isomerizations of *N*-acyl-2,3-disubstituted aziridines to Δ^2-oxazolines and the failure of *N*-benzoylcyclohexylimine to isomerize to this ring structure the present investigation was undertaken. We have studied the iodide ion induced isomerization of a number of *N*-acyl-2,3-disubstituted aziridines with respect to the stereochemical course of this reaction.

Experimental Section

Nmr spectra were obtained on a Jeolco CH-60 spectrometer.[9] Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (TMS). The samples were run as 10% solutions in chloroform-*d*. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrometer. Glpc was carried out on a Hewlett–Packard Model 810 gas chromatograph. Silica gel H (Brinkmann) was used for thin layer analyses. Spots were detected by heat charring after spraying with 50% sulfuric acid. Melting points were determined in a capillary and are uncorrected unless otherwise noted.

Preparation and Purity of Aziridines.—The synthesis of the aziridines used in this study was carried out by the iodine isocyanate route.[10,11] Their purity was shown to be >99% by gas–liquid (glpc) and thin layer chromatography (tlc) and by titration with perchloric acid.[12]

Preparation of 1-Aroylaziridines. General Procedure.—To a solution of the aziridine (1 equiv) and triethylamine (1.1 equiv) in benzene under an atmosphere of nitrogen gas was added a solution of the acid chloride (1 equiv) in benzene at 10–15°. The reaction mixture was stirred at ambient temperature for 1 hr, and then the triethylamine hydrochloride was filtered. The benzene filtrate was washed with dilute NaOH solution and water and dried, and the solvent was removed *in vacuo*.

***N*-Benzoyl-*cis*-2,3-diethylaziridine (7a).**—The crude benzoylaziridine obtained from *cis*-2,3-diethylaziridine and benzoyl chloride was chromatographed on Florisil. Elution with hexane gave the pure aziridine as a colorless oil, $n^{25}D$ 1.5216, in 73% yield: ir (neat) 3090 and 3025 (w) aziridine (C–H stretching), 1670 (s) carbonyl, 1315 and 1290 (s) cm^{-1}. The nmr spectrum consisted of two multiplets centered at 7.55 ppm (aromatic, 5 H), multiplets at 2.45 ppm (ring C–H, 2 H) and 1.60 ppm (methylene 4 H), and a triplet at 1.05 ppm (methyl 6 H). Elemental analysis is reported in Table I.

***N*-Benzoyl-*trans*-2,3-diethylaziridine (8a).**—Obtained from *trans*-2,3-diethylaziridine, the product was chromatographed on silica gel. Elution with 1% ether–benzene gave the aziridine as a colorless oil, $n^{25}D$ 1.5194, in 85% yield: ir (neat) 3095 and 3025 (w) aziridine, 1665 (s) carbonyl, and 1330 (s) cm^{-1}. Its nmr spectrum consisted of a multiplet centered at 7.60 ppm (aromatic, 5 H) and three multiplets centered at 2.40, 1.40, and 1.05 ppm in the ratio of 1:2:3.

***N*-*p*-Nitrobenzoyl-*cis*-2,3-diethylaziridine (7d).**—Obtained from the reaction of *cis*-2,3-diethylaziridine and *p*-nitrobenzoyl chloride, the pure product after recrystallization from methanol had mp 74–76°, 65% yield: ir (KBr) 3090 (m), 1660 (s) carbonyl, 1515 and 1340 (s) nitro, 1315 and 720 (s) cm^{-1}. The nmr spectrum consisted of 3 multiplets centered at 8.35 (5 H), 2.65 (2 H), and 1.80 (4 H) ppm and a triplet at 1.15 (6 H) ppm.

***N*-Benzoyl-*cis*-2,3-dioctylaziridine (7b).**—Obtained from the reaction of *cis*-2,3-dioctylaziridine[13] with benzoyl chloride, the crude product was chromatographed on Florisil. Elution with hexane gave the pure aziridine as a colorless oil, $n^{25}D$ 1.4940, in 85% yield: ir (neat) 3090 and 3025 (w) aziridine, 1675 (s) carbonyl, 1310 and 1280 (s) cm^{-1}. Its purity exceeded 99% as determined by tlc and ring titration.[12]

***N*-Benzoyl-*trans*-2,3-dioctylaziridine (8b).**—This compound was obtained from *trans*-2,3-dioctylaziridine.[13] Chromatography on Florisil, followed by elution with hexane gave the pure *N*-benzoylaziridine as a colorless oil, $n^{25}D$ 1.4940, in 90% yield:

(7) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31** 2662 (1966).

(8) P. E. Fanta and E. N. Walsh, *ibid.*, **30**, 3574 (1965).

(9) Mention of brand or firm names does not constitute an endorsement by the Department of Agriculture over others of a similar nature not mentioned.

(10) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

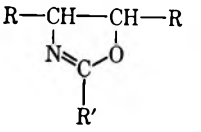
(11) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).

(12) G. Maerker, E. T. Haeberer, L. M. Gregory, and T. A. Foglia, *Anal. Chem.*, **41**, 1698 (1969).

(13) C. G. Gebelein, G. Swift, and D. Swern, *J. Org. Chem.*, **32**, 3314 (1967).

TABLE II

SUBSTITUTED Δ^2-OXAZOLINES



Compd	Stereochemistry	R	R′	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
9a	cis	C_2H_5	C_6H_5	52.78[a]	4.66[a]	12.96[a]	52.79[a]	4.45[a]	12.80[a]
10a	trans	C_2H_5	C_6H_5	52.78[a]	4.66[a]	12.96[a]	52.63[a]	4.44[a]	12.81[a]
9b	cis	C_8H_{17}	C_6H_5	80.80	11.12	3.77	80.92	11.29	3.64
10b	trans	C_8H_{17}	C_6H_5						
9c	cis	C_2H_5	CH_3	43.30[a]	5.19[a]	14.42[a]	43.22[a]	5.25[a]	14.27[a]
10c	trans	C_2H_5	CH_3	45.41[b]	4.90[b]	15.13[b]	45.62[b]	4.77[b]	15.18[b]
9d	cis	C_2H_5	p-NO_2-C_6H_4–	62.89	6.50	11.28	62.71	6.57	11.42
10d	trans	C_2H_5	p-NO_2-C_6H_4–	62.89	6.50	11.28	62.94	6.47	11.15
9e	cis	C_8H_{17}	p-NO_2-C_6H_4–	72.08	9.68	6.72	71.93	9.81	6.53
10e	trans	C_8H_{17}	p-NO_2-C_6H_4–						
9f	cis	C_8H_{17}	CH_3	77.61	12.70	4.53	77.82	12.77	4.51
10f	trans	C_8H_{17}	CH_3						

[a] Picrate salt monohydrate. [b] Picrate salt.

TABLE III

ISOMERIZATION OF *N*-AROYL-2,3-DIETHYLAZIRIDINES

Isomer	Δ^2-Oxazoline *cis*, %	Δ^2-Oxazoline *trans*, %	Solvent	Catalyst	Mole ratio, iodide:aziridine
cis-Benzoyl	53.1	46.9	Acetone	NaI	3.4:1
cis-Benzoyl	47.6	52.4	Acetone	NaI	5.0:1
cis-Benzoyl	75.0	25.0	Acetonitrile	NaI	5.0:1
cis-Benzoyl	57.6	42.4	Benzene	TBAI[a]	5.0:1
cis-Benzoyl	53.1	46.9	Acetone	TBAI	5.0:1
cis-Benzoyl	72.8	27.2	Acetonitrile	TBAI	5.0:1
cis-Benzoyl	78.8	21.2	2% water, acetone	NaI	5.0:1
cis-*p*-Nitrobenzoyl	58.5	41.5	Acetone	NaI	5.0:1
trans-Benzoyl	6.8	93.2	Acetone	NaI	3.4:1
trans-Benzoyl	7.2	92.8	Acetone	NaI	5.0:1

[a] Tetra-*n*-butylammonium iodide.

ir (neat) 3070 and 3015 (w) aziridine, 1670 (s) carbonyl, and 135 (s) cm^{-1}. Purity by tlc and by ring titration was >99%.

N-*p*-**Nitrobenozyl-*cis*-2,3-dioctylaziridine (7e)**.—The crude product from *cis*-2,3-dioctylaziridine and *p*-nitrobenzoyl chloride was chromatographed on Florisil. Elution with hexane gave the pure compound as a pale yellow oil, $n^{25}D$ 1.5070, in 81% yield: ir (neat) 3100 and 3050 (w), 1675 (s) carbonyl, 1525 and 1340 (s) nitro, 1300 (s), 1020, 870, and 850 (m) cm^{-1}. Its purity by tlc (methanol–ether–benzene, 1:13:86) and titration exceeded 99%.

N-**Acetyl-*cis*-2,3-diethylaziridine (7c)**.—The crude *N*-acetylaziridine obtained from *cis*-2,3-diethylaziridine and acetyl chloride was distilled: bp 40–41° (0.4 mm); $n^{25}D$ 1.4628; 93% yield; ir (neat) 2970 (s), 1690 (s) carbonyl, 1360 (m), 1290 and 1220 (s) cm^{-1}. The nmr spectrum showed a singlet (3 H) at 1.98 ppm, two multiplets centered at 2.28 (2 H) and 1.45 (4 H) ppm, and a triplet (6 H) centered at 1.05 ppm.

N-**Acetyl-*trans*-2,3-diethylaziridine (8c)**.—This compound was prepared from *trans*-2,3-diethylaziridine and acetyl chloride. The pure aziridine was obtained by distillation: bp 35° (0.25 mm); $n^{25}D$ 1.4575; 72% yield; ir (neat) 2960 (s), 1680 (s) carbonyl, 1365 (s), 1320 (s), and 1190 (s) cm^{-1}. The nmr spectrum showed a singlet (3 H) at 2.14 ppm and three multiplets centered at 2.18, 1.52, and 1.10 ppm in the ratio of 1:2:3.

N-**Acetyl-*cis*-2,3-dioctylaziridine (7f)**.—The crude product was obtained in nearly quantitative yield from the reaction of *cis*-2,3-dioctylaziridine and acetyl chloride. Chromatography on Florisil and elution with hexane gave the pure sample as a colorless oil: $n^{25}D$ 1.4545; 92% yield; ir (neat) 3080 and 3025 (w), 1690 (s) carbonyl, 1360, 1285, and 1215 (s) cm^{-1}. Its purity exceeded 99% by ring titration and tlc (methanol–ether–benzene, 3:13:84).

***cis*- and *trans*-4,5-Diethyl-2-phenyl-Δ^2-oxazoline (9a and 10a)**.—A solution of *N*-benzoyl-*cis*-2,3-diethylaziridine (**7a**, 1 mmol) and sodium iodide (5 mmol) in 25 ml of dry acetone was heated at reflux for 16 hr. The solvent was removed *in vacuo*, and the solid residue was extracted with hexane. Removal of the hexane gave a clear oil in nearly quantitative yield. Tlc of this residue showed the presence of only one component (R_f 0.55, methanol–ether–benzene, 7:13:80, starting material R_f 0.70). The ir spectrum contained an intense band at 1660 cm^{-1} which is generally characteristic of Δ^2-oxazoline structures.[14] Glpc of this material proved it to be a mixture of two components (ratio 48:52). They were separated by preparative glpc employing an 8 ft × 1/2 in. stainless steel column packed with 10% Carbowax 20M on Diatoport S 60–80 mesh at 180° with a helium flow of 150 ml/min.

The faster eluting component was identified as *trans*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**10a**) on the basis of its nmr spectrum (see Discussion). Its ir spectrum (neat) displayed bands at 2960 (s), 1650 (s) C=N, 1490 (m), 1450, 1345 (s), 1075 (m), 1060 (s), 1025 (s), 940 (m), 775 (m), and 690 (s) cm^{-1}. The picrate salt of this isomer had mp 133.5–134.5°. Elemental analysis is reported in Table II.

The slower component was identified as *cis*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**9a**) in analogous fashion as the trans isomer. Its ir spectrum (neat) showed bands at 2960 (s), 1656 (s) C=N, 1490 (m), 1450 (s), 1370 (m), 1345 (s), 1075 (m), 1060, 1025 (s), 940, 775 (m), and 690 (s) cm^{-1}. The picrate salt of this isomer had mp 144–145.5°. Elemental analysis is reported in Table II.

The isomerization of *N*-benzoyl-*trans*-2,3-diethylaziridine (**8a**) was carried out in the manner previously described for **7a**. This result as well as those obtained from the isomerization of the cis isomer under varying solvent and catalysis systems is summarized in Table III.

(14) A. R. Katritsky, Ed., "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p 218.

cis- and *trans*-**4,5-Diethyl-2-methyl-Δ²-oxazoline (9c and 10c).**—Isomerization of *N*-acetyl-*cis*-2,3-diethylaziridine (**7c**) to the isomeric Δ²-oxazoline structure was effected in the same manner as the isomerization of the *N*-benzoyl derivative **7a**. The crude product was distilled to give a clear oil, bp 42° (2 mm), yield 77%. Tlc of the distillate indicated one component (R_f 0.35, methanol–ether–benzene, 7:13:80, starting material R_f 0.61). The ir spectrum had a strong band at 1670 cm⁻¹. Glpc of this product, however, showed it to be a mixture of two components in 1:3 ratio. They were separated by preparative glpc employing an 8 ft × 1/2 in. stainless steel column packed with 10% Apiezon-L on Diatoport S 60–80 mesh at 125°, He flow 100 ml/min.

The minor component was identified as *trans*-4,5-diethyl-2-methyl-Δ²-oxazoline (**10c**) from its nmr spectrum (see Discussion). Its ir spectrum (neat) showed bands at 2960, 1670 (s) C=N, 1240 (m), 1225 and 950 (s) cm⁻¹. The picrate salt had mp 164–165°. Elemental analysis is reported in Table II.

The major component, *cis*-4,5-diethyl-2-methyl-Δ²-oxazoline (**9c**), was also identified on the basis of its nmr spectrum. Its ir (neat) displayed bands at 2960, 1670 (s) C=N, 1380 (s), 1260 (m), 1225 and 950 (s) cm⁻¹. The picrate salt had mp 131–132°. Elemental analysis is reported in Table II.

Table IV summarizes the results obtained on the isomerization of *N*-acetyl-*cis*- and -*trans*-3,4-epiminohexane under varying reaction conditions.

TABLE IV

ISOMERIZATION OF *N*-ACETYL-2,3-DIETHYLAZIRIDINES

Isomer	Δ²-Oxazoline, *cis*, %	Δ²-Oxazoline, *trans*, %	Solvent	Catalyst	Mole ratio, iodide: aziridine
cis	81.2	18.8	Acetone	NaI	2.4:1
cis	75.2	24.8	Acetone	NaI	4.7:1
cis	73.5	26.5	Acetonitrile	NaI	4.7:1
cis	48.9	51.1	Benzene	TBAI	4.7:1
trans	7.8	92.2	Acetone	NaI	4.7:1

cis- and *trans*-**4,5-Diethyl-2-*p*-nitrophenyl-Δ²-oxazoline (9d and 10d).**—The crude isomerization product of *N*-*p*-nitrobenzoyl-*cis*-2,3-diethylaziridine (**7d**) was found to be homogeneous by tlc (R_f 0.54, methanol–ether–benzene, 1:13:86, starting aziridine R_f 0.71). Glpc analysis, however proved the presence of two components in the ratio 3:2. Separation of the isomers was accomplished on a 6 ft × 1/4 in. column packed with 15% OV-1 at 220°, He flow 60 ml/min.

The less polar compound, *trans*-4,5-diethyl-2-*p*-nitrophenyl-Δ²-oxazoline (**10d**), was identified by comparison of its nmr spectrum with that of **10a**. The pure sample had mp 52–53°: ir (KBr) bands at 1640 (s) C=N, 1590 (s) C=C, 1155 and 1340 (s) NO_2, 1110, 1070 (s), 940, 850 (m), and 710 (s) cm⁻¹. Elemental analysis is reported in Table II.

The nmr spectrum of the more polar component established its structure as *cis*-4,5-diethyl-2-*p*-nitrophenyl-Δ²-oxazoline (**9d**). The pure compound had mp 78.5–80°: ir (KBr) bands at 1635 (s) C=N, 1595 (s) C=C, 1520 and 1340 (s) NO_2, 1075 (s), 930, 850 (m), and 700 (s) cm⁻¹.

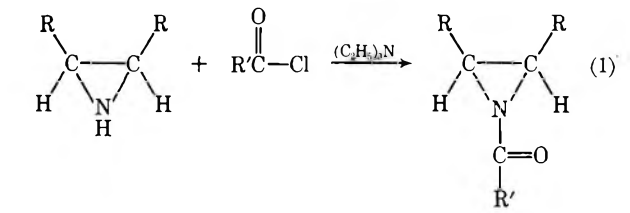
cis- and *trans*-**4,5-Dioctyl-2-phenyl-Δ²-oxazoline (9b and 10b).**—The crude isomerization product from *N*-benzoyl-*cis*-2,3-dioctylaziridine (**7b**) was chromatographed on a Florisil column. Elution with hexane gave the pure sample as a colorless oil, $n^{25}D$ 1.4943, in 92% yield. Tlc of this product indicated it to be homogeneous (R_f 0.58, methanol–ether–benzene, 1:13:86, starting material R_f 0.83). Its ir spectrum showed bands at 2830 (s), 1650 (s) C=N, 1080 (m), 1060 (s), 1025 (m), and 690 (s) cm⁻¹. Glpc of this oil on a 6 ft × 1/4 in. column packed with 10% Apiezon-L at 270°, He flow 60 ml/min, showed the presence of two components in ratio of 51:49. The two components were identified as the trans and cis isomers by comparison of their glpc retention times with authentic samples prepared by the thermal dehydration of the corresponding β-hydroxy amides.[15] Elemental analysis of the mixture is reported in Table II.

cis- and *trans*-**4,5-Dioctyl-2-methyl-Δ²-oxazoline (9f and 10f).**—Isomerization of *N*-acetyl-*cis*-2,3-dioctylaziridine (**7f**) was performed in the usual manner. The pure sample was obtained as a clear oil, $n^{27}D$ 1.4502, after chromatography on Florisil. Its ir spectrum (neat) showed absorption at 2960 (s), 1670 (s) C=N, 1385, 1375 (m), 1225 (s), 960 and 825 (m), cm⁻¹. Tlc showed this sample to be homogeneous (R_f 0.38, methanol–ether–benzene, 3:13:84, starting material R_f 0.58). Glpc of this oil on a 6 ft × 1/4 in. column packed with 10% Apiezon-L at 220°, He flow 60 ml/min, showed the presence of two components in ratio of 17:83. Identification as the trans and cis isomers was made by comparison of glpc retention times with authentic samples.[15] Elemental analysis of the mixture is reported in Table II.

cis- and *trans*-**4,5-Dioctyl-2-*p*-nitrophenyl-Δ²-oxazoline (9e and 10e).**—The crude product obtained from the isomerization of *N*-*p*-nitrophenyl-*cis*-2,3-dioctylaziridine (**7e**) was chromatographed on silica gel. Elution with benzene gave the pure product as a pale yellow oil, $n^{27}D$ 1.5077, in 77% yield. The material was homogeneous by tlc (R_f 0.52, ether–benzene, 5:95, starting material R_f 0.72). Glpc analysis on a 2 ft × 1/4 in. OV-17 column at 275°, He flow 60 ml/min, showed the presence of two closely related compounds in approximately equal amounts. The mixture was judged to consist of equal parts of the two isomeric oxazolines **9e** and **10e** by virtue of its elemental analysis (see Table II) and its ir spectrum (neat): bands at 2960, 1645 (s) C=N, 1600 (m) C=C, 1540 and 1340 (s) NO_2, 1075, 1015, 870, 850, 755, and 700 (m) cm⁻¹.

Results and Discussion

The acylated aziridines selected for this study were prepared by the reaction of the appropriate *cis*- or *trans*-dialkylaziridine obtained *via* the iodine isocyanate procedure,[10,11] with an acyl chloride in the presence of triethylamine (eq 1). Treatment of the *N*-acylaziridines (**7** and **8**) with sodium iodide in refluxing acetone gave the corresponding 2-alkyl- or 2-aryl-4,5-dialkyl-Δ²-oxazolines (**9** and **10**) in nearly quantitative yields as determined by tlc and ir (eq 2). Examination of the



(1)

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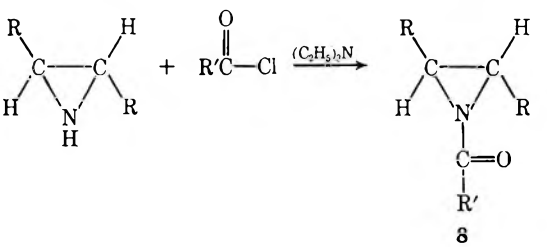

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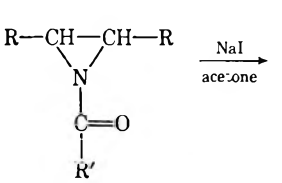

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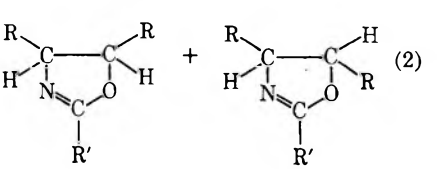

(2)

9 **10**

(15) W. E. Parker, private communication.

rearrangement products by analytical gas–liquid chromatography (glpc) showed that they were mixtures of the two geometric isomers, **9** and **10**. Mixtures of lower homologs of **9** and **10** were separated by preparative glpc and identified by elemental analysis, ir, and nmr. Higher homolog mixtures could be separated by analytical but not by preparative glpc, and in these cases the structures of the combined isomers were confirmed by elemental analysis and ir. The assignment of the stereochemistry of **9** and **10** was made from the nmr spectra of individual compounds as detailed below. In all glpc separations the trans isomer **10** was the faster eluting component.

The acylated aziridines which were studied are listed in Table I, and the resulting substituted Δ^2-oxazolines are shown in Table II. The rearrangement of the isomeric aziridines occurs with essentially equal facility, but the stereoselectivity of this conversion differs considerably for the cis and trans isomers. It is apparent from the data presented in Tables III–V that more than 90% of the Δ^2-oxazolines obtained have the trans configuration when *N*-aroyl-*trans*-aziridines are treated with sodium iodide in acetone. Under the same conditions the corresponding *cis*-aziridines give nearly equal amounts of *cis*- and *trans*-Δ^2-oxazolines. For instance, *N*-benzoyl-*trans*-2,3-diethylaziridine (**8a**) forms *trans*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**10a**) and the corresponding cis isomer **9a** in a ratio of 93:7. On the other hand, *N*-benzoyl-*cis*-2,3-diethylaziridine (**7a**) forms the same two oxazolines (**10a** and **9a**) in the ratio of 52:48.

TABLE V
ISOMERIZATION OF *N*-ACYL-2,3-DIOCTYLAZIRIDINES

Compd	—Δ^2-Oxazoline— *cis*-, %	*trans*-, %	Solvent	Catalyst	Mole ratio, iodide: aziridine
cis-*N*-Benzoyl	51.0	49.0	Acetone	NaI	5.0:1
cis-*N*-Acetyl	83.0	17.0	Acetone	NaI	5.0:1
cis-*p*-Nitrobenzoyl	60[a]	40[a]	Acetone	NaI	5.0:1
trans-*N*-Benzoyl	4.4	95.6	Acetone	NaI	5.0:1

[a] Estimated by glpc.

Isomerization of *N*-acetyl-*cis*- and -*trans*-2,3-diethylaziridines (**7c** and **8c**) also gave mixtures of *cis*- and *trans*-Δ^2-oxazolines. Again, the *trans*-aziridine (**8c**) gave predominantly *trans*-Δ^2-oxazoline, the ratio of **10c** to **9c** being 92:8. On the other hand, the *cis*-aziridine (**7c**) gave mostly *cis*-oxazoline, with a **10c** to **9c** ratio of 20:80. It therefore appears that the *cis*-alkanoylaziridines show a greater degree of stereoselectivity than the *cis*-aroyl derivatives.

The nmr data upon which the configurations of the 2-phenyl- and 2-methyl-4,5-diethyl-Δ^2-oxazolines are based are shown in Table VI. *trans*-4,5-Diethyl-2-phenyl-Δ^2-oxazoline (**10a**) showed protons H_a and H_b as quartets (J = 6.5 Hz) centered at 4.22 and 3.78 ppm, respectively. Since the coupling constant between H_a and H_b is of the same order of magnitude as the methylene coupling with H_a and H_b, all protons appear as equivalent hydrogens. Accordingly, H_a and H_b are observed as quartets. The more polar component of the mixture, *cis*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**9a**), was also identified from analysis of its nmr spectrum (Table VI). In this isomer protons H_a and H_b are seen at 4.62 and 4.10 ppm, respectively, as double triplets owing to the coupling of H_a with H_b (J_{ab} = 8.5 Hz) and each line being further coupled to the adjacent methylene protons ($J_{ac} = J_{bc}$ = 6.5 Hz). The observed difference in chemical shift of protons H_a and H_b in the two isomers is ascribed to the shielding effect of the alkyl groups attached to the adjacent carbon atoms in the trans isomer. The assignment as a cis or trans structure is made on the basis of the magnitude of the observed coupling constant between protons H_a and H_b in the two isomers. The trans configuration is assigned to the isomer with J_{ab} = 6.5 Hz while the isomer with J_{ab} = 8.5 Hz is assigned the cis configuration. This assignment of configuration is made by analogy with what has been previously observed in other five-membered heterocyclic ring systems, namely that cis proton coupling is generally larger than trans proton coupling.[16,17]

Further comment on the nmr spectra of the Δ^2-oxazolines would seem in order in view of what has been previously reported by Nishiguchi, *et al.*[18] These authors have reported that for *cis*- and *trans*-4,5-dimethyl-2-anilino-Δ^2-oxazoline the methine protons H_a and H_b appear as quintets with J_{ab} = 6.0 Hz for both isomers. Similar nmr spectral patterns were also observed for H_a and H_b in the corresponding sulfur analogs, *cis*- and *trans*-4,5-dimethyl-2-anilino-Δ^2-thiazoline. In these compounds the methine coupling constants were reported as 6.5 Hz for the cis derivative and 6.0 Hz for the trans isomer. Comparison of these J values with those observed in the present investigation reveals an apparent discrepancy in the methine coupling constant of *cis*-Δ^2-oxazolines. The observed J values for cis coupling in the present study were found to be on the order of 8.5 to 9.0 Hz, in contrast to the 6.0 and 6.5 Hz values previously reported. The J values for trans coupling are found to be of the same magnitude in both studies, being on the order of 6.0–6.5 Hz. This disparity in the magnitude of cis proton coupling in 4,5-disubstituted Δ^2-oxazolines cannot be explained at the present time until further work has been carried out to establish the general value of cis methine coupling.

To determine if a substituent effect could alter the stereochemical course of this iodide catalyzed isomerization of *N*-aroylaziridines, it was deemed advantageous to study the isomerization of *p*-nitrobenzoyl-*cis*-2,3-diethylaziridine (**7d**). This compound is structurally similar to those studied by Heine which reportedly rearranged stereospecifically.[7] Examination of the crude isomerization product of **7d** by glpc however confirmed the presence of two components (Table III). These materials were isolated and found to be the cis and trans isomers of 2-*p*-nitrophenyl-4,5-diethyl-Δ^2-oxazoline (**9d** and **10d**) by ir and elemental analysis. The assignment of stereochemistry was made by analysis of protons H_a and H_b in their nmr spectra and from their mass spectral fragmentation patterns.[19]

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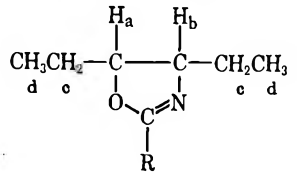
TABLE VI

NMR SPECTRA OF Δ^2-OXAZOLINES



Compd	H_a	H_b	H_c	H_d	R
trans-10a R = C_6H_5	4.22, quartet, $J_{ab} = J_{ac} = 6.5$ Hz	3.78, quartet, $J_{ba} = J_{bc} = 6.5$ Hz	1.64 (m)	0.98 (m)	7.38 (m) and 8.00 (m)
cis-9a R = C_6H_5	4.62, double triplet, $J_{ab} = 8.5$ Hz, $J_{ac} = 6.5$ Hz	4.10, double triplet, $J_{ba} = 8.5$ Hz, $J_{bc} = 6.5$ Hz	1.66 (m)	1.04 (t), $J_{dc} = 7.5$ Hz	7.44 (m) and 8.02 (m)
trans-10c R = CH_3	4.02, quartet, $J_{ab} = J_{ac} = 6.0$ Hz	3.54, quartet, $J_{ba} = J_{bc} = 6.0$ Hz	1.54 (m)	0.94 (t) $J = 7.5$ Hz	1.94
cis-9c R = CH_3	4.42, double triplet, $J_{ab} = 9.0$ Hz, $J_{ac} = 7.0$ Hz	3.90, double triplet, $J_{ba} = 9.0$ Hz, $J_{bc} = 7.0$ Hz	1.52 (m)	1.04 (m)	1.94

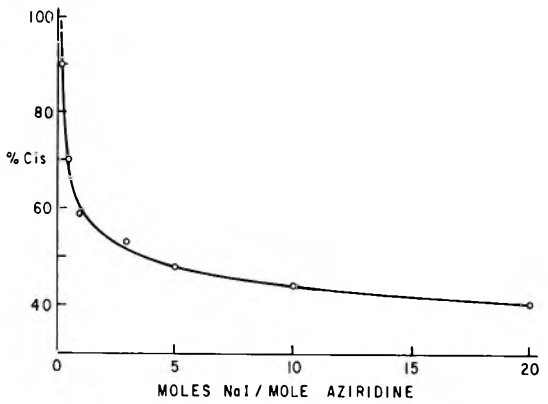


Figure 1.—Plot of per cent *cis*-oxazoline (**9a**) formed *vs.* mole ratio of NaI to aziridine (**7a**).

Verification that the above results were not caused by thermodynamic equilibration of the *cis*- and *trans*-oxazolines was obtained by subjecting the pure *cis*- and *trans*-2-*p*-nitrophenyl-Δ^2-oxazolines (**9d** and **10d**) to the reaction conditions. Glpc examination of the resulting reaction products confirmed the stability of the individual oxazoline isomers in that the presence of the other isomer could not be detected.

To determine whether the *cis*-:*trans*-oxazoline ratio could be affected by a change in the iodide ion concentration, the isomerization of *cis*-*N*-benzoyl-2,3-diethylaziridine (**7a**) with varying concentrations of iodide ion was studied. As can be seen from Figure 1 a pronounced change in the *cis*-:*trans*-oxazoline ratio was observed. At very high concentrations of iodide ion the amount of *cis*-oxazoline (**9a**) appears to approach a level of about 40%, while at very low concentrations of iodide ion the amount of *cis*-oxazoline (**9a**) formed increases asymptotically until nearly total selectivity is observed. As anticipated, it was found that as the iodide ion concentration decreased the rate of isomerization also decreased. For instance, at an iodide concentration of 0.1 mol–1.0 mol of aziridine less than 50% of the starting aziridine was isomerized after 60 hr of reaction. From the above data it can be concluded that the concentration of iodide ion not only affects the rate of isomerization, but more importantly that it can drastically alter the stereochemical outcome of the isomerization of *cis*-*N*-aroylaziridines to the isomeric Δ^2-oxazoline derivatives.

In order to determine whether the size of the alkyl substituents on the aziridine ring in any way influenced the stereoselectivity of the isomerization, the reactions of *N*-acyl-*cis*- and -*trans*-2,3-dioctylaziridine with iodide ion were investigated. As observed for the 2,3-diethylaziridine derivatives isomerization of *N*-phenyl-*cis*-2,3-dioctylaziridine (**7b**) gave a mixture of two components which were identified as the *trans*- and *cis*-4,5-dioctyl-2-phenyl-Δ^2-oxazoline isomers (**10b** and **9b**). The structural assignments were made on the basis of their glpc retention times (trans isomers less polar than cis isomers), elemental analysis, and mass spectral fragmentation data.[19] Isomerization of the trans isomer **8b** also gave a mixture of the two Δ^2-oxazolines, but as for the lower homolog a larger degree of stereoselectivity was observed (Table V). Also studied was the isomerization of *N*-acetyl- and *N*-*p*-nitrobenzoyl-*cis*-2,3-dioctylaziridine (**7f** and **7e**). The results obtained from the isomerization of these derivatives were comparable with the data obtained from the diethyl derivatives. The conclusion to be drawn from the above experiments is that the size of the alkyl substituent on the aziridine ring appears to have little if any effect in altering the stereochemical course of the iodide ion catalyzed isomerization of 2,3-dialkyl-*N*-acylaziridines to the isomeric Δ^2-oxazoline derivatives.

In order to determine whether solvent effects could be observed, the isomerization of the *N*-benzoyl-2,3-diethylaziridines (**7a** and **8a**) was repeated in acetonitrile and in acetone containing 2% water. No change was observed in the rearrangement of the *trans*-aziridine (**8a**), but for the cis isomer **7a** the change in solvent caused an increase in the amount of *cis*-oxazoline (**9a**) from 48% to 75–79% (see Table III). Increasing the water content in acetone further, however, had no addi-

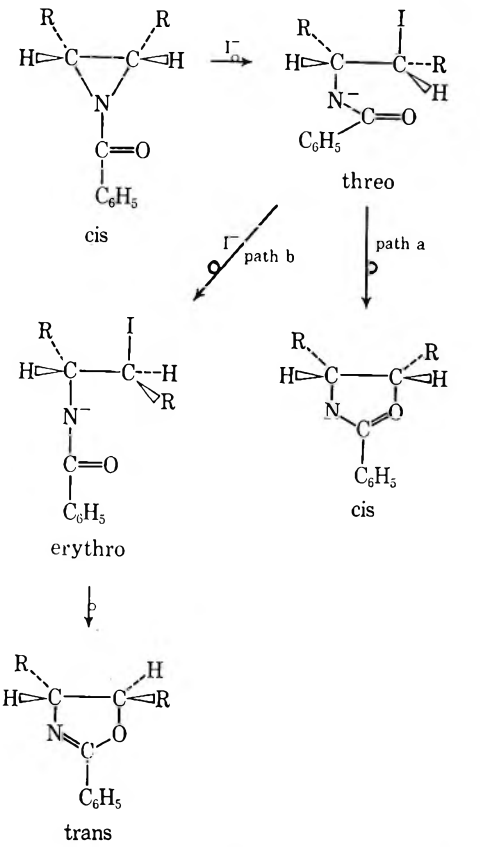
tional effect on the isomer distribution. For *N*-acetyl-*cis*-3,4-epiminohexane (**7c**) no change in isomer distribution was observed in going from acetone to acetonitrile solvent. The effect of water on the *N*-acetyl isomers could not be determined because of the propensity of 2-methyl-4,5-diethyl-Δ^2-oxazolines to hydrolyze.

Tetra-*n*-butylammonium iodide (TBAI), a catalyst which has been used previously in the rearrangement of aziridines to Δ^2-oxazolines,[20] was tested as an alternate source of iodide in acetone, acetonitrile, and benzene solution. TBAI and sodium iodide give similar results when applied to *N*-benzoyl-*cis*-2,3-diethylaziridine (**7a**) and to *N*-acetyl-*cis*-2,3-diethylaziridine (**7c**) in either acetone or acetonitrile solution. However, reaction of TBAI in benzene with acylated *cis*-aziridines results in a loss of selectivity in that a 1:1 mixture of *cis*- and *trans*-oxazolines is formed.

A mechanism which accounts for the lack of stereospecificity in the iodide ion catalyzed isomerization of *N*-acylaziridines, and which rationalizes the greater stereoselectivity observed in the rearrangement of the *trans*-aziridines than the *cis*-aziridines, is shown in Scheme I, using a *cis*-*N*-benzoylaziridine as a prototype. The initial step involves attack of the nucleophile on one of the carbon atoms of the aziridine ring with inversion of configuration to produce an intermediate *threo*-*N*-2-iodoalkylbenzamido ion. This ambident ion can now recyclize by a second nucleophilic inversion on the carbon atom bearing iodine to the *cis*-Δ^2-oxazoline structure (path a). An alternative reaction pathway for this threo intermediate, however, is for it to undergo an identity reaction (S$_N$2) with a second iodide ion to give the diastereomeric *erythro*-*N*-2-iodoalkylbenzamido ion (path b). The so-produced erythro intermediate can then cyclize to the isomeric *trans*-Δ^2-oxazoline. This proposed interconversion of threo–erythro isomers by various nucleophiles has been previously observed in other reaction processes.[6,10,16]

The lower stereoselectivity observed in the iodide catalyzed isomerization of *cis*-2,3-dialkyl-substituted *N*-acylaziridines can be attributed to a higher degree of crowding of alkyl groups in the intermediate *threo*-*N*-2-iodoalkylbenzamido ion in approaching the transition state leading to Δ^2-oxazoline formation (trans–anti parallel arrangement of the iodine and benzamido group). Thus in the intermediate, *threo*-*N*-2-iodoalkylbenzamido ions, the identity reaction appears to become more competitive with ring closure than in the corresponding erythro isomers.

SCHEME I



Registry No.—**7a**, 25942-96-5; **7b**, 25942-98-7; **7c**, 25942-99-8; **7d**, 25943-00-4; **7e**, 25943-01-5; **7f**, 25943-02-6; **8a**, 25942-97-6; **8b**, 25943-03-7; **8c**, 25943-04-8; **9a**, 25943-05-9; **9a** (picrate), 25943-06-0; **9b**, 26015-58-7; **9c**, 25943-07-1; **9c** (picrate), 26015-57-6; **9d**, 25943-08-2; **9e**, 25943-09-3; **9f**, 25943-10-6; **10a**, 25943-11-7; **10a** (picrate), 26015-59-8; **10b**, 25943-12-8; **10c**, 25943-13-9; **10c** (picrate), 25943-14-0; **10d**, 25943-15-1; **10e**, 25943-16-2; **10f**, 25943-17-3.

Acknowledgment.—The authors would like to thank Mrs. M. T. Lukasewycz and Mrs. Annette Kravitz for performing the carbon, hydrogen, and nitrogen analyses.

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Competitive Isomerization and Dealkylation of 2,4-Dialkoxypyrimidines in Aqueous and Nonaqueous Media[1]

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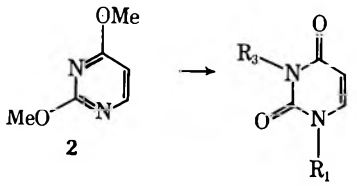
The competitive reactions of lactim–lactam isomerization and dealkylation of several 2,4-dialkoxypryimidines have been observed for the first time in aqueous solutions in the pH range of 1–5. In strong acids or alkali or at a high dilution of the pyrimidine base, dealkylations are singularly important. A rationale is presented for the specific partial hydrolysis of the 2-methoxy group in acid and the 4-methoxy moiety in basic conditions. Isomerizations are favored in nonaqueous media where dealkylations are limited to alkyl oxygen bond cleavage. Aqueous acid treatment of an equimolar mixture of 2,4-dimethoxy- (**2**) and 2,4-diethoxypyrimidine (**6**) confirms the intermolecular nature of the O → N alkyl migration. The alkyl rearrangement cannot be initiated by benzoyl peroxide and the reaction is postulated to proceed *via* alkylation of the free base pyrimidine at N_1 by the conjugate acid. The quaternary intermediate either dealkylates to the *N*-alkyl lactam or catalyzes further rearrangement.

Spectral and X-ray investigations[2] have shown conclusively that uracil (**1**) exists predominantly in the lactam form as pyrimidine-2,4-dione. The preference for the lactam structure is generally true of heterocycles containing an amide moiety.[3] Thus, there exists in 2,4-dimethoxypyrimidine (**2**) which contains two imidate groups a driving force to attain the keto structure by O-demethylation and/or O → N methyl migration to yield products **1**, **3**, **4**, **5**, etc., under appropriate conditions.



2

1, $R_1 = R_3 = H$
3, $R_1 = Me$, $R_3 = H$
4, $R_1 = H$, $R_3 = Me$
5, $R_1 = R_3 = Me$

We wish to report the novel finding of the competitive reactions of dealkylation and lactim–lactam isomerization of several 2,4-dialkoxypyrimidines in aqueous and nonaqueous media, and detail the reactivities of the pyrimidine lactim ethers under a variety of conditions. The results are relevant to the synthetic use of heteroaromatic lactim ethers such as in the Hilbert–Johnson procedure for the preparation of pyrimidine nucleosides,[4] and in the isolation of alkylated bases[5] from nucleic acid fractions which require aqueous acid treatments.[6]

Results and Discussion

Analyses of the dealkylation and isomerization products of 2,4-dimethoxy- (**2**), 2,4-diethoxy- (**6**), and 2,4-dimethoxy-5-methylpyrimidine (**7**) were carried out mainly by thin layer and gas–liquid phase chromatography. Major products were identified by actual isolation by preparative tlc and glpc and conventional means. These chromatographic methods in conjunction with uv and nmr spectroscopy for characterization of the isolated products permit an accurate identification and quantitation of the reaction products. A total of 21 mono- and dialkyl derivatives of uracil and thymine were prepared and characterized (*cf.* Experimental Section).

Aqueous Media —The isomerization of heteroaromatic lactim ethers to *N*-alkyl lactams has been effected by heating,[7] the catalytic function of the common alkylated cation,[8] and alkyl halides.[9] Treatment of 2,4-dialkoxypyrimidines with alkyl halide was first discovered by Hilbert and Johnson[10] to yield the isomerized products 1-alkyl-4-alkoxy-2-pyrimidones. Variations of the procedure include the use of Lewis acids[11] such as mercuric salts in aprotic solvents. Mineral acids have not been known to cause isomerization of any heteroaromatic lactim ether, and aqueous hydrochloric and sulfuric acids are routinely employed for the hydrolysis of alkoxypyrimidines.[12,13]

Our present study shows that dealkylation and isomerization of 2,4-dialkoxypyrimidines can occur concurrently under certain aqueous acid conditions. In refluxing 0.1 *N* aqueous hydrochloric acid, the pyrimidine lactim ether **2** at 0.18 *M* concentration and pH 2.7 gave rise to a substantial amount of the *N*-methylated products 1-methyl-4-methoxy-2-pyrimidone (**8**) and 1-

* To whom correspondence should be addressed.

(1) Support of this work by the Public Health Service Grant CA-10142 is gratefully acknowledged. Portion of this work was presented at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967.

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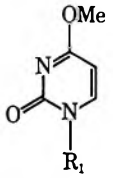
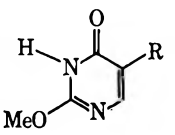
methyluracil (3) in addition to the demethylated compounds 4-methoxy-2-pyrimidone (9) and uracil (1).



8, R_1 = Me
9, R_1 = H



10, R = H
15, R = Me

In Table I is summarized the concentration effects of the pyrimidine 2 on the course of the two competing

Table I

Reaction of 2,4-Dimethoxypyrimidine (2) in 0.1 *N* Aqueous Hydrochloric Acid (100°, 3 Hr)

Concn, *M*	pH	Recovered 2, %	Mol % of products 8	3	9	1
0.018	1.1	21.1				100
0.18	2.7	38.8	13.5	16.2	1.4	68.9
0.18[a]	2.8	12.2	8.0	6.8		85.1
1.80	3.8	60.2	67.4	...[b]	...[b]	32.6

[a] Benzoyl peroxide (0.1 equiv) was added. [b] Trace amount detectable by glpc and tlc.

reactions. At 0.18 *M* concentration, the relative rate of O → N methyl migration to hydrolysis is 0.42. The ratio decreases to zero upon tenfold dilution but increases to 2.06 at ten times the original concentration. Since there was no 2-methoxy-4-pyrimidone (10) isolated at any stage of an acid treatment, and subjecting 4-methoxy-2-pyrimidone (9) to the same acid conditions produced only uracil (1), it appears that 1-methyluracil (3) does not owe its origin to either 9 or 10. It is reasonable to assume that 3 was derived from the "Hilbert–Johnson product" 8 for prolonged heating of 2 in acid led to a decrease of 8 with concomitant increase of 3. Thus, the isomerization products 8 and 3 were derived independent of the hydrolysates 9 and 1 and the reverse must also be true.

The reactivities of 2,4-dimethoxypyrimidine (2) and 2,4-dimethoxy-5-methylpyrimidine (7) in acids are compared in Table II. The bases were readily soluble

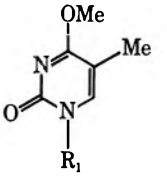
Table II

Comparison of the Reactions of 2,4-Dimethoxypyrimidines in Acids

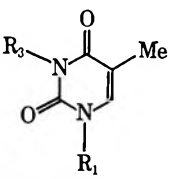
	pH	Pyrimidines recovered, %	Mol % of products			
A. 2,4-Dimethoxypyrimidine (2)			8	3	9	1
...[a]	4.1	25.1		27.5		72.5
...[b]		57.7	50.2	20.9	13.8	15.0
B. 2,4-Dimethoxy-5-methylpyrimidine (7)			11	12	13	14
...[a]	3.7	26.6	5.2	58.2	8.1	28.4
...[b]		21.3	68.7		24.3	7.0

[a] Pyrimidines (0.18 *M*) in 0.01 *N* HCl in 50% aqueous dioxane at 100° for 72 hr. [b] Pyrimidines (0.18 *M*) in 0.1 *N* HCl in anhydrous methanol under reflux for 48 hr.

in 0.01 *N* hydrochloric acid in 50% aqueous dioxane. A 0.18 *M* solution of the pyrimidine ether 7 was allowed to reflux for 72 hr. The isomerization products 1,5-dimethyl-4-methoxy-2-pyrimidone (11) and 1-methylthymine (12) outweighed the hydrolysis products 4-methoxy-5-methyl-2-pyrimidone (13) and thymine (14) by a factor of 1.73. The same reaction for the pyrimidine ether 2 gave a much smaller ratio of 0.38.



11, R_1 = Me
13, R_1 = H



12, R_1 = Me; R_3 = H
14, R_1 = R_3 = H

The pyrimidine ethers are practically inert when heated at reflux in 10^{-3} *N* acid (pH of 0.18 *M* solution 7.3) or in 0.1 *N* aqueous sodium hydroxide. In refluxing 5 *N* base prepared in 50% aqueous methanol, hydrolysis of the pyrimidine ethers 2 and 7 took place but no *N*-methylated products were produced. Apparently there is no base-catalyzed isomerization. It is interesting to note that thermal rearrangement (~200°) of 2-[14] and 4-alkoxypyrimidines[15] to 1-alkyl-2-pyrimidones and 3-alkyl-4-pyrimidones, respectively, are accelerated by tertiary bases, whose efficiencies vary according to their basic strengths. Since the aqueous base reactions of 2 and 7 were attempted at much lower temperature, the lack of isomerization may not be unexpected. Thus refluxing 2 for 48 hr in the 5 *N* base led to 68.1% yield of the following pyrimidines: 4-methoxy-2-pyrimidone (9) 2.3%, 2-methoxy-4-pyrimidone (10) 87.9%, and uracil (1) 9.8%. Similarly a 71.5% yield of hydrolysis products was obtained from the 5-methylpyrimidine 7: 4-methoxy-5-methyl-2-pyrimidone (13) 2.3%, and 2-methoxy-5-methyl-4-pyrimidone (15) 97.7%. The attack of the hydroxide anion appears to be selective at the 4 position of both 2 and 7; the 5-methyl group of the latter apparently poses no steric problem to the approaching nucleophile. Further hydrolysis of 10 and 15 to uracil or thymine was very slow indicating the lack of reactivity of the 2-methoxy group in alkaline conditions. Thus, the base treatment of 2,4-dimethoxypyrimidines constitutes a practical preparation of 2-methoxy-4-pyrimidones. The 4-methoxypyrimidines have been shown[16] to be more reactive in aminolysis than the 2-methoxy isomers and explanation has been advanced on the ground that approach of the amine nucleophile is discouraged at the 2 position by electronic repulsion by the two flanking nitrogen atoms. The anionic hydroxide would be expected to meet even more adamant opposition. This greater displaceability of the 4-methoxy group may also be attributed to maximal dispersal of the negative charge in the transition state favoring reaction opposite to rather than adjacent to the activating center.[17]

Nonaqueous Media.—In nonaqueous medium isomerization becomes very competitive. Alcoholic hydrogen chloride has been used[18] in the dealkylation of alkoxypyrimidines in the synthesis of pyrimidine nucleo-

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TABLE III

REACTION OF 2,4-DIMETHOXYPYRIMIDINE (2) WITH SODIUM IODIDE

Conditions, °C (hr)	Medium[a]	% yield of products	Mol % of products 5	8	3	9	1
100 (15)	2,4-Pentanedione	27.0		46.5	7.1	39.6	6.7
120 (15)	2,5-Hexanedione	45.1	100				
100 (15)	2,5-Hexanedione	40.0	48.0	52.0			
100 (15[b])	2,5-Hexanedione	64.7	8.3	53.8	37.9		

[a] Compound 2 (0.18 *M*) was dissolved. [b] Benzoyl peroxide (0.1 equiv) was added.

TABLE IV

REACTION OF EQUIMOLAR MIXTURE OF 2,4-DIMETHOXY- (2) AND 2,4-DIETHOXYPYRIMIDINE (6)

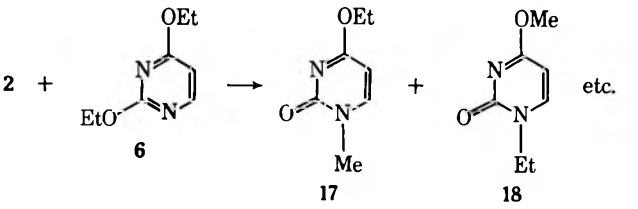
Concn, *M*	Conditions	pH	Mol % of products 8	17	18	19	3	16	9 20	1
0.018	0.05 *N* HCl[a]	1.3								100
0.18	0.05 *N* HCl	2.5					10.8	6.6		82.6
1.80	0.05 *N* HCl	3.6	8.5	11.5	2.3	2.2	17.3	8.9	1.5	47.9
0.36	NaI–2,5-hexanedione[b]		26	56	11	7				

[a] HCl (0.05 *N*) in 50% aqueous dioxane and refluxing for 72 hr. [b] At 100° for 24 hr.

sides. Dealkylation proceeds by alkyl oxygen ether cleavage only since ring substitution by alcohol (SNAr) gives no fruitful products. The former pathway resembles the Pinner cleavage of iminoester hydrochloride into the corresponding amides and alkyl chlorides.[19] This type of SN2 ether cleavage has been shown to be a minor route in the aqueous acid-catalyzed cleavage of 2-methoxypyrimidine.[13] Table II illustrates the reactions of the 2,4-dimethoxypyrimidine 2 and 7 in 0.1 *N* hydrochloric acid in anhydrous methanol under reflux. In both cases, the isomerization products prevail over that of demethylation by more than twofold.

In a mildly acidic nonaqueous medium comprised of excess sodium iodide dissolved in 2,4-pentanedione (pK_a 9.16), isomerization and demethylation of the pyrimidine ether 2 are equally facile as shown in Table III. In a neutral medium such as 2,5-hexanedione, sodium iodide catalyzed isomerization of 2 only. One or both of the imidate moieties were reacted depending on the temperature applied. Iodide anion was the catalyst in both cases. The latter result corroborates with the report[20] that 75% yield of 5-bromo-1,3-dimethyluracil was isolated from the treatment of 5-bromo-2,4-dimethoxypyrimidine in the NaI–2,5-hexanedione mixture. Methyl iodide was postulated[20] to be formed *in situ* and is therefore similar to the Hilbert–Johnson reaction.[10]

Intermolecular Reaction —Isomerization of the pyrimidine lactim ethers in aqueous or nonaqueous media increases dramatically over demethylation at increasing concentrations of the base. Since the isomerization of 2 is dependent on the concentration of the pyrimidine, the O → N methyl migration is reminiscent of the Lander rearrangement[21] of alkyl imidates to amides which is intermolecular. The thermal rearrangement of allyl pyrimidyl ethers has been shown[22] to be intramolecular and formally analogous with the ortho-Claisen rearrangement of allyl phenyl ethers, although, in the case of the thermal isomerization of 2-alkoxypyrimidines to 1-alkyl-2-pyrimidones,[14] the intra- or intermolecular nature of the reaction is uncertain. In order to provide evidence to this effect, a crossover experiment employing equimolar amounts of 2,4-dimethoxy- (2) and 2,4-diethoxypyrimidine (6) was run. A solution of 0.18 *M* of the pyrimidine ethers in 0.05 *N* hydrochloric acid in 50% aqueous dioxane was refluxed for 72 hr. The products tabulated in Table IV include uracil (1) as the major product and a considerable amount of 1-ethyluracil (16) as well as 1-methyluracil (3). A tenfold dilution led to uracil only, but, at 1.8 *M* concentration of the mixed pyrimidine ethers, the formation of uracil was suppressed in favor of the isomerization products. All of the possible N_1-alkyl-2-pyrimidones were isolated. The "mixed" isomerization products 1-methyl-4-ethoxy-2-pyrimidine (17) and 1-ethyl-4-methoxy-2-pyrimidone (18) demonstrate the occurrence of intermolecular *N*-alkylation. The N_1-methylpyrimidones 8, 17, and 3 surpassed the N_1-ethyl derivatives, *viz.*, 1-ethyl-4-ethoxy-2-pyrimidone (19), 18, and 16, by a ratio of 4.3. Small



amounts of partial hydrolysis products 4-methoxy-2-pyrimidone (9) and 4-ethoxy-2-pyrimidone (20) were also present. In the NaI–2,5-hexanedione system, the same equimolar mixture of 2 and 6 yielded only the isomerization products 8, 17, 18, and 19 with the N_1-methyl derivatives predominating over the N_1-ethyl derivatives by a factor of 4.6. The preponderance of *N*-methyl products 8 and 17 over the *N*-ethyl ones 18 and 19 is consistent with the greater reactivity[10] of methyl iodide over ethyl iodide, presumably generated *in situ*,[20] in *N*-alkylation.

Ionic Mechanism —The Hilbert–Johnson reaction of 2,4-dialkoxypyrimidines with alkyl halides or sodium iodide has been assumed to proceed *via* a quaternary

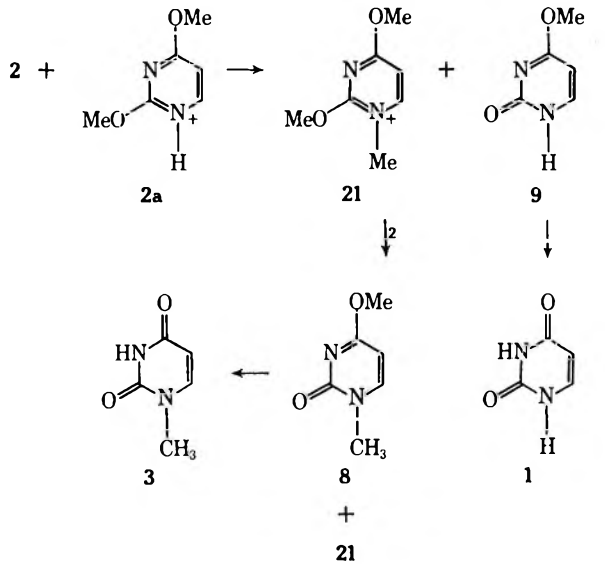
(19) (a) S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, **73**, 2233 (1951); (b) C. L. Stevens, D. Morrow, and J. Lawson, *ibid.*, **77**, 2341 (1955); (c) F. Cramer and H. J. Baldauf, *Chem. Ber.*, **92**, 370 (1959).

(20) T. L. V. Ulbricht, *J. Chem. Soc.*, 3345 (1961).

(21) J. W. Schulenberg and S. Archer, "Organic Reactions," Vol. 14, Wiley, New York, N. Y., 1965, p 24.

(22) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **28**, 1015 (1963).

salt derived from intermolecular *N*-alkylation followed by *O*-dealkylation.[4,10] A recent report[23] on the isolation of the intermediate 1-methyl-2,4-diethoxypyrimidinium salt from a mixture of **6** and methyl iodide in acetonitrile at room temperature lends support to this postulate. It is reasonable to assume that 2,4-dimethoxypyrimidine (**2**) in acid is protonated at the more basic N_1 nitrogen[10,23] to form the active methylating species **2a**. Combination of **2** and **2a** leads to the now established[23] pyrimidinium intermediate **21**, which is the common methylated derivative of the lactim **2** and lactam **8**. The quaternary salt **21** is capable of catalyzing a chain rearrangement of **2** but for the competitive demethylation in aqueous acids. It has been pointed out by Hilbert and Johnson[10] that methyl iodide needs to be present in quantities very much less than molecular proportions of the pyrimidine since the common methylated cation is continually regenerated. This situation is realized in the NaI–2,5-hexanedione system where demethylation was not observed. The following scheme summarizes the events of an acid-catalyzed isomerization of **2**.



The pK_a of **2** and **7**, previously unreported, are now determined to be 3.05 ± 0.05 and 3.63 ± 0.04, respectively, by potentiometric titration.[24] Thus, in the pH region of 1–5, significant quantities of both of the pyrimidine ethers and the conjugate acids are present, and intermolecular *N*-methylation will lead to lactim–lactam isomerization. The extremes of the pH spectrum such as in strong acids and bases (>1 *N*) are obviously not conducive to such methyl rearrangement.

An alternative route to the formation of the quaternary intermediate **21** is *via* a free-radical chain reaction. Such has been shown to be the mechanism for the thermal rearrangement of 2-methoxypyridine to 1-methyl-2-pyridone,[25] which can also be catalyzed by benzoyl peroxide. However, addition of 0.1 equiv of benzoyl peroxide to 0.1 *N* hydrochloric acid containing 0.18 *M* of **2** and refluxed led to much smaller ratio of methyl migration to hydrolysis as shown in Table I. Likewise, the presence 0.1 equiv of the peroxide in the NaI–2,5-hexanedione treatment of **2** caused cleavage of the 4-methoxy group yielding considerable amount of 1-methyluracil at the expense of the *N*,*N*-dimethyl derivative (*cf.* Table III). Apparently, O → N methyl migration of the pyrimidine ether cannot be initiated by peroxide, and a radical mechanism seems unlikely.

It has been pointed out earlier[10] that the two lactim configurations within the same pyrimidine molecule of **2** are different in their stability. Alkylation at the more basic 1-nitrogen appears to labilize selectively the 2-alkoxy group. Thus, when the pyrimidine lactim ethers **2**, **6**, and **7** were treated in aqueous acids, both isomerization and dealkylation initially took place at the lactim moiety comprised of 1-nitrogen and the 2-alkoxy group. Attempts to identify 3-methyluracil (**4**), 1,3-dimethyluracil (**5**), 3-methylthymine (**22**), and 1,3-dimethylthymine (**23**) were unsuccessful. There were no 2-methoxy-4-pyrimidones **10**, **15**, or 2-ethoxy-4-pyrimidone (**24**) detected under these conditions. The abundant literature[4] on Hilbert–Johnson type of reactions reflects the same general phenomenon of a greater reactivity of the N_1-lactim function. This provides an interesting contrast to the greater displaceability of the 4-methoxy group in alkaline conditions.

Dealkylation.—In aqueous acids, dealkylations of the pyrimidine lactim ethers probably follow the hydrolysis pathways elucidated[13] for 2-methoxypyrimidine-O^{18}. The cleavage proceeds predominantly *via* an aromatic nucleophilic substitution (SNAr) with a minor contribution (<10%) of the SN2 ether cleavage mechanism. However, the latter mode of ether cleavage is the only one operating in nonaqueous media such as anhydrous methanol and 2,4-pentanedione. A third possibility exists in the presence of benzoyl peroxide, which catalyzed homolytic cleavage of the alkyl oxygen bond in aqueous acid and in NaI–2,5-hexanedione mixture. Demethylations occur in alkaline conditions *via* nucleophilic aromatic substitution exclusively. In the absence of N-protonation, ring substitution is less facile and therefore requires more stringent conditions such as a high normality of the alkali.

Experimental Section

Instrumental.—Glpc analyses were performed on three gas chromatographs: F & M 5750B equipped with a flame-ionization detector, F & M 700 equipped with a thermal conductivity detector, and Perkin-Elmer 800 equipped with a flame ionization detector. All analyses unless otherwise mentioned were done on a 6 ft × 0.125 in. aluminum column packed with 10% Carbowax 20M on Anakrom ABS 60–70 mesh and at 30 cc/min of carrier gas. The more volatile 2,4-dialkoxypyrimidines, **2**, **6**, and **7** were done with T_I = 170°, T_C = 100°, and T_D = 260°. All others were done at T_I = 260°, T_C = 200°, and T_D = 260°. Products were determined by comparing their peak areas (planimeter five times) with those of reproduced peaks (trial and error) of authentic samples. Preparative glpc was performed on the F & M 700 using an aluminum 6 ft × 0.25 in. column packed with 10% UCW 98 on Anakrom ABS 60–70 mesh. Thin layer chromatography was done on silica gel G (Brinkman) with layers of 0.25 mm in thickness. Chloroform and methanol (19:1) was used in all cases as the solvent system unless otherwise noted. Development was accomplished by spraying a 0.5% fluorescein sodium salt solution then exposing to bromine vapor. Preparative thin layer chromatography was done on silica gel G with plates of 20 × 20 cm and 1.0 mm in thickness. No more than 10 mg was placed on the plate at one time. Nmr spectra were run on a Varian A-60A spectrometer with either D_2O as solvent,

(23) T. Ueda and H. Nishino, *J. Amer. Chem. Soc.*, **90**, 1678 (1968).

(24) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, Chapter 2. The pK_a values of **2** and **7** were determined by titrating 0.01 *M* of the base with standardized 0.100 *N* hydrochloric acid under nitrogen atmosphere.

(25) K. B. Wiberg, T. M. Shryne, and R. R. Kintner, *J. Amer. Chem. Soc.*, **79**, 3160 (1957).

TABLE V

PHYSICAL PROPERTIES OF ALKYL DERIVATIVES OF URACIL AND THYMINE

Compd no.	Mp, °C	Glpc[k] rrt	uv (H_2O) Ref	pH	λ_{max}	$\epsilon \times 10^{-3}$	Nmr (δ)[l] N_1-R, O_2-R	N_3-R, O_4-R	5-H, 5-CH_3	6-H
1	318[a]		[h]	4–7	259	8.2			5.71	7.60
				12–13	284	6.1				
2	18[b]	(1.00)	[i]	7	258	6.1	4.08[m]	3.97	6.42	8.24
3	233[a]	3.33	[h]	5–7	267	9.7	3.40		5.83	7.68
				12–14	265	7.0				
4	179[a]	6.80	[h]	3–7	258	7.3		3.31	5.96	7.59
				12–14	282	10.7				
5	121–122[a]	1.00	[h]	1–14	266	8.9	3.43	3.37	5.73	7.20
6	19–20[b]	(1.63)	[h]	7	259	6.1	4.23[m]	4.18	6.33	7.50
							1.33	1.33		
7	61[c]	(1.58)		7	264	6.3	4.00[m]	3.97	2.07	8.01
					215	7.9				
8	149–150[b]	1.93	[i]	7	274	5.2	3.42	3.87	6.10	7.82
9	206–208[d]	Dec		7	267	4.9		3.99	6.23	7.85
				11	276	5.4				
10	167–168	Dec		7	256	5.8	3.96		6.11	7.71
				11	263	6.0				
11	144[c]	2.47		5–12	280	5.6	3.51	3.99	1.95	7.47
12	292–293[e]	2.93	[j]	6	273	11.3	3.35		1.87	7.50
				12–13	271	7.9				
13	220–221	Dec		7	274	4.9		4.00	1.97	7.55
				11	283	5.8				
14	340[a]		[h]	4–7	265	7.9			1.83	7.42
				12–13	291	5.4				
15	198–199	Dec		7	260	7.1	3.98		1.94	7.62
					217	6.5				
				11	267	7.4				
16	148[a]	2.80		7	267	9.55	3.87		5.78	7.29
				11	265	7.00	1.33			
17	136[b]	2.00	[h]	7	274	6.1	3.45	4.33	5.71	7.56
								1.30		
18	91–92	1.60		7	272	5.3	3.98	3.99	5.98	7.68
							1.38			
19	88[f]	1.67		7	276	8.4	3.87	4.36	5.73	7.50
							1.30	1.30		
20	167–168[g]	1.64	[h]	4–7	269	5.1		4.25	6.17	7.90
				13	278	6.4		1.40		
22	209–210[e]	5.47	[j]	6	265	8.2		3.28	1.87	7.50
				13	290	11.4				
23	151–153[e]	0.93	[j]	5–12	272	9.8	3.46	3.43	1.83	7.57
24	128–129[g]	1.13	[h]	4–7	259	6.0	4.25		6.25	7.87
				10–13	265	6.7	1.40			

[a] D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, Table XXV–XXVII. [b] T. B. Johnson and G. E. Hilbert, *J. Amer. Chem. Soc.*, **52**, 2001 (1930). [c] T. B. Johnson and G. E. Hilbert, *ibid.*, **52**, 4511 (1930). [d] C. W. Noel and C. C. Cheng, *J. Heterocycl. Chem.*, **5**, 25 (1968). [e] E. Wittenburg, *Chem. Ber.*, **99**, 2380 (1966). [f] J. L. Rabinowitz and S. Gurin, *J. Amer. Chem. Soc.*, **75**, 5758 (1953). [g] G. E. Hilbert and E. J. Jansen, *ibid.*, **57**, 552 (1935). [h] D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952). [i] J. E. Austin, *J. Amer. Chem. Soc.*, **56**, 2141 (1934). [j] E. Wittenburg, *Chem. Ber.*, **99**, 2391 (1966). [k] Detailed conditions for glpc analysis are given in the Experimental Section. Relative retention times (rrt) were determined with a F & M 700 gas chromatograph (thermal couple detector). These values are slightly different from those derived with a Perkin-Elmer 800 equipped with a flame ionization detector, although the order of appearance of the pyrimidines remains unchanged. The three more volatile dialkoxypyrimidines were studied at lower Tc and the rrt are shown in parentheses. [l] Dialkylpyrimidines (*N,N*-; *O,O*-; *N,O*-) were taken in $CDCl_3$ with TMS and all others in D_2O using 3-(trimethylsilyl)propanesulfonic acid sodium salt as the internal standard. In the uracil series, 5-H and 6-H appear as doublets, $J = 7$ Hz, and in the thymine series 5-CH_3 appears as a doublet, $J = 1.5$–2 Hz. Other multiplicities follow normal patterns and are not mentioned. [m] Assignments uncertain.

with 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standard, or with deuteriochloroform, with internal tetramethylsilane as standard. Ultraviolet spectra were obtained on a Cary 14 recording spectrophotometer using water as solvent at known pH. Melting points are uncorrected and microanalyses were performed by M-H-W Laboratories, Garden City, Mich. 48135.

Materials.—The physical properties of the 21 mono- and dialkyl derivatives of uracil and thymine are tabulated in Table V. Preparations of the previous unreported pyrimidines **10**, **13**, **15**, and **18** are shown below.

2-Methoxy-4-pyrimidone (10).—2,4-Dimethoxypyrimidine (**2**) (0.98 g, 7 mmol) was added to 10 ml of 5 *N* sodium hydroxide in 50% aqueous methanol and the solution was refluxed for 72 hr. The solution was neutralized with acetic acid, continuously extracted with chloroform, dried, and evaporated to give 0.74 g of a white solid. Chromatography of the solid on 25 g silica gel (elution with 10% methanol in chloroform) gave 0.25 g (28% yield) of **10**. An analytical sample was prepared by recrystallization from ethanol, and physical properties are shown in Table V.

Anal. Calcd for $C_5H_6N_2O_2$: C, 47.6; H, 4.8; N, 22.2. Found: C, 47.7; H, 4.8; N, 22.2.

4-Methoxy-5-methyl-2-pyrimidone (13).—A mixture of 0.925 g (6 mmol) of 2,4-dimethoxy-5-methylpyrimidine (**7**) and 10 ml of freshly distilled acetyl chloride was stirred at 50° protected from moisture for 24 hr. The volatiles were evaporated and the residue washed with ether giving 0.7 g (68%) of 1-acetyl-4-methoxy-5-methyl-2-pyrimidone: mp 107°; nmr ($CDCl_3$) δ 1.95 (d,

3, J = 1.5 Hz), 2.75 (s, 3), 4.00 (s, 3), and 8.02 (m, 1, J = 1.5 Hz). The N_1-acetyl derivative (0.7 g, 4.1 mmol) was added to 5 ml of 5% sodium bicarbonate solution, stirred at room temperature for 3 hr, and extracted continuously with chloroform, dried, and evaporated to give 0.52 g of solid. Chromatography of the solid on 20 g of silica gel (elution with 10% methanol in chloroform) yielded 0.4 g (70%) of **13**, and physical properties are shown in Table V.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.1; H, 5.9; N, 20.1.

2-Methoxy-5-methyl-4-pyrimidone (15).—To 10 ml of 5 *N* sodium hydroxide in 50% aqueous methanol was added 0.308 g (2 mmol) of 2,4-dimethoxy-5-methylpyrimidine (**7**) and the solution was heated at reflux for 48 hr. The solution was neutralized with acetic acid, continuously extracted with chloroform, dried, evaporated to a solid, and recrystallized from ethanol to yield 0.19 g (69%) of **15**, and physical properties are shown in Table V.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.2; H, 5.9; N, 20.1.

1-Ethyl-4-methoxy-2-pyrimidone (18).—A mixture of 0.5 g (3.6 mmol) of 2,4-dimethoxypyrimidine (**2**) in 5 ml of freshly distilled ethyl iodide was stirred in the dark at room temperature for 1 week. The ethyl iodide and unreacted **2** were evaporated off and the residue was washed with petroleum ether to give 0.27 g of brown solid. Chromatography of the solid on a 12 g silica gel column with 10% acetone in ethyl acetate as eluents yielded 0.15 g (27%) of **18**. Sublimation (50°, 0.05 mm) gave pure sample, and physical properties are shown in Table V.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.5; H, 6.5; N, 18.2. Found: C, 54.7; H, 6.6; N, 18.0.

Reaction of 2,4-Dimethoxypyrimidine (2) in 0.1 *N* Aqueous Hydrochloric Acid.—A mixture of 25.2 mg (0.18 mmol) of **2** in 1.0 ml of 0.1 *N* aqueous hydrochloric acid was refluxed for 3 hr. The reaction was stopped by addition of saturated sodium bicarbonate solution. The reaction mixture was continuously extracted with chloroform for 14 hr, dried, and evaporated. Preparative tlc revealed the presence of 2,4-dimethoxypyrimidine (**2**), 1-methyl-4-methoxy-2-pyrimidone (**8**), 1-methyluracil (**3**), and 4-methoxy-2-pyrimidone (**9**) (relative R_f 4.5, 2.5, 2.0, and 1.0, respectively). To quantitate the pyrimidines, the experiment was repeated and the chloroform extracts diluted to 1.0 ml volumetrically. Analyses by glpc by comparing their peak areas with those of the authentic samples and normalized gave the following yields (mg, 10^{-2} mmol); **2**, (9.79, 6.98); **8**, (1.14, 0.82) **3**, (1.43, 1.13). Since 4-methoxy-2-pyrimidone (**9**) decomposed on the column under the conditions used, the chloroform extracts were evaporated to dryness and the residue silylated with 200 μl of *O,N*-bis(trimethylsilyl)acetamide and 600 μl of acetonitrile in a sealed tube at 150° for 1 hr.[26] A 1.0 ml solution of the acetonitrile was made up and chromatographed on a 6 ft × 0.125 in. column packed with 10% UCW 98 on Chromosorb W, 80–100 mesh: T_I = 210°, T_C = 150°, T_D = 260°, and 20 cc/min of nitrogen. The yield of **9**, determined in the usual manner, was 0.11 mg (0.087 × 10^{-2} mmol). The average results of four glpc analyses of these components are reported below (10^{-2} mmol): **2**, 6.98; **8**, 0.98; **3**, 1.18; and **9**, 0.098. The aqueous layer after continuous extraction with chloroform was diluted to 1000 ml volumetrically for ultraviolet assay of uracil (**1**) present: $OD_{259\ nm}$ = 0.41, and, using ϵ = 8200, yield of **1** was calculated to be 5.6 mg (5.00 × 10^{-2} mmol). The mole percentages of the products are shown in Table I, and 14.24 × 10^{-2} mmol (79%) of the starting material **2** was accounted for.

Reaction of 2,4-Dimethoxypyrimidine (2) in 0.1 *N* Methanolic Hydrogen Chloride.—A solution of 25.3 mg (0.181 mmol) of **2** in 1.0 ml of 0.1 *N* methanolic hydrogen chloride was allowed to reflux for 48 hr. The reaction was stopped by the addition of sodium bicarbonate, filtered and diluted to 1.0 ml volumetrically with methanol. Glpc analysis of the solution gave (mg, 10^{-2} mmol): 2,4-dimethoxypyrimidine (**2**) (14.29, 10.21); 1-methyl-4-methoxy-2-pyrimidone (**8**) (5.48, 3.91); 1-methyluracil (**3**) (2.12, 1.68). The average results of four glpc analyses are as follows (10^{-2} mmol): **2** 10.48, **8**, 4.04; **3**, 1.69. The methanol solution was evaporated followed by addition of water and continuous extraction with chloroform. The chloroform layer was dried, evaporated, and the residue chromatographed on a preparative silica gel plate. The band corresponding to 4-methoxy-2-pyrimidone (**9**) was eluted with methanol, diluted to 100 ml volumetrically, and assayed by ultraviolet absorption spectroscopy: $OD_{267\ nm}$ = 0.545, equivalent to 1.40 mg (1.11 × 10^{-2} mmol). The aqueous layer was made up to 1000 ml and uv determination showed 1.36 mg (1.21 × 10^{-2} mmol) of uracil (**1**). The pyrimidines analyzed totaled 18.5 × 10^{-2} mmol representing quantitative material balance. The mole percentages of the products are shown in Table II.

Reaction of 2,4-Dimethoxypyrimidine (2) with Sodium Iodide in 2,4-Pentanedione.—To a mixture of 1.0 ml of 2,4-pentanedione and 100 mg of sodium iodide was added 25.3 mg of **2** (0.181 mmol) and the mixture was heated at 100° for 24 hr, cooled, and evaporated. The reaction products were analyzed by the techniques elaborated above: glpc analyses gave 1-methyl-4-methoxy-2-pyrimidone (**8**), 3.11 mg (2.22 × 10^{-2} mmol), and 1-methyluracil (**3**), 0.43 mg (0.34 × 10^{-2} mmol); preparative tlc yielded 4-methoxy-2-pyrimidone (**9**), 2.38 mg (1.89 × 10^{-2} mmol), and uv analysis of the aqueous layer gave uracil (**1**), 0.36 mg (0.32 × 10^{-2} mmol). Total amounts of pyrimidines isolated were 4.77 × 10^{-2} mmol (27%); unreacted **2** was evaporated with 2,4-pentanedione. The mole percentages of the products are shown in Table III.

Reaction of Equimolar Mixture of 2,4-Dimethoxy- (2) and 2,4-Diethoxypyrimidine (6) in Aqueous Hydrochloric Acid.—A mixture of 125.4 mg (0.896 mmol) of **2** and 150.9 mg (0.898 mmol) of **6** in 1.0 ml of 0.05 *N* hydrochloric acid in 50% aqueous dioxane was heated at reflux for 72 hr. The solution was neutralized with saturated sodium bicarbonate solution, continuously extracted with chloroform for 15 hr, dried, and evaporated. The residue was taken up in 1.0 ml of methanol volumetrically. Glpc analyses gave the following yields (mg, 10^{-2} mmol): for 2,4-diethoxypyrimidine (**6**) (111.9, 66.56); 2,4-dimethoxypyrimidine (**2**) (69.3, 49.50); 1-ethyluracil (**16**) (3.39, 3.29); 1-methyluracil (**3**) (8.26, 6.55). The average results of four glpc analyses are as follows (10^{-2} mmol): **6**, 66.89; **2**, 49.95; **16**, 3.29; **3**, 6.36. The Hilbert–Johnson products **8**, **17**, **18**, and **19** gave an ill-resolved four-component trace, and analysis was achieved by matching it with a synthetic chromatogram prepared by trial and error mixing of authentic samples (mg, 10^{-2} mmol): 1-methyl-4-methoxy-2-pyrimidone (**8**) (4.36, 3.12); 1-methyl-4-ethoxy-2-pyrimidone (**17**) (6.50, 4.22); 1-ethyl-4-methoxy-2-pyrimidone (**18**) (1.33, 0.86); 1-ethyl-4-ethoxy-2-pyrimidone (**19**) (1.33, 0.79). Ultraviolet determination of the aqueous layer gave 19.7 mg (17.6 × 10^{-2} mmol) of uracil (**1**). Since 4-methoxy-2-pyrimidone (**9**) and 4-ethoxy-2-pyrimidone (**20**) cannot be effectively separated by either glpc or tlc, they were determined together as uracil by treating the chloroform extract in hot concentrated hydrochloric acid and isolating the uracil formed by preparative tlc to yield 0.604 mg, equivalent to 0.54 × 10^{-2} mmol of **9** and **20**. Total amounts of pyrimidines isolated were 156.37 × 10^{-2} mmol (87.2%), and the mole percentages of the products are shown in Table IV.

Registry No.—**1**, 66-22-8; **2**, 3551-55-1; **3**, 615-77-0; **4**, 608-34-4; **5**, 874-14-6; **6**, 20461-60-3; **7**, 5151-34-8; **8**, 7152-66-1; **9**, 18002-25-0; **10**, 25902-86-7; **11**, 25902-87-8; **12**, 4160-72-9; **13**, 25902-89-0; **14**, 65-71-4; **15**, 25902-91-4; **16**, 6490-42-2; **17**, 6220-46-8; **18**, 25902-94-7; **19**, 25902-95-8; **20**, 6220-43-5; **22**, 4160-77-4; **23**, 4401-71-2; **24**, 25957-58-8.

(26) C. W. Gehrke and C. D. Ruyle, *J. Chromatogr.*, **38**, 473 (1968).

A New Synthesis of *as*-Triazines and Pyrimido[4,5-*e*]-*as*-triazines (6-Azapteridines)

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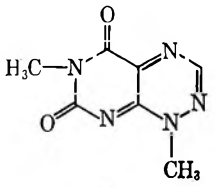
A new synthesis of *as*-triazines has been developed which involves Michael addition of diethyl azodicarboxylate to acyclic enamines, followed by base-catalyzed ring closure. By an appropriate choice of the enamine, *as*-triazines suitably substituted for subsequent annelation of a fused pyrimidine ring may be prepared. We describe in this paper the synthesis of a number of pyrimido[4,5-*e*]-*as*-triazines (6-azapteridines), including 2-methylisofervenulone (**20**) and 3,6,8-triaminopyrimido[4,5-*e*]-*as*-triazine (**23**), by this new route.

The discovery of the triad of naturally occurring antibiotics toxoflavin (**1**),[2,3] fervenulin (**2**),[4] and 2-methylfervenulone (MSD-92) (**3**),[5] and their identification by degradation and total synthesis as derivatives of the pyrimido[5,4-e]-*as*-triazine (7-azapteridine) ring system (**4**), has stimulated considerable recent interest in the synthesis and chemistry of further derivatives.



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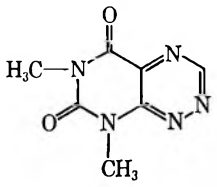

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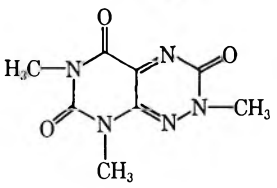

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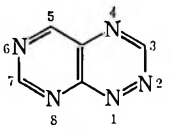

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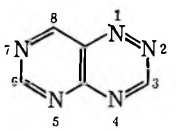

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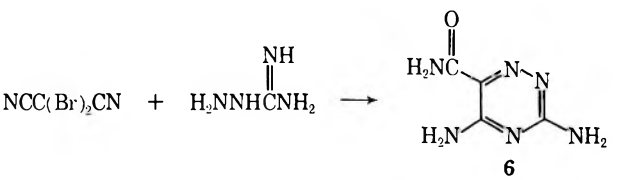
The isomeric pyrimido[4,5-e]-*as*-triazine (6-azapteridine) system (**5**) is also attracting recent attention because of the discovery that some derivatives exhibit antiviral activity.[6]

Almost all previous synthetic routes to pyrimidotriazines have involved the initial construction of a suitably substituted pyrimidine precursor and the eventual annelation of the condensed triazine ring in a terminal reaction step.[7-9] One exception to this order of construction of the bicyclic system was described by Taylor and Morrison,[10] who prepared 3,5-diamino-*as*-triazine-6-carboxamide (**6**) by condensation of dibromomalononitrile with aminoguanidine, and subsequently converted this intermediate to 6-azapteridines by cyclization with appropriate one-carbon reagents. We describe in this paper a further entry into the pyrimido[4,5-*e*]-*as*-triazine system *via* triazine intermediates.



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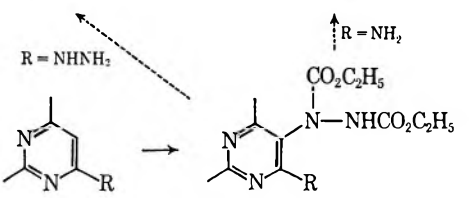

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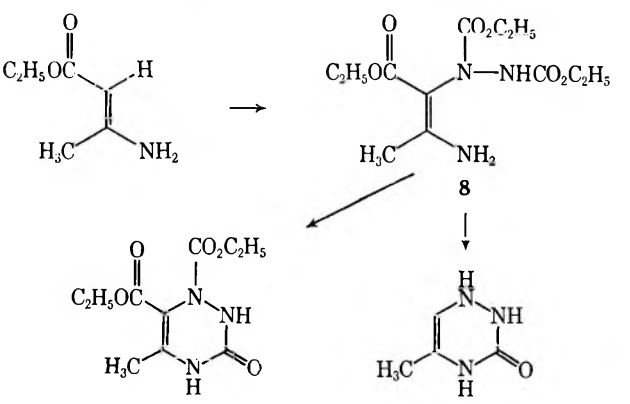
In our previously published total syntheses of fervenulin[4] and MSD-92,[5] a key step was the condensation of a 6-hydrazinopyrimidine with diethyl azodicarboxyl-



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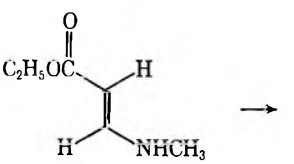

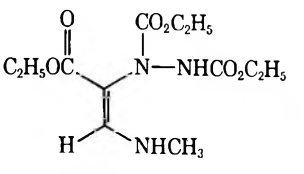

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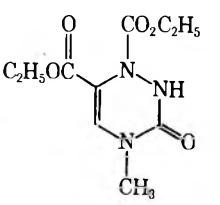

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* To whom correspondence should be addressed.

(1) NIH Predoctoral Fellow, 1969-1970.

(2) B. Levenberg and S. N. Linton, *J. Biol. Chem.*, **241**, 846 (1966).

(3) T. K. Liao, F. Baiocchi, and C. C. Cheng, *J. Org. Chem.*, **31**, 900 (1966), and references cited therein.

(4) E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, **90**, 1374 (1968), and references cited therein.

(5) E. C. Taylor and F. Sowinski, *ibid.*, **91**, 2143 (1969), and references cited therein.

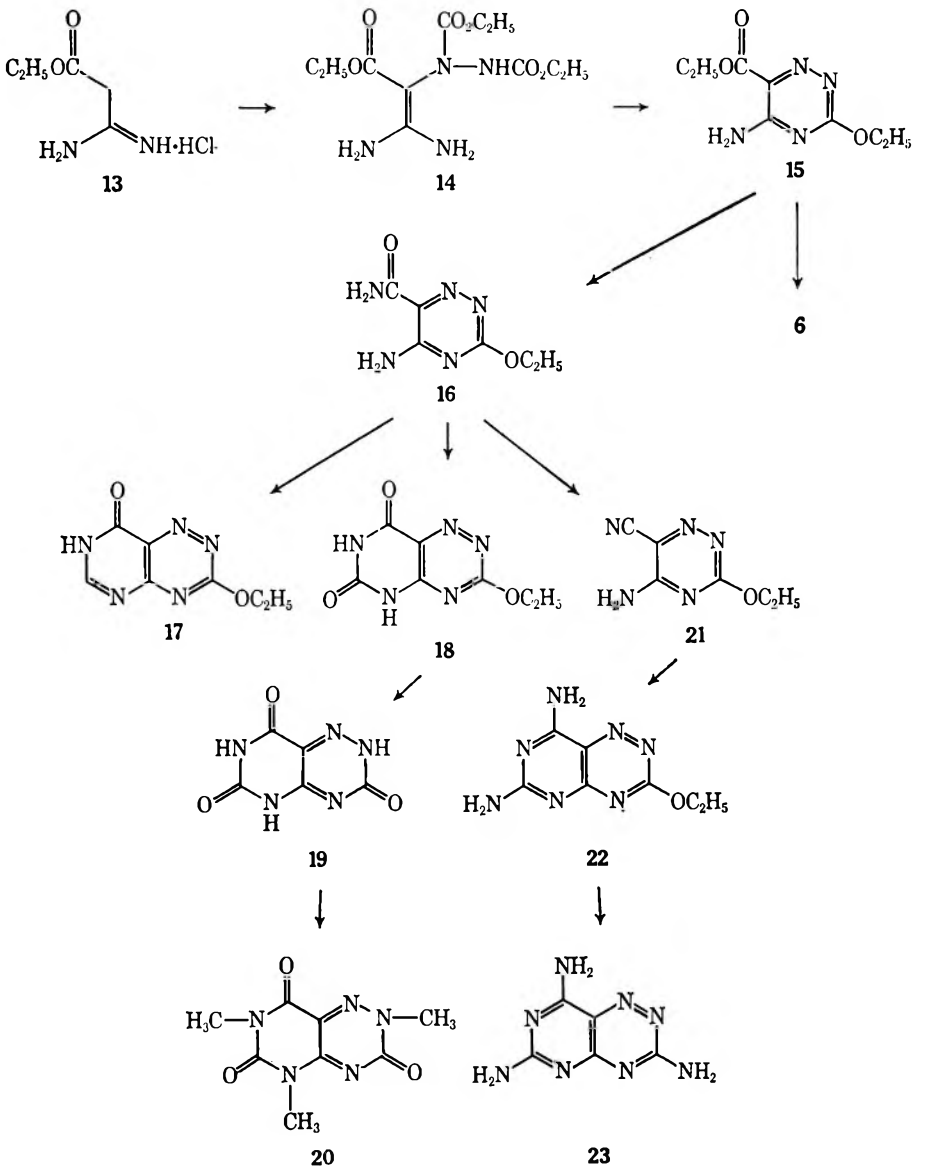
(6) C. Kuchler, W. Kuchler, and L. Heinisch, *Arzneim.-Forsch.*, **16**, 1122 (1966).

(7) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **34**, 2102 (1969), and references cited therein; these workers also described the ring cleavage of pyrimido[5,4-*e*]-*as*-triazin-5(6*H*)-one to 6-amino-*as*-triazine-5-carboxamide, and the subsequent recyclization of this latter compound to several 7-azapteridines.

(8) M. E. C. Biffin, D. J. Brown, and T. Sugimoto, *J. Chem. Soc. C*, 139 (1970).

(9) W. Pfleiderer and G. Blankenhorn, *Tetrahedron Lett.*, 4699 (1969).

(10) E. C. Taylor and R. W. Morrison, Jr., *J. Amer. Chem. Soc.*, **87**, 1976 (1965).



ate to give a Michael adduct (**7**, R = $NHNH_2$), which was subsequently modified to form the annelated *as*-triazine ring. The same principle was applied to the synthesis of 6-azapteridines by Michael addition of diethyl azodicarboxylate to 6-aminopyrimidines to give **7** (R = NH_2), followed by suitable ring closure techniques. In both instances, the initial Michael reaction leading to the adducts **7** (R = $NHNH_2$, NH_2) reflects enamine-type reactivity of the 6-hydrazino- (or amino-) 5-unsubstituted pyrimidines. It occurred to us that extrapolation of these reactions to acyclic enamines should provide an entry into *as*-triazines which, with an appropriate choice of substituents, might serve as precursors for subsequent closure of the annelated pyrimidine ring, and thus offer an alternate synthetic pathway to azapteridines.

The potential feasibility of this approach was demonstrated by the following sequence of reactions. Michael addition of diethyl azodicarboxylate to ethyl β-aminocrotonate gave ethyl α-(1,2-dicarbethoxyhydrazino)-β-aminocrotonate (**8**), which was cyclized in quantitative yield with thallium(I) ethoxide[11] in benzene to **9**. Cyclization of **8** could also be effected with aqueous sodium hydroxide, but under these conditions concomitant hydrolysis and decarboxylation of the carbethoxy group occurred to give **10**. In analogous fashion, ethyl β-methylaminoacrylate condensed with diethyl azodicarboxylate to give ethyl α-(1,2-dicarbethoxyhydrazino)-β-methylaminoacrylate (**11**), which was cyclized with thallium(I) ethoxide in benzene to **12**.

Efforts were then directed toward the preparation of an enamine so substituted that the resulting *as*-triazine could be subsequently cyclized to 6-azapteridines. Condensation of diethyl azodicarboxylate with carbethoxyacetamidine hydrochloride (**13**) in the presence of triethylamine gave α-(1,2-dicarbethoxyhydrazino)carbethoxyacetamidine (**14**). Although all attempts to effect cyclization of this intermediate to an *as*-triazine with basic reagents failed, it was found that a combination of bromine with Hünig's base (diisopropylethylamine)[12] smoothly afforded 3-ethoxy-5-amino-6-carbethoxy-*as*-triazine (**15**). The structure of this compound was confirmed by treatment with ethanolic ammonia at 150° to give 3,5-diamino-6-carbamoyl-*as*-triazine (**6**), identical with an authentic sample prepared by the alternate method of Taylor and Morrison.[10]

(11) E. C. Taylor, G. H. Hawks, III, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

(12) N. Finch and C. W. Gemenden, *Tetrahedron Lett.*, 1203 (1969).

Aminolysis of **15** at room temperature led to 3-ethoxy-5-amino-6-carbamoyl-*as*-triazine (**16**), which was then cyclized to a variety of 6-azapteridines. Thus, condensation with diethoxymethyl acetate gave 3-ethoxy-8(7*H*)-pyrimido[4,5-*e*]-*as*-triazinone (**17**), while reaction with diethyl carbonate in the presence of sodium ethoxide gave 3-ethoxy-6,8(5*H*,7*H*)-pyrimido[4,5-e]-*as*-triazinedione (**18**). Acid hydrolysis of this latter compound afforded 3,6,8(2*H*,5*H*,7*H*)-pyrimido[4,5-e]-*as*-triazinetrione (**19**), identical in physical properties with those reported for this same compound prepared independently *via* the pyrimidine annelation route.[13] Furthermore, methylation of **19** with methyl iodide and sodium hydride in anhydrous dimethylformamide gave 2-methylisofervenulone (**20**), identical with an authentic sample.[14]

Dehydration of the *o*-aminoamide **16** with phosphorus oxychloride in pyridine gave 3-ethoxy-5-amino-6-cyano-*as*-triazine (**21**), which was cyclized with guanidine to 3-ethoxy-6,8-diaminopyrimido[4,5-e]-*as*-triazine (**22**).[15] Subsequent treatment with ethanolic ammonia at 150° gave 3,6,8-triaminopyrimido[4,5-e]-*as*-triazine (**23**). This compound is of particular interest because of the known antifolic acid activity of 2,4-diaminopteridines and other condensed 2,4-diaminopyrimidine systems,[16] and the diuretic activity of 2,4,7-triaminopteridines.[17]

Experimental Section[18]

1,6-Dicarbethoxy-5-methyl-1,4-dihydro-*as*-triazin-3(2*H*)-one (9).[19]—To a solution of 6.45 g (0.05 mol) of ethyl β-aminocrotonate in 25 ml of anhydrous benzene was added, all at once, 8.70 g (0.05 mol) of diethyl azodicarboxylate. The reaction mixture was stirred at room temperature for 2.5 hr and evaporated under reduced pressure and the residual viscous oil dissolved in hot ethyl acetate. Cooling and scratching resulted in the crystallization of a colorless solid which was recrystallized from ethanol. The intermediate ethyl α-(1,2-dicarbethoxyhydrazino)-β-aminocrotonate (**8**) thus obtained weighed 9.10 g (60%) and melted at 92–96°.

To a suspension of 3.03 g (0.01 mol) of **8** in 15 ml of anhydrous ether was added a solution of 7.50 g (0.03 mol) of thallium(I) ethoxide[11] in 25 ml of anhydrous benzene. The mixture was refluxed for 2 hr, cooled, and neutralized with 1.80 g (0.03 mol) of glacial acetic acid. The thallium(I) acetate which separated was collected by filtration and washed thoroughly with methylene chloride, and the combined filtrate and washings were concentrated under reduced pressure. The residual solid was recrystallized from benzene–pentane to give 2.55 g (99%), mp 166°.

Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.34. Found: C, 46.71; H, 5.84; N, 16.31.

5-Methyl-1,4-dihydro-*as*-triazin-3(2*H*)-one (10).[19]—A solution of 10.00 g (0.34 mol) of ethyl α-(1,2-dicarbethoxyhydrazino)-β-aminocrotonate (**8**) (see above) in 30 ml of 5 *N* sodium hydroxide and 30 ml of ethanol was boiled (no reflux condenser) for approximately 2 hr, during which time most of the ethanol had evaporated. The resulting aqueous solution was cooled to room temperature, allowed to stand overnight, and then neutralized with glacial acetic acid. Constant extraction with hot chloroform, followed by evaporation of the extracts, gave a white solid which was recrystallized from ethanol to yield 1.98 g (52%), mp 222–224°.

Anal. Calcd for $C_4H_7N_3O$: C, 42.47; H, 6.24; N, 37.15. Found: C, 42.08; H, 6.11; N, 36.74.

Ethyl α-(1,2-Dicarbethoxyhydrazino)-β-methylaminoacrylate (11).—To a solution of 1.50 g (0.0116 mol) of ethyl β-methylaminoacrylate in 5 ml of anhydrous benzene was added, in one portion, 2.04 g (0.0116 mol) of diethyl azodicarboxylate. The reaction mixture was stirred at room temperature for 5 hr, the excess solvent removed by evaporation under reduced pressure, and approximately 10 ml of pentane added to the residual oil. Scratching and cooling induced the crystallization of a cream-colored solid which, upon recrystallization from a mixture of benzene and pentane, gave 2.68 g (77%), mp 90–92°.

Anal. Calcd for $C_{12}H_{21}N_3O_6$: C, 47.52; H, 6.98; N, 13.86. Found: C, 47.38; H, 6.92; N, 13.99.

1,6-Dicarbethoxy-4-methyl-1,4-dihydro-*as*-triazin-3(2*H*)-one (12).—Treatment of 2.55 g (0.0084 mol) of **11** with 6.30 g (0.0242 mol) of thallium(I) ethoxide in benzene, as described above for the conversion of **8** to **9**, gave colorless crystals which were recrystallized from a mixture of chloroform and pentane to give 1.61 g (75%), mp 172–173°.

Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.58; N, 16.34. Found: C, 46.64; H, 5.71; N, 16.08.

α-(1,2-Dicarbethoxyhydrazino)carbethoxyacetamidine (14).—To a suspension of 12.48 g (0.075 mol) of carbethoxyacetamidine hydrochloride (**13**)[20] in 45 ml of anhydrous benzene was added, in one portion, 13.08 g (0.075 mol) of diethyl azodicarboxylate, followed by dropwise addition of 7.56 g (0.075 mol) of triethylamine in 10 ml of anhydrous benzene. The resulting reaction mixture was stirred at room temperature for 3 hr, the triethylamine hydrochloride collected by filtration, and the filtrate concentrated under reduced pressure. The residual syrup was chromatographed on 500 g of silica gel (Baker) with ethyl acetate–benzene (1:3). The combined eluents were evaporated under reduced pressure and the residual gum recrystallized from chloroform–pentane to give 13.40 g (59%) of a colorless product, mp 110–111°.

Anal. Calcd for $C_{11}H_{20}N_4O_6$: C, 43.41; H, 6.63; N, 18.41. Found: C, 43.61; H, 6.55; N, 18.26.

3-Ethoxy-5-amino-6-carbethoxy-*as*-triazine (15).—To a solution of 15.20 g (0.05 mol) of **14** in 125 ml of methylene chloride, cooled in an ice–salt bath to 0°, was added 14.10 g (0.11 mol) of Hünig's base,[12] followed by dropwise addition of 8.90 g (0.055 mol) of bromine in 25 ml of methylene chloride. Stirring was continued at 0° for 1 hr and the resulting solution then extracted with three 150-ml portions of ice–water. The methylene chloride was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and the residual syrup chromatographed on 350 g of silica gel (Baker) using ethyl acetate–chloroform (1:10). The combined eluents were concentrated under reduced pressure and the residual solid recrystallized from benzene–pentane to give 4.45 g (42%), mp 127–128°.

Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.53; H, 5.44; N, 26.30.

3,5-Diamino-6-carbamoyl-*as*-triazine (6).—A solution of 0.20 g of **15** in 10 ml of ethanol saturated with dry ammonia was heated in a sealed tube at 150° (oil bath temperature) for 24 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue suspended in boiling water, and 1 *N* hydrochloric acid added until complete solution resulted. The resulting solution was decolorized with Norite and the pH of the filtrate then adjusted to neutrality with 5% ammonium hydroxide. The white solid which separated on cooling was collected by filtration to give 90 mg (62%), mp <350°. The product was identical with an authentic sample of 3,5-diamino-6-carbamoyl-*as*-triazine prepared independently.[10]

3-Ethoxy-5-amino-6-carbamoyl-*as*-triazine (16).—A solution of 2.50 g of **15** in 100 ml of anhydrous ethanol saturated with dry ammonia was stirred at room temperature for 24 hr. The reaction mixture was concentrated under reduced pressure to approximately 25 ml, cooled, and the white solid which separated collected by filtration, washed with ethanol, and recrystallized from aqueous dimethylformamide to yield 1.83 g (85%), mp 228–229°.

(13) L. Heinisch, W. Ozegowski, and M. Mühlstädt, *Chem. Ber.*, **97**, 5 (1964).

(14) F. Sowinski, Ph.D. Thesis, Princeton University, 1971.

(15) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Interscience, New York, N. Y., 1970.

(16) (a) "Experimental Chemotherapy," Vol. IV, Part I, R. J. Schnitzer and F. Hawking, Eds., Academic Press, New York, N. Y., 1966; (b) L. F. Larionov, "Cancer Chemotherapy," Pergamon Press, Oxford, 1965; (c) F. E. Knock, "Anticancer Agents," Charles C Thomas Publisher, Springfield, Ill., 1966.

(17) J. M. Sprague in "Topics in Medicinal Chemistry," J. L. Rabinovitz and R. M. Myerson, Eds., Vol. 2, Interscience, New York, N. Y., 1968, p 1.

(18) Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Uv spectra were determined on a Cary Model 11 instrument, and the nmr spectra on a Varian A-60. We are indebted for the microanalyses to the Baron Consulting Co., Orange, Conn.

(19) We are indebted to Dr. G. W. McClay for this preparation.

(20) S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, **73**, 2760 (1951).

Anal. Calcd for $C_6H_9N_5O_2$: C, 39.34; H, 4.95; N, 38.24. Found: C, 39.46; H, 4.97; N, 38.23.

3-Ethoxy-8(7*H*)-pyrimido[4,5-*e*]-*as*-triazinone (17).—A suspension of 0.50 g of **16** in 10 ml of diethoxymethyl acetate[21] was heated with stirring for 4 hr in an oil bath maintained at 100°. The resulting red solution was evaporated to dryness under reduced pressure and the residue triturated with 20 ml of chloroform and filtered. Recrystallization of the resulting solid from isopropyl alcohol then gave 0.37 g (69%), mp 204–205° dec: uv $\lambda_{max}^{C_2H_5OH}$ 321, 251 (sh), 244, 221 nm (ϵ 7700, 6500, 7300, 15,600); nmr (DMSO-d_6–TMS) δ 8.34 (s, 1 H).

Anal. Calcd for $C_7H_7N_5O_2$: C, 43.52; H, 3.65; N, 36.26. Found: C, 43.27; H, 3.88; N, 36.07.

3-Ethoxy-6,8(5*H*,7*H*)-pyrimido[4,5-*e*]-*as*-triazinedione (18).—To a suspension of 0.40 g (2.16 mmol) of **16** in ethanolic sodium ethoxide (prepared from 0.21 g of sodium and 15 ml of anhydrous ethanol) was added 1.05 g (8.80 mmol) of diethyl carbonate. The reaction mixture was heated under reflux for 5 hr and cooled, and the precipitated solid collected by filtration and washed well with ethanol. It was then dissolved in 10 ml of water and the resulting solution acidified with glacial acetic acid, cooled immediately, and filtered. The collected solid was recrystallized from ethanol to give 0.35 g (78%), mp 247–248°: uv $\lambda_{max}^{C_2H_5OH}$ 310, 232 nm (ϵ 12,000, 12,100).

Anal. Calcd for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.48. Found: C, 40.45; H, 3.41; N, 33.75.

3,6,8(2*H*,5*H*,7*H*)-Pyrimido[4,5-*e*]-*as*-triazinetrione (19).—A suspension of 0.10 g of **18** in 2 ml of 2 *N* hydrochloric acid was heated under reflux for 1 hr. Solution was initially achieved, but as heating progressed a solid gradually precipitated from the hot solution. The reaction mixture was cooled and filtered, and the collected solid recrystallized from water to give 0.08 g (92%), mp >300°.

Anal. Calcd for $C_6H_3N_5O_3$: C, 33.16; H, 1.67; N, 38.67. Found: C, 33.04; H, 2.07; N, 38.46.

The spectral data for this compound were essentially identical with those previously reported: uv $\lambda_{max}^{H_2O}$ 313 nm (ϵ 5500) [lit.[13] 306 nm (ϵ 5600)].

2,5,7-Trimethyl-3,6,8(2*H*,5*H*,7*H*)-pyrimido[4,5-*e*]-*as*-triazinetrione (2-Methylisofervenulone) (20).—To an ice-cooled suspension of 50 mg (0.28 mmol) of **19** in 1 ml of anhydrous dimethylformamide was added 60 mg (1.25 mmol) of a 50% dispersion of sodium hydride in mineral oil. The mixture was stirred at ice bath temperature for 30 min and then 310 mg (2.21 mmol) of methyl iodide added. The resulting mixture was heated under reflux for 30 min and evaporated under reduced pressure, and the residual solid partitioned between 5 ml of chloroform and 1 ml of water. The chloroform layer was separated, dried over anhydrous magnesium sulfate, and concentrated to a viscous oil under reduced pressure. Chromatography on 5 g of silica gel (Merck, 0.05–0.2 mm), using ethyl acetate as the eluting solvent, yielded 25 mg (30%), mp 184–185° dec, identical in all respects with an authentic sample.[14]

3-Ethoxy-5-amino-6-cyano-*as*-triazine (21).—To a suspension of 1.00 g of 3-ethoxy-5-amino-6-carbamoyl-*as*-triazine in 10 ml of anhydrous pyridine was added dropwise 2 ml of phosphorus oxychloride. The reaction mixture was warmed to 45–50°, maintained at that temperature for 10 min, and then poured slowly over 100 g of ice. The crude product was collected by filtration and recrystallized from acetonitrile to give 0.45 g (50%), mp 225° dec.

Anal. Calcd for $C_6H_7N_6O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.87; H, 4.41; N, 42.57.

3-Ethoxy-6,8-diaminopyrimido[4,5-*e*]-*as*-triazine (22).—Guanidine hydrochloride (0.27 g, 2.82 mmol) was dissolved in ethanolic sodium ethoxide (prepared from 0.065 g, 2.82 mmol, of sodium and 20 ml of anhydrous ethanol), the precipitated sodium chloride removed by filtration, and 0.30 g (1.87 mmol) of **21** added to the filtrate. The reaction mixture was stirred at room temperature for 10 min and then heated under reflux for 20 min and cooled, and the precipitated yellow solid was collected by filtration and washed well with water followed by ethanol. Recrystallization from ethanolic dimethylformamide gave 0.29 g (76%), mp >300°: uv $\lambda_{max}^{CH_3OH}$ 347, 325 (sh), 253 nm (ϵ 9700, 7500, 19,800).

Anal. Calcd for $C_7H_9N_7O$: C, 40.57; H, 4.38; N, 47.32. Found: C, 40.39; H, 4.33; N, 47.08.

3,6,8-Triaminopyrimido[4,5-*e*]-*as*-triazine (23).—A suspension of 0.15 g of **22** in 15 ml of anhydrous ethanol saturated with dry ammonia was heated in a sealed tube for 24 hr at 150° (oil bath temperature). The reaction mixture was then filtered and the collected yellow solid recrystallized from ethanolic dimethylformamide to give 0.11 g (85%), mp >300°.

The compound was most satisfactorily analyzed as its ditosyl salt, prepared by addition of 150 mg of *p*-toluenesulfonic acid to a suspension of 50 mg of the free base in 2 ml of boiling ethanol. The analytical sample of the ditosyl salt was prepared by recrystallization from methanol–ether, mp 278–279° dec: uv $\lambda_{max}^{CH_3OH}$ 343, 257 nm (ϵ 16,200, 28,400).

Anal. Calcd for $C_{19}H_{22}N_8O_6S_2$: C, 43.66; H, 4.24; N, 21.45. Found: C, 43.66; H, 4.22; N, 21.62.

Registry No.—**6**, 1501-48-0; **8**, 26154-44-9; **9**, 26154-45-0; **10**, 26154-46-1; **11**, 26154-47-2; **12**, 26154-48-3; **14**, 26154-49-4; **15**, 26154-50-7; **16**, 26154-51-8; **17**, 26154-52-9; **18**, 26154-53-0; **19**, 26154-54-1; **20**, 26154-55-2; **21**, 26154-56-3; **22**, 26154-57-4; **23**, 26154-58-5; **23** (ditosyl), 26154-59-6.

(21) N. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

Unsaturated Nitriles from *N*-Chlorosulfonyl-β-lactams[1]

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N-Chlorosulfonyl-β-lactams are converted into unsaturated nitriles (20–75%) with DMF and heat. Thus, the *N*-chlorosulfonyl derivatives of the following 2-azetidinones, 4,4-dimethyl- (**1**), 4,4-diethyl- (**3**), 3-ethyl-4,4-dimethyl- (**6**), 3-methyl-1-azaspiro[3.5]nonan-2-one (**9**), 3,3,4,4-tetramethyl- (**11**), 4-*tert*-butyl- (**13**), 4-phenyl- (**14**), *cis*- (**16**), and *trans*-3-methyl-4-phenyl- (**17**), 4,4-dimethyl-3-methylene- (**21**), and 4,4-dimethyl-3-isopropylidene (**25**), on treatment with DMF, afforded, respectively, the following products: 3-methyl-2-butenenitrile (**2**), a 9:1 mixture of 3-ethyl-2-pentenenitrile (**4**) and 3-ethyl-3-pentenenitrile (**5**), a 1:1 mixture of 2-ethyl-3-methyl-2-butenenitrile (**7**) and 2-ethyl-3-methylenebutanenitrile (**8**), 2-(1-cyclohexenyl)propanenitrile (**10**), 2,2,3-trimethyl-3-butenenitrile (**12**), *trans*-cinnamonitrile (**15**), α-methyl-*cis*-cinnamonitrile (**18**), 4-chloro-2,3-dimethyl-*trans*-2-butenenitrile (**23**), and 3-cyano-2,4-dimethyl-1,3-pentadiene (**26**). Without DMF, the conversion proceeds thermally in low yields (<5%). Replacement of the nucleophile DMF with DMSO as solvent–reactant afforded no nitriles. Working hypotheses for both the thermal and nucleophilic routes to unsaturated nitrile products are proposed.

The solvolytic conversion of *N*-chlorosulfonyl-β-lactams to α,β-unsaturated nitriles using DMF has been patented,[3,4] while a similar transformation of *N*-chlorosulfonylcarboxamides to nitriles with amides (DMF, formamide, dimethylacetamide, α-pyrrolidone, and *N*-methylpyrrolidone) has been reported.[5] Finally, treatment of *N*-chlorosulfonylcarboxamides with equimolar amounts of tertiary amines (triethylamine, diisopropylethylamine) also affords nitriles in good yields.[6] This latter technique is especially useful on acid-sensitive substrates. Mechanisms have been proposed for the *N*-chlorosulfonylcarboxamide → nitrile transformations,[5,6] but not for the *N*-chlorosulfonyl-β-lactam → α,β-unsaturated nitrile conversions. Further, while the reaction of 1-chlorosulfonyl-4-phenyl-2-azetidinone (**14**) with DMF has been reported, the geometry of the product cinnamonitrile has not been established [it is *trans* (**15**)].

It was the purpose of this research to enlarge the base of information available on the β-lactam–DMF reaction in order to determine its scope and limitations, and therefrom, perhaps to elucidate possible mechanisms for this conversion of β-lactams to unsaturated nitriles. The *N*-chlorosulfonyl derivatives of the following 2-azetidinones were chosen: 4,4-dimethyl- (**1**), 4,4-diethyl- (**3**), 3-ethyl-4,4-dimethyl- (**6**), 3-methyl-1-azaspiro[3.5]nonan-2-one (**9**), 3,3,4,4-tetramethyl- (**11**), 4-*tert*-butyl- (**13**), 4-phenyl- (**14**), *cis*- (**16**) and *trans*-3-methyl-4-phenyl- (**17**), *cis*- (**19**) and *trans*-3,4-diethyl- (**20**), 4,4-dimethyl-3-methylene- (**21**), and 4,4-dimethyl-3-isopropylidene (**25**).

In general, the procedure consisted of dissolution of the *N*-chlorosulfonyl-β-lactam in 3–4 mol equiv of DMF and stirring for 16–64 hr at 70–80°. After conventional work-up, the product nitriles were distilled and identified by comparison with authentic samples, synthesis, and/or degradation and spectral analysis.

Results

Treatment of **1** with DMF afforded solely the α,β-conjugated product 3-methyl-2-butenenitrile (**2**, 30%) (Scheme I). Conversely, **9** led exclusively to the β,γ-unsaturated nitrile, 2-(1-cyclohexenyl)propanenitrile (**10**, 65%). Intermediate between these extremes was the conversion of **3** and **6** to mixtures of both α,β- and β,γ-unsaturated nitriles. Thus **3** led to a separable 9:1 mixture (65–75%) of 3-ethyl-2-pentenenitrile (**4**) and 3-ethyl-3-pentenenitrile (**5**), while the trisubstituted β-lactam **6** was converted to a 1:1 mixture (63%) of 2-ethyl-3-methyl-2-butenenitrile (**7**) and 2-ethyl-3-methylenebutanenitrile (**8**).

In the case of the tetraalkyl-substituted β-lactam **11**, the only olefinic nitrile product possible, 2,2,3-trimethyl-3-butenenitrile (**12**), was isolated in 43% yield. Unexpectedly, this same β,γ-unsaturated nitrile **12** was obtained in 20% yield by treatment of the monosubstituted β-lactam **13** with DMF.

As noted, the reaction between β-lactam **14** and DMF led only to the isolation of *trans*-cinnamonitrile (**15**, 23%); further evidence for the lack of stereoselectivity in this transformation may be adduced by the fact that both *cis*- (**16**) and *trans*-β-lactam (**17**) afforded only α-methyl-*cis*-cinnamonitrile (**18**) in 20 and 25% yields, respectively.

The trans relation of vicinal protons in **15** was indicated by the strong out-of-plane absorption at μ 10.35[7a] in the ir and the magnitude of the coupling constant (J = 17 Hz) in the nmr. The α-styryl proton in **15** (cis to CN) appeared as a doublet at δ 7.20. In **18**, the analogous proton provided a more shielded signal at δ 6.80 indicative of its trans relation to the nitrile group (and/or that it is cis to the methyl group).[7b]

The reaction of *cis*- (**19**) and *trans*-β-lactam (**20**) with DMF led to an oil with no nitrile absorption.

Treatment of **21** with DMF under the usual conditions afforded 4-chloro-2,3-dimethyl-*trans*-2-butenenitrile (**23**, 35%), dehalogenation of which under hydrogen (5% Pd–C) afforded the known[8] and independently prepared 2,3-dimethyl-2-butenenitrile (**24**).

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(1) This research is supported by Public Health Service grants identified as RO1 AI08063-01-03 from the National Institute of Allergy and Infectious Diseases.

(2) Graduate Research Assistant (1966–1968) on a grant[1] supported by the NIH; taken entirely from the Ph.D. Thesis of C. Jalandoni, Fordham University, New York, N. Y., 1969.

(3) R. Graf, DBP 1,218,448, Farbwerke Hoechst AG (1963).

(4) K. Matterstock and G. Lohaus, DAS 1,253,704, Farbwerke Hoechst AG (1964).

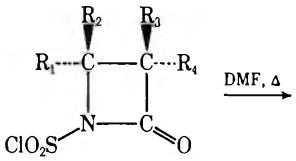
(5) G. Lohaus, *Chem. Ber.*, **100**, 2719 (1967).

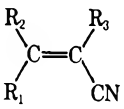
(6) H. Vorbruggen, *Tetrahedron Lett.*, 1631 (1968).

(7) (a) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 45. (b) In methacrylonitrile, *e.g.*, the protons cis and trans to the CN group appear at δ 5.82 and 5.73, respectively: Spectrum No. 97 in "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962; *cf.* also Spectra No. 64 (methyl acrylate) and No. 113 (methyl methacrylate).

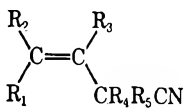
(8) Fr. de Laet, *Bull. Soc., Chim. Belges*, **38**, 168 (1929); *Chem. Abstr.*, **23**, 4443 (1929).

SCHEME I





and/or



1, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
2, $R_1 = R_2 = CH_3$; $R_3 = H$
3, $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = H$
4, $R_1 = R_2 = C_2H_5$; $R_3 = H$
5, $R_1 = R_4 = R_5 = H$; $R_2 = CH_3$; $R_3 = C_2H_5$
6, $R_1 = R_2 = CH_3$; $R_3 = C_2H_5$; $R_4 = H$
7, $R_1 = R_2 = CH_3$; $R_3 = C_2H_5$
8, $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$; $R_5 = C_2H_5$
9, $R_1R_2 = -(CH_2)_5-$; $R_3 = H$; $R_4 = CH_3$
15, $R_1 = R_3 = H$; $R_2 = C_6H_5$
10, $R_1 = R_4 = H$; $R_2R_3 = -(CH_2)_4-$; $R_5 = CH_3$
11, $R_1 = R_2 = R_3 = R_4 = CH_3$
18, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$
12, $R_1 = R_2 = H$; $R_3 = R_4 = R_5 = CH_3$
13, $R_1 = C(CH_3)_3$; $R_2 = R_3 = R_4 = H$
22, [$R_1 = R_2 = H$; $R_3 = C(CH_3)=CH_2$]
14, $R_1 = R_3 = R_4 = H$; $R_2 = C_6H_5$
23, $R_1 = R_3 = CH_3$; $R_2 = CH_2Cl$
16, $R_1 = R_4 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$
24, $R_1 = R_2 = R_3 = CH_3$
17, $R_1 = R_3 = H$; $R_2 = C_6H_5$; $R_4 = CH_3$
26, $R_1 = R_2 = CH_3$; $R_3 = C(CH_3)=CH_2$
19, $R_1 = R_4 = H$; $R_2 = R_3 = C_2H_5$
20, $R_1 = R_3 = H$; $R_2 = R_4 = C_2H_5$
21, $R_1 = R_2 = CH_3$; $R_3R_4 = =CH_2$
25, $R_1 = R_2 = CH_3$; $R_3R_4 = =C(CH_3)_2$

Both **23** and **24** displayed infrared absorptions at 4.50–4.51 (conj C≡N) and 6.08–6.10 μ (C=C). In the nmr, the two *trans*-methyl groups in **23** appeared as singlets at δ 2.11 and 1.99 with an additional two proton singlet at δ 4.23. The methyl protons in **24** appeared as singlets at δ 2.02 and 1.82 with intensity ratio 1:2, respectively. Since protons cis to electronegative substituents are more deshielded than their trans counterparts, the downfield signals at δ 2.11 and 2.02 are attributed to methyl protons cis to the nitrile group in **23** and **24**, respectively. The unusual response of **21** to DMF prompted a similar study of the effect of this nucleophile on similarly structured β-lactam **25**. The only product obtained was the conjugated diene, 3-cyano-2,4-dimethyl-1,3-pentadiene (**26**, 43%).

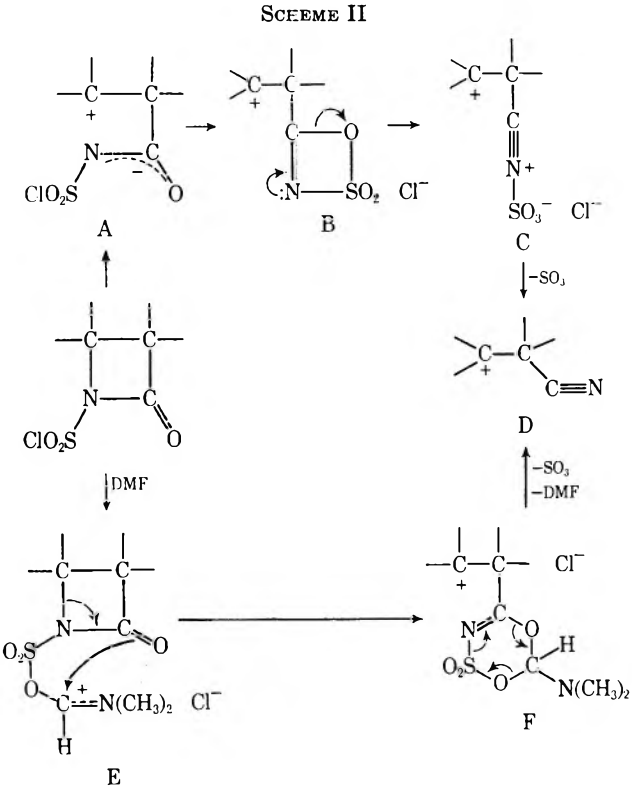
Effect of Nucleophile, Temperature, and Solvent.—Treatment of β-lactam **3** with DMSO, instead of DMF, as solvent–reactant, led to an exothermic reaction with rapid gaseous evolution. After stirring the reactants for several hours at room temperature, extensive polymerization was evident; the mixture darkened and became very viscous. The usual work-up afforded no nitriles.

When **3** and DMF were stirred at room temperature for 18 hr, a 25% yield of nitrile mixture **4** + **5** was obtained. Treatment of **3** (70–80°) for the same period of time in such solvents as hexane, benzene, and acetonitrile, but without DMF, also gave the nitrile mixture but in yields of less than 5%. Thus two mechanisms seem operative, one thermal and the other requiring the nucleophile DMF.

All reactions in this series were accompanied by extensive polymerization, some of which was probably caused by the acidic by-products generated (SO_3, HCl) under the reaction conditions. With DMF, some of this acidity may be neutralized since it forms a stable complex with SO_3.[9] With varying ratios 4–1:1 of β-lactam **3** to DMF, the product mixture yields were in the 10–20% range. When excess DMF was used (3–4 mol equiv), the yield of **4** + **5** rose to 71% which could be increased to 82% by the addition of the base pyridine.[6]

Reaction Mechanism.—Working mechanistic hypotheses for both the thermal and nucleophilic routes to unsaturated nitrile products are summarized in Scheme II. The former involves thermal β-lactam cleavage to

SCHEME II



the 1,4-dipolar species (A) with its delocalized anionic moiety. Isomerization of this primary dipole *via* the four-membered oxathiazete ring (B) to the nitrilium zwitterion C followed by elimination of SO_3 would lead to carbonium ion D, the progenitor of unsaturated ni-

(9) M. L. Wolfrom and T. M. Shenhan, *J. Amer. Chem. Soc.*, **81**, 1764 (1959).

trile products.[10] The cyclic mechanism E → F proposed involves precedented nucleophilic attack of DMF at the S site to give the iminium salt E,[5] followed by collapse of the β-lactam moiety to carbonium ion F. Loss of SO_3 and regeneration of DMF would lead to carbonium ion D. To account for the observed lack of stereoselectivity, β-lactam cleavage by both pathways to nitrilic carbonium ion D and its deprotonation to unsaturated nitriles must occur in step-wise fashion, albeit intermediate steps A → B → C → D ← F ← E may be synchronous.

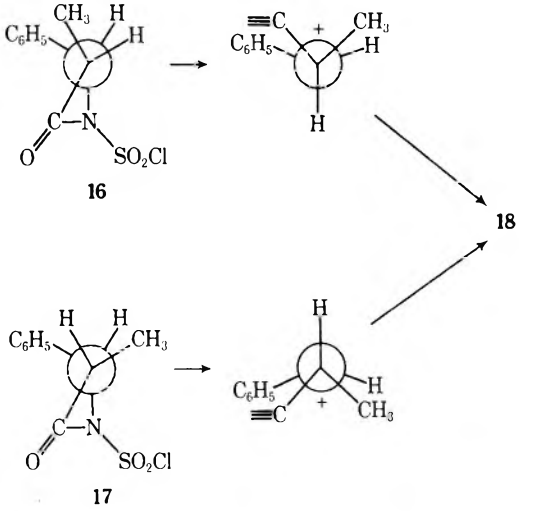
The formation of nitrile **2** and the predominance of **4**, from β-lactams **1** and **3**, respectively, suggests that when the conjugated nitrile is also the more substituted olefin, the preferred deprotonation of D is that which leads predominantly to α,β-unsaturated nitriles. The formation of **10** is in accord with the generalization that in simple hydrocarbons containing six-membered rings, endocyclic are far more stable than exocyclic double bonds.[11] A discernible pattern in the formation of equal amounts of nitrile products **7** and **8** from **7** is not evident. The formation of **8** is statistically favored over **7**; perhaps the relatively high acidity of the methine proton in **6** serves as an effective driving force in the deprotonation of D to the conjugated nitrile **7**.

The conversion of **21** to **23** presumably occurs *via* 1,4 addition of liberated HCl to intermediate 2-cyano-3-methyl-1,3-butadiene (**22**) which in turn would be a deprotonation product of D. This view of a dienic intermediate is supported by the actual isolation of the conjugated diene product **26** from **25**. Since the allylic, geminal methyl groups (R_1 and R_2 in **26**) apparently protect this double bond from further reaction, the results suggest that 1,4 addition of HCl to **22** (and its failure to do so in **26**) is initiated by protonation at the methylene carbon geminal to the nitrile function.

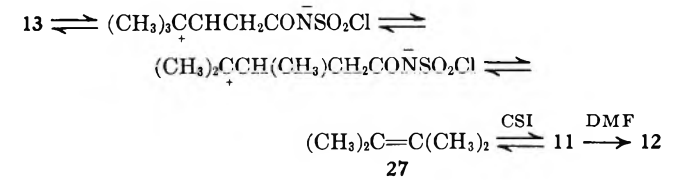
The formation of **18** from both **16** and **17** can be accounted for by deprotonation after the carbonium ion has assumed the most stable conformation; *i.e.*, the bulkier phenyl and methyl groups move farthest away from each other as the σ bond of the proton to be eliminated aligns trans to the vacant p orbital (Scheme III). If β-lactam cleavage and the deprotonation steps were synchronous, only **17** would lead to **18**.

The identity of nitrile product (**12**) resulting from **11** and **13** can be rationalized by a series of equilibria (Scheme IV) in which β-lactam **13** first rearranges, *via* the thermodynamically more stable olefin, tetramethylethylene (**27**), to β-lactam **11** followed by conversion to nitrile **12**. This rearrangement is reminiscent of the CSI-catalyzed rearrangement (slow) of 1,1,2,2-tetramethylcyclopropane to 2,3,3-trimethyl-1-butene followed by more rapid CSI addition to the formed olefin.[12]

SCHEME III



SCHEME IV

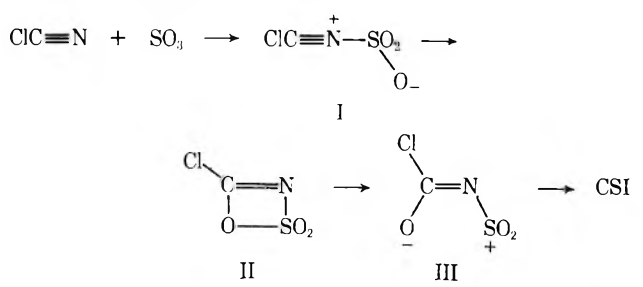


Experimental Section[13]

Reaction of β-Lactams with DMF.—The general procedure was as follows. The β-lactam was stirred at 70–80° with 3–4 mol equiv of DMF for 16–64 hr. The dark, viscous mixture was poured onto 50 ml of cold water and extracted continuously with 250 ml of pentane for 12 hr. The pentane extract was dried ($MgSO_4$), filtered, and evaporated. Distillation of the residue *in vacuo* afforded the nitrile product. Any variations in isolation procedure are noted under the appropriate β-lactam.

1-Chlorosulfonyl-4,4-dimethyl-2-azetidinone (**1**) (19.1 g, 0.10 mol) gave 2.4 g (30%) of **3-methyl-2-butenenitrile** (**2**). Vpc indicated the presence of a minor component as a shoulder on the main peak, presumably the β,γ-unsaturated nitrile. Nitrile **2** was obtained as colorless liquid: bp 39–41° (15.5 mm) [lit.[16] bp 141–142° (762 mm)]; ir (neat) 4.50 (conj C≡N) and 6.10 μ (C=C); nmr (neat) δ 1.88 (d, 3, J = 1.5 Hz, CH_3 trans to C≡N), 1.98 (s, 3, CH_3 cis to C≡N), and 5.08 (q, 1, J = 1.5 Hz, =CH).

(10) R. Graf's original mechanism for chlorosulfonyl isocyanate (CSI) preparation [*Ber.*, **89**, 107 (1956)] has been discussed in the framework of 1,4-dipolar cycloadditions by R. Huisgen [*Z. Chem.*, **8**, 290 (1968)], who suggests the following.



In this case, the primary 1,4 dipole is the nitrilium zwitterion (I) which proceeds to a new 1,4 dipole (III) *via* four-membered ring II. Our oxygen transfer step B → C is the reversal of II → III.

(11) H. C. Brown, J. H. Brewster, and H. Shecter, *J. Amer. Chem. Soc.*, **76**, 467 (1954); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(12) E. J. Moriconi, J. F. Kelly, and R. A. Salomone, *ibid.*, **33**, 3448 (1968).

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(14) (a) E. J. Moriconi and J. F. Kelly, *J. Amer. Chem. Soc.*, **88**, 3657 (1966); (b) E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).

(15) R. Graf, *Justus Liebigs Ann. Chem.*, **661**, 111 (1963).

(16) B. V. Ioffe and D. D. Tsitovich, *Dokl. Akad. Nauk SSSR*, **155**, 1348 (1964); *Chem. Abstr.*, **61**, 1849 (1964).

Anal. Calcd for C_5H_7N: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.84; H, 8.79; N, 16.92.

1-Chlorosulfonyl-4,4-diethyl-2-azetidinone (3)[16] (15.1 g, 0.07 mol) gave 5.2 g (71%) of **3-ethyl-2-pentenenitrile (4)** and **3-ethyl-3-pentenenitrile (5)** as colorless liquids in a 9:1 ratio by vpc: bp (of mixture) 68–69° (14.5 mm) [lit.[17] bp (of **4**) 66° (18 mm), lit.[18] bp (of **5**) 105–104° (72 mm)];[18] ir (neat) 4.46 (C≡N), 4.51 (conj C≡N), and 6.13 μ (C=C); nmr (neat) δ 1.02 (m, 9, CH_3), 1.60 (d, 3, J = 7 Hz, =$CHCH_3$), 2.18 (m, 6, CH_2CH_3), 3.05 (broad s, 2, CH_2CN), 5.07 (s, 1, =CHCN), and 5.41 (q, 1, J = 7 Hz, =$CHCH_3$).

Ancl. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.86; H, 10.04; N, 13.02.

The isomeric mixture was separated by preparative gas chromatography to yield **4** [ir strong bands at 4.52 (conj C≡N) and 6.06 μ (C=C)] and **5** [ir 4.46 (strong C≡N) and 5.99 μ (weak C=C)]. Recovery from preparative vpc was so poor that samples available were insufficient for individual nmr analysis.

When 5.3 g (0.07 mol) of pyridine was added dropwise to a stirred mixture of 15.1 g (0.07 mol) of **3** and 10.0 g (0.13 mol) of DMF at 60° for 24 hr, the yield of nitrile product mixture (**4** + **5**) rose to 6.0 g (82%), bp 69–71° (15 mm).

Finally, careful addition of 15.6 g (0.21 mol) of DMSO to 15.1 g (0.07 mol) of **3** led to an exothermic reaction accompanied by rapid gaseous evolution. After several hours, the dark brown viscous product displayed no CN band in the infrared.

1-Chlorosulfonyl-3-ethyl-4,4-dimethyl-2-azetidinone (6)[14b] (10.0 g, 0.04 mol) gave 3.0 g (63%) of **2-ethyl-3-methyl-2-butenenitrile (7)** and **2-ethyl-3-methylenebutanenitrile (8)** as colorless liquids in a 1:1 ratio by vpc, bp (of mixture) 61–62° (14.5 mm).

Anal. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.01; H, 10.21; N, 12.71.

Preparative vpc afforded pure **7**: ir (neat) 4.53 (conj C≡N) and 6.10 μ (C=C); nmr (neat) δ 1.08 (t, 3, J = 7 Hz, CH_2CH_3), 1.83 (s, 3, CH_3 trans to C≡N), 2.03 (s, 3, CH_3 cis to C≡N), and 2.21 (q, 2, J = 7 Hz, CH_2CH_3).

Isomer **8** with the shorter retention time could not be completely separated from **7**. Its spectral data was inferred from that of the product mixture: ir (neat) 4.47 (C≡N) and 6.04 μ (C=C); nmr (neat) δ 1.07 (t, 3, J = 7 Hz, CH_2CH_3), 1.81 (s, 3, =CCH_3), 2.20 (q, 2, J = 7 Hz, CH_2CH_3), 3.22 (t, 1, J = 7 Hz, CHCN), 4.97 and 5.04 (two singlets each with fine splitting, 2, =CH_2).

1-Chlorosulfonyl-3-methyl-1-azaspiro[3.5]nonan-2-one (9)[14b] (6.0 g, 0.02 mol) gave 2.1 g (65%) of **2-(1-cyclohexenyl)propanenitrile (10)**: bp 98–99° (12 mm) [lit.[19] bp 113° (13 mm)]; ir (neat) 4.47 μ (C≡N); nmr (CCl_4) δ 1.35 (d, 3, J = 7 Hz, CH_3), 1.63 (m, 4, C-4,5 protons of cyclohexene moiety), 2.03 (m, 4, C-3,6 allylic protons), 3.15 (q, 1, J = 7 Hz, CH), and 5.75 (broad singlet with fine splitting, 1, =CH).

Anal. Calcd for $C_9H_{13}N$: C, 79.75; H, 9.69; N, 10.36. Found: C, 79.76; H, 9.62; N, 10.38.

A repetition of Rajzman's procedure[20] for the preparation of **10** in three steps from cyclohexanone and ethyl cyanoacetate led to a product, bp 114° (19 mm), whose nmr [(CCl_4) δ 1.62 (s, 6, CH_2), 1.85 (s, 3, CH_3), and 2.37 (m, 4, CH_2)] clearly indicate it to be the α,β isomer, **2-cyclohexylidinepropanenitrile**.

1-Chlorosulfonyl-3,3,4,4-tetramethyl-2-azetidinone (11)[14b] (11.3 g, 0.05 mol) gave 2.3 g (43%) of **2,2,3-trimethyl-3-butenenitrile (12)** as a yellow oil: bp 48.5–49° (14.5 mm) [lit.[21] bp 51.3–51.5° (19 mm)]; ir (neat) 4.46 (C≡N) and 6.04 μ (C=C); nmr (neat) δ 1.42 [s, 6, $C(CH_3)_2$], 1.83 (s, 3, CH_3), 4.92 (broad s, 1, vinyl H), and 5.10 (s, 1, vinyl H).

Anal. Calcd for $C_7H_{11}N$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.00; H, 10.44; N, 12.76.

Hydrogenation of **12** (2.6 g, 0.024 mol) in 50 ml of ethanol at 39 psi over 5% Pd-C for 4 hr ultimately afforded 2.0 g (77%) of **2,2,3-trimethylbutanenitrile**: bp 46–47° (15 mm) [lit.[22] bp 152° (760 mm)]; ir (neat) 4.47 μ (C≡N); nmr (neat) δ 1.00 [d, 6, J = 6.5 Hz, $CH(CH_3)_2$], 1.26 [s, 6, $C(CH_3)_2CN$], and 1.65 (m, 1, CH).

1-Chlorosulfonyl-4-*t*-butyl-2-azetidinone (13)[15] (25.8 g, 0.11 mol) also gave 2.49 g (20%) of **12**, identical in every respect with that obtained from **11**.

1-Chlorosulfonyl-4-phenyl-2-azetidinone (14)[15] (12.2 g, 0.05 mol) gave 1.48 g (23%) of *trans*-cinnamonitrile (**15**): bp 94–95° (2 mm); ir (neat) 4.51 (C≡N), 6.15 (C=C), and 10.35 μ (*trans* -CH=CH-); nmr (CCl_4) δ 5.74 (d, 1, J = 17 Hz, =CHCN), 7.20 (d, 1, J = 17 Hz, =CHC_3H_5), and 7.30 (s, 5, C_6H_5).

Anal. Calcd for C_9H_7N: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.97; H, 5.34; N, 10.76.

***cis*-3-Methyl-4-phenyl-2-azetidinone (16)**[14b] (13 g, 0.05 mol) and 8 ml (0.10 mol) of DMF in 25 ml of benzene were refluxed for 3 days. The dark viscous mixture was added to cold water and stirred until the benzene layer separated. The benzene moiety was washed twice with water, decolorized (Norit), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Distillation at 90–92° (1 mm) afforded 1.4 g (20%) of **α-methyl-*cis*-cinnamonitrile (18)**: lit.[23] bp 120° (14 mm); ir (neat) 4.51 (C≡N) and 6.15 μ (C=C); nmr (CCl_4) δ 2.06 (s, 3, CH_3), 6.80 (broad s, 1, =CH), 7.30 (m, 3, *meta*- and *para*-aromatic H), and 7.60 (m, 2, *ortho*-aromatic H). The analytical sample was prepared by preparative vpc.

Anal. Calcd for $C_{10}H_9N$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.57; H, 6.43; N, 9.65.

Similarly, 6.5 g (0.02 mol) of ***trans*-3-methyl-4-phenyl-2-azetidinone**[14b] **(17)**, 4 ml (0.05 mol) of DMF, and 15 ml of benzene, after refluxing for 2 days, gave 0.86 g (25%) of **18**, bp 88–90° (1 mm). The ir and nmr spectra of **18** obtained from **16** and **17** were superimposable.

cis- (**19**) and *trans*-**1-Chlorosulfonyl-3,4-diethyl-2-azetidinone (20)**[14b] (2.2 g, 0.01 mol), each dissolved in 20 ml of benzene, were heated at 80° for 4 days with 5 ml of DMF. After extraction of DMF with H_2O, the organic layer was dried ($MgSO_4$) and filtered, and the benzene was removed by distillation *in vacuo*. The residual oil showed no nitrile absorption in the ir.

1-Chlorosulfonyl-3-methylene-4,4-dimethyl-2-azetidinone (21)[14] (21.0 g, 0.10 mol) gave 4.5 g (35%) of **4-chloro-2,3-dimethyl-*trans*-2-butenenitrile (23)**: bp 99.5–101° (13.5 mm); ir (neat) 4.51 (C≡N) and 6.10 μ (C=C); nmr (neat) δ 1.99 [s, 3, =$C(CH_3)CN$], 2.11 [s, 3, =$C(CH_3)CH_2Cl$], and 4.23 (s, 2, CH_2).

Anal. Calcd for C_6H_8NCl: C, 55.60; H, 6.22; N, 10.82; mol wt, 129. Found: C, 55.81; H, 6.31; N, 10.82; mol wt, 131.

Catalytic hydrogenation of **23** (1.02 g, 0.008 mol) in 30 ml of absolute ethanol over 5% Pd-C at 32 psi hydrogen pressure ultimately afforded **2,3-dimethyl-2-butenenitrile (24)**: bp 48–49° (14 mm) [lit.[8] bp 157° (766 mm)]; ir (neat) 4.50 (C≡N), 6.08 μ (C=C); nmr (neat) δ 1.82 (s, 6, *cis*-CH_3 groups) and 2.02 (s, 3, CH_3 cis to CN).

Anal. Calcd for C_6H_9N: C, 75.74; H, 9.54; N, 14.71. Found: C, 75.81; H, 9.73; N, 14.68.

The considerable discrepancy between our boiling point for **24** and the extrapolated literature value[8] led us to repeat the preparation of **24** from **3-methyl-2-butanone**. A solution of 65 g (1.0 mol) of KCN in 125 ml of water was added slowly to a cooled (ice bath) mixture of 102 g (1.0 mol) of acetic anhydride and 43 g (0.5 mol) of **3-methyl-2-butanone**. Stirring was continued for 16 hr at room temperature after which saturated Na_2CO_3 solution was added until the mixture was alkaline to litmus. The whole was extracted with three 100-ml portions of benzene. The combined extracts were washed with 30% aqueous $NaHSO_3$ and dried ($MgSO_4$), and the benzene was removed *in vacuo* (15 mm). The residual oil was distilled at 89–91° (11 mm) to yield 33.9 g (60%) of the **cyanohydrin**.

A solution of 15.6 g (0.14 mol) of this cyanohydrin in 100 ml of dry benzene was refluxed for 12 hr with 10 g of P_2O_5. The liquid was decanted from the solid material and the solvent distilled. Fractionation at 49–50° (14 mm) gave 10.5 g (79%) of a colorless liquid identical with **24**.

1-Chlorosulfonyl-4,4-dimethyl-3-isopropylidine-2-azetidinone[14] **(25)** (7.0 g, 0.03 mol) gave 1.6 g (43%) of **3-cyano-2,4-dimethyl-**

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(22) C. R. Harris and W. W. De Atley, U. S. Patent 2,455,995 (1948); *Chem. Abstr.*, **43**, 3439*h* (1949).

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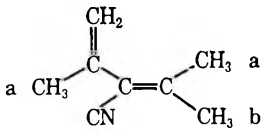

26

1,3-pentadiene (26): bp 71–74° (14.5 mm); ir (neat) 4.52 (C≡N), 6.08 and 6.14 μ (C=C); nmr (neat) δ 1.89 (split s, 6, a protons), 2.07 (s, 3, b protons), 4.87 (broad s, 1, vinyl proton), and 5.17 (m, 1, vinyl proton).

Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.33; H, 9.61; N, 11.34.

Registry No.—**2,** 4786-24-7; **4,** 5631-82-3; **5,** 26157-47-1; **7,** 26157-48-2; **8,** 26154-39-2; **10,** 26157-49-3; **12,** 4786-26-9; **15,** 1885-38-7; **18,** 26157-51-7; **23,** 26157-52-8; **24,** 4786-37-2; **26,** 26154-42-7; 2,2,3-trimethylbutanenitrile, 26154-43-8.

Phosphoramidate Analogs of Oligonucleotides[1]

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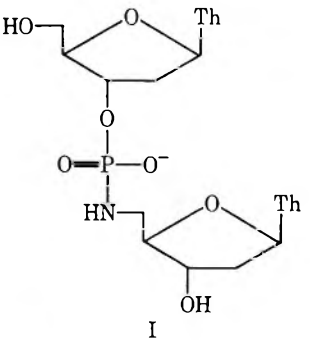
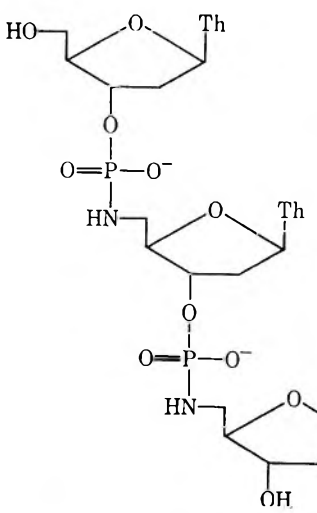
Some dinucleoside phosphate and trinucleoside diphosphate analogs that possess internucleotide phosphoramidate bonds [-OP(O)NH-] are described. These compounds are stable in neutral and alkaline solution, but they hydrolyze in acidic solutions and in solutions containing snake venom phosphodiesterase or spleen phosphodiesterase. A possible role for substances of this type in the synthesis of defined polynucleotides is suggested.

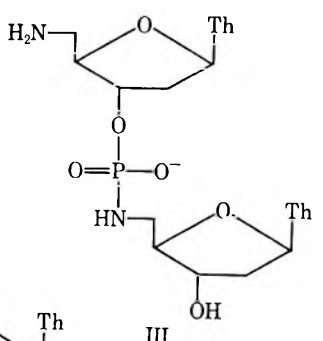
We describe in this paper the synthesis and some chemical properties of the oligonucleotide analogs thymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (Tp_NT, compound I), thymidylyl-(3′–5′)-5′-amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (Tp_NTp_NT, compound II), and 5′-amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine ($_NTp_NT$, compound III). These compounds were prepared as models to explore the accessibility and stability of polymers containing nucleoside units joined by O–P–N bonds. Our interest in this class of compounds was stimulated by the prospect that the stepwise chemical synthesis of such analogs might be more readily achieved than the synthesis of the natural polynucleotides and that the phosphoramidate analogs might serve as templates for enzymatic synthesis of defined polynucleotides from the nucleoside triphosphates and the polymerase enzymes.



I



II



III

The general synthetic approach was patterned after the phosphotriester method for oligonucleotides[3] as modified by Reese and Saffhill.[4] Thymidine was first protected by reaction with isobutyl chloroformate, a reagent that reacts selectively at the 5′ oxygen.[5] Treatment of the resulting ester, 5′-*O*-isobutyloxycarbonylthymidine, with phenyl phosphorodichloridate and pyridine in dioxane, followed by 5′-amino-5′-deoxythymidine[6] and triethylamine in dioxane, afforded the protected derivative, compound IV. This phosphoramidate was isolated in 83% yield by chromatography on silica gel. In agreement with expectations, the condensation of the phosphoryl monochloride with the amino group of 5′-amino-5′-deoxythymidine proceeded rapidly, being complete in less than 30 min. This feature is advantageous since it would facilitate the synthesis of a long chain poly(aminodeoxy nucleotide), both by reducing the time (relative to the time for synthesizing a natural polynucleotide *via* phosphoryl chlorides) and by eliminating the necessity for blocking the oxygen function at the 3′ position of the nucleosides.

One of the major questions concerning the utility of polynucleotide phosphoramidate analogs pertained to the stability of the internucleoside links. Simple phosphoramidates are known to be relatively labile; they hydrolyze readily in aqueous acid[7] and are suffi-

(1) Part XVI in series on Nucleotide Chemistry; for XV, see R. L. Letsinger, K. K. Ogilvie, and P. S. Miller, *J. Amer. Chem. Soc.*, **91**, 3360 (1969). This research was supported in part by a research grant (GM 10265) from the Division of General Medical Sciences of the National Institutes of Health.

(2) National Science Foundation Predoctoral Fellow, 1968–present.

(3) R. L. Letsinger and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **91**, 3350 (1969); **89**, 4801 (1967).

(4) C. B. Reese and R. Saffhill, *Chem. Commun.*, 767 (1968).

(5) K. K. Ogilvie and R. L. Letsinger, *J. Org. Chem.*, **32**, 2365 (1967).

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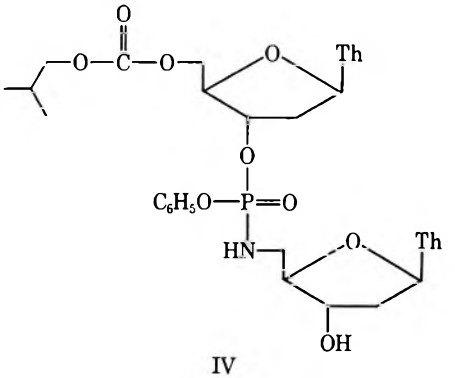
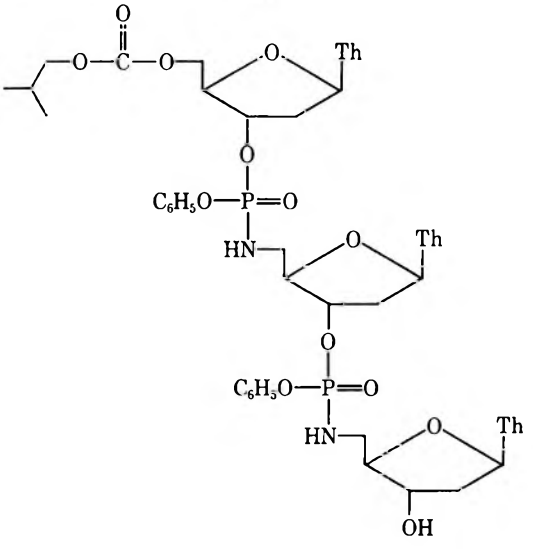
(7) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1966, p 71; (b) A. W. Garrison and C. E. Boozer, *J. Amer. Chem. Soc.*, **90**, 3486 (1968).

ciently reactive toward nucleoside phosphates and pyrophosphate[8] to serve as reagents for preparation of dinucleoside pyrophosphates and nucleoside triphosphates. Jastorff and Hettler[9] recently synthesized an N-phosphorylated 5′-amino-5′-deoxy nucleoside and found that it hydrolyzed readily in neutral aqueous solution. Fortunately, the internucleoside phosphoramidate link in IV proved to be relatively stable. Thus we found that IV was unchanged for extended periods (48 hr) in anhydrous pyridine and in a mixture of 4 parts of pyridine and 1 part of acetic acid at room temperature. Furthermore, there was no evidence of decomposition when IV was chromatographed on silica gel with ethyl acetate.



IV



V

On alkaline hydrolysis, the isobutyloxycarbonyl and phenoxy groups were cleanly removed from IV to give I. This substance did not degrade further when heated with 0.5 *M* aqueous sodium hydroxide at 98° for 1 hr. Compound I was also stable in 50% aqueous pyridine (64 hr) and in concentrated ammonium hydroxide (84 hr) at room temperature; however, it exhibited some degradation when heated with 50% aqueous pyridine at 100° for 25 min. That this latter reaction involves nucleophilic attack by pyridine rather than a base-catalyzed reaction is suggested by the observation that I is stable when heated with 50% aqueous 2,6-lutidine under the same conditions.[10] Especially important for the projected study of template activity of polynucleotide phosphoramidate analogs is the observation that I is stable in aqueous solutions containing phosphate (0.5 *M* at pH 8.6) or a nucleoside triphosphate (no reaction found over a period of 9 days for 10^{-2} *M* Tp_NT in the presence of 2×10^{-2} *M* adenosine triphosphate in 0.1 *M* Tris-HCl buffer at pH 8).

Successive treatment of compound IV with phenyl phosphorodichloridate and 5′-amino-5′-deoxythymidine afforded the protected trinucleotide analog, compound V. Like IV, this compound was relatively stable in neutral and in weakly alkaline solutions. On treatment with strong alkali (0.1 *M* sodium hydroxide in 50% aqueous dioxane), it was smoothly converted to II without any cleavage of P–N bonds.

Both I and II were completely hydrolyzed when heated at steam bath temperature in 80% aqueous acetic acid for 20 min. Compound I gave equimolar amounts of thymidine 3′-phosphate (Tp) and 5′-amino-5′-deoxythymidine ($_NT$), as determined by the absorbance of material eluted from paper chromatograms. Compound II similarly afforded equimolar amounts of Tp, $_NT$, and 5′-amino-5′-deoxythymidine 3′-phosphate ($_NTp$).

Of especial interest are the hydrolyses effected by the exonucleases, snake venom phosphodiesterase and spleen phosphodiesterase. Whereas a P–O bond in the sequence O–P–O is broken in a reaction of a natural substrate, P–O or P–N in the sequence O–P–N must be broken if I or II is hydrolyzed. Both enzymes in fact attacked the phosphoramidates, though at a reduced rate relative to attack on TpT or TpTpT. Snake venom phosphodiesterase degraded both I and II completely, yielding T and $_NT$ (1:1 ratio for I; 1:2 ratio for II). Formation of aminodeoxythymidine in these reactions may be rationalized on the basis that 5′-amino-5′-deoxythymidine 5′-phosphate, the expected product, hydrolyzes spontaneously in water to orthophosphate and aminodeoxythymidine.[9] Spleen phosphodiesterase, which attacks an oligonucleotide from the 5′ terminus, converted I to Tp and $_NT$ (P–N cleavage). In the case of II, the first nucleotide unit was removed from the 5′ end; however, the reaction then slowed down markedly. At the end of 18 hr (compare with I, which was completely degraded within 12 hr) the products were Tp, $_NTp$, $_NT$, and a fourth substance which exhibited properties expected for $_NTp_NT$. This result indicates that a terminal 5′-amino group inhibits the action of spleen phosphodiesterase.

To test the conclusion that a 5′-amino group in the nucleotide substrate inhibits the action of spleen phosphodiesterase, we prepared 5′-amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (III). This compound was made from 5′-*N*-isobutyloxycarbonyl-5′-amino-5′-deoxythymidine by the procedure used to prepare I from 5′-*O*-isobutyloxycarbonylthymidine. In agreement with expectations based on the behavior of II, compound III was completely hydrolyzed to 5′-amino-5′-deoxythymidine by an aqueous solution of snake venom phosphodiesterase, and the reaction with spleen phosphodiesterase was slow. With the spleen enzyme, 13% of the sample of III remained at the end of 18 hr; otherwise the hydrolysis proceeded normally, yielding equivalent amounts of 5′-amino-5′-deoxythymidine 3′-phosphate and 5′-amino-5′-deoxythymidine.

(8) J. G. Moffatt and H. G. Khorana, *J. Amer. Chem. Soc.*, **83**, 649 (1961).
(9) B. Jastorff and H. Hettler, *Tetrahedron Lett.*, 2543 (1969).
(10) Compare ref 7a, p 78.

These synthetic and degradative experiments demonstrate that the phosphoramidate analogs of oligothymidylates can be made and that they are stable in aqueous neutral and alkaline solutions. Work is now in progress to synthesize long-chain oligonucleotide analogs to test the template activity of such compounds.

Experimental Section

Infrared spectra were recorded on a Beckman IR-5 spectrophotometer and ultraviolet spectra were recorded on a Cary 11 spectrophotometer. Melting points were determined with a Kofler hot-stage microscope apparatus and are uncorrected. Elemental analyses were made by Micro-Tech Laboratories, Skokie, Ill.

Reagent grade pyridine was distilled from *p*-toluenesulfonyl chloride, redistilled from calcium hydride, and stored over Linde 4-A molecular sieves. Reagent grade 1,4-dioxane was distilled from lithium aluminum hydride and stored over molecular sieves. Triethylamine was distilled from *p*-toluenesulfonyl chloride, redistilled from calcium hydride, and stored over barium oxide. DEAE-cellulose (0.69 equiv/g) was a product of Bio-Rad Laboratories. ChromAR 1000, a preparative thin layer chromatography (tlc) medium, was purchased from Mallinckrodt Chemical Co. For analytical tlc, Eastman 6060 sheets were used.

Paper electrophoresis was performed on a Savant flatbed apparatus at 2000 V using Whatman 3MM paper and a 0.05 *M* sodium phosphate buffer (pH 7.2). Nucleosides and their derivatives were located under uv light. In addition, 5′-amino-5′-deoxythymidine was detected by the 2,4-dinitrofluorobenzene color test.[11] Paper chromatography was carried out on Whatman 3MM paper by the descending technique. The solvent systems were: A, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2 v/v/v); C, ethanol–1 *M* aqueous ammonium acetate (7:3, pH 7.5); F, *n*-propyl alcohol–concentrated ammonium hydroxide–water (55:10:35). For quantitative determinations the bands were cut out, eluted with water, and diluted to a known volume. Absorbances were determined with a Gilford spectrophotometer, and the values were corrected by subtraction of the absorbancy for a blank cut from the paper adjacent to the product spot. The extinction coefficients used in calculating yields are 9.7×10^3 at 267 nm for T, Tp, and pT[12] and 9.3×10^3 at 266 nm for $_N$T.[6]

Phenyl Ester of 5′-*O*-Isobutyloxycarbonylthymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (IV).—5′-*O*-Isobutyloxycarbonylthymidine[5] (68 mg, 0.20 mmol) was dried by evaporation of three 1-ml portions of pyridine under reduced pressure. The resulting gum was dissolved in 4 ml of dioxane and treated with pyridine (0.032 ml, 0.40 mmol) and phenyl phosphorodichloridate (0.031 ml, 0.20 mmol); then the solution was stirred 48 hr at room temperature. Triethylamine (0.056 ml, 0.40 mmol) and 5′-amino-5′-deoxythymidine[6] (72 mg, 0.30 mmol) in 18 ml of dioxane were added, the mixture was stirred for 30 min, aqueous sodium hydroxide (0.7 ml of 0.5 *M* solution) was added, and the solution was concentrated (<30°) at reduced pressure. Following addition of 2 ml of saturated aqueous sodium chloride, the mixture was extracted three times with 10-ml portions of ethyl acetate. On concentration of the ethyl acetate extracts and chromatography on two sheets of ChromAR 1000 (20 × 20 cm, developed twice with ethyl acetate), three bands were observed: a dark band at the origin consisting of excess $_N$T, a dark product band centered at R_f 0.3, and a faint band near the solvent front. Elution of the product band with tetrahydrofuran and precipitation by addition of hexane afforded 120 mg (83%) of compound IV, mp 108–111°, homogeneous on tlc in tetrahydrofuran (R_f 0.67), 1:1 tetrahydrofuran–ethyl acetate (R_f 0.44), acetone (R_f 0.36), and ethyl acetate (R_f 0.05). For analysis, a sample was reprecipitated from tetrahydrofuran with hexane, mp 108–111°, λ_{max} (CH_3OH) 265 nm (ϵ 1.9×10^4), and λ_{min} 234 nm.

Anal. Calcd for $C_{31}H_{40}N_5O_{13}P \cdot H_2O$: C, 50.33; H, 5.72; N, 9.47. Found: C, 50.29; H, 5.40; N, 9.49.

Thymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (I).—Compound IV (99 mg) was dissolved in 6 ml of 0.1 *M* sodium hydroxide in 50% aqueous dioxane and kept at room temperature for 6 hr. The solution was then neutralized with a minimum of pyridinium Dowex 50 resin, filtered to remove the resin (which was then washed with water), concentrated to 10 ml (<25°), diluted to 20 ml with water, concentrated again to remove dioxane, and applied to a DEAE-cellulose column (3 × 34 cm) in the bicarbonate form. The column was eluted with 2 l. of a linear gradient solution ranging from 10^{-3} *M* ammonium bicarbonate (in 10% aqueous ethanol adjusted to pH 8 with ammonium hydroxide) to 10^{-1} *M* ammonium bicarbonate (also in 10% aqueous ethanol, pH 8). Fractions of 13 ml were collected at the rate of 80 ml/hr. Two uv absorbing bands were eluted: the first (fractions 8–26) contained unhydrolyzed phenyl ester; the second (fractions 39–58) contained the desired Tp_NT (I). This material was obtained as the ammonium salt by concentrating the solution under reduced pressure, lyophilizing, redissolving the solid in water, and lyophilizing again to remove residual ammonium bicarbonate: weight 55 mg (70%); mp 205–208° dec; λ_{max} (H_2O) 267 nm (ϵ 1.9×10^4). It was homogeneous on chromatography in solvent A (R_f 0.28), C (R_f 0.55), F (R_f 0.67), and on electrophoresis (R_m 0.33 relative to pT).

Anal. Calcd for $C_{20}H_{31}N_6O_{11}P \cdot 3H_2O$: C, 38.96; H, 6.04; N, 13.63. Found: C, 39.34; H, 5.36; N, 13.38.

Diphenyl Ester of 5′-*O*-Isobutyloxycarbonylthymidylyl-(3′–5′)-5′-amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (V).—This compound was prepared from IV (361 mg, 0.50 mmol) by reaction with the same reagents in the same relative molar amounts as used for conversion of 5′-*O*-isobutyloxycarbonylthymidine to IV. On chromatography on a silica gel column (3 × 35 cm) with ethyl acetate and tetrahydrofuran, three substances were found: $_N$T, V, and IV. Compound V was eluted from the column with 50% ethyl acetate–tetrahydrofuran and precipitated with hexane, weight 320 mg (58%). It was homogeneous on tlc with acetone (R_f 0.19) and tetrahydrofuran–ethyl acetate (1:1, R_f 0.32).

Anal. Calcd for $C_{47}H_{58}N_8O_{19}P_2 \cdot H_2O$: C, 50.44; H, 5.40; N, 10.01. Found: C, 50.48; H, 5.35; N, 10.14.

Compound V (2 mg) was treated with 0.2 ml of 0.1 *M* sodium hydroxide in 50% aqueous dioxane for 6 hr at room temperature. The solution was carefully neutralized with 1 *M* hydrochloric acid and samples were withdrawn for testing. A single nucleotide spot was found on paper chromatography in solvents A (R_f 0.06) and C (R_f 0.32) and on paper electrophoresis (R_m 0.52 relative to pT). For enzyme assay, compound II was further purified by electrophoresis and by paper chromatography in solvent A and was collected as a dry powder by lyophilization.

Hydrolytic Degradation.—Acid-catalyzed hydrolyses were carried out by heating the nucleotidic material (1 mg) in a solution of acetic acid–water (80:20 v/v) at steam bath temperature for 20 min. The products were then separated by chromatography on paper with solvent A.

Enzymatic reactions were patterned after procedures described in the literature.[13] Standard solutions of the enzymes were prepared by dissolving commercial snake venom phosphodiesterase (200 units, Calbiochem) in 0.1 *M* Tris buffer (1 ml, adjusted to pH 9.2 with hydrochloric acid) and by adding spleen phosphodiesterase (10–15 units, Nutritional Biochemical Co.) to a 0.01 *M* sodium pyrophosphate buffer (1 ml, adjusted to pH 6.5 with phosphoric acid). For reaction with the snake venom enzyme, 0.1 ml of the standard enzyme solution was added to the solid nucleotidic sample (~10 OD units) and the solution was incubated at 37° for 12 hr. Additional enzyme solution (0.1 ml) was added and the reaction was continued for another 6 hr. The solution was then frozen, lyophilized, and subjected to chromatography with solvent A. The reactions with the spleen enzyme were similarly carried out by mixing 0.1 ml of the standard enzyme solution with a solution of the substrate (~10 OD units) in 0.2 ml of 0.5 *M* ammonium acetate buffer (pH 6.5). After 12 hr, additional enzyme solution (0.1 ml) was added and the reaction was continued another 6 hr before work-up. Data on the products are summarized in Tables I and II. When the reaction of I with the snake venom enzyme was terminated at the end of 12 hr, 13% of I remained. Also, the reaction of I with spleen phosphodiesterase was incomplete after 7 hr. In contrast, under the same conditions TpT and TpTpT were completely hy-

(11) N. D. Cheronis and J. B. Entrikin, "Identification of Organic Compounds," Interscience, New York, N. Y., 1963, p 131.

(12) H. G. Khorana and J. P. Vizsolyi, *J. Amer. Chem. Soc.*, **83**, 675 (1961).

(13) H. G. Khorana, A. F. Turner, and J. P. Vizsolyi, *ibid.*, **83**, 686 (1961); M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *ibid.*, **84**, 430 (1962).

TABLE I
PROPERTIES OF HYDROLYTIC PRODUCTS OF I, II, III

Compd	R_f[a]	R_m[b]
T	0.60	−0.11
Tp	0.11	1.00
Tp_NT	0.28	0.33
Tp_NTp_NT	0.07	0.55
$_NT$	0.47	−0.69
$_NTp$	0.05	0.45
$_NTp_NT$	0.14	−0.10

[a] Paper chromatograph, solvent A, ~23°. [b] Electrophoretic mobility relative to pT.

drolyzed by both enzymes within 7 hr. Control experiments showed that no hydrolysis occurred when I or II was subjected to the action of the buffers in the absence of enzymes.

5′-*N*-Isobutyloxycarbonyl-5′-amino-5′-deoxythymidine.—To a solution of 5′-amino-5′-deoxythymidine (120 mg, 0.50 mmol) in pyridine (5 ml) was added isobutyl chloroformate (0.07 ml, 0.5 mmol). After standing 15 min at room temperature, the solution was mixed with water (0.5 ml), concentrated to a syrup, and mixed with ethyl acetate (60 ml) and water (5 ml). The organic layer was separated, washed with water, and evaporated. Recrystallization of the residue from acetonitrile afforded 147 mg (88%) of the title compound, mp 181–183°, homogeneous on tlc with ethyl acetate (R_f 0.16), acetone (R_f 0.61), and tetrahydrofuran–ethyl acetate (1:1, R_f 0.62). The analytical sample, mp 184–185°, was obtained by recrystallization from acetonitrile–ethyl ether (3:1).

Anal. Calcd for $C_{15}H_{23}N_3O_6$: C, 52.78; H, 6.79; N, 12.31. Found: C, 59.92; H, 6.72; N, 12.56.

5′-Amino-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (III).—The procedure used to prepare IV was followed except that 5′-*N*-isobutyloxycarbonyl-5′-amino-5′-deoxythymidine (68 mg, 0.20 mmol) was used in place of 5′-*O*-isobutyloxycarbonylthymidine. The product was applied to two sheets of ChromAR 1000 (20 × 20 cm) and developed four successive times with ethyl acetate. At this point the desired material had moved about a quarter the length of the sheet. It was removed by elution with tetrahydrofuran and was precipitated by addition of hexane, weight 76 mg (53%), homogeneous on tlc with acetone (R_f 0.34), tetrahydrofuran–ethyl acetate (1:1, R_f 0.31), and tetrahydrofuran (R_f 0.65). The analytical sample was obtained by dissolving the sample in tetrahydrofuran, filtering, and precipitating with hexane, mp 128–130°.

Anal. Calcd for $C_{31}H_{41}N_6O_{12}P \cdot H_2O$: C, 50.40; H, 5.87; N, 11.38. Found: C, 50.55; H, 5.78; N, 11.15.

TABLE II
HYDROLYTIC PRODUCTS

		Relative molar amounts[a]				
Substrate	Catalyst	T	$_NT$	$_NTp_NT$	Tp	$_NTp$
Tp_NT	H^+		1.0		0.91	
	Venom	0.92	1.0			
	Spleen		1.0		1.05	
Tp_NTp_NT	H^+		1.0		1.07	0.99
	Venom	1.00	1.98			
	Spleen		0.42	0.38	1.00	0.49
$_NTp_NT$	H^+		1.0			0.94
	Venom		1.0			
	Spleen		1.0	0.13		1.1

[a] Relative to one of the products, usually $_NT$.

For removal of the isobutyloxycarbonyl and phenyl groups, a sample (1.61 mg) was treated with 2 *M* aqueous sodium hydroxide (0.2 ml) for 2 hr on a steam bath. The solution was neutralized to a phenolphthalein end point with dilute hydrochloric acid and diluted with 2 vol of methanol to precipitate most of the sodium chloride. On application of the solution to paper (3MM) and development with solvent A, a single nucleotidic spot was observed (R_f 0.15–0.20). The band was cut out and compound III was eluted with water. It was homogeneous on paper chromatography in solvent A and C (R_f 0.23) and on electrophoresis (R_m −0.1 relative to pT). For hydrolytic studies, the sample was rechromatographed on paper with solvent F and recovered from the paper in the usual way. The reactions with acetic acid and the hydrolytic enzymes were carried out as in the case of compounds I and II (Table II).

Registry No.—I, 25383-42-0; II, 25383-43-1; phenyl ester of 5′-*N*-isobutyloxycarbonyl derivative of III, 25383-44-2; IV, 25442-41-5; V, 25383-45-3; 5′-*N*-isobutyloxycarbonyl-5′-amino-5′-deoxythymidine, 25383-46-4.

Routes to Substituted Methyl β-Maltosides[1]

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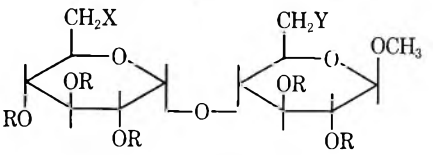
Reaction of methyl β-maltoside (**1**) with *p*-toluenesulfonyl (tosyl) chloride in a 1:1.1 molar ratio gave 28% of the 6,6′-ditosylate (**2a**) (isolated as an ethanolate **2b**), 18% of the 6′-tosylate (**3**), and 1% of the 6-tosylate (**4**). Acetylation of **2a** (or **2b**), **3**, and **4** produced the corresponding peracetates **5**, **6**, and **7**, which on treatment with sodium iodide in acetone were converted to 6,6′-dideoxy-6,6′-diiodo acetate (**8**), 6′-deoxy-6′-iodo acetate (**9**), and 6-deoxy-6-iodo acetate (**10**), respectively. Catalytic hydrogenolysis of the iodo acetates **8**, **9**, and **10** gave the corresponding deoxy acetyl maltosides **11**, **12**, and **13**. Reaction of methyl 2,2′,3,3′,4′-penta-*O*-acetyl-6,6′-di-*O*-*p*-tolylsulfonyl-β-maltoside (**5**) with sodium iodide in a 1:1 molar ratio produced methyl 2,2′,3,3′,4′-penta-*O*-acetyl-6-deoxy-6-iodo-6′-*O*-*p*-tolylsulfonyl-β-maltoside (**14**) as the major iodo product. Structures were assigned on the basis of catalytic hydrogenolysis of **14** to the related 6-deoxy-6′-tosylate (**15**), which on treatment with sodium hydroxide gave methyl 3′,6′-anhydro-6-deoxy-β-maltoside (**16**). Structures were also assigned by nmr evidence that located the C_5-CH_3 doublet for the α anomer in a higher field than the β anomer in a 6-deoxypyranoside.

Many studies during the past 5 years have reported on the hydrolytic behavior of substituted and unsubstituted glycosides in dilute acid solution.[3] Little work, however, has been done on disaccharides. We wished to determine the effect of substitution on the rate of hydrolysis of the 1′-4 glycosidic bonds of methyl β-maltoside, since we felt that results could be extrapolated to starch. Alteration of substituents in the 6 position was known to affect the rate of hydrolysis of glycopyranosides.[3d] Consequently, we undertook the synthesis of 6,6′-mono- and disubstituted derivatives of methyl β-maltoside and report here the details leading to the syntheses of these derivatives (Table I).

TABLE I
COMPOUNDS INVESTIGATED[a]



Compd no.	R	X	Y
1	H	OH	OH·H_2O
2a	H	OTs	OTs
2b	H	OTs	OTs·C_2H_5OH
3	H	OTs	OH
4	H	OH	OTs
5	Ac	OTs	OTs
6	Ac	OTs	OAc
7	Ac	OAc	OTs
8	Ac	I	I
9	Ac	I	OAc
10	Ac	OAc	I
11	Ac	H	H
12	Ac	H	OAc
13	Ac	OAc	H
14	Ac	OTs	I
15	Ac	OTs	H
17	Ac	OBz	H

[a] Ac, acetyl; Ts, *p*-tolylsulfonyl; Bz, benzoyl.

Wolfrom and Koizumi,[4] using maltose and trityl chloride, isolated the three 6,6′-di- and monosubstituted trityl derivatives. Because the procedure envisioned for transforming these 6,6′-trityl derivatives to the related maltosyl sulfonate derivatives was multistepped, a direct reaction of methyl β-maltoside to form the sulfonates was deemed more convenient. Preferential reaction at a primary hydroxyl group by *p*-toluenesulfonyl (tosyl) chloride was known[5] and had been used previously to synthesize methyl 6,6′-di*O*-*p*-tolysulfonyl-β-maltoside.[6] The related 6,6′-dimethanesulfonate had been prepared by Newth, *et al.*[7] For convenience tosyl chloride was selected as the reagent of choice for entry into the series.

After work-up and recrystallization, a 6,6′-ditosylate derivative was obtained in 28% yield when tosyl chloride and methyl β-maltoside (**1**) were allowed to react in a 1.1:1 molar ratio. Both nmr spectroscopy and chemical analysis[8] established that this ditosylate contained 1 mol of ethanol of crystallization. Consequently, the ditosylate was methyl 6,6′-di-*O*-*p*-tolylsulfonyl-β-maltoside monoethanolate (**2b**). Our results on this ditosyloxymaltoside differed from those reported[6] in that the ethanol of crystallization was not previously indicated.

By column chromatography[9] and acetylation, 18% of **6** and 1% of **4** were obtained. This result was in accord with the expected influence of steric hindrance. The ratio of 6′- to 6-tosyl substitution agreed with results reported for analogous tritylation.[10]

The corresponding iodides of **2a**, **3**, and **4** were produced in over 90% yield with excess sodium iodide in acetone following acetylation of the substrates (Figure 1B). Without acetylation these iodide displacements resulted in a large number of spots on tlc plates and the desired products were isolated in low yield (<20%). The iodo acetates **8**, **9**, and **10** were, in turn, catalytically hydrogenolyzed to produce **11**, **12**, and **13** (Figure 1B).

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(2) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(3) (a) T. E. Timell, *Can. J. Chem.*, **42**, 1456 (1964); (b) R. J. Ferrier, L. R. Hatton, and W. G. Overend, *Carbohyd. Res.*, **8**, 56 (1968); (c) M. D. Saunders and T. E. Timell, *ibid.*, **6**, 12 (1968); (d) T. E. Timell, W. Enterman, F. Spencer, and E. J. Soltes, *Can. J. Chem.*, **43**, 2296 (1965); (e) M. S. Feather and J. F. Harris, *J. Org. Chem.*, **30**, 153 (1965); (f) J. T. Edward, *Chem. Ind. (London)*, 1102 (1955).

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(5) D. H. Ball and F. W. Parrish, *Advan. Carbohyd. Chem.*, **23**, 240 (1968); **24**, 139 (1969).

(6) M. L. Wolfrom, Y.-L. Hung, P. Chakravarty, G. U. Yuen, and D. Horton, *J. Org. Chem.*, **31**, 2227 (1966).

(7) F. H. Newth, S. D. Nicholas, F. Smith, and L. F. Wiggins, *J. Chem. Soc.*, 2552 (1949).

(8) In ref 6 an incorrect chemical formula was used to calculate the analytical values.

(9) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

(10) In ref 4 some conflict exists between values reported in the abstract and those given in the experimental section. We believe this error to be typographical.

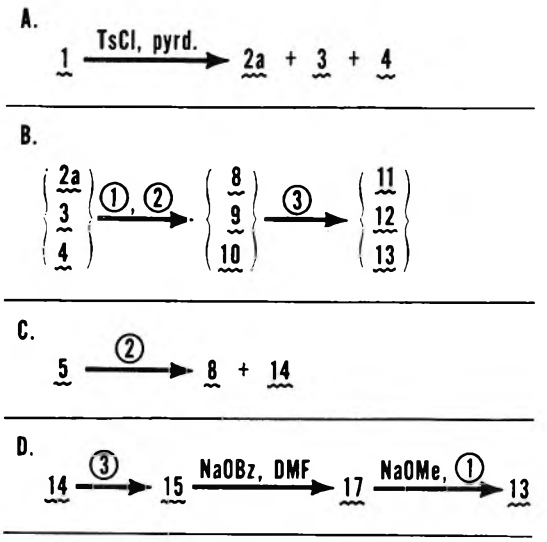

Figure 1.—Reaction sequences: ① = Ac_2O, pyridine; ② = NaI, refluxing acetone; ③ = H_2, Pd-C, KOH; pyrd. = pyridine; DMF = N,N-dimethylformamide.

Proof of structure of the three deoxy sugars **11**–**13** was obtained in two ways. The first was a new nmr correlation method,[1,11] which held that, for C-6-deoxypyranosides, the doublet for the C-5 methyl was always located at higher field for the α anomer than the doublet for the β anomer. Examples are given in Table II. Thus **11** had two doublets: δ 1.16 for the C-5′ methyl and 1.39 for the C-5 methyl. The doublet at δ 1.15 in the spectrum of **12** was indicative of the C-5′ methyl. The doublet at δ 1.39 in the spectrum of **13** corresponded to the C-5 methyl (Figure 2).

TABLE II

C_5-CH_3 RESONANCE PEAK IN ANOMERIC 6-DEOXYPYRANOSIDES

	Anomer			
Compd	α	J, Hz	β	J, Hz
6-Deoxy-L-mannose	1.60	6	1.65	6
Methyl 6-deoxy-L-mannoside	1.26	6	1.28	6
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-L-mannoside	1.20	6	1.28	6
6-Deoxy-D-galactose	1.19	7	1.22	7
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy D-galactoside	1.13	6	1.21	6

The second proof of structure was established by chemical conversions, generally known to give unrearranged products[5] that are observed when **5** was treated with sodium iodide in a 1:1 molar ratio. Preferential displacement of the 6-*O*-tosyl group gave the products shown in Figure 1C. Catalytic hydrogenolysis of **14** gave **15**, which had a doublet for the C-5 methyl at δ 1.34. Compound **15** was converted to **13** by the sequence shown in Figure 1D. Reaction of **15** with ethanolic sodium hydroxide (Figure 3) gave methyl 3′,6′-anhydro-6-deoxy-β-maltoside (**16**) as the only product (~90%). Compound **16**, having the C-5 methyl doublet at δ 1.39, was oxidized by sodium metaperiodate with an uptake to 1.06 equiv of periodate per mol of anhydro substrate. The only other possible structure that could have consumed 1 mol equiv of periodate was methyl 3′,6-anhydro-6′-deoxy-β-maltoside. Such eight-membered anhydro rings are not known to occur by base elimination of tosylate groups in carbohydrates;[7] it is unlikely that an eight-membered ring would be formed in as high yield as found. Any other anhydro structure would have consumed 2 mol equiv of sodium metaperiodate.

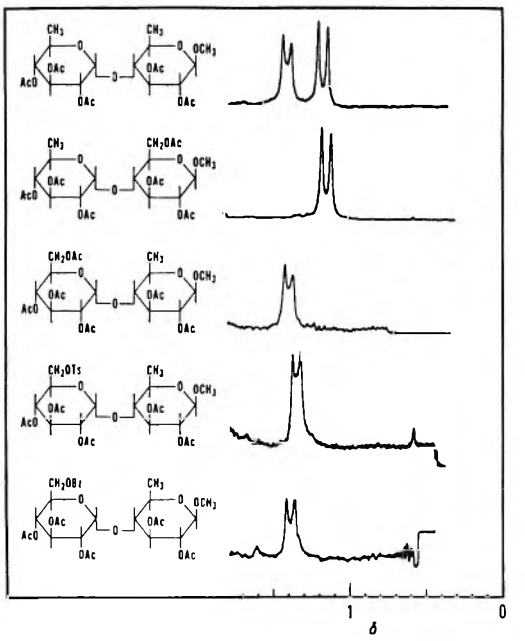

Figure 2.—Nmr spectra (100 MHz) in chloroform-*d* with internal tetramethylsilane.

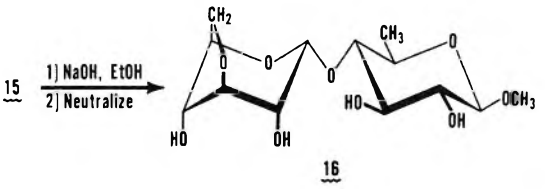

Figure 3.—3′,6′-Anhydro formation.

Partial tosylation of **1** and partial tritylation of maltose[4] and benzyl β-maltoside[12] resulted in a 6′ derivative. This difference in reactivity of the two primary hydroxyl groups, 6 and 6′, was attributed to a steric effect. Although considerations of the steric accessibility would have predicted that the 6′-tosylate to be more reactive than the 6-tosylate, the latter proved to be more reactive in the partial displacement of the 6,6′-ditosylate **5** by sodium iodide. Dutton and Slessor[13] report their attempts were unsuccessful at selective tosylation of the primary hydroxyl group in benzyl 4′,6′-*O*-benzylidene-β-maltoside.

Little systematic work has been carried out on the selective sulfonation of disaccharides and on the displacement reactions of these sulfonyl disaccharides. The present investigations show that reactions usually classed as typical with monosaccharides become altered when applied to disaccharides.

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(12) B. Helferich and W. Speicher, *Justus Liebigs Ann. Chem.*, **579**, 106 (1953).

(13) G. G. S. Dutton and K. N. Slessor, *Can. J. Chem.*, **44**, 1069 (1966).

Experimental Section

Tlc was performed on silica gel G[14] with air-equilibrated plates of 0.25-mm thickness. For unacetylated compounds benzene:absolute ethanol 2:1 (v/v) was used; for acetylated compounds, toluene:methanol 50:1 (v/v). The spots were detected by spraying with 5% ethanolic sulfuric acid and heating until charred. Uv spectra were measured with a Cary Model 14 spectrophotometer. Ir spectra were determined as KBr pellets with a Perkin-Elmer Model 621 spectrophotometer. Nmr spectra were obtained with a Varian Model HA-100 spectrometer. The chemical shifts were measured in chloroform-*d* unless otherwise specified and were compared against internal tetramethylsilane. Melting points of samples of capillary tubes was measured on a Mel-Temp apparatus. All analytical samples were dried in the presence of sodium hydroxide and sulfuric acid at room temperature and at 1–10 mm vacuum for 24–48 hr unless otherwise specified. Acetylations were carried out in dry pyridine with excess acetic anhydride for 16 hr at room temperature.

Methyl β-Maltoside Monohydrate (1).—The procedure of Newth, *et al.*,[7] was followed for the preparation of the title compound in 27.4% overall yield: mp 108–111°, $[\alpha]^{22.3}D$ +77.5° (*c* 1.65, chloroform) (lit.[7] mp 110–111°, $[\alpha]^{19}D$ +81°).

Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6,6′-di-*O*-*p*-tolylsulfonyl-β-maltoside (5).—Tosyl chloride (5.34 g, 28 mmol) was added to a solution of dry **1** (4.76 g, 13.3 mmol) in dry pyridine (50 ml). The reaction mixture was kept 3 hr at −10° and 16 hr at 5°, when acetic anhydride (20 ml) was added to acetylate. Partitioning the mixture between water (~500 ml) and chloroform (three 50-ml portions) gave after evaporating the chloroform a solid, which on dissolving in boiling ethanol and cooling deposited crystalline **5** (6.8 g, 59%): mp 186–189°; $\lambda_{max}^{95\%\ EtOH}$ 263 nm (ε 1240); $[\alpha]^{23}D$ +60.4° (*c* 1.63, chloroform); λ_{max}^{KBr} 1752 (acetate), 1355, 1157 cm^{-1} (sulfonate); nmr δ 7.86–7.24 (m, aryl, 8 H), 5.40–3.40 (m, maltoside, 14 H), 3.30 (s, –OCH_3, 3 H), 2.42 (s, aryl–CH_3, 6 H), and 1.96 (s, –OAc, 15 H).

Anal. Calcd for $C_{37}H_{46}O_{20}S_2$: C, 50.80; H, 5.30; S, 7.33. Found: C, 50.69; H, 5.52; S, 7.42.

Methyl 6,6′-di-*O*-*p*-Tolylsulfonyl-β-maltoside (2a) and Its Ethanolate (2b).—The procedure for the tosylation was the same as for **5**. The mixture was vacuum concentrated (bath temperature <40°) to a syrup that was partitioned between water (200 ml) and chloroform (four 200-ml portions). Drying and concentrating the organic extract yielded a solid that was recrystallized four times from ethanol to give **2b**, 4.95 g (56%); mp 120–121;[15] nmr δ 7.85–7.11 (m, aryl, 8 H), 5.14–2.82 (m, maltoside H, OH, CH_2, 22 H), 2.55 (s, aryl–CH_3, 6 H), 1.18 (t, CH_3 of ethanol, 3 H); $\lambda_{max}^{95\%\ EtOH}$ 262.5 nm (ε 1189); λ_{max}^{KBr} 3430 (OH), 1358, 1176 cm^{-1} (sulfonate); $[\alpha]^{22}D$ +46.3° (*c* 1.76, chloroform).

Anal. Calcd for $C_{29}H_{42}O_{16}S_2$: C, 49.00; H, 5.96; S, 9.02. Found: C, 48.82; H, 5.88; S, 9.00.

Heating **2b** at 78° and 2 Torr for 7 hr gave **2a**, mp 123–124° (lit.[6] mp 124–126°).

Anal. Calcd for $C_{27}H_{36}O_{15}S_2$: C, 48.78; H, 5.46; S, 9.65. Found: C, 48.74; H, 5.73; S, 9.49.

Methyl 6-*O*-*p*-Tolylsulfonyl-β-maltoside (4) and Methyl 6′-*O*-*p*-Tolylsulfonyl-β-maltoside (3).—Dry **1** (4.78 g, 13.4 mmol) and tosyl chloride (2.81 g, 14.7 mmol) were allowed to react in dry pyridine (50 ml) as in the preparation of **5** but at −10° for 48 hr. Concentration of the mixture under aspirator pressure (bath temperature <50°), followed by addition of absolute ethanol (~50 ml), and two similar concentrations resulted in a yellow syrup, which was dissolved in absolute ethanol (20 ml) and divided in half. Each half was treated as follows: silica gel (15 g, Davison Grade 12, Mesh 28–200) was deactivated by adding sufficient 95% ethanol to cover the solid and after cooling, the ethanolic reaction solution was added, and the mixture was swirled and then concentrated under aspirator pressure to a dry mass which was rendered free flowing and dry column[9] chromatographed on silica gel G (200 g, 4 × 40 cm) using benzene:absolute ethanol 2:1 (v/v) as the developing solvent. The elution order was polytosyl substituted maltoside (which were not examined), **2b**, **3**, and **4**.

The front-running monosubstituted product **3** was obtained as a syrup, which could not be crystallized; it was characterized as a crystalline acetate (see below).

The slow-running monosubstituted product **4** was crystallized (seed crystals were obtained from the last fractions containing **4**). Recrystallization from 95% ethanol gave crystalline **4** (1%): mp 154–155° dec; λ_{max}^{KBr} 3400 (OH), 1355, 1154 cm^{-1} (sulfonate); $\lambda_{max}^{95\%\ EtOH}$ 262 nm (ε 521); nmr (25% in DMSO-*d*) δ 7.82–7.32 (m, aryl, 4 H), 5.58–2.12 (m, maltoside-H-OH, 23 H), and 2.39 (s, aryl–CH_3, 3 H).

An average yield of methyl 6,6′-di-*O*-*p*-toluenesulfonyl-β-maltoside for five reactions was 24.0%.

Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acetyl-6′-*O*-*p*-tolylsulfonyl-β-maltoside (6).—Crude **3** was acetylated and worked up in the usual manner by partitioning between water and chloroform. Removal of the chloroform left a syrup that on dissolving in a minimum amount of hot ethanol and cooling deposited crystalline **6**: mp 143–144°; λ_{max}^{KBr} 1750 (acetate), 1372, 1174 cm^{-1} (sulfonate); $\lambda_{max}^{95\%\ EtOH}$ 262 nm (ε 578); $[\alpha]^{23}D$ +55.3° (*c* 5.128, chloroform); nmr δ 7.84–7.26 (m, aryl, 4 H), 5.40–3.50 (m, maltoside, 14 H), 3.45 (s, –OCH_3, 3 H), 2.43 (s, aryl CH_3, 3 H), and 2.23–1.90 (4 s, –OAc, 18 H).

Anal. Calcd for $C_{32}H_{42}O_{19}S$: C, 50.39; H, 5.55; S, 4.20. Found: C, 49.98; H, 5.48; S, 4.21.

The average yield (calculated on the basis of methyl β-maltoside monohydrate) in five runs was 17.4%.

Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6,6′-dideoxy-6,6′-diiodo-β-maltoside (8).—Compound **5** (4.011 g, 4.58 mmol), sodium iodide (3.75 g, 25 mmol), and acetone (60 ml) were heated to reflux under anhydrous conditions. Tlc monitoring with toluene:methanol 50:1 (v/v) easily revealed the progress of the displacement from **5** to methyl 2,2′,3,3′,4′-penta-*O*-acetyl-6-deoxy-6-iodo-6′-*O*-*p*-tolylsulfonyl-β-maltoside to **8** as spots with increasing R_f values. When monitoring revealed the displacement was complete (~4–5 days), the mixture was transferred with water (50 ml) and chloroform (50 ml) to a separatory funnel and extracted with two additional 50-ml portions of chloroform. The combined extracts were dried and concentrated to crude crystalline **8**. Recrystallization from absolute ethanol gave pure **8**, 3.58 g (98%): mp 196–197°; positive Beilstein halogen test; λ_{max}^{KBr} 1755, 1245 cm^{-1} (acetate); $[\alpha]^{24}D$ +48.2° (*c* 7.63, chloroform); nmr δ 5.46–3.00 (m, maltoside, 14 H), 3.51 (s, –OCH_3, 3 H), and 2.10–1.90 (4 s, –OAc, 15 H).

Anal. Calcd for $C_{23}H_{32}I_2O_{14}$: C, 35.13; H, 4.10. Found: C, 34.79; H, 4.21.

Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6-deoxy-6-iodo-6′-*O*-*p*-tolylsulfonyl-β-maltoside (14).—Sodium iodide (0.180 g, 1.2 mmol), **5** (0.965 g, 1.1 mmol), and acetone (15 ml) were heated to reflux under anhydrous conditions for 2 days. On removal of the acetone a solid remained. Trituration of this solid with boiling absolute ethanol (~60 ml) left undissolved nearly pure **14**; an additional recrystallization from ethanol gave **14**, 0.197 g (21%): mp 203–204°; λ_{max}^{KBr} 1350, 1240 (acetate), 1361, 1172 cm^{-1} (sulfonate); $\lambda_{max}^{95\%\ EtOH}$ 252 nm (ε 970); positive Beilstein halogen test; nmr δ 7.84–7.24 (m, aryl, 4 H), 5.46–3.12 (m, maltoside, 14 H), 3.49 (s, –OCH_3, 3 H), 2.44 (s, aryl–CH_3, 3 H), 1.99 and 1.97 (s, OAc, 15 H); $[\alpha]^{24.0}D$ +50.1° (*c* 2.565, chloroform).

Reworking the mother liquor followed by trituration increased the yield to 28%. In boiling absolute ethanol the solubility of **14** is 1 g/250 ml, qualitatively much less soluble than **5** or **7**.

Anal. Calcd for $C_{30}H_{39}IO_{17}S$: C, 43.38; H, 4.73. Found: C, 43.60; H, 5.08.

Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acetyl-6′-deoxy-6′-iodo-β-maltoside (9).—We used the same procedure employed to prepare **8** with **6** (4.09 g, 5.38 mmol), sodium iodide (4.3 g, 28 mmol), and acetone (80 ml). Recrystallization from absolute ethanol gave **9**: 3.80 g (98%); mp 170–171°; $[\alpha]^{24.0}D$ +52.4° (*c* 5.815, chloroform); λ_{max}^{KBr} 1753, 1230 cm^{-1} (acetate); nmr δ 5.46–3.00 (m, maltoside, 14 H), 3.45 (s, –OCH_3, 3 H), 2.12 and 2.06–1.97 (4 s, –OAc, 18 H).

Anal. Calcd for $C_{25}H_{35}IO_{16}$: C, 41.80; H, 4.91. Found: C, 41.89; H, 4.99.

Methyl 2,2′,3,3′,4′,6′-Hexa-*O*-acetyl-6-deoxy-6-iodo-β-maltoside (10).—Compound **4** (310 mg, 0.6 mmol) was acetylated with acetic anhydride (5 ml) in dry pyridine (5 ml) and worked up in the usual manner by partitioning between water and chloroform. Removal of the chloroform left syrupy **7**, which could not

(14) The mention of firm names or trade products does not imply an endorsement or recommendation by the Department of Agriculture over other firms or similar products not mentioned.

(15) At first the small difference in melting point between **2a** and **2b** was attributed to a trace impurity. However, a consistently low per cent of sulfur after each crystallization resulted in the conclusion this compound was an ethanolate, which nmr spectroscopy confirmed.

be crystallized. Syrupy **7**, sodium iodide (0.27 g, 1.8 mmol), and acetone (10 ml) were heated to reflux for 4 days, and worked up according to the procedure employed to prepare **8**. Recrystallization from absolute ethanol gave **10**, 0.228 g (52%): mp 129–130°; λ_{max}^{KBr} 1750, 1238 cm^{-1} (acetate); nmr δ 5.47–3.16 (m, maltoside, 14 H), 3.49 (s, $-OCH_3$, 3 H), 2.08 and 2.03–1.90 (4, s, –OAc, 18 H).

Anal. Calcd for $C_{26}H_{35}IO_{16}$: C, 41.80; H, 4.91. Found: C, 41.59; H, 5.09.

Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6,6′-dideoxy-β-maltoside (**11**).—Compound **8** (0.502 g, 0.63 mmol) was added to a mixture of potassium hydroxide (0.147 g, 2.54 mmol), 5% Pd–C (0.202 g), and methanol (50 ml), pressured to 50 psi with hydrogen, and mechanically shaken at room temperature for 7 hr. After separation of the catalyst by filtration, the methanolic solution was concentrated to leave a syrup, which was acetylated. Work-up and recrystallization from ethanol gave **11**: mp 186–187°; $[\alpha]^{24}D$ +50.0° (c 3.04, chloroform); λ_{max}^{KBr} 1350, 1242 cm^{-1} (acetate); nmr δ 5.44–3.36 (m, maltoside-ring, 10 H), 3.46 (s, $-OCH_3$, 3 H), 2.10–1.93 (3 s, –OAc, 15 H), 1.16 (d, J = 6.2 cps, C5′–CH_3, 3 H), and 1.39 (d, J = 6 cps, C_5–CH_3, 3 H).

Anal. Calcd for $C_{23}H_{34}O_{14}$: C, 51.68; H, 6.41. Found: C, 51.30; H, 6.45.

Methyl 2,2′,3,3′,4′,6-Hexa-*O*-acetyl-6′-deoxy-β-maltoside (**12**).—Compound **9** (0.504 g, 0.70 mmol) was hydrogenolyzed according to the procedure given for **11**. Recrystallization from absolute ethanol deposited **12**, 0.340 g (82%); mp 176–177°; λ_{max}^{KBr} 1750, 1232 cm^{-1} (acetate); nmr δ 5.39–3.52 (m, maltoside-ring, 10 H), 3.43 (s, $-OCH_3$, 3 H), 2.09, 2.04–1.88 (4 s, –OAc, 18 H), 1.15 (d, J = 6 cps, C5′–CH_3, 3 H).

Anal. Calcd for $C_{25}H_{36}O_{16}$: C, 50.68; H, 6.12. Found: C, 50.78; H, 6.24.

Methyl 2,2′,3,3′,4′,6′-Hexa-*O*-acetyl-6-deoxy-β-maltoside (**13**).—Compound **10** (89 mg, 0.121 mmol) was hydrogenolyzed according to the procedure for **11**. Recrystallization gave **13**: 12 mg (17%); mp 120–121°; λ_{max}^{KBr} 1350, 1240 cm^{-1} (acetate); nmr δ 5.45–3.30 (m, maltoside-ring, 10 H), 3.46 (s, $-OCH_3$, 3 H), 2.06, 2.04–1.90 (3 s, –OAc, 18 H), 1.39 (d, J = 6 cps, C-5–CH_3, 3 H).

Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6-deoxy-6′-*O*-*p*-tolylsulfonyl-β-maltoside (**15**).—Compound **14** (113.3 mg, 0.136 mmol) was hydrogenolyzed following the procedure for **11** for 2.5 hr. Recrystallization from absolute ethanol gave **15**, 54 mg (57%): mp 143–144°; $\lambda_{max}^{95\% EtOH}$ 262 nm (ϵ 579); λ_{max}^{KBr} 1750, 1240 (acetate), 1372, 1174 cm^{-1} (sulfonate); $[\alpha]^{23}D$ +43.2° (c 2.37, chloroform); nmr δ 7.84–7.20 (m, aryl, 4 H), 5.42–3.20 (m, maltoside, 10 H), 3.43 (s, $-OCH_3$, 3 H), 2.43 (s, aryl-CH_3, 3 H), 2.02–1.80 (3 s, –OAc, 15 H), 1.34 (d, J = 5 cps, C-5–CH_3, 3 H).

Anal. Calcd for $C_{30}H_{40}O_{17}S$: C, 51.14; H, 5.72. Found: C, 50.71; H, 6.01.

Methyl 2,2′,3,3′,4′-Penta-*O*-acetyl-6′-*O*-benzoyl-6-deoxy-β-maltoside (**17**).—Compound **15** (53 mg, 0.075 mmol) and sodium benzoate (23.5 mg, 0.15 mmol) were heated to 100 ± 1° with stirring in anhydrous N,N-dimethylformamide (30 ml) for 16 hr. After vacuum concentrating (bath temperature <70°) the reaction mixture, it was extracted with chloroform. Removal of the chloroform and recrystallization from ethanol gave **17**: 41 mg (83%); mp 196–197°; λ_{max}^{KBr} 1750, 1246 (acetate), 1735, 1280, 1125 cm^{-1} (benzoate); nmr δ 8.19–7.24 (m, aryl, 5 H), 5.49–3.30 (m, maltoside, 10 H), 3.43 (s, $-OCH_3$, 3 H), 2.20–1.84 (3 s, –OAc, 15 H), 1.39 (d, J = 5 cps, C-5–CH_3, 3 H).

Anal. Calcd for $C_{30}H_{38}O_{16}$: C, 55.05; H, 5.85. Found: C, 55.26; H, 6.23.

Conversion of 17 to 13.—Compound **17** (20.4 mg, 0.031 mmol) was dissolved in dry methanol (30 ml) and a few granules of sodium–lead alloy (J. T. Baker Chemical Co., "dri-Na") were added. After the solution was held 48 hr at room temperature, methanol was removed from it and the resulting syrup covered with anhydrous pyridine (~5 ml) and acetic anhydride (~5 ml). Work-up in the usual manner gave a product whose nmr spectrum was identical with **13**.

Methyl 3′,6′-Anhydro-6-deoxy-β-maltoside (**16**).—Compound **15** (200 mg, 0.284 mmol) was dissolved in a mixture of ethanol (5 ml) and 1 *N* sodium hydroxide (0.2 ml) and heated to 60° for 3.5 hr. After diluting with an equal volume of water, the solution was adjusted to pH 7.10 with 0.1 *N* hydrochloric acid and concentrated to a dry solid. Dry silica gel G column (100 g, 4 × 21 cm) chromatography developed with benzene:absolute ethanol 2:1 (v/v) gave only one compound, a yellowish oil (81.5 mg, 90%), which could not be rendered crystalline. An nmr spectrum established that the tosyl group was absent, a glycosidic methoxyl was present, a C-5 methyl proton resonance was present, and the proton integral was consistent with the title compound: nmr δ 5.36–2.95 (m, maltoside H–OH, 14 H), 3.50 (s, $-OCH_3$, 3 H), 1.38 (d, J = 5 cps, C-5–CH_3, 3 H).

Periodate Oxidation of 16.—A weighed amount of **16** (~1–5 mg) when oxidized by the procedure of Dixon and Lipkin[16] consumed 1.06 mol equiv after 24 hr. Methyl α-D-glucopyranoside and methyl α-L-rhamnopyranoside when oxidized under the identical conditions consumed 1.95 and 1.98 mol equiv, respectively.

Registry No.—**2b**, 25787-29-5; **4**, 25834-66-6; **5**, 25787-30-8; **6**, 25834-67-7; **8**, 25787-31-9; **9**, 25834-68-8; **10**, 25787-32-0; **11**, 25787-33-1; **12**, 25787-34-2; **13**, 25787-35-3; **14**, 25787-36-4; **15**, 25787-37-5; **16**, 25787-38-6; **17**, 25787-39-7.

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(16) J. S. Dixon and P. Lipkin, *Anal. Chem.*, **26**, 1092 (1954).

Nucleosides from 3-Deoxy-3-methylamino-D-ribofuranose[1]

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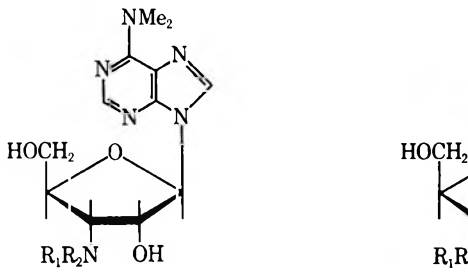
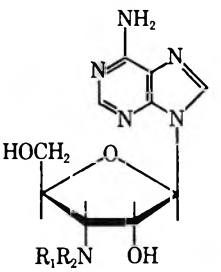
A number of 9-(3-deoxy-3-methylamino-β-D-ribofuranosyl)-6-substituted purines have been prepared with the 6 substituent being amino, dimethylamino (**2**), oxygen, and sulfur (**31**). Compound **31** is the first example of a nucleoside with purine-6-thione bonded to an amino sugar. Compound **2** was further substituted at the 3′-methylamino position with a *p*-methoxyphenyl-L-alanyl group to give 3′-*N*-methylpuromycin (**2a**). Eschweiler–Clarke methylation, carried out for the first time on a nucleoside, of the 6-dimethylaminopurine nucleoside **2** gave the 3′-deoxy-3′-dimethylamino-D-ribofuranose derivative **3**. The key intermediate required for the nucleoside condensations, 1,2,5-tri-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-D-ribofuranose (**20**) was prepared from methyl 2,3-anhydro-α-D-lyxofuranoside (**6**) by a sequence of seven steps that included an intramolecular displacement by an *N*-methylacetamido neighboring group.

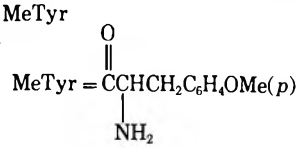
Puromycin (**1a**), an antibiotic with antitumor activity,[2] has been used as an important biochemical tool in the study of protein synthesis. The amino nucleoside **1** from puromycin and its adenine analog **4** also exhibit antitumor[3a,b] and other biological activity.[3c] In view of the great interest in the potential biological activity of puromycin analogs,[4] we have synthesized some 3′-*N*-methyl derivatives of **1** and **4** (*e.g.* **2**, **3**, and **5**) as well as 3′-*N*-methylpuromycin (**2a**).



1, $R_1 = R_2 = H$
1a, $R_1 = H$; R_2 = MeTyr
2, R_1 = Me; $R_2 = H$
2a, R_1 = Me; R = MeTyr
3, $R_1 = R_2$ = Me

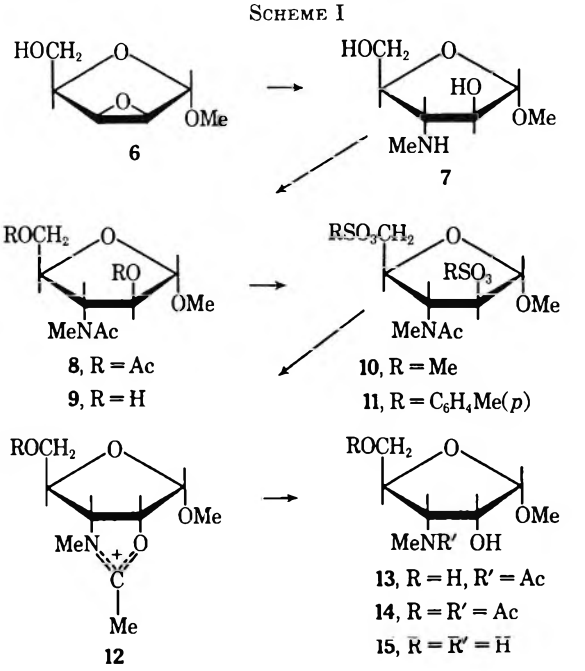


4, $R_1 = R_2 = H$
5, R_1 = Me; $R_2 = H$
5a, R_1 = Me; R_2 = Ac



The 3-deoxy-3-methylamino-D-ribofuranose moiety was prepared from the epoxide **6**[5] by the method (see Scheme I) used for 3-deoxy-3-aminoribose.[5] Aqueous methylamine cleaved **6** at the 3 position to give **7** with no detectable opening at C-2. Acetylation to **8** and selective deacylation gave crystalline **9**. In **9** the *N*-methylacetamido group existed in *cis* and *trans* forms according to the nmr spectrum.[6] Upon raising the

SCHEME I



temperature, the two *N*-acetyl signals collapsed to one signal. A number of the other *N*-methylacetamides also showed two forms, but the nmr spectra have not been examined at higher temperatures. While sulfonation of **9** with methanesulfonyl chloride afforded syrupy **10**, *p*-toluenesulfonyl chloride gave crystalline, stable **11** in good yield. Inversion of **11** at C-2 on treatment with sodium acetate in hot aqueous 2-methoxyethanol proceeded *via* the oxazolinium ion **12**. No relatively stable uncharged imidazoline intermediate[5] was possible with this amide. This appears to be the first carbohydrate example of a neighboring group participation reaction utilizing an N,N-disubstituted amide.[7,8] The inversion proceeded very cleanly,

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(2) B. L. Hutchings in "Chemistry and Biology of Purines. CIBA Foundation Symposium," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957.

(3) (a) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Amer. Chem. Soc.*, **77**, 5911 (1955); (b) N. N. Gerber and H. A. Lechevalier, *J. Org. Chem.*, **27**, 1731 (1962); (c) J. T. Truman and S. Frederiksen, *Biophys. Biochim. Acta*, **182**, 36 (1969).

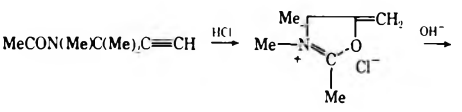
(4) See L. V. Fisher, W. W. Lee, and L. Goodman, *J. Med. Chem.*, **13**, 775 (1970), and references there.

(5) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 7 (1955).

(6) (a) H. Paulson and K. Todt, *Chem. Ber.*, **100**, 3385 (1967), have reported a carbohydrate amide showing two forms in its nmr spectrum. (b) R. C. Neumann, Jr., and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968), have studied the hindrance to internal rotation of *N*,*N*-dimethylacetamide-d_3 by nmr.

(7) See L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 109 (1967), for a recent review on participation reactions in sugars.

(8) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **28**, 2465 (1963), have reported the following tertiary amide participation reaction

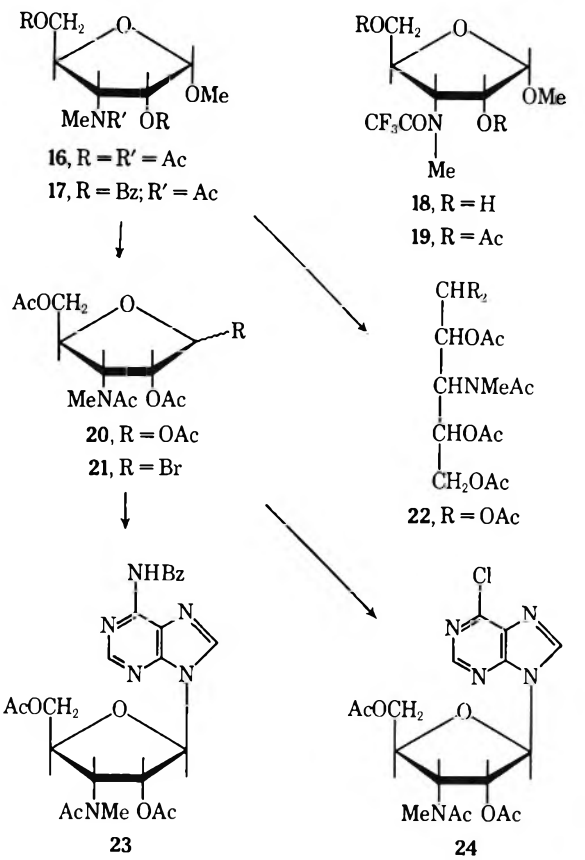


MeCON(Me)C(Me)$_2$COMe

for acetylation of the reaction mixture (**13**–**15**) gave only the syrupy ribose derivative **16**; none of the arabinoside **8** could be detected (limit of detection, <0.5%) by glc. Selective deacylation of **16** gave crystalline **13** which was unlike the arabinoside **9** in all its properties, but also like compound **9** showed two isomeric forms by nmr. Hot sodium hydroxide hydrolyzed **13** to **15** which was analyzed as the crystalline hydrochloride.

For the nucleoside condensations, the blocked methyl riboside **16** needed to be converted to the 1-*O*-acetate **20** or the halo sugar **21** (see Scheme II). The

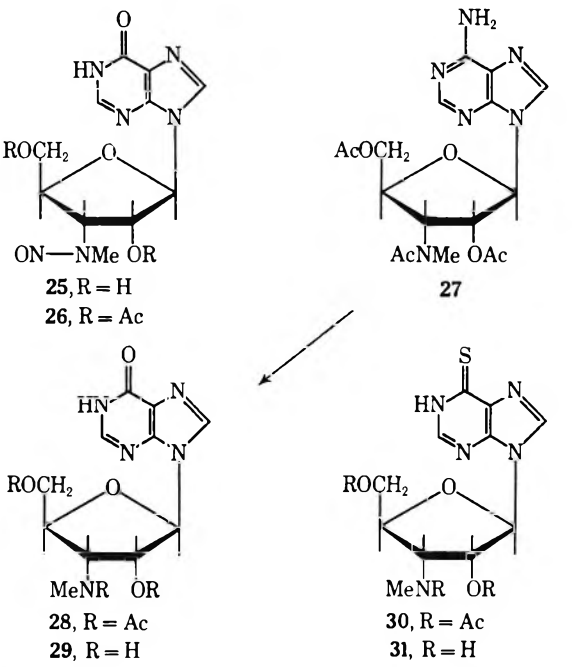
SCHEME II



acetolysis of **16** did not proceed in high yields, but **20** could be obtained in reproducible yields under carefully controlled conditions. The acyclic aldehyde diacetate **22**, one of the acetolysis by-products, could be isolated and characterized after being carried through the nucleoside condensation. The use of other blocking groups as in **17** and **19** was considered but was not found to be advantageous. Chloromercuri-6-benzamidopurine was condensed with the 1-*O*-acetate **20** by the titanium tetrachloride method[9] to afford the crystalline blocked nucleoside **23**. The combined yield of **23** and acyclic **22** was over 80%. An attempt to prepare the bromo sugar **21** gave a precipitate[10] which, when condensed with chloromercuri-6-benzamidopurine, gave a poorer yield of **23** than the first method. Heating **23** with 1.5 equiv of sodium methoxide in methanol for 8 hr gave the completely deblocked nucleoside **5** in high yield. The *N*-acetyl group was relatively easy to remove from this N,N-disubstituted amide in contrast to other monosubstituted amides on nucleosides.[11] In fact, attempts to hydrolyze **23** selectively to the 3′-*N*-acetyl derivative **5a** always gave some **5** also.

The chloropurine nucleoside **24** would seem to be a versatile intermediate for other nucleosides. The fusion of the 1-*O*-acetate **20** with 6-chloropurine afforded **24** in better yield than reaction of **20** with chloromercuri-6-chloropurine in the presence of titanium tetrachloride. The noncrystalline **24**, accompanied by small amounts of another nucleoside and the acetolysis by-products, could be converted to the crystalline **5**. The yields of **5** from the 1-*O*-acetate **20** *via* either **23** or **24** were equal. This established the amount of **24** present in the crude mixtures which were not readily purified and decomposed slowly on ordinary storage (probably because the acetolysis by-products gradually reacted with the chloropurine). In the future, it may be worthwhile to purify **24** by column chromatography to improve its shelf life.

The hypoxanthine nucleoside **29** could not be obtained by direct nitrosation of **5**; the product was the nitroso derivative **25** which was characterized as the



crystalline diacetate **26**. To prevent 3′-*N*-nitrosation, **5** was first converted to the triacetyl derivative **27** which reacted with nitrous acid to afford **28**; deacylation gave the desired **29**. Attempts to convert the triacetyl hypoxanthine nucleoside **28** to the chloronucleoside **24** by treatment with thionyl chloride and *N*,*N*-dimethylformamide (DMF)[12] gave mainly decomposition products with little or none of the chloro nucleoside **24**.

The mercaptopurine nucleoside **31** could be obtained by several routes, but in relatively poor yield. Thus,

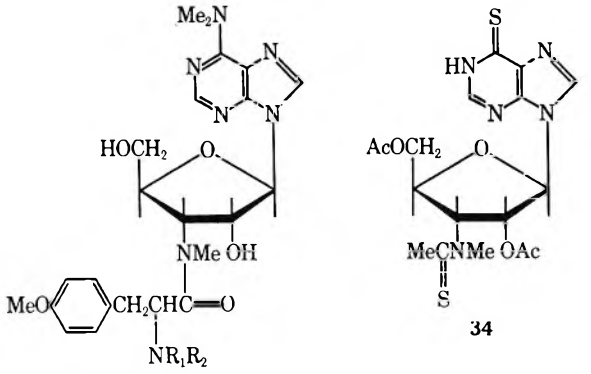
(9) (a) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 12 (1955); (b) D. H. Murray and J. Prokop, *J. Pharm. Sci.*, **54**, 1468 (1965).

(10) This may be the insoluble HBr salt of the weakly basic amide group (see ref 9a for a similar insoluble salt) of **20** with perhaps some being converted to **21** or its salt.

(11) (a) B. R. Baker and R. E. Schaub, *J. Amer. Chem. Soc.*, **77**, 2396 (1955); (b) M. L. Wolfrom, P. J. Conigliaro, and E. J. Soltes, *J. Org. Chem.*, **32**, 653 (1967), discussed the removal of *N*-acetyl groups and the choice of other N-blocking groups for amino sugar nucleoside synthesis. (c) K. A. Watanabe, J. Beránek, H. A. Friedman, and J. J. Fox, *ibid.*, **30**, 2735 (1965), have converted *N*-acetyls of nucleosides to *N*-thioacetyls for easier removal.

(12) J. Pliml and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 546 (1963).

thiation of the acetylated hypoxanthine nucleoside **28** with phosphorus pentasulfide in hot pyridine afforded the crystalline 3′-thioacetamido-6-mercaptopurine nucleoside **34**. Deacylation in refluxing methanolic



32, R_1 = Cbz; R_2 = H
33, R_1; R_2 = Me_2C=

sodium methoxide under various conditions was either incomplete or gave **31** accompanied by some by-products. The chloropurine nucleoside **24** could be treated with either thiourea or sodium hydrogen sulfide, preferably with the latter, to give the desired **31** after deacylation. Compound **31** sometimes required purification *via* the lead salt since **31** was not as readily crystallized as **2** or **5** from the reaction mixtures that contained appreciable amounts of by-products. Compound **31** is the first example of a mercaptopurine nucleoside of an amino sugar.

Reaction of the chloropurine nucleoside **24** with hot methanol and dimethylamine readily afforded, after sodium methoxide treatment, the dimethylaminopurine nucleoside **2**. Omission of the sodium methoxide step resulted in incomplete 3′-*N*-deacylation. The nucleoside **2** was coupled to *N*-benzyloxycarbonyl-*p*-methoxy phenyl-L-alanine[13] by the dicyclohexylcarbodiimide–*N*-hydroxysuccinimide method[14] to afford the blocked nucleoside peptide **32** in excellent yield. Other coupling methods gave much less or no **32**. Hydrogenolysis readily yielded **2a** which is 3′-*N*-methylpuromycin. Attempts to crystallize **2a** from acetone afforded the crystalline azomethine derivative **33**. This was stable in acetone or as a crystalline solid. In other solvents, it reverted back to **2a**.

Treatment of **2** with formaldehyde and formic acid gave the crystalline 3′-dimethylamino nucleoside **3**. This is apparently the first time that the Eschweiler–Clarke methylation procedure[15a] has been applied to a nucleoside, although it has been employed with aminosugars.[15b] That **3** cannot undergo 3′-*N*-acylation may make it an interesting analog of the puromycin nucleoside **1**.

All the nucleosides have been assigned as β anomers on the basis that **5**, predictably the β anomer when produced from the bromo sugar **21** and chloromercuri-6-benzamidopurine,[16] was the same when prepared from the chloropurine nucleoside **24**. If **24** and **5** are β anomers, so must be all the other nucleosides derived from them. This conclusion is supported by circular dichroism (CD) measurements[17] showing that **2**, **3**, and **5** have the same anomeric configuration as **1**, which is known to be the β anomer.[18] In addition, Eschweiler–Clarke methylation of **1** gave the same product, **3**, obtained from **2**.

Experimental Section[19]

Methyl 3-Deoxy-3-methylamino-α-D-arabinofuranoside (7).—Methyl 2,3-anhydro-α-D-lyxofuranoside **6**[5] (3.00 g, 20.5 mmol) and 21 ml of anhydrous methylamine were heated in a bomb at steam bath temperature for 28 hr. After evaporation for 20 hr at 60°, there was left 3.66 g (100%) of **7** as a homogeneous syrup, R_f 0.58 in solvent TA. This was immediately used in the next step. The use of 40% aqueous methylamine was more convenient and gave the same results.

A 1.31-g portion of **7** from another run was dissolved in an equivalent amount of 1 *N* HCl (7.43 ml) and evaporated to give 1.57 g (100%) of the hydrochloride of **7**, mp 120–122.5°. Crystallization from 100 ml of acetonitrile gave 1.29 g (84%) of white crystals of **7**·HCl: mp 126–127°; $[\alpha]^{20}D$ 99° (c 1.0, H_2O); nmr (D_2O) δ 5.10 (s, 1, H-1), 3.44 (s, 3, OCH_3), and 2.87 (s, 3, NCH_3); R_f 0.47 in solvent TB.

Anal. Calcd for $C_7H_{15}NO_4$·HCl: C, 39.4; H, 7.55; Cl (ionic), 16.6; N, 6.56. Found: C, 39.6; H, 7.64; Cl (ionic), 16.3; N, 6.58.

Methyl 3-Deoxy-2,5-di-*O*-acetyl-3-*N*-methylacetamido-α-D-arabinofuranoside (8).—The above 3.66 g of **7** was stirred with 23.2 ml of acetic anhydride and 50 ml of pyridine at room temperature for 24 hr to give, after work-up and thorough drying *in vacuo*, 5.12 g (82%) of **8** as a syrup: $[\alpha]^{24}D$ +89° (*c* 0.87, $CHCl_3$); nmr ($CDCl_3$) δ 5.10 (m, 2, H-2 and H-3), 4.95 (s, 1, H-1), 4.23 (m, 3, H-4 and 2 H-5), 3.44 (s, 3, OCH_3), 3.07 (s, 2.3, N-CH_3 one form), 2.95 (s, 0.7, N-CH_3 another isomer), and 2.12 (s, 3, $NCOCH_3$); R_f 0.73 in solvent TC.

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.5; H, 6.98; N, 4.62. Found: C, 51.2; H, 7.01; N, 4.26.

Methyl 3-Deoxy-3-*N*-methylacetamido-α-D-arabinofuranoside (9).—A 10.2 g (33.7 mmol) portion of **8** in 50 ml of dry methanol containing 3 ml of 1 *N* sodium methoxide in methanol was kept overnight, neutralized with acetic acid and filtered to give 3.34 g of **9**, mp 155–156°, and a second crop of 2.43 g of **9**, mp 152–154° (total yield 78%).

A sample from an earlier run was recrystallized from ethanol to give the analytical sample of **9**: mp 155–156°; $[\alpha]^{23}D$ +89° (*c* 0.99, H_2O); nmr (D_2O) δ 5.05 (d, 1, $J_{1,2}$ = 2 Hz, H-1), 3.55 (s, 3, OCH_3), 3.15 and 2.99 (both s, 3, N-CH_3, two forms), 2.30 and 2.25 (both s, 3, NAc, two forms); at 95° the protons of the NAc group had collapsed to a singlet at 2.25, but the two N-CH_3 peaks were only slightly changed; R_f 0.13 in solvent TD.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.3; H, 7.82; N, 6.39. Found: C, 49.5; H, 7.84; N, 6.15.

Further recrystallizations did not change the rotation or

(13) (a) R. P. Rivers and J. Lerman, *J. Endocrinol.*, **5**, 223 (1948); (b) H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).

(14) (a) F. Weygand, D. Hoffman, and E. Wünsch, *Z. Naturforsch.*, **21b**, 426 (1966); (b) J. E. Zimmerman and G. W. Anderson, *J. Amer. Chem. Soc.*, **89**, 7151 (1967).

(15) (a) M. L. Moore in "Organic Reactions" Vol. V, R. Adams, *et al.*, Ed., Wiley, New York, N. Y., 1949, p 301; (b) C. Richardson, *J. Chem. Soc.*, 5364 (1964).

(16) B. R. Baker in ref 2, pp 120–129.

(17) R. H. Iwamoto, *et al.*, manuscript in preparation, describing CD studies of a number of nucleosides.

(18) C. W. Waller, P. W. Fryth, B. L. Hutchings, and J. H. Williams, N. Y. Meeting in Miniature, Feb 1954.

(19) Melting points were determined on a Fisher–Johns apparatus and are corrected. Optical rotations were obtained with a Perkin-Elmer Model 141 automatic polarimeter; nmr, with a Varian A60 or HA 100; CD, with a Jasco Model ORD/UV-5, Sproule Scientific SS 107 CD modification. Evaporations were carried out *in vacuo* at or below 45° unless specified otherwise. Anhydrous magnesium sulfate was used as drying agent. Celite is a diatomaceous earth product of Johns–Manville. Glc was run on a Varian 2100-20. Paper chromatograms were run by the descending technique on Whatman No. 1 paper in these solvent systems: PA, *n*-butyl alcohol–water (saturated); PC, 5% aqueous disodium hydrogen phosphate, pH 8.9; PE, *n*-butyl alcohol–acetic acid–water (5:2:3); PF, *t*-butyl alcohol–water (5:1); PG, 3% aqueous ammonium chloride; PP, aqueous saturated ammonium sulfate–2-propanol–water (2:28:70). Tlc was run on silica gel HF (E. Merck AG Darmstadt) in these solvent systems: TA, methanol–ethyl acetate (4:6); TB, methanol; TC, ethanol–ethyl acetate (1:9); TD, chloroform–methanol (19:1); TE, same (4:1); TF, same (9:1). The spots were detected under uv light or by iodine vapor and reported as R_f or R_{Ad} in relation to solvent front or adenine, respectively.

melting point of **9**. Its 2,5-di-*O*-*p*-nitrobenzoate (**9**, R = $OCC_6H_4NO_2$-*p*) had mp 150–151°, $[\alpha]^{24}D$ +16.6° (c 0.99, $CHCl_3$).

Anal. Calcd for $C_{23}H_{23}N_3O_{11}$: C, 53.4; H, 4.48; N, 8.12. Found: C, 53.6; H, 4.61; N, 8.25.

Methyl 3-Deoxy-3-(*N*-methylacetamido)-2,5-di-*O*-*p*-toluenesulfonyl-α-D-arabinofuranoside (11).—To a cold (0°) stirred solution of 8.37 g (40 mmol) of the arabinofuranoside (**9**) in 200 ml of dry pyridine was added 30.5 g (160 mmol) of *p*-toluenesulfonyl chloride. After stirring at 0° for 1 hr, the solution was stored at 5°, protected from moisture, for 65 hr. The solution was cooled to 0°, diluted with 20 ml of ice water, and stirred at 0° for 15 min. The mixture was then poured into 600 ml of cold water and extracted with two 100-ml portions of chloroform. The chloroform extracts were washed with 150 ml of saturated sodium bicarbonate solution and with two 200-ml portions of water. After drying, the chloroform solution was treated with charcoal and evaporated; the residue was suspended in 50 ml of toluene and reevaporated to a reddish-white solid, 19.9 g. The crude product was dissolved in 300 ml of preheated methanol and cooled to 5° to afford **11** as yellowish-white fibrous needles, 15.4 g (73%), mp 132.5–133.5°; R_f 0.65 in solvent TD. The product from another run was triturated with methanol to afford the analytical sample of **11** as white needles, mp 134–135°.

Anal. Calcd for $C_{23}H_{29}NO_9S_2$: C, 52.4; H, 5.54; N, 2.66; S, 12.2. Found: C, 52.5; H, 5.65; N, 2.84; S, 12.1.

Crystalline **11** can be kept at 5° for 1 year without decomposition. A chloroform solution of **11** showed two new spots by tlc after 1 week. A refluxing absolute ethanol solution of **11** is 50% decomposed after 30 min, and 90% after 1 hr. By ir, one decomposition product may be the toluenesulfonic acid salt of methyl 2-*O*-acetyl-3-deoxy-3-methylamino-5-*O*-tosyl-α-D-ribofuranoside.

The dimesyl sugar **10** could be prepared by the same procedure as a homogeneous oil which was unstable.

Methyl 2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-α-D-ribofuranoside (16).—A stirred suspension of 15.8 g (30 mmol) of the ditosylate **11** and 12.3 g (150 mmol) of anhydrous sodium acetate in 200 ml of 95% aqueous 2-methoxyethanol was heated at reflux for 21 hr. The solution was evaporated; the residue was suspended in 75 ml of toluene and reevaporated. A suspension of the residue in a mixture of 50 ml of acetic anhydride and 100 ml of dry pyridine was stirred and heated at 100° for 1 hr. The mixture was worked up to leave 8.42 g (93%) of **16** as an orange-yellow syrup: $[\alpha]^{22}D$ +163° (*c* 0.61, $CHCl_3$); ir (neat) 5.71 (C=O ester), 6.02 (C=O amide), 8.10 μ (ester); nmr ($DCCl_3$) δ 5.14 (m, 3, H-1, 2,3), 4.25 (m, 3, H-4 and 2 H-5), 3.48 and 3.45 (both s, 3, OCH_3), 3.09 and 2.97 (both s, 3, N-CH_3), 2.14 and 2.10 (both s, 9, 3 $COCH_3$); glc (packing: 5% STAP on 80–100 Chromosorb W, acid washed, 6 ft × 2 mm; column temperature 215°; injection temperature 240°; H_2 flame detector temperature 300°; flow rate, 26 ml/min of He) retention time 250 sec (99.2%) for **16**; no **8**, retention time 228 sec was detected (limit of detection, 0.5%); a minor unidentified peak (0.8%) occurred at a retention time of 296 sec; R_f 0.50 in solvent TD.

Anal. Calcd for $C_{13}H_{21}NO_7 \cdot {}^1/_4H_2O$: C, 50.7; H, 7.04; N, 4.55. Found: C, 50.8; H, 7.07; N, 4.55.

Methyl 3-Deoxy-3-(*N*-methylacetamido)-α-D-ribofuranoside (13).—A cold (0°) solution of 8.29 g (27.4 mmol) of the triacetate **16** in 150 ml of methanol was saturated with ammonia, allowed to stand at 25° for 16 hr, and evaporated. Crystallization of the product from 65 ml of ethyl acetate afforded 4.49 g (75%) of **13**, mp 107.5–109°. Recrystallization from ethyl acetate gave analytically pure **13**, melting point unchanged; $[\alpha]^{19}D$ +221° (*c* 0.99, H_2O); nmr (D_2O) δ 5.08 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 3.48 (s, 3, OCH_3), 3.12 and 2.97 (both s, 3, N-CH_3), and 2.18 (s, 3, $NCOCH_3$); R_f 0.12 in solvent TD.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.3; H, 7.82; N, 6.39. Found: C, 49.5; H, 8.02; N, 6.47.

Methyl 3-Deoxy-3-(methylamino)-α-D-ribofuranoside Hydrochloride (15·HCl).—A solution of 7.84 g (25.8 mmol) of the triacetate **16** in 78 ml of 1.0 *N* sodium hydroxide was heated on the steam bath for 15 hr. The solution was cooled to 0°, acidified with 104 ml of 1.0 *N* hydrochloric acid, treated with charcoal, and evaporated. The residue was triturated with 75 ml of hot absolute ethanol; the sodium chloride was removed by filtration and washed with two 20-ml portions of absolute ethanol. The combined ethanol solution was evaporated; the residue was crystallized from 40 ml of hot absolute ethanol, to afford 4.60 g (83%) of **15**·HCl as white needles, mp 120–121.5°. The mother liquors gave an additional 0.68 g of **15**·HCl [total 5.28 g (95%)], mp 120–121°. The analytical sample of **15**·HCl, recrystallized from absolute ethanol, had mp 120.5–121.5°; $[\alpha]^{20}D$ +112° (*c* 0.99, H_2O); nmr (D_2O) δ 5.11 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 3.48 (s, 3, OCH_3), and 2.83 (s, 3, NCH_3); R_f 0.29 in solvent TB.

Anal. Calcd for $C_7H_{15}NO_4 \cdot HCl$: C, 39.4; H, 7.55; Cl (ionic), 16.6; N, 6.56. Found: C, 39.5; H, 7.54; Cl (ionic), 16.2; N, 6.48.

Methyl 2,5-Di-*O*-benzoyl-3-deoxy-3-(*N*-methylacetamido)-α-D-ribofuranoside (17).—A solution of 3.16 g (14.4 mmol) of the acetamidoribofuranoside (**13**) in 30 ml of dry pyridine was treated with 3.7 ml (31.8 mmol) of benzoyl chloride and kept at 25° for 17 hr, to leave, after work-up, 5.53 g (90%) of **17** as a pale yellow gum. For analysis, a sample was dried at 100° (0.1 Torr) for 15 hr; $[\alpha]^{18}D$ +98° (*c* 1.88, $CHCl_3$); R_f 0.70 in solvent TD.

Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.6; H, 5.90; N, 3.27. Found: C, 64.3; H, 6.00; N, 3.40.

Attempts to prepare the 1-*O*-acetate derived from **17** by treatment with acetic anhydride, acetic acid, and sulfuric acid, resulted in some replacement of benzoyl by acetyl according to nmr data.

Methyl 3-Deoxy-3-(*N*-methyltrifluoroacetamido)-α-D-ribofuranoside (18).—A solution of 2.14 g (10 mmol) of the aminoribofuranoside hydrochloride **15**·HCl in 10 ml of trifluoroacetic anhydride was allowed to stand at 5° for 15 hr and then evaporated. The residue was dissolved in 50 ml of methanol, refluxed for 25 min, and then evaporated to a crystalline residue. The product was dissolved in 10 ml of hot methanol, diluted with 50 ml of hot chloroform, and allowed to cool to afford 2.11 g (73%) of **18** as white fibrous needles, mp 153–154.5°. The mother liquors yielded an additional 0.47 g [total 2.58 g (88%)], mp 153–154°. For analysis, a sample was recrystallized from methanol–chloroform (1:5) to give **18**, melting point unchanged: ir (Nujol) 3.06 (OH), 5.90 μ (amide); $[\alpha]^{16}D$ +83° (c 0.84, H_2O); R_f 0.10 in TE.

Anal. Calcd for $C_9H_{14}F_3NO_5$: N, 5.13. Found: N, 4.97.

Attempts to convert **18** to the diacetyl **19** with acetic anhydride in pyridine resulted in conversion to the triacetyl sugar **16** according to ir data.

Acetolysis of Methyl 3-Deoxy-2,5-di-*O*-acetyl-3-(*N*-methylacetamido)-α-D-ribofuranose (16).—To a cold (0°) stirred solution of 15.00 g (49.5 mmol) of the methyl riboside (**16**) in 70 ml each of acetic anhydride and acetic acid was added 8.25 ml (148.5 mmol) of sulfuric acid dropwise over a 1-hr period. The solution was stirred and protected from moisture at 25° for 23 hr. The reaction mixture was cooled to 0°, 26.0 g (317 mmol) of anhydrous sodium acetate was added, and the mixture was stirred at 25° for 30 min and then evaporated (≤30°). The residue was suspended in 200 ml of methanol and reevaporated; the evaporation with methanol was repeated. A solution of the residue in 200 ml of chloroform was washed with two 300-ml portions of saturated sodium bicarbonate solution and with two 50-ml portions of water. The dried chloroform solution was treated with charcoal and evaporated to leave 14.0 g of a pale yellow syrup. [The product was a mixture of ~29% of **16**, ~55% of **20**, ~11% of aldehyde (*e.g.*, **22**, R_2 = O), and ~5% of other products as estimated by nmr analysis; the yield of **20** was 47%.] The above product mixture was treated a second time with 5.90 ml (106 mmol) of sulfuric acid in 50 ml each of acetic acid and acetic anhydride at 25° for 23 hr; the mixture was worked up as described above to leave 12.6 g of a pale yellow syrup. [This product was a mixture of ~11% of **16**, ~63% of the 1-*O*-acetate (**20**), ~7% of the aldehyde (**22**, R_2 = 0), and ~19% of the aldehyde diacetate (**22**); the yield of **20** was 48%]: ir (neat) 5.70 (C=O, ester), 6.02 (C=O, amide), 8.12 μ (acetate); nmr ($CDCl_3$) δ 9.49 (s, CHO), 6.15 (H-1 of **20**), and various amounts of H-1 of **22**, 1-OCH_3 of **16**, and $COCH_3$ (for δ values see under particular compound) which were used to estimate mixture composition; R_f 0.40 and 0.60 in solvent TD.

Various acetolysis conditions were studied and found less satisfactory than the above. For example, pouring the acetolysis mixture into ice water[20] in the work-up gave little or no chloroform soluble product.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]-6-benzamidopurine (23).—Using a literature procedure,[9b] 22.6 g (47.6 mmol) of chloromercuri-6-benzamidopurine (35.3 g of a 36% Celite mixture) and 7.94 g (24.0 mmol)

(20) K. J. Ryan and E. M. Acton in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 165.

of the tetraacetate **20** (12.6 g of a 63% pure sample) in 1,2-dichloroethane were treated with 5.25 ml (47.7 mmol) of titanium tetrachloride in the same solvent and refluxed for 22 hr, then worked up to give 11.4 g of **23** as a foam. Crystallization from 20 ml of warm alcohol diluted with 200 ml of warm water gave 5.66 g (46%) of **23** as fibrous needles, mp 95.5–98.5°. Recrystallization from water gave the analytical sample of **23**: mp 96.5–99.5°; $[\alpha]^{20.5}D$ −27° (*c* 0.99, EtOH); ir 5.71 (C=O, acetate) 5.87 (C=O, benzamide), 6.02 (C=O, acetamide), 6.22, 6.32 (purine), 8.14 μ (ester); uv max (pH 1) 252 mμ (ε 11,400), 291 (26,300); (EtOH) 231 mμ (ε 13,200), 253 sh (~11,700), 262 sh (~13,100), 279 (21,300); (pH 13) 303 mμ (ε 13,900); nmr ($DCCl_3$) δ 9.64 (s, 1, NHBz), 8.71 and 8.23 (both s, 2, H-2/H-8), 8.04 and 7.5 (both m, 5, C_6H_5CO), 6.40 (d, 1, $J_{1',2'}$ = 4 Hz, H-1'), 3.11 and 3.06 (both s, NCH_3); R_f 0.30 in solvent TD.

Anal. Calcd for $C_{24}H_{26}N_6O_7$: C, 56.5; H, 5.13; N, 16.5. Found: C, 56.3; H, 5.33; N, 16.3.

1,1,2,4,5-Penta-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-D-ribose (22).—The aqueous ethanolic mother liquors, from the crystallization of the 6-benzamidonucleoside (**23**), were concentrated to approximately 75 ml and then extracted with six 35-ml portions of ether. The combined ether extract was washed with 20 ml of water, dried, treated with charcoal, and evaporated to a partially crystalline residue, 1.69 g. The residue was dissolved in 10 ml of hot benzene, diluted with 40 ml of hot cyclohexane, filtered, and allowed to cool to afford 0.95 g (40%) of light yellow crystals, mp 112.5–115.5°. Recrystallization from benzene–cyclohexane (1:4) gave the analytical sample of **22**: mp 115–116.5°; $[\alpha]^{20}D$ +41° (*c* 1.99, $CHCl_3$); ir (Nujol) 5.61, 5.70 (C=O, ester), 6.02 (C=O, amide), 8.00, 8.10, 8.20 μ (COOR); nmr ($CDCl_3$) δ 6.85 (d, $J_{1,2}$ = 7 Hz, H-1), 3.17 (s, 3, NCH_3), 2.08 and 2.04 (both s, 18 $COCH_3$); R_f 0.64 in solvent TD.

Anal. Calcd for $C_{18}H_{27}NO_{11}$: C, 49.9; H, 6.28; N, 3.23. Found: C, 50.2; H, 6.51; N, 3.34.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]-6-chloropurine (24).—A mixture of 3.09 g (20 mmol) of 6-chloropurine and 6.27 g (19 mmol) of the tetraacetate **20** [11.0 g of a 57% pure sample of **20**] was stirred and heated in an oil bath at 135–140°, 0.100 g of *p*-toluenesulfonic acid monohydrate was added, and the flask was evacuated to 0.25 Torr. The melt was stirred at 135–140° (0.25 Torr) for 20 min and then cooled. A solution of the fusion product in 150 ml of methylene chloride was washed with 25 ml of saturated sodium bicarbonate solution and with two 25-ml portions of water. The dried organic solution was treated with charcoal and evaporated to a foam, 11.80 g (uv indicated a purity of approximately 60%): uv max (EtOH) 250 mμ sh (ε 4460), 264 (5960); R_f 0.40 [chloronucleoside (**24**)], 0.48 and 0.63 (acetolysis by-products) in solvent TD.

9-(3-Deoxy-3-methylamino-β-D-ribofuranosyl)adenine (5).—A solution of 5.66 g (11.1 mmol) of the 6-benzamidonucleoside (**23**) and 17 ml of 1.0 *M* methanolic sodium methoxide in 225 ml of methanol was stirred and refluxed for 8 hr, during which time the aminonucleoside (**5**) crystallized from the reaction mixture. The mixture was cooled and adjusted to pH 8–9 with acetic acid; the crystalline precipitate was collected and washed with four 5-ml portions of methanol and three 5-ml portions of methylene chloride to afford 2.74 g (89%) of **5**, mp 244–247° dec. An additional 0.14 g [total 2.88 g (93%)] of **5**, mp 243–245°, was obtained from the mother liquors. The analytical sample of **5**, recrystallized twice from water, had mp 247.5–250° dec: $[\alpha]^{19}D$ −103° (*c* 1.00, 1.0 *N* NaOH); uv max (pH 1) 206 mμ (ε 22,100), 256 (14,800); (pH 7) 207 mμ (ε 20,400), 259 (15,100); (pH 13) 259 mμ (ε 15,200); nmr (DMSO-d_6, D_2O exchanged) δ 8.39 and 8.15 (both s, 2, H-2 and H-8), 5.95 (d, $J_{1',2'}$ = 3 Hz, H-1'), 2.32 (s, 3, NCH_3); R_f 0.37 in solvent TB; R_{Ad} 0.79, 1.56, and 0.78 in solvents PA, PC, and PE, respectively.

Anal. Calcd for $C_{11}H_{16}N_6O_3$: C, 47.1; H, 5.76; N, 30.0. Found: C, 46.9; H, 5.93; N, 30.1.

Attempts to selectively deacylate **23** at room temperature to the 3'-*N*-acetyl derivative (**5a**) of **5** were not successful. Treatment with 1 equiv of sodium methoxide in methanol for 16 hr gave **5a**:**5** in the ratio of 1:1; 0.2 equiv for 45 hr, a ratio of 9:1.

Treatment of the chloropurine **24** with methanolic ammonia at 100° for 15 hr followed by methanolic sodium methoxide deacylation as above gave **5** in 43% yield overall from **20**; the same yields as *via* **23** to **5** are obtained from **20**.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-nitrosomethylamino)-β-D-ribofuranosyl]hypoxanthine (26).—A solution of 1.40 g (5.0 mmol) of the aminonucleoside **5** and 2.07 g (30 mmol) of sodium nitrite in 10 ml of acetic acid and 30 ml of water was kept at 25° for 24 hr and then evaporated. The residue of **25** was acetylated with 10 ml of acetic anhydride in 50 ml of pyridine at 25° for 23 hr and evaporated. The residue was triturated several times with water (5-ml portions), three times with methanol (4-ml portions), and dried to afford 1.82 g (92%) of **26**, mp 244–245.5° dec. Two recrystallizations from water gave the analytical sample of **26**: mp 247.5–249° dec; $[\alpha]^{20}D$ −36° (*c* 0.99, pyridine); uv max (pH 1) 243 mμ (ε 17,600); (pH 7) 242 mμ (18,000); (pH 13) 252 mμ (18,000); R_f 0.34, in solvent TF; R_{Ad} 2.18 and 1.43 in solvents PC and PE, respectively.

Anal. Calcd for $C_{15}H_{18}N_6O_7$: C, 45.7; H, 4.60; N, 21.3. Found: C, 45.7; H, 4.79; N, 21.1.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]adenine (27).—A suspension of 2.80 g (10 mmol) of the aminonucleoside **5** and 5.0 ml (53 mmol) of acetic anhydride in 100 ml of pyridine was stirred at 25° for 4 hr, during which time **5** dissolved. After the solution was worked up the residue was crystallized from 220 ml of absolute ethanol to give 2.93 g (72%) of **27** as white crystals, mp 222.5–224.5°. The mother liquors gave another 0.73 g [total 3.66 g (90%)] of **27**, mp 220–223°. A recrystallization from absolute ethanol afforded the analytical sample of **27**: mp 224–225.5°; $[\alpha]^{21.5}D$ −15° (*c* 0.99, pyridine); uv max (pH 1) 257 mμ (ε 13,800); (pH 7) 259 mμ (ε 13,900); (pH 13) 260 mμ (ε 14,200); R_f 0.70 in solvent TE; R_{Ad} 1.39, 1.95, and 1.38 in PA, PC, and PE, respectively.

Anal. Calcd for $C_{17}H_{22}N_6O_6 \cdot 1/4H_2O$: C, 49.7; H, 5.52; N, 20.5. Found: C, 49.8; H, 5.60; N, 20.6.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]hypoxanthine (28).—A 2.80 g (10 mmol) portion of **5** was acetylated as before, but the product **27** was immediately treated with 2.76 g (40 mmol) of sodium nitrite in 10 ml of acetic acid and 30 ml of water by the procedure used for **26**. Crystallization of the product, **28**, from 100 ml of methanol gave 3.06 g (75%) of **28** as white crystals, mp 239–241°, with a second crop of 0.37 g (total 84%), mp 238–240°. Recrystallization from methanol afforded the analytical sample of **28**: mp 240–241°; $[\alpha]^{21.5}D$ −24° (*c* 0.92, pyridine); uv max (pH 1) 248 mμ (ε 12,100); (pH 7) 248 mμ (ε 12,300); (pH 13) 253 mμ (ε 13,500); R_f 0.54 and 0.22 in solvents TE and TF, respectively; R_{Ad} 1.02, 2.38, and 1.25 in solvents PA, PC, and PE, respectively.

Anal. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.1; H, 5.20; N, 17.2. Found: C, 50.1; H, 4.94; N, 17.3.

9-(3-Deoxy-3-methylamino-β-D-ribofuranosyl)hypoxanthine (29).—A solution of 2.04 g (5.00 mmol) of the triacetyl **28** and 7.5 ml of 1.0 *N* methanolic sodium methoxide in 100 ml of methanol was refluxed for 8 hr, neutralized with acetic acid, and evaporated. Crystallization of the residue from 50 ml of methanol gave 1.01 g (72%) of **29** as white crystals, mp 217–219° dec, and a second crop, 0.09 g (total 79%), mp 215.5–219° dec. Recrystallization from the same solvent yielded the analytical sample of **29**: mp 218–219.5° dec; $[\alpha]^{22}D$ −25° (*c* 0.97, H_2O); uv max (pH 1) 249 mμ (ε 12,000); (pH 7) 249 mμ (ε 12,400); (pH 13) 254 mμ (ε 13,300); R_f 0.32 in solvent TB, R_{Ad} 0.33, 2.15, and 0.60 in solvents TA, TC, and TE, respectively.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 47.0; H, 5.38; N, 24.9. Found: C, 47.1; H, 5.48; N, 25.1.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylacetamido)-β-D-ribofuranosyl]-6-mercaptopurine (30).—A solution of 0.705 g (1.65 mmol) of the chloronucleoside **24** (1.31 g of 54% pure **24**), 0.19 g (2.48 mmol) of thiourea, and 0.27 ml (3.35 mmol) of pyridine in 25 ml of absolute ethanol was refluxed for 10 hr and evaporated and the residue triturated with ether to give 0.372 g (54%) of chromatographically pure, amorphous **30**. Crystallization from absolute ethanol gave two crops of **30**, 0.136 g (20%) of mp 210.5–212.5° dec and 0.036 g (total 25%) of mp 186–190° dec. Recrystallization of the first crop afforded **30**: mp 215.5–217.5° dec; $[\alpha]^{20}D$ −58° (*c* 0.49, pyridine); uv max (pH 1) 227 mμ sh (ε 9850), 321 (23,500); (pH 7) 228 mμ sh (ε 9500), 319 (20,500); (pH 13) 235 mμ sh (ε 14,600), 311 (22,200); R_f 0.42 in solvent TF.

Anal. Calcd for $C_{17}H_{21}N_5O_6S$: C, 48.2; H, 5.00; N, 16.5; S, 7.57. Found: C, 47.9; H, 4.87; N, 16.5; S, 7.13.

Reaction of **24** with excess thiourea in hot ethanol without pyridine cleaved the nucleoside product to 6-mercaptopurine. With 1.5 mol of thiourea and 2 of pyridine, crystalline **30** could be obtained in 23% yield together with 30% 6-mercaptopurine. On larger scale, the yield of **30** was not reproducible. With larger excesses of pyridine, the product **30**, though present,

could not be isolated. Replacement of pyridine with sodium bicarbonate resulted mostly in de-*O*-acylation of **24**.

9-(3-Deoxy-3-methylamino-β-D-ribofuranosyl)-6-mercaptopurine (31).—To a solution of 1.31 g (3.08 mmol) of the chloronucleoside **24** (2.30 g of 57% pure **24**) in 40 ml of methanolic hydrogen sulfide was added 9.3 ml of 1.0 *M* methanolic sodium hydrogen sulfide. The solution was refluxed for 1 hr during which time hydrogen sulfide was bubbled through the mixture. Then nitrogen was bubbled through the refluxing mixture for 15 min, 6.2 ml of 1.0 *M* methanolic sodium methoxide was added, and refluxing under nitrogen was continued for 7 hr more. After cooling, the mixture was adjusted to pH 7–8 with acetic acid to afford 0.43 g of **31**. Crystallization from water yielded 0.21 g (23%) of **31**, mp 221–223° dec. A further crystallization gave the analytical sample of **31**: mp 228–230.5° dec; $[\alpha]^{19}D$ −93° (c 0.46, 0.1 *N* NaOH); uv max (pH 1) 224 mμ (ε 9500), 321 (23,900); (pH 7) 229 mμ (ε 11,200), 315 (21,600); (pH 13) 232 mμ (ε 16,400), 310 (26,800); R_f 0.50 in solvent TB; R_{Ad} 1.88 and 0.73 in solvents PC and PE, respectively.

Anal. Calcd for $C_{11}H_{15}N_6O_3S$: C, 44.4; H, 5.09; N, 23.6; S, 10.8. Found: C, 44.5; H, 5.16; N, 23.3; S, 10.7.

9-[2,5-Di-*O*-acetyl-3-deoxy-3-(*N*-methylthioacetamido)-β-D-ribofuranosyl]-6-mercaptopurine (34).—To a stirred suspension of 1.70 g (4.17 mmol) of the triacetate **28** in 85 ml of dry pyridine was added 3.80 g (17 mmol) of phosphorus pentasulfide. The mixture was stirred vigorously and refluxed for 4 hr. The two-phase reaction mixture was evaporated and the residue was triturated with a solution of 2.86 g (34 mmol) of sodium bicarbonate in 40 ml of water. The precipitate was collected and washed with water to yield 1.32 g of **34**. Crystallization from 50 ml of ethanol gave 0.95 g (52%) of a crystalline powder, mp 191–196° dec, and an additional 0.15 g (total 60%), mp 185–191° dec. The analytical sample of **34**, recrystallized from water, had mp 207.5–209.5° dec: $[\alpha]^{21.5}D$ −93° (c 1.00, pyridine); uv max (pH 1) 223 mμ sh (ε 13,300), 272 (17,300), 321 (26,000); (EtOH) 228 mμ sh (ε 10,700), 275 (16,900) 324 (24,200); (pH 13) 235 mμ sh (ε 25,100) 311 (24,400), R_f 0.47 in solvent TF; R_{Ad} 1.55, 1.72, and 1.52 in solvents PA, PC, and PE, respectively.

Anal. Calcd for $C_{17}H_{21}N_5O_5S_2$: C, 46.5; H, 4.82; N, 15.9; S, 14.6. Found: C, 46.1; H, 4.86; N, 15.9; S, 14.5.

9-[3-Deoxy-3-methylamino-β-D-ribofuranosyl)-6-dimethylamino]purine (2).—Treatment of 5.85 g (13.7 mmol) of the chloronucleoside **24** (9.76 g of a 60% pure sample of **24**) with 15 ml of anhydrous dimethylamine in 150 ml of methanol in a bomb at 100° for 2 hr followed by deacylation with methanolic sodium methoxide (as for **5**) afforded crude **2**. Crystallization from 40 ml of water gave 2.65 g (63%) of **2** as white crystals, mp 215–216.5°, with a second crop of 0.20 g (total 68%), mp 213–215°. Recrystallization from water afforded **2**: mp 216.5–218°; $[\alpha]^{23}D$ −52° (c 0.97, EtOH); uv max (pH 1) 208 mμ (ε 20,100), 267 (19,200); (pH 7) 214 mμ (ε 17,100) and 275 (19,400); (pH 13) 275 mμ (ε 19,700): R_f 0.42 in solvent TB; R_{Ad} 1.47, 1.89, and 1.00, in solvents PA, PC, and PE, respectively; nmr (DMSO-d_6) δ 8.28 and 8.10 (both s, 2, H-8, H-2), 5.89 (d, 1, $J_{1,2}$ = 3 Hz, H-1′), 3.31 [s, 6, N^6-$(CH_3)_2$], 2.20 (s, 3, $HNCH_3$).

Anal. Calcd for $C_{13}H_{20}N_6O_3$: C, 50.6; H, 6.54; N, 27.3. Found: C, 50.7; H, 6.69; N, 27.1.

9-{3-Deoxy-3-[*N*-(benzyloxycarbonyl-*p*-methoxyphenyl-L-alanyl)methylamino]-β-D-ribofuranosyl}-6-dimethylaminopurine (32).—To a cooled (0°) stirred solution of 1.43 g (4.64 mmol) of the 3′-methylaminonucleoside (**2**), 1.61 g (4.9 mmol) of *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine,[13] and 0.565 g (4.9 mmol) of *N*-hydroxysuccinimide in 45 ml of dry DMF was added 1.01 g (4.9 mmol) of dicyclohexylcarbodiimide. The solution was stirred at 0° for 30 min and then at 25° for 3 days, protected from moisture. The reaction mixture was filtered, the dicyclohexylurea was washed with ethyl acetate, and the combined filtrate was evaporated. A solution of the residue in 40 ml of ethyl acetate was cooled at 0° for 1 hr and then filtered to remove the precipitated dicyclohexylurea. The filtrate was diluted to 100 ml with ethyl acetate and then washed successively with 25-ml portions of water, one-half saturated sodium bicarbonate solution, and two portions of water. The dried ethyl acetate solution was treated with charcoal and evaporated; the residual syrup was azeotroped with several 20-ml portions of methylene chloride to leave 2.79 g (91%, calcd as **32**·$^1/_2CH_2Cl_2$) of a pale yellowish-white solid foam: nmr (DCl_3) δ 8.17 (s, 1, $NHCO_2R$), 8.03 (s), and 7.85 (s, H-8, H-2), 7.25 (s, C_6H_5), 6.94 (q, $MeOC_6H_4$), 6.13 (d, H-1′), 5.27 (s, CH_2Cl_2) and remainder of spectrum compatible with structure of **32**; R_f 0.32 in solvent TD.

9-{3-Deoxy-3-[*N*-(*p*-methoxyphenyl-L-alanyl)methylamino]-β-D-ribofuranosyl}-6-dimethylaminopurine (3′-*N*-methylpuromycin) (2a).—A 2.08-g (3.14 mmol) sample of the amino acid nucleoside **32** and 0.31 g of 5% palladium on carbon in 50 ml of ethanol was stirred under hydrogen, 1 atmosphere, at 25° for 20 hr. After filtration through Celite, the filtrate was evaporated. The residue was dissolved in 10 ml of ethanol, diluted with 25 ml of water, and allowed to stand 1 day to precipitate the last traces of dicyclohexylurea. After filtration the filtrate was concentrated to about 20 ml, and extracted with three 20-ml portions of methylene chloride. The combined extracts were washed with two 10-ml portions of water, dried, treated with charcoal, and evaporated to a solid foam. This was dissolved in 50 ml of hot benzene, filtered, and allowed to crystallize at 25°. The very fine needles were collected, washed with benzene, and dried at 56° (0.1 Torr) for 15 hr to give 1.34 g (81% as **2a**·$^1/_2C_6H_6$) with mp 98–108°. Recrystallization from benzene did not change the melting point of **2a**·$^1/_2C_6H_6$: $[\alpha]^{19}D$ +30° (c 0.97, EtOH); uv max (pH 1) 268 mμ (ε 20,100); (EtOH) 213 mμ sh (ε 27,400), 276 (20,600); (pH 13) 276 mμ (ε 20,300); nmr ($DCCl_3$) δ 8.13 and 7.90 (both s, 2, H-8, H-2), 6.91 (q, 4, $MeOC_6H_4$), 5.86 (d, 1, $J_{1',2'}$ = 5.5 Hz, H-1′), remainder of spectrum showed overlapping with discernible singlets at δ 3.76 (OCH_3), 3.46 [$N^6(CH_3)_2$], and 2.90 ($N^{3'}CH_3$) as well as 0.5 C_6H_6 at δ 7.34; R_f 0.31 in solvent TE; R_{Ad} 1.65 in solvent PA.

Anal. Calcd for $C_{23}H_{31}N_7O_5 \cdot {}^1/_2C_6H_6$: C, 59.5; H, 6.53; N, 18.7. Found: C, 59.3; H, 6.25; N, 18.5.

9-{3-Deoxy-3-[*N*-(*N*-isopropylidene-*p*-methoxyphenyl-L-alanyl)methylamino]-β-D-ribofurnaosyl}-6-dimethylaminopurine (33).—A 0.181-g (0.37 mmol) sample of 3′-*N*-methylpuromycin (**2a**) was dissolved in 2 ml of acetone and allowed to stand at 25° (crystals began to form after approximately 15 min) for 17 hr. The fine white fibrous needles were collected, washed with acetone, and dried to give 0.149 g (76%) of **33**, mp 164–168°. For analysis, a sample was recrystallized from acetone and dried at 56° (0.15 Torr) for 15 hr: mp 166.5–170.5°; $[\alpha]^{19}D$ +5° (c 0.98, EtOH); after 17 hr at 25° the solution had $[\alpha]^{19}D$ +30°; like **2a**; ir (Nujol) 6.00 μ (C=N); uv max (pH 1) 268 mμ (ε 20,800); (EtOH) 213 mμ (ε 27,000), 276 (21,100); (pH 13) 276 mμ (ε 20,900); nmr ($DCCl_3$) δ 2.11 [s, 6, $N{=}C(CH_3)_2$]; remainder of spectrum like that of **2a**; **33** had the same chromatographic behavior as **2a**.

Anal. Calcd for $C_{26}H_{35}N_7O_5 \cdot H_2O$: C, 57.5; H, 6.86; N, 18.0. Found: C, 57.8; H, 6.80; N, 18.1.

9-[3-Deoxy-3-(dimethylamino)-β-D-ribofuranosyl]-6-dimethylaminopurine (3).—A solution of 0.925 g (3.00 mmol) of **2** in 5 ml of 88% formic acid and 5 ml of 37% aqueous formaldehyde was stirred and heated at reflux for 10 min (CO_2 evolution had ceased after ~8 min) and then evaporated. After adding and evaporating successively three 10-ml portions of water, the gelatinous residue was dissolved in 30 ml of water and filtered through Celite, and the filter was washed with water. The combined filtrates, about 40 ml, were adjusted to pH 9.5 with 1.0 *N* sodium hydroxide (4.9 ml needed), and evaporated. A solution of the residue in 10 ml of hot water gave, after standing at 5°, 0.645 g (67%) of **3**, mp 184–185°, and a second crop of 0.112 g (total 78%), mp 183.5–185°. Recrystallization of 0.15 g of **3** from 1 ml of water afforded, after drying at 56° and 0.15 Torr for 15 hr, 0.132 g of **3**: mp 184.5–186°; $[\alpha]^{25}D$ −27° (c 1.00, H_2O); uv max (pH 1) 209 mμ (ε 17,700), 267 (18,600); (pH 7) 214 mμ (ε 16,100), 275 (19,000); (pH 13) 276 mμ (ε 18,700); nmr (D_2O) δ 8.00 and 7.74 (both s, 2, H-8, H-2), 5.86 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1′), 3.07 [s, 6, $N^6(CH_3)_2$], 2.42 [s, 6, $N^{3'}(CH_3)_2$]; R_{Ad} 1.39, 1.96, and 1.64 in solvents PF, PG, and PP, respectively, where **2**, on the same sheet, had R_{Ad} 1.33, 1.91, and 1.70, respectively.

Anal. Calcd for $C_{14}H_{22}N_6O_3$: C, 52.2; H, 6.88; N, 26.1. Found: C, 52.2; H, 7.20; N, 26.0.

Registry No.—**2**, 25787-40-0; **2a**, 25787-41-1; **3**, 25787-42-2; **5**, 25787-43-3; **7** HCl, 25787-44-4; **8**, 25787-45-5; **9**, 25787-46-6; **11**, 25787-47-7; **13**, 25787-48-8; **15** HCl, 25787-49-9; **16**, 25787-50-2; **17**, 25787-51-3; **18**, 25787-52-4; **22**, 25787-53-5; **23**, 25787-54-6; **24**, 25834-69-9; **26**, 25834-70-2; **27**, 25834-71-3; **28**,

25787-55-7; **29**, 25787-56-8; **30**, 25787-57-9; **31**, 25791-57-5; **32**, 25791-58-6; **33**, 25791-59-7; **34**, 25791-60-0; 3-deoxy-3-methylamino-D-ribofuranose, 25791-61-1.

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2-Phenylaspartic Acid Derivatives from β-Lactams

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Intramolecular cyclization of an *N*-chloroacetyl-2-phenylglycine ethyl ester occurs in the presence of various bases to produce the corresponding 2-phenyl-4-oxoazetidine. A similar cyclization of the *N*-(3-chloropropionyl) homolog to an oxopyrrolidine has been observed. The facile ring cleavage of the oxoazetidines yielded a series of novel 2-phenylaspartic acid derivatives. Large geminal coupling constants from the pmr spectra of the *N*-phenyl- and *N*-benzyl-2-phenylaspartic acid derivatives support restricted rotational conformations for these compounds.

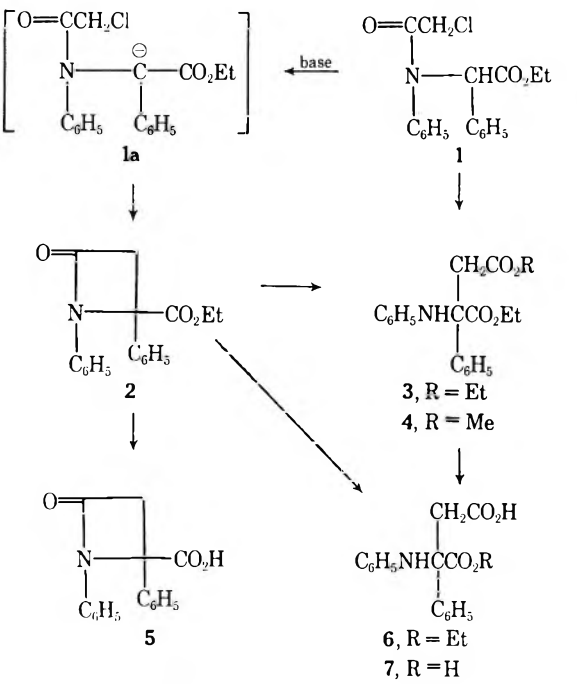
When *N*-chloroacetyl-*N*,2-diphenylglycine ethyl ester (**1**)[1] reacts with sodium cyanide, ethyl 4-oxo-1,2-diphenylazetidine-2-carboxylate (**2**)[2] is formed in good yield, rather than the *N*-cyanoacetyl derivative. Although **1** fails[1] to yield **2** in the presence of triethylamine, the reaction is successful[2] when carried out in the presence of basic anion exchange resin. Sheehan and Bose[3] report the intramolecular cyclization of diethyl *N*-arylhaloacetamidomalonates in the presence of triethylamine to 1-aryl-2,2-dicarbethoxy-4-oxoazetidines. Similarly, Deshpande, Mukerjee, and Dey[1,4] prepare 2,2-dicarbethoxy-1-phenyl-3-phthalimidomethyl-4-oxoazetidine from diethyl *N*-(3-phthalimido)-2-bromo-*N*-phenylpropionamidomalonate.

Sodium cyanide is apparently a strong enough base to form the carbanion (**1a**) which by intramolecular nucleophilic displacement of Cl gives **2**. Other bases (*e.g.*, NaH, NaOR, NaOAc, and NH_3) behave similarly, and may be preferred cyclization reagents (Scheme I).

1,4-Diethyl *N*,2-diphenylaspartate (**3**) was obtained in 84% yield by the addition of an excess (1.3 equiv) of NaOEt to **1** in EtOH. When 1 equiv of NaOEt was added rapidly to **1**, compound **3** was the major reaction product. The localized excess of NaOEt presumably opens up the initially formed azetidine ring to give **3** and a lesser amount (26%) of **2**. As expected, when **2** was treated with NaOMe–MeOH the analogous ester, 1-ethyl 4-methyl *N*,2-diphenylaspartate (**4**), was obtained.

Mild hydrolysis[2-4] of **2** (1 equiv) at room temperature in a 0.5% solution of KOH (1 equiv) in 95% EtOH produced the azetidinecarboxylic acid **5**. When the reaction was repeated with MeOH as solvent, the chief product was the ring-opened diester **4** with only a minor amount of **5** being isolated. Refluxing **3** for 5 min in a 1.6% NaOH (2.4 equiv) aqueous EtOH solution allowed selective hydrolysis of the 4-carbethoxy group, giving an 80% yield of 1-ethyl *N*,2-diphenylaspartate (**6**). Compound **6** was prepared by: (a) selective hydrolysis of **3** with hot dilute H_2SO_4, or (b)

SCHEME I



the ring cleavage of **2** with concentrated H_2SO_4. More drastic hydrolysis of either **2** or **3** with excess NaOH in refluxing aqueous dioxane produced *N*,2-diphenylaspartic acid (**7**).

Other investigators[3] obtained *N*-phenylaspartic acid by hydrolysis of 2,2-dicarbethoxy-1-phenyl-4-oxoazetidine with KOH, followed by decarboxylation. The dimethyl ester was obtained[3] by treatment with diazomethane. α esters are less readily available than β or γ esters of monoaminodicarboxylic acids. Klieger and Gibian[5] found that benzyloxycarbonyl-L-glutamic acid anhydride reacts with ROH in the presence of dicyclohexylamine to produce the α ester dicyclohexylammonium salt. The α esters may also be prepared[6] by taking advantage of the difference in the dissociation constants of the α- and γ-carboxyl groups of *N*-acylglutamic acids. The reaction is carried out

* Author to whom correspondence should be addressed.

(1) A. K. Bose, B. N. G. Mazumdar, and B. G. Chatterjee, *J. Amer. Chem. Soc.*, **82**, 2382 (1960).

(2) B. G. Chatterjee, V. V. Rao, and B. N. G. Mazumdar, *J. Org. Chem.*, **30**, 4101 (1965).

(3) J. C. Sheehan and A. K. Bose, *J. Amer. Chem. Soc.*, **72**, 5158 (1950).

(4) S. M. Deshpande, A. K. Mukerjee, and P. M. Dey, *Indian J. Chem.*, **6**, 238 (1968).

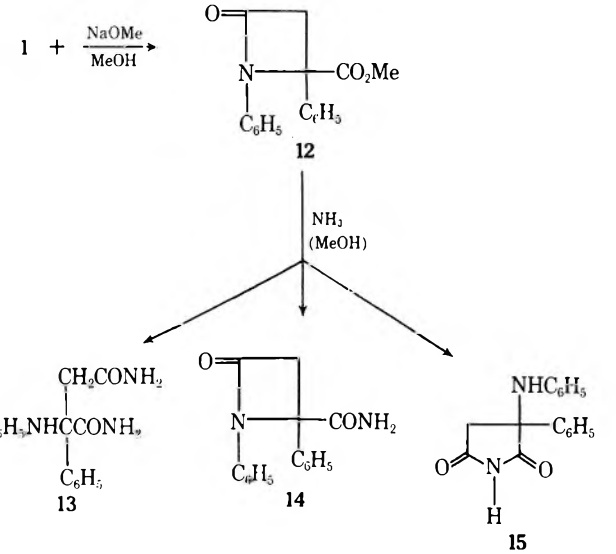
(5) E. Klieger and H. Gibian, *Justus Liebigs Ann. Chem.*, **655**, 195 (1962).

(6) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," G. A. Olah, Ed., Interscience, New York, N. Y., 1966, p 52.

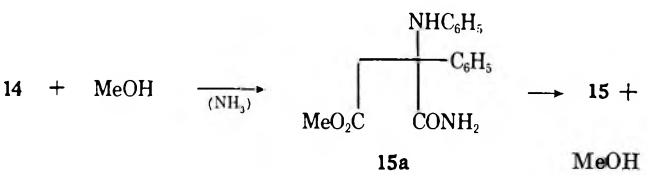
with RX in the presence of 1 equiv of a strong base. The mixed diesters can be obtained[6] from the α esters by several procedures.

The *N*-methyl and *N*-benzyl analogs of **1** were also prepared for cyclization to the corresponding oily oxoazetidines of type **2**. The crude oxoazetidines were treated with excess alkali in a manner similar to that used for the preparation of **7** from **2**. In both examples, however, the azetidine ring was more resistant to cleavage than **2** as shown by the isolation of azetidinecarboxylic acids **8** and **9** (Table I). The N-substituted 2-phenylaspartic acids **10** and **11** were obtained in lower yield.

During the intramolecular cyclization of **1** with NaOMe, transesterification also occurred giving **12**. The reaction of **12** with NH_3 in MeOH under pressure at room temperature gave three products: the succinamide **13**, the 4-oxoazetidine-2-carboxamide **14**, and the succinimide **15**. Compound **14** is believed to be the

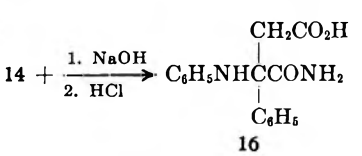


initial product of ammonolysis which reacts further with ammonia to produce the ring-cleavage product **13**. Pathways to **15** might include (a) ring cleavage of **14** with MeOH to yield an hypothetical intermediate **15a**, followed by the loss of MeOH, or (b) the intramolecular



rearrangement of **14**. Sheehan and Bose[3] prepared *N,N'*-dibenzyl-2-anilinosuccinamide by the action of benzylamine upon (a) *N*-phenylaspartic acid dimethyl ester or (b) 2-carbethoxy-2-carboxy-1-phenyl-4-oxoazetidine.

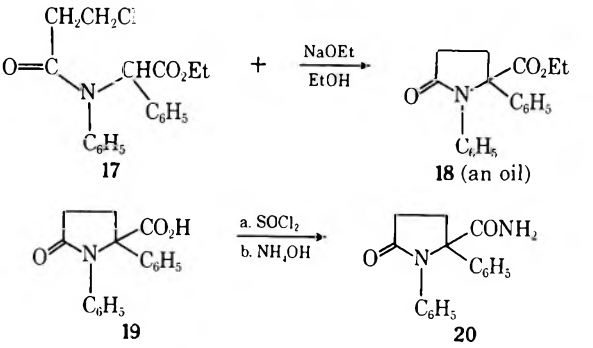
Ring cleavage of **14** with alkali has afforded a method for preparing the α amide, 3-anilino-3-phenylsuccinamic acid (**16**). A standard method[7] for preparing



(7) S. W. Tanenbaum, *J. Amer. Chem. Soc.*, **75**, 1754 (1953).

3-aminosuccinamic acid has involved the reaction between *N*-phthaloylaspartic anhydride and ammonia. As ring opening of the anhydride may occur in two different ways, mixtures may result by this method.

Using *N*-(3-chloropropionyl)-*N*,2-diphenylglycine ethyl ester (**17**) as the intermediate, ethyl 5-oxo-1,2-



diphenylpyrrolidine-2-carboxylate (**18**) was prepared under conditions similar to those used for the preparation of **2**. Compound **18** (an oil) was readily hydrolyzed to the crystalline acid **19**, which was then converted to the amide **20**. Similarly, the cyclization of diethyl *N*-(3-bromopropionyl)anilinomalonate to 2,2-dicarbethoxy-1-phenyl-5-oxopyrrolidine is reported.[1,2]

A method[8] for the preparation of 2,5-dioxopiperazines by the action of NH_3 in MeOH upon α-haloacetyl derivatives of amino acid esters was applied to the chloroacyl intermediates **1** and **17**. However, the products isolated were compounds **14** and **21** (Table I), respectively, resulting from expected intramolecular cyclizations.

Pmr Spectra.—The proton magnetic resonance spectra of the substituted 4-oxoazetidines show marked magnetic nonequivalence of the two protons in position 3 caused by the asymmetric carbon atom 2 (Table II). The geminal coupling constants are in the normal range for methylene protons in four-membered ring compounds[9] having a planar configuration and one adjacent π bond.[10] No cross-ring coupling was observed in **8** or **9** between the hydrogens at position 3 and the methyl or benzylic protons as was reported by Barrow and Spotswood.[9] The two substituents at position 2 must force the N substituent into the plane of the ring thereby destroying the transoid pathway necessary for long-range coupling.

The absolute values of the geminal coupling constants observed for the *N*-phenyl- and *N*-benzyl-2-phenylaspartic acid derivatives are very large, especially for those spectra taken in trifluoroacetic acid solution. These values require a large population of restricted rotational conformations with the plane of the carbonyl group bisecting the H–C–H bonds of the methylene group.[10] Conformational restrictions imposed by rotational hindrance of the two benzene rings, and probably enhanced by intramolecular hydrogen bonding of the acidic hydrogen to the adjacent carbonyl group, allow a preferred conformation for the 2-phenylaspartic acid derivatives which approaches that of the cyclic compounds.

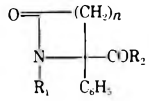
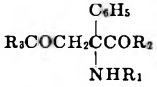
(8) Y. T. Pratt in *Heterocycl. Compounds*, **6**, 438 (1957).

(9) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, **37**, 3325 (1965).

(10) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).

TABLE I

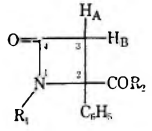
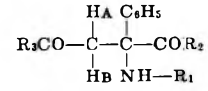
THE LACTAMS AND ASPARTIC ACID DERIVATIVES

Compd no.	R_1	R_2	(n) or R_3	Prepn method (variation)[a]	Yield, %	Recrystn solvent[b]	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
														
2	C_6H_5	OEt	(1)	A, B, C	65, 93, 56	B	80–81.5	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	73.48	5.93	4.65
5	C_6H_5	OH	(1)	G	37	B	127.5–129	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.60	4.79	5.11
8	Me	OH	(1)	BH (1)	10	A	210.5–211 dec	...[a(1)]	62.89	6.50	11.28	63.19	6.40	11.30
9	$C_6H_5CH_2$	OH	(1)	BH (5)	77	C	145.5–146	$C_{17}H_{15}NO_3$	72.58	5.38	4.98	72.48	5.44	5.09
12	C_6H_5	OMe	(1)	B (2)	78	A	112–114	$C_{17}H_{15}NO_3$	72.58	5.37	4.98	72.49	5.33	4.93
14	C_6H_5	NH_2	(1)	K, L	18, 31	A	197–198.5	$C_{16}H_{14}N_2O_2$	72.16	5.30	10.52	72.11	5.45	10.45
19	C_6H_5	OH	(2)	BH (3)	18	C	249–251 dec	$C_{17}H_{15}NO_3$	72.58	5.38	4.98	72.88	5.86	4.86
20	C_6H_5	NH_2	(2)	(4)	71	C, D	213–214.5	$C_{17}H_{16}N_2O_2$	72.83	5.75	10.00	72.62	5.76	9.99
21	C_6H_5	OMe	(2)	M	28	C	129–130	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	73.17	6.00	4.71
														
3	C_6H_5	OEt	OEt	D, E	84, 62	F	139.5–141.5	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.43	6.63	4.38
4	C_6H_5	OEt	OMe	E (2)	61	A	147–148	$C_{19}H_{21}NO_4$	69.70	6.46	4.28	69.79	6.19	4.59
6	C_6H_5	OEt	OH	F	80	C	190–191.5 dec	$C_{18}H_{19}NO_4$	68.90	6.11	4.47	68.92	5.89	4.65
7	C_6H_5	OH	OH	H	70, 56	B	180–180.5 dec	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	67.32	5.58	4.88
10	Me	OH	OH	H (6)	63	E	232[c]	$C_{11}H_{13}NO_4$	59.21	5.87	6.28	58.95	5.83	6.35
11	$C_6H_5CH_2$	OH	OH	H (7)	18	H	198.5 dec	$C_{17}H_{17}NO_4$	68.21	5.73	4.68	68.22	5.72	4.61
13	C_6H_5	NH_2	NH_2	J	17	G	253.5–255.5 dec	$C_{16}H_{17}N_3O_2$	67.82	6.05	14.83	67.53	6.26	14.74
16	C_6H_5	NH_2	OH	N	70	C	160–161 dec	$C_{16}H_{16}NO_2O_3$	67.59	5.67	9.86	67.42	5.75	9.57

[a] See Experimental Section for the letters: (1) isolated from the EtOAc soluble fraction in method H as the piperazinium salt formula, $(C_{11}H_{11}NO_3)_2 \cdot C_4H_{10}N_2$; (2) MeOH was employed as the reaction solvent; (3) 75% aqueous 2-PrOH was used as the reaction solvent in method H; (4) prepared by the action of $SOCl_2$ on **19**, followed by treatment with NH_4OH; (5) concentration of the reaction mixture in method H, followed by solution of the residual oil in H_2O and adjusting pH to ~4–5 gave the solid; (6) precipitated by concentrating the aqueous layer from **8**; (7) H_2O soluble fraction from **9**. [b] A = MeOH, B = EtOAc–Skellysolve B, C = EtOH, D = DMF–MeOH, E = 50% aqueous MeOH, F = EtOAc–EtOH, G = DMF–H_2O, H = aqueous EtOH. [c] Indefinite.

TABLE II

PMR SPECTRAL DATA

Compd no.[a]	Solvent	Chemical shifts (ppm from TMS) R_1	H_A	H_B	$J_{A,B}$, cps	Compd no.[a]	Solvent	Chemical shifts (ppm from TMS) R_1	H_A	H_B	$J_{A,B}$, cps
											
2	CCl_4	C_6H_5	3.05	3.77	15.2	3	$CDCl_3$	C_6H_5	3.54	3.78	16.4
8	CF_3COOH	CH_3, 3.17	3.62	3.91	15.5	6	$CDCl_3$	C_6H_5	3.62	3.84	17.0
9	CF_3COOH	$C_6H_5CH_2$, 4.74	3.62	3.90	16.0	7	CF_3COOH	C_6H_5	3.58	3.90	18.9
12	CCl_4	C_6H_5	3.08	3.80	15.1	10	CF_3COOH	CH_3, 2.79	3.98	3.98	None observed
14	CF_3COOH	C_6H_5	3.80	4.04	15.7	11	CF_3COOH	$C_6H_5CH_2$, 4.20	3.87	4.05	18.7
						13	CF_3COOH	C_6H_5	3.64	3.81	18.0
						16	CF_3COOH	C_6H_5	3.75	3.92	19.0

[a] See Table I.

The coupling constants were obtained directly from the spectra, while the chemical shift values were adjusted using the formula[11] for the deviation from first-order treatment. The signs of the coupling constants were not determined, but the geminal coupling constants are probably negative.

Experimental Section

The ir spectra of all the described compounds are consistent with the assigned structures. The β-lactam carbonyl bands were in the expected range[2] of 5.65–5.75 μ. The pmr data were obtained from spectra taken with a Varian A-60A spectrometer, using TMS as internal reference. The melting points are corrected (Thomas–Hoover capillary apparatus).

The N-substituted 2-phenylglycine ethyl esters were prepared as described.[12,13] ***N*-Benzyl-2-phenylglycine ethyl ester·HCl** was obtained in a yield of 75%, mp 182.5–183.5° dec, after recrystallizing from anhydrous EtOH.

Anal. Calcd for $C_{17}H_{19}NO_2 \cdot HCl$: C, 66.77; H, 6.59; N, 4.58; Cl, 11.60. Found: C, 66.76; H, 6.72; N, 4.49; Cl, 11.77.

The *N*-chloroacyl derivatives were prepared in warm (50–60°) benzene solution according to a similar procedure.[14] ***N*-Chloroacetyl-*N*-methyl-2-phenylglycine ethyl ester** was obtained in a yield of 69%, mp 50–52°, after recrystallizing from EtOAc–Skellysolve B.

Anal. Calcd for $C_{13}H_{16}ClNO_3$: C, 57.88; H, 5.98; N, 5.19. Found: C, 57.77; H, 6.06; N, 5.22.

***N*-Benzyl-*N*-chloroacetyl-2-phenylglycine ethyl ester** was obtained in yield of 35%, mp 82.5–84.5°, after recrystallizing from EtOAc–Skellysolve B.

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05; Cl, 10.26. Found: C, 66.15; H, 5.90; N, 4.14; Cl, 9.85.

***N*-(3-Chloropropionyl)-*N*,2-diphenylglycine ethyl ester** (**17**) was obtained in a yield of 35%, mp 84.5–85.5°, after recrystallizing from EtOAc–Skellysolve B.

Anal. Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; Cl, 10.26. Found: C, 65.79; H, 5.46; Cl, 10.32.

A. Ethyl 4-Oxo-1,2-diphenylazetidine-2-carboxylate (2).[2]—A suspension of 0.025 mol of the chloro intermediate 1,[1] 1.5 g (0.0305 mol) of NaCN, and 18 ml of dimethylformamide (DMF) was heated at 50–60° for 2 hr. After adding 10 ml of H_2O, the resulting solution was heated at 95–100° for 0.5 hr. The reaction mixture was diluted with H_2O to give an oil which crystallized from aqueous EtOH, yield 4.8 g (65%).

B.—A solution of 1 g (0.0435 g-atom) of Na dissolved in 60 ml of anhydrous EtOH was added slowly (10 min) to a stirred suspension of 14.4 g (0.0435 mol) of 1 in 80 ml of anhydrous EtOH. The reaction temperature increased from 25 to 30° during the addition. After slowly heating the mixture to reflux and maintaining this temperature for 1 hr, the neutral suspension was allowed to stand overnight. The solid (chiefly NaCl) was collected on a filter, washed with EtOH, and discarded. The filtrate was concentrated to a small volume and the resulting white solid was collected, yield 12 g (93%). When this reaction was repeated, omitting the heating step, a 79% yield was obtained. When the reaction was carried out under rapid addition of NaOEt, this compound was obtained in only 26% yield. The major product was ring-cleaved 1,4-diethyl *N*,2-diphenylaspartate (**3**).

C.—An equivalent of NaH (dispersion 54.3% in mineral oil) was added to a cold (3–5°) mixture of 8.3 g (0.025 mol) of 1 and 25 ml of DMF. After 3 hr at room temperature and 1 hr at 50–55°, the resulting neutral reaction mixture was diluted with 15% NaCl solution. The compound was isolated by extracting with C_6H_6, yield 4.1 g (56%).

D. 1,4-Diethyl *N*,2-Diphenylaspartate (3).—A solution of 100 ml of anhydrous EtOH containing 2.3 g (0.1 g-atom) of dissolved Na was added to a suspension of 25.5 g (0.077 mol) of 1 and 200 ml of anhydrous EtOH. The reaction temperature increased from 25 to 30°. The mixture was warmed at 35–40° for 0.5 hr and then heated under reflux for 1 hr. After standing overnight at room temperature, the solid was collected and washed first EtOH and then with H_2O, yield 22 g (84%) of white solid.

E.—A mixture of 2.5 g (0.0085 mol) of 2 and 50 ml of anhydrous EtOH containing 0.1 g (0.0044 g-atom) of dissolved Na was warmed slowly to 50° and the reaction temperature was maintained at 50–60° for 1 hr. During the heating time, solution resulted followed by precipitation of the product. After cooling, the white solid was collected and washed with EtOH, yield 1.8 g (62%).

F. 1-Ethyl *N*,2-Diphenylaspartate (6).—A mixture of 3.4 g (0.01 mol) of **3**, 50 ml of EtOH, and 12 ml of 2 *N* NaOH was heated under reflux for 5 min. After cooling, the precipitate was collected and dried to give 1.2 g of white solid of mp >300°. It was dissolved in warm H_2O, and 5 ml of 1 *N* HCl was added to precipitate **6**, yield 0.6 g. An additional quantity (1.9 g) was obtained by acidification of the original filtrate, total yield 2.5 g (80%).

Compound **6** was also prepared by acid hydrolysis from either compound **3** or **2**. Compound **3** (6.5 g, 0.019 mol) was heated to 90° in 56 g of 65% H_2SO_4. The solution was poured onto ice water. The product was extracted with EtOAc to give 5 g (85%). Similarly, a solution of 3 g (0.01 mol) of **2** in 6 ml of concentrated H_2SO_4 was allowed to stand overnight, yield 1.4 g (45%).

G. 4-Oxo-1,2-diphenylazetidine-2-carboxylic Acid (5).—Hydrolysis[2] of the carbethoxy group in **2** was achieved by slowly adding 100 ml of 95% EtOH containing 1.1 g (0.020 mol) of KOH to a stirred suspension of 6 g (0.02 mol) of **2** in 100 ml of 95% EtOH. After 5 min, a complete solution resulted. The reaction mixture was allowed to stand overnight and concentrated to a white solid, yield 5.5 g (90%) of the K salt. A solution of this solid in 30 ml of H_2O was acidified. The product was isolated by extracting with Et_2O and concentrating the extract to give an oil. This material was slurried with EtOAc–Skellysolve B to give 2 g (73%) of product.

When this reaction was repeated using anhyd MeOH as the solvent, only 0.4 g (7%) of **5** was obtained. Compound **4** was isolated as the chief product (2.4 g, 37%).

H. *N*,2-Diphenylaspartic Acid (7).—A mixture of 15 g (0.05 mol) of **2** and 0.16 mol of NaOH in 230 ml of 65% aqueous dioxane was heated under reflux for 3 hr and then concentrated. After adding 160 ml of 1 *N* HCl, 10 g (70%) of **7** precipitated. When **3** was employed as the intermediate, a 56% yield of **7** was obtained.

J. 2-Anilino-2-phenylsuccinamide (13).—To 300 ml of MeOH saturated with NH_3 at 10° was added 11.7 g (0.041 mol) of **12**. The cold suspension was stoppered and allowed to stand at room temperature for 4 days with careful agitation at the end of the first day to complete the solution. The flask was cooled and opened and the white solid was collected, yield 1.5 g (13%). A second crop was recovered from the filtrate by concentrating to one-half volume, slurrying the resulting solid with hot MeOH, total yield 2 g (17%).

K. 4-Oxo-1,2-diphenylazetidine-2-carboxamide (14).—The solid, which precipitated from the above methanolic filtrate, was recrystallized twice from MeOH to give 2 g (18%) of product.

2-Anilino-2-phenylsuccinimide (15).—A third crop (3.2 g) of crude material was obtained from the above filtrate (method K). Three recrystallizations from MeOH gave 1.2 g (11%) of purified solid. An additional recrystallization by dissolving the sample in 15 ml of DMF, followed by dilution with 5 ml of H_2O, gave **15** melting at 212.5–214°: λ_{max}^{KBr} 2.95, 5.58, 5.82, 6.24, 6.64, 13.32, 14.38 μ; $\delta^{(CF_3COCH)}$ 3.89, 4.08 (J = 18.8 cps), 10.08 (NH).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.18; H, 5.60; N, 10.36.

L.—Compound **14** was also obtained by bubbling NH_3 into a stirred mixture of 33.2 g (0.1 mol) of **1** and 300 ml of MeOH. The resulting solution was allowed to stand at room temperature for 5 days at the end of which time a solid had formed, yield 8.3 g (31%).

M. Methyl 5-Oxo-1,2-diphenylpyrrolidine-2-carboxylate (21).—Compound **17** (10.4 g, 0.03 mol) was added to 150 ml of MeOH saturated with NH_3 at 10°. After standing at room temperature for 10 days, the solution was concentrated to an oily solid. This material was slurried with EtOAc to give 1.5 g of NH_4Cl. The filtrate was diluted with Skellysolve B to precipitate 2.5 g (28%) of product. Its structure was further supported by hydrolysis to **19** as follows: A mixture of 0.1 g of **21**, 1 ml of 2 *N* NaOH, and 2 ml of MeOH was warmed slightly for a few minutes and then allowed to stand for 3 hr. The carboxylic acid **19** was

(11) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 120.

(12) J. Klosa, *Arch. Pharm.*, **285**, 401 (1952).

(13) C. Bischoff, *Ber.*, **30**, 2305 (1897).

(14) T. A. Martin, D. H. Causey, A. L. Sheffner, A. G. Wheeler, and J. R. Corrigan, *J. Med. Chem.*, **10**, 1172 (1967).

isolated by concentrating the reaction mixture to yield a solid, dissolving in H_2O, and acidifying, yield 0.1 g.

N. 3-Anilino-3-phenylsuccinamic Acid (16).—A solution of 2.7 g (0.01 mol) of **14** and 40 ml each of EtOH, dioxane, and 1 *N* NaOH was allowed to stand overnight. After neutralizing with 40 ml of 1 *N* HCl, the reaction mixture was concentrated, yield 2 g (70%).

Registry No.—**2**, 5634-62-8; **3**, 25791-42-8; **4**, 25791-43-9; **5**, 13327-23-6; **6**, 25791-45-1; **7**, 25791-46-2; **8** (piperazinium salt), 25791-47-3; **9**, 25791-48-4; **10**, 25791-49-5; **11**, 25791-50-8; **12**, 25791-51-9; **13**, 25791-52-0; **14**, 25791-53-1; **15**, 25791-54-2; **16**, 25791-55-3; **17**, 25834-64-4; **19**, 25791-56-4; **20**, 25791-62-2; **21**, 25791-63-3; *N*-benzyl-2-phenylglycine ethyl ester·HCl, 25791-64-4; *N*-chloroacetyl-*N*-methyl 2-phenylglycine ethyl ester, 25791-65-5; *N*-benzyl-*N*-chloroacetyl-2-phenylglycine ethyl ester, 25791-66-6.

Acknowledgment.—The authors are grateful to Mr. C. I. Kennedy and Mr. J. G. Schmidt for analytical and ir spectral data, and to Mr. D. H. Causey and Mr. W. F. Kavanaugh for technical assistance.

Synthesis of a Bicyclohydantoin

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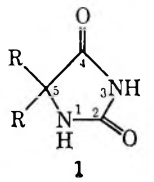
The preparation and intramolecular cyclizations of 5-phenyl-5-(3-hydroxypropyl)hydantoin tosylate, **4**, and 5-phenyl-5-(4-hydroxybutyl)hydantoin tosylate, **5**, are described. No products involving the imide nitrogen in the cyclizations could be obtained. Proof of structure of the compounds involving the amide nitrogen in the cyclization is discussed.

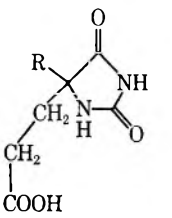
Previous reports have indicated that intermolecular alkylations of 5,5-disubstituted hydantoins, **1**, proceed exclusively at the imide nitrogen (N-3).[2] Amino-



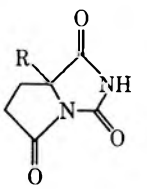
1

methylations utilizing formaldehyde,[3] aminoethylations with ethylenimine,[4] and Michael condensations[5] have also demonstrated a preference for the acidic imide function. Amide nitrogen (N-1) alkylations occur under more rigorous reaction conditions during which both nitrogens are alkylated. Mono N-1-alkylated hydantoins can be obtained by protecting the imide nitrogen with an aminomethyl group followed by alkylation of the amide nitrogen and then the removal of the protecting group by mild aqueous base hydrolysis.[6]

Intermolecular acylations have been reported to occur exclusively at the amide nitrogen and the intramolecular cyclization of the hydantoin propionic acids **2a**[7] and **2b**[8] yield only the amide cyclized products **3a** and **3b**, respectively.

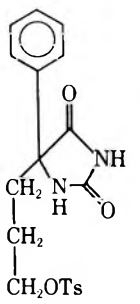


2a, R = H
b. R = CH_3, C_3H_5



3

In these laboratories the base-catalyzed cyclizations of 5-phenyl-5-(3-hydroxypropyl)hydantoin tosylate, **4**, and 5-phenyl-5-(4-hydroxybutyl)hydantoin tosylate, **5**, produced only amide cyclized monomers. The synthesis of **4** and **5** and the proof of structure of the cyclized products are described below.



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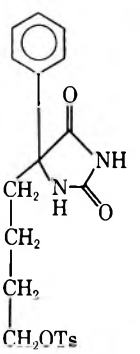

5

The conversion of 3-benzoylpropionic acid, **6a**, and 4-benzoylbutyric acid, **6b**, to 4-hydroxybutyrophenone, **8a**, and 5-hydroxyvalerophenone, **8b**, was performed by a lithium aluminum hydride reduction of the corresponding ethylene ketal monoethylene glycol esters **7a** and **7b** followed by acid hydrolysis according to the method of Pasto and Serve[9] (Scheme I).

The two keto alcohols, **8a** and **8b**, were converted to the 5-phenyl-5-(hydroxyalkyl)hydantoins, **9a** and **9b**,

* Author to whom correspondence should be addressed.

(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of The University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) (a) E. Ware, *Chem. Rev.*, **46**, 403 (1950); (b) M. B. Winstead and C. R. Hamel, *J. Med. Chem.*, **8**, 120 (1965).

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(6) O. O. Orazi and R. A. Corral, *Experientia*, **21**, 508 (1965).

(7) J. L. Szabo and J. V. Karabinos, *J. Amer. Chem. Soc.*, **66**, 650 (1944).

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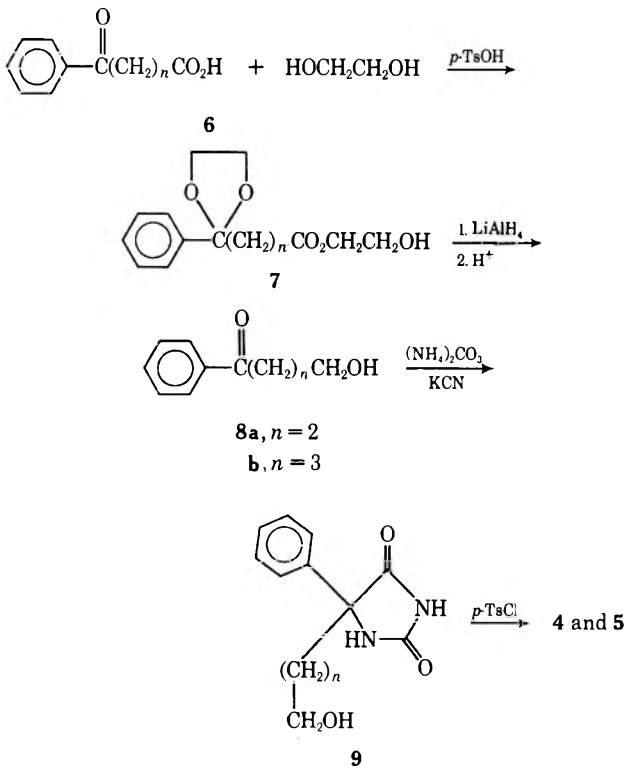
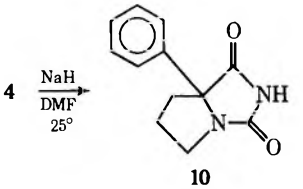
SCHEME I

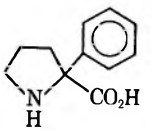


by condensation with ammonium carbonate and potassium cyanide.[10] The resulting hydantoin alcohols were converted to their respective tosylates **4** and **5**. The nmr spectra of **4** and **5** showed absorption at δ 8.5–8.7 and 10.7–10.9, indicating the amide and imide protons[11] to be present, thus excluding the possibility of alkylation having occurred during the formation of the tosylates.

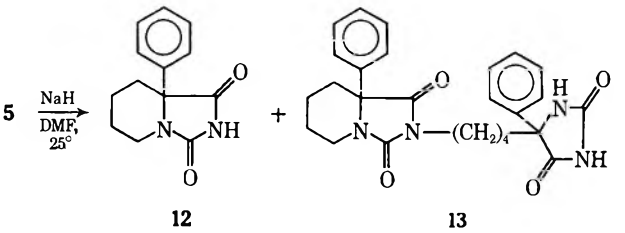
When the tosylate, **4**, was treated with sodium hydride, the products were the amide-alkylated hydantoin, 7(a)-phenylpyrrolidino[1,2-*d*]-1,3-(2*H*)-imidazolidinedione, **10**, and polymeric material.



The infrared spectrum of **10** exhibited strong absorptions at 3250 and 3150 cm^{-1} which are characteristic absorption bands for N-3-substituted hydantoins.[12] The nmr spectrum of **10** showed a broad singlet at δ 10.90 (imide proton)[11] and a molecular ion *m/e* 216. Base hydrolysis of **10** in ammonium hydroxide–hydrogen sulfide[13] or in barium hydroxide solution[14] afforded the amino acid, 2-phenylproline, **11**. Under conditions



analogous to the cyclization of **4**, the hydantoin tosylate **5** afforded 8(a)-phenylpiperidino[1,2-*c*]-1,3-(2*H*)-imidazolidinedione, **12**. The infrared spectrum of **12** showed absorption at 3270 and 3160 cm^{-1} (imide NH stretching frequency).[12] The nmr (broad singlet at δ 10.98)[11] and the mass spectrum (molecular ion *m/e* 230)



confirmed the assigned structure. A crystalline dimer (molecular ion *m/e* 460) was also obtained from the reaction. Its nmr spectrum showed single amide and imide protons. Structure **13** is the most plausible assignment based on the preferred routes of inter- and intramolecular alkylation in the hydantoins.

The use of higher temperatures and different base catalysts, in general, had no effect on the ring closure of **4** except to lower the overall yield of **10**. The use of potassium carbonate in dimethylformamide at elevated temperatures did raise the yield of the cyclic monomer, **12**. No evidence for intramolecular cyclization *via* the imide nitrogen to the [4.2.1]bicyclodiazanonane system could be obtained under any of the various conditions utilized.

Experimental Section[15]

4-Hydroxybutyrophenone (8a).—Essentially the method of Pasto and Serve was followed.[9] A mixture of 3-benzoylpropionic acid, **6a** (58.2 g, 0.33 mol), ethylene glycol (40.0 g, 0.65 mol), and TsOH (3.0 g) yielded a yellow oil, **7a** (68.2 g), whose spectra were consistent with the assigned structure.

A solution of the oil, **7a** (68.0 g; 0.30 mol), in Et_2O was added dropwise to a stirred suspension of $LiAlH_4$ (27.7 g; 0.75 mol) in Et_2O at room temperature. The reaction yielded the desired product **8a** (32.3 g; 61% overall from **6a**).

The 2,4-dinitrophenylhydrazone of **8a** was prepared and recrystallized from EtOH–H_2O, mp 128–130° (lit.[16] mp 137°).

5-Hydroxyvalerophenone (8b).—A solution of 4-benzoylbutyric acid, **6b** (50.0 g, 0.26 mol), ethylene glycol (48.4 g, 0.68 mol), and TsOH (3.00 g) yielded **7b** (67.1 g) when subjected to the same procedure as above.[9] The ketal ester **7b** was allowed to react with excess $LiAlH_4$ in the manner utilized for **7a** to give the desired product **8b** (35.4 g; 76% from **6b**).

The 2,4-dinitrophenylhydrazone of **8b** was prepared and recrystallized from EtOH–H_2O, mp 136–141° (lit.[17] mp 145°).

5-Phenyl-5-(3-hydroxypropyl)hydantoin (9a).—A mixture of **8a** (20.0 g, 0.12 mol), KCN (15.9 g, 0.24 mol), and $(NH_4)_2CO_3$ (47.0 g, 0.49 mol) in EtOH–H_2O (500 ml) was heated at 55–60° with stirring for 22 hr. Part of the solvent was removed *in vacuo* and the reaction mixture cooled, diluted with ice–H_2O (200 ml), and acidified to congo red with 10% HCl. The precipitate was collected, washed repeatedly with water, and dried. Re-

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(13) W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 546 (1935).
(14) H. D. Daken, *J. Biol. Chem.*, **45**, 368 (1911).
(15) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data were recorded on Beckman IR-8 and IR-10 spectrophotometers and are reported in cm^{-1}. Nmr data were recorded on Varian Associates Model A-60, A-60A, and HA-100 spectrophotometers (TMS) and are reported as ppm (δ) in the organic solvent specified. If D_2O was used as the solvent, sodium 3-trimethylpropanesulfonate was employed as an internal standard. Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind. and on an F & M Model 185, The University of Kansas. Molecular weights were determined on a Finnigan 1015 mass spectrometer.
(16) B. C. Subba Rao and G. P. Thaker, *Curr. Sci.*, **32**, 404 (1963).
(17) J. Cologne, G. Descartes, and J. C. Saula, *C.R. Acad. Sci.*, **354**, 887 (1962).

crystallization from EtOH-Me_2CO gave **9a** (14.6 g; 52%): mp 205–206°; nmr (DMSO-d_6) 1.06–1.72 (2 H, multiplet, CH_2), 1.74–2.30 (2 H, multiplet, CH_2), 3.40 (2 H, triplet, CH_2OH), 4.08–4.70 (1 H, multiplet, –OH), 7.20–7.68 (5 H, multiplet, aromatic), 8.63 (1 H, broad singlet, amide), 10.73 (1 H, broad singlet, imide).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.09; H, 6.04; N, 12.08.

5-Phenyl-5-(4-hydroxybutyl)hydantoin (9b).—A solution of **8b** (15.0 g, 0.084 mol), KCN (10.9 g, 0.17 mol), and $(NH_4)_2CO_3$ (32.3 g, 0.34 mol) in 50% EtOH-H_2O was allowed to react according to the above procedure. The desired product **9b** (19.2 g, 83%) was isolated: mp 168–170° (EtOH-Me_2CO); nmr (DMSO-d_6) 1.05–1.70 (4 H, multiplet, CH_2), 1.80–2.20 (2 H, multiplet, CH_2,) 3.20–3.60 (2 H, multiplet, CH_2OH), 4.20–4.50 (1 H, multiplet, –OH), 7.20–7.68 (5 H, multiplet, aromatic), 8.60 (1 H, broad singlet, amide), 10.70 (1 H, broad singlet, imide).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.29. Found: C, 62.92; H, 6.61; N, 11.35.

5-Phenyl-5-(3-hydroxypropyl)hydantoin *p*-Toluenesulfonate (4).—A solution of **8a** (2.34 g, 0.01 mol) in pyridine (30 ml) was cooled to 0°, treated with TsCl (5.70 g, 0.03 mol), and allowed to stand at 0° for 18 hr. The reaction mixture was poured into ice–H_2O and extracted with Et_2O. The Et_2O extracts were washed repeatedly with cold 10% HCl, H_2O, and dried ($MgSO_4$). Evaporation of the Et_2O afforded **4** (3.40 g, 88%): mp 153–154° (MeCO); nmr (DMSO-d_6) 1.15–2.65 (7 H, multiplet), 4.10 (2 H, multiplet, CH_2–OTs), 7.20–7.92 (9 H, multiplet, aromatic), 8.70 (1 H, broad singlet, amide), 10.80 (1 H, broad singlet, imide).

Anal. Calcd for $C_{19}H_{20}N_2O_5S$: C, 58.75; H, 5.19; N, 7.21; S, 8.26. Found: C, 58.67; H, 5.02; N, 7.40; S, 8.34.

5-Phenyl-5-(4-hydroxybutyl)-hydantoin *p*-Toluenesulfonate (5).—Compound **9b** (10.0 g, 0.40 mol) was allowed to react with TsCl (23.0 g, 0.120 mol) according to the procedure described for **9a**. The tosylate, **5** (14.2 g; 86%), crystallized from $CHCl_3$–Me_2CO: mp 187–188°; nmr (DMSO-d_6) 1.10–2.70 (9 H, multiplet), 4.01 (2 H, multiplet, CH_2OTs), 7.20–7.90 (9 H, multiplet, aromatic), 8.63 (1 H, broad singlet, amide), 10.75 (1 H, broad singlet, imide).

Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.68; H, 5.51; N, 6.96; S, 7.97. Found: C, 59.39; H, 5.41; N, 7.06; S, 8.09.

Cyclization of 5-Phenyl-5-(3-hydroxypropyl)hydantoin *p*-Toluenesulfonate.—To a stirred solution (under N_2) of **4** (0.500 g, 1.29 mmol) in DMF (75 ml) was added NaH (0.056 g, 1.29 mmol) (50% in mineral oil). The reaction mixture was stirred at room temperature for 24 hr, poured into ice–H_2O, and acidified to congo red with 10% HCl. The acidic mixture was extracted with $CHCl_3$ and the $CHCl_3$ extracts were washed with 5% $NaHCO_3$ and H_2O and dried ($MgSO_4$). The solvent ($CHCl_3$ and DMF) was removed *in vacuo* to give an amorphous gum which partially dissolved in $CHCl_3$. The mixture was filtered to give 0.091 g of a solid (mp 260° dec) which was insoluble in common organic solvents and in 10% NaOH. The substance was assumed to be a polymer.

Chromatography of the $CHCl_3$ layer on silica gel (80% $CHCl_3$, 20% EtAc) gave the bicyclo[3.3.0] derivative, 7(a)-phenylpyrrolidino[1,2-*d*]-1,3-(2*H*)-imidazolidinedione, **10** (0.120 g; 56%): mp 187–188° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3250, 3150, 2710, 1670–1760; nmr (DMSO-d_6) 1.55–2.45 (4 H, multiplet, CH_2), 3.00–3.86 (2 H, multiplet, CH_2), 7.25–7.66 (5 H, multiplet, aromatic), 10.88 (1 H, broad singlet, imide).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.35; H, 5.46; N, 13.30.

2-Phenyproline (11).—Compound **10** (1.00 g, 0.426 mmol) in H_2O (90 ml) and 35% NH_4OH (10 ml) was saturated with H_2S, placed in a steel autoclave, and heated at 100–105°. After 72 hr the reaction was cooled, and the contents were removed. The aqueous solution was heated to boiling and decolorized with charcoal. The water was removed *in vacuo* and the crude residue recrystallized from 95% EtOH to give **11** (0.540 g; 61%): mp 260–265° (dec); ir (KBr) 3390, 1600, 1433; nmr (D_2O) 2.00–3.80 (6 H, multiplet, $-CH_2-$) 7.50 (5 H, singlet, aromatic).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.59; N, 7.33. Found: C, 68.92; H, 6.63; N, 7.01.

Compound **11** was also prepared in 34% yield by refluxing **10** in 8% aqueous $Ba(OH)_2$.

Cyclization of 5-Phenyl-5-(4-hydroxybutyl)hydantoin *p*-Toluenesulfonate.—To a solution of 5-phenyl-5-(4-hydroxybutyl)hydantoin *p*-toluenesulfonate, **5** (3.00 g, 7.45 mmol), in DMF (500 ml) (under N_2) was added NaH (0.338 g, 7.45 mmol) (50% mineral oil). The reaction mixture was stirred for 24 hr, poured into ice–H_2O, and acidified to congo red with 10% HCl. The acidic mixture was extracted with $CHCl_3$ and the extracts were washed with 5% $NaHCO_3$ and water and dried ($MgSO_4$). Removal of the solvent ($CHCl_3$ and DMF) *in vacuo* gave a residue which partially dissolved in $CHCl_3$. The $CHCl_3$–insoluble material was filtered to give a white solid (1.41 g) (250° dec) which was insoluble in common organic solvents and in 10% NaOH. The $CHCl_3$-soluble fraction was chromatographed on silica gel.

Elution with 90% $CHCl_3$–10% EtAc gave the bicyclo[4.3.0]-hydantoin, 8(a)-phenylpiperidino[1,2-*c*]-1,3-(2*H*)-imidazolidinedione, **12** (0.041 g; 2.5%): mp 199–200°; ir (KBr) 3270, 3160, 1690–1790; nmr (DMSO-d_6), 1.15–2.05 (6 H, multiplet, CH_2), 2.35–3.00 (2 H, multiplet, CH_2), 7.45 (5 H, singlet, aromatic), 10.78 (1 H, broad singlet, imide); *m/e* 230.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.97; H, 6.24; N, 12.42.

Further elution with 50% $CHCl_3$–50% EtAc gave the dimer, **13** (0.341 g; 20%): mp 230–234°; nmr (DMSO-d_6), 0.80–2.40 (12 H, multiplet, CH_2), 2.45–3.70 (4 H, multiplet, CH_2), 7.30–7.70 (10 H, multiplet, aromatic), 8.63 (1 H, broad singlet, amide), 10.73 (1 H, broad singlet, imide).

Anal. Calcd for $C_{26}H_{28}N_4O_4$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.02; H, 6.13; N, 12.05.

The reaction was repeated in the presence of K_2CO_3 (1 equiv) and DMF at 100° for 12 hr. The yields of **12** and **13** were 12% and 7%, respectively.

Registry No.—**4**, 25860-39-3; **5**, 25860-40-6; **9a**, 25860-41-7; **9b**, 25860-42-8; **10**, 25860-43-9; **11**, 25860-44-0; **12**, 25860-45-1; **13**, 25860-46-2.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health Grant GM-9254.

The Synthesis and Rearrangement of 5-Phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane

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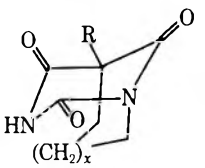
The synthesis and proof of structure of the bicyclobarbiturate, 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**2**), is described. An attempt was made to demethylate **2** utilizing boron trichloride and resulted in the formation of a γ-lactone. A plausible mechanism for this transformation is given.

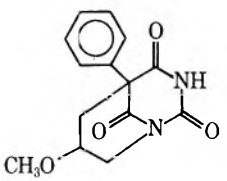
A study of the steric aspects of antiepileptic drug action was initiated by investigating the synthesis of bridged barbituric acids (**1**).



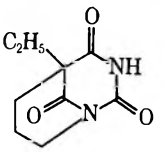
1

R = alkyl, aryl
$x = 0, 1, 2$

The initial approach to this desired system involved a base catalyzed intramolecular attack by an imide nitrogen on a suitable substituent located on a 5-alkyl side chain of a barbituric acid. In these laboratories 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo-[3.3.1]nonane (**2**) was prepared by this route. Baumler and coworkers[2] have reported the synthesis of 5-ethyl-



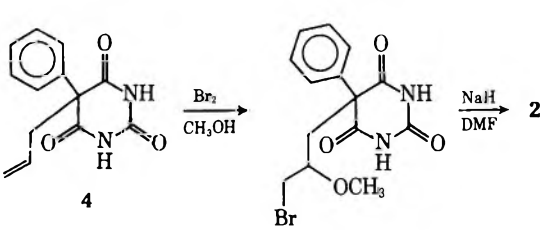
2



3

2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**3**) by a similar method; however, there is reason to believe that their structure assignment was erroneous[3] and thus a rigorous structure proof of the bicyclic system was undertaken.

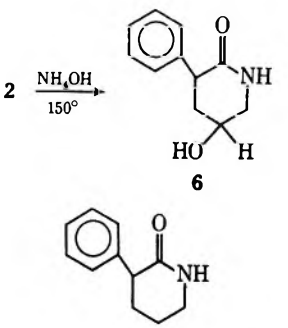
The synthesis of the bicyclic barbiturate **2** involved the conversion of 5-phenyl-5-allylbarbituric acid (**4**) to 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid (**5**) by treatment with bromine in methanol. The structure of the bromo ether, **5**, was confirmed by nmr



4 **5**

in that the spectrum had a doublet at δ 3.10–3.30 ($-CH_2Br$) and a broad multiplet at δ 4.50–4.90 ($>CHOCH_3$). Treatment of the bromo ether, **5**, with sodium hydride produced the desired bicyclic barbiturate, **2**. The absence of absorption at 1625–1650 cm^{-1} (>C=N– stretch) in the infrared spectrum of **2** eliminated the possibility of an *O*-alkylated product.[3]

Further proof of *N*-alkylation was obtained by degradation of the barbiturate ring under basic conditions. When the bicyclic system, **2**, was treated with ammonium hydroxide, 5-hydroxy-3-phenyl-2-piperidone (**6**) was obtained. Its infrared spectrum showed a band at 3390 cm^{-1} (OH stretch) while the remainder of the spectrum was almost identical with that of 3-phenyl-2-piperidone (**7**).[4]



6

7

The demethylation of **2** during the hydrolysis constitutes a somewhat anomalous situation, considering the basic conditions utilized. The degradation product, however, supports the assignment of compound **2** as the *N*-alkylated structure.

An attempt to demethylate **2** utilizing boron trichloride[5] resulted in the formation of a γ-lactone **8**. The nmr spectrum of **8** showed the absence of *O*-methyl-protons and a shift of one NH proton from δ 10.0 (observed for barbituric acid imide protons in DMSO)[6] to δ 7.90. Infrared spectroscopy indicated the presence of a γ-lactone carbonyl (1780 cm^{-1}).

The formation of this lactone in high yield indicates that the methyl ether in **2** is probably in an exo configuration (in relation to the C-9 ketone) since cleavage of methyl ethers with other strong Lewis acids has been shown to proceed with retention of configuration.[7] A

* Author to whom correspondence should be addressed.

(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of The University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) J. Baumler, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 459 (1951).

(3) E. E. Smissman and R. A. Robinson, *J. Org. Chem.*, **35**, 3532 (1970).

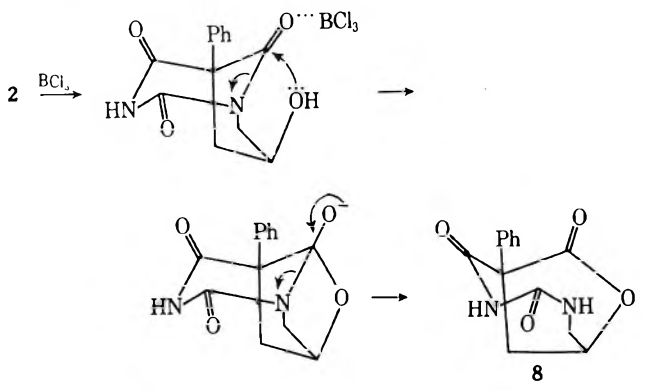
(4) R. K. Hill, C. E. Glassik, and E. J. Fleinder, *J. Amer. Chem. Soc.*, **81**, 737 (1959).

(5) F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1966).

(6) G. M. Kheifets, N. V. Khromov, A. I. Borison, A. I. Koltsov, and M. V. Volkenstein, *Tetrahedron*, **23**, 1197 (1967).

(7) C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, **30**, 1734 (1965).

plausible mechanism for this transformation is shown below.



The syntheses of bicyclic hydantoins, oxazolidindiones, glutarimides, and succinimides are currently being investigated.

Experimental Section[8]

5-Phenyl-5-(2-methoxy-3-bromopropyl)barbituric Acid (5).—A solution of 5-phenyl-5-allylbarbituric acid (4) (6.10 g, 0.025 mol) in MeOH (90 ml), cooled to 10°, was slowly added to a cold solution of Br_2 (4.00 g, 0.025 mol) in MeOH (20 ml). The mixture was stirred for 2 hr at 10° and allowed to warm to 25°. The precipitate was filtered and air dried. Recrystallization from EtOH gave 5 (7.70 g, 87%): mp 209–209.5°; ir (Nujol) 3310, 1745, 1735; nmr (CF_3CO_2H) 2.40–2.80 (2 H, multiplet, CH_2), 3.10–3.30 (2 H, doublet, $-CH_2Br$), 3.58 (3 H, singlet, $-OCH_3$), 4.50–4.90 (1 H, multiplet, $HCOCH_3$), 7.10 (5 H, aromatic).

Anal. Calcd for $C_{14}H_{15}N_2O_4Br$: C, 47.34; H, 4.26; N, 7.89; Br, 22.50. Found: C, 47.44; H, 4.48; N, 7.95; Br, 22.20.

5-Phenyl-7-methoxy-7-2,4,9-triketo-1,3-diazabicyclo[3.3.1]-nonane (2).—To 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid (4.00 g, 0.011 mol) in DMF (100 ml) (anhydrous) at 25° was added 50% NaH–mineral oil suspension (0.54 g, 0.011 mol). The mixture evolved H_2 immediately and was stirred at 25° for 20 hr. The DMF was removed at 100° under a stream of N_2 to afford a solid and a reddish-brown oil. The oil was dissolved in acetone, filtered, and cooled to afford a white solid, mp 237–240°. The filtered solid was washed with H_2O, and crystallization (MeOH) afforded 2 (0.78 g, 25.2%): mp 240.5–242.5°; ir (KBr) 3390, 3180, 3080, 1740, 1700; nmr (CF_3CO_2H) 3.10–3.70 [5 H, singlet ($-OCH_3$) and multiplet ($-CH_2$)], 3.80–4.80 (2 H, multiplet, CH_2), 5.00 (1 H, multiplet, CH), 7.40 (5 H, singlet, aromatic).

Anal. Calcd $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21; mol wt, 274. Found: C, 60.91; H, 5.41; N, 10.11; mol wt, 274 (mass spectrum).

3-Phenyl-5-hydroxy-2-piperidone (6).—A suspension of 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane, 2 (0.50 g, 1.41 mmol), in a solution of 30% NH_4OH (6 ml) and H_2O (34 ml) was heated at 150° in a steel autoclave. After 48 hr the reaction was cooled to 25°, and evaporation of the aqueous solution gave a red residue which was dissolved in 95% EtOH, filtered, and was allowed to stand. The hydroxypiperidone (6) (0.18 g, 65%) crystallized: mp 202–205°; ir (KBr) 3390 (OH), 3178, 3025, 2900, 1625 (lactam >C=O); nmr (DMSO-d_6) 1.83–2.20 (2 H, multiplet, CH_2), 3.00–4.18 (4 H, multiplet), 5.00 (1 H, multiplet, OH), 7.20 (5 H, singlet, aromatic), 7.41 (1 H, broad singlet, amide).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.34. Found: C, 68.68; H, 6.92; N, 7.33.

Reaction of 5-Phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo-[3.3.1]nonane (2) with Boron Trichloride.—To a stirred suspension of 2 (0.10 g, 0.73 mmol) in methylene chloride (50 ml) at −70° was added an excess of BCl_3. The mixture was stirred for 2 hr and allowed to warm to 25°. The solvent was removed *in vacuo* and the residue was washed several times with hot H_2O, filtered, and dried. Recrystallization (Me_2CO–Et_2O) yielded lactone 8 (0.08 g, 85%): mp 182–184°; ir (KBr) 3250, 3050, 2875, 1780 (lactone >C=O), 1660–1680; nmr (DMSO-d_6) 2.80–3.10 (4 H, multiplet, CH_2), 4.80–5.10 (1 H, multiplet, methine), 7.20–7.90 (6 H, multiplet, aromatic and amide), 10.0 (1 H, broad singlet, imide).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.64; N, 10.77; mol wt, 260. Found: C, 59.75; H, 4.42; N, 10.80; *m/e* 217 [loss of HNCO (43)].

(8) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data were recorded on Beckman IR-8 and IR-10 spectrophotometers and are reported in cm^{-1}. Nmr data were recorded on Varian Associated Model A-60, A-60A, and HA-100 spectrophotometers (TMS) and are reported as ppm (δ). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, University of Kansas. Molecular weights were determined on a Finnigan 1015 mass spectrometer.

Registry No.—2, 25860-23-5; 5, 25860-24-6; 6, 25860-25-7; 8, 25860-26-8.

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The Synthesis of Pyrano- and Furanopyrimidines from 3-Halopropyl- and 2-Halopropylbarbituric Acids

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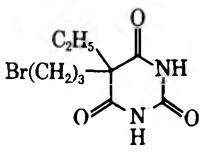
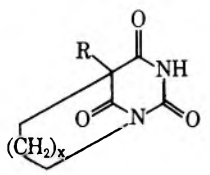
Received March 31, 1970

In attempts to obtain intramolecular *N*-alkylated bicyclo compounds from 5-haloalkylbarbituric acids, only *O*-alkylated compounds could be obtained. The resulting pyranopyrimidine, **7**, and furanopyrimidine, **9**, could be opened with alcohols to give the corresponding ether in the side chain of the barbituric acid. With water the side chain alcohol was obtained.

Baumler and coworkers reported the intramolecular nitrogen alkylation of 5-ethyl-5-(3-bromopropyl)barbituric acid (**1**) in the presence of pyridine.[2] A program designed to prepare bridged bicyclic barbituric acids, **2**, as potential anticonvulsants was initiated in these laboratories and it was thought that Baumler's method could be applied in this work.

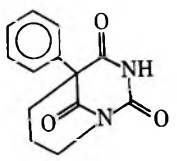


1



2

The initial compound desired for pharmacologic testing was 5-phenyl-2,4,9-triketo-1,3-diazobicyclo-[3.3.1]nonane (**3**). Light-catalyzed addition of hydrogen bromide to 5-phenyl-5-allybarbituric acid (**4**) produced the primary bromo derivative, **5a**, in quantitative yield.



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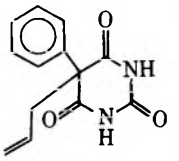
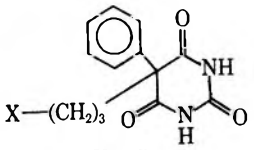
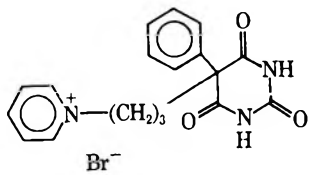


4

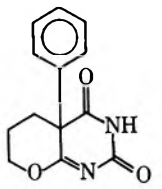


5a, X = Br
b, X = I
c, X = OC_2H_5
d, X = OCH_3
e, X = OH
f, X = OTs

Attempts to cyclize the tosylate derivative, **5f**, utilizing pyridine as the catalyst, resulted in the formation of a water soluble pyridinium salt, **6**. The iodo compound **5b** was treated in a similar manner and also failed to give the cyclized compound **3**. Various other bases also failed to give the desired bicyclic compound. When dry silver oxide in dimethylformamide (DMF) was used, 5-phenyl-5-(3-ethoxypropyl)barbituric acid (**5c**) was obtained on chromatographing on silica gel. This primary ether was also obtained by the ring opening of the intermediate pyranopyrimidine (**7**).



6



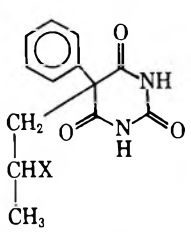
7

When **5a** was allowed to react with Triton B in refluxing methanol, the major product was the primary ether, 5-phenyl-5-(3-methoxypropyl)barbituric acid (**5d**). With **5b** a mixture of the primary alcohol, **5e**, and the ether, **5d**, was obtained.

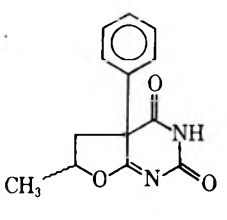
When **5b** was treated with silver benzoate in benzene, the product isolated from the reaction was 4(*a*)-phenyl-6*H*,7*H*-pyrano[2,3-*d*]-$\Delta^{1,8a}$-2,4-(3*H*)-pyrimidinedione (**7**). Hydrolysis of **7** with acid gave the primary alcohol **5e** and with anhydrous methanol the methyl ether **5d**.

The use of sodium hydride and DMF favored *N*-alkylation; however, the reactions were complicated by the formation of polymeric products resulting from intermolecular alkylation and no intramolecularly alkylated compound could be found.

A secondary bromobarbituric acid, 5-phenyl-5-(2-bromopropyl)barbituric acid (**8a**), was prepared by the addition of hydrogen bromide to alphenal (**4**). Treatment of **8a** with bases such as sodium ethoxide in ethanol and sodium hydride in DMF yielded the secondary alcohol, **8b**. When **8a** was refluxed in absolute ethanol



8a, X = Br
b, X = OH



9

* Author to whom correspondence should be addressed.

(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of The University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) J. Baumler, E. Sorkin, and H. Erlenmeyer, *Helv. Chim. Acta*, **34**, 459 (1951).

followed by treatment with water, only the secondary alcohol, **8b**, was obtained.

The formation of **8b** proceeds *via* the enol ether intermediate **9**. The *O*-alkylated barbituric acid, 4(a)-phenyl-6-methyl-5*H*,6*H*-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4-(3*H*)pyrimidindione (**9**), was prepared and isolated by treating the bromo derivative **8a** with silver benzoate in refluxing benzene. Acid hydrolysis of **9** produced **8a**.

Baumler, *et al.*,[2] presented no spectral data in support of their proposed structure. In light of our inability to obtain compound **3** by their method, no attempt was made to ascertain whether they reported an incorrect structure or whether there is a steric effect involved in the cyclization of the 5-ethyl- and 5-phenylbarbituric acids investigated.

Experimental Section[3]

5-Phenyl-5-(3-bromopropyl)barbituric Acid (5a).—A suspension of 5-phenyl-5-allybarbituric acid (**4**) (50.0 g, 0.163 mol) in toluene (1000 ml) was irradiated (G. E. Sunlamp, 275 W, 110–125 V) for 90 min with stirring. HBr was added over a 45-min interval with irradiation, followed by additional stirring for 45 min. The reaction vessel was opened and the excess HBr was allowed to evaporate. The solids were removed by filtration and washed with toluene. Recrystallization [Me_2CO–petroleum ether (60–68°)] gave **5a** (51.1 g, 96%): mp 202–205°; ir (KBr) 3.12, 3.22, 5.70–5.85; nmr (CF_3CO_2H) 2.01 (2 H, multiplet, CH_2), 2.78 (2 H, multiplet, CH_2), 3.45 (2 H, triplet, CH_2Br), 7.45 (5 H, singlet, aromatic).

Anal. Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.02; H, 4.03; N, 8.62; Br, 24.50. Found: C, 48.25; H, 3.93; N, 8.49; Br, 25.60.

5-Phenyl-5-(3-iodopropyl)barbituric Acid (5b).—A solution of NaI (4.62 g, 30.8 mol) in Me_2CO (50 ml) was added with stirring to 5-phenyl-5-(3-bromopropyl)barbituric acid (**5a**) (10.0 g, 30.8 mmol) in Me_2CO (50 ml). The reaction was heated for 15 min and the NaBr was filtered. The Me_2CO was removed *in vacuo* and the product was washed repeatedly with H_2O and dried. Recrystallization [Me_2CO–petroleum ether (60–68°)] afforded **5b** (10.9 g, 95%): mp 224.5–226.5°; ir (KBr) 3.12, 3.22, 5.60–5.92; nmr (CF_3CO_2H) 1.83 (2 H, multiplet, CH_2), 2.50 (2 H, multiplet, CH_2), 3.05 (2 H, triplet, CH_2I), 7.30 (5 H, singlet, aromatic).

Anal. Calcd for $C_{13}H_{13}N_2O_3I$: C, 41.95; H, 3.52; N, 7.53. Found: C, 42.21; H, 3.70; N, 7.56.

5-Phenyl-5-(3-pyridiniumpropyl)barbituric Acid Bromide (6).—A solution of **5a** (4.00 g, 13 mmol) in C_5H_5N (100 ml) was placed in a glass, high-pressure reaction flask and allowed to stand for 7 days. No precipitate appeared. The flask was heated on a steam bath for 3 hr and allowed to cool to room temperature. The solid material was filtered, washed with $CHCl_3$ and Me_2CO, and dried. Recrystallization (absolute EtOH) afforded **6** (4.87 g, 95%): mp 261–263°; ir (KBr) 2.90–2.95, 5.70–5.95; nmr (D_2O) 1.83–2.75 (4 H, multiplet, CH_2), 4.70–4.95 (multiplet, H_2O and CH_2), 7.45 (5 H, singlet, aromatic), 8.00–8.36 (2 H, multiplet, meta-aromatic), 8.51–8.75 (1 H, multiplet, para-aromatic), 8.78–9.08 (2 H, multiplet, ortho-aromatic).

Anal. Calcd for $C_{18}H_{18}N_3O_3Br \cdot H_2O$: C, 51.19; H, 4.77; N, 9.95. Found: C, 51.05; H, 4.50; N, 9.97.

5-Phenyl-5-(3-methoxypropyl)barbituric Acid (5d).—Triton B (2.57 g, 15.4 mmol, 40% in MeOH) was added to a solution of 5-phenyl-5-(3-bromopropyl)barbituric acid (**5a**) (5.00 g, 15.4 mmol) in anhydrous MeOH (100 ml). The reaction mixture was refluxed for 12 hr, cooled, and neutralized with 10% HCl. The MeOH was evaporated and solids were washed with H_2O and dried. Recrystallization [Me_2CO–petroleum ether (60–68°)] afforded **5d** (3.87 g, 89%): mp 182–183°; ir (KBr) 3.10, 3.23, 5.75–5.90, 9.55; nmr (CF_3CO_2H) 2.00 (2 H, multiplet, CH_2), 2.65 (2 H, multiplet, CH_2), 4.04 (3 H, singlet, OCH_3), 4.55 (2 H, triplet, $-CH_2OMe$), 7.42 (5 H, singlet, aromatic).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.96; H, 5.65; N, 10.23.

5-Phenyl-5-(3-ethoxypropyl)barbituric Acid (5c).—A mixture of 5-phenyl-5-(3-iodopropyl)barbituric acid (**5b**) (2.00 g, 5.37 mmol) in DMF (200 ml) and Ag_2O (0.712 g, 3.08 mmol) was stirred at 80° for 2 hr. The reaction mixture was cooled to room temperature and the silver salts were filtered off. The DMF was removed *in vacuo*, and the residue was extracted with hot absolute EtOH (200 ml) and filtered. Silica gel was added and the EtOH was removed *in vacuo* below 80°. Chromatography on silica gel ($CHCl_3$–10% 2-propanol) gave **5c** (0.496 g, 32%): mp 204–206° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3.10, 3.23, 5.77–5.90, 9.65; nmr (CF_3CO_2H) 1.48 (3 H, triplet-fine splitting, CH_3), 1.70–2.90 (4 H, multiplet, CH_2), 4.50 (2 H, multiplet, CH_3CH_2–O), 5.05 (2 H, triplet, CH_2CH_2–OEt), 7.45 (5 H, singlet, aromatic).

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24; N, 9.65. Found: C, 61.97; H, 6.39; N, 9.79.

5-(2-Bromopropyl)-5-phenylbarbituric Acid (8a).—A solution of allylphenylbarbituric acid (24.4 g, 0.1 mol) in Et_2O (240 ml) was stirred for several minutes and cooled. Gaseous HBr was added. After 7 hr the reaction mixture was allowed to warm to room temperature. On filtration, a cream colored material, mp 218–220° dec, was obtained. The solid was washed successively with $NaHCO_3$ solution and H_2O, and recrystallized (EtOH) to give white, solid **8a** (22 g, 68.8%): mp 221–222° dec.

Anal. Calcd for $C_{13}H_{13}N_2O_3Br$: C, 48.02; H, 4.03; N, 8.62; Br, 24.58. Found: C, 48.36; H, 4.13; N, 8.52; Br, 24.76.

4(a)-Phenyl-6*H*,7*H*-pyrano[2,3-*d*]-$\Delta^{1,8a}$-2,4-(3*H*)-pyrimidinedione (7).—A suspension of 5-phenyl-5-(3-iodopropyl)barbituric acid (**5b**) (2.00 g, 5.36 mmol) and AgOBz (1.23 g, 5.36 mmol) in anhydrous C_6H_6 (100 ml) was allowed to refluxed for 2 hr. The reaction mixture was cooled and filtered, and the C_6H_6 was removed *in vacuo*. The residue was taken up in hot C_6H_6 (40 ml) and filtered, and the filtrate was allowed to stand. Crystallization from the solvent gave **7** (0.862 g, 62%): mp 208–211°; ir (KBr) 3.28, 3.42, 5.85, 5.92, 6.24; nmr (DMSO-d_6) 1.15–2.40 (4 H, multiplet), 3.60–4.50 (2 H, multiplet), 7.20–7.70 (5 H, multiplet, aromatic), 9.83 (1 H, imide), *m/e* 244.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.86; H, 4.96; N, 11.35.

Treatment of **7** in either H_2O or CH_3OH with a trace of CF_3CO_2H gave the primary alcohol, **5e**, or methyl ether, **5d**, respectively. The ir, nmr, and tlc (silica gel, 80% $CHCl_3$–20% EtAc) of **5d** and **5e** were identical with the known compounds prepared by alternate methods.

4(a)-Phenyl-6-methyl-5*H*,6*H*-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4-(3*H*)-pyrimidinedione (9).—A mixture of 5-phenyl-5-(2-bromopropyl)barbituric acid (**8a**) (2.00 g, 6.16 mmol) and AgOBz (1.41 g, 6.16 mmol) in C_6H_6 (250 ml) was allowed to react according to the procedure outlined for **7**. The furopyrimidine **9** (0.511 g, 34%) crystallized from C_6H_6: mp 170–174°; ir (KBr) 3.25, 3.35, 5.75, 5.90, 6.15; nmr (DMSO-d_6) 1.00 (3 H, doublet, CH_3), 2.40–3.50 (2 H, multiplet, CH_2), 4.80–5.20 (1 H, multiplet, CH), 7.46 (5 H, singlet, aromatic), 11.16 (1 H, imide).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.57; H, 4.76; N, 11.26.

Acid hydrolysis of **9** gave the alcohol **8b**, mp 229–231°, which gave a positive iodoform test.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.78; H, 5.42; N, 10.76.

Registry No.—**5a**, 25860-47-3; **5b**, 25907-99-7; **5c**, 25860-48-4; **5d**, 25860-49-5; **6**, 25860-50-8; **7**, 25860-51-9; **8a**, 25860-52-0; **8b**, 25860-53-1; **9**, 25860-54-2.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health Grant GM-9254.

(3) All melting points were taken on the Thomas–Hoover capillary melting point apparatus and are corrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., by Weiler and Strauss Microanalytical Laboratory, Oxford, England, and on an F & M Model 185, The University of Kansas. Infrared spectra were recorded on Beckman IR-8 and IR-10 spectrophotometers. Nuclear magnetic resonance spectra were recorded and A-60, A-60A, and HA-100 analytical spectrophotometers with tetramethylsilane as a standard or in deuterium oxide when 3-trimethylpropanesulfonic acid sodium salt was employed. Nuclear magnetic resonance data are reported as δ values (ppm). Molecular weights were determined on the Finnigan 1015 mass spectrometer.

Photochemical Cyclizations. II. Effect of Structural Features on the Photocyclization of 2-Stilbazole Derivatives[1,2]

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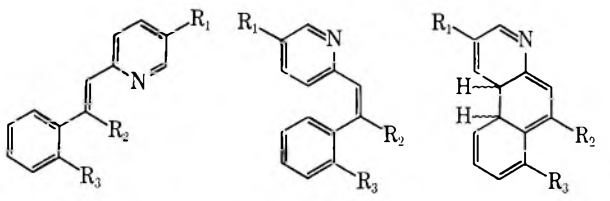
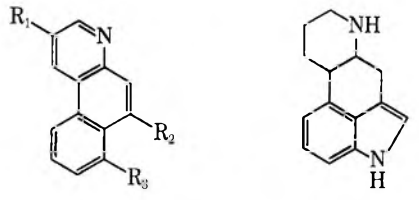
The photochemical behavior of a series of 2-stilbazole derivatives has been investigated as part of a synthetic scheme leading to the ergoline ring system of the ergot alkaloids. In general, these compounds undergo facile oxidative photocyclization to benzo[*f*]quinoline derivatives; it has been found, however, that certain structural features can prevent the desired photocyclization.

As part of a continuing program directed toward the synthesis of various ergot alkaloids[4] we are investigating the feasibility of utilizing photochemical cyclizations of suitably substituted stilbazoles **1** or **2**.

Irradiation of the trans[5] isomer **1** would be expected to cause initial trans–cis isomerization (**1** → **2**) and



1 **2** **3**



4 **5**

	R_1	R_2	R_3
a	H	H	H
b	H	CN	H
c	OCH_3	CN	H
d	H	$COOCH_3$	H
e	H	H	$NHCOCH_3$
f	H	H	NO_2
g	OCH_3	CN	Cl

subsequent cyclization to the dihydrobenzo[*f*]quinolines **3**,[7] which should be readily oxidized to the benzo[*f*]-quinolines **4**. The oxidative photocyclization of various stilbenes to phenanthrenes has received considerable attention[9,10] but the photocyclization of stilbazole derivatives has not been as thoroughly investigated.[11]

All of the alkaloids thus far isolated from the filamentous fungus *Claviceps purpurea* are collectively referred to as the ergot alkaloids.[12] The structures of all of these alkaloids are based upon the same tetracyclic ring system **5** that Jacobs and Gould[13] called ergoline. It was felt that successful preparation of suitably substituted benzo[*f*]quinolines **4** by photocyclization reactions would allow very facile entry into the tetracyclic ring system **5**.

Results and Discussion

In the previous paper in this series[4] we reported the successful photocyclization of the 2-stilbazole derivatives **1a–1d** to the benzo[*f*]quinolines **4a–4d**. At the same time we reported unsuccessful attempts at the photocyclization of **1e** and **1f** and discussed the reasons for lack of success in these cases. In addition we investigated the effect of various experimental parameters (wavelength of light, nature of the solvent, nature of the oxidizing agent) to determine the optimum conditions for the photocyclization of 2-stilbazoles. A notable result of this work was the very definite advantage of utilizing *tert*-butyl alcohol as solvent for the photocyclization of stilbazoles and various possible reasons for this effect were discussed.[14]

With a view toward utilizing substituents R_2 and R_3 to construct the five-membered ring present in the

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(1) Abstracted in part from the dissertations submitted by P. L. Kumler and R. A. Dybas to the Graduate School of the University of Rochester in partial fulfillment of the requirements for the Ph.D. degree, May 1967 (P. L. K.) and Jan 1970 (R. A. D.).

(2) For paper I in this series, see ref 4.

(3) (a) National Institutes of Health Predoctoral Fellow, 1966–1967. To whom correspondence should be addressed: Department of Chemistry, Saginaw Valley College, University Center, Mich. 48710. (b) National Institutes of Health Predoctoral Fellow, 1968–1969.

(4) P. L. Kumler and R. A. Dybas, *J. Org. Chem.*, **35**, 125 (1970).

(5) The stereochemistry about the double bond of compounds of this type will be described as being derived from *trans*- and *cis*-2-stilbazole, **1a** and **2a**, respectively. Use of the descriptors *E* and *Z*[6] to define the configuration about the double bond in compounds of this type, although always leading to a completely unambiguous stereochemical assignment, sometimes leads to opposite descriptors for compounds having the same geometry of the two aromatic rings around the central stilbazole double bond. For example, stilbazole **1d** is of the *Z* configuration while **1e** is of the *E* configuration but both compounds contain a *trans*-2-stilbazole moiety.

(6) J E Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968); J. E. Blackwood, C. L. Gladys, A. E. Petrarca, W. H. Powell, and J. E. Rush, *J. Chem. Doc.*, **8**, 30 (1968).

(7) There is apparently only one well documented example of isolation of a *stable* dihydro intermediate from a stilbene photocyclization[8] but this work appears to have been overlooked in recent reviews of this field.[9,10]

(8) D. Banes, *J. Ass. Offic. Agr. Chem.*, **44**, 323 (1961).

(9) F. R. Stermitz in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, pp 247–282.

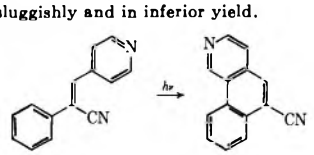
(10) E. V. Blackburn and C. J. Timmons, *Quart. Rev.* (*London*), **23**, 482 (1969).

(11) See ref 4 and references contained therein.

(12) For a comprehensive review of the chemistry of the ergot alkaloids, see R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press, New York, N. Y.: Vol. II, 1952, pp 375–392, and Vol. VII, 1960, pp 9–36.

(13) W. A. Jacobs and R. G. Gould, *J. Biol. Chem.*, **120**, 141 (1937).

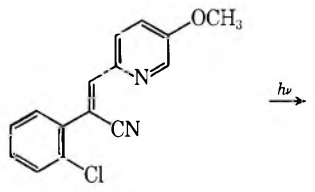
(14) As another example of the utility of this solvent for stilbazole photocyclizations, irradiation of the 4-stilbazole derivative i in oxygen-saturated *tert*-butyl alcohol through a Corex filter for 4 hr resulted in isolation of benz[*h*]isoquinoline-6-carbonitrile (ii) in 58% yield. Previous workers[15] have noted that 4-stilbazole derivatives (in contrast to 2-stilbazole derivatives) cyclize very sluggishly and in inferior yield.



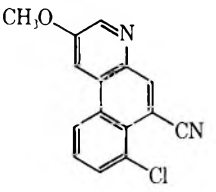
i ii

(15) C. E. Loader and C. J. Timmons, *J. Chem. Soc. C*, 1078 (1966).

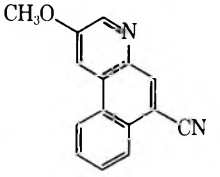
ergoline skeleton **5** we investigated the photochemical behavior of the 2-stilbazole derivative **1g**. Photolysis of **1g**, using a variety of experimental conditions, proceeded at a slow rate with the formation of large amounts of polymeric material, to give two major products, **4g** and **4c**, in low yield (at least two other products were detected by tlc but not characterized). Of the experimental conditions investigated (*tert*-butyl alcohol, oxygen, Corex; benzene, oxygen, Corex; acetonitrile, oxygen, Pyrex) the *tert*-butyl alcohol solvent system gave the best results. Thus, photolysis of **1g** in this solvent through Corex for 5 hr, followed by column chromatography of the complex photolysate on alumina, led to isolation of both **4g** (11%) and **4c** (6%). The formation of **4c**, which formally corresponds to loss



1g



4g

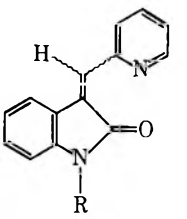


4c

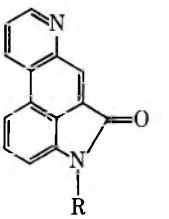
of the elements of HCl, can be rationalized in a number of ways. Loss of substituents other than hydrogen during photocyclizations have been seen in a number of cases and the substituents "lost" include Cl, Br, CH_3, COOH, I, and OCH_3.[16,17] In almost all cases (loss of I appears to be an exception) the substituent which is "lost" is at a position on the ring where cyclization occurs. Whether the Cl substituent in the present cases is lost prior to the photocyclization (photoinduced homolytic cleavage of the C–Cl bond in **1g** or **2g**), by elimination of HCl from a dihydro intermediate of the type **3**, or by photoinduced homolytic cleavage of a C–Cl bond in the product **4g**, was not however investigated. It is possible that the presence (assumed) of HCl during photolysis could account for the inferior yields in the present case although this reaction was not investigated in any more detail.

The most desirable type of benzo[*f*]quinoline consistent with the rest of our anticipated scheme for the synthesis of the various ergot alkaloids would be one in which R_2 and R_3 form a five-membered lactam, that is compounds of the type **7**. Consistent with this idea we investigated the solution photochemistry of the stilbazole derivatives **6**.

Irradiation of the stilbazole derivative **6a**[18] under a wide variety of experimental conditions (see Experimental Section) failed to give any detectable evidence



6



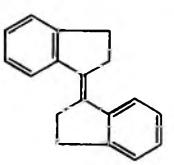
7

a, R = H
b, R = CH_2Ph

(ultraviolet spectra or tlc versus authentic **7a**) for the desired photocyclization. At wavelengths longer than 290 nm an unstable photoproduct (presumably the isomeric cis or trans olefin) could be detected by tlc but it was converted back to starting material upon attempted isolation. At wavelengths shorter than 290 nm extensive decomposition occurred but no photocyclization could be detected by tlc or ultraviolet spectroscopic analysis. However, control studies suggested that the expected photocyclization product **7a** might not survive the reaction conditions (see Experimental Section). It is of course possible that some structural feature present in **6a** was prohibiting the photocyclization from occurring at all (see below).

As in the case of **6a**, the irradiation of **6b** under a wide variety of experimental conditions led to extensive decomposition, but no detectable photocyclization, if light of wavelength shorter than 290 nm was utilized.

Examination of the literature revealed the successful photocyclization of various compounds containing *some* of the structural features present in **6a** (or **6b**). For example, various groups have reported the photocyclization of compounds incorporating five-membered rings;[19–21] photocyclization of systems in which the stilbene-like double bond is exocyclic to a fused ring system have also been reported.[22–24] However, none of these cases have the stilbene-like double bond exocyclic to a fused five-membered ring. During the preparation of this manuscript, three reports concerning the photochemistry of stilbene systems in which the stilbene double bond is exocyclic to a fused five-membered ring system have appeared. Goedicke and Stegemeyer[25] reported that the stilbene derivative **8** did



8

9

10

not undergo either isomerization to the cis isomer or photocyclization to the dicyclopentanophenanthrene. At about this same time Gunst reported on the

(16) See ref 9, p 261, for pertinent references.

(17) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.*, **35**, 175 (1970).

(18) The stereochemistry around the double bond in compounds **6a** and **6b** is uncertain but does not affect the present results since the initial step in the photocyclization sequence involves cis–trans isomerization.[9,10] Our work suggests, in fact, that the two isomers interconvert readily in solution (see Experimental Section).

(19) C. S. Wood and F. B. Mallory, *J. Org. Chem.*, **29**, 3373 (1964).

(20) A. A. Lamola, G. S. Hammond, and F. B. Mallory, *Photochem. Photobiol.*, **4**, 259 (1965).

(21) M. V. Sargent and C. J. Timmons, *J. Amer. Chem. Soc.*, **85**, 2186 (1963).

(22) M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Lett.*, 2937 (1966); also, see ref 17.

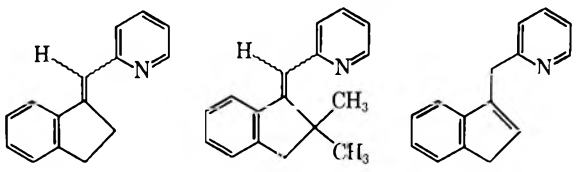
(23) N. C. Yang, G. R. Lenz, and A. Shani, *Tetrahedron Lett.*, 2941 (1966).

(24) For a review of the photcyclization of anthrone and bianthrone derivatives, see ref 9, pp 248–253.

(25) C. Goedicke and H. Stegemeyer, *Ber. Bunsenges. Phys. Chem.*, **73**, 782 (1969).

photochemistry of 9,9′-bifluorenylidene (**9**)[26] and reported the isolation, in very low yield, of a compound tentatively identified as the phenanthrene derivative **10**. Other workers have not, however, detected this product during an independent study of the same stilbene derivative **9**.[27]

In light of the above considerations, it was decided to investigate whether the stilbazole derivative **11** would undergo the desired photocyclization. The failure or success of this photocyclization would allow a more



11 **12** **13**

a = *cis*

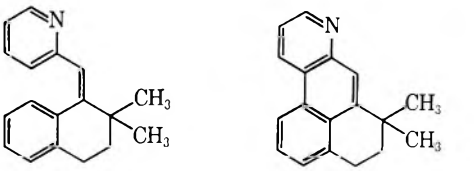
b = *trans*

realistic assessment of the effect of the fused five-membered ring. Under various conditions (see Experimental Section) the exocyclic olefin **11** was converted in moderate yield (20–35%) to the endocyclic olefin **13**. Although other products were formed none of these appeared to contain the benzo[*f*]quinoline skeleton (by uv spectroscopic examination of the photolysate and lack of the blue fluorescence on tlc plates which seems to be characteristic of the benzo[*f*]quinoline system). Although there are a number of examples of photoinduced isomerization of 1-alkylcycloalkenes to their analogous exocyclic isomers,[28] to our knowledge this represents one of the very few examples of the isomerization proceeding in the opposite direction under photochemical conditions.[29] The original purpose of this particular experiment (*i.e.*, is it the presence of the fused five-membered ring which prevents the desired photocyclization?) was not however fulfilled. It is possible that the availability of another reaction path (exo to endo isomerization), perhaps of lower energetic requirements, effectively masks the desired photocyclization. Therefore, a study of the photochemical behavior of the stilbazole derivative **12**, in which the exo to endo isomerization cannot occur, was undertaken.

Irradiation of **12a** in *tert*-butyl alcohol containing 7.5% benzene[30] through a Corex filter in the presence of oxygen led to very rapid trans–cis isomerization (photostationary state reached in 0.5 hr). Continued irradiation for a total of 6 hr led to no further changes as evidenced both by tlc and ultraviolet spectroscopy. Column chromatography of the photolysate resulted in isolation of **12b** (57%) and **12a** (38%).

At this stage of the investigation it was felt that one of the major factors contributing to the failure of photocyclizations in systems of the present type was the presence of the stilbazole double bond exocyclic to a fused *five-membered* ring. As a test of this empirical hypothesis we investigated the photochemical behavior of the stilbazole derivative **14**, in which the stilbazole double bond is exocyclic to a fused *six-membered* ring.

As expected, irradiation of the stilbazole derivative **14** in the presence of oxygen through a Corex filter led to isolation of the desired photocyclization product **15** in 53% yield.

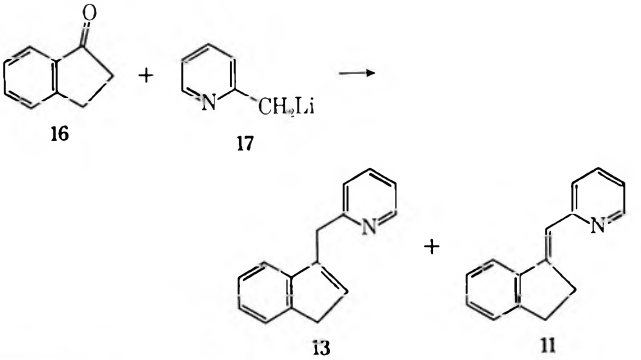


14 **15**

In summary, we have shown that in systems of the type considered in the present work one of the major reasons for failure to observe the desired photocyclization is the presence of the stilbazole double bond in a position exocyclic to a fused five-membered ring. This suggests that in order for photocyclization to occur, the stilbazole system (*i.e.*, the benzene and pyridine rings and the linking double bond) must be able to attain a geometry which approximates that of *cis*-2-stilbazole; the presence of any structural element (such as that described above) which precludes the attainment of such geometry will effectively inhibit the desired photocyclization.[31] To our knowledge the present study reports the first elucidated example of a structural feature which effectively prohibits the photocyclization reaction; the suggestion of Stermitz concerning the generality of the photocyclization reaction[32] should not be taken as an inviolable rule.

Syntheses and Structural Assignments.—Stilbazole **1g** was prepared by base-catalyzed condensation of 2-chlorophenylacetonitrile with 5-methoxy-2-pyridinecarboxyaldehyde. The oxindole derivative **6a** was prepared in an analogous fashion from oxindole and 2-pyridinecarboxaldehyde. The oxindole derivative **6b** was most conveniently prepared by condensation of 1-benzylisatin with 2-picoline in the presence of acetic anhydride.

Preparation of the stilbazole derivative **11** was attempted by the reported method.[33] Condensation of 1-indanone (**16**) with 2-picolyllithium (**17**) gave a



16 **17** **13** **11**

(26) G. P. de Gunst, *Recl. Trav. Chim. Pays-Bays*, **88**, 801 (1969).

(27) J. Nasielski, M. Jauquet, E. Vander Donckt, and A. Van Sinoy, *Tetrahedron Lett.*, 4859 (1969).

(28) (a) P. J. Kropp, *J. Amer. Chem. Soc.*, **88**, 4091 (1966); (b) P. J. Kropp, *ibid.*, **89**, 3650 (1967); (c) P. J. Kropp and H. J. Krauss, *ibid.*, **89**, 5199 (1967); (d) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967); (e) P. J. Kropp, *J. Amer. Chem. Soc.*, **91**, 5783 (1969).

(29) A similar phenomenon has been briefly reported in ref 25.

(30) This solvent system seems to be the preferred one for photocyclizations in systems of this type. For a discussion of this solvent effect, see ref 4.

(31) The only apparent exception to this generality appears to be that concerning the isolation of **10** from the irradiation of the stilbene derivative **9**[26] which may be an anomalous case since this molecule contains two separate stilbene systems sharing the same central double bond.

(32) "... the cyclization seems to be so general that a proper outlook in regard to failures would perhaps be that the proper conditions for the particular cyclization have not yet been found." Reference 9, p 259.

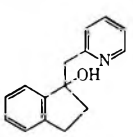
(33) J. Sam, J. Plampin, and D. Alwami, *J. Org. Chem.*, **27**, 4543 (1962).

mixture of the desired exo olefin **11** and the endo olefin **13** in the ratio 1:4 (exo:endo). The composition of the olefin mixture was determined by comparison of the spectral properties of the mixture with those of pure samples of each of the olefins (see below). Treatment of the olefin mixture with hydrogen bromide in ether resulted in the formation of a single hydrobromide in 77% yield. This hydrobromide salt was, in fact, the hydrobromide of the exo olefin **11**. Thus, from a mixture which was originally 80% endo olefin approximately 80% of the exo olefin hydrobromide was obtained. Pure exocyclic olefin **11** was obtained as a crystalline solid by treatment of the hydrobromide with dilute base.[34]

The exo olefin **11** gave satisfactory analytical data, the melting point of the hydrobromide salt was the same as that reported by previous workers,[33] and it gave a picrate which also exhibited the correct analytical data. The nmr, ir, and uv spectra were consistent with the assigned structure (see Experimental Section) with the following pertinent points. The ultraviolet spectrum was very similar to that of *trans*-2-stilbazole (see ref 4) and the ir spectrum showed characteristic absorption at 1635 cm^{-1} assigned to the exocyclic olefinic linkage. Both the picrate and the hydrobromide salts showed this same ir absorption.

The endo olefin **13** was a yellow liquid which gave unsatisfactory analytical data and was subject to decomposition at room temperature. Treatment of the endo olefin with hydrogen bromide in ether gave the hydrobromide of the exo olefin **11** as expected (see above). However, treatment of the endo olefin with picric acid in ethanol led to a picrate which was different from that of the exo olefin and satisfactory analytical data were obtained on the picrate. Spectral data consistent with the structural assignment were obtained on samples of olefin freshly regenerated from the picrate. The ir spectrum showed a band at 1615 cm^{-1} assigned to the endocyclic olefin and this band was also present in the ir spectrum of the picrate. The ultraviolet spectrum is very similar to that of indene[36] and the nmr spectrum is very similar to that reported for 1-benzylindene.[37]

(34) The previous workers[33] had not characterized the product of the original condensation between 2-picolyllithium and 1-indanone (only a boiling point is reported) but had assumed the product to be



iii

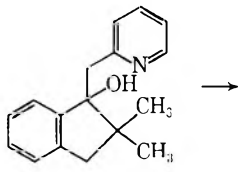
the carbinol iii which is certainly the immediate precursor of the olefin mixture. In order to dehydrate the "alcohol" iii they heated the condensation product in molten phosphorus pentoxide for 7 hr.[35] After distillation of the reaction mixture from the P_2O_5 treatment they obtained the desired exo olefin (probably the same mixture described in the present work) as a liquid. Again, only a boiling point is recorded and this olefin was analyzed in the form of the hydrobromide salt. Therefore, Sam and coworkers had probably carried out the same sequence observed in this study but did not realize it because of their failure to characterize both the initial product of the condensation and the product resulting from the molten phosphorus pentoxide treatment.

(35) Control experiments in the present work have shown that the composition of the olefin mixture is not changed by this rather drastic treatment and hence this mixture probably reflects the thermodynamic stability of the two isomers.

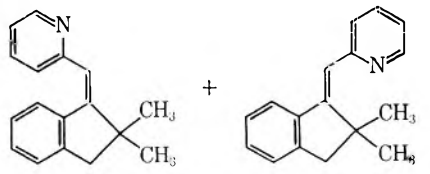
(36) Sadtler Standard Spectra, Sadtler Research Associates, Spectrum No. 308 UV.

(37) A. M. Weidler, *Acta Chem. Scand.*, **17**, 2724 (1963).

The stilbazole derivative **12** was prepared by dehydration of the carbinol **18**, formed by condensation of 2,2-dimethyl-1-indanone with 2-picolyllithium. If refluxing acetic anhydride is used for the dehydration a



18



12a 12b

54% yield of the olefin mixture is formed (considerable amounts of 2,2-dimethyl-1-indanone and 2-picoline are formed by reversal of the initial condensation) and the composition of this mixture is 77% **12a** and 23% **12b** as analyzed by nmr (see below). Dehydration with *p*-toluenesulfonyl chloride led to quantitative formation of the olefin mixture (72% **12a**, 28% **12b**). The two olefins could be separated by column chromatography and were each completely characterized. The stereochemical assignments were based upon ultraviolet spectra (similarity to *cis*- and *trans*-2-stilbazole; see Experimental Section and ref 4) and nmr spectra. The nmr resonance due to the vinyl proton of **12a** was at τ 3.47 while that due to the vinyl proton of **12b** was at τ 2.92. These values are quite consistent with those for a series of cis and trans stilbene derivatives.[38]

The stilbazole derivative **14** was prepared by condensation of 2,2-dimethyl-1-tetralone with 2-picolyllithium and dehydration of the resultant carbinol with *p*-toluenesulfonyl chloride in pyridine. The resultant olefin **14** gave consistent analytical and spectral data and was exclusively of the cis configuration as assigned by nmr analysis.[38]

Experimental Section[39]

2-(2-Chlorophenyl)-3-(5-methoxy-2-pyridyl)acrylonitrile (1g).—A mixture of 2-chlorophenylacetonitrile[40] (1.51 g, 0.01 mol) and 5-methoxy-2-pyridinecarboxaldehyde[4] (1.37 g, 0.01 mol) in 15 ml of absolute methanol was warmed to 50°. A sodium methoxide solution (3.66 *M* in methanol, 2.75 ml, 0.01 mol) was added and the reaction mixture was maintained at 55–60° for 1 hr and then cooled. The resultant crystals were removed by filtration. Recrystallization from pentane gave 1g as colorless crystals (1.11 g, 41%): mp 82–83°; ir ($CHCl_3$) 2200 cm^{-1} (C≡N); uv max (95% ethanol) 318 nm (ϵ 26,900), 291 (sh, 16,250), and 210 (24,250); uv max (C_6H_{12}) 310 nm (21,400), and 208 (21,900); nmr ($CDCl_3$) τ 6.10 (s, 3 H, OCH_3), 1.55 (d, J = 2.9 cps, 1 H,

(38) H. Gusten and M. Salzwedel, *Tetrahedron*, **23**, 173, 187 (1967).

(39) Melting points were obtained on a Fisher-Johns apparatus and are reported uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 137 Infracord or a Perkin-Elmer Model 421 spectrophotometer; all spectra were calibrated with polystyrene. Ultraviolet spectra were measured with a Model 11 or Model 14 Cary recording spectrophotometer. Nuclear magnetic resonance spectra were taken on a Varian Associates A-60 spectrometer or on a Japan Electron Optics Model JNM-4H-100 spectrometer; chemical shifts are reported in ppm (τ) relative to tetramethylsilane as internal standard. Elemental analyses are by Micro-Tech Laboratories (Skokie, Ill.) or by Orcbaugh Laboratories (Cleveland, Ohio).

(40) C. Viel, R. Dorme, and P. Rumpf, *Bull. Soc. Chim. Fr.*, **6**, 1956 (1966).

pyridyl H_3), 2.08 (d, J = 9 cps, 1 H, pyridyl H_6), and 2.38–2.87 (m, 6 H, vinyl and other aromatic protons).

Anal. Calcd for $C_{16}H_{11}N_2OCl$: C, 66.55; H, 4.09; N, 10.35. Found: C, 66.42; H, 4.11; N, 10.21.

Isatinylidene-3-(2-picoline) (6a).—To a solution of oxindole (40.0 g, 0.30 mol) and 2-pyridinecarboxaldehyde (32.1 g, 0.30 mol) in 95% ethanol was added 2 ml of piperidine. The solution was refluxed for 4 hr and then cooled to room temperature. The resultant red crystals (58.4 g, 87%, mp 199–201°) were removed by filtration, air dried, and then eluted through a short column of Woelm alumina (activity III) with methylene chloride to give bright orange needles which were recrystallized from 95% ethanol. This gave **6a** as orange needles: mp 202.5–203° (lit.[41] mp 205–207°); ir ($CHCl_3$) 1712 (C=O), and 3350 cm^{-1} (NH); uv max (95% ethanol) 347 nm (sh, ϵ 7840), 333 (11,470), 325 (sh, 9800), 257 (11,500), and 209 (20,900); nmr (CF_3COOH) τ 0.57–2.95 (m, 10 H, amide, vinyl, and aromatic protons).

1-Benzylisatinylidene-3-(2-picoline) (6b).—A mixture of 1-benzylisatin[42] (11.8 g, 0.05 mol) and 2-picoline (24 ml, 0.27 mol) was refluxed for 6 hr in the presence of acetic anhydride (30 ml). The warm reaction mixture was poured over ice and, after 5 hr, was basified with ammonium hydroxide. The orange-brown precipitate was filtered, washed with water, and air dried. The crude product was eluted through 125 g of activity I Woelm alumina to give, after removal of the eluting solvent, **6b** as bright orange needles (6.0 g, 40%), mp 134–136°. Recrystallization from 95% ethanol gave the analytical sample as yellow needles: mp 139–140°; ir (KBr) 1705 (C=O) and 1630 cm^{-1} (C=C); uv max (C_6H_{12}) 346 nm (sh, ϵ 13,900), 330 (16,500), 317 (13,000), 268 (14,400), and 210 (15,000); uv max (CH_3OH) 328 nm (ϵ 12,000), 256 (12,700), and 207 (27,000); nmr ($CDCl_3$) τ 0.8–1.3 (m, 2 H), 2.2–3.5 (m, 12 H) and 5.00 (s, 2 H, CH_2—N); the aromatic protons of the benzyl group gave a singlet at τ 3.30 easily discernible from the other resonances in this region.

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 79.98; H, 5.37. Found: C, 80.15; H, 5.27.

1-Indanylidene-(2-picoline) (11).—Freshly cut lithium strips (3.45 g, 0.50 g-atom) were placed in 200 ml of anhydrous ether and then bromobenzene (39.2 g, 0.25 mol) was added at a rate sufficient to keep the ether at reflux. After all of the bromobenzene had been added the reaction mixture was stirred at reflux for 1 hr. To the resultant phenyllithium solution, 2-picoline (23.2 g, 0.25 mol) was added dropwise over a period of 5–10 min. The deep-red solution was stirred for 1 hr, cooled in an ice bath, and 1-indanone (30.0 g, 0.23 mol) dissolved in 75 ml of ether was added dropwise. The light-gray mixture was then immediately decomposed by the addition of 50 ml of concentrated hydrochloric acid and 50 ml of water, and the two phases were separated. The ether phase was extracted once with 10% HCl and the combined aqueous phases were added to a saturated solution of sodium carbonate. The oily layer which separated was extracted into ether and dried over Na_2SO_4. Evaporation of the ether gave a yellow oil (43.9 g) which was distilled under reduced pressure. After removal of a forerun (~8 g) of 1-indanone, the two major fractions [12.9 g, bp 123–129° (0.5 mm), and 14.9 g, bp 129–131° (0.5 mm)] were combined after their infrared spectra and tlc behavior were shown to be essentially identical. The dark brown distillation residue (6.8 g) was not characterized.

The tlc and spectral properties of the distillate were consistent with a mixture of endo (**13**) and exo (**11**) olefins in the ratio of 4:1 (endo:exo).

A 15.6-g sample of the olefin mixture was dissolved in 800 ml of anhydrous ether and the solution was saturated with gaseous hydrogen bromide. Removal of the ether gave a bright yellow amorphous residue, mp 248–256° dec, which was recrystallized from methanol (600 ml) to give the exo olefin hydrobromide (14.4 g) as very large (~1 × 1 × 10 mm) straw colored rods, mp 259–260° (lit.[33] mp 258–260°); an additional crop (2.3 g, mp 256–259°) was obtained by concentration and cooling of the mother liquor, making the total yield 16.7 g (77%).

The tlc behavior of the free base was determined by partitioning the salt between ether and 10% KOH and looking at the tlc of the ether layer. The free base was homogeneous and the R_f value was identical (2 solvent systems) with one component (that with the larger R_f value) of the original olefin mixture. The ir spectrum of the hydrobromide showed medium intensity absorption at 1640 cm^{-1} (exo C=C).

The above hydrobromide (14.4 g, 0.05 mol) was partitioned between 150 ml of 10% KOH–H_2O and 150 ml of ether. The ether phase was washed to neutrality with water, then with saturated salt solution, and dried over sodium sulfate. Evaporation of the ether gave 1-indanylidene-(2-picoline) as off-white crystals (9.9 g, 95%), mp 69–71°. Recrystallization from 100 ml of hexane gave colorless rosettes (8.7 g), mp 69–70°. Two additional recrystallizations gave the analytical sample as colorless needles: mp 72–73°; ir (KBr) 1635 cm^{-1} (exo C=C); uv max (C_6H_{12}) 343 nm (ϵ 17,300), 325 (22,100), 295 (sh, 10,000) 283 (11,700), 244 (6000), 236 (7350), and 228 (430); nmr ($CDCl_3$) τ 1.55 (br d, J = 6 cps, 1 H, pyridyl H_6), 2.2–3.2 (m, 8 H, vinyl proton and other aromatic protons), and 7.07 (m, 4 H, aliphatic protons).

Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.75; H, 6.30; N, 6.48.

The picrate of the exo olefin was prepared by addition of a solution of the exo olefin (207 mg, 1.0 mmol) in 10 ml of ethanol to a saturated solution of picric acid in ethanol (25 ml). Heating for 10 min on a steam bath and cooling gave the picrate as bright yellow needles (380 mg, 87%), mp 207–209° dec. For analysis the picrate was sublimed [185° (0.01 mm)] and the sublimate was recrystallized from a large volume of ethanol to give bright yellow crystals: mp 208–209°; ir (KBr) 1635 cm^{-1} (exo C=C).

Anal. Calcd for $C_{21}H_{16}N_4O_7$: C, 57.80; H, 3.70; N, 12.84. Found: C, 57.65; H, 3.72; N, 12.71.

1-(2-Pyridylmethyl)-2,2-dimethyl-1-indanol (18).—A solution of 2-picolyllithium was prepared as above from lithium (2.71 g, 0.39 g-atom), bromobenzene (30.6 g, 0.195 mol), and 2-picoline (18.1 g, 0.195 mol). To the ether solution of 2-picolyllithium at 0° was added 2,2-dimethyl-1-indanone[43] (25.0 g, 0.156 mol) in 30 ml of ether over a 25-min period. After 15 min, 40 ml of water and 40 ml of concentrated hydrochloric acid were added successively. The aqueous phase was separated and poured with stirring into 350 ml of saturated aqueous sodium carbonate. The resultant red oil was extracted into benzene and the benzene was washed with water and dried over sodium sulfate. Evaporation of the solvent gave the carbinol as an orange oil (40.0 g) which solidified on standing. The crude carbinol was eluted through a pad of Woelm activity V alumina with benzene; removal of the solvent gave a homogeneous (tlc) pale yellow solid (38.0 g, 96%), mp 70–77°. A further elution through activity III alumina and two recrystallizations from hexane gave colorless plates, mp 82–83°; ir ($CHCl_3$) 3150 (OH), and 1110 cm^{-1} (C—O stretch, 3° alcohol); nmr ($CDCl_3$) τ 9.01 (s, 3 H, CH_3), 8.82 (s, 3 H, CH_3), 7.21 (s, 2 H, Ar-CH_2), 6.93 (AB q, J = 14 cps, 2 H, Py-CH_2), 1.38 (m, 1 H, pyridyl α proton), and 2.25–3.52 (m, 8 H, hydroxyl and other aromatic protons).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.66; H, 7.52; N, 5.52.

2-(2,2-Dimethyl-1-indanylidenemethyl)pyridine (12). Method A.—A solution of **18** (25.3 g, 0.10 mol) and acetic anhydride (40.8 g, 0.40 mol) was stirred overnight at room temperature followed by refluxing for 1 hr. The acetic anhydride was removed by distillation and the residue was partitioned between water and benzene. The benzene solution was extracted with 10% HCl (200 ml), washed with water, and dried over sodium sulfate. Evaporation of the solvent gave a red oil (6.9 g, 43%) whose tlc, ir, and nmr were identical with that of 2,2-dimethyl-1-indanone.

The acid solution from above was basified with 10% NaOH and extracted with benzene. The combined benzene extracts were washed with water, dried over Na_2SO_4, and evaporated to give the olefin as an orange oil (12.6 g, 54%). Analysis by nmr indicated the oil to be a mixture of 77% cis isomer **12a** and 23% trans isomer **12b**. Vacuum distillation of the crude olefin gave a pale yellow oil (10.9 g), bp 130–135° (0.005 mm), which was dissolved in 30 ml of ethanol and added to a saturated solution of picric acid in ethanol to give the picrate of the cis isomer **12a** as bright yellow needles (10.6 g), mp 154.5–158.5°. Regeneration of the free base by partitioning the picrate between chloroform and 0.5 N lithium hydroxide solution gave the cis olefin **12a** as a colorless oil (4.5 g); ir (film) 1640 cm^{-1} (trisubstituted C=C); uv max (C_6H_{12}) 314 nm (ϵ 14,500), 282 (11,800), and 225 (15,400); uv max (95% ethanol) 310 nm (ϵ 10,800), 267 (sh, 7700), and 224 (14,000); nmr ($CDCl_3$) τ 8.70 (s, 6 H, gem CH_3), 7.14 (s, 2 H, CH_2), 3.47 (s, 1 H, vinyl proton), 1.28 (br d, 1 H, pyridyl α proton), and 2.13–3.08 (m, 7 H, other aromatic protons).

(41) M. Akkerman and H. Veldstra, *Recl. Trav. Chim. Pays-Bas*, **73**, 629 (1954).

(42) R. L. Autrey and F. C. Tahk, *Tetrahedron*, **23**, 901 (1967).

(43) M. Mousseron, R. Jacquier, and H. Christol, *Bull. Soc. Chim. Fr.*, **24**, 346 (1957).

Anal. Calcd for $C_{17}H_{17}N$ (olefin): C 86.76; H, 7.28; N, 5.95. Found: C, 86.39; H, 7.25; N, 5.92.

Anal. Calcd for $C_{23}H_{20}N_4O_7$ (picrate): C, 59.48; H, 4.34; N, 12.07. Found: C, 59.59; H, 4.35; N, 11.99.

The ethanolic mother liquors from cis picrate formation were partitioned between 0.5 *N* lithium hydroxide and chloroform as above, giving a pale yellow oil (5.5 g) which consisted of 56% cis isomer **12a** and 44% trans isomer **12b**. Column chromatography on grade III Woelm alumina and elution with hexane gave the trans isomer as a colorless oil (1.91 g) which was purified through its picrate (mp 181–182°); the purified trans olefin **12b** was a colorless oil: ir (film) 1665 cm^{-1} (C=C); uv max (C_6H_{12}) 346 nm (ϵ 13,400), 332 (23,100), 319 (21,700), 307 (sh, 15,400), 299 (sh, 13,000), 282 (13,000), 246 (7600), 238 (10,300), and 230 (10,000); uv max (95% ethanol) 340 nm (sh, ϵ 6950), 323 (sh, 13,400), 313 (14,800), 304 (14,500), 278 (br sh, 11,900), 245 (7750), 236 (sh, 8500), and 224 (sh, 10,300); nmr ($CDCl_3$) τ 8.48 (s, 6 H, gem CH_3), 7.10 (s, 2 H, CH_2), 2.92 (s, 1 H, vinyl proton), 1.33 (br d, 1 H, pyridyl α proton), and 2.23–3.17 (m, 7 H, other aromatic protons).

Anal. Calcd for $C_{17}H_{17}N$ (olefin): C, 86.76; H, 7.28; N, 5.95. Found: C, 86.48; H, 7.33; N, 5.91.

Anal. Calcd for $C_{23}H_{20}N_4O_7$ (picrate): C, 59.48; H, 4.34; N, 12.07. Found: C, 59.54; H, 4.34; N, 12.03.

Method B.—The carbinol **18** (1.27 g, 0.005 mol) was dissolved in 25 ml of dry pyridine, *p*-toluenesulfonyl chloride (1.90 g, 0.01 mol) was added, and the solution was heated at reflux for 8 hr. The pale yellow reaction mixture was poured over ice and basified with saturated sodium carbonate solution. The aqueous solution was extracted with benzene (two 75-ml portions); the benzene extracts were washed with water and then saturated salt solution, and then dried over sodium sulfate. Evaporation of the solvent gave a pale yellow oil (1.19 g, 100%) shown to contain only the isomeric (cis–trans) olefins by tlc analysis. Analysis by nmr indicated the mixture to be 72% cis (**12a**) and 28% trans (**12b**). The two olefins were separated by column chromatography on Woelm activity III alumina (**12b** eluted with hexane; **12a** eluted with hexane:benzene, 1:1). The isolated amounts were 300 mg **12b** (27%) and 812 mg **12a** (73%). All spectral properties of the two olefins were the same as those prepared by method A and they both gave picrates identical with those of method A.

2-(2,2-Dimethyl-1-tetralylidenemethyl)pyridine (14).—To a solution of 2-picolyllithium (prepared from 1.46 g of lithium, 16.5 g of bromobenzene, and 9.78 g of 2-picoline; theoretical yield of 2-picolyllithium, 0.105 mol) at 0° was added a solution 2,2-dimethyl-1-tetralone[43] (14.6 g, 0.084 mol) over a 20-min period. Then water (25 ml) and concentrated hydrochloric acid (25 ml) were successively added. After the excess lithium had reacted, the two phase mixture was separated. The ether phase was extracted once with 6 *N* hydrochloric acid and the combined aqueous extracts were poured with stirring into excess aqueous potassium carbonate. The basic solution was extracted several times with benzene; the benzene extracts were washed with saturated salt solution and dried over sodium sulfate. Evaporation of the solvent gave the crude carbinol as a red-brown oil (19.6 g, 87%); ir (film) 3180 (OH) and 1124 cm^{-1} (C—O stretch, tertiary alcohol).

The crude carbinol was dissolved in 175 ml of dry pyridine and *p*-toluenesulfonyl chloride (27.9 g, 0.146 mol) was added. The reaction mixture was refluxed for 72 hr, cooled, and poured into excess potassium carbonate. The basic solution was extracted several times with benzene and the combined benzene extracts were extracted with 10% hydrochloric acid. The acidic solution was basified with 15% sodium hydroxide and extracted with benzene. The benzene extract was washed with water and saturated salt solution and then dried over sodium sulfate. Evaporation of the solvent and subsequent vacuum distillation gave the olefin as a pale yellow oil (5.07 g, 28%), bp 134–139° (0.25 mm).

This olefin was purified by picrate formation (mp 152–153°) and regeneration of the free base. The olefin prepared in this way (only the cis isomer) was a colorless oil: ir (film) 1631 cm^{-1} (C=C); uv max (95% ethanol) 295 nm (ϵ 11,700), 220 (sh, 17,300), and 209 (21,700); uv max (C_6H_{12}) 293 nm (ϵ 13,600), 221 (sh, 19,800), and 210 (25,600); nmr ($CDCl_3$) τ 8.82 (s, 6 H, gem CH_3), 8.27 (t, 2 H, CH_2), 7.20 (t, J = 7 cps, 2 H, Ar-CH_2), 3.42 (s, 1 H, vinyl proton), 3.33–2.67 (m, 7 H, aromatic protons), and 1.53 (br d, 1 H, pyridyl α proton).

Anal. Calcd for $C_{18}H_{19}N$ (olefin): C, 86.70; H, 7.68; N, 5.62. Found: C, 86.64; H, 7.59; N, 5.57.

Anal. Calcd for $C_{24}H_{22}N_4O_7$ (picrate): C, 60.24; H, 4.64; N, 11.71. Found: C, 60.40; H, 4.56; N, 11.83.

Photolyses. General Considerations.—Unless stated otherwise, the substrate was dissolved in solvent and oxygen was bubbled through the solution for 0.5 hr prior to and then during the irradiation. The light source was a 450 W Hanovia medium-pressure mercury arc placed in a water-cooled quartz immersion well containing the appropriate filter sleeve (where indicated). All photolyses were monitored by tlc and by periodic scanning of the ultraviolet spectrum. The irradiations were generally continued until most of the starting material was consumed as evidenced by tlc.

Photolysis of 1g. Method A.—The stilbazole derivative **1g** (2.000 g, 0.0074 mol) was dissolved in 50 ml of spectrograde benzene and 925 ml of *tert*-butyl alcohol and irradiated through Corex for 5 hr. After evaporation of the solvent the photolysate was dissolved in chloroform and the chloroform was washed with 10% NaOH. Evaporation of the solvent gave a brown solid residue which was purified by column chromatography on 90 g of activity III alumina. Elution with benzene:hexane (1:1) gave 2-methoxybenzo[*f*]quinoline-6-carbonitrile (**4c**) as an off-white solid (101 mg, 6%), mp 192–198°. Formation of the picrate (mp 223.5–227°) and regeneration of the free base gave **4c** as colorless needles, mp 200–201° (lit.[4] mp 200–201°); this sample was identical (ir, nmr, tlc, mixture melting point) with an authentic sample.[4]

Elution with benzene gave 2-methoxy-7-chlorobenzo[*f*]quinoline-6-carbonitrile (**4g**) as an off-white solid (225 mg, 11.3%): mp 214–216°; ir ($CHCl_3$) 2195 cm^{-1} (C≡N); uv max (C_6H_{12}) 362 nm (ϵ 9750), 345 (8800), 330 (8300), 324 (16,000), 318 (14,300), 310 (15,200), 298 (sh, 10,100), 285 (15,400), 262 (27,900), 256 (sh, 26,800), 241 (37,600), and 223 (sh, 22,500); nmr (CF_3COOH–$CDCl_3$) τ 5.67 (s, 3 H, OCH_3), and 0.78–2.08 (m, 6 H, aromatic protons).

Anal. Calcd for $C_{15}H_9N_2OCl$: C, 67.05; H, 3.38; N, 10.43. Found: C, 67.17; H, 3.43; N, 10.32.

Method B.—The stilbazole **1g** (2.000 g, 0.0074 mol) was dissolved in 950 ml of spectrograde benzene and photolyzed through a Corex filter for 37 hr. A considerable amount of polymeric material formed during the irradiation and the photolysate was filtered before evaporation to give a tan residue (473 mg). Chromatography as in method A gave 24 mg (1.4%) of a tan solid whose tlc and uv spectrum were identical with that of **4c** and 37 mg (1.9%) of a tan solid whose tlc and uv spectrum were identical with **4g**.

Method C.—The stilbazole **1g** (400 mg, 1.48 mmol) was dissolved in 200 ml of spectrograde acetonitrile and photolyzed for 1.25 hr through Pyrex. Evaporation of the solvent gave a dark red glassy solid (500 mg) which was chromatographed on 70 g of activity III alumina. Elution with benzene:hexane (1:1) gave **4c** (10 mg, 3%); elution with benzene gave **4g** (22 mg, 6%).

Photolysis of 6a.—The photolysis of the oxindole derivative **6a** was investigated under a wide variety of conditions. One irradiation will be described in detail, while the others will only be briefly summarized.

Method A.—The stilbazole **6a** (1.600 g, 0.0072 mol) was dissolved in 950 ml of iropropyl alcohol and irradiated through Pyrex for 24 hr. At this stage the uv spectrum showed only very minor changes and tlc indicated (in addition to starting material) trace amounts of a product (henceforth called photo-A) which was probably the isomeric (cis–trans) olefin. Removal of the solvent gave an orange solid, mp 194–198° (some melting and resolidification occurred at 181–182°). The uv and ir spectra of this material were essentially identical with that of the starting material.

Method B.—Same as method A but deoxygenation before and during irradiation was carried out by bubbling nitrogen through the irradiation vessel. Chromatography of the photolysate on activity III alumina gave a mixture in which photo-A was the main product, but removal of the solvent gave starting material.

Method C.—Same as method B, but through a Vycor filter for 35 hr. Extensive decomposition occurred, but photo-A was detected by tlc at intermediate stages of irradiation.

Method D.—Photolysis in benzene, in the presence of oxygen, through Pyrex for 17 hr (no change by tlc or uv) and then through Corex for an additional 17 hr resulted in no change (tlc or uv).

Method E.—Photolysis in acetonitrile, in the presence of oxygen, through Vycor for 42 hr resulted in extensive decomposition but no evidence (tlc or uv) for photocyclization.

Method F.—A saturated solution of the stilbazole in cyclohexane was placed in a quartz tube and irradiated at 2537 Å in a Rayonet reactor in the presence of oxygen. Extensive decomposition occurred but there was no evidence (uv) for photocyclization.

Method G.—Photolysis in 0.1 *N* hydrochloric acid, in the presence of oxygen, through quartz for 4 hr led to extensive decomposition but no evidence (tlc or uv) for photocyclization.

Method H.—Photolysis in 0.1 *N* hydrochloric acid, in the presence of oxygen, through Pyrex for 7 hr led to no apparent (tlc or uv) change. Continued irradiation for 90 hr led to disappearence of the orange color with loss of the uv maximum at 333 nm (no other obvious spectral changes from 200 to 300 nm). No further characterization was attempted.

Method I.—Photolysis in cyclohexane (with or without iodine present), in the presence of oxygen, through quartz for 4 hr led to extensive decomposition but no evidence (tlc or uv) for photocyclization.

Method J.—Photolysis in a KBr matrix (standard ir pellet) through quartz for 16 hr led to no change in the ir spectrum.

Control Photolyses of 7a. Method A—A saturated solution of **7a**[44] in cyclohexane was irradiated in a quartz uv cell by placing the cell 2 in. from a 450 W Hanovia medium-pressure lamp contained in a quartz immersion well. The progress of the irradiation was followed by periodic scanning of the uv spectrum. After 4 hr of irradiation the solution exhibited an unstructured spectrum with a complete loss of the 282 nm band characteristic of the starting material; the spectrum was dominated by intense end absorption at ~210 nm. No further characterization was attempted.

Method B.—A 1-mg sample of authentic **7a**[44] was dissolved in 50 ml of 0.1 *N* hydrochloric acid and an aliquot (~3 ml) of this solution was photolyzed as in method A. Irradiation for 5 hr led to the same results described in method A.

Photolyses of 6b. Method A.—A 119-mg sample of the olefin was irradiated in 120 ml of methanol through quartz for 2 hr. Analysis by tlc showed the complete disappearance of starting material and formation of a complex mixture (minimum of 6 components by tlc). However, there was no evidence (tlc or uv) for photocyclization.

Method B.—Photolysis in benzene, in the presence of oxygen, through quartz for 122 hr led to formation of a complex mixture from which only recovered starting material (37%) could be isolated.

Method C.—Photolysis of the olefin in cyclohexane (with or without added iodine) through Vycor for 5 hr led to extensive decomposition but no evidence (tlc or uv) for photocyclization.

Photolyses of 11. Method A.—The exo olefin **11** (1.00 g) was dissolved in 950 ml of spectrograde cyclohexane and irradiated through Vycor for 70 hr (considerable amounts of polymeric material were present). Filtration of the photolysate and evaporation of the solvent gave a dark brown oil (834 mg) which showed a minimum of 7 components by tlc (none having the same R_f as starting material). Initial chromatography on activity III alumina gave a bright yellow oil (506 mg) which showed three components by tlc. Further attempts at chromatography led to no separation of this three-component mixture. The oil was dissolved in 30 ml of absolute ethanol and a saturated solution of picric acid in ethanol was added until no further precipitation took place. After heating on a steam bath for 5 min and then cooling, filtration gave a bright yellow solid which was washed with a small amount of ethanol, then with ether, and air dried to give the picrate of **13** as an amorphous yellow solid (364 mg), mp 170–173°. Recrystallization from methanol:dimethyl sulfoxide followed by sublimation [145° (0.05 mm)] gave the analytical sample as a bright yellow microcrystalline powder: mp 179–180°; ir (KBr) 1615 cm^{-1} (endo C=C). Regeneration of the free base from its picrate could be accomplished either by partitioning the picrate between methylene chloride and 1% aqueous lithium hydroxide or by chromatographing the picrate on activity III alumina (elution with methylene chloride containing 1% tetrahydrofuran). The endo olefin **13**, recovered from its picrate by either of the above methods, was distilled in a short-path still [~130° (0.1 mm)] to give a mobile yellow liquid, homogeneous by tlc, which slowly decomposed in air. (After 24 hr it was converted to a dark brown viscous gum.) Satisfactory analytical data could not be obtained on this olefin, but consistent spectral data were obtained on a sample freshly recovered from its picrate: ir (film) 1615 cm^{-1} (endo C=C); uv max (C_6H_{12}) 320 (ϵ 770), 278 (1420), and 253 (11,500); nmr ($CDCl_3$) τ 1.42 (br d, 1 H, pyridyl α proton), 2.1–3.3 (m, 7 H, other aromatic protons), 3.75 (br d,[45] 2 H, vinyl proton), 5.90 (d,[45] 2 H, "exo" CH_2), and 6.64 (d,[45] 2 H, ring CH_2).

Anal. Calcd for $C_{21}H_{16}N_4O_7$ (picrate): C, 57.80; H, 3.70; N, 12.84. Found: C, 57.90; H, 3.73; N, 12.83.

Method B.—Exo olefin **11** (1.000 g) was dissolved in 1000 ml of spectrograde cyclohexane in a quartz vessel and the solution was saturated with oxygen; irradiation was carried out in a Rayonet reactor at ~3000 Å (RUL-3000 lamps) for 12.5 hr. Filtration of the photolysate and evaporation of the solvent gave 888 mg of a dark brown oil which showed 5 components (in addition to starting material) by tlc. Preliminary chromatography on activity III alumina gave the same three component mixture described in method A. Formation of the picrate as in method A gave the picrate of **13** (590 mg, 33%), which was identical with that prepared in method A.

Photolysis of 12a.—The stilbazole cis isomer **12a** (1.800 g, 0.0076 mol) was dissolved in a mixture of 75 ml of spectrograde benzene and 925 ml of *tert*-butyl alcohol and irradiated through Corex for 6 hr. After the initial rapid cis–trans isomerization took place within 0.5 hr, no other tlc or ultraviolet spectral changes were detected throughout the photolysis. Removal of the solvent gave an orange oil which was dissolved in benzene and washed through a column of activity III alumina (100 g). Evaporation of the solvent gave a yellow-orange oil (1.73 g, 96%) which showed only two spots on tlc. Analysis by nmr indicated that the mixture consisted of trans isomer **12b** (60%) and cis isomer **12a** (40%). The olefin mixture was chromatographed on activity III alumina; elution with hexane gave **12b** (1.021 g, 60%) as a colorless oil whose nmr and tlc were identical with previously characterized material (see preparation of **12** above). Elution with hexane:benzene (1:1) gave **12a** as a colorless oil (0.686 g, 40%) whose nmr and tlc were identical with that of starting material.

Photolysis of 14.—The stilbazole **14** (1.75 g, 0.007 mol) was dissolved in a mixture of 75 ml of spectrograde benzene and 925 ml of *tert*-butyl alcohol and irradiated through Corex for 5.5 hr. Removal of the solvent gave a red-orange oil which was dissolved in benzene and washed through a column of activity III alumina. Removal of the solvent gave the crude benzo[*f*]quinoline derivative **15** as a pale yellow oil (913 mg, 53%) which slowly solidified on standing, mp 134–139°. Recrystallization from hexane gave colorless needles, mp 138.5–140°: uv max (C_6H_{12}) 353 nm (ϵ 5340), 337 (4590), 322 (2480), 300 (9660), 286 (sh, 12,600), 277 (sh, 18,300), 270 (22,100), 255 (24,800), 245 (sh, 27,500), 240 (32,700), 220 (29,100), and 213 (29,500); nmr ($CDCl_3$) τ 8.60 (s, 6 H, gem CH_3), 8.18 (t, J = 7 cps, 2 H, CH_2), 6.88 (t, J = 7 cps, 2 H, Ar—CH_2), 2.76–2.30 (m, 3 H, H_2, H_8 and H_9), 1.92 (s, 1 H, H_5), 1.57 (br d, 1 H, H_{10}), and 1.20 (br d, 1 H, H_3).

Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.34; H, 6.93; N, 5.52.

Registry No.—**1g**, 25791-26-8; **4g**, 25791-27-9; **6b**, 25791-28-0; **11**, 25791-29-1; **11** picrate, 25791-30-4; **12a**, 25791-31-5; **12a** picrate, 25791-32-6; **12b**, 25791-33-7; **12b** picrate, 25791-34-8; **13**, 25791-35-9; **13** picrate, 25791-36-0; **14**, 25791-39-3; **14** picrate, 25791-40-6; **15**, 25791-38-2; **18**, 25791-41-7.

Acknowledgments.—We acknowledge the financial support of the National Institutes of Health in the form of Predoctoral Fellowships to both authors and we would like to thank Dr. Marshall Gates for many helpful discussions throughout the duration of this work.

(44) We thank D. J. Werber of these laboratories for this sample.

(45) This spectrum shows significant amounts of second-order splitting and hence is not very susceptible to simple first order analysis, but the spectrum is very similar to that of 1-benzylindene.[37]

Alanylactinobolone. A Basic Hydrolysis Product of the Antibiotic Actinobolin[1]

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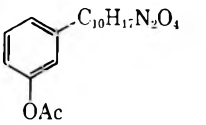
The structure elucidation of *N*-acetylalanylactinobolone, the product derived from the mild basic hydrolysis of *N*-acetylactinobolin, is described. The molecule was shown to possess three secondary hydroxyl groups and a methylene-flanked ketone group ($-CH_2COCH_2-$). Aromatization of the molecule demonstrated the incorporation of the methylene-flanked ketone in a cyclohexane ring and the presence of a side chain array, $CH_3CH(NHCOCH_3)CONHCH(CHOHCH_3)$, β to the carbonyl group. The presence of one of the hydroxyl groups in the side chain demanded placement of the remaining hydroxyl groups at the β' and γ positions of the cyclohexanone ring to give expression 1 for *N*-acetylalanylactinobolone.

The mild basic hydrolysis of the crystalline *N*-acetate of the broad spectrum antibiotic actinobolin[2] leads to the destruction of the parent chromophore, 1 mol of carbon dioxide, and a labile degradation product, *N*-acetylalanylactinobolone, which is the precursor of a second more stable degradation product, *N*-acetylalanylactinobicyclone.[3] The former, *N*-acetylalanylactinobolone, proved to be an important link in the chain of information that led to the elucidation of the structure of the intact antibiotic. Its chemistry, structure, configuration, and preferred conformation comprise the subject of this report.

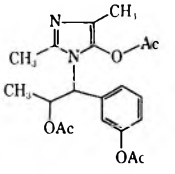
Elemental analysis and a mass spectral determination establish the moleuclar formula $C_{14}H_{24}N_2O_6$ for *N*-acetylalanylactinobolone (**1**). The presence of three secondary hydroxyl groups is suggested by the nmr spectrum[4a] (dimethyl sulfoxide-d_6) of **1** which displays doublet signals (J = 3.5–4.5 Hz), each equivalent to a single hydrogen, at δ 4.58, 4.98, and 5.04 that rapidly disappear upon addition of deuterium oxide to the nmr probe.[5] Single hydrogen doublets at δ 7.54 (J = 9 Hz) and 8.10 (J = 7 Hz) disappear more slowly and provide evidence for the presence of two secondary amide groups, each bonded to carbon bearing a single hydrogen. Other prominent signals are assigned to *N*-acetate methyl (δ 1.87, s) and to a pair of secondary methyl groups (δ 1.26, d, J = 7 Hz, and δ 1.02, d, J = 6 Hz). The remaining hydrogen resonances fall into one of two discrete sets of overlapping signals; the region from δ 2.5 to 1.9 contains signals for five hydrogens as does the region from δ 4.5 to 3.1. A base-catalyzed deuterium exchange experiment, monitored by nmr, suggested the presence of a $-CH_2COCH_2-$ unit. The absence in the nmr spectrum of a signal characteristic of a methyl ketone militates against the presence of CH_3COCH-. The infrared spectrum of **1**, in addition to the bands associated with hydroxyl and amide groups, displays an unstrained ketone carbonyl band at 1715 cm^{-1}.

Direct esterification as a means of verifying the presence of three secondary hydroxyl groups proved unsuccessful. However, by masking the ketone group as its dimethyl ketal, followed by pyridine-catalyzed acetylation, it was possible to isolate the tri-*O*-acetyldimethyl ketal **2**. Elemental analysis and mass spectral data confirm the molecular formula of **2** as $C_{22}H_{36}N_2O_{10}$. The nmr spectrum of **2** (see Experimental Section) provides support for the required structural features. As expected, the infrared spectrum displays no bands characteristic of ketone or hydroxyl groups.

Acetylation of **1** in acetic anhydride in the presence of perchloric acid leads to an easily isolable product, **3** ($C_{18}H_{24}N_2O_6$).[6] Spectroscopic data (nmr, uv, and ir, see Experimental Section) indicate **3** to be a meta-substituted phenyl acetate. Conversion of the phenyl acetate **3** to the corresponding phenyl methyl ether **5**, followed by basic permanganate oxidation to *meta*-anisic acid confirms the assignment. These data implicate the following partial structure for compound **3**.



Chemical and spectral evidence lead to the arrangement of atoms in the side chain. The vigorous acid hydrolysis of the aromatic compound **3** gives rise to the amino acid alanine. In the nmr spectrum[4a] of **3** (dimethyl sulfoxide-d_6) those signals not associated with the 3-acetoxyphenyl residue indicate the presence of an *N*-acetate and an *O*-acetate methyl group (δ 1.87, 3 H, s, and δ 1.95, 3 H, s, respectively) together with two methyl groups (δ 1.10, 3 H, d, and δ 1.17, 3 H, d), each bonded to carbon bearing a single hydrogen, *i.e.*, CH_3CH-. The presence of two secondary amide groups, each bonded through nitrogen to carbon bearing a single hydrogen, *i.e.*, $-CONHCH-$, is suggested by the two low-field one-hydrogen doublets centered at δ 8.03 and 8.38. The remaining signals appear in the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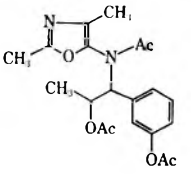

ii

* Author to whom correspondence should be addressed.

(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 large part on the Ph.D. Dissertation of D. B. Nelson, Arizona State University. (c) A portion of this work has been published in preliminary form: M. E. Munk, D. B. Nelson, F. J. Antosz, D. L. Herald, Jr., and T. H. Haskell, *J. Amer. Chem. Soc.*, **90**, 1087 (1968).

(2) M. E. Munk, C. S. Sodano, R. L. McLean, and T. H. Haskell, *ibid.*, **89**, 4158 (1967).

(3) D. B. Nelson, M. E. Munk, K. B. Gash, and D. L. Herald, Jr., *J. Org. Chem.*, **34**, 3800 (1969).

(4) (a) Reported in parts per million (δ) downfield of tetramethylsilane. (b) Reported in parts per million (δ) downfield of 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt.

(5) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

(6) A chromatographic separation of the mother liquids afforded a second compound. Spectroscopic studies suggest the tentative assignment of structure i or ii; however, the problem has not been pursued.

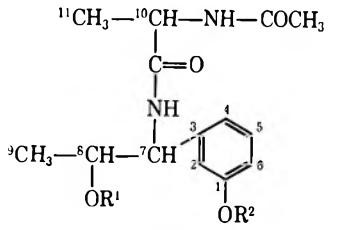
region attributed to hydrogens on carbon bearing oxygen and nitrogen; an unsymmetrical multiplet of two overlapping one-hydrogen signals centered at δ 5.05 and a one-hydrogen quintet at 4.45 (J = 7 Hz).

Exchange of the amide hydrogens for deuterium (addition of deuterium oxide to the sample tube) results in the collapse of the quintet at δ 4.45 to a quartet (J = 7 Hz), an observation consistent with the assignment of this signal to the methine hydrogen of an *N*-acetylalanyl residue, *i.e.*, $CH_3CH(NHCOCH_3)CO-$. A quintet, discernible in the nmr spectrum of compound **1** (dimethyl sulfoxide-d_6) at nearly identical field strength, δ 4.37, behaves similarly upon addition of deuterium oxide. Therefore, it appears unlikely that the signal at δ 4.45 in the spectrum of **3** reflects a benzylic hydrogen, since, in that case, a paramagnetic shift would have been expected for that signal upon aromatization of the ring component of **1**. Additional confirmation of the unit proposed was obtained by double resonance studies[7] which demonstrated coupling between the methine hydrogen quartet at δ 4.45 and the methyl doublet at δ 1.38.

Since a second secondary amide function is required, the unit $CH_3CH(NHCOCH_3)CONH-$ is indicated. To complete the side chain array only the point of attachment of this unit and the $-OCOCH_3$ unit to the remaining $CH_3CH<$ and $>CH$ units requires resolution.

Methoxide-catalyzed *O*-deacetylation of compound **3** results in the shift of *one* of the two overlapping nmr signals centered at δ 5.05 to higher field. Addition of deuterium oxide (to exchange hydroxyl and amide hydrogen for deuterium) to the nmr sample tube of the *O*-deacetylated compound **4** in acetone-d_6[4a] leads to the immediate simplification of the diamagnetically shifted signal to a quintet centered at δ 4.07 (J = 6 Hz). The *rapid* resolution of this signal upon addition of deuterium oxide (consistent with *rapid* exchange of hydroxylic hydrogen), its observed multiplicity after deuterium exchange and the diamagnetic shift experienced upon *O*-deacetylation[8] of **3** permits identification of a $CH_3CH(OCOCH_3)-$ unit in **3**, *i.e.*, the $-OCOCH_3$ group is assigned to C-8 of the side chain of **3**.

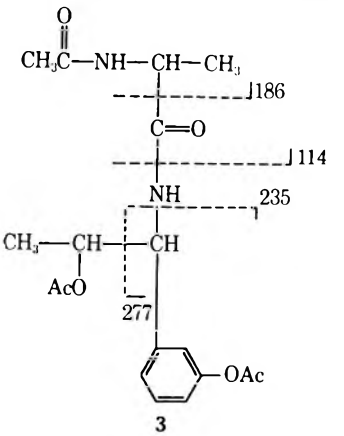
The chemical shift of the *second* of the two signals of the original δ 5.05 multiplet of **3** remains at low field



3, $R^1 = R^2 = COCH_3$
4, $R^1 = R^2 = H$
5, $R^1 = H$; $R^2 = CH_3$

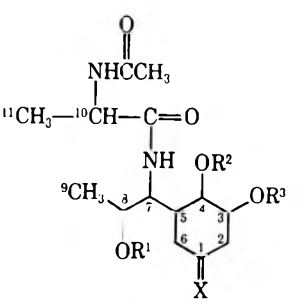
upon *O*-deacetylation and in the presence of deuterium oxide only *slowly* resolves to a doublet centered at δ 4.78 (J = 5 Hz). The slow resolution of this signal (consistent with *slow* exchange of amide hydrogen) allows its assignment to hydrogen on the benzylic carbon (C-7), the carbon atom bearing the *N*-acetylalanylamido group. In this nmr spectrum of **4** the methine proton of the *N*-acetylalanyl residue appears as a quartet centered at δ 4.25 (J = 7 Hz). The implications of these data permit the assignment of structure **3** to the aromatic compound derived directly from acid-catalyzed acetylation of **1**. The well-resolved nmr spectrum of aromatic compound **5**, obtained by treatment of **4** with diazomethane, and the related double resonance experiments (see Experimental Section) provide verification of the assignment.

Further support for the side chain assignment is found in the mass spectrum of **3** which displays peaks at *m/e* 86 and 114, associated with the *N*-acetylalanyl portion of the side chain, and at *m/e* 235 and 237 (base peak) resulting from benzylic fragmentation.



3

The structure of the aromatic compound **3** implicates the presence in **1** of these structural features: (1) a cyclohexanone ring, (2) an *N*-(*N*-acetylalanyl)propanolamine side chain, and (3) a β relationship of side chain to the ketone carbonyl, progenitor of the phenolic hydroxyl group. The methylene-flanked ketone (CH_2-$COCH_2-$) and the presence of one hydroxyl group on the side chain require that the remaining two hydroxyl groups occupy the unsubstituted β and γ positions of the cyclohexanone ring. These structural requirements are met by expression **1** for *N*-acetylalanylactinobolone.



1, $R^1 = R^2 = R^3 = H$; $X = O$
2, $R^1 = R^2 = R^3 = COCH_3$; $X = OCH_3$, OCH_3
6, $R^1 = H$; $R^2 = R^3 = (CH_3)_2C<$; $X = O$
7, $R^1 = COCH_3$; $R^2 = R^3 = (CH_3)_2C<$; $X = O$

The formation of an isopropylidene derivative **6**, which can be best characterized as its mono-*O*-acetate **7**, is consistent with the vicinal relationship of two of the hydroxyl groups. In the nmr spectrum[4a] (acetone-d_6) of **7** the low-field signal assigned to H_8 appears as a quartet of doublets ($J_{8,9}$ = 6 Hz, $J_{8,7}$ = 3 Hz)

(7) Field-swept spin decoupling at 60 MHz.
(8) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 77.

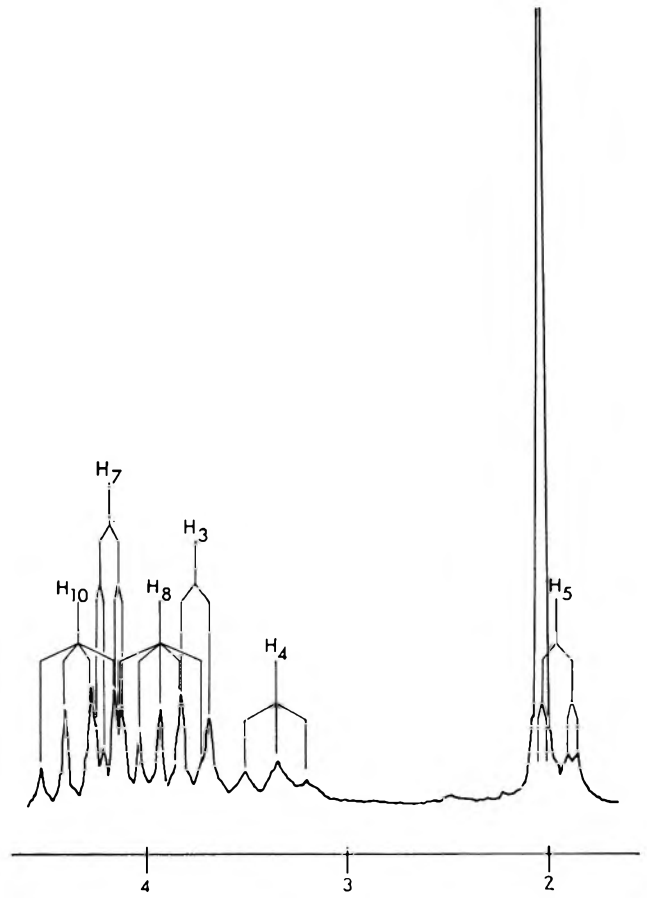
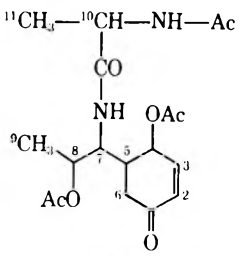


Figure 1.—Nmr spectrum of nonadeuterio *N*-acetylalanylactinobolone.

centered at δ 5.29, an observation consistent with the assignment of the side chain hydroxyl group of **1** to C-8 rather than C-7.

Pyridine-catalyzed acetylation of **1** gives rise to an elimination product which is isolated as its di-*O*-acetate, **8**. The nmr spectrum[4a] (chloroform-*d*) fea-



8

tured well-separated signals amenable to complete analysis (Table I) and spin decoupling studies.

The chemical shifts of the olefinic hydrogens (δ 6.84 and 6.04) and the size of the olefinic coupling constant (J = 10 Hz) are those expected for an α,β-unsaturated cyclohexenone system.[9] Double resonance experiments[7] demonstrate that irradiation of the signal assigned to H_4 results in the collapse of both olefinic hydrogen signals (doublet of doublets) to a simple doublets (J = 10 Hz). Hence, the H_4 signal is coupled equally to the olefinic hydrogens H_2 and H_3. Irradiation of the three-hydrogen signal at δ 2.6 (H_5 and H_6) results in the collapse of the H_4 signal to a triplet (J =

(9) See ref 8, p 90.

TABLE I

NMR ASSIGNMENTS, COMPOUND 8[a]

δ	Number of protons	Multiplicity	Assignment
1.25	3	d, $J_{9,8}$ = 6 Hz	$^{9}CH_3$
1.38	3	d, $J_{11,10}$ = 7 Hz	$^{11}CH_3$
1.99	3	s	$-NHCOCH_3$
2.02	3	s	$-^{8}COCOCH_3$
2.19	3	s	$-^{4}COCOCH_3$
2.59	3	m	^{5}CH, $^{6}CH_2$
4.41[b]	1	d of broad d, $J_{7,NH}$ = 9.5, $J_{7,8}$ = 6, $J_{7,5}$ = <1 Hz	^{7}CH
4.63[c]	1	quintet, $J_{10,NH}$ = 8, $J_{10,11}$ = 7 Hz	^{10}CH
5.04	1	quintet, $J_{8,9}$ = 6, $J_{8,7}$ = 6 Hz	^{8}CH
5.40[d]	1	multiplet	^{4}CH
6.04	1	d of d, $J_{2,3}$ = 10, $J_{2,4}$ = 2 Hz	^{2}CH
6.62[e]	1	d, $J_{NH,10}$ = 8 Hz	NH
6.84	1	d of d, $J_{3,2}$ = 10, $J_{3,4}$ = 2 Hz	^{3}CH
7.35[e]	1	d, $J_{NH,7}$ = 9.5 Hz	NH

[a] In $CDCl_3$ *vs.* TMS = 0. [b] Exchange of NH for ND results in a broad doublet, $J_{7,8}$ = 6 Hz, $J_{7,5}$ = <1 Hz. [c] Exchange of NH for ND results in a quartet, $J_{10,7}$ = 7 Hz. [d] When examined in D_2O *vs.* 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt = 0, this signal appears as a doublet of triplets at δ 5.40, $J_{4,5}$ = 9 Hz, $J_{4,3} = J_{4,2}$ = 2 Hz. [e] Signal disappears on addition of D_2O.

2 Hz). The observed behavior is consistent with the chemical environment of the ring hydrogens in **8**. The nmr data (Table I) also confirm the nature of the side chain array.

The nmr spectrum[4b] of **1** in deuterium oxide containing sodium deuterioxide (to exchange the hydrogens at C-2 and C-6 for deuterium), in which the signals for the five hydrogens on carbon bearing oxygen and nitrogen overlap in the δ 4.7 to 3.0 region (Figure 1), is completely explicable in terms of the structure proposed and, in addition, reveals the preferred conformation of the molecule in solution. After complete deuterium exchange H_3 appears as a doublet at δ 3.77 ($J_{3,4}$ = 8.5 Hz). The H_4 signal is now more clearly visible and appears at δ 3.36 as a triplet ($J_{4,3} = J_{4,5}$ = 8.5 Hz). The magnitude of $J_{3,4}$ and $J_{4,5}$ requires an axial-axial-axial relationship between H_3, H_4, and H_5 of the cyclohexane ring.[10] These observations are consistent with a preference for the chair-like conformation of the cyclohexanone ring of N-acetylalanylactinobolone (**1**) where the substituents at C-3, C-4, and C-5 each occupy the equatorial position.[11] In the α,β-unsaturated ketone **8**, a preference for the half-chair conformation with equatorial-like acetoxyl at C-4 and equatorial-like side chain at C-5 may be inferred from the $J_{4,5}$ value of 9 Hz derived from the H_4 signal (D_2O, see Table I).

A total of three hydrolysis products of the antibiotic actinobolin (**9**) have now been reported: *N*-acetyl-

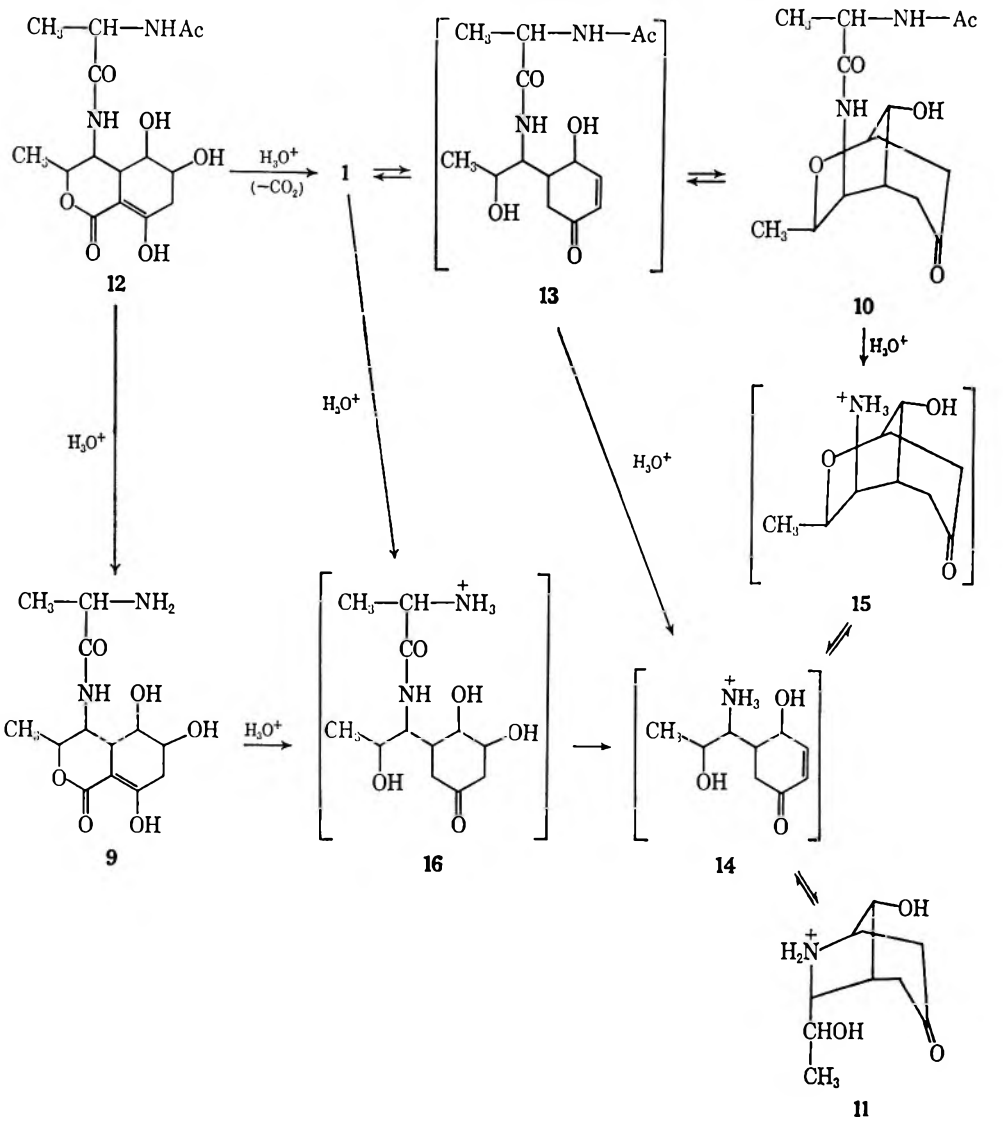
(10) In dimethyl sulfoxide-d_6 solution[4a] the H_4 signal is visible (δ 3.28) as a triplet with a coupling constant of similar magnitude ($J_{4,3} = J_{4,5}$ = 8 Hz).

(11) The recently suggested conformation of *N*-acetylactinobolin,[12] a derivative of the intact antibiotic, is comparable at sites equivalent to C-3, C-4, and C-5. Such an observation together with the mild conditions employed in the cleavage of the lactone ring and subsequent decarboxylation of *N*-acetylactinobolin suggest a retention of configuration in the formation of *N*-acetylalanylactinobolone. Thus, centers C-10, C-8, C-7 C-5, C-4, and C-3 are tentatively assigned as *S*, *R*, *R*, *R*, *R*, and *R*, respectively.

(12) F. J. Antosz, D. B. Nelson, D. L. Herald, Jr., and M. E. Munk, *J. Amer. Chem. Soc.*, **92**, 4933 (1970).

SCHEME I

PATHWAYS OF ACID-INDUCED CLEAVAGE OF ACTINOBOLIN



alanylactinobolone (**1**), *N*-acetylalanylactinobicyclone (**10**),[3] and actinobolamine (**11**).[2] It was of interest to determine the pathways relating these compounds. The original conditions employed in a study of the basic hydrolysis of *N*-acetylactinobolin (**12**), *i.e.*, a 30-min reflux in 1 *N* aqueous ammonia, gave a mixture of **1** and **10** in the ratio of one to two. Under milder conditions, 20 hr at room temperature in 5 *N* aqueous ammonia, both products were again formed but **1** predominated; the observed ratio of **1** to **10** being two to one. Refluxing *N*-acetylactinobolin in 5 *N* aqueous ammonia for 1 hr resulted in the formation of **1** and **10** in the ratio of one to twelve. These observations suggest that the monocyclic system **1** is the direct product of basic hydrolysis of *N*-acetylactinobolin and the precursor of the bicyclic hydrolysis product **10**. The conversion of **1** to **10** during the course of a 30-min reflux period in 1 *N* aqueous ammonia, conditions to which **10** is stable, confirms the base-induced reaction sequence: **12** → **1** → **10**.

A reasonable route for the transformation of **1** to **10** would involve the base-catalyzed β elimination of water to form the α,β-unsaturated ketone **13** followed by base-catalyzed 1,4 addition of the side chain hydroxyl group. The α,β-unsaturated ketone **13** necessary to test the plausibility of this pathway was available as its di-*O*-acetate **8**. Under the mild basic conditions of ester cleavage, 0.1 *N* sodium methoxide in methanol at room temperature, compound **8** was converted to **10**, thus providing support for the elimination–addition sequence **1** → **13** → **10**.

A related α,β-unsaturated ketone, **14**, may serve as the precursor of actinobolamine (**11**), the product derived from the vigorous acid hydrolysis of both actinobolin (**9**)[2] and *N*-acetylalanylactinobicyclone (**10**).[3] Mild acid treatment, 2 *N* sulfuric acid at 60°, results in the conversion of *N*-acetylactinobolin (**12**) to a mixture of *N*-acetylalanylactinobolone (**1**), *N*-acetylalanylactinobicyclone (**10**), and actinobolamine (**11**). Treatment of either **1** or **10** under the same conditions, but for a shorter period of time, leads to a mixture of both compounds. Thus, the interconvertibility of **1** and **10** under acidic conditions, probably *via* the unsaturated ketone **13**, is demonstrated. The possible pathways for acid-induced cleavage of actinobolin and its *N*-acetate are summarized in Scheme I.

No direct or indirect evidence is available to support the intervention of **14**, **15**, or **16**, although, as indicated

above, the α,β-unsaturated ketone **14** appears to be a likely precursor of actinobolamine (**11**), the apparent energy well of the system.

Experimental Section

All melting points are corrected and were taken on a Thomas–Hoover capillary melting point apparatus. Infrared spectra were determined on a Perkin-Elmer Model 237B Infracord and ultraviolet spectra on a Cary Model 14 spectrophotometer. Nuclear magnetic resonance spectra were run in an appropriate solvent on a Varian Associates A-60 spectrometer with tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standards and are reported in δ units. Field-sweep decoupling experiments utilized a Varian Associates Model V-6058A spin decoupler. Rotations at the sodium D line were determined on a Rudolf Model 80 polarimeter and optical rotatory dispersion curves were determined with a Jasco Model ORD/UV-5 spectropolarimeter in 10-mm cells. Mass spectra were obtained on an Atlas CH-4B mass spectrometer using a heated direct inlet system, ionizing current of 19 μA, and ionizing energy of 70 eV. Thin layer chromatographic (tlc) plates were prepared with Bio-Sil A(10-30 μ) with 5% binder (purchased from Bio-Rad Laboratories). Mallinckrodt ChromAR sheets (silicic acid) were used for preparative tlc. Solvent systems for tlc and visualization methods are listed where used. Column chromatography separations were performed with Bio-Sil A, 100–200 mesh, silicic acid (purchased from Bio-Rad Laboratories). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Basic Hydrolysis of Actinobolin. Determination of Carbon Dioxide.—A three-necked flask was fitted with a dropping funnel, a West condenser, and a gas inlet. Nitrogen gas was passed through an Ascarite-filled tube into the reaction flask, exited through the condenser, passed through a drying clyinder containing concentrated sulfuric acid and into a removable tube containing Ascarite and magnesium perchlorate (protected from the atmosphere by a two-stage mineral oil-filled gas exit). Carbon dioxide liberated in the reaction flask was swept into and adsorbed in the Ascarite magnesium perchlorate tube and determined by weight difference. The apparatus was shown to provide a reasonably accurate (5%) estimate of carbon dioxide resulting from the acidification of carbonate salt solutions and carbon dioxide liberated in the acid hydrolysis of actinobolin[2] (1 mol of carbon dixode *per* mol of actinobolin). An example of the procedure used in determining carbon dioxide liberated in the basic hydrolysis of actinobolin is described below.

After addition to the reaction flask of 368.4 mg (1.00 mmol) of actinobolin sulfate the flask was flushed under slow nitrogen flow. The Ascarite magnesium perchlorate tube was removed, weighed, and reconnected as 25 ml of 1 *N* ammonium hydroxide was added to the reaction flask. The flask was heated to reflux and maintained at reflux for 30 min under a slow nitrogen flow. The heating mantle was removed, the flask allowed to cool, and a 1 *N* hydrochloric acid solution containing phenolphthalein was added *via* the dropping funnel until the reaction solution was slightly acidic. The reaction flask was allowed to remain at room temperature for 4 hr under a slow nitrogen flow. The Ascarite magnesium perchlorate tube was removed and weighed. The weight difference indicated 42.2 mg of carbon dioxide (0.96 mmol).

Preparation of *N*-Acetylalanylactinobolone (1).—A solution of 1.475 g (4.32 mmol) of *N*-acetylactinobolin in 45 ml of 5 *N* ammonium hydroxide was stirred for 20 hr at room temperature. The solution was passed over a column containing 15 ml of Bio-Rad AG 21-K anion-exchange resin (hydroxide form), and the water eluent was freeze-dried to yield a residue of 1.128 g. The freeze-dried solid was adsorbed onto silicic acid, dry loaded into a column containing 90 g of silicic acid and eluted with ethyl acetate containing increasing amounts of ethyl alcohol. Elution with ethyl acetate–ethyl alcohol (25/4, v/v) gave first a homogeneous product band followed by a mixed component zone and then a second homogeneous product band. Crystallization of the first band from ethyl acetate gave 298 mg of *N*-acetylalanylactinobicyclone. The second homogenous band on crystallization from acetone gave 627 mg (46%) of *N*-acetylalanylactinobolone (1), mp 161.5–162.5° (resolidifies and melts at 178–180°). Vacuum drying gave an analytical sample: mp 179–180°; $[\alpha]^{25}D$ −57.1° (*c* 3.1, H_2O); ν_{max}^{KBr} 3550–3250 (broad, OH and amide NH), 3070 (amide NH), 1715 (unstrained ketone C=O), 1665 and 1640 (amide C=O), 1540 cm^{-1} (amide II); ORD (*c* 3.7, MeOH) negative plain curve; nmr (DMSO-d_6) (see discussion) (D_2O) δ 4.7–3.0 (5 H, m, hydrogen on carbon bearing heteroatoms), 3.0 to 1.7 (5 H, m, methine H and CH_2COCH_2), 2.05 (3 H, s, $NCOCH_3$), 1.43 (3 H, d, J = 7 Hz, $CHCH_3$), and 1.19 (3 H, d, J = 6 Hz, $CHCH_3$);[13] mass spectrum *m/e* (rel intensity) 316 (<1), 298 (6), 272 (27), 186 (21), 168 (44), 158 (69), 141 (61), 140 (56), 131 (53), 123 (41), 114 (100), 87 (93), 86 (87).

Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86; O, 30.35; mol wt, 316. Found: C, 53.09; H, 7.73; N, 8.88; O, 30.46; mol wt, 316 (mass spectrum).

N-Acetylalanylactinobolone Dimethyl Ketal Tri-*O*-acetate (2).—The procedure of Lorette and Howard[14] was used. A solution of 121 mg (0.38 mmol) of **1**, 12.3 g of dimethoxypropane ($n^{25}D$ 1.2748), 5 mg of *p*-toluenesulfonic acid monohydrate, and 10 ml of methanol was refluxed for 45 min, then set for distillation. After 15 ml of distillate had been collected at ~60°, 10 ml of methanol was added to the solution and an additional 10 ml of distillate taken. On cooling, 1 ml of methanol-washed Bio-Rad AG 21-K anion-exchange resin (hydroxide form) was added to the pot liquid. The mixture was stirred and filtered. The filtrate was taken to dryness under reduced pressure to give 137 mg of a clear film whose ir (film from methanol) displayed no ketone carbonyl stretch.

A solution composed of the filtrate film, 1.5 ml of acetic anhydride and 1.5 ml of pyridine was allowed to sit at room temperature for 12 hr. Removal of solvent under reduced pressure gave an oil which crystallized from ethyl acetate–methylcyclohexane to give 123 mg (64%) of **2**, mp 173–175°. Recrystallization gave analytically pure material: mp 176–178°; $[\alpha]^{26}D$ +6.8° (c 4.3, MeOH); nmr (DMSO-d_6) three of the five hydrogen signals in the δ 4.5–3.1 region of the spectrum of **1** experience a paramagnetic shift[8] and appear as an overlapping set of signals in the δ 5.1–4.5 region, other pertinent signals appear at δ 1.88 (3 H, s, $-OCOCH_3$), 1.91 (3 H, s, $-OCOCH_3$), 1.93 (3 H, s, $-OCOCH_3$), 3.10 (3 H, s, OCH_3), and 3.15 (3 H, s, OCH_3); mass spectrum *m/e* (rel intensity) 457 (<1), 428 (<1), 397 (<1), 369 (8), 309 (83), 190 (51), 164 (61), and 136 (100).

Anal. Calcd for $C_{22}H_{36}N_2O_{10}$: C, 54.08; H, 7.43; N, 5.74; O, 32.75; mol wt, 488. Found: C, 54.08; H, 7.56; N, 5.64; O, 32.77; mol wt, 488 (mass spectrum *m/e* 457, 488 $-OCH_3$).

Acetylation of 1. Preparation of the Aromatic *O*-Acetate 3.—To a three-necked flask equipped with a gas inlet, a pressure-equalizing dropping funnel containing 70% perchloric acid, and a gas outlet was added 250 mg (0.79 mmol) of **1** and 4 ml of acetic anhydride. The slurry was stirred magnetically at 0° for 30 min under nitrogen flow. A drop of perchloric acid was added and followed 5 min later with a second drop. The solution was allowed to come to room temperature over a period of 20 min and poured onto ice and the water layer extracted three times with 25-ml portions of dichloromethane. The combined dichloromethane extracts were dried over anhydrous magnesium sulfate and filtered. Volatile solvent was removed from the filtrate under reduced pressure. Further solvent removal under high vacuum left a crystalline mass which was triturated with cold ethyl acetate and filtered to give 33 mg of **3**, mp 141–143°. The filtrate was loaded into a column containing 20 g of silicic acid. Elution with ethyl acetate gave first a difficult-to-crystallize oil[6] followed by cuts containing 85 mg of readily crystallizable **3**, mp 141–143°, to bring the crude yield of **3** to 118 mg (41%). Recrystallization from ethyl acetate gave analytically pure material: mp 146–147°; $[\alpha]^{25}D$ −79° (*c* 4.1, MeOH); λ_{max}^{EtOH} 262, 269 mμ (ϵ 300, 246);[15] ν_{max}^{KBr} 1770 (aromatic acetate

(13) Addition of sodium deuteroxide to a chilled solution of **1** in deuterium oxide (Figure 1) results in the immediate loss of signals equivalent to four hydrogens in the δ 3.0–1.7 region (leaving a signal at δ 1.98) and the simplification of the δ 4.7–3.0 region. The signal assignment for H_3 and H_4 discussed in the text can then be made, as can the assignment of H_{10} at δ 4.35 (1 H, q, $J_{10,11}$ = 7 Hz), H_7 at δ 4.20 (1 H, d of d, $J_{7,8}$ = 6 Hz, $J_{7,5}$ = 2.5 Hz), H_8 at δ 3.94 (1 H, quintet, $J_{8,9}$ = $J_{8,7}$ = 6 Hz), and H_5 at δ 1.98 (1 H, d of d, $J_{5,4}$ = 8.5 Hz, $J_{5,7}$ = 2.5 Hz). Assignment of side-chain methine signals is aided by spin decoupling studies[7] which fortuitously allow the decoupling of both H_{10} from H_{11}, and H_8 from H_9 at the same chemical shift difference. The H_7 pattern is then clearly visible as a doublet of doublets while H_{10} appears as a singlet and H_8 is a doublet ($J_{8,7}$ = 6 Hz).

(14) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

(15) Found for *m*-cresyl acetate: λ_{max}^{EtOH} 262, 269 mμ (ϵ 324, 296).

C=O),[16] 1735 (aliphatic acetate C—O), 1630 (amide (C=O), 1540 (amide II), 1210 cm^{-1} (C—O)[16]; nmr (DMSO-*d*) δ 8.38 (1 H, d, J = 9 Hz, NH), 8.03 (1 H, d, J = 7 Hz, NH), 7.2 (4 H, aromatic),[17] 5.05 (2 H, m, H-7, H-8), 4.45 (1 H, quintet, J = 7 Hz, H-10), 2.28 (3 H, s, $ArOCOCH_3$),[18] 1.95 (3 H, s, $OCOCH_3$), 1.86 (3 H, s, $NHCOCH_3$), 1.17 (3 H, d, J = 7 Hz, H-11), 1.10 (3 H, d, J = 6 Hz, H-9); mass spectrum *m/e* (rel intensity) 364 (<1), 277 (100), 235 (1), 164 (74), 114 (5), 87 (7), 86 (5).

Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69; mol wt, 364. Found: C, 59.58; H, 6.69; N, 7.59; mol wt (mass spectrum), 364.

Deacetylation of 3. Preparation of the Phenol 4.—A solution of 348 mg (0.96 mmol) of **3** in 15 ml of 0.1 *N* sodium methoxide in methanol was stirred at room temperature for 35 min. The reaction solution was passed through a column containing 20 ml of methanol-washed Amberlite 120 cation-exchange resin (proton form). The eluent and column washing were combined and taken to dryness under reduced pressure to give 198 mg (74%) of **4**: homogeneous to tlc (acetone, H_2SO_4 char); λ_{max}^{EtOH} 275, 280 mμ (ϵ 1870, 1700); $\nu_{max}^{EtOH,\ -OH}$ 294 mμ (ϵ 2950); nmr (acetone-d_6) δ 1.11 (3 H, d, J = 6 Hz, H-9), 1.30 (3 H, d, J = 7 Hz, H-11), 1.96 (3 H, s, $NCOCH_3$), 4.12 (2 H, H-^{6}C-OH), 4.58 (1 H, quintet, J = 7 Hz, H-10), 4.81 (1 H, d of d, J = 9 and 5 Hz, H-7), 7.4 to 6.5 (4 H, aromatic,[17] 7.59 (1 H, d, J = 8 Hz, NH), 7.82 d, J = 9 Hz, NH), and 8.47 (1 H, s, phenol OH). Addition of D_2O causes signals at δ 8.47, 7.82, and 7.59 to disappear while these signals are altered: δ 4.07 (1 H, quintet, J = 6 Hz, H-8), 4.52 (1 H, q, J = 7 Hz, H-10), and 4.78 (1 H, d, J = 5 Hz, H-7).

Methylation of 4. Preparation of the Methyl Ether 5.—To a solution of 138 mg (0.49 mmol) of **4** and 3 ml of methanol in a 25-ml round-bottomed flask fitted with a Dry Ice condenser was added ~300 mg of diazomethane in 15 ml of ether and the resulting solution was stirred at room temperature for 8 hr. Removal of solvent under reduced pressure gave 152 mg of a slightly yellow solid. Crystallization from ethyl acetate gave 120 mg (83%) of **5** as analytically pure material: mp 134–135°; $[\alpha]^{26}D$ −120° (c 4.9, MeOH); λ_{max}^{EtOH} 212 mμ (ϵ 8900), 272 (2000), 280 (1900); nmr (D_2O) δ 7.6 to 6.8 (4 H, aromatic), 4.85 (1 H, d, J = 5.5 Hz, H-7), 4.45 (1 H, q, J = 7 Hz, H-10), 4.20 (1 H, quintet, J = 6 Hz, H-8), 3.86 (3 H, s, OCH_3), 2.12 (3 H, s, $NCOCH_3$), 1.38 (3 H, d, J = 7 Hz, H-11), 1.19 (3 H, d, J = 6.5 Hz, H-9); spin decoupling studies[7] (signal irradiated, signal observed, multiplicity change) H-8, H-9, d → s; H-8, H-7, d → s; H-7, H-8, quintet → q (J = 6 Hz), H-9, H-8, quintet → d (J = 5 Hz); mass spectrum *m/e* (rel intensity) M + 1 = 295 (4), 276 (8), 251 (24), 250 (100), 249 (27), 232 (16), 191 (20), 163 (24), 136 (35), 114 (22), 91 (13), 87 (17), 86 (18).

Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.54; mol wt, 294. Found: C, 60.97; H, 7.54; mol wt, 294 (mass spectrum, M + 1 = 295).

Oxidation of 5 to *meta*-Anisic Acid.—A solution of 105 mg (0.36 mmol) of **5**, 330 mg of potassium permanganate, and 210 mg of sodium hydroxide in 2 ml of H_2O was heated at steam bath temperature for 1 hr, an additional 2 ml of H_2O added, and heating continued for 2 hr. The reaction solution was cooled and filtered. The filtrate and the water washes were combined and acidified with concentrated sulfuric acid. Sodium bisulfite was added until color decreased to a constant level, the solution cooled and extracted three times with 25-ml portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate and filtered. The filtrate was taken to dryness under reduced pressure to give 75 mg of a tan residue. A tlc examination (EtOAc, bromocresol green visible) revealed a mixture of acidic components. Preparative tlc on an 1 ft × 8 ft Chrom-AR-1000 sheet (developed with EtOAc; visible *via* uv) revealed a major band with R_f comparable with *meta*-anisic acid. The major band was cut out and eluted with ethyl acetate–ethyl alcohol (3:1, v/v). Removal of solvent under reduced pressure gave 34 mg of a slightly colored crystalline mass. Purification by vacuum sublimation gave 20 mg of *meta*-anisic acid, mp 106–107° (lit.[19] mp 109–110°). The ir spectrum could be superimposed upon that of authentic *meta*-anisic acid, and the nmr ($CDCl_3$) was identical with an nmr of *meta*-anisic acid.

Preparation of the Isopropylidene Derivative of *N*-Acetylactinobolin.—In a 500-ml round-bottom flask fitted with a Soxhlet condenser containing Linde 3A Molecular Sieves in the thimble was placed 1.193 g (3.48 mmol) of *N*-acetylactinobolin, 250 ml of acetone, and 60 mg of *p*-toluenesulfonic acid monohydrate. The solution was refluxed for 22 hr, cooled, and passed through a column containing 20 ml of Amberlite IR-45 weakly basic anion-exchange resin. The eluent was taken to dryness under high vacuum. The resultant solid was triturated with cold acetone and filtered to give 657 mg of N-acetylactinobolin, identified by tlc (ethyl acetate–ethyl alcohol, 2:1, v/v). The filtrate was loaded into a column containing 20 g of silicic acid and eluted with acetone. The first 125 ml of acetone contained 557 mg (1.46 mmol) of the isopropylidene derivative of *N*-acetylactinobolin. Further elution gave an additional 13 mg of *N*-acetylactinobolin to bring the yield of recovered *N*-acetylactinobolin to 670 mg (1.96 mmol). The crude yield of product based on starting material utilized was 95%. Recrystallization from acetone followed by vacuum drying at 78° gave an analytical sample: mp 238–240° dec; $[\alpha]^{26}D$ + 26.3 (*c* 3.6, MeOH); λ_{max}^{EtOH} 262 mμ (ϵ 9000); $\lambda_{max}^{EtOH,\ OH^-}$ 287 mμ (ϵ 17,400); ν_{max}^{KBr} 3340, 3300–3250 and 3055 (amide NH), 1687, 1660–1630 (C=O), 1625 (amide C=O), 1525 (amide II), 1390, 1380 cm^{-1} (gem-methyl).

Anal. Calcd for $C_{18}H_{26}N_2O_7$: C, 56.53; H, 6.85; O, 29.29; mol wt, 382. Found: C, 56.71, H, 6.99; O, 29.13; mol wt, 382 (mass spectrum).

Preparation of 6. A. Hydrolysis of Isopropylidene *N*-Acetylactinobolin.—A solution of 380 mg (0.95 mmol) of isopropylidene *N*-acetylactinobolin in 25 ml of 1 *N* ammonium hydroxide was refluxed for 35 min, cooled, and freeze-dried. The freeze-dried residue was diluted with water and passed over a column of 5 ml of Bio-Rad AG 21-K anion-exchange resin (hydroxide form). The water eluents were freeze-dried to give 262 mg. Crystallization from acetone gave 131 mg; chromatography of the mother liquor on silicic acid using ethyl acetate–ethyl alcohol (25:2, v/v) as eluent gave an additional 50 mg of **6** for a total yield of 181 mg (51%): mp 160–161°; nmr (DMSO-d_6) δ 4.6 (1 H, d, ^{8}C-OH, diappears on addition of D_2O), 1.37 (6 H, gem-methyl). It should be noted that the presence of **10** could not be detected in the hydrolysis mixture.

B. From 1.—In a 25-ml round-bottom flask fitted with a micro Soxhlet containing Linde 3A molecular Sieves in the thimble was placed 23 mg (0.07 mmol) of **1**, 15 ml of acetone, and 8 mg of *p*-toluenesulfonic acid monohydroate. The solution was refluxed for 26 hr, cooled, and passed over a column containing 5 ml of Amberlite IR-45 weakly basic anion-exchange resin. The eluent was taken to dryness under vacuum. A tlc examination (ethyl acetate–ethyl alcohol, 2:1, v/v, sulfuric acid char) revealed the presence of **1**, **6**, and *N*-acetylalanylactinobicyclone (**10**). The formation of **6** (in ~35% yield) and **10** was confirmed by isolation *via* silicic acid column chromatography and comparison of the ir spectrum of each product with an ir spectrum of authenic **6** and **10**.[3]

Preparation of Isopropylidene *N*-Acetylalanylactinobolone *O*-Acetate (7).—A solution of 222 mg (0.63 mmol) of **6** in 4 ml of acetic anhydride and 4 ml of pyridine was stirred at 5° for 12 hr. solvent was removed under reduced pressure to give a white solid which crystallized from acetone–methylcyclohexane to give 183 mg (80%) of **7**, mp 145–147°. Recrystallization and extensive drying gave a sample for analysis: mp 147–148°; $[\alpha]^{25}D$ −25.0 (*c* 4.1, MeOH); ν_{max}^{KBr} 1730 (acetate C=O), 1715 (ketone C=O), 1375 cm^{-1} (gem-dimethyl); nmr (acetone-d_6) δ 5.29 (1 H, q of d, J = 6 and 3 Hz, H-8), 1.37 (3 H, s, gem CH_3), 1.42 (3 H, s, gem CH_3), 1.98 (3 H, s, $OCOCH_3$), and 1.95 (3 H, s, $-NHCOCH_3$); mass spectrum *m/e* (rel intensity) peaks characteristic of an isopropylidene group[20] at 383 (4) M − CH_3 340 (2) M − CH_3COCH_3, and 323 (1) M − (CH_3 + CH_3CO_2H).

Anal. Calcd for $C_{19}H_{39}N_2O_7$: C, 57.27; H, 7.59; O, 28.12; mol wt, 398. Found: C, 56.74; H, 7.67; O, 27.96; mol wt, 398 (mass spectrum, M + 1 = 399).

Acetylation of 1 under Basic Conditions. Preparation of the α,β-Unsaturated Ketone 8.—A solution of 202 mg (0.64 mmol) of

(16) Ascribed to an aromatic acetoxy unit: see K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 44.

(17) The nature of the aromatic substitution pattern is most clear in the nmr of **4** (acetone-d_6) which displays a four hydrogen aromatic region very similar in chemical shift and pattern to that reported for *m*-cresol. "Varian Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, number 160.

(18) A chemical shift about 0.3 ppm downfield of the methyl group of an aliphatic acetate. See ref 8, p 98.

(19) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. III, Part B, Elsevier, Amsterdam, 1956, p 768.

(20) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectroscopy," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 228.

1 in 2 ml of acetic anhydride and 2 ml of pyridine was heated at steam bath temperature for 3.5 hr under a nitrogen blanket. Solvent was removed under reduced pressure and the resulting residue was loaded into a column containing 25 g of silicic acid. Elution with benzene–ethyl alcohol (95:5, v/v) gave a homogeneous material which was crystallized from benzene to give 137 mg of 8 holding benzene as solvent of crystallization. Drying to constant melting point gave analytically pure material: mp 131–132°; $[\alpha]^{26}D$ +51° (c 5.2, MeOH); λ_{max}^{EtOH} 211 (ε 9500); ν_{max}^{KBr} 1750 and 1730 (acetate C=O), 1685 cm^{-1} (ketone C=O); mass spectrum *m/e* (rel intensity) M + 1 = 383 (<1), 322 (1), 295 (16), 235 (35), 182 (85), 150 (35), 123 (45), 122 (100), 116 (71), 114 (72), 87 (72), 86 (69); nmr, see discussion.

Anal. Calcd for $C_{18}H_{26}N_2O_7$: C, 56.53; H, 6.85; O, 29.29; mol wt, 382. Found: C, 56.35; H, 6.95; O, 29.34; mol wt, 382 (mass spectrum, M + 1 = 383).

Basic Hydrolysis of Actinobolin.—A solution of 1.602 g (4.42 mmol) of the sulfate salt of actinobolin in 75 ml of 1 *N* ammonium hydroxide was refluxed for 35 min, cooled, and passed through a column containing 40 ml of Bio-Rad AG 21-K anion-exchange resin (hydroxide form). The water eluent was freeze-dried and the resulting solid was taken up in 25 ml of ethyl alcohol contining 1.5 ml of acetic anhydride. The solution was stirred at room temperature for 12 hr. Solvent was removed *via* high vacuum and the resulting clear glass was adsorbed onto silicic acid, dry loaded into a column containing 50 g of silicic acid and eluted with ethyl acetate containing increasing amounts of ethyl alcohol. Elution with ethyl acetate–ethyl alcohol (25:3, v/v) gave 616 mg of crystalline solid whose physical and spectral properties were identical with those of *N*-acetylalanylactinobicyclone (10), isolated from the basic hydrolysis of *N*-acetylactinobolin. Further elution with ethyl acetate–ethyl alcohol (25:4, v/v) gave cuts which contained a second less mobile product. Rechromatography of the mixed product cuts resulted in the isolation of an additional 17 mg of 10 and 112 mg of a second product whose physical and spectral properties were identical with those of *N*-acetylalanylactinobolone (1) isolated from the basic hydrolysis of *N*-acetylactinobolin.

Basic Hydrolysis of 1.—A solution of 5 mg of 1 in 5 ml of 1 *N* ammonium hydroxide was refluxed for 35 min, cooled, and freeze-dried. A tlc examination (ethyl acetate–ethyl alcohol, 2:1, v/v, sulfuric acid char) revealed the presence of a single compound, *N*-acetylalanylactinobicyclone (10). In a parallel experiment 10 was shown to be stable to the reaction conditions.

Methanolysis of 8.—A solution of 67 mg (0.18 mmol) of 8 in 4 ml of 0.1 *N* sodium methoxide in methanol was stirred at room temperature for 30 min and passed through a column containing 5 ml of methanol-washed Amberlite 1R-120 cation-exchange resin (proton form). The eluent was taken to dryness under reduced pressure. A tlc examination (Merck HF 254,[21] ethyl acetate–ethyl alcohol, 2:1 v/v, sulfuric acid char) revealed the absence of 8 and the presence of *N*-acetylalanylactinobicyclone (10) as the major product. Preparative tlc (ethyl acetate–ethyl alcohol, 2:1, v/v) of the methanolysis products gave 31 mg (0.10 mmol) of 10 identified by melting point and ir.

Vigorous Acid Hydrolysis of 1.[22]—A solution of mg of 1 in 2 ml of 4 *N* sulfuric acid was refluxed for 15 hr, cooled, and passed through a column containing 15 ml of Bio-Rad AG 21-K anion-exchange resin (hydroxide form). The column was eluted with water until the eluents were neutral and then with a 10% acetic acid solution. The residue left after freeze-drying of the water eluent was *N*-acetylated in ethyl alcohol–acetic anhydride. After removal of solvent *via* high vacuum a tlc examination (ethyl acetate–ethyl alcohol, 2:1, v/v, sulfuric acid char) demonstrated the product to be the *N*-acetyl derivative of actinobolamine (11).[2] A tlc examination (iso propyl alcohol, pyridine, acetic acid, water, 8:8:1:1, v/v/v/v and methyl ethyl ketone, propionic acid, water, 75:25:30, v/v/v, ninhydrin visible) of the residue left after freeze-drying of the acetic acid eluent demonstrated the product to be alanine.

Vigorous Acid Hydrolysis of 3.[22]—Hydrolysis of 2 mg of 3 using the conditions described for 1, followed by a parallel work-up led to an amphoteric product which was shown to be alanine by a tlc examination.

Mild Acid Hydrolysis of *N*-Acetylalanylactinobolone (1).—A solution of 12 mg of 1 in 5 ml of 2 *N* sulfuric acid was heated at 60°. After 0.5 hr (1 ml), 1.5 hr (2 ml), and 2.5 hr (2 ml) of heating, a sample was removed, diluted with water, stirred with 10 ml of Bio-Rad AG 21-K anion-exchange resin (hydroxide form), and filtered. The filtrates were freeze-dried and the resulting residues examined *via* tlc (ethyl acetate–ethyl alcohol, 2:1, v/v, sulfuric acid char). All samples revealed the absence of low R_f material (*i.e.*, 11), the presence of 1, and the presence of 10 (as the major product at 1.5 and 2.5 hr).

Mild Acid Hydrolysis of *N*-Acetylalanylactinobicyclone (10).—A solution of 11 mg of 10 in 5 ml of 2 *N* sulfuric acid was heated at 60°. Samples were removed, worked up, and examined *via* tlc as in the mild acid hydrolysis of 1. All samples revealed the absence of low R_f material, the presence of 10 as the major product, and the presence of a lesser amount of 1 at 1.5 and 2.5 hr.

Mild Acid Hydrolysis of *N*-acetylactinobolin (12).[23]—A solution of 22 mg of 12 in 2 ml of 2 *N* sulfuric acid was heated at 60° for 27 hr, cooled, and passed through a column containing 15 ml of Bio-Rad AG 21-K anion-exchange resin (hydroxide form). The water eluent (75 ml) was freeze-dried. The resulting residue was dissolved in water and passed through a column containing 10 ml of Bio-Rad AG 50W-X8 cation-exchange resin (proton form). The column was eluted with water (70 ml) and 5% aqueous ammonia (100 ml). The solid left after freeze-drying of the basic eluent was *N*-acetylated in 1 ml of ethyl alcohol containing 0.5 ml of acetic anhydride. A tlc examination (ethyl acetate–ethyl alcohol, 2:1 and 3:1, v/v, sulfuric acid char) indicated the neutral fraction (freeze-dried water eluent) contained both 1 and 10 while the *N*-acetylated basic fraction contained 10 and the *N*-acetyl derivative of actinobolamine (11).

Registry No.—1, 25834-39-3; 2, 25834-40-6; 3, 25834-41-7; 4, 78802-19-2; 5, 25834-43-9; 6, 25834-44-0; 7, 25834-45-1; 8, 25834-46-2; *N*-acetylactinobolin isopropylidine derivative, 25834-47-3; alanylactinobolone, 25834-48-4.

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(21) Merck Ag. Darmstadt HF 254 silicic acid distributed by Brinkmann Instruments.

(22) Studied by Mr. Chidambar L. Kulkarni.

(23) Studied by Mr. Fredrick J. Antosz.

Photochemical Decarboxylation of Sodium Glycidates[1]

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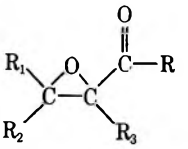
The photolysis of sodium phenylglycidates yielded decarboxylated products analogous to those generated in the presence of acids, although photoprotonation was probably not involved. Aliphatic sodium glycidates did not photolyze, even in the presence of sensitizers.

The photochemistry of epoxy ketones (**1**) has been intensively investigated, showing the formation of β diketones to be the major process.[3] The photochemistry of glycidic acids (**2**), on the other hand, was hitherto unknown. Because of the close formal relationship between the two series, we had hoped that



1, R = alkyl or aryl
2, R = OH

they would behave similarly and that the photolysis of glycidic acids would convert them into β-keto acids and finally into acetophenones after decarboxylation, in contrast with the acid-catalyzed decarboxylation which places the carbonyl at the α position.[4] We now report that the photochemical behavior of sodium glycidates in aqueous solution closely parallels that in presence of mineral acids.

Discussion

Saponification of the glycidic esters prepared by the Darzens synthesis provides a convenient preparation of sodium glycidates.[5] Acid treatment is usually accompanied by epoxide ring opening and does not yield the corresponding glycidic acids, except with simple aliphatic salts.[6] After several disappointing attempts to isolate the aromatic acids required in this study, we decided to investigate the behavior of the sodium salts in aqueous solution.

Aromatic sodium glycidates show a typical absorption maximum near 260 nm. When sodium β-phenylglycidate (**3**) was irradiated at 253.7 nm under nitrogen, carbon dioxide was immediately evolved and a polymeric precipitate coated the walls of the reaction vessel preventing extensive photolysis. No acetophenone was detected by nmr or glc in the neutral products of the reaction, which consisted almost exclusively of phenylacetaldehyde (**4**), with some bibenzyl and traces of benzaldehyde.

Phenylacetaldehyde (**4**) could have been generated from primary products resulting either from decarboxylation or from isomerization, namely from epoxystyrene (**5**) or phenylpyruvate (**6**), respectively. Neither **5** nor **6**, however, produced **4** upon irradiation in the above conditions.[7] When the photolysis of **3** was performed in deuterium oxide, the nmr of **4** showed that one deuterium had been incorporated at the methylene position and that no exchange had taken place at the aldehyde. This result further confirmed that a pyruvate had not been an intermediate since a deuterium would have been introduced at the carbon bearing the aldehyde in the product.

The formation of bibenzyl in the irradiation of **3** is most probably the result of further photolysis of **4**, which was found to decarbonylate and to yield bibenzyl upon irradiation in the above conditions.[9a] The detection of traces of benzaldehyde in the photolysis of **3** is in line with the results obtained by Griffin and coworkers in their studies on the photochemical cleavage of oxiranes.[9] Another route to benzaldehyde is through photohydration of **3** to sodium 2,3-dihydroxy-3-phenylpropionate followed by a retroaldol reaction. This is considered much less likely since it requires generating an unstabilized negative charge adjacent to the carboxylate, and since the photohydration of epoxides to glycols is still without precedent. Group migrations accompanying the opening of oxiranes are well known, both in photochemical[3] and in acid-catalyzed reactions.[10] It was desirable, therefore, to check for phenyl migration in the decarboxylation–epoxide opening of **3**. Had it taken place, it would have led to the observed products, both in normal and in deuterated water. The starting material was chemically labeled with a methyl at the β position, but, when **7a** was irradiated, it yielded 2-phenylpropionaldehyde (**8a**) rather than a ketone, thereby proving that no substituent had migrated.[11] Similarly, the ketones **8b** and **8c** were the major products in the photolysis of **7b** and **7c**. The latter example again indicated the absence of group migration in the reaction. It is also noteworthy that carbonyl products analogous to benzaldehyde were not detected with sodium β-phenylglycidates more substituted than **3**.

Aliphatic sodium glycidates, such as **7d** and **7e**, have an absorption maximum below 210 nm and have no measurable absorption above 230 nm; as expected, they did not photolyze upon irradiation. We also

(1) Presented, in part, at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, Abstracts of Papers, ORGN 46.

(2) Author to whom inquiries should be addressed.

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(7) Styrene oxide does isomerize to phenylacetaldehyde, however, when irradiated in benzene.[8]

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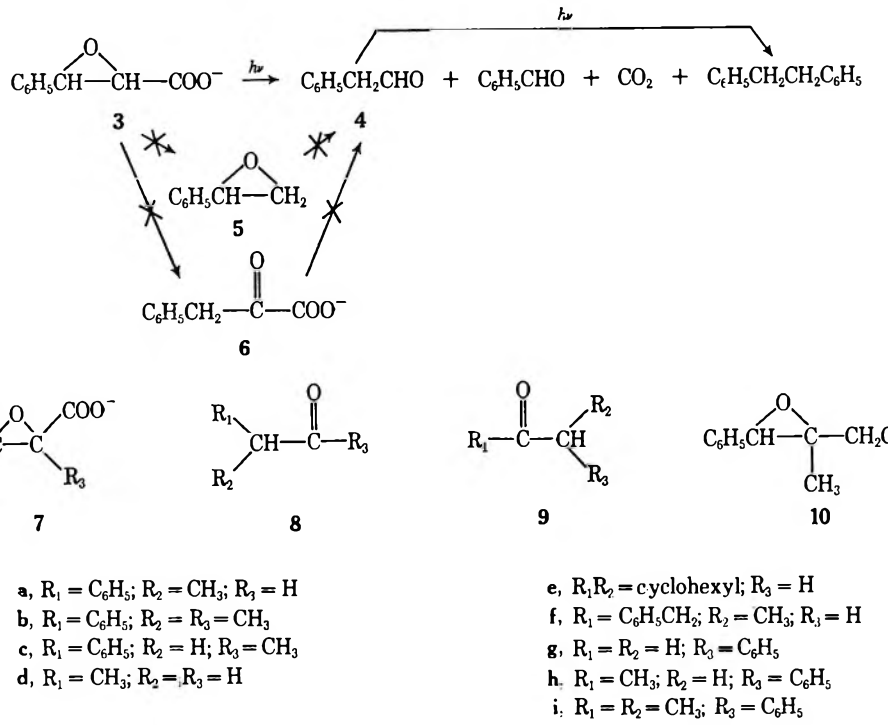
(11) This is in agreement with the lack of phenyl migration reported in the rearrangement of styrene oxide to phenylacetaldehyde.[8a]



a, $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = H$
b, $R_1 = C_6H_5$; $R_2 = R_3 = CH_3$
c, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$
d, $R_1 = CH_3$; $R_2 = R_3 = H$
e, R_1R_2 = cyclohexyl; $R_3 = H$
f, $R_1 = C_6H_5CH_2$; $R_2 = CH_3$; $R_3 = H$
g, $R_1 = R_2 = H$; $R_3 = C_6H_5$
h, $R_1 = CH_3$; $R_2 = H$; $R_3 = C_6H_5$
i, $R_1 = R_2 = CH_3$; $R_3 = C_6H_5$

failed in our attempts to induce their decarboxylation by triplet energy transfer from sensitizers such as benzoic acid, benzene, and rose bengal. We also tried unsuccessfully to transfer the energy from an aromatic sodium glycidate, by photolyzing **7c** in presence of **7e**. Finally, even an internal sensitizer proved ineffective, as in **7f** where one methylene separates the phenyl from the epoxide and which was unaffected by uv light.

The observed photochemistry of aromatic sodium glycidates must be a consequence of initial excitation of the aromatic moiety. After finding that **7f** did not photolyze, we tried to determine the requirements for decarboxylation in the aromatic series. Since there was no reaction upon irradiation of **10**, it was clear that the direct attachment of both the phenyl and the carboxylate to the epoxide ring was a prerequisite for decarboxylation. We therefore investigated representatives, **7g**, **7h**, and **7i**, of the sodium α-phenylglycidate series which are not accessible through the usual Darzens synthesis[12] and were prepared from the corresponding unsaturated esters by epoxidation followed by saponification. Photolysis proceeded smoothly, accompanied by decarboxylation. The products, **9g**, **9h**, and **9i**, respectively, indicated that fission of the benzylic carbon–oxygen bond had taken place, placing the new carbonyl at the original β position of the glycidate, unlike the β-phenylglycidate series in which the carbonyl is formed at the α position.

These observations led us to investigate the acid-catalyzed decomposition of sodium α-phenylglycidates, and we have already reported that they yielded "abnormal" products, identical with those obtained photochemically.[1,13] We explained the results in terms of a benzylic carbonium ion intermediate which was formed after protonation of the epoxide, in conflict with the accepted concerted mechanism for the decarboxylation of glycidic acids.[14]

The photodecarboxylation of carboxylic acids and their anions is currently receiving much attention, but the multiplicity of the reactive excited states during decarboxylation has not been established.[15] We failed in all our attempts to sensitize the decarboxylation of aliphatic sodium glycidates, but we achieved limited success in similar experiments in the aromatic series using acetophenone as sensitizer. This suggests to us that although decarboxylation can take place from a triplet state in this latter case, it normally proceeds from a singlet state. The failure which we experienced with the sensitized experiments in the aliphatic series may also be due to a requirement for a singlet excited state or to a prohibitively high triplet energy.

If the epoxide ring cleavage were an homolytic process, products of radical trapping would be expected in solvents which are better hydrogen radical donor than water.[16] Decarboxylation of **7a** in methanol, however, did not yield any hydroxymethylated product. This finding also appears to rule out the possibility of initial decarboxylation of the carboxylate anion accompanied by the expulsion of one electron, yielding an oxirane radical, as it was suggested in the decarboxylation of 1-naphthaleneacetic acid.[15c,17] The absence of radical intermediates was further indicated by observing that oxygen had no effect on the course of photolysis of **3**.

Heterolytic cleavage of the benzylic carbon to oxygen epoxide bond is an attractive possibility to account for the identity of products obtained in the acid-catalyzed and in the photolytic decarboxylation of aromatic so-

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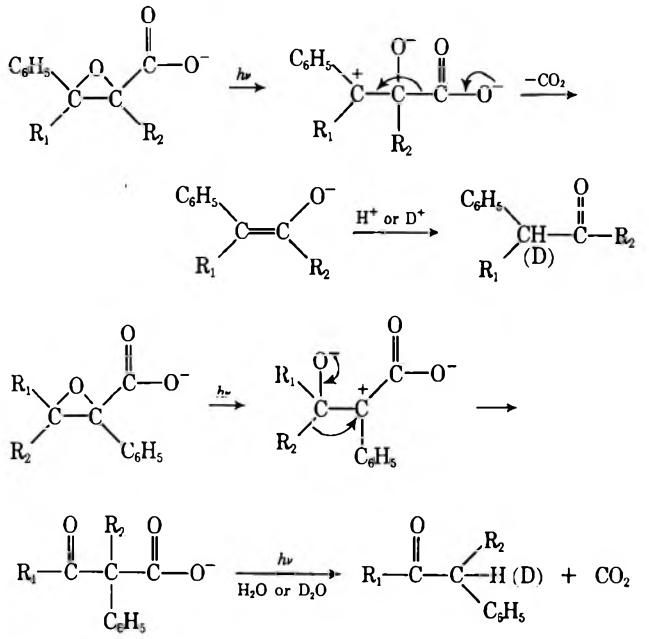
(16) P. J. Kropp, *ibid.*, **91**, 5783 (1969).
(17) L. I. Grossweiner and H. I. Joscheck, p 286 in "Solvated Electron," Advances in Chemistry Series, No. 50, American Chemical Society, Washington, D. C., 1965.

SCHEME I



dium glycidates (Scheme I). However, when **7c** was irradiated in aqueous solutions containing an excess of sodium hydroxide, the photolysis proceeded smoothly indicating that photoprotonation does not precede decarboxylation.[18] Furthermore, the decarboxylation of **7h** which took place with the loss of the β proton in acid[13] occurred photochemically with migration of that hydrogen from the β to the α position, and finally the formation of glyceric acids which was prominent in the acid-catalyzed treatment of sodium α-phenylglycidates did not occur during photolysis of these salts. These results indicate that the mechanisms of the acid-catalyzed and photochemical decarboxylation reactions are fundamentally different.

Speculations concerning the detailed mechanism(s) of the photochemical decarboxylation of sodium glycidates will be more fruitful when additional experiments, especially those carried out at low temperature, will have been performed.

Experimental Section

All irradiations were performed at 253.7 nm in a quartz vessel using a Rayonet reactor equipped with 16 8-W low pressure Hg lamps. The solutions were deoxygenated by bubbling nitrogen through, for 30 min prior to each run and during the course of each irradiation. The exit stream was bubbled through a $Ba(OH)_2$ solution when the detection of CO_2 was required. The nmr spectra were recorded on a Varian A-60A or T-60 spectrometer, and are expressed on the δ scale. The mass spectra were recorded at 70 and at 12 eV with a Perkin-Elmer 270 gas chromatograph–mass spectrometer, equipped with a column of 20% SE-30 on Chromosorb. A F & M 402 gas chromatograph equipped with SE-52 and DEGS columns was also used for comparing the retention times of reaction products with standards.

The ethyl glycidates corresponding to **3**,[5] **7a**,[5,20] **7b**,[21] **7e**,[5] and **7f**[22] were the products of Darzens condensations using potassium *tert*-butoxide as the base. Ethyl glycidates corresponding to **7c**[23] and **7d**[24] were obtained according to the literature methods, whereas the ethyl esters of **7g**, **7h**, **7c**, and **10** were prepared in 90, 78, 77, and 85% yields, respectively, by epoxidation of ethyl atropate,[25] ethyl-α-phenylcrotonate,[26] ethyl dimethylatropate,[27] and ethyl 3-methyl-4-phenylbutenoate[28] with 85% *m*-chloroperoxybenzoic acid in refluxing $CHCl_3$ for 15 hr. Each reaction mixture was cooled, extracted with 5% aqueous bicarbonate, dried, concentrated, and chromatographed over silica gel. The nmr and mass spectra of these glycidates were satisfactory. The saponification of the ethyl glycidates was performed according to Claisen[29] with 1 equiv each of sodium ethoxide and water. After standing overnight, the solid was filtered, washed thoroughly with ether, and dried. The salts, obtained in 60–90% yield, had satisfactory nmr spectra in D_2O and also in DMSO-d_6 which indicated the absence of hydroxylated impurities. The usual work-up of the irradiated solutions consisted in thoroughly extracting with chloroform or ether, drying the organic phase over $MgSO_4$, and concentrating it under reduced pressure. The per cent composition of the major decarboxylation product(s) was determined by the integration of the nmr spectra of the crude neutral product. The glc analysis and the signals in the nonaromatic part of the nmr spectra accounted for all the reaction products herein reported. However, integration of the aromatic protons was always too high and in calculating the amounts of products, we assumed the presence of polymeric aromatic substances which were not characterized.

Irradiation of 3.—The starting material had nmr (D_2O) at 7.35 (s, 5 H), 3.92 (d, J = 2 Hz, 1 H), and 3.45 (d, J = 2 Hz, 1 H). A solution of 1 g of **3** in 200 ml of water became turbid and evolved CO_2 after 30 min of irradiation. The milky white mixture was extracted with ether (four 100-ml portions) after 4 hr of irradiation, yielding 120 mg of a fragrant smelling liquid. It consisted mostly of **4** (59%): nmr (CCl_4) 9.60 (t, J = 2.5 Hz) and 3.60 (d, J = 2.5 Hz) in addition to phenyl protons; gc–mass spectrum major peaks at *m/e* 120, 92, and 91. The minor products (less than 5%) were identified as benzaldehyde (major peaks at *m/e* 106, 105, and 77) and bibenzyl (major peaks at *m/e* 182 and 91.) The aqueous layer was concentrated under vacuum and yielded 0.7 g of residue identical with the starting material by nmr. Bubbling oxygen instead of nitrogen during the irradiation did not affect the course of the photolysis, which yielded **4** as the major product.

Irradiation of 3 in D_2O.—A solution of 540 mg of **3** in 10 ml of D_2O was irradiated for 4 hr. Work-up yielded **4** which had nmr (CCl_4) signals at 9.60 (d, J = 2.5 Hz, –CDHCHO) and a broad signal at 3.60 (–CDHCHO) in addition to the phenyl protons.

Irradiation of 4.—A suspension of 1 g of **4** in 250 ml of water was irradiated for 4 hr. Work-up yielded a mixture of **4** (57%) and bibenzyl (15%) by nmr and gc–mass spectrum analysis.

Irradiation of 5.—The starting material was obtained according to literature method.[30] A suspension of 200 mg of **5** in 250 ml of water was irradiated for 3 hr. Neither **4** nor bibenzyl was detected by nmr and gc in a $CHCl_3$ extract.

Irradiation of 6.—A solution of 1 g of the salt in 250 ml of water was irradiated for 3 hr. Extraction with ether and usual work-up did not yield any neutral residue.

Irradiation of 7a.—The starting material was a mixture of cis and trans isomers showing nmr signals (D_2O) at 7.25 (s, 5 H), 3.57, and 3.37 (each a s, 1 H) and at 1.57 (s, 3 H). A solution of 1 g of **7a** was irradiated for 4 hr. Work-up yielded 221 mg of a neutral mixture from which the only volatile product was identified as **8a** (59%). It was characterized by its nmr (CCl_4) at 9.6 (d, J = 1 Hz, aldehydic proton), 3.52 (q, J = 7 Hz, showing poorly resolved coupling with the aldehyde), and 1.38 (d, J = 7 Hz) in addition to phenyl protons, and by a gc–mass spectrum comparison with an authentic sample (major peaks at *m/e* 134, 105, and 77.)

Irradiation of 7a in Methanol.—A solution of 500 mg of **7a** in 150 ml of methanol was irradiated for 30 min. After removing

(18) Although we have no knowledge of the acidity of the excited state of the glycidate anion, it is reasonable to assume that a strong alkaline solution would prevent the photoprotonation.[19]

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the solvent under vacuum, the residue was washed thoroughly with CCl_4 and filtered, and the solvent was evaporated to leave a residue (50 mg) which was found to be **8a** by gc–mass spectrum and nmr. The CCl_4 insoluble portion was identical with the starting material.

Irradiation of 7b.—The starting material (mixture of isomers) had nmr signals (D_2O) at 7.30 (s, 5 H), 1.62, 1.53, 1.10 (all s, total of 6 H). A solution of 500 mg of **7b** in 150 ml of water was irradiated for 4 hr. Work-up yielded 80 mg of residue containing **8b** as the only volatile product (66%). It was identified by gc–mass spectrum (*m/e* at 148, 105, 79, 77, and 43) and nmr at 7.20 (b), 3.60 (q, J = 7 Hz), 1.98 (s), and 1.35 (d, J = 7 Hz).

Irradiation of 7c.—The starting material had nmr (D_2O) signals at 7.28 (s, 5 H), 3.90 (s, 1 H), 1.60 (s, 3 H). A solution of 1 g of **7c** in 200 ml of water was irradiated for 4 hr. Ether extraction provided 135 mg of residue consisting mostly of **8c** (83%). It was identified by its nmr (CCl_4) signals at 7.20 (s), 3.52 (s), and 2.00 (s), as well as by its gc–mass spectrum analysis using an authentic sample (*m/e* 134, 92, 91, and 43). The other volatile product (5%) was identified as bibenzyl by direct comparison with a standard sample.

Irradiation of Phenylacetone.—A suspension of 1 g of **8c** in 200 ml of water was irradiated for 3 hr. Ether extraction yielded a mixture of starting material and bibenzyl (14%).

Irradiation of 7c in Basic Solutions.—Irradiation of 0.5 g of **7c** in 200 ml of water containing few drops of NaOH solution (pH 10) for 3 hr and work-up yielded 82 mg of residue consisting of **8c** (40%) and bibenzyl (38%). When the above experiment was repeated in pH 12, 89 mg of residue was obtained which consisted of 50% bibenzyl and 10% **8c**. Repeating the experiment in 200 ml of 1 *N* NaOH solution yielded 91 mg of neutral residue consisting of bibenzyl (52%) with a trace of **8c**.

Irradiation of 7c in Presence of Acetophenone.—A solution of 1 g of **7c** and 150 mg of acetophenone in 150 ml of water was irradiated using a 450-W medium pressure mercury arc with a Pyrex filter for 6 hr. Usual work-up yielded a mixture of **8c** (6 mg) and acetophenone. Identical irradiation of **7c**, but without acetophenone, did not provide any **8c**.

Irradiation of 7d.—The starting material had nmr (D_2O) signals at 3.00 (m, 2 H) and 1.30 (n, J = 5 Hz, 3 H). A solution of 580 mg of **7d** in 5 ml of water was deoxygenated and irradiated in a closed quartz tube for 4 hr. After cooling in ice and extracting with cold ether, glc analysis of the ether layer indicated the absence of propionaldehyde or any other volatile product. Upon concentration of the aqueous phase to dryness, the starting material was recovered quantitatively. Identical results were obtained upon irradiation with a Hanovia 450-W medium pressure lamp.

Irradiation of 7e.—The starting material had nmr (D_2O) at 3.42 (s, 1 H) and 1.61 (s, 10 H). A solution of 800 mg of **7e** in 200 ml of water was irradiated for 3 hr. Usual work-up did not provide any neutral product. Similar results were obtained when the irradiation was carried out in presence of either rose bengal (800 mg) or sodium benzoate (1.5 g) or benzene (saturating the water solution) as sensitizers. When a solution of 500 mg each of **7e** and **7c** in 250 ml of water was irradiated for 3.5 hr, usual work-up yielded 135 mg of neutral product consisting of **8c** (25%) and bibenzyl (48%). The evaporation of the aqueous layer left a mixture of **7e** and **7c** (nmr). Identical results were obtained upon irradiation with a Hanovia 450-W medium pressure lamp.

Irradiation of 7f.—The starting material was a mixture of isomers, with nmr (D_2O) signals at 7.38 (s, 5 H), 3.40 and 3.38 (each a s, 1 H), 2.85 and 2.83 (each a s, 2 H), and 1.22 (s, 3 H). A solution of 750 mg of **7f** in 200 ml of water was irradiated for 4 hr. Usual work-up did not yield any neutral product.

Irradiation of 10.—The starting material was a mixture of cis and trans isomers with nmr (D_2O) signals at 7.20 (s, 5 H), 3.38 and 3.34 (each a s, 1 H), 2.78 and 2.75 (each a s, 2 H), and 1.20 and 1.12 (each a s, 3 H). A solution of 750 mg of **10** in 150 ml of water was irradiated for 4 hr. Usual work-up did not provide any neutral product. The starting material was recovered quantitatively after the evaporation of the aqueous layer.

Irradiation of 7g.—The starting material had nmr (DMSO-d_6) signals at 7.20 (s, 5 H), 3.18 (d, J = 6 Hz, 1 H), and 2.75 (d, J = 6 Hz, 1 H). A solution of 300 mg of **7g** in 150 ml of water was irradiated for 3 hr. Work-up yielded 48 mg of a mixture consisting mostly of **9g** (57%) and bibenzyl (18%) by nmr and gc–mass spectrum analysis. Evaporation of the aqueous layer left a residue which was found to be identical with **7g** by nmr in DMSO-d_6.

Irradiation of 7h.—The starting material had nmr (D_2O) signals at 7.30 (b, 5 H), 3.40 (q, J = 6 Hz, 1 H), and 0.94 (d, J = 6 Hz, 3 H). A solution of 590 mg of **7h** in 150 ml of water was irradiated for 2.5 hr. Usual work-up yielded 65 mg of a mixture of phenylacetone (70%) and bibenzyl (13%), characterized by gc–mass spectrum and nmr.

Irradiation of 7h in D_2O.—A solution of 100 mg of **7h** in 30 ml of D_2O was irradiated for 3.5 hr. Usual work-up yielded 8 mg of residue, which showed nmr (CCl_4) signals at 3.52 (b) and 2.00 (s) in addition to phenyl protons; major peaks at *m/e* 136, 135, 94, 93, 92, and 43. A sample of $C_6H_5CD_2COCH_3$ was prepared by refluxing 100 mg of **8c** in 10 ml of D_2O and a drop of concentrated HCl for 3 hr. Usual work-up offered a product showing nmr (CCl_4) signals at 7.20 and 2.00; major peaks at *m/e* 138, 137, 136, 93, and 44.

Irradiation of 7i.—The starting material had nmr (D_2O) signals at 7.40 (b, 5 H), 1.48 (s, 3 H), and 1.10 (s, 3 H). A solution of 400 mg of **7i** in 150 ml of water was irradiated for 3 hr. Ether extraction yielded 40 mg of neutral product which was identified as **9i** by gc–mass spectrum and direct comparison with an authentic sample.

Registry No.—**3,** 25957-39-5; **4,** 122-78-1; **5,** 96-09-3; **6,** 114-76-1; **7a,** 25957-43-1; **7b,** 25957-44-2; **7c,** 5449-12-7; **7d,** 25957-46-4; **7e,** 25957-47-5; **7f,** 25957-48-6; **7g,** 24568-17-0; **7h,** 24568-16-9; **7i,** 24568-18-1; **10,** 25966-54-5.

Acknowledgments.—We thank the National Science Foundation for financial support of this research, directly as well as indirectly through the award of a departmental development grant. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. S. P. S. thanks the University of Kurukshetra (India) for a leave of absence.

The Total Synthesis of (±)-Dasycarpidone, (±)-Epidasycarpidone, and (±)-Epiuleine[1,2]

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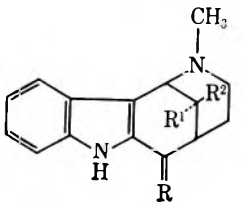
Received May 5, 1970

The syntheses of the indole alkaloids dasycarpidone, epidasycarpidone, and epiuleine in racemic form are described. The important intermediate in the synthetic scheme is *N*-methyl-3-ethyl-4-carbomethoxy-2-piperidone which is prepared by decarbomethoxylating *N*-methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone obtained from the condensation of dimethyl malonate with *N*-methyl-*N*-(2-chloroethyl)-α-bromobutyramide. Vilsmier condensation of *N*-methyl-3-ethyl-4-carbomethoxy-2-piperidone with indole followed by sodium borohydrate reduction afforded 3-[2-(*N*-methyl-3-ethyl-4-carbomethoxypiperidyl)]indole which was saponfied and cyclized with polyphosphoric acid to give (±)-dasycarpidone and (±)-epidasycarpidone. Racemic epiuleine was obtained from (±)-epidasycarpidone by treatment with methyl lithium followed by dehydration on alumina.

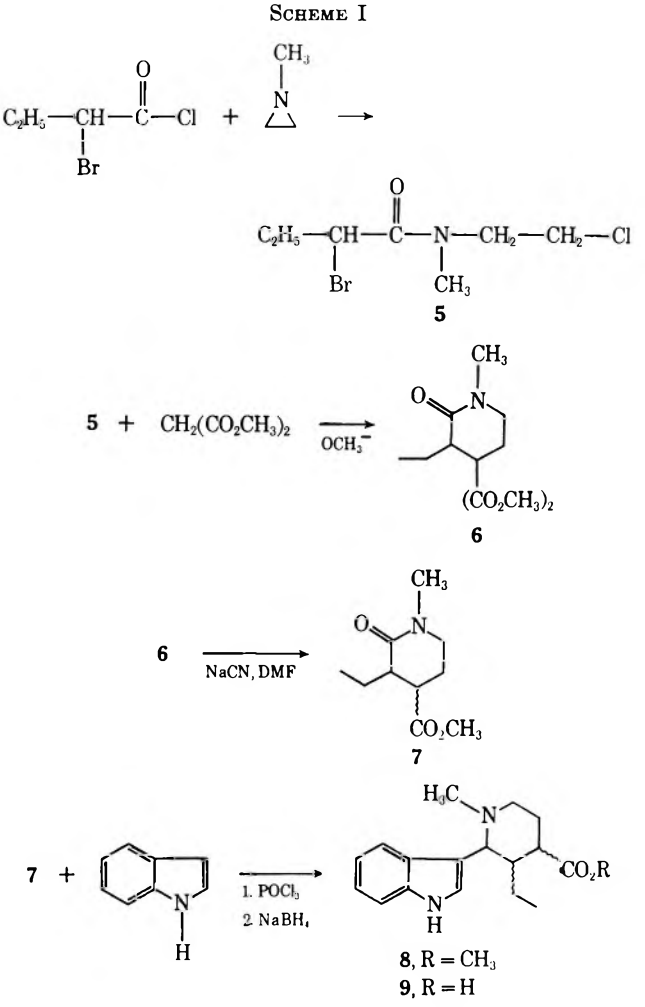
Of the large number of indole alkaloids which have been found in nature only a few lack a tryptamine moiety as part of their structures. Four closely related members of this group are uleine,[4] epiuleine,[5] dasycarpidone,[6] and epidasycarpidone.[5] We wish to report the total synthesis of the latter three of these compounds in racemic form and, since dasycarpidone has been converted to uleine, this work constitutes a formal total synthesis of the fourth member as well. The total synthesis of this group has also been achieved by a quite different route.[7]



	R	R¹	R²
Uleine (1)	CH_2	C_2H_5	H
Epiuleine (2)	CH_2	H	C_2H_5
Dasycarpidone (3)	O	C_2H_5	H
Epidasycarpidone (4)	O	H	C_2H_5

Our approach takes advantage of the ease of electrophilic substitution at both the α and β positions of the indole ring. Thus the synthetic scheme consists of simply attaching an appropriately substituted piperdine derivative at the α and β positions of indole itself. The key steps leading to (±)-dasycarpidone and (±)-epidasycarpidone are outlined in Scheme I. *N*-methylaziridine reacts smoothly in cold benzene solution with α-bromobutyrl chloride to afford *N*-(2-chloroethyl)-*N*-methyl-α-bromobutyramide (**5**) which was used directly in the next step. The amide **5** was condensed with dimethyl malonate under conditions similar to those used for the preparation of ethyl 1,1-cyclobutanedicarboxylate.[8] The expected product, *N*-methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone (**6**), was obtained in 65% yield based on *N*-methylaziridine. All of the spectral properties of **6** (Experimental Section) are in accord with the piperidone structure. This efficient synthesis of the required piperidine derivatives provides a new and perhaps generally useful approach to 1,3,4-trisubstituted 2-piperidones.[9]

Scheme I



Our hope was that the piperidone diester **6** could be combined with indole in a Vilsmier condensation. A

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(2) A portion of this work was published in preliminary form: L. J. Dolby and H. Biere, *J. Amer. Chem. Soc.*, **90**, 2699 (1968).

(3) Alfred P. Sloan Fellow, 1965–1967.

(4) G. Buchi and E. W. Warnhoff, *ibid.*, **81**, 4433 (1959).

(5) A. J. Gaskell and J. A. Joule, *Chem. Ind. (London)*, 1089 (1967). See also M. Shamma, J. A. Weiss, and R. J. Shine, *Tetrahedron Lett.*, 2489 (1967).

(6) J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, **21**, 1717 (1955).

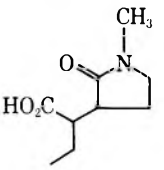
(7) A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc. C*, 2738 (1969).

(8) G. B. Heisig and F. H. Stodola, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 213.

(9) Some preliminary experiments indicated that condensation of α-bromobutanoyl chloride with aziridine did yield the dihaloamide. However, the desired alkylation of malonic ester was prevented by oxazoline formation.

previous study by Szmuszkovicz and coworkers illustrated the synthetic utility of the condensation of lactams and indole by means of phosphorus oxychloride.[10] However, the diester **6** proved to be very unreactive and we were not able to obtain useful material from attempted condensations with indole. In order to increase the reactivity of the amide grouping, the piperidone diester was decarbomethoxylated in 70% yields by treatment with sodium cyanide in hot *N*,*N*-dimethylformamide (DMF), a modification of the procedure reported by Krapcho, Glynn, and Grenon.[11]

More usual hydrolysis and decarboxylation procedures gave material which showed complex carbonyl absorption in its infrared spectrum. In particular absorption at 1680 cm^{-1} was ascribed to the presence of pyrrolidones which is not unexpected since hydrolysis of the piperidone ring followed by cyclization involving the C-4 carboxyl group would give a mixture of stereoisomers of the pyrrolidonecarboxylic acid **10**.

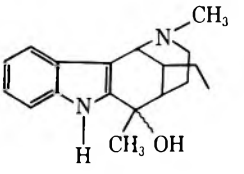


10

The *N*-methyl-3-ethyl-4-carbomethoxy-2-piperidone obtained from the sodium cyanide treatment of **6** was clearly a mixture of diastereomers as indicated by its nmr spectrum. The ester mixture was used directly in the Vilsmier condensation with indole since the remaining stages of the synthesis allow ample opportunity for epimerization. The product from the Vilsmier condensation was not isolated. The reaction mixture was diluted with ammonia and treated with sodium borohydride to give in about 65% yield a mixture of stereoisomers of ester **8**. This mixture was suitable for the next steps in the conversion to dasycarpidone and epidasycarpidone. One diastereomer was obtained in pure form by chromatography over alumina, but the stereochemistry of this material was not established.

Preliminary attempts to effect the final ring closure using ester **8** were quite discouraging. Reasonable mechanisms can be written for base induced cyclization as well as acid-catalyzed cyclization. However, treatment of the ester **8** with sodium hydride, methylmagnesium iodide, or polyphosphoric acid gave no materials showing 2-acylindole absorption in the ultraviolet region. Accordingly, the ester was saponified and it was quickly found that polyphosphoric acid cyclization gave a mixture of 2-acylindoles. The best cyclization conditions we found gave a 2-acylindole mixture in 65% yield and pure (±)-epidasycarpidone could be as obtained in 54% yield. The (±)-epidasycarpidone was identified from its spectral properties and tlc comparison with a sample of (±)-epidasycarpidone kindly provided by Professor J. A. Joule. (±)-Dasycarpidone was also present in the products from some of the cyclization reactions. The dasycarpidone was extremely difficult to separate from some of the by-products from the cyclization. In one cyclization experiment using carefully recrystallized amino acid 9, (±)-epidasycarpidone was isolated in 47% yield by direct crystallization and dasycarpidone could not be detected by tlc. In a similar experiment using crude amino acid, pure (±)-dasycarpidone was isolated in 0.7% yield by repeated preparative tlc. These results suggest that the purified amino acid has the trans–cis stereochemistry which leads directly to epidasycarpidone and dasycarpidone is formed from all cis isomer which is present in relatively small amounts in the crude acids prepared from the ester mixture **8**. However, it is not impossible that the amino acid **8** is epimerized in polyphosphoric acid solution and prior to cyclization Moreover, a plausible mechanism can be written for the interconversion of dasycarpidone and epidasycarpidone in acid solution although Joule and his coworkers found no evidence of this interconversion in hot acetic acid. In any event, all samples of the amino acid **8** gave predominantly (±)-epidasycarpidone which could easily be isolated in 40% yields and improved by chromatographic separation of the mother liquors.

The remaining synthetic problem was the conversion of the carbonyl group to an *exo*-methylene. Preliminary studies with 1-ketotetrahydrocarbazole indicated that the Wittig reaction would not be useful for this transformation although Joule and coworkers successfully converted dasycarpidone into uleine in 13% yield by this method. Moreover, we were unable to effect the addition of methylmagnesium iodide to the carbonyl group of 1-ketotetrahydrocarbazole but methyllithium reacted quite normally. Accordingly, (±)-epidasycarpidone was treated with methyllithium to give the carbinol **11** in excellent yields.



11

The nicely crystalline carbinol appeared to be a single diastereomer, but the stereochemistry was not determined. The carbinol could be dehydrated in poor yield to (±)-epiuleine by exposure to 85% phosphoric acid, but the conversion was quite efficient using alumina as the dehydrating agent. A very simple procedure converted the carbinol to (±)-epiuleine in 77% yield. The (±)-epiuleine thus obtained was identical with the (±)-epiuleine prepared by Joule and his coworkers.

Experimental Section[12]

***N*-Methyl-*N*-(2-chloroethyl)-α-bromobutyramide (5).**—α-Bromobutyryl chloride (185 g, 1 mol), prepared as previously

(10) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DaVanzano, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964).

(11) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).

(12) Melting points and boiling points are uncorrected. Ultraviolet spectra were measured on ethanol solutions using a Cary Model 15 spectrophotometer and infrared spectra were determined with a Beckman IR-5A infrared spectrophotometer. A Varian Associates A-60 instrument was used for nmr spectra. Chemical shifts are reported as δ values with tetramethylsilane as internal standard. Mass spectra were measured with a CEC 101 mass spectrometer. Combustion analyses were performed by Berkeley Analytical Laboratories, Berkeley, Calif.

described,[13] and freshly distilled *N*-methylaziridine (57 g, 1 mol) dissolved in 50 ml of dry benzene were added concurrently from two dropping funnels to 300 ml of dry benzene cooled to the freezing point with vigorous stirring. The rate of addition was adjusted so the temperature did not rise above 10°. The benzene solution was filtered to remove a small amount of polymer and used directly in the next step: nmr (benzene) 2.74 (singlet, three protons, *N*-CH_3), 3.44 ppm (broad singlet, four protons, *N*-CH_2CH_2Cl).

***N*-Methyl-3-ethyl-4,4-dicarbomethoxy-2-piperidone (6).**—The benzene solution of *N*-methyl-*N*-(2-chloroethyl)-α-bromobutyramide obtained above and 500 ml of 2 *N* sodium methoxide were added concurrently to a stirred and refluxing solution of sodium dimethyl malonate prepared from 500 ml of 2 *N* sodium methoxide and 132 g (1 mol) of dimethyl malonate. After completion of the addition (*ca.* 2 hr) the mixture was heated under reflux for 75 min. The cooled mixture was neutralized with acetic acid, filtered, and concentrated under reduced pressure. The residue was taken up in chloroform, filtered, and washed with water. Distillation under reduced pressure afforded 170 g (*ca.* 65%) of material, bp 120–160° (1.0 mm), collected in several fractions. The material appeared to be nearly pure 6 and the higher boiling fractions crystallized on standing. Tlc on silica gel G (according to Stahl) with ethyl acetate indicated diester (R_f 0.3) and monoesters (R_f 0.6). In a similar experiment on 0.75 mol scale the crystalline diester (mp 78–79° from ether–*n*-hexane) was isolated in 51% yield. The infrared spectrum showed $\nu_{max}^{CHCl_3}$ 1730 and 1640 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.60; H, 7.52; N, 5.59.

***N*-Methyl-3-ethyl-4-carbomethoxy-2-piperidone (7).**—To a solution of sodium cyanide (6.5 g, 0.13 mol) in DMF (100 ml) was added 23 g (0.09 mol) of 6. The solution was heated under reflux and gas evolution was monitored with a gas burette. In 10 min 250 ml of gas was evolved (calculated for 1 equiv of carbon dioxide 2 l.) and gas evolution stopped. A white precipitate formed during this time. The mixture was heated at 150° for an additional 2 hr. The solution was filtered and concentrated under reduced pressure. The residue was taken up in chloroform and washed with water. The crude product was distilled under reduced pressure to yield 12.4 g (70%) of 7 as a mixture of diastereomers, bp 110–120° (0.4 mm). The infrared spectrum showed $\nu_{max}^{CHCl_3}$ 1730 and 1630 cm^{-1}; nmr ($CDCl_3$) 3.72 ppm (singlet, three protons, CO_2CH_3), 2.95 (singlet, three protons, *N*-CH_3), and *ca.* 0.9 (two overlapping triplets, three protons, CH_2CH_3).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03 Found: C, 59.71; H, 8.67; N, 6.98.

3-[2-(*N*-Methyl-3-ethyl-4-carbomethoxypiperidyl)]indole (8).—Piperidone 7 (12 g, 0.06 mol) was added to freshly distilled phosphorus oxychloride (12 g). The mixture was stirred at room temperature for 2 hr after which 7 g (0.06 mol) of indole was added. The mixture was then heated at 80° for 1 hr during which it became very viscous. After dilution with 1,2-dichloroethane heating was continued for 10 hr. Aliquots of the reaction mixture showed increasing absorption at 335 mμ which disappeared on addition of sodium borohydride. The cooled reaction mixture was diluted with methanol (50 ml) and made slightly alkaline by addition of 25% aqueous ammonia after which it was slowly added to a solution of sodium borohydride (4.0 g) in aqueous methanol. The methanol was boiled off and the resulting mixture was extracted with chloroform. The chloroform solution was extracted several times with 12% hydrochloric acid. The hydrochloric acid extracts were made strongly alkaline and extracted with chloroform to afford 11.8 g (66%) of crude 8 which was suitable for preparation of the amino acid 9. A portion of crude 8 was filtered through neutral activity II alumina and crystallized to give a pure diastereomer of 8: mp 140–141° (from benzene–hexane); nmr ($CDCl_3$) 0.64 (triplet, three protons, J = 6 Hz, CH_2CH_3), 2.01 (singlet, three protons, *N*-CH_3), and 3.72 ppm (singlet, three protons, CO_2CH_3).

Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.78; H, 8.16; N, 9.01.

Amino Acid 9.—A solution of crude 8 (11.8 g, 0.039 mol) in dioxane (50 ml) was added to 400 ml of 1.1 *N* barium hydroxide (aqueous) and the resulting mixture was refluxed under nitrogen for 6 hr after which it was filtered and neutralized while hot with 20% sulfuric acid. The barium sulfate was collected and washed with hot water. The combined aqueous solutions were lyophilized to yield 6.8 g (59%) of the amino acid mixture as a white solid. A single isomer, mp 235–238° dec, could be obtained by crystallization from ethyl acetate–methanol: nmr (pyridine-d_5–D_2O) 0.83 (triplet, three protons, J = 7 Hz, CH_2CH_3) and 2.76 ppm (singlet, three protons, *N*-CH_3).

Anal. Calcd for $C_{17}H_{22}N_2O_2.2H_2O$: C, 63.33; H, 8.13; N, 8.69. Found: C, 62.86; 63.00; H, 7.14. 7.60; N, 8.62, 8.74.

(±)-Epidasycarpidone (4).—A sample of pure recrystallized amino acid 9 (0.318 g, 0.97 mmol) was mixed with 4 g of polyphosphoric acid and slowly heated to 75° with stirring and maintained at that temperature for 1 hr. The mixture was poured into 150 g of ice–water with vigorous stirring and then basified with 25% aqueous ammonia. The basic solution was extracted with ether and the ether extracts were washed with water, dried, and concentrated to a small volume. (±)-Epidasycarpidone, mp 168–169° (0.122 g, 47%), crystallized in large cubes. The (±)-epidasycarpidone was identified by comparison of its mass spectrum with the published spectrum of dasycarpidone.[6] Epidasycarpidone and dasycarpidone are reported to show the same mass spectrum in accord with our observations.[5] Comparison of the behavior on tlc of our (±)-epidasycarpidone with a sample provided by Professor Joule confirmed the identification. The mother liquors from the isolation of (±)-epidasycarpidone contained additional epidasycarpidone and several other side products but (±)-dasycarpidone could not be detected by tlc. Using silica gel G and benzene–ethyl acetate–ethanol (2:2:1 v/v) epidasycarpidone (R_f 0.50) and dasycarpidone (R_f 0.3) are readily separated.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.99; H, 7.46; N, 10.01.

The picrate, mp 230 dec from ethyl acetate, was obtained by treatment with saturated picric acid in 95% ethanol.

Anal. Calcd for $C_{23}H_{23}N_5O_8$: C, 55.53; H, 4.66; N, 14.08. Found: C, 55.37; H, 4.52; N, 13.97.

(±)-Dasycarpidone.—A sample of crude amino acid (0.790 g, 3.3 mmol) was cyclized as described above. Preparative tlc of the entire crude product afforded 350 mg (54%) of (±)-epidasycarpidone and 100 mg of crude (±)-dasycarpidone. The crude dasycarpidone was subjected to repeated preparative tlc to give 5 mg (0.7%) of amorphous (±)-dasycarpidone (dasycarpidone has never been obtained in crystalline form) which showed the same infrared spectrum as natural dasycarpidone[14] and the same mass spectrum as observed for epidasycarpidone.

1-Methyl-3-epi-dasycarpidol.—A solution of (±)-epidasycarpidone (300 mg) in 3 ml of dry tetrahydrofuran under nitrogen was treated with 2 ml of 2 *N* methyllithium in ether. After 10 min the ultraviolet spectrum of the reaction mixture showed no 2-acylindole absorption at 314 mμ. The reaction mixture was hydrolyzed with water and extracted with ether to yield 0.310 g (97%) of carbinol 11, mp 165–167° dec from methylene chloride.

Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.80; H, 8.36; N, 9.68.

(±)-Epiuleine.—An ether solution of the carbinol obtained above (0.100 g, 0.35 mmol) in ether was added to 3.5 g of activity I neutral alumina in an erlenmeyer flask. The ether was removed with a nitrogen stream and the material was heated for 30 min at 90–95° in an oven. The material was extracted from the alumina with ether and chromatographed over activity II neutral alumina with ether–benzene to give (±)-epiuleine, 50 mg (77% based on unrecovered carbinol), and recovered carbinol (30 mg). (±)-Epiuleine shows mp 135–136° after crystallization from petroleum ether (bp 30–60°). The (±)-epiuleine thus obtained was identical by uv, ir, mass spectrum, mixture melting point, and tlc with a sample prepared by Joule and coworkers and compared with natural epiuleine.[15]

Registry No.—2, 19775-51-0; 3, 18700-27-1; 4, 18688-38-5; 4 picrate, 26146-13-4; 6, 26154-16-5; 7, 18813-70-2; 8, 18688-39-6; 9, 26154-19-8; 11, 26211-02-9.

(13) S. R. Safir, H. Dalalian, W. Fanshawe, K. Cyr, R. Lopresti, R. Williams S. Upham, L. Goldman, and S. Kushner, *J. Amer. Chem. Soc.*, **77**, 4840 (1955).

(14) We are indebted to Professor Carl Djerassi for providing us with spectra of dasycarpidone.

(15) We are grateful to Professor J. A. Joule, University of Manchester, for carrying out this comparison and for communicating his results to us before publication.

Novel Products from the Oxidation of Δ^5 Steroids with Potassium Permanganate in Pyridine[1]

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Received May 4, 1970

The oxidation of pregnenolone acetate with potassium permanganate in pyridine yields pregnane-3β,5,6-triol-7,20-dione 3-acetate (**3a**) (ketotriol) and other products. Similar oxidation of 7-ketopregnenolone acetate also gave **3a**. Similar results were obtained with cholesteryl acetate and with androst-5-ene-3β,17β-diol diacetate. The respective ketotriols were dehydrated to diosphenols **5**, and also were oxidized to give unusual seven-membered ring anhydrides **7**.

An attempt to prepare a 5,6-*cis*-diol of pregnenolone acetate (**1a**) was made by treating it with a modification of the potassium permanganate–periodic acid reagent of Lemieux and von Rudloff.[2] However, instead of the desired diol, a number of unusual and interesting oxidation products were obtained. The structures and some of their chemistry are described in this and subsequent papers.

The reaction was conducted in pyridine–water solution, but for solubility reasons, the ratio was changed from the usual 1:3 pyridine–water[2] to approximately 5:1. It is not known at present whether this change is responsible for the different results obtained. In addition to an acid fraction which has not yet been studied, a complex neutral fraction was obtained from which so far three compounds have been isolated and identified. They are 5β,6β-oxidopregnan-3β-ol-20-one 3-acetate (**2**) ("5,6-oxide") (3–14%), pregnane-3β,5,6,7-tetrol-20-one 3-acetate (5–15%), and pregnane-3β,5,6-triol-7,20-dione 3-acetate (**3a**) (7-ketotriol) (10–24%) (Chart I).

The 5,6-oxide was identical with an authentic sample prepared as reported by Akhtar and Barton,[3] and appears to be the first reported example of the formation of an oxide from an olefin with the permanganate–periodate reagent.

The structure and chemistry of the 7-ketotriol is the subject of this paper. Microanalysis indicated the presence of six oxygen atoms, and the infrared spectrum showed hydroxyl absorption and the presence of three carbonyl groups. The peak at 7.99 μ indicated that one of these was an acetate carbonyl (assigned to C-3) and a second carbonyl group was assigned to C-20. The nmr spectrum showed peaks at δ 1.98 (21-CH_3), 2.09 (3-acetate methyl), and 5.05 (at least six peaks, one proton, 3α-H on carbon carrying an acetate group) in confirmation of these assignments. There was no significant ultraviolet absorption.

It therefore appeared that there remained two hydroxyl groups and one carbonyl group to be characterized. The nmr spectrum also showed two doublets, δ 3.80 (J = 3 Hz) and 3.89 (J = 2.5 Hz) which integrated for two protons. When D_2O was added to the sample, the doublets disappeared and a one-proton singlet appeared at δ 4.09. The same behavior was observed when D_2O–pyridine or D_2O–sodium methoxide–methanol was added. These doublets have been assigned to coupling of the 6-hydrogen and the 6-hydroxyl hydrogen, and further evidence for this assignment is given below.

Acetylation of the ketotriol with acetic anhydride in pyridine introduced one more acetyl group, and the infrared spectrum of this compound **3b** showed the presence of three carbonyl groups, two acetate groups, and still showed hydroxyl absorption. Therefore, one of the hydroxyl groups must be tertiary, since it did not acetylate, and most probably is at C-5. The nmr spectrum had peaks at δ 2.02, 2.10, and 2.17 (3- and 6-acetoxy and 21-methyl groups). The two doublets in the parent compound were gone, and in addition to the broad complex absorption at δ 5.0 to 5.8 for the 3α-hydrogen, there was a single sharp one-proton peak at δ 5.17, assigned to the 6-hydrogen.

Confirmation of the structure of the ketotriol was obtained by the permanganate–periodate oxidation of 7-ketopregnenolone acetate (**4a**) which gave the ketotriol in 32% yield. None of the other oxidation products obtained from pregnenolone acetate could be isolated from this reaction mixture.

In order to gain further information about the oxidation reaction, various modifications were tried. When the oxidation was conducted under an atmosphere of nitrogen, the same products were obtained and there was no significant variation in the yields, indicating that atmospheric oxygen was not involved.

When the oxidation of pregnenolone acetate was conducted with potassium permanganate in pyridine–water, without the periodate, the ketotriol was obtained in 26% yield, and none of the other products could be isolated. When 7-ketopregnenolone acetate (**4a**) was oxidized with potassium permanganate in pyridine–water, again only the ketotriol was obtained, in 20% yield.[4]

From these results, it appears that the permanganate–periodate reagent[2] is not necessary for formation of the ketotriol and that permanganate is effecting both hydroxylation of the 5,6 double bond and allylic oxidation at the 7-carbon atom.

Studies currently in progress in this laboratory (R. Hanninen and G. Starkey) indicate that the conformation of the 5- and 6-hydroxyl groups is α.

When cholesteryl acetate was oxidized with the permanganate–periodate reagent, results similar, but not identical, with those from pregnenolone acetate were obtained. From the complex neutral fraction was isolated cholestane-3β,5,6-triol-7-one 3-acetate (**3c**) ("7-ketotriol") (8%) and cholestane-3β,5,6,7-tetrol 3-ace-

* To whom correspondence should be addressed.

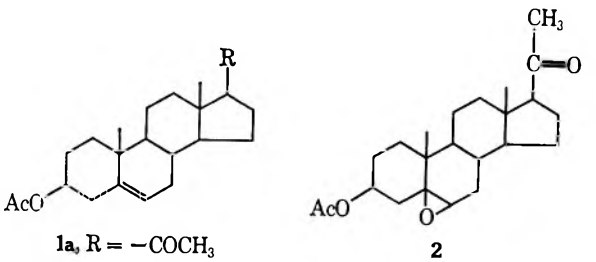
(1) Grateful acknowledgment is made to the W. S. Merrell Co. for financial support of this work.

(2) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710, 1714 (1955).

(3) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).

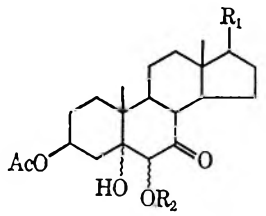
(4) The oxidation has also been carried out with periodic acid alone, and none of the ketotriol was formed. The products will be described in a subsequent paper.

CHART I

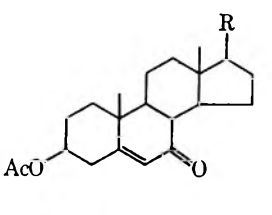


1a, R = $-COCH_3$
b, R = $-C_8H_{17}$
c, R = $-OCOCH_3$

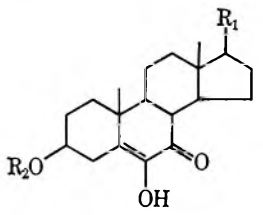
2



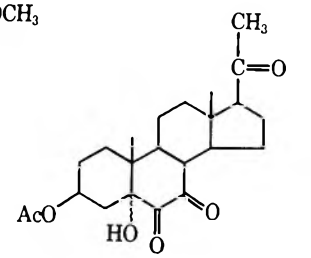
3a, $R_1 = -COCH_3$; $R_2 = -H$
b, $R_1 = R_2 = -COCH_3$
c, $R_1 = -C_8H_{16}$; $R_2 = -H$
d, $R_1 = -C_8H_{17}$; $R_2 = -COCH_3$
e, $R_1 = -OCOCH_3$; $R_2 = -H$
f, $R_1 = -OCOCH_3$; $R_2 = -COCH_3$



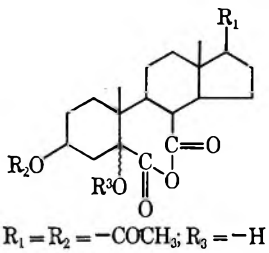
4a, R = $-COCH_3$
b, R = $-C_8H_{17}$



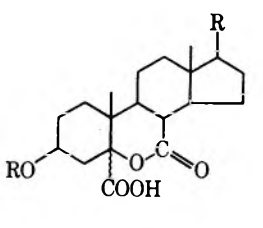
5a, $R_1 = -COCH_3$; $R_2 = -H$
b, $R_1 = -COCH_3$; $R_2 = -COCH_3$
c, $R_1 = -C_8H_{17}$; $R_2 = -H$
d, $R_1 = -C_8H_{17}$; $R_2 = -COCH_3$
e, $R_1 = -OCOCH_3$; $R_2 = -COCH_3$
f, $R_1 = OH$; $R_2 = H$



6



7a, $R_1 = R_2 = -COCH_3$; $R_3 = -H$
b, $R_1 = R_2 = R_3 = -COCH_3$
c, $R_1 = -COCH_3$; $R_2 = -H$; $R_3 = -CH_3$
d, $R_1 = -C_8H_{17}$; $R_2 = -COCH_3$; $R_3 = -H$
e, $R_1 = -C_8H_{17}$; $R_2 = R_3 = -COCH_3$
f, $R_1 = -OCOCH_3$; $R_2 = R_3 = -COCH_3$



8

tate (4%). None of the 5,6-oxide, observed with pregnenolone acetate, could be isolated.

The structure of the 7-ketotriol was established in the same manner as in the pregnane series (see Experimental Section).

Again, confirmation of the structure of the 7-ketotriol was obtained by permanganate–periodate oxidation of 7-ketocholesteryl acetate (**4b**), which gave the 7-ketotriol in 36% yield.

When cholesteryl acetate was oxidized with permanganate only in pyridine, the 7-ketotriol was obtained in 18% yield, and 7-ketocholesteryl acetate under the same conditions gave the 7-ketotriol in 23% yield.

In view of the above findings, the permanganate–periodate reagent was not used in the androstane series. Instead, androst-5-ene-3β,17β-diol diacetate (**1c**) was treated with potassium permanganate in pyridine–water and androstrane-3β,5,6,17β-tetrol-7-one 3,17-diacetate (**3e**) was isolated from the neutral fraction in 23% yield.

Reactions of the 7-Keto Compounds.—Hydrolysis of pregnane-3β,5,6-triol-7,20-dione 3-acetate (**3a**) with potassium hydroxide in aqueous methanol was carried out with the intention of removing the 3-acetate group. However, elemental analysis of the product indicated that dehydration had also occurred. The infrared spectrum was characteristic of a diosphenol, as was the ultraviolet spectrum, with a peak at 274.2 mμ (ϵ 16,700).[5,6] The product, obtained in 64% yield, was therefore assigned the structure pregn-5-ene-3β,6-diol-7,20-dione (**5a**) and must have arisen by β elimination of the 5-hydroxyl group, which is β to the 7-carbonyl group. The diosphenol gave a positive ferric chloride test and application of Woodward's rules[7] to the ultraviolet spectrum gave a calculated value of 279 mμ, compared to the observed value of 274.2 mμ.

The nmr spectrum showed a broad poorly defined multiplet centered at approximately δ 3.34 which was assigned to the 3α-hydrogen and the allylic 4-hydrogens, and a one-proton singlet at δ 6.13 which was assigned to the hydrogen of the 6-hydroxyl group, since it disappeared in the presence of deuterium oxide (see below).

When the 7-ketotriol was treated with thionyl chloride in pyridine a product was obtained which differed from the starting material by one less molecule of water and which still contained the acetate group. The infrared and ultraviolet (maximum at 274.7 mμ, ϵ 9920) spectra and a positive ferric chloride test again indicated a disophenol,[5,6] to which the structure pregn-5-ene-3β-6-diol-7,20-dione 3-acetate (**5b**) was assigned. When the diosphenol acetate was hydrolyzed with potassium carbonate in aqueous ethanol a disophenol was obtained which was identical with the one described above.

The same reactions were carried out with the 7-ketotriol in the cholestane series and the same results were obtained. Basic hydrolysis gave cholest-5-ene-3β,6-diol-7-one (**5c**) in 32% yield and the infrared, ultraviolet, and nmr spectra showed the same characteristic features. Thionyl chloride in pyridine again gave the 3-acetate (**5d**) of the diosphenol, identical with the one reported in the literature.[8] This identity thus provides good evidence for the structures of the diosphenols in the pregnane and androstane series, and provides additional evidence for the structure of the 7-ketotriol, since it is difficult to visualize any other structures which would give the diosphenol and also be in accord with the other evidence. The nmr spectrum of the acetylated diosphenol showed two doublets centered at δ 3.33 assigned to the 4-hydrogens, a single proton as a broad

(5) H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).
(6) H. R. Nace and D. H. Nelander, *ibid.*, **29**, 1677 (1964).
(7) R. B. Woodward, *J. Amer. Chem. Soc.*, **64**, 72 (1942); see also L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.
(8) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 801 (1937).

multiplet centered at 4.78, assigned to the 3α-hydrogen, and a single-proton singlet at 6.30, assigned to the hydrogen of the 6-hydroxy group, since it disappeared in the presence of deuterium oxide. Spin decoupling experiments on this compound gave further evidence for the assignments, since irradiation in the δ 4.78 region caused marked changes in the appearance of the two doublets assigned to the C-4 hydrogens.

In the androstane series the dehydration with thionyl chloride in pyridine was carried out and the acetylated disophenol **5e** was obtained in 64% yield. It showed the same characteristics as the two described above.

In an attempt to gain additional information about the 7-ketotriol (pregnane series) it was subjected to Jones oxidation.[9] However, instead of the expected 6,7-α-diketone **6** (or its diosphenol isomer), a compound was obtained which gave a negative ferric chloride test, a weak ultraviolet spectrum, and contained one more oxygen atom. The infrared spectrum had bands at 5.52 and 5.74 μ, characteristic of a cyclic anhydride,[10] and accordingly, the compound, formed in 66% yield, has been assigned structure **7a**. In the nmr spectrum, in addition to the various methyl peaks, a sharp one-proton singlet was present at δ 4.74 which disappeared on the addition of D_2O. This peak has been assigned to the hydrogen atom on the 5-hydroxyl group.

Such an anhydride could be formed from the 6,7-diketone **6** by cleavage to the secodicarboxylic acid and subsequent formation of the anhydride. The seven-membered ring anhydride exhibited unusual stability in that it would not dissolve in sodium bicarbonate or sodium hydroxide solution, and no carbon dioxide was liberated when it was dissolved in aqueous methanol containing sodium bicarbonate. It did dissolve in ammonium hydroxide solution but apparently with decomposition since no discrete compounds could be recovered.

When the anhydride was treated with acetic anhydride and pyridine, one more acetate group was introduced, as shown by microanalysis and the nmr spectrum. Since the one-proton singlet at δ 4.74 had disappeared, the new acetate group was assigned to the 5-hydroxyl group to give **7b**. The hydroxyl absorption was no longer present in the infrared spectrum, but the two anhydride bands were still present.

When the anhydride was treated with methanol containing a small amount of concentrated hydrochloric acid, methanolysis of the tertiary 5-hydroxyl group apparently occurred, and the corresponding 5-methyl ether **7c** was obtained in 25% yield. In the process, the 3-acetate group was also hydrolyzed. The infrared spectrum showed hydroxyl absorption and in the nmr spectrum, the 3α-hydrogen was shifted upfield to δ 3.63. The methoxyl methyl group appeared at δ 3.42, and the anhydride bands were still present in the infrared spectrum.

Jones oxidation[9] of the ketotriol **3c** in the cholestane series gave similar results. The anhydride **7d**, obtained in 39% yield, showed the same type of infrared and nmr spectra and the same type of behavior on acetylation (methanolysis was not attempted). In the androstane series, Jones oxidation of the ketotriol **3e** also gave an anhydride **7f** with similar properties but only stable when the 5-hydroxyl group was acetylated.

In all three series, an isomeric lactone structure can be written instead of the anhydride. The structure, **8**, can be ruled out, however, on the basis of the infrared spectra, since it would contain a free carboxyl group which should show O–H absorption at 3.33–4.00 μ (KBr), and which should liberate carbon dioxide from sodium bicarbonate. It also seems unlikely that it would behave in the observed manner on acetylation (although rearrangement to the hydroxy anhydride is possible) and it would not show infrared absorption in the 5.5–5.7 μ region. Although the structures of the anhydrides have not been unequivocally established by relating them to known compounds they are quite reasonable on the basis of the evidence at hand.

Experimental Section[11]

Potassium Permanganate–Periodic Acid Oxidation of Pregnenolone Acetate (1a).—A solution of 6.0 g (0.18 mol) of pregnenolone acetate in 400 ml of pyridine, a suspension of 5.60 g (0.035 mol) of potassium permanganate in 80 ml of water, and a solution of 18.0 g (0.079 mol) of periodic acid in 50 ml of water were prepared. The permanganate suspension was added to the pyridine solution and any remaining permanganate was washed in with the periodic acid solution. The reaction mixture was stirred at room temperature for 43 hr and then filtered through an asbestos pad, and the pad was washed thoroughly with hot methanol. The combined filtrate and washings were cooled in an ice bath and acidified with hydrochloric acid. (In a separate experiment the filtrate and washings were treated separately and no significant difference in product ratios in the two fractions was noted.) The acid solution was decolorized with sodium bisulfite and then extracted thoroughly with ether. The extract was washed with water, 5% sodium bicarbonate solution, and water and dried ($MgSO_4$), and the ether was evaporated to give 4.17 g of solid neutral fraction. The sodium bicarbonate wash was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to give 0.403 g of a complex mixture of acids which was not investigated further.

The neutral fraction was chromatographed on a column of silica and the various fractions eluted were checked for purity and identity by tlc. The first fraction, eluted with 10:1–9:1 benzene–ether, was a mixture of unreacted pregnenolone acetate and an as yet unidentified compound.

The next fraction, eluted with 9:1–8:1 benzene–ether, was 5β,6β-oxidopregnan-3β-ol-20-one acetate (**2a**): yield 0.25 g (3.8%) (in other experiments, 3–14%); mp (after recrystallization from aqueous methanol) 136–137°; ir (KBr) 5.80, 5.90, 8.04 μ; homogeneous to tlc; mp (with an authentic sample,[3] mp 136–137.5°), 136–137°.

The next fraction, eluted with 8:1–7:1 benzene–ether, gave 0.984 g (13.4%) (in other experiments, 5–15%) of pregnane-

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

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 128.

(11) Melting points were determined with a Hershberg apparatus and Anschutz thermometers and are corrected. Analytical samples were recrystallized to constant melting point and then dried at 100° (0.3 mm) unless stated otherwise. Analyses by Dr. S. M. Nagy and Associates, Micro-Chemical Laboratories, Massachusetts Institute of Technology, Micro-Tech Laboratories Inc., Skokie, Ill., and by the Analytical Research Department, The Wm. S. Merrell Co., Cincinnati, Ohio.

Thin layer chromatography (tlc) was carried out with glass plates coated with silica gel (Brinkman silica gel G) 0.025 mm thick. The plates were eluted with various solvent systems and developed with a spray of 2,4-dinitrophenylhydrazine in phosphoric acid and ethanol, followed by heating at 80–100°.

Column chromatography was done with Baker's analyzed silica, packed in benzene, and the samples were put on the column in benzene. Anhydrous magnesium sulfate was used as a drying agent.

Infrared spectra were determined with a Perkin-Elmer Infracord or with a Perkin-Elmer Model 337 spectrophotometer. Ultraviolet spectra were determined with a Bausch and Lomb Spectronic 505. Nmr spectra were obtained with a Varian HA-60A or A-60 spectrometer, using 12–30-mg samples in 0.4 ml of deuteriochloroform with TMS as an internal standard.

The infrared and nmr spectrometers were purchased with funds granted to the chemistry department by the National Science Foundation, and grateful acknowledgment is hereby made.

3β,5,6,7-tetrol-20-one 3-acetate, which will be described in a subsequent paper.

The last fraction, eluted with 5:1 benzene–ether, gave 0.907 g (12%) (in other experiments 10–24%) of pregnane-3β,5,6-triol-7,20-dione 3-acetate (**3a**). The analytical sample was prepared by recrystallization from benzene–petroleum ether, and had mp 189–189.5°: ir (KBr) 2.85, 5.75, 5.82, 5.92, and 7.99 μ; homogeneous to tlc; nmr δ 0.61 (18-CH_3), 1.27 (19-CH_3), 1.98 (21-CH_3), 2.09 (3-acetate CH_3), 2.17 (s, 1, disappears on addition of D_2O), 2.37 (center of quartet, 17α-hydrogen), two doublets, which integrate for two protons at 3.80 (J = 3 Hz), and 3.89 (J = 2.5 Hz) (disappear on addition of D_2O or D_2O–pyridine, or D_2O–sodium methoxide–methanol, and a one-proton singlet appears at 4.09), and 5.05 (m, 1, 3α-H).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.98; H, 8.64.

Pregnane-3β,5,6-triol-7,20-dione 3,6-Diacetate (3b).—A solution of 0.406 g (0.974 mmol) of the ketotriol in 8 ml of pyridine and 8 ml of acetic anhydride was heated on a steam bath for 2 hr and then poured onto ice. The white solid was collected and weighed 0.417 g (95%), mp 267–269 dec. The analytical sample was prepared by chromatography on silica, elution with 4:1 benzene–ether and recrystallization from aqueous methanol, and had mp 271–272°: ir (KBr) 2.94, 5.68, 5.77, 5.91, 8.00, and 8.07 μ; homogeneous to tlc; nmr δ 0.65 (18-CH_3), 1.32 (19-CH_3), 2.02 (21-CH_3), 2.10 (3-acetate CH_3), 2.17 (6-acetate CH_3), 2.37 (center of quartet, 17α-H), 5.17 (s, 1, 6-H), 5.0–5.8 (m, 3α-H).

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.13; H, 8.38.

Potassium Permanganate–Periodic Acid Oxidation of 7-Ketopregnenolone Acetate (4a).—To a solution of 1.00 g (2.68 mmol) of 7-ketopregnenolone acetate in 100 ml of pyridine was added 3.00 g (13.1 mmol) of periodic acid in 15 ml of water and 0.60 g of potassium permanganate in 30 ml of water. The reaction mixture was stirred at room temperature for 48 hr and then worked up as in the previous oxidation to give 0.788 g of solid neutral material and 0.255 g of acidic material, not further investigated.

Tlc of the neutral material showed that it contained four components, with the major one having the same R_f value as the ketotriol. Chromatography on silica and elution with 5:1 benzene–ether gave small amounts of a mixture of two unidentified compounds, and finally elution with 5:1–4:1 benzene–ether gave 0.35 g (32%) of the ketotriol **3a**. Its identity with the ketotriol described above was established by melting point, mixture melting point and comparison of the infrared spectra and tlc R_f values.

Potassium Permanganate–Periodic Acid Oxidation of Pregnenolone Acetate under a Nitrogen Atmosphere.—Purified nitrogen was bubbled through a solution of 3.88 g (10.8 mmol) of pregnenolone acetate in 350 ml of pyridine for 1 hr. A suspension of 2.34 g (1.48 mmol) of potassium permanganate in 75 ml of water was added and any remaining permanganate was rinsed in with a solution of 12.74 g (5.58 mmol) of periodic acid in 50 ml of water. Nitrogen was bubbled through the solution for 30 min, the flask was stoppered, and the solution was stirred for 40.5 hr. The reaction was then worked up as above and a neutral fraction of 2.69 g and an acid fraction of 0.483 g were obtained. Chromatography of the neutral fraction as above gave starting material, 0.093 g of unidentified material, 0.244 g (6.0%) of the 5,6-oxide **2a**, 0.361 g (8.2%) of the tetrol, and 0.805 g (18.5%) of the ketotriol **3a**.

Potassium Permanganate in Pyridine Oxidation of Pregnenolone Acetate.—To a solution of 10 g (27 mmol) of pregnenolone acetate in 600 ml of pyridine was added a suspension of 10 g of potassium permanganate in 150 ml of water, and the mixture was stirred for 47 hr and then worked up as in the previous oxidations. A neutral fraction of 5.7 g and an acid fraction of 1.4 g were obtained. The neutral fraction was chromatographed on 200 g of silica and 100-ml eluates were collected. Nothing was eluted with 700 ml of benzene and 500 ml of 20:1 benzene–ether. The next 500 ml of the latter solvent gave 1.87 g of starting material. The next 200 ml, followed by 400 ml of 10:1 benzene–ether eluted nothing, and then 400 ml gave 49 mg of impure material. The next 2500 ml gave 2.85 g (26%) of the ketotriol **3a**, which had mp 185.5–187° after one recrystallization from benzene–petroleum ether.

Potassium Permanganate in Pyridine Oxidation of 7-Ketopregnenolone Acetate (4a).—To a solution of 1.13 g (3.00 mmol) of 7-ketopregnenolone acetate in 75 ml of pyridine was added a suspension of 0.515 g of potassium permanganate in 15 ml of water and the mixture was stirred for 52.5 hr and then worked up as above to give 0.61 g of neutral material and 0.11 g of acid material. Chromatography of the neutral material on silica and elution with 8:1 benzene–ether gave 0.13 g of starting material. Elution with 6:1 benzene–ether gave 0.25 g (20%) of the ketotriol **3a**.

Potassium Permanganate–Periodic Acid Oxidation of Cholesteryl Acetate (1b).—To a solution of 7.0 g (16.3 mmol) of cholesteryl acetate in 450 ml of pyridine was added a suspension of 5.6 g of potassium permanganate in 80 ml of water and a solution of 18 g of periodic acid in 40 ml of water. The reaction mixture was stirred for 39.5 hr and then worked up as for the previous oxidations to give 3.23 g of neutral material and 0.44 g of acidic material.

The neutral fraction was chromatographed on silica gel and elution with 10:1 benzene–ether gave 0.46 g of starting material, mp 111–112.5° after two recrystallizations from methanol; ir spectrum identical with that of starting material. Elution with 9:1 benzene–ether gave 0.47 g of a mixture of starting material, an unknown material, and cholestane-3β,5,6,7-tetrol 3-acetate, as determined by tlc. Further elution with the same solvent gave 0.34 g of the latter compound. Finally, elution with 8:1–6:1 benzene–ether gave 0.65 g (7.7%) of cholestane-3β,6,7-triol-7-one 3-acetate (**3c**), whose physical constants and analysis are given below.

Potassium Permanganate–Periodic Acid Oxidation of 7-Ketocholesteryl Acetate (4b).—To a solution of 6.0 g (14 mmol) of 7-ketocholesteryl acetate in 600 ml of pyridine was added a suspension of 5.6 g of potassium permanganate in 120 ml of water, followed by 18 g of periodic acid in 60 ml of water, and the mixture was stirred for 67 hr and then worked up as above to give 3.98 g of neutral material and 0.49 g of acidic material.

The neutral fraction was chromatographed on silica and elution with 9:1–7:1 benzene–ether gave 2.23 g (36%) of cholestane-3β,5,6-triol-7-one 3-acetate (**3c**), mp 181–182° after one recrystallization from methanol. Recrystallization from ether and then methanol gave an analytical sample: mp 180–181°; ir (KBr) 3.11, 3.03, 5.81, 5.83, and 8.04–8.1 μ; nmr δ 0.64 (18-CH_3), 0.79 (20-CH_3), 0.89 (25-methyls), 1.27 (3-acetate CH_3), 2.23 (s, 1, which disappears on the addition of D_2O), 3.83 (d, J = 2.4 Hz), 4.04 (d, J = 4 Hz) (the pair of doublets disappeared on the addition of D_2O and a one-proton singlet appeared at 4.08), and 5.00 (m, 3α-H).

Anal. Calcd for $C_{29}H_{48}O_5$: C, 73.06; H, 10.10. Found: C, 72.40; H, 10.33.

Cholestane-3β,5,6-triol-7-one 3,6-Diacetate (3d).—A solution of 0.21 g (0.44 mmol) of the ketotriol **3c** in 4 ml of anhydrous pyridine and 4 ml of acetic anhydride was heated on a steam bath for 2 hr and then poured on ice. The precipitate was collected to give 0.22 g (95%) of the diacetate. A sample was recrystallized from methanol for analysis to mp 221–222°: ir (KBr) 2.88, 5.78, 5.80, and 7.98 μ; homogeneous to tlc; nmr δ 0.67 (18-CH_3), 0.82 (20-CH_3), 0.92 (25-methyls), 1.32 (19-CH_3), 2.04, 2.18 (3- and 6-$OCOCH_3$), 2.35 (s, 1), 5.15 (s, 1, 6-H, and a broad multiplet, 3α-H).

Anal. Calcd for $C_{31}H_{50}O_6$: C, 71.78; H, 9.74. Found: 72.14; H, 9.77.

Potassium Permanganate in Pyridine Oxidation of Cholesteryl Acetate.—To a solution of 6.0 g (14 mmol) of cholesteryl acetate **1b** in 350 ml of pyridine was added 6.0 g of potassium permanganate in 40 ml of water, and the resulting mixture was stirred for 65.5 hr. After the usual work-up, 4.32 g of neutral material and 0.65 g of acidic material were obtained.

The neutral fraction was chromatographed on 200 g of silica and 100-ml eluates were collected. Elution with 1000 ml of benzene gave 1.04 g of starting material, mp 114–115° after recrystallization from benzene. Nothing was eluted with 700 ml of 20:1 benzene–ether. Elution with 900 ml of 15:1 benzene–ether gave 0.19 g of impure material. Elution with 700 ml of 8:1 benzene–ether gave 1.37 g (21%) of ketotriol **3c**, mp 181–182° after one recrystallization from methanol.

Potassium Permanganate in Pyridine Oxidation of 7-Ketocholesteryl Acetate.—To a solution of 6.00 g (13.6 mmol) of 7-ketocholesteryl acetate **4b** in 250 ml of pyridine was added 5.60 g of potassium permanganate in 100 ml of water and the resulting mixture was stirred for 88 hr. After the usual work-up, 2.47 g of neutral material and 0.92 g of acidic material were obtained.

The neutral material was chromatographed on silica, and elution with 9:1 benzene–ether gave small amounts of impure fractions and, finally, 1.50 g (23%) of the ketotriol **3c**, mp 180–181°.

Potassium Permanganate in Pyridine Oxidation of Androst-5-ene-3β,17β-diol 3β,17-Diacetate (1c).—To a solution of 4.10 g (10.9 mmol) of the androstene **1c** in 400 ml of pyridine was added 4.6 g of potassium permanganate in 65 ml of water and the resulting mixture was stirred for 19 hr. Work-up in the usual manner gave 2.84 g of neutral material and 0.62 g of acidic material.

The neutral fraction was chromatographed on silica and elution with 10:1 benzene–ether gave 1.25 g of starting material. As the proportion of ether was gradually increased a number of impure fractions were collected, and finally 5:1 benzene–ether gave 1.04 g (23%) of androstane-3β,5,6,17β-tetrol-7-one 3,17-diacetate (**3e**). Two recrystallizations from benzene–petroleum ether gave an analytical sample: mp 158.5–159°; ir (KBr) 2.82, 2.92, 5.73, 5.75, 5.81, 7.96, and 8.06 μ; nmr δ 0.78 (18-CH_3), 1.27 (19-CH_3), 1.98 and 1.99 (3- and 17-$OCOCH_3$), 2.35 (s, 1 disappears on the addition of D_2O), 3.78 (d, J = 3 Hz), and 4.03 (d, J = 3 Hz) (the two doublets disappear on the addition of D_2O, and a sharp s, 1, appears at 4.01, 6-**H**), and 4.83 (m, 3α- and 17α-**H**'s).

Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.40, H, 8.11.

Androstane-3β,5,6,17β-tetrol-7-one 3,6,17-Triacetate (3f).—A solution of 114 mg (0.27 mmol) of the above compound **3e** in 3 ml of pyridine and 3 ml of acetate anhydride was heated on a steam bath for 4 hr and then poured over ice. The precipitate was recrystallized from methylene chloride–petroleum ether to give an analytical sample: mp 127–128.5°; ir (KBr) 2.90, 5.73, 5.75, 7.93, and 8.12 μ.

Anal. Calcd for $C_{26}H_{36}O_8$: C, 64.87; H, 7.81. Found: C, 64.46; H, 7.85.

Pregn-5-ene-3,6-diol-7,20-dione (5a).—To a solution of 0.704 g (1.73 mmol) of the ketotriol **3a** in 55 ml of methanol was added a solution of 0.85 g of potassium hydroxide in 20 ml of water and 25 ml of methanol, and the resulting solution was allowed to stand for 18 hr. It was then poured into ice water, the resulting mixture was acidified with hydrochloric acid, sodium chloride was added, and the mixture was refrigerated for 12 hr. The resulting white solid, 0.338 g (64%) was recrystallized from methanol to give an analytical sample of the diosphenol **5a**: mp 252–255°; ir (KBr) 2.90 (broad), 5.89, 5.98, and 6.11 μ; uv max (CH_3OH) 209 mμ (ε 15,400), 224 (10,900), and 274.2 (16,700); homogeneous to tlc, strong positive ferric chloride test; nmr δ 0.65 (18-CH_3), 1.12 (19-CH_3), 2.12 (21-CH_3), 2.34–2.50 (q, 17α-**H**), 3.00–3.42 (m, 3α- and 4-**H**'s), and 6.13 (s, 1, 6-O**H**).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73. Found: C, 72.89; H, 8.75.

Pregn-5-ene-3β,6-diol-7,20-dione 3-acetate (5b).—A solution of 0.405 g (1.00 mmol) of the ketotriol in 4 ml of anhydrous pyridine was cooled to 0° and 4 ml of thionyl chloride was added dropwise with swirling. The reaction mixture was kept in an ice bath for 15 min and then added slowly to an ice and water mixture. The resulting tan solid was chromatographed on a column of silica, and elution with 10:1 benzene–ether gave 0.062 g (16%) of diosphenol **5b**, which had mp 184–185.5° after recrystallization from methanol, was homogeneous to tlc, and gave a positive ferric chloride test.

An analytical sample was obtained by recrystallization from methanol: mp 193–193.5°; ir (KBr) 2.89, 5.74, 5.90, 5.95, 6.07, and 7.98 μ; uv max (CH_3OH) 206.8 mμ (ε 1350) and 274.7 (9920); nmr δ 0.67 (18-CH_3), 1.17 (19-CH_3), 2.03 and 2.11 (3-$OCOCH_3$ and 21-CH_3), 2.89–3.49 (eight peaks, 4-H's), 5.33 (m, 3α-**H**), and 5.33 (6-O**H**).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 71.10; H, 8.30. Found: C, 70.92; H, 8.92.

A solution of 20 mg of the diosphenol **5b** and 31 mg of potassium carbonate in 5 ml of 95% ethanol and 1 ml of water was allowed to stand for 16 hr and then was acidified with concentrated hydrochloric acid. The white solid was collected and had mp 232–235°. Tlc gave the same R_f value as the disophenol **5a**. One recrystallization from methanol gave mp 245–247°, mmp (with diosphenol **5a**) 253–254°, ir spectra superimposable.

Cholest-5-ene-3β,6-diol-7-one (5c).—To a solution of 0.480 g (1.0 mmol) of the ketotriol **3c** in 90 ml of methanol was added a solution of 0.511 g of potassium hydroxide in 10 ml of methanol and 10 ml of water and the resulting solution was allowed to stand for 14 hr and then poured into 100 ml of water. The mixture was acidified with hydrochloric acid and extracted with ether, and the ether extract was washed with water, dried ($MgSO_4$), and evaporated. The residue, 0.343 g, was chromatographed on silica, and elution with 9:1 benzene–ether gave 0.142 g (32%) of the diosphenol **5c**. Recrystallization from methanol gave an analytical sample: mp 155–156°; homogeneous to tlc; ir (KBr) 2.94, 5.97, and 6.07 μ; uv max (MeOH) 213.2 mμ (ε 5920) and 273.5 (15,600) [lit.[8] mp 156–157°; uv max 274.5 mμ (ε 19,956)]; nmr δ 0.69 (18-CH_3), 0.81 (20-CH_3), 0.91 (25-CH_3's), 1.17 (19-CH_3), four d at 3.10 (J = 9.6 Hz), 3.27 (J = 2 Hz), 3.42 (J = 2 Hz), 3.50 (J = 2.5 Hz) (C-4 H's coupled to the 3α-**H**). Spin decoupling experiments with irradiation at 4.78 caused marked changes in the appearance of the doublets, with some coalescing to singlets: 4.78 (m, 3α-hydrogen) and 6.3 (s, 1, 6-O**H**, disappears on the addition of D_2O).

Androst-5-ene-3β,6,17β-triol-7-one 3,17-Diacetate (5e).—A solution of 0.153 g (0.36 mmol) of the ketotriol **3e** in 2 ml of anhydrous pyridine was cooled in an ice bath and 2 ml of thionyl chloride was added dropwise over a period of 5 min. The solution was allowed to warm to room temperature and poured onto crushed ice and the precipitate collected to give 0.128 g which was chromatographed on silica. Elution with 20:1 benzene–ether gave 93 mg (64%) of the diosphenol **5e**. An analytical sample was obtained by recrystallization from benzene–petroleum ether, and had mp 216.5–217°: uv max (MeOH) 274.5 mμ (ε 16,900); positive ferric chloride test; nmr δ 0.85 (18-CH_3), 1.22 (19-CH_3), 2.05 (six protons, 3- and 17-$OCOCH_3$), four doublets at 3.14 (J = 2 Hz), 3.22 (J = 2 Hz), 3.37 (J = 2 Hz), 3.45 (J = 2.5 Hz) (1.8 protons, 4-H's), 4.45 (m, 2, 3α- and 17α-**H**), and 6.18 (s, 1, disappears when D_2O is added, 6-O**H**).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98. Found: C, 68.56; H, 7.98.

Androst-5-ene-3β,6,17β-triol-7-one (5f).—To a solution of 177 mg (0.419 mmol) of androstane-3β,5,6,17β-tetrol-7-one 3,17-diacetate (**3e**) in 35 ml of methanol was added a solution of 758 mg of potassium hydroxide in 2 ml of water. The resulting solution was heated on a steam bath for 2 hr and then allowed to stand at room temperature for 12 hr. After acidification with concentrated hydrochloric acid the solution was extracted with ether, the extract was dried ($MgSO_4$), and the solvent was evaporated to give 92 mg of solid which gave a positive ferric chloride test. The solid was taken up in benzene and chromatographed on 20 g of silica. Nothing was eluted with eleven 50-ml fractions of benzene, six 50-ml fractions of 10:1 benzene–ether, and three 50-ml fractions of 5:1 benzene–ether. One more 50-ml fraction of the latter gave 8 mg of impure material and the next five fractions gave 88 mg (69%) of homogeneous (tlc) diosphenol **5f** (positive ferric chloride test). Recrystallization from benzene–petroleum ether gave mp 220–232°: ir (KBr) 2.91, 5.97 (sh), 6.05 (sh), and 6.06 μ; uv max (MeOH) 215 mμ (ε 7000) and 269.5 (21,600).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.21; H, 8.81. Found: C, 71.39; H, 9.44.

Jones' Oxidation of the Ketotriol 3a in the Pregnane Series.—To a solution of 302 mg (0.742 mmol) of the ketotriol in 20 ml of dry acetone was added 1.2 ml of Jones' reagent over a period of 2.5 min. The solution was stirred for 20 min, 10 ml of methanol was added, stirring was continued for 20 min, and then the solution was diluted with water and extracted thoroughly with chloroform. The extract was washed with water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 207 mg (66%) of the anhydride **7a**. The analytical sample, prepared by chromatography on silica, elution with 4:1–2:1 benzene–ether, and two recrystallizations from benzene–petroleum ether, had mp 199–200°: ir (KBr) 2.90–3.05, 5.52, 5.74, 5.84 (sh), 5.94 and 8.03 μ; a complex but weak uv spectrum; a negative ferric chloride test; nmr δ 0.69 (18-CH_3), 1.13 (19-CH_3), 2.04 (21-CH_3), 2.10 (3-$OCOCH_3$), and 4.74 (s, 1, lost on addition of D_2O, 5-O**H**, and a broad multiplet, 3α-**H**).

Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: 65.22; H, 7.68.

Acetylation of the Anhydride 7a in the Pregnane Series.—A solution of 66 mg (0.15 mmol) of the anhydride in 2 ml of dry pyridine and 2 ml of acetic anhydride was heated on a steam bath for 1.75 hr and then poured onto cracked ice. The resulting solid, 52 mg, was collected and chromatographed on 8 g of silica. Elution with 8:1 benzene–ether gave 59 mg (67%) of the acetylated anhydride **7b**. The analytical sample was obtained by recrystallization from acetone–water containing 1 drop of concentrated hydrochloric acid, or from methanol, and had mp 191–192°: ir (KBr) 5.52, 5.62, 5.75, 5.87, and 7.89–7.99 μ; nmr δ 0.72 (18-CH_3), 1.12 (19-CH_3), 2.03 (21-CH_3), 2.14 (six protons, 3- and 5-$OCOCH_3$), 5.16 (m, 1, 3α-**H**).

Anal. Calcd for $C_{25}H_{34}O_8$: C, 64.95; H, 7.41. Found: 65.51; H, 7.50.

Acid Hydrolysis of the Anhydride 7a in the Pregnane Series.—A solution of 190 mg (0.45 mmol) of the anhydride **7a** in 40 ml of methanol containing 25 drops of concentrated hydrochloric acid was boiled under reflux for 1 hr, allowed to cool, and poured into 200 ml of water. The resulting solution was saturated with salt, and the white precipitate which formed was collected and recrystallized from methanol to give 42 mg, (25%) of **7c**: mp 180–182°; ir (KBr) 2.80, 2.90, 5.54, 5.84, and 5.90 μ; nmr δ 0.69 (18-CH_3), 1.12 (19-CH_3), 2.12 (21-CH_3), 3.42 (s, 3, 5-OCH_3), and 3.63 (m, 3α-H).

Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.54; H, 8.31.

Jones Oxidation of the Ketotriol 3c in the Cholestane Series.—To a solution of 408 mg (0.855 mmol) of the ketotriol in 35 ml of dry acetone was added dropwise with stirring 1.2 ml of Jones' reagent. The reaction mixture was stirred for 8 min and then 50 ml of methanol was added and the reaction mixture was worked up as above to give 315 mg of an oily solid. The solid was chromatographed on 30 g of silica and elution with 10:1 benzene–ether gave 160 mg (39%) of anhydride **7d**: mp (after recrystallization from benzene–petroleum ether) 185.5–187°; ir (KBr) 3.01–3.03, 5.54, 5.62, 5.73, 5.87, and 8.11–8.18 μ; nmr δ 0.73 (18-CH_3), 1.12 (19-CH_3), 2.04 (3β-$OCOCH_3$), and 3.89 (5-OH, disappears on the addition of D_2O).

Anal. Calcd for $C_{29}H_{46}O_6$: C, 70.82; H, 9.45. Found: C, 70.58; H, 9.23.

Acetylation of the Anhydride 7d in the Cholestane Series.—A solution of 58 mg (0.012 mmol) of **7d** in 2 ml of acetic anhydride and 2 ml of pyridine was heated on a steam bath for 3.5 hr and poured onto ice. The resulting precipitate was collected and chromatographed on silica. Elution with benzene gave 41 mg of **7e** which was recrystallized from aqueous methanol and then had mp 147–148°: ir (KBr) 5.52, 5.63, 5.71, 8.04, and 8.07 μ; nmr δ 0.74 (18-CH_3), 1.12 (19-CH_3), 2.05 and 2.12 (3- and 5-$OCOCH_3$'s), and 5.00 (m, 1, 3α-H).

Anal. Calcd for $C_{31}H_{48}O_7$: C, 69.90; H, 9.08. Found: C, 70.26; H, 9.14.

Jones Oxidation of the Ketotriol 3e in the Androstane Series.—To a solution of 243 mg (0.575 mmol) of the ketotriol in 25 ml of dry acetone was added dropwise with stirring over a period of 5 min 1 ml of Jones reagent. After an additional 15 min of stirring 10 ml of methanol was added and the solution was allowed to stand for 2 hr more and worked up as above to give 232 mg of oily solid. Earlier experiments indicated that partial deacetylation had occurred, so the material was dissolved in 5 ml of pyridine and 5 ml of acetic anhydride and heated on a steam bath for 14.5 hr. The solution was then poured into water and the resulting solid was collected to give 144 mg, mp 209–210.5°, homogeneous to tlc. The solid was chromatographed on 20 g of silica. Nothing was eluted with twelve 50-ml fractions of benzene and two 50-ml fractions of 20:1 benzene–ether. Elution with four more fractions of the latter solvent gave 107 mg which was recrystallized from methanol to give 61 mg (22%) of **7f**: mp 215–215.5°; ir (KBr) 5.53, 5.62, 5.75, 7.95, and 8.03 μ; nmr δ 0.85 (18-CH_3), 1.13 (19-CH_3), 2.03 (nine protons, 3-, 5-, and 17-$OCOCH_3$'s), 4.48 (t, 1 17α-H), and 5.08 (m, 3α-H).

Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.77; H, 7.18. Found: C, 63.22; H, 7.18.

Registry No.—Potassium permanganate, 7722-64-7; **3a**, 26145-85-7; **3b**, 26145-86-8; **3c**, 26145-87-9; **3d**, 26145-88-0; **3e**, 26145-89-1; **3f**, 26145-90-4; **5a**, 26145-91-5; **5b**, 26210-96-8; **5c**, 26145-92-6; **5e**, 26145-93-7; **5f**, 26210-97-9; **7a**, 26145-94-8; **7b**, 26145-95-9; **7c**, 26145-96-0; **7d**, 26145-97-1; **7e**, 26145-98-2; **7f**, 26145-99-3.

Synthesis and Photocycloadditions of Compounds Related to 3-Carboxycyclohexenone[1]

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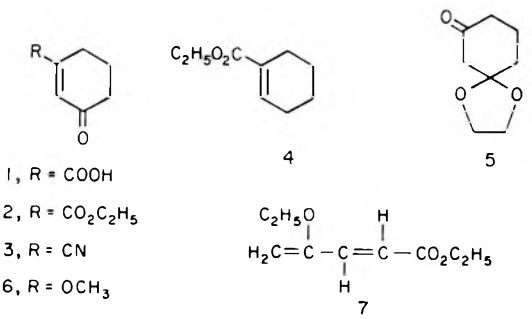
Irradiation of **1**, **2**, and **3** in the presence of ethylene, acetylene, and 2-butyne leads to formation of cycloaddition products **22–26**. Bromination–dehydrobromination of **23** yields the cyclooctadienone **27**. The 3-carbethoxycyclohexenones **16** and **17** are prepared from the Diels–Alder adduct **13** of maleic anhydride with the new diene **7**. Reaction of 3-methoxycyclohexenone (**6**) with diethylaluminum cyanide gives the corresponding nitrile **3** in a single step.

We have explored the chemistry of derivatives of 3-carboxycyclohex-2-enone (**1**) as synthetic intermediates and as models for more highly substituted compounds. Some of our observations appear to be of general interest, and we record these below. They include the smooth photochemical cycloaddition of ethylene, acetylene, and 2-butyne to three of the simplest examples of this system, **1**, **2**, and **3**; a one-step preparation of nitrile **3** which may be broadly applicable; and a new route to ring-substituted derivatives of **1** employing the Diels–Alder reaction. Previous preparations of simple derivatives of **1** have involved either chromic acid oxidation of the unsaturated ester **4** to give **2**,[3] or addition of hydrogen cyanide to the ketal (**5**) of dihydroresorcinol, followed by hydrolysis and dehydration to **3**.[4] The exact conditions in the former reaction are critical and the method is inherently limited in applicability. The cyanide addition gives only moderate overall yields but presumably could be applied to substituted cyclohexane-1,3-diones. In our hands the published procedures for both these reactions were not wholly satisfactory, and in the Experimental Section we report details of improved conditions.



(1) A portion of this work has been published in preliminary form: W. C. Agosta and W. W. Lowrance, Jr., *Tetrahedron Lett.*, 3055 (1969).

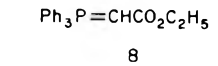
(2) Fellow of the Alfred P. Sloan Foundation. Author to whom correspondence should be addressed.

(3) M. Mousseron, R. Jacquier, A. Fontaine, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1246 (1954).

(4) M. W. Cronyn and J. E. Goodrich, *J. Amer. Chem. Soc.*, **74**, 3331 (1952).

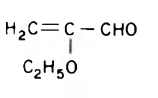
We have found a simple alternative preparation of **3** from the readily available enol ether **6**.[5] This compound reacts with diethylaluminum cyanide[6] in benzene at room temperature to yield **3** directly in a Michael-type addition–elimination reaction. Hydrolysis of **3**, protected as the ethylene ketal, or of **2** gives the previously unknown parent acid **1**.

As an approach to ring-substituted derivatives of **1**, we have prepared diene **7** and investigated its Diels–Alder addition to suitable dienophiles. Wittig reaction of carbethoxymethylenetriphenylphosphorane (**8**) with α-ethoxyacrolein (**9**)[7] gives exclusively the trans isomer of **7**, as expected.[8] The nuclear magnetic resonance (nmr) spectrum of the reaction product showed that a single isomer is formed, and a vicinal coupling constant of 15 Hz indicated[9] this to be the trans compound. Derivatization of **7** gave the known[10] 2,4-dinitrophenylhydrazone of ethyl β-acetoacrylate. With the pyrrolidine enamine of cyclopentanone, **7** formed an adduct which on treatment with acid underwent loss of pyrrolidine and oxidative aromatization to the indan **11**.[11]



$Ph_3P{=}CHCO_2C_2H_5$

8



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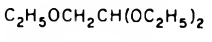
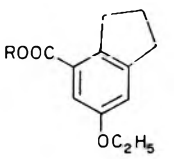


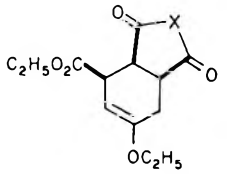
$C_2H_5OCH_2CH(OC_2H_5)_2$

10



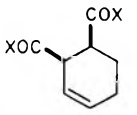
11, R = C_2H_5

12, R = H



13, X = O

14, X = N–Ph



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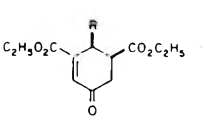
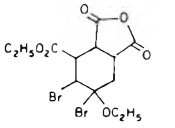
The conditions used lead to ester hydrolysis, and the product was isolated as the parent acid **12**. Reaction of diene **7** with the active dienophiles maleic anhydride and N-phenylmaleimide at 110° yielded the nicely crystalline cyclohexenes **13** and **14**. The related condensation of vinylacrylic acid with acrylic acid and that of vinylacrylyl chloride with acrylyl chloride have been examined[12] with care, and it is known that the cis adducts **15** are preferentially formed. Similarly, reaction of vinylacrylic acid or ester with quinone leads only to cis,cis addition.[13] These experimental observations are completely in accord with theoretical prediction,[14] and we assume then that the single isomers (**13** and **14**) obtained from **7** in greater than 60% yield have the cis,cis stereochemistry indicated.

The maleic anhydride adduct **13** was employed for further transformation and could be converted into triester **16** and diester **17**, examples of ring-substituted 3-carbethoxycyclohexenones. Compound **13** absorbed 1 equiv of bromine quite readily; the crude product (**18**) was treated first with hot ethanol containing hydrogen chloride and then briefly with aqueous sulfuric acid at room temperature. Exposure to acidic alcohol presumably serves three functions, esterification of the succinic anhydride, conversion of the α-bromo ether of **18** into a ketal, and dehydrobromination of the intermediate β-bromo ester. Final treatment with mild aqueous acid allows hydrolysis of the ketal and formation of the isolated cyclohexenone **16**. Although there is opportunity for epimerization to the trans isomer in this sequence, this apparently does not occur. In the nmr spectrum of **16** at 220 MHz the geminal protons adjacent to the ketone carbonyl group are separated cleanly from all other signals and are seen as the AB portion of a typical ABX system with $J_{AB} = 17$, $J_{AX} = 5.0$, and $J_{BX} = 3.5$ Hz. Examination of molecular models of **16** and its trans diastereomer, and application of the Karplus relation[15] show that the observed coupling constants are reasonable only for the cis isomer shown. An alternative preparation of **16** was possible through keto-triester **19**, formed on esterification[16] of **13** with ethanol



16, R = $CO_2C_2H_5$

17, R = H



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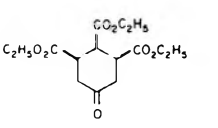

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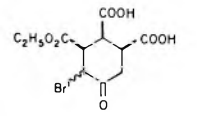

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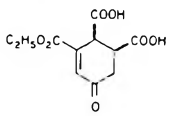

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containing *p*-toluenesulfonic acid and subsequent mild hydrolysis of the intermediate ketal. Bromination of **19** in acetic acid, followed by dehydrobromination using lithium bromide and lithium carbonate in dimethylformamide,[17] gave **16**, identical with the material described above. Successful reaction conditions were considerably less critical in this case than in direct bromination of **13**; the sequence is less interesting, however, since its application to a ketone lacking the symmetry

(5) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).

(6) W. Nagata and M. Yoshioka, *Tetrahedron Lett.*, 1913 (1966).

(7) M. F. Shostakovskii and N. A. Keiko, *Dokl. Akad. Nauk SSSR*, **162**, 362 (1965). α-Ethoxyacrolein (**9**) is prepared by condensation of formaldehyde with ethoxyacetaldehyde; in the course of this work we observed that readily available ethoxyacetal (**10**) may be hydrolyzed and used *in situ* for this reaction without intermediate isolation of the unstable aldehyde. This simple modification should make **9**, which has been little studied, a much more conveniently available compound.

(8) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957); S. S. Novikov and G. A. Shvekhgelmer, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 673 (1960); V. F. Kuckerov, B. G. Kovalev, G. A. Kogan, and L. A. Yanovskaya, *Dokl. Akad. Nauk SSSR*, **138**, 1115 (1961).

(9) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, pp 301–302, and references cited therein.

(10) S.-O. Lawesson, M. Dahlén, and C. Frisell, *Acta Chem. Scand.*, **16**, 1191 (1962).

(11) For similar reactions of vinylacrylic ester with enamines, see S. Danishefsky and R. Cunningham, *J. Org. Chem.*, **30**, 3676 (1965), and G. A. Berchtolb, J. Ciabattoni, and A. A. Tunick, *ibid.*, **30**, 3679 (1965).

(12) K. Alder, M. Schumacher, and O. Wolff, *Justus Liebigs Ann. Chem.*, **564**, 79 (1949).

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(14) A. S. Onishchenko, "Diene Synthesis," Daniel Davey and Co., New York, N. Y., 1964, Chapter 1, and refrences cited therein.

(15) Reference 9, pp 281–298, and references cited therein.

(16) A. C. Cope and E. C. Herrick, *J. Amer. Chem. Soc.*, **72**, 983 (1950).

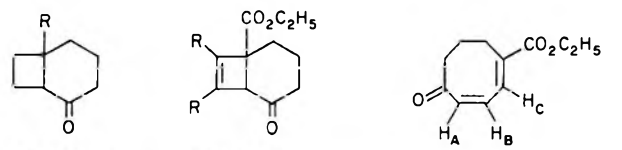
(17) R. P. Holysz, *ibid.*, **75**, 4432 (1953); R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. Fr.*, 366 (1958).

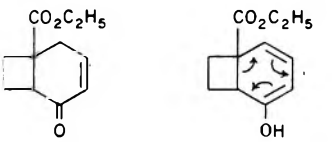
of **19** would undoubtedly lead to a mixture. The path from **13** first outlined, on the other hand, may be of some general use in preparing 3-carboxycyclohexenones.

The bromination–dehydrobromination conditions just described for **13** involved direct ethanolysis after bromination. If instead the crude bromide **18** was treated with water, a different sequence of reactions ensued. Water apparently opens the anhydride and converts the α-bromo ether to the corresponding ketone. The resulting bromoketo acid **20** was heated directly at 80° in hexamethylphosphoramide[18] and underwent dehydrobromination to give intermediate **21**, followed by thermal decarboxylation of this vinylogous β-keto acid.[19] Subsequent esterification gave the diester **17**.

We now turn attention to photochemical cycloadditions of the simple unsaturated systems **1**, **2**, and **3**. These are the first examples of addition of an alkene or alkyne to cyclohexenones having strongly electron-withdrawing groups in the β position; the reaction is clearly quite favorable in comparison with additions involving other cyclohexenones.[20-22] Ethylene, an olefin generally unreactive in cycloadditions, condenses with compounds **1**, **2**, and **3** on irradiation through Pyrex[23] in benzene solution to give the expected bicyclic products **22**, **23**, and **24**, respectively. Hydrolysis of ester **23** and nitrile **24** yielded **22**, and the structures of all three adducts are secure from spectroscopic properties. For carboxylic acid **1** and ester **2** the addition of ethylene is rapid and very clean; the yield of ester **23** is 98%. Nmr spectra indicate that **22** and **23** are unchanged by treatment with mild aqueous base or contact with alumina, and we conclude that only cis-fused bicyclic systems are isolated in these additions.[20-22] In similar fashion irradiation of **2** in the presence of 2-butyne or acetylene itself leads to the unsaturated adducts, **25** and **26**. Previous attempts[24] to form cyclobutenes by photoaddition of acetylene to activated olefins have met with quite limited success, and the 30% yield of **26** observed here is unusually high.

Reaction of **23** with bromine in chloroform–acetic acid followed by treatment[17] with lithium bromide and lithium carbonate in hot dimethylformamide gave carbethoxycyclooctadienone **27** as the only isolated product. We suggest that α-bromination followed by loss of hydrogen bromide leads to the expected unsaturated ketone **28**, which undergoes enolization, rearrangement (**29**),[25] and ketonization. The structure of **27** follows from spectroscopic measurements; ultraviolet [λ_{max} = 282 mμ (ϵ 9700)[26]] and infrared (1710, 1662 cm^{-1}) absorptions are consistent with the assignment, and the nmr spectrum is particularly informative. At 220 MHz signals for the three olefinic protons are well separated and interpretable upon inspection (H_A 5.95 ppm, d, J_{AB} = 12.5 Hz; H_B 6.50 ppm, dd, J_{AB} = 12.5, J_{BC} = 5.5 Hz; H_C 7.30 ppm, d, J_{BC} = 5.5 Hz). Using this observed J_{BC} in the modified Karplus equation appropriate[27] to such systems in medium rings, we estimate the dihedral angle between H_B and H_C to be about 45°, a value that appears reasonable in molecular models of **27**. This sequence of cycloaddition followed by bromination–dehydrobromination provides rather convenient access to this substituted cyclooctadienone.





Experimental Section

Materials and Equipment.—Irradiations were carried out at about 15° using a 450-W medium-pressure mercury arc lamp, Hanovia type L, No. 679A-36, contained in a water-cooled quartz immersion well fitted with a Pyrex filter sleeve. In reactions involving ethylene or acetylene the hydrocarbon was bubbled through the reaction mixture before and during the irradiation. Saturated solutions of ethylene and acetylene in benzene at 15° are 0.16 and 0.24 *M*, respectively.[28]

Vapor phase chromatography (vpc) was carried out using a Varian Aerograph Model 700 Autoprep equipped with a 20 ft × 0.25 in. stainless steel column packed with 30% SE-30 on Chromosorb W support. Spectra were recorded using a Perkin-Elmer 237B grating ir spectrophotometer, a Cary 14 PM uv spectrophotometer, and Varian A-60 (60 MHz) and HR-220 (220 MHz) nmr spectrometers. Measurement of pH was performed with a Radiometer TTT1 pH meter equipped with a type GK2021-B glass membrane–calomel electrode. All reactions and distillations were conducted with care to exclude air and moisture, under a blanketing stream of prepurified nitrogen.

3-Oxo-1-cyclohexene-1-carboxylic Acid Ethyl Ester (2).—In a modification of the method of Mousseron,[3] chromic anhydride (15.0 g) was added over 30 min to a mechanically stirred solution of 1-carboethoxycyclohexene (15.0 g) in 100 ml of acetic acid and 2 ml of water while the reaction temperature was maintained at 40° by external cooling. After another 60 min at 40–50°, the mixture was cooled by addition of ice, neutralized cautiously with a concentrated solution of KOH, and extracted with ether. The ether extract was washed with saturated $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Distillation provided 7.9 g (48%) of slightly yellow oil: bp 143° (20 mm); ir ($CHCl_3$) 1720, 1685, 1615 (w) cm^{-1}; uv (95% ethanol) λ_{max} 240 mμ (ϵ 12,000), 345 (28); nmr (CCl_4) δ 1.33 (t, J = 7 Hz, 3 H), 1.7–2.7 (m, 6 H), 4.24 (q, J = 7 Hz, 2 H), 6.60 (t, J = 2 Hz, 1 H).

The melting behavior and uv spectrum of the 2,4-dinitrophenylhydrazone were as reported:[3] mp 201° (ethanol); uv (95% ethanol) λ_{max} 260 mμ (ϵ 33,100).

3-Oxo-1-cyclohexene-1-carbonitrile (3). A. From the Monoethylene Ketal of Cyclohexane-1,3-dione (5).—Reaction of the

(18) H. Normant, *Bull. Soc. Chim. Fr.*, 791 (1968).

(19) P. Rabe and E. Pollock, *Ber.*, **45**, 2924 (1912); E. C. Horning, M. O. Denekas, and R. E. Field, *J. Org. Chem.*, **9**, 547 (1944).

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(22) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969). This paper contains a more complete list of references and also a brief review of the reaction.

(23) Similar conditions using unfiltered light are described in ref 21.

(24) G. Koltzenburg, P. G. Fuss, and J. Leitich, *Tetrahedron Lett.*, 3409 (1966); S. Farid, W. Kothe, and G. Pfundt, *ibid.*, 4147 (1968); I. W. J. Still, M-H. Kwan, and G. E. Palmer, *Can. J. Chem.*, **46**, 3731 (1968).

(25) Equilibration of the parent bicyclo[4.2.0]octa-2,4-diene with cycloocta-1,3,5-triene at 80–100° was described by A. C. Cope, A. C. Haven, Jr., F. L. Ramp, and E. R. Trumbull, *J. Amer. Chem. Soc.*, **74**, 4867 (1952).

(26) The parent cycloocta-2,4-dienone shows λ_{max} 278 mμ (ϵ 5770): N. Heap, G. E. Green, and G. H. Whitham, *J. Chem. Soc., C*, 160 (1969); see also J. K. Crandall and L-H. Chang, *J. Org. Chem.*, **32**, 532 (1967).

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

(28) J. Horiuti, *Sci. Papers Inst. Phys. Chem. Res. (Tokyo)*, **17**, 125 (1931).

monoethylene ketal of cyclohexane-1,3-dione[29] (20 g) with aqueous NaCN as described by Cronyn[4] gave the cyanohydrin ketal, which was extracted into ether, concentrated, and then stirred vigorously at 25° for 72 hr with 10 ml of 6.0 *M* HCl. The product was extracted with ether, washed with 5% Na_2CO_3, water, and brine, and dried over Na_2SO_4. Distillation provided 7.2 g (46%) of 3-cyanocyclohexenone: bp 80° (0.5 mm); ir (CCl_4) 2225 (w), 1700, 1605 cm^{-1}; nmr (CCl_4) δ 1.9–2.8 (m, 6 H), 6.58 (t, J = 2 Hz, 1 H).

B. From 3-Methoxycyclohexenone (6).—3-Methoxycyclohexenone[5] (vpc purified, 38 mg, 0.30 mmol) in 2 ml of benzene and 1.5 ml of toluene was added dropwise over 15 min to a magnetically stirred benzene solution of diethylaluminum cyanide[5] (CAUTION: toxic and possibly pyrophoric) (approximately 1.5 mmol) at 0°. The solution was allowed to warm to 25° over 1 hr, poured into 40 ml of 0.0125 *M* MaOH at 0°, then extracted with ether. The ether extract was washed with 5% Na_2CO_3, water, and brine and dried over Na_2SO_4. The heavy oil left after removal of solvent was chromatographed on a column of Woelm grade II neutral alumina to give 20 mg (55%) of 3-cyclocyclohexenone.

The 2,4-dinitrophenylhydrazones of the ketones made by methods A and B melted at the same temperature (204–205°, ethanol) singly and in mixture (lit.[4] 204–204.5°), and had identical ir spectra (KBr disk).

3-Oxocyclohexene-1-carboxylic Acid (1). **A. From 3-Cyanocyclohexenone** (3).—Removing water with a Dean–Stark trap from a refluxing solution of 3-cyanocyclohexenone (726 mg, 6.0 mmol) and ethylene glycol (372 mg, 6.0 mmol) in 30 ml of benzene containing a trace of *p*-toluenesulfonic acid gave the ethylene ketal.[4] The nitrile function was then hydrolyzed by heating at reflux with 3 ml of 2.5 *M* NaOH for 12 hr; the ketone was then regenerated from the ketal by stirring with 3 ml of 1.0 *M* HCl at 0° for 1 hr. The resulting keto acid was extracted into ether, washed with brine, and dried over Na_2SO_4. Crystallization from hot benzene gave 270 mg (45%) white needles: melting behavior, sinters 100–129°, melts 129°; ir ($CHCl_3$) 3500–2600, 1700, 1680, 1620 (w) cm^{-1}; nmr ($CDCl_3$) δ 1.9–2.8 (m, 6 H), 6.87 (t, J = 2 Hz, 1 H), 10.80 (s, 1 H).

Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.03; H, 5.70.

B. From 3-Carbethoxycyclohexenone (2).—3-Carbethoxycyclohexenone (60 mg, 0.39 mmol) in 2 ml of methanol was stirred with a solution of K_2CO_3 (215 mg, 1.60 mmol) in 2 ml of water for 12 hr at 25°. The mixture was acidified and extracted with ether. The ether extract was washed with brine and dried over Na_2SO_4. The 30 mg (80%) of white needles left after evaporation of solvent and recrystallization from hot benzene was identical with the carboxylic acid prepared by method A.

2-Ethoxyacrolein (9).—1,1,2-Triethoxyethane[30] (22.0 g) was stirred with 3.0 *M* HCl at 25° for 45 min, then neutralized at 0° with 6.0 *M* NaOH. This solution was added in one portion to 37% formalin (11.6 ml), diethylamine hydrochloride (14.9 g), and hydroquinone (100 mg) in a flask maintained at 60° equipped with a mechanical stirrer, condenser, and pH electrode. The apparent pH, which fluctuated over the first 10 min, was adjusted to 7.6 by addition of 6.0 *M* NaOH; the reaction was stirred for 2.5 hr at 60°. It was then cooled to 0° and extracted with pentane. The pentane extract was washed with water and brine and dried over Na_2SO_4. Evaporation of solvent through a Vigreux column and subsequent distillation provided 5.90 g (44%) of the lacrymatory 2-ethoxyacrolein:[7] bp 41° (18 mm); ir (CCl_4) 1712, 1614 cm^{-1}; nmr (CCl_4) δ 1.39 (t, J = 7 Hz, 3 H), 3.87 (q, J = 7 Hz, 2 H), 5.02 (s, 2 H), 9.16 (s, 1 H).

***trans*-4-Ethoxy-2,4-pentadienoic Acid Ethyl Ester** (7).—2-Ethoxyacrolein (9) (4.65 g) was heated at reflux with carbethoxymethylenetriphenylphosphorane (8) (16.20 g) in 35 ml of CH_2Cl_2 for 4.5 hr. The reaction was cooled, freed of solvent using a rotary evaporator, and poured into 300 ml of ligroin; after 12 hr at 0° the liquid was decanted from the triphenylphosphine oxide and concentrated. Rapid distillation from a small amount of hydroquinone gave 3.85 g (48%) of colorless sweet-smelling oil, bp 87° (5 mm), which could not survive vpc at 150°: ir ($CHCl_3$) 1700, 1640, 1590 cm^{-1}; uv (95% ethanol) λ_{max} 218 mμ (ε 8500), 270 (13,500); nmr (CCl_4) δ 1.30 (t, J = 7 Hz, 3 H), 1.38 (t, J = 7 Hz, 3 H), 3.85 (q, J = 7 Hz, 2 H), 4.16 (q, J = 7 Hz, 2 H), 4.41 (s, 2 H), 6.12 (d, J = 15 Hz, 1 H), 6.96 (d, J = 15 Hz, 1 H). A second distillation gave an analytical sample.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.46; H, 8.37.

Treatment of the enol ether with 2,4-dinitrophenylhydrazine in methanol containing a few drops of 6.0 *M* HCl produced the 2,4-dinitrophenylhydrazone of ethyl 3-acetylacrylate, mp 148° (ethanol) (lit.[10] 148°).

Anal. Calcd for $C_{13}H_{14}N_4O_6$: C, 48.45; H, 4.38; N, 17.39. Found: C, 48.36; H, 4.43; N, 17.46.

6-Ethoxy-4-indancarboxylic Acid (12).—The pyrrolidine enamine of cyclopentanone (328 mg, 2.4 mmol), prepared by the method of Stork,[31] was heated at reflux with ethyl 4-ethoxypentadienoate (7) (204 mg, 1.2 mmol) in 2 ml of benzene for 72 hr. The reaction mixture was then extracted with pentane, and the extract was washed with 5% w/v HCl, water, and brine, and dried over Na_2SO_4. In order to eliminate any remaining pyrrolidine,[11] the oil was stirred with 10 ml of 95% ethanol containing 0.05 ml of concentrated HCl at 25° for 4 hr. The product was extracted into ether, washed with brine, and dried over Na_2SO_4. Solvent was evaporated to leave 170 mg (69%) white solid which was recrystallized from aqueous methanol to give white needles: mp 121–122° (sinters 90–100°); ir ($CHCl_3$) 3400–2900, 1685, 1605 cm^{-1}; nmr ($CDCl_3$) δ 1.48 (t, J = 7 Hz, 3 H), 1.9–2.4 (broad m, 2 H), 2.98 (t, J = 8 Hz, 2 H), 3.30 (t, J = 8 Hz, 2 H), 4.1 (q, J = 7, 2 H), 7.0 (m, 1 H), 7.45 (d, J = 2.5 Hz, 1 H), 13.0 (s, 1 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.02; H, 6.87.

5-Ethoxy-4-cyclohexene-1,2,3-tricarboxylic Acid 1,2-Anhydride 3-Ethyl Ester (13).—Maleic anhydride (210 mg, 2.1 mmol) and ethyl 4-ethoxypentadienoate (7) (374 mg, 2.1 mmol) were heated at reflux for 4 hr in 7 ml of toluene containing 2,5-di-*tert*-butylhydroquinone (20 mg). The Diels–Alder product was recrystallized from hot ethyl acetate–cyclohexane to yield 340 mg (63%) of colorless square plates: mp 92° dec; ir ($CHCl_3$) 1865 (w), 1787, 1725, 1653 cm^{-1}; nmr ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 1.32 (t, J = 7 Hz, 3 H), 2.40–2.55 (m, 2 H), 2.8–3.3 (m, 1 H), 3.80 (broad s, 2 H), 3.87 (q, J = 7 Hz, 2 H), 4.25 (q, J = 7 Hz, 2 H), 4.72 (broad s, 1 H).

Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.32; H, 6.05.

***N*-Phenyl-5-ethoxy-4-cyclohexene-1,2-dicarboximide-3-carboxylic Acid Ethyl Ester** (14).—*N*-Phenylmaleimide (173 mg, 1.0 mmol) and ethyl 4-ethoxypentadienoate (7) (170 mg, 1.0 mmol) were heated at reflux for 4.5 hr in 5 ml of toluene containing 2,5-di-*tert*-butylhydroquinone (5 mg). Evaporation of solvent left gummy material which was crystallized from hot ethyl acetate–cyclohexane to 227 mg (66%) white needles: mp 94–95° dec; ir ($CHCl_3$) 1780, 1710, 1647, 1595 cm^{-1}; nmr ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 2.5–2.8 (m, 2 H), 3.2–3.7 (m, 3 H), 3.75 (q, J = 7 Hz, 2 H), 4.18 (q, J = 7 Hz, 2 H), 4.8–5.1 (m, 1 H), 7.1–7.6 (m, 5 H).

Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.45; H, 6.08; N, 3.98.

5-Oxocyclohexane-1,2,3-tricarboxylic Acid Triethyl Ester (19).—The Diels–Adler adduct **13** (500 mg) was heated at reflux for 12 hr with 2 ml of ethanol containing *p*-toluenesulfonic acid (20 mg). Toluene (0.5 ml) was then added and the ethanol–water–toluene azeotrope distilled away until the vapor temperature fell to 65°. Another 2-ml portion of ethanol was added and the esterification cycle repeated.[16] In order to hydrolyze the ketal formed under these conditions, the oil was stirred with 2.7 *M* H_2SO_4 (2 ml) in 15 ml of tetrahydrofuran at 25° for 4 hr. The ketone was extracted into ether, washed with $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Evaporation of the solvent left 580 mg (100%) of heavy oil, ir ($CHCl_3$) 1730 (broad). Short path distillation gave an analytical sample.

Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.18; H, 7.43.

5-Oxo-3-cyclohexene-1,2,3-tricarboxylic Acid Triethyl Ester (16). **A. From the Enol Ether 13.**—Bromine (0.082 ml, 1.5 mmol) was added to the enol ether (400 mg, 1.5 mmol) in 50 ml of dry ether at 25°; the solution blanched immediately. After the solvent had been evaporated using a rotary evaporator,

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(30) S. M. McElvain and C. H. Stammer, *J. Amer. Chem. Soc.*, **73**, 915 (1951).

(31) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

ethanol (40 ml) and acetyl chloride (4 ml) were added to the residue; the solution was heated at reflux for 36 hr, cooled to 25°, and stirred with 4 ml of 0.4 *M* H_2SO_4 for 20 min. The ketone was extracted into ether, washed with $NaHCO_3$, water, and brine, and dried over Na_2SO_4. The product recovered from the solvent was purified for analysis by vpc at 215° to a slightly yellow oil (40%): ir ($CHCl_3$) 1730 (broad), 1695 cm^{-1}; 220 MHz nmr (CCl_4) δ 1.15–1.50 (m, 9 H), 2.45 (dd, J = 7 Hz, J = 5.0 Hz, 1 H), 2.76 (dd, J = 17 Hz, J = 3.5 Hz, 1 H), 3.43–3.50 (broad s, 1 H), 4.05–4.40 (m, 7 H), 6.64 (s, 1 H).

Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.79; H, 6.41.

B. From the Ketone 19.—The keto triester (300 mg, 0.96 mmol) in 10 ml of acetic acid was treated with bromine (0.060 ml, 1.10 mmol) for 15 min at 25°. After neutralization with saturated $NaHCO_3$ the reaction mixture was extracted with ether. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated to give 372 mg (98%) oily bromo ketone. The crude bromo ketone was dissolved in 20 ml of dimethylformamide previously flushed with nitrogen. After addition of anhydrous LiBr (500 mg) and Li_2CO_3 (500 mg), the reaction was stirred at 120° for 1 hr.[17] The mixture was diluted with cold water and extracted repeatedly with ether. The ether extracts were washed with water and brine and dried over Na_2SO_4. The ketone was purified for analysis by vpc at 215° (55%). Its ir and 220 MHz nmr spectra as well as vpc retention time were identical with those of the ketone prepared by method A.

Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.95; H, 6.44.

5-Oxo-3-cyclohexene-1,3-dicarboxylic Acid Diethyl Ester (17).—To the enol ether **13** (400 mg, 1.50 mmol) in 20 ml of $CHCl_3$ at 0° was added bromine (0.084 ml., 1.54 mmol) in 3 ml of $CHCl_3$ over 15 min; the product was stirred with water (0.5 ml) at 25° for 4 hr. The solvents were evaporated *in vacuo* for 12 hr. The yellow glassy residue was dissolved in 2 ml of hexamethylphosphoramide and heated at 80° for 15 min. The cooled reaction was added to water and extracted with ether; the extract was washed with brine, dried over Na_2SO_4, and concentrated.

The oil dissolved in 20 ml of ethanol containing *p*-toluenesulfonic acid hydrate (50 mg) was heated for 24 hr in a Soxhlet apparatus whose extraction thimble was charged with Linde type 3A molecular sieves.[32] The solution was then concentrated, stirred for 1 hr with 0.6 *M* HCl to hydrolyze the ketal, and extracted with ether. The extracts were washed with $NaHCO_3$, water, and brine and dried over Na_2SO_4. From the concentrated product mixture the major volatile component was isolated by vpc at 220° (approximately 20%, analytically pure): ir (CCl_4) 1740, 1725, 1690 cm^{-1}; 220 MHz nmr (CCl_4) δ 1.30 (t, J = 7 Hz, 3 H), 1.37 (t, J = 7 Hz, 3 H), 2.4–2.9 (m, 5 H), 4.12 (q, J = 7 Hz, 2 H), 4.22 (q, J = 7 Hz, 2 H), 6.68 (s, 1 H).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.08; H, 6.68.

5-Oxobicyclo[4.2.0]octane-1-carboxylic Acid (22).—Irradiation of 3-carboxycyclohexenone (1) (200 mg) in 200 ml of benzene saturated with ethylene for 2 hr gave, after evaporation of benzene, a 90% yield of distillable oil: ir ($CHCl_3$) 3500–2500, 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.8–2.8 (m, 10 H), 3.0–3.3 (m, 1 H), 10.0 (broad s, 1 H). Short path distillation gave an analytical sample.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.12; H, 7.20.

There was no change in the nmr spectrum on treatment of the adduct with 5% w/v K_2CO_3.

5-Oxobicyclo[4.2.0]octane-1-carboxylic Acid Ethyl Ester (23).—A solution of 3-carbethoxycyclohexenone (2) (2.0 g) in 200 ml of benzene was saturated with ethylene and irradiated for 3.5 hr. Evaporation of the benzene left 2.3 g (98%) of the ethylene adduct which was purified for analysis by vpc at 175°: ir (CCl_4) 1726, 1712 cm^{-1}; uv (95% ethanol) λ_{max} 290 mμ (ε 7); mass spectrum parent peak (calcd, 196.10994; found, 196.10916); nmr (CCl_4) δ 1.30 (t, J = 7 Hz, 3 H), 1.6–2.6 (m, 10 H), 3.18 (broad m, 1 H), 4.15 (q, J = 7 Hz, 2 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.11; H, 8.25.

Exposure of the adduct to Woelm grade I neutral alumina for 30 min and to ethanolic sodium ethoxide at 25° for 12 hr left the nmr spectrum unaffected.

The ester (59 mg, 0.32 mmol) was saponified for 26 hr in 2 ml of refluxing methanol containing 1.0 *M* NaOH (0.65 ml, 0.65 mmol). The solution was acidified and extracted with ether; the extract was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent provided 49 mg (98%) of carboxylic acid **22** as evidenced by identity of ir and nmr spectra.

5-Oxobicyclo[4.2.0]octane-1-carbonitrile (24).—A solution of 3-cyanocyclohexenone (**3**) (200 mg) in 200 ml of benzene was saturated with ethylene and irradiated for 2.5 hr; polymer formation was evident. The crude product was distilled bulb-to-bulb at 0.2 mm, and then purified by vpc at 180° to give 149 mg (62%) analytically pure oil: ir (CCl_4) 2220, 1712 cm^{-1}; mass spectrum parent peak (calcd, 149.08406; found, 149.08420); nmr (CCl_4) δ 1.8–2.8 (m, 10 H), 3.0–3.3 (m, 1 H).

Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.44; H, 7.50; N, 9.33.

The nmr spectrum of the ketone was not altered by treatment with refluxing 5% w/v K_2CO_3 for 3 hr.

The nitrile (47 mg) was heated at reflux with 1.0 *M* NaOH (2 ml) and 0.5 ml of methanol for 36 hr. The reaction mixture was acidified and extracted with ether; the extract was washed with water and brine, and dried over Na_2SO_4. Removal of solvent left 40 mg (76%) 22 as evidenced by identity of ir and nmr spectra.

7,8-Dimethyl-5-oxobicyclo[4.2.0]oct-7-ene-1-carboxylic Acid Ethyl Ester (25).—Irradiation of a solution of 3-carbethoxycyclohexenone (**2**) (200 mg) and 2-butyne (5.0 g) in 200 ml of benzene for 2.5 hr resulted in formation of one volatile product, which was purified by vpc at 180° to give 132 mg (50%) of analytically pure adduct: ir (CCl_4) 1727, 1702 cm^{-1}; uv (95% ethanol) end absorption, shoulder 284 mμ (ε 122); nmr (CCl_4) δ 1.29 (t, J = 7 Hz, 3 H), 1.65 (s, 6 H), 1.7–2.5 (m, 6 H), 3.3 (broad s, 1 H), 4.16 (q, J = 7 Hz, 2 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.16; H, 8.13.

5-Oxobicyclo[4.2.0]oct-7-ene-1-carboxylic Acid Ethyl Ester (26).—Acetylene (Matheson) was freed of acetone by being passed through a Dry Ice–acetone cold trap, a mercury safety valve, an empty bottle, a large bottle of H_2SO_4, NaOH pellets, then another empty bottle;[33] it was then bubbled through a solution of 3-carbethoxycyclohexenone (**2**) (200 mg) in 180 ml of benzene. Irradiation for 14 hr resulted in optimum formation of volatile product; amorphous, insoluble material was also formed. The solution was filtered, concentrated, distilled bulb to bulb at 110° (0.2 mm), and purified by vpc at 180° to give 70 mg (30%) of the cyclobutene. This was further purified by vpc to give an analytical sample: ir (CCl_4) 1730, 1705 cm^{-1}; uv (95% ethanol) end absorption, shoulder 287 mμ (ε 121); nmr (CCl_4) δ 1.28 (t, J = 7, 3 H), 1.7–2.6 (m, 6 H), 3.50 (s, 1 H), 4.15 (q, J = 7 Hz, 2 H), 6.18 (s, 2 H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.03; H, 7.45.

In a parallel experiment the crude product remaining after removal of benzene was dissolved in 40 ml of ethanol containing 5% palladium on carbon (20 mg) and hydrogenated at room temperature and 1 atm pressure. The reaction consumed 0.3 equiv of H_2 based on starting **2**. After removal of catalyst and solvent the product was distilled bulb to bulb and then purified by vpc to give cyclobutane **23** in 30% yield. Nmr and ir spectra and vpc retention time of the product were identical with those of **23** prepared above.

5-Oxo-1,3-cyclooctadiene-1-carboxylic Acid Ethyl Ester (27).—Bromine (0.112 ml, 2.05 mmol) in 5 ml of $CHCl_3$ was added at −15° over 15 min to the ketone **23** (400 mg, 2.0 mmol) in 25 ml of $CHCl_3$ containing 1 ml of acetic acid. The solution was then washed with $NaHCO_3$, water, and brine and dried over Na_2SO_4. The concentrated product was dissolved in 10 ml of dimethylformamide containing anhydrous LiBr (800 mg) and Li_2CO_4 (800 mg) and then stirred at 160° for 1.5 hr.[17] The organic material was extracted into ether, washed with water and brine, dried over Na_2SO_4, and freed of solvent. Following bulb-to-bulb distillation at 1.0 mm, the mixture was subjected to vpc at 190°. The product, isolated in approximately 20% yield as a colorless oil was analytically pure: ir (CCl_4) 1710, 1662, 1620 (weak),

(32) H. R. Harrison, W. M. Haynes, P. Arthur, and E. J. Eisenbraun, *Chem. Ind. (London)*, 1568 (1968).

(33) R. H. Wiley in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 853.

1598 (weak) cm^{-1}; uv (95% ethanol) λ_{max} 282 mμ (ε 9700); 220 MHz nmr (CCl_4) δ 1.33 (t, J = 7 Hz, 3 H), 2.0–2.15 (m, 2 H), 2.45–2.60 (m, 4 H), 4.15–4.30 (m, 2 H), 5.95 (d, J = 12.5 Hz, 1 H), 6.50 (dd, J = 12.5 Hz, J = 5.5 Hz, 1 H), 7.30 (d, J = 5.5 Hz, 1 H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.36; H, 7.34.

Registry No.—**1**, 24079-79-6; **2**, 25017-79-2; **3**, 25017-78-1; **7**, 25942-83-0; **9**, 2648-49-9; **12**, 25942-85-2; **13**, 25942-86-3; **14**, 25942-87-4; **16**, 25942-88-5; **17**, 25942-89-6; **19**, 25942-90-9; **22**, 24079-80-9; **23**, 24079-81-0; **24**, 24079-82-1; **25**, 25942-93-2; **26**, 25942-94-3; **27**, 25942-95-4.

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Preparation and Reactions of 2,2-Dimethyl-4-cyclopentene-1,3-dione

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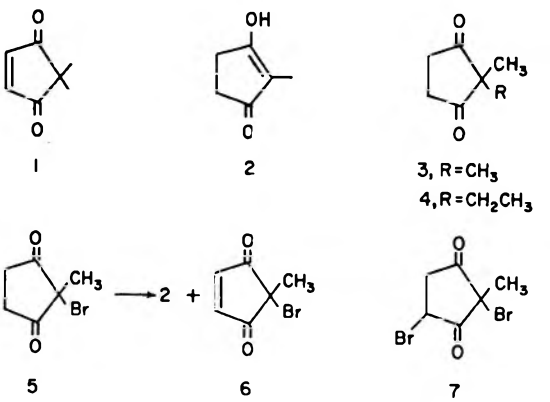
Treatment of **3** with *N*-bromosuccinimide yields **1**. Simple addition–elimination reactions of **1** and the related ketone **6** give **9**, **10**, **11**, and **14**. Enedione **1** is a sluggish dienophile relative to the parent compound **18**, but it behaves as a normal dipolarophile. The mechanistic implications of these observations are noted and the structure and stereochemistry of adducts of **1** with cyclopentadiene, three anthracenes, two aziridines (**24** and **25**), and diazomethane are recorded.

We describe here the preparation and a number of reactions of 2,2-dimethyl-4-cyclopentene-1,3-dione (**1**). These studies include simple addition–elimination reactions at the carbon–carbon double bond to provide substituted derivatives, as well as both Diels–Alder and 1,3-dipolar addition reactions. This compound (**1**) is a rather poor dienophile but a normal 1,3 dipolarophile, and we have previously discussed[2] the mechanistic implications of these observations for the 1,3-dipolar addition reaction.

Earlier investigators have described[3] methylation of the readily available enol **2**[4] to give 2,2-dimethylcyclopentane-1,3-dione (**3**) in 11% yield. By modification and careful control of the alkylating conditions we have improved this yield to 51%. Attempted use of similar conditions for ethylation, however, gave only a poor yield of the corresponding methylethyldione **4**. Reaction of **3** with *N*-bromosuccinimide in hot carbon tetrachloride gave the desired enedione **1** directly, presumably *via* α-bromination followed by dehydrobromination. The nuclear magnetic resonance (nmr) spectrum of the mixture during reaction showed only **3** and **1** with no evidence of the α-bromo ketone. Loss of hydrogen bromide from this intermediate under the reaction conditions then must be relatively rapid. Parallel behavior is apparent in a number of related transformations described below. The structure of **1** was confirmed by spectroscopic properties and its reduction back to **3** with zinc in acetic acid. The compound is a bright yellow liquid at room temperature and stable in the absence of base. Solutions of **1** exposed to amines, ammonia, or aqueous alkali quickly turn black.

An unexpected reaction similar to transformation of **3** to **1** occurs with the previously known[3] 2-bromo-2-methylcyclopentane-1,3-dione (**5**). On standing in the solid state at 4° this ketone undergoes slow conversion to a mixture of **2** and the bromoenedione **6**. Bromo ketone **5** apparently suffers bimolecular reaction with itself (perhaps through the intermediacy of molecular bromine) to give **2** and the unobserved dibromo ketone **7**, which then loses hydrogen bromide to form **6**.



We have followed the reaction of **1** with bromine in carbon tetrachloride solution by nmr and observed rapid formation of a dibromide which must be the trans isomer **8**, since its nmr spectrum consists of two singlets, one for the methyl groups and one for the ring protons. This substance can be obtained as a white solid by low temperature removal of solvent, but it fumes readily in air with formation of bromo ketone **9**. In similar fashion, but more slowly, **9** also reacts with bromine and yields dibromo ketone **10**. Absorption of bromine by **6** also proceeds at room temperature. In this case, however, addition of a second mole of halogen is relatively fast; the major product isolated, even with bromine as limiting reagent, is the fully brominated enedione **11**. This is accompanied by a small amount of **12**, which may be accounted for by reaction of liberated hydrogen bromide with the intermediate **13**.

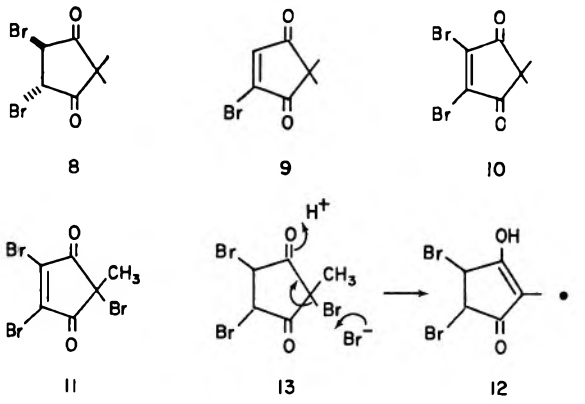
(1) Fellow of The Alfred P. Sloan Foundation. Author to whom correspondence should be addressed.

(2) W. C. Agosta and A. B. Smith, III, *Chem. Commun.*, 685 (1970).

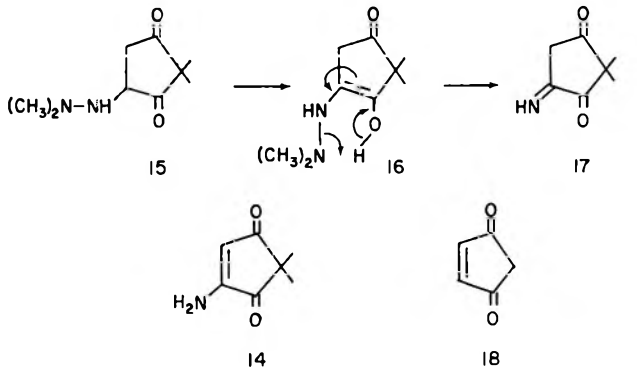
(3) G. V. Kondrat'eva, G. A. Kogan, T. M. Fadeeva, and S. I. Saz'yalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1648 (1964).

(4) H. Schick, G. Lehmann, and G. Hilgetag, *Ber.*, **102**, 3238 (1969), and references cited therein.

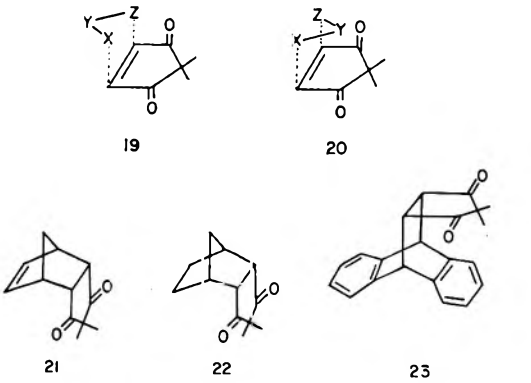
Since bromination of **1** gives **8** with no nmr evidence for the cis dibromide, it is probable that **12** also is the trans isomer.[5]



As noted above, attempts to add ammonia to **1** were unrewarding; this compound does react smoothly, however, with 1,1-dimethylhydrazine in dry ethanol to give enamine **14**. We may account for this rather unexpected result by assuming enolization of the initial Michael adduct **15** to form **16**, followed by elimination of dimethylamine and tautomerization of the resulting imine **17** to **14**. This sequence is mechanistically reminiscent of the long-known oxidation of α-hydroxy aldehydes and ketones by phenylhydrazine to yield osazones and aniline.[6] The amino ketone **14** was alternatively available in quantitative yield by Michael addition–elimination of ammonia with bromo ketone **9**. Reduction of **14** with zinc in acetic acid furnished **3**.



The most interesting reactions we have carried out with **1** have been Diels–Alder and 1,3-dipolar additions. We have already reported[2] that **1** is a sluggish dienophile relative to the parent compound, 4-cyclopentene-1,3-dione (**18**),[7] but a normal 1,3 dipolarophile, and we have attributed this difference to steric retardation by the methyl groups in the transition state leading to Diels–Alder, but not dipolar, addition. These observations led to the conclusion that, if the generally accepted concerted mechanism[8] for 1,3-dipolar additions is operative here, the orientation of addends in the transition state must be that shown in **19** rather than **20**. We shall not present again the arguments involved, but simply note the assignment of structure and stereochemistry to the various adducts



employed in our comparisons. Diels–Alder addition of **1** to cyclopentadiene affords adduct **21**. The endo configuration expected for this compound on the basis of the Alder–Stein rules[9] was confirmed by comparison of the nmr spectrum of **21** with that of its dihydro derivative **22** available on catalytic hydrogenation. Shielding of one methyl group by the double bond in **21**, an effect[10] possible only in the endo adduct, is indicated by the change in separation of the methyl singlets on hydrogenation. This separation ($\Delta\delta$) decreases from 0.20 ppm in **21** to 0.07 ppm in **22**. Also, the protons adjacent to the carbonyl groups show the upfield displacement ($\Delta\delta$ = 0.19 ppm) expected[11] for exo protons on passing from **21** to **22**. For endo protons the change anticipated[11] is smaller and in the opposite direction.[12] Addition of enedione **1** to anthracene proceeds smoothly with aluminum chloride catalysis[13] to form **23**. Similar adducts are formed with 2,6-dimethylanthracene[14] and 2,6-dichloroanthracene.[15] In each of these compounds the methyl group directly over the aromatic ring is quite shielded[16] magnetically and appears at about 0.2 ppm in the nmr spectrum.

As a dipolarophile, ketone **1** reacts normally and in good yield with the 1,3 dipoles formed in hot toluene from 1,2,3-triphenylaziridine (**24**)[17] and *trans*-1-cyclohexyl-2,3-dibenzoylaziridine (**25**).[18] In each case the adduct isolated (**26** and **27**, respectively), had trans disposed substituents on a cis-fused ring system, an assignment unambiguously clear from nmr spectra. In the spectra of **26** and **27** the protons at the ring junction

(5) As a result of rapid shift of the acidic proton, the ring hydrogen atoms are equivalent in **12** and in **2**, and they appear as a singlet in the nmr spectrum in both cases. This fact precludes an assignment of stereochemistry in **12** based on nmr measurements.

(6) A. Hassner and P. Catsoulacos, *Tetrahedron Lett.*, 489 (1967), and numerous references cited therein.

(7) C. H. DePuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, **81**, 4920 (1959); C. H. DePuy and C. E. Lyons, *ibid.*, **82**, 631 (1960).

(8) R. Huisgen, *Angew. Chem.*, **75**, 742 (1963); R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968). For an opposing point of view, see R. A. Firestone, *ibid.*, **33**, 2285 (1968).

(9) A. S. Onishchenko, "Diene Synthesis," Daniel Davey and Co., New York, N. Y., 1964, Chapter 1, and references cited therein.

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 83, and references cited therein.

(11) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(12) The more convenient distinction between endo and exo protons at these positions based (see ref 10, pp 288–289) on their observed coupling constants with the adjacent bridgehead protons fails with **19**. The four protons in question appear fortuitously as a sharp singlet even at 220 MHz. For successful application of this method in a closely related system, see M. Green and E. A. C. Lucken, *Helv. Chim. Acta*, **45**, 1870 (1962).

(13) P. Yates and P. Eaton, *J. Amer. Chem. Soc.*, **82**, 4436 (1960).

(14) G. T. Morgan and E. A. Coulson, *J. Chem. Soc.*, 2203 (1929).

(15) Preparation of this compound by reduction of the known related quinone is detailed in the Experimental Section.

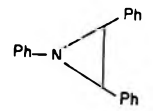
(16) Reference 10, p 94, and references cited therein.

(17) H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966).

(18) A. B. Turner, H. W. Heine, J. Irving, and J. B. Bush, Jr., *J. Amer. Chem. Soc.*, **87**, 1050 (1965); R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966).

are coupled with a vicinal coupling constant of 10 Hz, indicating[19] cis rather than trans fusion of the two rings, just as expected on mechanistic grounds.[8] Furthermore, each proton on the pyrrolidine ring in **26** and **27** shows a unique chemical shift and unique coupling constants with its neighbors. This is possible only with trans disposition of phenyl (in **26**) or benzoyl (in **27**) groups, since both alternative isomers with these substituents cis possess structural symmetry inconsistent with four unique protons. The specific vicinal coupling constants derivable from the spectra are recorded in the Experimental Section and are fully consistent with the stereochemistry assigned.

In similar fashion **1** adds diazomethane[20] at room temperature to give the rather unstable pyrazoline **28**. Also here the expected[8] cis-fused system is signaled[19] by the vicinal coupling constant (9 Hz) of the two methine protons. As predicted from previous observations,[21] **28** loses nitrogen on pyrolysis to give only the trimethyl ketone **29**, but yields a mixture of **29** and the isomeric cyclopropane **30** on photolysis.



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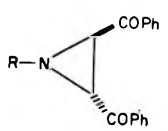
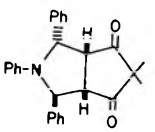


25, R=cyclohexyl



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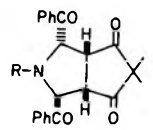
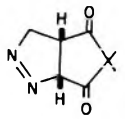


27, R=cyclohexyl



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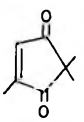

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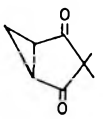

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Experimental Section

Materials and Equipment.—Unless otherwise noted, both ir and nmr spectra were obtained for carbon tetrachloride solutions, the former on a Perkin-Elmer 237B spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) nmr spectrometer. Spectra at 220 MHz are so marked; others are at 60 MHz. Ultraviolet spectra were obtained for solutions in 95% ethanol using a Cary Model 14PM spectrophotometer. Vpc was carried out using a Varian Aerograph Model 700 Autoprep equipped with a 20 ft × 0.25 in. stainless steel column packed with 30% FFAP on Chromosorb W and operated at 170° with a helium carrier gas flow rate of 100–150 ml/min. Photolysis was carried out at about 15° using a 450-W medium pressure mercury arc lamp, Hanovia type L, No. 679A-36, contained in a water-cooled quartz immersion well fitted with a Pyrex sleeve. Melting points are corrected.

2,2-Dimethylcyclopentane-1,3-dione (3).—A solution of 10 g of enone **2**,[4] 5 g of potassium hydroxide, and 13.4 g of methyl iodide was heated at reflux in 75 ml of dioxane and 25 ml of water. After 5 hr and again after 8.5 hr, 2.0 g of potassium hydroxide and 5.4 g of methyl iodide in 15 ml of dioxane and 5 ml of water was added to the refluxing mixture. After a total of 12 hr the mixture was cooled and extracted several times with ether. After removal of ether this extract was heated with 50 ml of 10% aqueous hydrochloric acid to the boiling point, cooled, and treated with excess 10% aqueous sodium carbonate. This solution was extracted four times with chloroform, and the organic extract was dried. The crude product remaining after removal of solvent was recrystallized from petroleum ether to give 51.5% **3** in two crops: ir ($CHCl_3$) 1770 (w), 1730 (s) cm^{-1}; nmr δ 1.05 (s, 6 H), 2.75 (s, 4 H). If no additional potassium hydroxide and methyl iodide were added during the reaction, the yield was 34%. The melting point of **3** was 45–47.

2-Ethyl-2-methylcyclopentane-1,3-dione (4).—This compound was prepared from **2**[4] and ethyl iodide as above. No additional base and ethyl iodide were added during the reaction. The crude yield was 14%. A sample was purified by vpc for analysis: ir (neat) 1765 (w), 1725 (s) cm^{-1}; nmr δ 0.77 (t, J = 7 Hz, 3 H), 1.00 (s, 3 H), 1.60 (q, J = 7 Hz, 2 H), 2.75 (s, 4 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.79; H, 8.66.

2,2-Dimethyl-4-cyclopentene-1,3-dione (1).—A mixture of 1.754 g of **3** and 2.44 g of *N*-bromosuccinimide in 40 ml of carbon tetrachloride was irradiated and heated with a 100-W incandescent bulb for 2 hr. The solution was cooled, filtered to remove succinimide, washed with sodium bicarbonate solution and then water, and dried. After removal of solvent there remained 1.28 g of yellow liquid product (74%), bp 90° (44 mm). On a larger scale the yield was 85%. Preparative vpc gave an analytical sample: ir 1750 (m), 1710 (vs), 1470 (m), 1315 (m), 1285 (m), 1135 (m), 1125 (m), 1038 (m), 845 (m) cm^{-1}; nmr δ 1.12 (s, 6 H), 7.15 (s, 2 H); uv λ_{max} 219 mμ (log ϵ 3.78), 345 (sh, 1.26), 389 (1.42).

Anal. Calcd for $C_7H_8O_2$: C, 67.74; H, 6.49. Found: C, 67.73; H, 6.66.

This compound could be stored at 4° for at least 1 year without change.

Reduction of 1 to 3.—A mixture of 200 mg of **1**, 2 g of zinc dust, and 10 ml of acetic acid was heated at 85° for 45 min. The solution was cooled and treated with excess 10% sodium carbonate solution and the product extracted into chloroform. This was washed with water and dried; removal of solvent gave 189 mg (92%) of **3**, identical with material prepared above by ir and nmr spectral comparisons.

2-Bromo-2-methyl-4-cyclopentene-1,3-dione (6).—A sample of **5** was stored at 4° for several months, during which time it turned quite yellow. It was treated with chloroform, and an insoluble white material was filtered off. Recrystallization of this material from water gave **2**, identical in ir spectrum, melting points and mixture melting point with authentic material. The chloroform filtrate yielded a yellow solid which was twice recrystallized from cyclohexane for analysis: mp 72–73°; ir 1760 (m), 1730 (s), 1715 (s), 1690 (w) cm^{-1}; nmr ($CDCl_3$) δ 1.80 (s, 3 H), 7.44 (s, 2 H).

Anal. Calcd for $C_6H_5O_2Br$: C, 38.13; H, 2.67. Found: C, 37.98; H, 2.66.

4-Bromo-2,2-dimethyl-4-cyclopentene-1,3-dione (9).—A solution of 380 mg of bromine in 5 ml of carbon tetrachloride was added dropwise to 300 mg of enedione **1** in 5 ml of carbon tetrachloride. Solvent and excess bromine were evaporated *in vacuo* to leave off-white crystals which fumed and turned to a yellow oil over 15 min. This oil crystallized spontaneously to give 434 mg (88%) of yellow crystals which could be recrystallized from petroleum ether. A sample was recrystallized for analysis: mp 75–76°; ir 1770 (w, sh), 1760 (w), 1715 (s) cm^{-1}; nmr δ 1.19 (s, 6 H), 7.40 (s, 1 H).

Anal. Calcd for $C_7H_7O_2Br$: C, 41.40; H, 3.48; Br, 39.36. Found: C, 41.33; H, 3.61; Br, 39.6.

In a similar experiment carried out in an nmr tube 100 mg of **1** was treated with 130 mg of bromine in 1 ml of carbon tetrachloride. The bromine color rapidly disappeared, and the nmr spectrum was then determined. This indicated that about 5% of both **1** and **9** was present and that the remaining material was the *trans*-dibromide **8** [δ 1.48 (s, 6 H), 4.72 (s, 2 H)]. Upon work-up the material described above was obtained.

4,5-Dibromo-2,2-dimethyl-4-cyclopentene-1,3-dione (10).—A mixture of 200 mg of bromo ketone **9** and 157 mg (1.0 equiv) of bromine was heated at reflux in 8 ml of carbon tetrachloride for 12 hr. From the nmr spectrum it was clear that starting material remained. The mixture was returned to reflux for an additional 36 hr with 100 mg more bromine. The crude product remaining on removal of solvent and excess bromine showed mp 135–142°. Three recrystallizations from carbon tetrachloride gave an analytical sample of yellow needles: mp 149–150.5°; ir (KBr disk) 1760 (s), 1735 (m), 1715 (vs), 1265 (s), 1210 (s),

(19) Reference 10, pp 286–288, and references cited therein.

(20) Dipolar additions of diazomethane are reviewed by R. Huisgen, *Angew. Chem.*, **75**, 604 (1963), and R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Wiley, New York, N. Y., 1964, Chapter 11, pp 806–878.

(21) Cyclopropane **30** is known to rearrange to **29** on pyrolysis: H. Stetter and H.-J. Sandhagen, *Ber.*, **100**, 2837 (1967). For decomposition of a related pyrazoline forming a thermally stable cyclopropane, see T. Sasaki and S. Eguchi, *J. Org. Chem.*, **33**, 4389 (1968).

1150 (s), 1110 (s) cm^{-1}; nmr δ 1.28 (s); uv λ_{max} 277 mμ (log ϵ 2.06), 325 (0.94).

Anal. Calcd for $C_7H_6O_2Br_2$: C, 29.82; H, 2.14; Br, 56.69. Found: C, 29.69; H, 2.16; Br, 57.0.

Bromination of 2-Bromo-2-methyl-4-cyclopentene-1,3-dione (6).—A solution of 200 mg of diketone 6 in 5 ml of chloroform was stirred at room temperature with 169 mg (1.0 equiv) of bromine. The color faded to yellow over 1.5 hr. The solvent was removed to leave a crystalline mass which was extracted with cyclohexane. This separated the reaction product into colorless needles (65 mg) insoluble in cyclohexane and a solution which yielded yellow needles (144 mg, 78% based on available bromine) on removal of solvent. Recrystallization of the colorless needles from benzene several times gave an analytical sample of 12: mp 142.5–143.5°; ir ($CHCl_3$) 3450–2500 (m, broad), 1705 (m), 1625 (s, broad), 1395 (s), 1360 (m) cm^{-1}; nmr ($CDCl_3$) δ 1.83 (s), 4.86 (s).

Anal. Calcd for $C_6H_6O_2Br_2$: C, 26.70; H, 2.24. Found: C, 26.76; H, 2.25.

Recrystallization of the yellow needles from cyclohexane gave an analytical sample of 11: mp 128–130°; ir 1770 (s), 1730 (vs), 1645 (s), 1545 (s), 1245 (m), 1120 (m), 1075 (m), 885 (m) cm^{-1}; nmr δ 1.87 (s).

Anal. Calcd for $C_6H_3O_2Br_3$: C, 20.78; H, 0.87. Found: C, 21.04; H, 0.93.

4-Amino-2,2-dimethyl-4-cyclopentene-1,3-dione (14). A. From 1,1-Dimethylhydrazine and Enedione 1.—A solution of 309 mg of enedione 1 and 174 mg of 1,1-dimethylhydrazine (freshly distilled and having ir identical with that reported[22]) in 5 ml of absolute ethanol stood at room temperature overnight. The solution was diluted with aqueous hydrochloric acid and the product extracted into ether. This was washed with water and brine and then dried. Removal of solvent gave 279 mg (80%) of solid. Recrystallization from benzene gave a sample with mp 169–170°, mmp (with material described below) 169–170°, ir and nmr spectra identical with those of material described below.

B. From Ammonia and Bromo Ketone 9.—A solution of 102 mg of bromo ketone 9 in 3 ml of ethanol and 1 ml of concentrated aqueous ammonia stood at room temperature for 3.5 hr. It was then evaporated to dryness, and the residue was extracted with ether to give 70 mg of product (100%). Recrystallization from benzene gave an analytical sample: mp 169–171°; ir 3510 (w), 3400 (w), 1745 (w), 1690 (m), 1635 (s) cm^{-1}; nmr ($CDCl_3$) δ 1.18 (s, 6 H), 5.50 (broad, 2 H, exchanges with D_2O), 5.90 (s, 1 H); uv λ_{max} 220 mμ (log ϵ 4.04), 309 (4.03).

Anal. Calcd for $C_7H_9O_2N$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.50; H, 6.48; N, 10.00.

Reduction of Amino Ketone 14 with Zinc in Acetic Acid.—A solution of 101 mg of amino ketone 14 in 5 ml of acetic acid containing 5 drops of concentrated hydrochloric acid and 1.00 g of zinc dust was stirred at room temperature for 2 hr. The solution was poured into water, neutralized with sodium bicarbonate solution, and extracted with chloroform. Removal of chloroform after drying left 29 mg of diketone **3** which was recrystallized from petroleum ether, mp and mmp (with authentic **3**) 46–48°, ir and nmr spectra identical with those of authentic **3**.

Reaction of Cyclopentadiene with Enedione 1.—A solution of 1.24 g of enedione 1 in 15 ml of benzene containing 1 ml of cyclopentadiene was heated at reflux under nitrogen for 19 hr. The mixture was concentrated *in vacuo*, treated with 10 ml of pentane, and then kept at −20° for several hours. Filtration then gave 900 mg (45%) of off-white crystals. Three recrystallizations from pentane at −20° gave an analytical sample of adduct **21**: mp 70–72°; ir 1770 (w), 1720 (s), 1112 (m), 1080 (m), 710 (m) cm^{-1}; nmr (220 MHz) δ 0.79 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.49 (d, J = 9 Hz, 1 H, CHH), 1.64 (d, J = 9 Hz, 1 H, CHH), 3.40 (s, $w_{1/2}$ = 3 Hz, 4 H), 5.98 (s, 2 H, olefinic H).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.67; H, 7.44.

Hydrogenation of Adduct 21.—A solution of 84 mg of adduct **21** in 5 ml of methanol containing 7 mg of 5% palladium on carbon was reduced with hydrogen at 1 atm. After removal of catalyst and solvent, the residue was treated with pentane and kept at −20° for several hours to give colorless crystals. Recrystallization from pentane gave an analytical sample of **22**: mp 60–61.5°; ir 1765 (m), 1720 (s) cm^{-1}; nmr (220 MHz) δ 0.99–1.23 (s, s, m, 8 H, CH_3, CH_3, bridge CH_2), 1.41–1.73 (m, 4 H, CH_2CH_2), 2.74 (broad, 2 H, bridgehead CH), 3.21 (s, $w_{1/2}$ = 7 Hz, 2 H, COCH).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.81; H, 8.37.

Reaction of Anthracene with Enedione 1.—A solution of 140 mg of enedione 1 in 5 ml of dichloromethane containing 200 mg of anthracene and 140 mg of aluminum chloride was heated at reflux for 2 hr. The mixture was poured into 20 ml of water and the layers separated. The organic layer, plus two washings of the aqueous layer with dichloromethane, was washed with water and dried. Removal of solvent left a foam which crystallized from petroleum ether to yield 282 mg (82%) of adduct **23**. This was recrystallized from cyclohexane–benzene (3:1) to furnish an analytical sample: mp 176–177°; ir (Nujol) 1765 (m), 1715 (s), 755 (s), 740 (m) cm^{-1}; nmr (ppm downfield from external tetramethylsilane) 0.10 (s, 3 H), 0.97 (s, 3 H), 3.32 (m, 2 H), 4.83 (m, 2 H), 7.0–7.7 (m, 8 H).

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.52; H, 5.91.

Reaction of 2,6-Dimethylanthracene with Enedione 1.—This reaction was carried out just as the preparation of **23** and gave an 82% yield. The product was best purified by elution from grade I neutral alumina with ethyl acetate. Two subsequent recrystallizations from ethanol gave an analytical sample of the desired adduct: mp 149.5–151.5°; ir (KBr disk) 1770 (w), 1730 (s), 1460 (m), 1120 (w), 1070 (m), 805 (w) cm^{-1}; nmr ($CDCl_3$, ppm downfield from external tetramethylsilane) 0.092 (s, CH_3), 0.95 (s, CH_3), 2.25 (s, $ArCH_3$), 2.35 (s, $ArCH_3$), 3.39 (m, COCH), 4.80 (m, ArCH), 6.85–7.50 (m, ArH).

Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.86; H, 6.70.

A bishydrazone was prepared using hydrazine and hydrazine hydrochloride in diethylene glycol at 130° (95%), mp 116–121° and 207–208° from ether.

Anal. Calcd for $C_{23}H_{26}N_4$: C, 77.06; H, 7.31; N, 15.63. Found: C, 77.14; H, 7.38; N, 15.75.

2,6-Dichloroanthracene.—A mixture of 2.74 g of 2,6-dichloro-9,10-anthraquinone,[23] 19.2 ml of concentrated aqueous ammonia, and 35.6 ml of water was heated on the steam bath for 7 hr and treated with 13.7 g of zinc dust in portions. The mixture was then filtered, and the product was extracted from the filter cake with several portions of hot acetone. This solvent was removed, and the crude product was dissolved in boiling 1-propanol, treated with a few drops of concentrated hydrochloric acid (to dehydrate any anthrol present), and allowed to cool. This gave 1.61 g of yellow plates. Several recrystallizations from benzene gave an analytical sample: mp 271–272°; ir (KBr disk) 1612 (m), 1440 (m), 1070 (m), 1055 (m), 920 (m), 895 (s), 790 (m) cm^{-1}.

Anal. Calcd for $C_{14}H_8Cl_2$: C, 68.05; H, 3.26. Found: C, 68.00; H, 3.41.

Reaction of 2,6-Dichloroanthracene with Enedione 1.—This reaction was carried out just as the preparation of **23** and gave an 83% yield. The adduct was purified by several recrystallizations from ethanol: mp 168–169.5°; nmr ($CDCl_3$, ppm downfield from external tetramethylsilane) 0.28 (s, CH_3), 1.07 (s, CH_3), 3.46 (m, COCH), 4.88 (m, ArCH), 7.08–7.51 (m, ArH).

Anal. Calcd for $C_{21}H_{16}O_2Cl_2$: C, 67.93; H, 4.35. Found: C, 68.04; H, 4.37.

Reaction of 1,2,3-Triphenylaziridine (24) with Enedione 1.—A solution of 124 mg of enedione 1 in 10 ml of toluene containing 271 mg of **24** was heated at reflux for 10 hr. Filtration of the cooled and somewhat concentrated solution gave 355 mg (90%) of solid product. One recrystallization from toluene gave 261 mg (66%) of adduct **26**. Two more recrystallizations furnished an analytical sample: mp 269–271°; ir (KBr disk) 1765 (w), 1725 (s), 1600 (m), 1500 (s), 1340 (s), 1330 (s), 735 (s), 680 (s) cm^{-1}; nmr ($CDCl_3$, 220 MHz) δ 0.080 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 3.46 (dd, J_{AB} = 10 Hz, J_{AC} = 1 Hz, 1 H, $COCH_A$), 4.16 (app t, J_{BA} = 10 Hz, J_{BD} = 10 Hz, 1 H, $COCH_B$), 5.66 (d, J_{DB} = 10 Hz, 1 H, $ArCH_D$), 5.84 (d, J_{CA} = 1 Hz, 1 H, $ArCH_C$), 6.34 (d, J = 8 Hz, 2 H, ArH), 6.52 (app t, J = 7 Hz, 1 H, ArH), 6.9–7.4 (m, 12 H, ArH).

Anal. Calcd for $C_{27}H_{25}O_2N$: C, 82.00; H, 6.37; N, 3.55. Found: C, 82.01; H, 6.46; N, 3.39.

(22) E. R. Shull, J. L. Wood, J. G. Aston, and D. H. Rank, *J. Chem. Phys.*, **22**, 1191 (1954).

(23) H. E. Fierz-David, *Helv. Chim. Acta*, **10**, 197 (1927); K. Lauer, *J. Prakt. Chem.*, [2] **130**, 185 (1931).

Reaction of *trans*-1-Cyclohexyl-2,3-dibenzoylaziridine (25) with Enedione 1.—A solution of 62 mg of enedione **1** in 5 ml of toluene containing 165 mg of aziridine **25** was heated at reflux for 2.75 hr. Concentration and filtration gave 181 mg (80%) of crude solid product. This was recrystallized several times from benzene to yield an analytical sample of adduct **27**: mp 175.5–177°; ir (KBr disk) 1765 (m), 1720 (s), 1675 (s), 1660 (s), 1230 (s) cm^{-1}; nmr ($CDCl_3$) δ 0.5–2.0 (m, 10 H, CH_2), 1.12 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 2.28–2.80 [broad, 1 H, C(1)H of cyclohexyl], 3.55 (dd, J_{BA} = 10.5 Hz, J_{BC} = 3 Hz, 1 H, $COCH_B$), 3.92 (dd, J_{AB} = 10.5 Hz, J_{AD} = 8 Hz, 1 H, $COCH_A$), 5.52 (d, J_{CB} = 3 Hz, 1 H, $ArCOCH_C$), 5.78 (d, J_{DA} = 8 Hz, 1 H, $ArCOCH_D$), 7.2–8.6 (m, 10 H, ArH).

Anal. Calcd for $C_{29}H_{31}O_4N$: C, 76.13; H, 6.84; N, 3.07. Found: C, 76.14; H, 6.91; N, 2.96.

Reaction of Diazomethane with Enedione 1.—A solution of 500 mg of enedione **1** in 20 ml of ether was treated with 30 ml of 0.14 *M* ethereal diazomethane. After 3 hr at room temperature excess diazomethane was distilled out on the steam bath and the solvent removed. The resulting crystals were washed with cyclohexane and filtered to give 514 mg (77%) of pyrazoline **28**. This was recrystallized by dissolution in benzene at room temperature, addition of cyclohexane, and subsequent cooling. Four such operations gave an analytical sample: mp 86–88°; ir 1770 (w), 1730 (s), 1545 (w) cm^{-1}; nmr ($CDCl_3$) δ 0.97 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 3.40 (six lines, 1 H, CH_2CH_BCO), 4.9–5.2 (m, 2 H, CH_XH_Y), 5.80 (broad dt, J_{AB} = 9 Hz, J_{AX} = 2.5 Hz, $J_{AY} \sim$ 0.5 Hz, 1 H, NCH_ACO). This compound is light sensitive.

Anal. Calcd for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.91; H, 5.87; N, 16.76.

Pyrolysis of Pyrazoline 28.—A solution of 200 mg of adduct **28** in 10 ml of toluene was heated at reflux for 1.5 hr. The solvent was evaporated to leave 135 mg (81%) of crude product which was purified by preparative vpc to give an analytical sample of ketone **29**: ir 1750 (m), 1710 (s), 1620 (m), 1280 (m), 1120 (m) cm^{-1}; nmr δ 1.10 (s, 6 H), 2.10 (d, J = 1 Hz, 3 H), 6.84 (broad, 1 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.25; H, 7.25.

Photolysis of Pyrazoline 28.—A solution of 200 mg of adduct **28** in 400 ml of ether was photolyzed for 1 hr. Most of the solvent was removed and the product was purified by preparative vpc to give a small amount of **29** plus analytically pure cyclopropane **30**; ir 1763 (m), 1727 (s), 1265 (m), 1130 (m), 990 (m), 875 (m), 850 (m) cm^{-1}; nmr δ 1.03 (s, 3 H), 1.07 (s, 3 H), 1.17–1.92 (m, 2 H), 2.3–2.7 (m, 2 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.14; H, 7.22.

Registry No.—**1**, 26154-22-3; **3**, 3883-58-7; **4**, 25112-87-2; **6**, 26154-25-6; **9**, 26154-26-7; **10**, 26154-27-8; **11**, 26154-28-9; **12**, 26157-42-6; **14**, 26154-29-0; **21**, 26157-43-7; **22**, 26157-44-8; **23**, 26154-30-3; **26**, 26145-73-3; **27**, 26145-74-4; **28**, 26145-75-5; **29**, 15972-27-7; **30**, 15973-50-9; reaction product of 2,6-dimethylanthracene with **1**, 26154-33-6; reaction product of 2,6-dimethylanthracene with bishydrazone, 26154-34-7; 2,6-dichloroanthracene, 26154-35-8; reaction product of 2,6-dichloroanthracene with **1**, 26154-36-9.

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The Preparation and Properties of Cage Polycyclic Systems. I. Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane and Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane Derivatives

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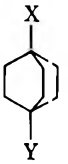
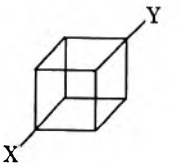
Reliable syntheses of some pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (**22**) and pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (**23**) derivatives are described. The nmr spectra of several of them and the nmr spectra of the *endo*-dicyclopentadiene precursors are discussed; magnetic shielding of some of the cage methine protons is observed for certain ketones and ethylene ketals, a dimethyl ketal, and a hydrate, and even 5,9-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane has a two-proton absorption at higher field than that of the main group of protons. The cleavage of a nonenolizable α-bromo ketone, 5,9-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione 6-ethylene ketal (**5**) to give a lactone (**17**), and several attempted Favorskii rearrangements on 5,9-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-deca-6,10-dione (**6**) and 1-bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one-4-carboxylic acid (**10**) are described.

Recently[1] we have prepared some 1,4-disubstituted bicyclo[2.2.2]octanes in order to study the polar effects of substituents X in a system such that they have no influence on the steric effect experienced by the reaction site Y. In these compounds the substituent



is hidden from the reaction site by the bulk of the cyclic system and changing the substituent does not alter the steric effect at the reaction site. 1,4-Disubstituted cubanes[2] offer the same possibilities for studying polar effects without the intervention of steric effects,[3] and, after the preparation of 1,4-dimethoxy-



* Author to whom correspondence should be addressed.

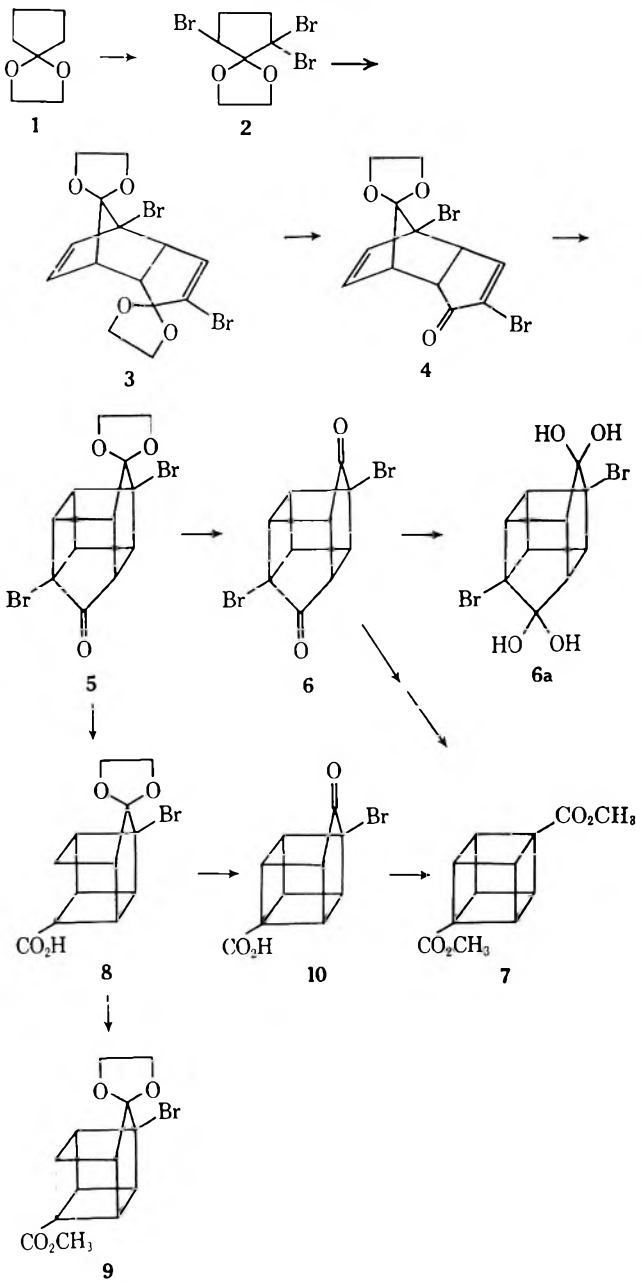
(1) (a) S. Sotheeswaran, Ph.D. Thesis 1967, University of Hull, England; (b) N. B. Chapman, S. Sotheeswaran, and K. J. Toyne, *J. Org. Chem.*, **35**, 917 (1970).

(2) J. M. Key, Ph.D. Thesis, 1968, University of Hull, England.

(3) F. W. Baker, R. C. Parish, and L. M. Stock, *J. Amer. Chem. Soc.*, **89**, 5677 (1967).

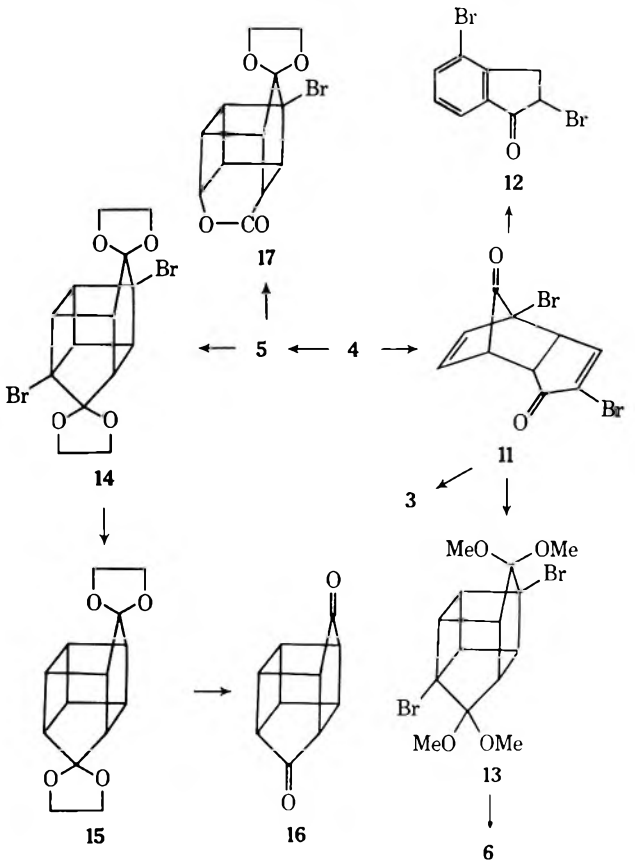
carbonylcubane was reported by Eaton and Cole,[4,5] we planned to prepare some 1,4-disubstituted cubanes for this purpose. However, we met numerous difficulties in following the preparative method reported by Eaton and Cole, arising from (a) the need to prepare cyclopent-2-en-1-one on a large scale, (b) the instability of the compounds leading to *endo*-2,4-dibromodicyclopentadiene-1,8-dione (**11**), which meant that many reactions gave tarry by-products, thus making purification difficult and causing low yields, and (c) the discovery that irradiation of **11** in 4% methanolic hydrogen chloride[6] gave the bisdimethyl ketal (**13**) and not the bishemimethyl ketal of **6** (see Schemes I and II).

SCHEME I



The Favorskii rearrangement of **6** gave variable yields; a 50% yield of **7** was isolated on one occasion but we were never able to repeat this and the usual yield was about 9%. The synthesis outlined in Scheme I was finally used as this avoids the difficulties a, b, and c mentioned above.

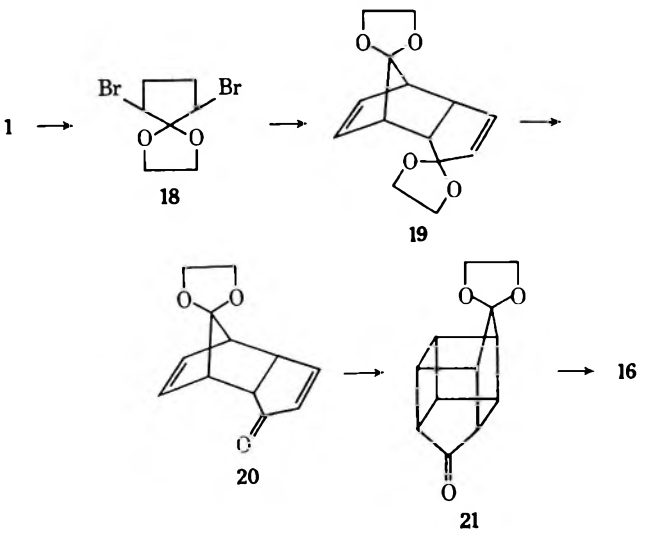
SCHEME II



Eaton and Hudson[7] brominated cyclopentanone ketals by using pyridinium bromide perbromide[8] in the alcohol from which the ketal had been derived; our attempts with this reagent failed. Various other established methods for the bromination of ketals were tried without success, *e.g.*, pyridinium bromide perbromide or trimethylphenylammonium perbromide in tetrahydrofuran,[9-12] and molecular bromine in a range of solvents. Dioxane dibromide, however, has been used[13] as a brominating agent and the initial isolation and purification of dioxane dibromide are unnecessary if bromine is added to the ketal in dioxane as solvent. This method proved successful and dibromination and tribromination of **1** gave good yields, and intermediates which were stable and relatively easy to purify (see Schemes I and III). This method is therefore a convenient way of preparing intermediates required for the synthesis of simple pentacyclodecane and pentacyclononane derivatives, and can be generalized to provide intermediates for the synthesis of complex substituted pentacyclodecanes[14] and pentacyclononanes, which

(4) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 962 (1964).
(5) P. E. Eaton and T. W. Cole, Jr., *ibid.*, **86**, 3157 (1964).
(6) P. E. Eaton, personal communication.
(7) P. E. Eaton and R. A. Hudson, *J. Amer. Chem. Soc.*, **87**, 2769 (1965).
(8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1957, p 65.
(9) A. Marquet, H. B. Kagan, M. Dvolaitzky, L. Mamlok, C. Weidmann, and J. Jacques, *C. R. Acad. Sci., Ser. C*, **248**, 984 (1959).
(10) A. Marquet and J. Jacques, *Tetrahedron Lett.*, 24 (1959).
(11) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).
(12) A. Marquet and J. Jacques, *ibid.*, 90 (1962).
(13) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3596 (1953).
(14) W. L. Dilling and M. L. Dilling, *Tetrahedron*, **23**, 1225 (1967).

SCHEME III



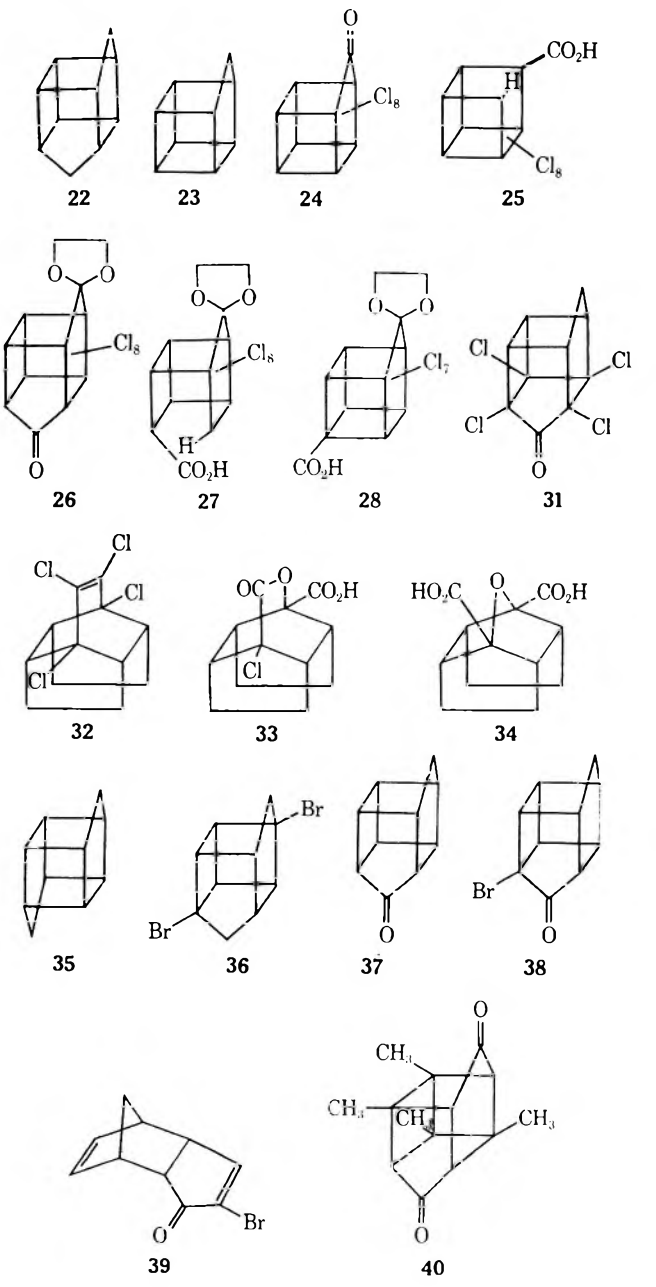
have attracted attention as potential antiviral agents.[15,16]

As we had obtained a poor yield of **7** from the Favorskii rearrangement of **6** by using the conditions recommended by Eaton and Cole,[4] we tried the reaction under various conditions as follows: aqueous potassium hydroxide 25–75% w/w, 90° up to reflux temperature, 20 hr–15 days, maximum yield 9%; powdered potassium hydroxide in xylene,[17,18] 25° up to reflux temperature, 1 day, no product; powdered potassium hydroxide in dimethyl sulfoxide, 50° up to 100°, 1 day, no product; powdered potassium hydroxide or sodium hydroxide in tetrahydrofuran,[19,20] 5° up to reflux temperature, 5 hr–2 days, no product; sodium methoxide in methanol, 25% w/w, reflux temperature, 1 day, no product; sodium methoxide–methanol in dimethyl sulfoxide, aqueous potassium hydroxide in dioxane, aqueous silver nitrate,[21] negligible yield.

Other workers[20,22,23] have experienced similar difficulties in the attempted Favorskii rearrangements of polychlorinated caged ketones. The attempted Favorskii rearrangement of **24** failed and the reaction gave a ring-cleaved product (**25**) which remained unchanged on treatment with base. Compound **26**, in a similar way, gave a ring-cleaved intermediate product (**27**), which in the presence of strong base gave the expected product (**28**).

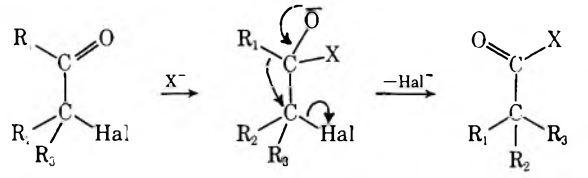
The preparation[4] of **7** from **6** involves two successive Favorskii rearrangements and an alternative approach was to find the optimum conditions for each of these rearrangements by preparing **7** *via* **8** and **10**. The Favorskii rearrangement of **5** with 10% aqueous potassium hydroxide[4] was found to be unsatisfactory and the best yield (34%) was obtained by heating a 4% solution of **5** in 10% aqueous potassium hydroxide for 4 hr at 110°. It was more satisfactory to use a more concentrated base for a shorter time and a 4% solution of **5** in 25% aqueous potassium hydroxide for 2.5 hr at 110° gave consistent yields of **8** of 70–85%.

Compound **10** was subjected to a wide range of bases to see whether the yield of cubane-1,4-dicarboxylic acid could be improved. The use of aqueous potassium hydroxide, powdered potassium hydroxide in dimethyl sulfoxide or tetrahydrofuran, sodium methoxide in methanol or dimethyl sulfoxide, aqueous potassium hydroxide in dioxane, and aqueous silver nitrate, with a range of concentrations, reaction times and temperatures failed to improve the yield of **7**. A complication arising from the use of Pyrex vessels was the large amount of silicic acid formed on acidification of the reaction product, which made extraction of the cubane-1,4-dicarboxylic acid difficult. Reactions were tried in silica or 'Nalgon' tubes, or in sealed stainless steel tubes at high temperatures, but the optimum yield was still only 9%.



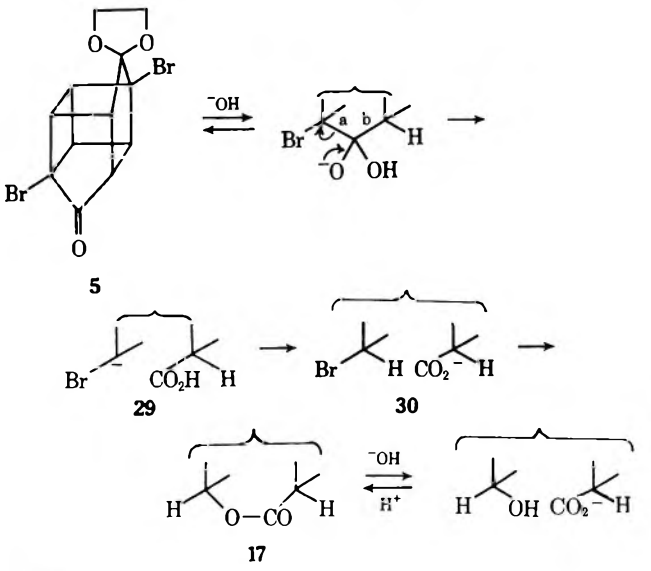
(15) British Patent 1,068,655 (1967); *Chem. Abstr.*, **68**, 2640m (1968).
(16) G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Org. Chem.*, **33**, 1454 (1968).
(17) K. V. Scherer, Jr., R. S. Lunt, III, and G. A. Ungefug, *Tetrahedron Lett.*, 1199 (1965).
(18) R. J. Stedman, L. S. Miller, and J. R. E. Hoover, *ibid.*, 2721 (1966).
(19) K. V. Scherer, Jr., *ibid.*, 5685 (1966).
(20) K. V. Scherer, Jr., personal communication.
(21) A. C. Cope and E. S. Graham, *J. Amer. Chem. Soc.*, **73**, 4702 (1951).
(22) R. S. Lunt, III, Ph.D. Dissertation, University of California, Berkeley, Calif., 1968.
(23) G. A. Ungefug, Ph.D. Dissertation, University of California, Berkeley, Calif., 1968.

The proposed mechanism for the Favorskii rearrangement of nonenolizable α-halogeno ketones is similar to the mechanism of the benzilic acid rearrangement[4,24-26] and it seems reasonable that any nucleophile capable of producing the intermediate (I) may cause a Favorskii



I

rearrangement. A reaction which is mechanistically similar to the Favorskii reaction is the cleavage of nonenolizable ketones by potassium *tert*-butoxide–water in an aprotic solvent.[27-29] We decided to study this reaction to see whether a nonenolizable α-halogeno ketone would give a Favorskii rearrangement under these conditions. The Favorskii rearrangement of **5** gives acceptable yields and we tried its reaction with potassium *tert*-butoxide–water in dimethyl sulfoxide to see whether ring cleavage or Favorskii rearrangement occurred. The reaction gave the lactone **17** (see Scheme II) indicating that ring cleavage (breakage of bond a) rather than Favorskii rearrangement (breakage of bond b) had occurred, probably as shown. In



addition to the lactone produced, the cleavage of **5** leads to the acid **8** and possibly to the *tert*-butyl ester of **8**, which may arise from the reactions of **5** with hydroxide ion and *tert*-butoxide ion, respectively, to give a Favorskii rearrangement.

The action of alkali on cage chloro ketones has been reported to give several products. For example, Scherer, Lunt, and Ungefug[17] describe a normal Favorskii rearrangement, ring cleavage without displacement of chlorine, and ring cleavage followed by an olefin-forming elimination of chlorine; Stedman, Miller, and Hoover[18] describe a normal Favorskii product; and Dunn, DiPasquo, and Hoover[16] report the reaction of 4,5,7,8-tetrachloropentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (**31**) with solid sodium hydroxide in benzene to give ring cleavage and the Favorskii product, and to give ring cleavage almost exclusively with aqueous alkali or solid potassium hydroxide in benzene. In none of these reactions did the presence of the carboxylate anion group in the cleaved product lead to displacement of chlorine to yield the lactone, but Akhtar, Fray, and Yarrow[30] have recently shown that the oxidation of 9,10,11,12-tetrachlorotetracyclo[6.4.0.0^{4,12}.0^{5,9}]dodec-10-ene (**32**) with potassium permanganate in refluxing acetone leads to 9-carboxy-10-chlorotricyclo[4.2.1.1^{2,5}]-decane-9-hydroxy-10-carboxy lactone (**33**), which is formed by transannular nucleophilic displacement of chlorine. When this chlorolactone carboxylic acid (**33**) was heated with aqueous potassium hydroxide another internal nucleophilic substitution led to an oxygen-bridged dicarboxylic acid (**34**).

Lunt[22] attributes the formation of the ring-cleaved products in the attempted Favorskii reactions of the polychlorinated cage ketones (see above) to a combination of factors arising from the severe ring strain and from the stability of the chlorocarbanions. The difference in the type of ring-cleaved product obtained by Lunt and that reported here may be explained in the following way. The initial ring-cleaved anion (**29**) is a stronger base than the chlorocarbanion and will lead to **30** which is then capable of producing the lactone because bromine is more easily displaced than chlorine. The bromocarbanion (**29**) is not able to give a ring-closed product because of the absence of a leaving group on the carbon atom to which the carboxy group is attached. When the intermediate product (**27**) obtained by Lunt is treated with strong base it will give the chlorocarbanion, which is not susceptible to attack by the carboxylate anion group, and the alternative displacement of the chloride ion from the carbon atom to which the carboxy group is attached will give the ring-closed acid (**28**). Oxidation of **32**, however, does not lead to chlorocarbanion formation and the displacement of chloride ion by the carboxylate anion group is the only displacement possible.

The thermal decarbonylation of **11** gave 2,4-dibromoindanone. Baggiolini, *et al.*,[31] obtained *cis*-8,9-dihydroindenone from the thermal decomposition of *endo*-dicyclopentadiene-1,8-dione, and DePuy, *et al.*,[32] by decarbonylating the chloro compound analogous to the bromo compound **11**, have obtained the 8,9-dihydroindenone initially, which then aromatized at room temperature to give 2,4-dichloroindanone. The nmr spectrum of compound **12** agrees very closely with that reported by DePuy, *et al.*,[32] for 2,4-dichloroindanone.

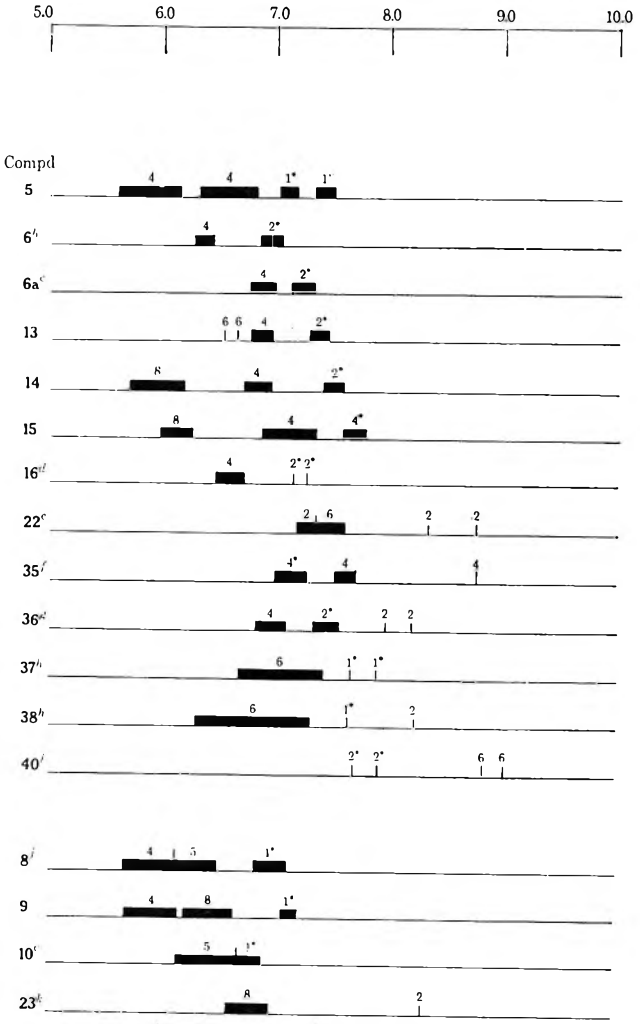
Nmr Spectra.—One notable feature of the nmr spectra of cage compounds is that the presence of carbonyl or ethylene ketal groups causes shielding of some of the hydrogen atoms.[4,5,33-35] Stedman and Davis[33] have considered the nmr spectra of ketones and ketals of

(24) A. S. Kende, *Org. React.*, **11**, 261 (1960).
(25) J.-M. Conia and J. Salaün, *Tetrahedron Lett.*, 1175 (1963).
(26) J.-M. Conia and J.-L. Ripoll, *Bull. Soc. Chim. Fr.*, 755, 773 (1963).
(27) G. A. Swan, *J. Chem. Soc.*, 1408 (1948).
(28) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Amer. Chem. Soc.*, **89**, 946 (1967).
(29) P. G. Gassman and F. V. Zalar, *Tetrahedron Lett.*, 3031, 3251 (1964).
(30) I. A. Akhtar, G. I. Fray, and J. M. Yarrow, *J. Chem. Soc. C*, 812 (1968).
(31) E. Baggiolini, E. G. Herzog, S. Iwasaki, R. Schorta, and K. Schaffner, *Helv. Chim. Acta*, **50**, 297 (1967).
(32) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964).
(33) R. J. Stedman and L. D. Davis, *Tetrahedron Lett.*, 1871 (1968).
(34) G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *ibid.*, 3737 (1966).
(35) R. J. Stedman and L. S. Miller, *J. Org. Chem.*, **32**, 35 (1967).

pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**35**) and have concluded that for the ketones the α protons are held in the shielding zone of the carbonyl group[36,37] and for the ethylene ketals the shielding may arise from some long range anisotropic effect associated with the oxygen atom.[33] We have prepared several substituted pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decanes (**22**), all of which show the characteristic high-field resonance for protons at the position α to a carbonyl or ketal functional group, but the nmr results indicate that the high-field resonance is not confined to ketones and ethylene ketals, but also appears in the spectra of a dimethyl ketal (**13**), a hydrate (**6a**), and a halo compound (**36**). In Chart I are collected the bar diagrams for the nmr spectra of several pentacyclodecanes and their derivatives. For all derivatives shown the resonances for the hydrogen atoms at C_1, C_9, C_5, and C_7 (when present) appear at higher field than those of the remaining cage methine protons. As would normally be expected, the introduction of a carbonyl group into the molecule causes most of the cage protons to resonate at lower field [*e.g.*, **22**, **37**; and **36**, **6**] but the protons at the positions α to the carbonyl group appear at higher field than the main group. Compounds **36** and **6**, however, show that the carbonyl groups have little relative effect on cage protons, and the α protons and the remaining cage protons are moved downfield to approximately the same extent. Similarly, the ethylene ketal group causes the resonance of several protons to move to lower field but the α protons resonate at approximately the same position as in the parent hydrocarbon (see **22**, **15**, **14**). Bromine atoms cause all resonances to move to slightly lower field (**36**, **22**; **14**, **15**; **38**, **37**) but surprisingly **36** shows high-field methine protons although C_6 and C_{10} are unsubstituted. Compounds **14**, **5**, and **6** show that replacing the ethylene ketal group by a carbonyl group causes all the resonances to move to lower field, but the peculiar high-field behavior of the α proton remains. For a similar system, Stedman and Davis[33] have suggested that the shielding of α protons would only be observed for ketals when the ketal oxygen atoms form part of a rigid ring; indeed they found that for a dimethyl ketal none of the cage protons were greatly shielded with respect to those of the hydrocarbon. From Chart I it can be seen that a bisdimethyl ketal (**13**) and even a bishydrate (**6a**) still show 2 protons at higher field than the main group, as is observed for the bisethylene ketal **14**, although there is an indication that the separation of the high-field protons from the main group decreases from compounds **14** to **13** to **6a**.

CHART I

NMR SPECTRA OF PENTACYCLODECANE AND PENTACYCLONONANE DERIVATIVES[a]



[a] Chemical shifts (τ values), with deuteriochloroform as solvent and tetramethylsilane as internal standard. The number of hydrogen atoms responsible for each resonance is indicated and the probable assignments of resonances arising from protons α to the carbonyl or ketal groups are indicated by an asterisk. [b] See also ref 4. [c] In hexadeuterioacetone. [d] See also ref 31. [e] See also ref 43. [f] See also ref 33 and 43. [g] Preparation to be reported later (J. R. Bell, N. B. Chapman, and K. J. Toyne). [h] See ref 34. [i] See G. Maier and U. Mende, *Angew. Chem., Int. Ed. Engl.*, **8**, 132 (1969). [j] See also ref 5. [k] See ref 1b and 16.

It does not seem likely that the high-field resonances of the ethylene ketals arise because of a long-range anisotropic effect of oxygen since compound **36** shows the high-field resonances, although oxygen atoms are not present in the molecule, and compounds **13** and **6a**, in which rotation about the carbon–oxygen bonds is possible, still show high-field absorption.

In the formal conversion of the *endo*-dicyclopentadienes **3**, **4**, and **11** into the pentacyclodecane derivatives **14**, **5**, and **6**, respectively, the protons at positions C_7 and C_{7a} in the diene become the protons showing the high-field absorption. From Table I and Chart I it can be seen that the changes of chemical shift for this conversion are always to higher field, and for the formation of compound **14** are τ 0.11 and 0.47, for compound **5**, 0.11 and 0.53, and for compound **6**, 0.52 and 0.15. The methine resonance at highest field for **19** (see Table I) and for *endo*-2-bromodicyclopentadien-1-one (**39**)[16] is at τ 7.31 and 7.25, respectively, and for the cage compounds the high-field absorption is at τ 7.51 and 7.6,[16] respectively, which corresponds to a shift to high field of at least τ 0.20 and 0.35, respectively.

The nmr spectra of appropriately substituted pentacyclononanes, *e.g.*, compounds **8**, **9**, and **10**, also show a high-field proton resonance, which appears basically as a triplet because the symmetry of these molecules is such that the hydrogen atoms on C_3 and C_7 are chemically identical.

(36) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, A. K. G. Nasser, L. Saunders, and W. B. Whalley, *Chem. Commun.*, 754 (1966).

(37) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

TABLE I

NMR SPECTRA OF *endo*-DICYCLOPENTADIENE DERIVATIVES[a]

Compd	Proton chemical shifts 1	2	3	3a	4	7	7a	5	6	8
endo-Dicyclopentadiene[b]	7.85									8.75
	8.40	—4.55—		6.82	—7.16, 7.27—		7.33	—4.08—		8.73
3			3.95	6.50		7.29	6.93	4.19	3.83	
4			2.38	6.35		6.95	6.81	4.09	4.00	
11			2.34	6.47		6.43	6.80	3.76	3.64	
19		4.43	4.23	—6.55, 7.13, 7.31, 7.31—				—3.85, 4.20—		
20		3.91	2.64	—6.43, 6.99, 7.07, 7.19—				—4.00, 4.14—		

[a] Chemical shifts (τ values) with deuteriochloroform as solvent and tetramethylsilane as internal standard. [b] See R. G. Foster and M. C. McIvor, *J. Chem. Soc. B*, 188 (1969).

It is clear from these observations that the anomalous high-field shift in the nmr spectra of these cage systems does not admit of a simple explanation and in any one case a number of opposing factors may be important. In an attempt to rationalise these results we are extending our studies to a wider range of cage compounds.

Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded at 100 MHz with a Varian HA-100 or JEOL 4H-100 spectrometer, with tetramethylsilane as internal standard and deuteriochloroform as solvent; the chemical shifts and coupling constants were obtained by first-order analysis. The molecular ion peaks in the mass spectra are given for the bromine 79 isotope. Glpc analyses were achieved by using a Perkin-Elmer F11 gas-liquid chromatograph fitted with a column (72 in. × 1/8 in. o.d.) packed with 20% silicone gum rubber, SE-301, on Chromosorb W. Thin layer chromatography plates were spread with 0.1 mm of silica gel G, Merck 7731, and developed by spraying them with an ethanolic solution of phosphomolybdic acid and heating them to 180–200° for 30 min. Whenever a preparation leading to a useful yield of product is described, the reported yield was obtained reproducibly in several (up to 10) separate experiments.

Cyclopentanone Ethylene Ketal (1).—This compound was prepared by the method described by DePuy, *et al.*,[38] for the preparation of 2-chlorocyclopentanone ethylene ketal; it had bp 152–155° [lit.[39] 57–57.2° (18 mm)].

2,2,5-Tribromocyclopentanone Ethylene Ketal (2).—Cyclopentanone ethylene ketal (1) (128.0 g, 1.0 mol) in pure dioxane (1 l.) under a dry atmosphere was cooled to 10–15°. Bromine (480 g, 3.0 mol) was added dropwise with stirring during 1.5 hr, keeping the mixture below 15°. The mixture was then stirred at room temperature for 2 days and poured into 5% aqueous sodium bicarbonate (6 l.) and stirred, and the product was kept for 1 hr. The yellow solid was filtered off and washed with water, dried ($CaCl_2$) *in vacuo* overnight, and recrystallized twice (ethanol) to give 2,2,5-tribromocyclopentanone ethylene ketal (**2**) (253.7 g, 69.5%): mp 76–78°; nmr τ 5.21 (q, 1 H), 5.42–5.90 (m, 4 H), 6.77–8.33 (m, 4 H); ir (KCl) 1210, 1057, 1039, 950, 660 cm^{-1}; *m/e* 362 (M^+).

Anal. Calcd for $C_7H_9O_2Br_3$: C, 23.04; H, 2.49; Br, 65.70. Found: C, 23.06; H, 2.57; Br, 65.40.

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione Bisethylene Ketal (3).**—For large scale preparations, the most convenient method involved the dehydrobromination of compound **2** with methanolic sodium methoxide.

Compound **2** (253.7 g, 0.73 mol) in pure dioxane (500 ml) was added dropwise at room temperature during 1.5 hr with stirring to sodium (92.0 g, 4.0 g-atoms) dissolved in methanol (1.1 l.). The mixture was heated under reflux with stirring for 2.5 hr and cooled, and water (3 l.) was added. The aqueous mixture was kept at room temperature for 1 hr and the solid was filtered off, dried ($CaCl_2$) *in vacuo*, and recrystallized twice (ethanol) to give *endo*-2,4-dibromodicyclopentadiene-1,8-dione bisethylene ketal (**3**) (106.6 g, 76%): mp 172–174°; nmr τ 3.83 (q, H_6), 3.95 (d, H_3), 4.19 (q, H_5), 5.68–6.21 (m, 8 H), 6.50 (q, H_{3a}), 6.93 (q, H_{7a}), 7.29 (m, H_7); $J_{3,3a}$ = 2.5, $J_{3,7}$ = 0.5, $J_{3a,7a}$ = 7.3, $J_{5,6}$ = 6.5, $J_{5,7}$ = 1.0, $J_{6,7}$ = 3.5, $J_{7,7a}$ = 4.8 Hz; ir (KCl) 3060, 3000, 1617, 1050, 1032, 1012 cm^{-1}; *m/e* 404 (M^+).

Anal. Calcd for $C_{14}H_{14}O_4Br_2$: C, 41.40; H, 3.48; Br, 39.36. Found: C, 41.50; H, 3.40; Br, 39.23.

The dehydrobromination of **2** with potassium *tert*-butoxide in dimethyl sulfoxide at 18–20°, potassium *tert*-butoxide in *tert*-butyl alcohol at 18–20°, or piperidine at reflux temperature gave compound **3** in 67, 63, and 89% yield, respectively. Compound **3** was also prepared (64% yield) by the reaction of **11** with ethylene glycol in benzene, with toluene-*p*-sulfonic acid as catalyst.

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione 8-Ethylene Ketal (4).**—Concentrated hydrochloric acid (100 ml) was added dropwise at room temperature to a stirred solution of compound **3** (100 g, 0.246 mol) in tetrahydrofuran (1 l.). The mixture was stirred for 18 hr and then poured into 10% aqueous sodium bicarbonate (6 l.) and kept at room temperature for 1 hr. The product was filtered off, dried ($CaCl_2$) *in vacuo*, and recrystallized twice (toluene) to give compound **4** (81.4 g, 91%): mp 171–172° (lit.[4] 172–173°); nmr τ 2.38 (q, H_3), 4.00 (q, H_6), 4.09 (q, H_5), 5.68–6.13 (m, 4 H), 6.35 (q, H_{3a}), 6.81 (t, H_{7a}), 6.95 (m, H_7); $J_{3,3a}$ = 2.9, $J_{3,7}$ = 0.5, $J_{3a,7a}$ = 5.4, $J_{5,6}$ = 6.7, $J_{5,7}$ = 1.9, $J_{6,7}$ = 3.3, $J_{7,7a}$ = 5.3 Hz; ir (KCl) 2990, 1714, 1584, 1481 cm^{-1}; *m/e* 360 (M^+).

Anal. Calcd for $C_{12}H_{10}O_3Br_2$: C, 39.81; H, 2.78; Br, 44.15. Found: C, 40.01; H, 2.65; Br, 44.30.

5,9-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione 6-Ethylene Ketal (5).—Compound **4** (17.0 g, 0.047 mol) in dry benzene (500 ml) in a Pyrex tube (40 × 5 cm) fitted with a condenser and nitrogen inlet tube was placed 1 cm from the quartz water-cooled jacket of a 450-W Hanovia medium-pressure mercury vapor lamp for 16–24 hr. The progress of the reaction was followed by using glpc (column temperature 220°) or tlc (benzene); compounds **4** and **5** have R_f values of 0.11 and 0.76, respectively. The benzene was removed and the residue was recrystallized twice (1:1 carbon tetrachloride–hexane) to give compound **5** (15.1 g, 89%): mp 148–150° (lit.[5] 148–150°); nmr τ 5.62–6.15 (m, 4 H), 6.31–6.81 (m, 4 H), 6.98–7.14 (m, 1 H), 7.26–7.42 (m, 1 H); ir (KCl) 2990, 2880, 1768 cm^{-1}; *m/e* 360 (M^+).

Anal. Calcd for $C_{12}H_{10}O_3Br_2$: C, 39.81; H, 2.78; Br, 44.15. Found: C, 39.80; H, 2.80; Br, 44.20.

5,9-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione (6). Method 1.—A solution of compound **5** (10.0 g, 0.0276 mol) in concentrated sulfuric acid (100 ml) was stirred for 2 days. The reaction was followed by using tlc (1:19 methanol–benzene); compounds **5** and **6** have R_f values of 0.45 and 0.01, respectively. The dark solution was poured onto crushed ice and shaken with ether (three 50-ml portions). The ethereal extracts were discarded and the aqueous phase was diluted to 500 ml with water and washed continuously with ether (400 ml) for 20 hr. The ethereal solution was dried (Na_2CO_3) and the ether was removed to give the hydrate of **6** (7.3 g). Recrystallization (methylene chloride), followed by desiccation ($CaCl_2$) at 40° (1 mm), gave compound **6** (6.2 g, 71%): mp 230–232° dec (lit.[4] 232–233° dec); nmr τ 6.28–6.44 (m, 4 H), 6.86–7.02 (m, 2 H); ir (KCl) 3030, 1782 cm^{-1}; *m/e* 316 (M^+).

Method 2.—Compound **13** (0.5 g, 0.0012 mol) in tetrahydrofuran (5 ml) was heated under reflux overnight with hydrochloric acid (1 ml of concentrated acid, 1 ml of water). The solution was cooled, added to 10% aqueous sodium bicarbonate (20 ml), and shaken with ether (three 20-ml portions), and the ethereal solutions were dried ($MgSO_4$). Evaporation of the ether and crystallization (methylene chloride) of the residue gave the hydrate of

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6. Desiccation (P_2O_5) at 48° (1 mm) for 24 hr gave compound **6** (0.21 g, 54%) with the physical properties given above.

1,4-Dimethoxycarbonylpentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (7).—Compound **6** (1.0 g, 0.032 mol) or compound **10** (1.0 g, 0.00394 mol) in aqueous potassium hydroxide (30 ml of 50% w/w, *i.e.*, 20 g of potassium hydroxide in 20 g of water) was heated under reflux for 30 hr. The solution was poured into water (30 ml) and brought to pH 1 with hydrochloric acid. The solid was treated with ethereal diazomethane, the mixture was filtered, and the filtrate was washed with water and dried ($MgSO_4$). The ether was removed and the solid was crystallized (hexane) to give compound **7**, mp 161–162° (lit.[4] 161–162°). From compound **6** or compound **10** the yields were 0.072 g (10.4%) and 0.086 g (9.9%), respectively.

1-Bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one Ethylene Ketal 4-Carboxylic Acid (8).—A solution of compound **5** (44.0 g, 0.1255 mol) and potassium hydroxide (275.0 g) in water (1.1 l.) was stirred at room temperature for 20 min; most of the solid had then dissolved. During 45 min the temperature was raised to and then kept at 110–120° for 2 hr. The solution was cooled and acidified with hydrochloric acid, and the product was filtered off, washed, and crystallized twice (ethanol) to give compound **8** (28.6 g, 79%): mp 187–189° (lit.[5] 187–189°); nmr τ −0.98 (s, 1 H), 5.68–6.11 (sym m, 4 H), 6.12–6.50 (m, 5 H), 6.79–7.02 (m, 1 H); ir (CH_2Cl_2) 1730, 1688 cm^{-1}; *m/e* 298 (M$^+$).

Anal. Calcd for $C_{12}H_{11}O_4Br$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 48.30; H, 3.60; Br, 26.50.

Methyl 1-Bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one Ethylene Ketal 4-Carboxylate (9).—Compound **8** (12.7 g, 0.0425 mol) was dissolved in ether (500 ml) and esterified with ethereal diazomethane. The ethereal solution was washed with water, sodium bicarbonate solution, water, and dried ($MgSO_4$). The ether was removed *in vacuo* and a solution of the solid in hot hexane was treated with decolorizing charcoal and allowed to cool to give methyl 1-bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one ethylene ketal 4-carboxylate (**9**) (11.6 g, 87%): mp 106–108°; nmr τ 5.69–6.11 (sym m, 4 H), 6.14–6.52 (m, includes a singlet at 6.33, 8 H), 6.92–7.01 (m, 1 H); ir (KCl) 2998, 2960, 2910, 2895, 1725, 1300, 1230, 650 cm^{-1}; *m/e* 312 (M$^+$).

Anal. Calcd for $C_{13}H_{13}O_4Br$: C, 49.86; H, 4.18; Br, 25.52. Found: C, 49.90; H, 4.00; Br, 25.60.

1-Bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one-4-carboxylic Acid (10).—A solution of compound **8** (20.0 g, 0.0669 mol) in aqueous sulfuric acid (360 ml of 75% w/w, *i.e.*, 143 ml of water and 252 ml of concentrated sulfuric acid) was stirred for 3 days at room temperature. The reaction was followed by using tlc [ethanol–water–ammonium hydroxide (2 *N*), 100:6:8], spraying with saturated aqueous ammonium bisulfate, and development at 200°. The mixture was poured onto crushed ice and diluted to 1 l. with water. The aqueous solution was shaken with ether (100 ml) to remove unchanged acid **8**. The aqueous phase was washed continuously with ether (400 ml) for 20 hr and then dried ($MgSO_4$). The ether was removed to give the crude hydrate of compound **10** (16.4 g) which was heated for 1 hr under reflux in toluene in an apparatus having a Dean–Stark separator. When cooled, the toluene solution gave 1-bromopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonan-9-one-4-carboxylic acid (**10**) (15.1 g, 87%): mp 219–220°; nmr τ (CD_3COCD_3) 6.17–6.71 (m, 5 H), 6.72–6.86 (m, 1 H); ir (KCl) 3350, 3000, 2950, 1683, 1652, 1256, 1224 cm^{-1}; *m/e* 254 (M$^+$).

Anal. Calcd for $C_{10}H_7O_3Br$: C, 47.08; H, 2.77; Br, 31.33. Found: C, 47.03; H, 2.80; Br, 31.65.

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione (11).**—A solution of compound **4** (2.65 g, 0.00736 mol) in concentrated sulfuric acid (10 ml) was stirred at room temperature for 2 days. The reaction mixture was poured onto crushed ice and the aqueous mixture was kept in the refrigerator overnight. The solid was filtered off and the filter cake was washed with water and dried ($CaCl_2$) *in vacuo* overnight. The solid was dissolved in hot carbon tetrachloride and treated with decolorizing charcoal. Compound **11** crystallized as fine white needles from the cold solution (1.71 g, 73%): mp 154–155° dec (lit.[4] 154–155° dec); nmr τ 2.34 (q, H_2), 3.64 (q, H_6), 3.76 (q, H_5), 6.43 (m, H_7), 6.47 (q, H_{3a}), 6.80 (q, H_{7a}); $J_{3,3a}$ = 3.0, $J_{3,7}$ = 0.5, $J_{3a,7a}$ = 6.5, $J_{5,6}$ = 7.0, $J_{5,7}$ = 1.5, $J_{6,7}$ = 3.5, $J_{7,7a}$ = 5.0 Hz; ir (KCl), 1795, 1722, 1585, 1556, 690 cm^{-1}; *m/e* 316 (M$^+$).

Anal. Calcd for $C_{10}H_6O_2Br_2$: C, 37.77; H, 1.90; Br, 50.27. Found: C, 37.70; H, 2.0; Br, 50.20.

2,4-Dibromoindanone (12).—Compound **11** (1.0 g, 0.00315 mol) in freshly distilled tetralin (50 ml) under nitrogen was heated slowly to and kept at 180° for 3 hr. The tetralin was removed *in vacuo* [42° (0.7 mm)] and the oily residue was dried ($CaCl_2$–paraffin wax) *in vacuo*. The solid in hot ethanol was treated with decolorizing charcoal and 2,4-dibromoindanone (**12**) crystallized from the cold solution (0.58 g, 64%): mp 80–82°; nmr τ 2.12–2.26 (m, 2 H), 2.62 (d, 1 H), 5.29 (q, H_2, $J_{H_2,H_{cis}}$ = 7.5 Hz, $J_{H_2,H_{3\ trans}}$ = 3.5 Hz), 6.26 [q, H_3 (cis to H_2), J_{gem} = 18.5 Hz], 6.66 [q, H_3 (trans to H_2)]; ir (KCl) 3037, 2960, 1728, 1600, 1572 cm^{-1}; *m/e* 288 (M$^+$).

Anal. Calcd for $C_9H_6OBr_2$: C, 37.27; H, 2.09; Br, 55.12. Found: C, 37.30; H, 2.05; Br, 54.92.

5,9-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione Bisdimethyl Ketal (13).—A solution of compound **11** (5.0 g, 0.016 mol) in methanolic hydrogen chloride (72 g of a 4% w/w solution)[6] in a Pyrex tube (18.5 × 3.2 cm), fitted with a condenser and calcium chloride guard tube, was placed 1 cm from a 450-W Hanovia medium-pressure mercury vapor lamp and was irradiated for 24 hr, whereupon no olefinic stretching absorption (1585 cm^{-1}) could be detected. The solution was poured into 10% aqueous sodium bicarbonate (300 ml) and shaken with ether (three 100-ml portions) and the combined ethereal solutions were washed with water and dried ($MgSO_4$). The ether was removed and the residual brown oily solid was heated under reflux with water for 1 hr. The mixture was cooled, the water was decanted off, and the solid was dried ($CaCl_2$) *in vacuo*. Chromatography on a neutral alumina column (32 × 2.4 cm) and elution with petroleum ether (bp 40–60°) gave a white solid (2.9 g) which was crystallized (cyclohexane) to give 5,9-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione bisdimethyl ketal (**13**) (1.6 g, 25%): mp 123–124°; nmr τ 6.58 (s, 6 H), 6.61 (s, 6 H), 6.76–6.90 (m, 4 H), 7.22–7.35 (m, 2 H); ir (KCl) 2990, 2870, 650 cm^{-1}; *m/e* 408 (M$^+$).

Anal. Calcd for $C_{14}H_{18}O_4Br_2$: C, 41.00; H, 4.42; Br, 38.97. Found: C, 41.14; H, 4.46; Br, 38.60.

5,9-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione Bisethylene Ketal (14).—Compound **5** (23.0 g, 0.064 mol), redistilled ethylene glycol (23.0 g, 0.37 mol) and toluene-*p*-sulfonic acid (0.1 g) in dry benzene (600 ml) were heated under reflux for 36 hr in an apparatus having a Dean–Stark water separator. The solution was cooled, washed with aqueous potassium hydroxide and water, and dried ($MgSO_4$). The benzene was removed *in vacuo* and the residue was crystallized twice (tetrahydrofuran) to give 5,9-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-deca-6,10-dione bisethylene ketal (**14**) (20.5 g, 80%): mp 188–190°; nmr τ 5.69–6.15 (m, 8 H), 6.68–6.85 (m, 4 H), 7.33–7.46 (m, 2 H); ir (KCl) 2990, 1304, 1035, 657 cm^{-1}; *m/e* 404 (M$^+$).

Anal. Calcd for $C_{14}H_{14}O_4Br_2$: C, 41.40; H, 3.48; Br, 39.36 Found: C, 41.30; H, 3.50; Br, 39.60.

Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione Bisethylene Ketal (15).—Compound **14** (13.1 g, 0.0323 mol) in tetrahydrofuran (250 ml) and *tert*-butyl alcohol (9.55 g, 0.130 mol) was stirred rapidly and finely cut pieces of lithium (1.34 g, 0.193 g-atom) were added in portions during 30 min. The mixture was heated under reflux for 2 hr and then allowed to cool. Water (50 ml) was added and the mixture was stirred vigorously for 4 hr. The solution was poured into water (1.1 l.), shaken with ether (three 150-ml portions) and the ethereal solutions were combined, washed with water, and dried ($MgSO_4$). The ether was evaporated off slowly through a Vigreux column (20 cm) to leave a residue which was crystallized twice (ethanol) to give pentacyclo-[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione bisethylene ketal (**15**) (7.3 g, 91%): mp 94–96°; nmr τ 5.96–6.22 (m, 8 H), 6.81–7.24 (m, 4 H), 7.44–7.59 (m, 4 H); ir (KCl) 2990, 1473, 1330, 948, 899 cm^{-1}; *m/e* 248 (M$^+$).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.80; H, 6.50.

Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]deca-6,10-dione (16). Method 1.—A solution of compound **21** (3.0 g, 0.0147 mol) in concentrated sulfuric acid (35.0 ml) was stirred at room temperature for 30 hr. The solution was then poured onto crushed ice and shaken with ether (three 150-ml portions), and the ethereal solutions were washed with water (three 50-ml portions) and dried ($MgSO_4$). The ether was removed and the residue was crystallized (1:1 acetic acid–water) to give compound **16** (1.76 g, 75%): mp 162–163° (lit.[31] 163°); nmr τ 6.50–6.70 (m, 4 H), 7.14 (s, 2 H), 7.24 (s, 2 H); *m/e* 160 (M$^+$).

Method 2.—A solution of compound **15** (3.0 g, 0.0121 mol) in concentrated sulfuric acid (35 ml) was stirred at room tempera-

ture for 24 hr. The extraction and isolation were similar to those described in method 1; the yield of **16** was 1.36 g (70%).

1-Bromotetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonan-9-one Ethylene Ketal 4-Hydroxy-7-carboxy Lactone (17).—Compound **5** (1.08 g, 0.003 mol) in dry dimethyl sulfoxide (15 ml) was added during 1 hr, with ice-water cooling, to a stirred mixture of potassium *tert*-butoxide (3.36 g, 0.030 mol), water (0.162 g, 0.009 mol) and dimethyl sulfoxide (10 ml). The mixture was stirred overnight at room temperature and then poured into water (300 ml). The solution was saturated with salt and shaken with ether (three 50-ml portions) and the ethereal solutions (ethereal washings of the alkaline solution) were dried ($MgSO_4$). The aqueous solution was brought to pH 1 with hydrochloric acid and then shaken with ether (three 50-ml portions); the ethereal solutions (ethereal washings of the acidic solution) were dried ($MgSO_4$).

Ethereal Washings of the Alkaline Solution.—The ether was removed to give a pale yellow solid (0.18 g). Glpc analysis (column temperature 236°) showed the presence of three components (8:1:1) with retention times different from that of compound **5**. The solid was heated under reflux with potassium hydroxide (0.6 g) in water (0.6 ml) and methanol (6 ml) for 24 hr. The solution was cooled, poured into water (20 ml), and shaken with ether (three 10-ml portions), and the ethereal solutions were dried ($MgSO_4$). [Evaporation of the ether gave a solid (0.03 g) which was shown by glpc to contain the same distribution of components as the mixture before hydrolysis]. The aqueous solution was brought to pH 1 with hydrochloric acid and shaken with ether (three 10-ml portions), and the ethereal solutions were dried ($MgSO_4$). Evaporation of the ether gave a solid (0.11 g) which was treated with an ethereal solution of diazomethane. Analysis of the ethereal solution by glpc showed one main component (85%) which was identified with the methyl ester **9** by their identical retention times.

Ethereal Washings of the Acid Solution.—The ether was removed to give a colorless solid (0.53 g); glpc analysis showed the product to consist mainly of one component. However, when a small portion was dissolved in ether and treated with an ethereal solution of diazomethane, glpc showed the original major component and a small amount of another component which corresponded to the methyl ester **9** (identical retention times). The remaining solid (0.50 g) was purified by chromatography on a neutral alumina column (32 × 1.2 cm) (elution with ethyl acetate). The solvent was removed and the residue was crystallized (carbon tetrachloride) to give 1-bromotetracyclo[4.3.0.0^{2,5}.0^{3,8}]-nonan-9-one ethylene ketal 4-hydroxy-7-carboxy lactone (**17**) (0.29 g, 32%): mp 143–145°; nmr τ 4.65 (q, 1 H), 5.71–6.01 (m, 4 H), 6.76 (t, 1 H), 7.02 (q, 1 H), 7.46–7.86 (m, 3 H), 8.33 (q, 1 H); ir (KCl) 2978, 2905, 1786, 1775 cm^{-1}; ir (KCl disk of solid from reaction with LiOD–D_2O) 1555, 1500, 1440, 867, 500 cm^{-1}; *m/e* 298 (M^+), main peaks at 219 (100%, $C_{12}H_{11}O_4^+$), 191 ($C_{11}H_{11}O_3^+$), 175 ($C_{11}H_{11}O_2^+$), 156 ($C_6H_5Br^+$), 147 ($C_9H_7O_2^+$), 131 ($C_9H_7O^+$), 103 ($C_8H_7^+$), 98 ($C_4H_6O_2^+$); the formulas of all the ions in parentheses were confirmed by mass marking.

Anal. Calcd for $C_{12}H_{11}O_4Br$: C, 48.18; H, 3.71; Br, 26.72. Found: C, 47.92; H, 3.70; Br, 26.90.

2,5-Dibromocyclopentanone Ethylene Ketal (18).—This compound was prepared by the method described for compound **2**, using 2.0 mol of bromine. The mixture was allowed to attain room temperature and then stirred for a further hour. The colorless solution was poured into 5% aqueous sodium bicarbonate (5 l.) and shaken with ether (three 300-ml portions). The combined ethereal solutions were washed with water and dried ($MgSO_4$). Evaporation of the ether *in vacuo* gave a pale brown oil which usually solidified when kept in the refrigerator overnight. Recrystallization thrice (ethanol) gave 2,5-dibromocyclopentanone ethylene ketal (**18**) (194.7 g, 68.1%): mp 62–64°; nmr τ 5.75 (s, 6 H), 7.67–7.83 (m, 4 H); ir (KCl) 2980, 2954, 2892, 1304, 1212, 695 cm^{-1}; *m/e* 284 (M^+).

Anal. Calcd for $C_7H_{10}O_2Br_2$: C, 29.40; H, 3.52; Br, 55.89. Found: C, 29.65; H, 3.55; Br, 55.65.

Sometimes the product failed to solidify but the oil still gave satisfactory yields when used for the preparation of compound **19**. Garbisch[40] reported a method of brominating cycloalkanone ketals in ether which we found satisfactory for the preparation of 2,5-dibromocyclopentanone ethylene ketal (**18**), but which was not successful for the preparation of 2,2,5-tribromocyclopentanone ethylene ketal (**2**).

***endo*-Dicyclopentadiene-1,8-dione Bisethylene Ketal (19).**—A solution of compound **18** (190.0 g, 0.664 mol) in methanol (400 ml) was added dropwise with stirring to sodium (92.0 g, 4.0 g-atoms) in methanol (1.1 l.) cooled in ice water. The mixture was then heated under reflux for 9 hr, cooled, poured into water (5 l.), and shaken with ether (three 300-ml portions). The ethereal solutions were washed with water and dried ($MgSO_4$). The ether was removed and the residue was crystallized (ethanol) three times to give compound **19** (56.8 g, 69%): mp 91–92° (lit.[41] 92°); nmr τ 3.80–3.90 (m, 1 H), 4.15–4.27 (m, 2 H), 4.43 (q, 1 H), 5.98–6.13 (m, 8 H), 6.46–6.64 (m, 1 H), 7.13 (q, 1 H), 7.22–7.39 (m, 2 H); ir (KCl) 3040, 2982, 2888, 1695 cm^{-1}; *m/e* 248 (M^+).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.70; H, 6.60.

***endo*-Dicyclopentadiene-1,8-dione 8-Ethylene Ketal (20).**—This compound was prepared by the partial hydrolysis of compound **19** at room temperature for 5 hr as described by Vogel and Wyes:[41] yield 92%; mp 93–94° (lit.[41] 94–95°); nmr τ 2.64 (q, 1 H), 3.91 (q, 1 H), 3.91–4.20 (m, 2 H), 5.94–6.24 (sym m, 4 H), 6.32–6.52 (m, 1 H), 6.91–7.25 (m, 3 H); *m/e* 204 (M^+).

Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]deca-6,10-dione 6-Ethylene Ketal (21).—This compound was prepared from compound **20** as described by Vogel and Wyes:[41] yield 50%; mp 58–60° (lit.[41] 58–60°).

Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (22).—This compound was prepared as described by Schenck and Steinmetz,[42] and by Dilling, Braendlin, and McBee.[43] The residue was sublimed twice [90° (760 mm)] to give compound **22**: yield 14%; mp 139–141° (lit.[42] 134–136°,[43] 138–141°, and 142–143°); nmr τ 7.20–7.36 (m, 2 H), 7.38–7.58 (m, 6 H), 8.36 (d, 2 H), 8.79 (d, 2 H); *m/e* 132 (M^+).

Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (35).—This compound was prepared by the dechlorination of dodecachloropentacyclo-[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane[44,45] as described by Dilling, Braendlin, and McBee.[43] The crude product was purified by chromatography on a neutral alumina column (elution with cyclohexane). The cyclohexane was removed *in vacuo* and the residue was sublimed [40° (40 mm)] to give compound **35**: yield 52%; mp 125–127° (sealed tube) (lit.[43] 125–127°); nmr τ 7.00–7.24 (m, 4 H), 7.43–7.57 (m, 4 H), 8.64 (s, 4 H); *m/e* 132 (M^+).

Registry No.—**2**, 25834-49-5; **3**, 25834-50-8; **4**, 25834-51-9; **5**, 25867-84-9; **6**, 25867-85-0; **6a**, 25834-60-0; **8**, 25867-86-1; **9**, 25867-87-2; **10**, 25867-88-3; **11**, 25834-52-0; **12**, 25834-53-1; **13**, 25834-54-2; **14**, 25867-89-4; **15**, 25834-55-3; **16**, 74725-77-0; **17**, 25915-60-0; **18**, 25834-57-5; **19**, 4576-45-8; **20**, 4576-44-7; **22**, 6707-86-4; **35**, 6707-88-6.

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(45) E. T. McBee, C. W. Roberts, J. D. Idol, Jr., and R. H. Earle, Jr., *ibid.*, **78**, 1511 (1956).

Synthesis of *gem*-Dimethylcycloheptadienes *via* Homoallylic Ring Expansion

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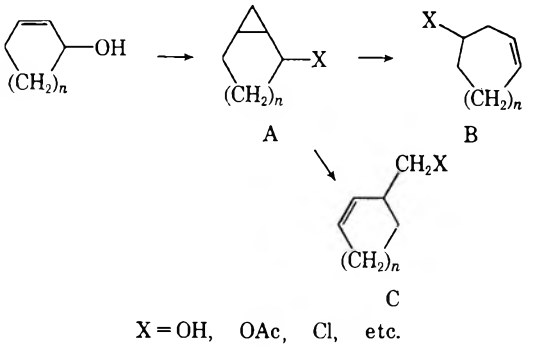
Several synthetic routes to *gem*-dimethylcycloheptadienes involving cyclopropanation of 5,5-dimethyl-2-cyclohexenol (4) coupled with homoallylic ring expansion have been investigated. Satisfactory conversions were effected either by bromination of *cis*-4,4-dimethylbicyclo[4.1.0]heptan-2-ol (*cis*-5) with 48% hydrogen bromide followed by base-promoted dehydrobromination or by acetylation of *cis*-5 followed by pyrolysis. The diene product distributions in the former route are subject to both kinetic and thermodynamic control and the importance of these factors is discussed with respect to several base–solvent systems.

There are many examples of the acid-catalyzed opening of cyclopropyl carbinols to afford acyclic olefins,[1] sometimes in a highly stereoselective manner.[2,3] In addition, the conversion of cyclic allylic alcohols to the corresponding cyclopropyl alcohols, coupled with acid-catalyzed opening of the latter (to give type B products), has been shown to be a useful method for ring



expansion.[3] However, depending on the conditions, bicyclic products (type A) may be formed[4] or cleavage may occur at a perimetrical cyclopropyl bond to give type C products.[5] Because of the potential synthetic utility of these reactions and because of a need for several previously unknown *gem*-dimethyl-substituted cycloheptadienes, we decided to employ a route which would further extend the scope of homoallylic ring expansion reactions.

(1) For reviews, see (a) S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem., Int. Ed. Engl.*, **7**, 577 (1968); (b) M. Hanack and H.-J. Schneider, *ibid.*, **6**, 666 (1967); *Fortschr. Chem. Forsch.*, **8**, 554 (1967); (c) H. G. Richey, Jr., in "Carbonium Ions," Vol. 3, G. A. Olah and P. von R. Schleyer, Ed., Wiley, New York, N. Y., 1969.

(2) S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, **90**, 2882 (1968).

(3) (a) M. Gašić, D. Whalen, B. Johnson, and S. Winstein, *ibid.*, **89**, 6382 (1967); (b) D. Whalen, M. Gašić, B. Johnson, H. Jones, and S. Winstein, *ibid.*, **89**, 6384 (1967).

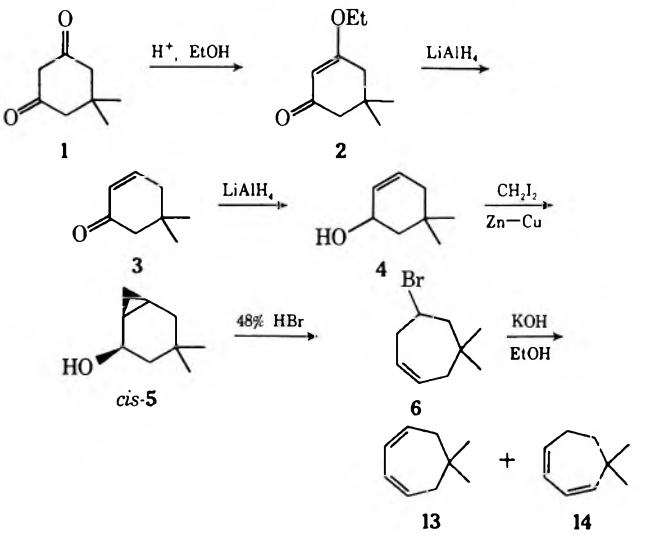
(4) For examples involving bicyclo[4.1.0]heptyl products, see (a) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 1735 (1967); (b) J. Tadanier, *J. Org. Chem.*, **31**, 2124 (1966); (c) L. Birladeanu, T. Hanafusa, and S. Winstein, *J. Amer. Chem. Soc.*, **88**, 2315 (1966); (d) L. Birladeanu, T. Hanafusa, B. Johnson, and S. Winstein, *ibid.*, **88**, 2316 (1966); (e) H. L. Goering and K. E. Rubenstein, Abstracts, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., 1966, p K11; (f) S. W. Pelletier, S. Nakamura, and Y. Shimizu, *Chem. Commun.*, 727 (1966); (g) A. C. Cope, C. H. Park, and P. Scheiner, *J. Amer. Chem. Soc.*, **84**, 4862 (1962).

(5) For examples related to those in ref 4 see ref 4a, b, and f and (a) E. C. Friedrich, *J. Org. Chem.*, **34**, 528 (1969); (b) H. Laurent, H. Muller, and R. Wiechert, *Chem. Ber.*, **99**, 3836 (1966); (c) Y. Hikino and P. de Mayo, *Chem. Commun.*, 550 (1965); (d) M. Julia, S. Julia, T. S. Yu, and C. Neuville, *Bull. Soc. Chim. Fr.*, 1381 (1960), and earlier papers; (e) W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, **34**, 2512 (1969).

Results and Discussion

The reaction sequence which was employed with the most success is outlined in Scheme I. All of the reac-

SCHEME I



tions occur in good yield (>70%) to afford reasonably pure products (>92% in each case); the overall yield of cycloheptadienes is ~40%.

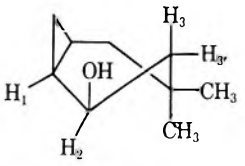
5,5-Dimethyl-2-cyclohexenone (**3**) was prepared from 5,5-dimethyl-1,3-cyclohexanedione (dimedon or methone) (**1**) by the method of Frank and Hall.[6] Greatly increased yields (~90%) can be obtained with the use of fresh reducing agent in the reduction of 3-ethoxy-5,5-dimethyl-2-cyclohexenone (**2**) (see Experimental Section).

The third step, which entails a lithium aluminum hydride reduction of the α,β-unsaturated ketone **3**, must be carefully controlled in order to obtain a good yield of reasonably pure allylic alcohol **4**. We have obtained satisfactory conversions by treating **3** with a 10% equiv excess of fresh reducing agent for 20 min. When **3** is stirred for 8 hr with a twofold excess of lithium aluminum hydride the product mixture contains a substantial quantity of a saturated alcohol, 3,3-dimethylcyclohexanol. The use of sodium borohydride leads to even more extensive reduction of the double bond. Similar behavior of α,β-unsaturated

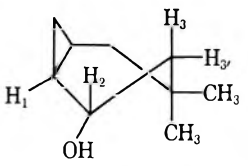
(6) R. L. Frank and H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **72**, 1645 (1950).

carbonyl compounds has been noted by other workers.[7,8]

A cyclopropyl ring was next introduced adjacent to the hydroxyl group by treatment of **4** with methylene iodide and zinc–copper couple.[4g,9] By analogy with the majority[9b–d] of previous reports of the cyclopropanation of 2-cyclohexenol,[4g,9b–d] the product was expected to be essentially all cis isomer. This is confirmed by the nmr spectrum of the single bicyclo[4.1.0]heptanol product (*cis*-**5**), particularly by the splitting of the C_2 proton at τ 5.82 which is a five-line multiplet (two overlapping doublets of doublets) with a line separation of 5.8 Hz. Thus H_1, H_3, and $H_{3'}$ are all



cis-**5**

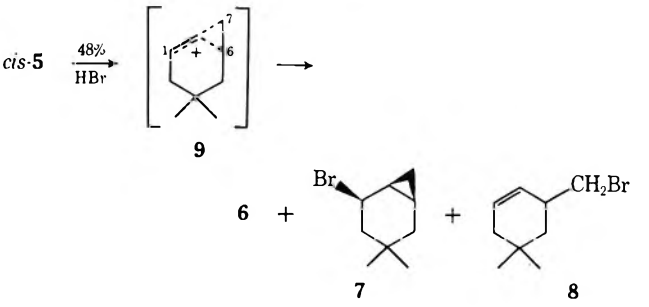


trans-**5**

coupled reasonably strongly with H_2 (see Experimental Section). On the other hand, the signal for H_2 (τ 5.93) in the trans isomer of **5** (*trans*-**5**)[10] is an apparent triplet (*i.e.*, overlapping doublets) with a line separation of 5.3 Hz. Since the dihedral angle between H_1 and H_2 is ~40° in *cis*-**5** and ~80° in *trans*-**5** (from Dreiding models) the stereochemical assignments are consistent with the much larger value of J_{12} in *cis*-**5** (5.8 Hz as opposed to <1 Hz in *trans*-**5**).[11]

Under favorable reaction conditions (0.5 hr in ether at reflux) *cis*-**5** is obtained in ~70% yield contaminated with only minor amounts of unchanged **4** and a second product. If the reaction is allowed to proceed for longer periods the latter compound can constitute a significant portion of the product mixture. It has been identified as 3-iodomethyl-5,5-dimethylcyclohexene, primarily on the basis of the mass (molecular ion at *m/e* 250.022) and nmr [doublet at τ 6.92 (2 H, iodomethyl, J = 6 Hz)] spectra.[10] We are currently investigating the mechanism of this novel reaction.

The critical step in this reaction sequence is the one involving ring expansion. We have found that the conversion of *cis*-**5** to 6-bromo-4,4-dimethylcycloheptene (**6**) can be effected in >90% yield with only slight contamination by two isomeric products (**7** and **8**) by stirring with 48% hydrogen bromide at room temperature for 6 hr.[12] The bromo and cyclopropyl groups are cis to each other in **7** since the C_2 proton (–CHBr–) signal at τ 5.2 is a broadened five-line pattern similar to that in *cis*-**5** (*vide supra*). This

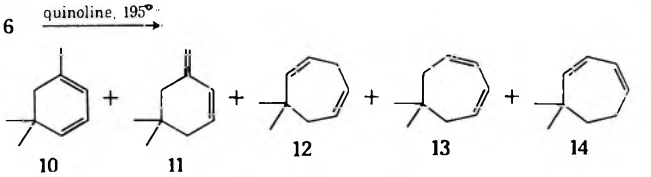


isomer is actually the major product for short reaction times (10 min or less) but is converted to **6** upon stirring with acid. In addition, the third isomer (**8**) is the major product after about 3 days at room temperature (or after 15 min at 195°).[10]

If one assumes that the reaction proceeds *via* the delocalized homoallylic ion **9**, in which the positive charge is located primarily at C_1, C_6, and C_7,[3a,13,14] it can be seen that products resulting from attack of bromide at each of these positions are observed.[15] This reaction represents an interesting example of the use of both kinetic and thermodynamic control for synthetic purposes since it is necessary to convert the initially formed but least stable isomer (**7**) into the desired product (**6**) without the latter in turn being converted into the most stable isomer (**8**).

We have investigated the dehydrobromination of **6** by employing several base systems which vary over a wide range of base strength. These include a weak base (quinoline), a medium-strength base (potassium hydroxide in ethanol), and a strong base (potassium amide in liquid ammonia).[16]

On heating **6** with quinoline at 195° for 20 min a 72% yield of at least five C_9H_{14} isomers is obtained (Table I). These isomers were isolated by gas chromatography and identified on the basis of spectroscopic evidence (see Experimental Section). Two of the isomers were identified as six-membered-ring dienes, *viz.*, 1,5,5-trimethyl-1,3-cyclohexadiene (**10**)[17] and 5,5-dimethyl-3-



(7) (a) M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 1042 (1952), and references cited; (b) J. W. Wheeler and R. H. Chung, *J. Org. Chem.*, **34**, 1149 (1969), and references cited; (c) W. L. Dilling and R. A. Plepys, *Chem. Commun.*, 417 (1969); (d) H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969), and references cited. The greater amount of double bond reduction which we observe with sodium borohydride (relative to lithium aluminum hydride) is in accord with the results in the latter three papers, and in (e) F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkranz, *Chem. Ind. (London)*, 1482 (1954); (f) H. L. Goering, R. W. Greiner, and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1391 (1961). (g) See K. E. Wilson, R. T. Seidner, and S. Masamune, *Chem. Commun.*, 213 (1970), for a potentially useful reagent.

(8) It was previously reported [A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 3723 (1953)], that **4** is obtained from the lithium aluminum hydride reduction of **1**. However, in our hands this procedure afforded a 2:1 mixture of **4** and 3,3-dimethylcyclohexanol. We have not investigated this reaction in detail but it may be possible, by using less reducing agent, to obtain reasonably pure **4** in good yield by this more convenient route.

(9) (a) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959); (b) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); (c) S. Sawada, K. Takehana, and Y. Inouye, *J. Org. Chem.*, **33**, 1767 (1968); (d) J. H.-H. Chan and B. Rickborn, *J. Amer. Chem. Soc.*, **90**, 6406 (1968).

(10) S. W. Staley and F. L. Wiseman, Jr., to be published.

(11) H. Conroy, *Advan. Org. Chem.*, **2**, 265 (1960).

(12) This is an extension of the method of M. Julia, S. Julia, and R. Guégan, *Bull. Soc. Chim. Fr.*, 1072 (1960).

(13) P. von R. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, **88**, 2321 (1966).

(14) It should be recognized, however, that several closely related, but different, ions may be involved. See ref 1b, 5e, and K. B. Wiberg and A. J. Ashe, III, *J. Amer. Chem. Soc.*, **90**, 63 (1968).

(15) We, of course, are not able to observe migration of the cyclopropyl group, as has been observed or suggested by others (ref 4a, b and f and 5b and c) since this merely interconverts enantiomeric ions in the present case.

(16) For a listing of base strengths, see J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, pp 219–21.

(17) This compound may contain a small amount of 2,6,6-trimethyl-1,3-cyclohexadiene. At equilibrium **10** has been found to predominate over the latter isomer by a factor of 5:2 in potassium-*t*-butoxide–hexamethylphosphoramide at 25°: S. W. Staley, W. L. Maloy, and J. P. Erdman, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968, p P129.

TABLE I

PRODUCT DISTRIBUTIONS FOR THE BASE-PROMOTED DEHYDROBROMINATION OF 6-BROMO-4,4-DIMETHYLCYCLOHEPTENE (6) IN VARIOUS BASE–SOLVENT SYSTEMS

Product	Quinoline, 195°, 20 min[a]	KNH_2–NH_3, 25°, 5 min[a]	KOH–EtOH, 80°, 30 min[a]
10[b]	26.5	0	2[c]
11	13.5	0	1[c]
12	12	15	0
13	25	30	89
14	23	55	8

[a] Approximate percentage of isolated product. [b] Probably contains ~15% 2,6,6-trimethyl-1,3-cyclohexadiene. [c] Probably arises from ~2–3% 3-bromomethyl-5,5-dimethylcyclohexene present as an impurity in **6**.

methylenecyclohexene (**11**). Both compounds exhibit ir, uv, and mass spectra which are essentially identical with those of authentic samples.[18]

The remaining three isomers are cycloheptadienes; **12** is nonconjugated, as shown by its uv spectrum which displays only end absorption, whereas **13** and **14** are both conjugated [λ_{max}^{hexane} 246 (ϵ 6160) and 248 nm (13,200), respectively].[19] The latter two isomers are readily distinguished by their nmr spectra since that of **13** indicates four allylic protons whereas that of **14** shows two allylic and two methylene protons.

The presence of a large quantity of six-membered-ring dienes in the product mixture is of considerable interest. Control experiments which employed conditions similar to those used for dehydrobromination have established that the cycloheptadienes are not converted to the C_6-ring dienes, although the reverse process does occur. Diene **11** is the major C_6-ring product in low conversion dehydrobrominations of **6** (Table II), thereby indicating

TABLE II

DEHYDROBROMINATION OF 6-BROMO-4,4-DIMETHYLCYCLOHEPTENE (6) WITH QUINOLINE

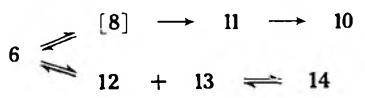
Reaction time	Percentage dehydrobromination	Product distribution[a] 10[b]	11	12	13	14
30 sec	10	0	25	10	58	7
1 min	60	2	26	14	37	21
2 min	87	8	21	16	29	26

[a] Approximate percentage (of the isomers listed) as measured by gas chromatography; obtained by placing a 20% (v/v) solution of **6** in quinoline (at 25°) in an oil bath at 215° for the indicated length of time. [b] May contain some 2,6,6-trimethyl-1,3-cyclohexadiene.

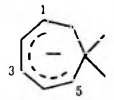
that this isomer is formed initially and then converted to **10**.[20] Since we have shown that bromide **6** is isomerized to bromide **8** in 48% hydrogen bromide or in sulfuric acid–dioxane,[10] the latter isomer is a reasonable intermediate in the formation of **11** (Scheme II). The ratio of **10** to **11** (Table I) is essentially that expected at equilibrium.[18b]

1,2-Dehydrobromination of **6** would lead to **12** and **13** and these are the major cycloheptadiene products in the initial stages of the reaction (Table II). The nonconjugated isomer is substantially less stable than **13** and **14** (*vide infra*) and therefore is formed in a kinetically controlled process. In contrast, the ratio of **13** to **14** is approximately that expected at equilibrium.[10] There are several possible mechanisms for the interconversion of the latter two isomers; these include catalysis by quinoline hydrobromide–quinoline, and a concerted [1,5]-suprafacial sigmatropic migration of hydrogen.[21]

SCHEME II



Dehydrobromination with the strongest base, potassium amide in liquid ammonia, affords only cycloheptadienes as products but the recovery is rather poor (27%). In this case potassium cycloheptadienyl anion (**15**) is an intermediate and the distribution of products

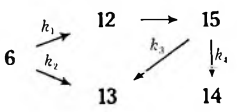


15

is governed by the relative rates of protonation at C_1, C_3, and C_5 upon quenching (accompanied, perhaps, by some isomerization during the brief quenching process). Anion **15** is known to be present under these conditions since it can be generated in high yield (by adding a mixture of **12**, **13**, and **14** to a twofold excess of potassium amide in liquid ammonia) and directly observed by nmr spectroscopy.[10]

The highest yield of cycloheptadienes (78%) was obtained by heating **6** in potassium hydroxide–ethanol at reflux (~95°); the product was isolated as an 11:1 mixture of **13** and **14**. Since **14** cannot arise directly from **6** by 1,2 elimination and since it was established that **13** and **14** are not interconverted to a significant extent under the reaction conditions, the most reasonable pathway for the formation of the latter isomer is *via* **12** (Scheme III). This mechanism is supported by

SCHEME III



the fact that **12** in a mixture with **13** and **14** is converted virtually completely into the latter two isomers when treated under the reaction conditions (Table V). Since there was little material loss (as shown by use of an internal standard) this establishes that **12** is substantially less stable than **13** and **14**,[22] and allows one to estimate that $k_3/k_4 = \sim 2.3$. With this figure and the data in Table I, k_2/k_1 (in potassium hydroxide–ethanol) can be estimated to be 3. The greater value of

(18) (a) H. Pines and R. H. Kozlowski, *J. Amer. Chem. Soc.*, **78**, 3776 (1956); (b) S. W. Staley and J. P. Erdman, unpublished results.

(19) 1,3-Cycloheptadiene has $\lambda_{max}^{isooctane}$ 248 nm (ϵ 7400): E. Pesch and S. L. Friess, *ibid.*, **72**, 5756 (1950).

(20) We have also shown by a control experiment that this isomerization occurs in quinoline hydrobromide–quinoline at 200°.

(21) (a) This isomerization can occur either as in ref 20 or in pentane at 200°. (b) For a similar thermal rearrangement, see V. A. Mironov, O. S. Chizhov, Ia. M. Kimelfeld, and A. A. Akhrem, *Tetrahedron Lett.*, 499 (1969).

(22) (a) The heat of hydrogenation of 1,4-cycloheptadiene is 6.0 kcal/mol greater than that of 1,3-cycloheptadiene (both in acetic acid at 25°): R. B. Turner, personal communication. (b) 1,4-Cycloheptadiene is isomerized to 1,3-cycloheptadiene in refluxing potassium ethoxide–ethanol: W. von E. Doering and G. Schröder, cited by W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

k_2 relative to k_1 may be due in part to the fact that the respective transition states reflect the stabilities of the products. However, the role of steric factors in these two processes is unclear at the present time.

It can be seen that both kinetic and thermodynamic control of the cycloheptadiene product mixtures are operative. The type of control for a given product varies with the dehydrobrominating conditions; the results are summarized in Table III.

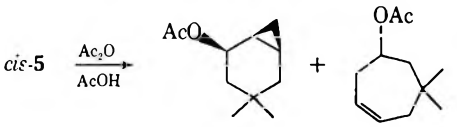
TABLE III
TYPE OF PRODUCT CONTROL (K = KINETIC, T = THERMODYNAMIC) FOR THE BASE-PROMOTED DEHYDROBROMINATION OF 6-BROMO-4,4-DIMETHYLCYCLOHEPTENE (6)

Product	Quinoline	KNH_2–NH_3[a]	KOH–EtOH
12	K	K	T
13	T	K	K + T[b]
14	T	K	T

[a] Some equilibration may occur during the quenching process. [b] Kinetic control predominates; 12, but not 14, is isomerized to 13.

Alternate Routes.—Two other routes from alcohol *cis*-5 to cycloheptadienes 12–14 were explored. Although they were not studied as extensively as the bromination–dehydrobromination route, it is nevertheless of value to discuss our initial results.

Behavior analogous to that observed on treatment with 48% hydrogen bromide was noted when *cis*-5 was heated at reflux with acetic anhydride–acetic acid. When the reaction is allowed to proceed for 6 hr a 6:4 mixture of acetates 16 and 17 is obtained as the major product, but after 26 hr the ring expanded acetate (17) predominates by a factor of >20. This represents yet another example of kinetic *vs.* thermodynamic control in this system.

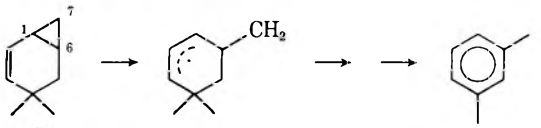


16 17

When ~92% pure 17 is pyrolyzed at 516° in a flow system a >50% yield of a mixture which contains 11% 12, 37% 13, and 37% 14 is obtained. The first two isomers are probably formed by concerted cis elimination of acetic acid; 14 is undoubtedly formed from 13 *via* a 1,5 hydrogen shift mechanism.[21b] In contrast, pyrolysis of a sample which was predominantly a 3:2 mixture of 16 and 17 gave *m*-xylene as the major product. This could arise by pyrolysis of a primary product, 4,4-dimethylbicyclo[4.1.0]hept-2-ene (18) (*vide infra*).

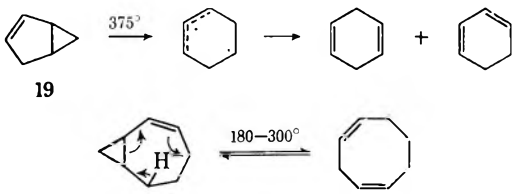
When alcohol *cis*-5 was heated at 230° in the presence of a catalytic amount of *p*-toluenesulfonic acid, complex mixtures of products were obtained. The product ratios varied somewhat between two runs but the yield of cycloheptadienes never exceeded 20% of the isolated products. This reaction therefore appears to have much less synthetic potential than the two which have already been discussed (dehydrobromination and acetate pyrolysis).

The major component in the product mixtures from dehydration of *cis*-5 was identified as 18 on the basis of its nmr spectrum. The presence of this compound allowed us to test the supposition that the *m*-xylene obtained from the pyrolysis of a 3:2 mixture of acetates 16 and 17 is formed from 18 (which would arise by pyrolysis of 16). Thus, when a dehydration product mixture containing 45% 18 was heated in a sealed tube at 320° or in a flow system at 490°, *m*-xylene comprised about half the product mixture. Apparently cleavage occurs predominantly at C_1–C_7 instead of at C_1–C_6.[23]



18

These results can be contrasted with those for bicyclo[3.1.0]hex-2-ene (19)[24] and bicyclo[5.1.0]oct-2-ene (20).[25] It can be rationalized that the biradical mechanism suggested[24b] for 19 is less likely in the case of 18



19 20

because the bridge C–C bond is less strained in the latter compound. Furthermore, a concerted 1,5 hydrogen migration is more probable for 20 than for 18 since there will be better overlap (less strain) in the activated complex for the former compound.[26]

Summary

It is apparent that acid-catalyzed ring expansion of α-cyclopropyl alcohol *cis*-5 followed by base-promoted dehydrobromination of bromide 6 constitutes a convenient high-yield synthesis of *gem*-dimethylcycloheptadienes. Considerations of kinetic and thermodynamic control are important in both of the key steps. Particular attention must be paid to this point if a specific cycloheptadiene is desired since different bases afford markedly different product ratios.

Experimental Section

General Comments.—Infrared (ir) spectra (neat) were obtained in a 0.025-mm sodium chloride or potassium bromide cell on a Perkin-Elmer 337 instrument; nuclear magnetic resonance (nmr) spectra of ~10% solutions in carbon tetrachloride with internal tetramethylsilane were recorded on a Varian A-60A spectrometer; ultraviolet (uv) spectra of Spectrograde hexane solutions were obtained on a Cary 14 instrument, and mass spectra were recorded at 70 eV on a Varian M-66 mass spectrometer. Boiling points are uncorrected. Elemental analyses were performed by Dr. Franz Kasler of the University of Maryland.

Analyses by gas chromatography (gc) were performed on an Aerograph 1200 (1/8-in. columns, flame ionization detector) or A90-P3 (1/4-in. columns, thermal conductivity detector) instru-

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ment and are not corrected for response factors. Gc columns were generally made with copper tubing. The following were employed (outside diameter and length are given): CW20M-1, 15% Carbowax 20M on 80–100 acid washed and silanized (AW-S) Chromosorb P (1/8 in. × 5 m); CW20M-2, 8% Carbowax 20M on 100–120 AW-S Chromosorb P (1/8 in. × 3 m); CW20M-3, same as CW20M-1 except 1/4 in. × 1.5 m; m; CW20M-4, 20% Carbowax 20M on 60–80 Diatoport S (1/4 in. × 5 m); SE30-1, 5% SE-30 silicone oil on 60–80 Chromosorb W (1/8 in. × 1.7 m, stainless steel); SE30-2, 20% SE-30 silicone oil on 60–80 AW-S Chromosorb P (1/8 in. × 1.5 m, stainless steel); TCEP-1, 15% 1,2,3-tris(2-cyanoethoxy)propane on 100–120 AW-S Chromosorb P (1/4 in. × 2 m); TCEPE-1, 7% tetracyanoethoxypentaerithritol on 80–100 AW-S Chromosorb P (1/8 in. × 0.6 m).

3-Ethoxy-5,5-dimethyl-2-cyclohexenone (2) was prepared by the method of Frank and Hall[6] in 98% yield, bp 97–105° (2 mm) [lit.[6] bp 93° (1 mm)]. The nmr spectrum displays signals at τ 4.79 (s, 1, C=C-H), 6.08 (q, 2, J = 7 Hz, OCH_2), 7.77 (s, 2, CH_2), 7.92 (s, 2, CH_2), 8.65 (t, 3, J = 7 Hz, CH_3), and 8.93 (s, 6, CH_3); no other peaks were observed.

5,5-Dimethyl-2-cyclohexenone (3) was prepared as described previously[6] except that a 15% equiv excess of fresh lithium aluminum hydride was employed. A 90% yield of material with bp 40–48° (1.6 mm) [lit.[6] bp 75° (15 mm)] was obtained: nmr τ 3.17 (doublet of triplets, 1, J = 10 and 4 Hz, respectively, CH=CH-CH_2), 4.08 (doublet of triplets, 1, J = 10 and 2 Hz, respectively, CH=CH-CH_2), 7.70 (doublet of doublets, 2, J = 2 and 4 Hz, CH_2), 7.80 (s, 2, CH_2), and 8.93 (s, 6, CH_3); no other signals were detected. Yields of 45–55% (similar to that reported by Frank and Hall[6]) were obtained when reducing agent which had been on the shelf for months in an inadequately sealed container was used.

5,5-Dimethyl-2-cyclohexenol (4).—5,5-Dimethyl-2-cyclohexenone (25 g, 0.20 mol) was added over 0.5 hr to a cooled suspension of 2.2 g (0.23 equiv) of fresh lithium aluminum hydride in 300 ml of dry ether. The reaction mixture was then heated at reflux for 20 min, cooled, and treated with water followed by saturated aqueous ammonium chloride. The aqueous layer was extracted twice with ether and the combined ether layers were dried over anhydrous magnesium sulfate. The ether was distilled and the residue vacuum distilled to afford 22.6 g [bp 86–88° (17 mm)] of 93% pure 4 (83% yield).[7b] This material was shown to contain a trace of 3 by gas chromatography (gc) (column CW20M-3 at 100°) and ir (small carbonyl band at 1698 cm^{-1}) and ~6% 3,3-dimethylcyclohexanol (21) by gc and nmr. After purification by gc on this same column [retention time (rt) relative to 21 was ~1.2], 4 gave the following spectral data: ir 3340, 3035, 1650, 1385, 1370, 1282, 1089, 1035, 1000, 934, 800, and 725 cm^{-1}; nmr τ 4.39 (s, 2, C=CH), 5.9 (broad m, 1, CHOH), 6.95 (s, 1, COH), 8.21 (m, 2, C=C-CH_2), 8.50 (d, 1, J = 8.5 Hz, CH_2), 8.75 (1, broadened d, J = 3.5 Hz, CH_2), 9.00 (s, 3, CH_3), and 9.10 (s, 3, CH_3).

Anal. Calcd for $C_8H_{14}O$: C, 76.15; H, 11.17. Found: C, 75.88; H, 10.92.

When 20.1 g (0.16 mol) of 3 was added to 4.7 g (0.5 equiv, threefold excess) of lithium aluminum hydride in 250 ml of dry ether, stirred at reflux for 41 hr, and worked up as above (except that quenching was effected with water followed by dilute sulfuric acid), 20 g of product was obtained. This was shown by nmr to be a 1:1 mixture of 4 and 21.

When 3 was stirred with a fivefold excess of saturated sodium borohydride in 0.2 N sodium hydroxide–ethanol for 20 hr at room temperature, a crude product was obtained whose nmr showed no vinyl hydrogens.

A sample of 21 which was purified by gc has ir and nmr spectra which agree with reported data:[27] ir 3340, 1380, 1365, 1062, 1022, 970, 944, 923, 899, 852, and 812 cm^{-1}; nmr 6.0–6.7 (m, 1, CHOH), 7.42 (s, 1, COH), 7.8–9.0 (m, 8, CH_2), 9.05 (s, 3, CH_3), and 9.11 (s, 3, CH_3).

***cis*-4,4-Dimethylbicyclo[4.1.0]heptan-2-ol** (*cis*-5) was synthesized by the procedure described by Dauben and Berezin,[9b] except that the zinc–copper couple was prepared by the method of LeGoff.[28] From 22 g (~0.34 g-atom) of zinc–copper couple, 0.1 g of iodine, 66 g (0.25 mol) of methylene iodide, and 12.6 g (equivalent to 0.093 mol) of 4 (from the previous preparation) in 140 ml of dry ether was obtained 9.9 g of product, bp 65° (1.5 mm), which was ~92% *cis*-5 (71% yield). The impurities were [by nmr and gc (column SE30-1 at 100°)] 6% unchanged 4 and a trace of 3-iodomethyl-5,5-dimethylcyclohexene. A forefraction [bp 55–65° (1.5 mm)] which weighed 2.4 g and was 2/3 *cis*-5 was also obtained; the total yield of *cis*-5 was therefore 82%. Relative retention times on column SE30-1 at 100° were methylene iodide, 0.8; 4, 1.0; *cis*-5, 2.5; 3-iodomethyl-5,5-dimethylcyclohexene, 6.2. Gc analysis (column TCEPE-1) of the main fraction showed that no (*i.e.* <0.5%) *trans*-5 was present.

After gc purification (column SE30-2) *cis*-5 exhibits the following spectral data: ir 3340, 3070, 3005, 1465, 1385, 1365, 1291, 1167, 1114, 1035, 983, 945, 919, 852, 807, and 743 cm^{-1}; nmr τ 5.76 (5 line m, 1, J_{21} = 6, J_{23} = 12, and $J_{23'}$ = 6 Hz, CHOH), 6.41 (s, 1, OH), 8.0–9.7 (m, 7, CH_2 and cyclopropyl), 9.10 (s, 3, CH_3), 9.17 (s, 3, CH_3), and 9.83 (t, 1, J = 5 Hz, cyclopropyl).

Anal. Calcd for $C_9H_{16}O$: C, 77.11; H, 11.49. Found: C, 76.99; H, 11.16.

6-Bromo-4,4-dimethylcycloheptene (6).—Five grams (0.03 mol) of 90% *cis*-5 was stirred with 20 ml of 48% hydrogen bromide for 6 hr at room temperature, after which time the organic layer was separated and the aqueous layer extracted with pentane. The combined organic layers were shaken with aqueous sodium carbonate and then dried over anhydrous magnesium sulfate. The pentane was distilled and the residue distilled *in vacuo* to afford 6.7 g at 45–51° (1.0 mm). Analysis by nmr and gc (column SE30-2 at 100°) showed the distillate to be 93% 6 (95% yield), 5% *cis*-2-bromo-4,4-dimethylbicyclo[4.1.0]heptane (7),[10] and 1–2% 3-bromomethyl-5,5-dimethylcyclohexene (8).[10] A sample of 6 was obtained in ~97% purity by gc (column TCEP-1 at 60°; a small amount of isomerization to 8 occurred even under these mild conditions): ir 3025, 1705, 1645, 1385, 1370, 1315, 1173, 867, 788, 716, 679, and 630 cm^{-1}; nmr τ 4.3 (m, 2, C=CH), 6.9 (broad m, 1, CHBr), 7.28 (m, 2, C=CCH_2CBr), 7.5–8.5 (m, 4, C=CCH_2 and CH_2CBr), 9.02 (s, 3, CH_3), and 9.04 (s, 3, CH_3); mass spectrum m/e 202.025 [calcd for $C_9H_{15}Br(^{79}Br)$: 202.036; 202:204 intensity ratio = 0.9], 67 (base peak).

Anal. Calcd for $C_9H_{15}Br$: C, 53.19; H, 7.45. Found: C, 53.50; H, 7.46.

Dehydrobromination of 6-Bromo-4,4-dimethylcycloheptene (6).

A. With Quinoline.—A solution of 15 g (0.07 mol) of 93% 6 and 35 ml of distilled quinoline was heated at 195° for 20 min, cooled, and then added to enough dilute hydrochloric acid to produce an acidic solution. The hydrocarbon layer was separated and the aqueous layer extracted twice with pentane. After distillation of the pentane the residue was distilled *in vacuo* to afford a fraction, bp 60–70° (16 mm), which weighed 7.4 g (82% yield). analysis by gc (column CW20M-4 at 90°) showed the distillate to consist of at least five compounds, the relative amounts of which are given in Table I; analyses for 1 and 2 min reaction times in small-scale runs are given in Table II. The products were purified by using the above column and had the following relative retention times: 10, 1.00; 11, 1.25; 12, 1.47; 13, 1.59; 14, 1.68. A mixture of these five isomers gave the following analysis.

Anal. Calcd for C_9H_{14}: C, 88.44; H, 11.56. Found: C, 88.28; H, 11.57.

1,5,5-Trimethyl-1,3-cyclohexadiene (10).—The uv spectrum of this isomer [λ_{max}^{hexane} 261 nm (ϵ 5400)] agrees with previously determined data[18] as does the mass spectrum [m/e 122.107 (calcd for C_9H_{14}:122.109), 79 (base peak)]. The ir spectrum agrees with previously determined spectra[18] except that it shows additional small peaks at 1030, 997, and 818 cm^{-1} which are also present in the spectrum of 2,6,6-trimethyl-1,3-cyclohexadiene (23) and which we attribute to a ~15% impurity of the latter isomer. The nmr spectrum of pure 10[18b] exhibits signals at τ 4.18–4.83 (complex m, 3, C=CH), 8.05 (narrow m, 2, C=C-CH_2), 8.25 (narrow m, 3, C=C-CH_3), and 8.87 (s, 6, CH_3).

5,5-Dimethyl-3-methylenecyclohexene (11).—The ir spectrum is in excellent agreement with previously determined spectra,[18] as are the uv spectrum [λ_{max}^{hexane} 231 nm (ϵ 19,900)] and mass spectrum [m/e 122.108 (calcd for C_9H_{14}: 122.109), 107 (base peak)]. The nmr spectrum[18b] exhibits signals at τ 3.88 (doublet of triplets, 1, J = 10 and 2 Hz, respectively, CH=C-CH_2), 4.33 (doublet of triplets, 1, J = 10 and 4 Hz, respectively, C=CH-CH_2), 5.23 (complex m, 2, C=CH_2), 7.95 (doublet of doublets, 2, J = 1.3 and 1.5 Hz, CH_2-C=CH_2), 8.08 (complex m, 2, J = 1.2 and and 4 Hz, CH_2CH=CH), and 9.09 (s, 6, CH_3); mass spectrum m/e 122.108 (calcd for C_9H_{14}: 122.109), 107 (base peak).

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6,6-Dimethyl-1,4-cycloheptadiene (12) shows only end absorption in the uv ($\epsilon_{210\,nm}^{hexane}$ 1700): ir 3035, 3010, 1650, 1375, 1365, 1133, 988, 812, 696, and 662 cm^{-1}; nmr τ 4.27 (m, 2, C=CH, 4.68 (s, 2, C=CH), 7.23 (broad s, 2, $(C=C)_2CH_2$), 7.80 (broad d, 2, J = 5 Hz, C=C-CH_2), and 8.98 (s, 6, CH_3); mass spectrum m/e 122.105 (calcd for C_9H_{14}: 122.109), 79 (base peak).

6,6-Dimethyl-1,3-cycloheptadiene (13) gave the following: λ_{max}^{hexane} 246 nm (ϵ 6160); ir 3060, 3020, 1615, 1385, 1370, 992, 789, 690, and 654 cm^{-1}; nmr τ 4.24 (broadened s, $W_{1/2}$ = 3.5 Hz, 4, C=CH), 7.93 (broadened d, 4, J = 3 Hz, $C=CCH_2$), and 9.03 (s, 6, CH_3); mass spectrum m/e 122.108 (calcd for C_9H_{14}: 122.109), 79 (base peak).

5,5-Dimethyl-1,3-cycloheptadiene (14) gave the following: λ_{max}^{hexane} 248 nm (ϵ 13,200); ir 3055, 3005, 1610, 1375, 1360, 1125, 976, 866, and 700 cm^{-1}; nmr τ 4.31 (apparent d, 2, line separation = 3.5 Hz, C=CH), 4.49 (apparent d, 2, line separation = 2.5 Hz, C=CH), 7.55–8.0 (m, 2, $C=CCH_2$), 8.45 (doublet of doublets, 2, J = 5 and 6.5 Hz, CH_2), and 8.96 (s, 6, CH_3); mass spectrum m/e 122.111 (calcd for C_9H_{14}: 122.109), 79 (base peak).

B. Dehydrobromination of 6 with Potassium Amide in Liquid Ammonia.—To a 5 mm × 10 cm Pyrex tube at ~ −78° was added ~0.2 ml of liquid ammonia and ~0.02 g of potassium metal. The tube was sealed, warmed to room temperature until formation of potassium amide was complete (color change from blue to gray), cooled, and opened. A solution (0.015 ml) of 6 and tridecane in a molar ratio of 2.2:1 was then added and the tube resealed and warmed to room temperature for 5 min (during which time a red color developed). The tube was then cooled and opened, and the solution quenched in water and extracted with pentane. Gc analysis (column CW20M-1 at 90°) showed a trace of unchanged 6 and three cycloheptadienes (see Table I) with a cycloheptadiene to tridecane ratio of 0.6:1 (27% recovery). an even lower recovery (~5%) was obtained when this reaction was run for 20 min at −33°.

C. Dehydrobromination of 6 with Potassium Hydroxide in Ethanol.—To a solution of 10 g of potassium hydroxide in 12 ml of absolute ethanol (in an argon atmosphere) was added 5.0 g (0.024 mol) of 98% pure 6 containing ~2% 8. The reaction mixture was stirred at reflux for 0.5 hr, cooled, diluted with 30 ml of water, and extracted three times with pentane. The pentane solution was dried over anhydrous magnesium sulfate and distilled to afford 2.14 g (73% yield), which was shown by gc (column CW20M-1 at 90°) to contain 89% 13, 8% 14, and ~3% 10 and 11 (which probably arose from 8 present as an impurity). Less than 1% 6 remained, as shown by gc analysis on column SE30-1 at 90°.

Control Experiments. A.—Solutions of 5 μl of various dienes (along with tridecane as an internal standard) and 200 μl of quinoline or 0.1 M quinoline hydrobromide in quinoline were heated in a sealed tube under argon at 200° for 1 hr. The tubes were cooled and opened, and dilute hydrochloric acid was added until the quinoline had dissolved and the solution was acidic. The product mixtures were than extracted with 50 μl. of pentane and the pentane layers analyzed by gc (column CW20M-2 at 90°). When a mixture of 96% 11 and 4% 10 [which may have contained some 2,6,6-trimethyl-1,3-cyclohexadiene (23)] was heated in quinoline hydrobromide-quinoline at 200° for 1 hr the product mixture contained 33% 10 (+23), 49% 11, 3% 12, 8% 13, and 7% 14; no cycloheptadienes were formed when the initial mixture was heated for 1 hr at 200° in quinoline alone. Additional control experiments are given in Table IV.

TABLE IV
ISOMERIZATION OF CYCLOHEPTADIENES AT 200° FOR 1 HR

	Relative amount, %		
Isomer	Initial mixture	Final mixture (in quinoline)[a]	Final mixture (in 0.1 M quinoline hydrobromide in quinoline)[b]
10 + 11	<0.5	<0.5	<0.5
12	9	7	8
13	55	51	48
14	37	41	43

[a] 28% material loss. [b] 12% material loss.

B.—Solutions of 5 μl of cycloheptadienes (along with tridecane as an internal standard) in saturated potassium hydroxide–absolute ethanol were sealed in tubes under argon and immersed in refluxing saturated solutions of potassium hydroxide–ethanol (95°) for 30 min. The tubes were cooled and opened and dilute hydrochloric acid was added until the reaction mixtures became acidic. The contents of the tubes were then shaken with 50 μl of pentane and the pentane layers were analyzed by gc (column CW20M-2 at 90°). When a mixture of 97% 13 and 3% 14 was treated as above there was no change in the ratio of isomers. The results of additional experiments are given in Table V.

TABLE V
ISOMERIZATION OF CYCLOHEPTADIENES IN POTASSIUM HYDROXIDE–ETHANOL AT 95° FOR 30 MIN

	Relative amounts, %		
Isomer	Initial mixture[a]	Run 1 final mixture[a]	Run 2 final mixture[a,b]
12	24	0.6	0.6
13	43	58	62
14	32	41	38

[a] Average of two gc analyses. [b] There was <10% material loss.

6-Acetoxy-4,4-dimethylcycloheptene (17).—A solution of 1.0 ml of acetic acid, 3.3 ml of freshly distilled acetic anhydride, and 0.5 g (0.0032 mol) of ~90% *cis*-4,4-dimethylbicyclo[4.1.0]-heptan-2-ol (*cis*-5) was stirred at reflux for 26 hr, cooled, and carefully added to saturated aqueous sodium carbonate. The organic layer was separated and the aqueous layer extracted with pentane. The solvent was distilled from the combined organic layers and the residue flash distilled *in vacuo* to afford 0.4 g of product. Analysis by gc (column SE30-1 at 90°) showed this to be 92% 17 (63% yield) with ~4% each of two impurities, one of which had a retention time which corresponded to that of 16.

After gc purification (column SE30-2 at 120°) 17 had ir 3030, 1735, 1645, 1365 (broad), 1240, 1020, 955, 863, 790, 695, and 680 cm^{-1}; nmr τ 4.26 (m, 2, C=CH), 5.27 (broad 7 line m, 1, J = 4.5, 4.5, 9, and 9 Hz, CHOAc), 7.55–8.55 (m, 6, CH_2), 8.07 (s, 3, $COCH_3$), and 9.01 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 73.50; H, 9.97. Found: C, 73.20; H, 9.84.

In a peliminary experiment, a sample of *cis*-5 [which contained 25% 3-iodomethyl-5,5-dimethylcyclohexene (22) and 10% 3,3-dimethylcyclohexanol (21)] was treated as above for 6 hr and worked up in a similar manner. Gc analysis of the crude reaction mixture (column CW20M-3 at 100°) showed a major component (65%), 19% 22 (by comparison of nmr spectra), 9% 3-acetoxy-1,1-dimethylcyclohexane, and several other peaks. The major component was isolated on the same column and was shown by nmr spectroscopy to be a 3:2 mixture of *cis*-2-acetoxy-4,4-dimethylbicyclo[4.1.0]heptane (16) and 17: nmr τ 4.3 (broad m, 0.8, C=CH of 17), 4.73 (5 line m, 0.6, J = 6.6 and 12 Hz, AcOCH of 16), 5.3 (broad m, 0.4, AcOCH of 17), 8.05 (s, 1.8, $COCH_3$ of 16), 8.08 (1.2, $COCH_3$ of 17), 7.6–9.6 (m), 8.99 (s, CH_3 of 16 and 17), 9.14 (s, CH_3 of 16), and 9.83 (t, 0.6, cyclopropyl H of 16).

The component present as 9% of the mixture was purified by gc (column CW20M-3) and identified as 3-acetoxy-1,1-dimethylcyclohexane on the basis of spectral data: ir 1735, 1365 (broad), 1240, 1052, 1023, 980, 872, and 606 cm^{-1}; nmr τ 5.0–5.6 (m, 1, CHOAc), 8.06 (s, 3, OCH_3), 8.1–9.0 (m, 8, CH_2), and 9.05 (s, 6, CH_3).

Pyrolysis of 6-acetoxy-4,4-dimethylcycloheptene (17) was performed by passing 0.12 ml of 17 through a 12 cm × 1 cm Pyrex tube filled with glass helicies and heated to 516°. A flow rate of 30 ml/min of nitrogen was employed. Pentane was added to the pyrolysate and this mixture was washed with dilute sodium carbonate. The product (recovered in >50% yield) was shown by gc (column CW20M-2 at 90°) to consist of 11% 12 (by peak enhancement), 37% 13, 37% 14 (both by comparison of ir spectra), and 15% of several unidentified compounds. No 17 remained and there was a maximum of 2% *m*-xylene present.

When an acetate sample which was predominantly a 3:2 mixture of 16 and 17 was pyrolyzed and worked up as above, the product mixture was shown by gc (column CW20M-4 at 90°) to consist of 38% *m*-xylene (by comparison of ir and nmr spectra), 11% 13 and 14 (by peak enhancement), and at least seven other components. At 506° there was ~30% unchanged starting

TABLE VI
PRODUCTS OF DEHYDRATION OF *cis*-4,4-DIMETHYLBICYCLO[4.1.0]HEPTAN-2-OL

Product	% of mixture Run 1	% of mixture Run 2	Relative retention time (column CW20M-2 at 90°)
18	45[a]	14	1.00
12	2	5	1.37
13	9	9	1.27
14	6	6	1.15

[a] Isolated along with 9% 11 (as determined by gc and nmr).

material, whereas at 528° there were no acetates and some charring was evident.

Dehydration of *cis*-4,4-dimethylbicyclo[4.1.0]heptan-2-ol (*cis*-5) was effected by heating 2.0 g (0.014 mol) of the alcohol with a few crystals of *p*-toluenesulfonic acid at ~230°. Products were slowly distilled from the reaction mixture (~1 g in 4.5 hr). In a second run a similar yield was produced in 0.5 hr by heating at 235° with a Wood's metal bath.

The product mixtures were analyzed by gc (column CW20M-2 at 90°; see Table VI) and several components were collected (column CW20M-4 at 90°). Cycloheptadienes **13** and **14** were identified by comparison of their ir spectra with those of authentic samples, **12** was tentatively identified by gc peak enhancement, and the major component in each run was identified as 4,4-dimethylbicyclo[4.1.0]hept-2-ene (**18**) on the basis of its nmr spectrum: τ 4.29 and 4.67 (AB quartet, 2, J = 10 Hz, CH=CH), 8.0–9.6 (m, 5, CH_2 and cyclopropyl H), 8.96 (s, 3, CH_3), 9.06 (s, 3, CH_3), and 9.72–10.02 (m, 1, cyclopropyl H).

Pyrolysis of 4,4-Dimethylbicyclo[4.1.0]hept-2-ene (18).—When the product mixture from dehydration run 1 was pyrolyzed, either in a sealed tube under argon at 320° for 5.5 hr, or in a flow system (described above) at 490°, analysis by gc (column CW-20M-2) and nmr showed that, in each case, about 50% of the product mixture was *m*-xylene.

Registry No.—**2**, 6267-39-6; **3**, 4694-17-1; **4**, 25866-56-2; *cis*-**5**, 25866-57-3; **6**, 25866-58-4; **10**, 25866-59-5; **11**, 25907-92-0; **12**, 25866-60-8; **13**, 25866-61-9; **14**, 25866-62-0; **16**, 25866-63-1; **17**, 25866-64-2; **18**, 25866-65-3; 3-acetoxy-1,1-dimethylcyclohexane, 25866-66-4.

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Hydroboration of Terpenes. VII. Hydroboration of (−)-Thujopsene. Configurations of the Isomeric 3-Thujopsanols and 3-Thujopsanones[1]

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Conformational analysis suggests that thujopsene (**1**) can exist in two possible conformations, steroidal I and nonsteroidal II. In the steroidal conformation, the side (α) away from the cyclopropane ring should be relatively inaccessible to reactions sensitive to steric requirements, whereas, in the nonsteroidal conformation, it is the side (β) toward the cyclopropane ring that should be relatively inaccessible. Hydroboration of (−)-thujopsene takes place exclusively from the β side, as indicated by the isolation of a single alcohol (+)-3-thujopsanol (**2**). The structure of (+)-3-thujopsanol has been established by determining the absolute configuration of the alcohol by Horeau's method. Similarly, epoxidation of thujopsene takes place predominantly from the β side to yield not the epoxide, but the rearranged product (−)-3-isothujopsanone (**5**). An equilibration study indicates nearly equal stability for (−)-3-thujopsanone and (−)-3-isothujopsanone. Consequently, it is concluded that thujopsene (**1**) reacts preferentially in the steroidal conformation I and probably exists preferentially in that conformation. In the course of this study all four of the isomeric 3-thujopsanols and both the two isomeric 3-thujopsanones were prepared and characterized.

The chemistry and structure of the sesquiterpene, thujopsene, has been the subject of considerable interest in the recent years. The structure of thujopsene was correctly deduced, in 1960, by Erdtman and Norin,[3] who assigned the relative stereochemistry shown in **1**. The cis relationship of the angular methyl substituent and the cyclopropane ring has subsequently been confirmed by a further degradative study[3d] and by a stereospecific synthesis.[4] Recently thujopsene has become of interest with respect to the problem of classical and nonclassical carbonium ion structures. Recognition of the existence of four rapidly equilibrating cyclopropyl carbinyl cations, from *cis*- and *trans*-thujopsenes, points to the essentially classical nature of these cations.[5]

Conformation and Steric Course of Reaction in Thujopsene.—Thujopsene is an interesting molecule, whose molecular model indicates the presence of considerable flexibility arising from the cis ring junction. The molecule (Figure 1) may adopt either the steroidal I or the nonsteroidal conformation II.[6] In the steroidal conformation I, the β side[7] provides a less crowded environment for the double bond. Hence the approach of any reagent with large steric requirements should be preferred from this side. On the other hand, in the nonsteroidal conformation II, the β side of the molecule is congested by the bridgehead 4a-methyl. However, the α side is relatively open to the reagent.

Hydroboration of olefins is highly sensitive to the steric environment of the double bond, taking place from the less hindered side.[8] The reaction is also highly exothermic but is remarkably free of skeletal rearrange-

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(1) Presented in part at the International Symposium on the Chemistry of Natural Products (IUPAC), London, July 1968.

(2) Postdoctoral Research Associate, 1966–1968, on Grant GM-10937 of the National Institutes of Health.

(3) (a) H. Erdtman and T. Norin, *Chem. Ind. (London)*, 622 (1960); (b) T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961); (c) S. Farsen and T. Norin, *ibid.*, **15**, 592 (1961); (d) T. Norin, *ibid.*, **17**, 738 (1963).

(4) (a) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963); (b) G. Büchi and J. D. White, *ibid.*, **86**, 2884 (1964).

(5) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, **18**, 1735 (1967).

(6) For steroidal and nonsteroidal conformations, see C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960, p 186 ff.

(7) It is convenient to use β to indicate the side of the molecule toward the cyclopropane ring and the bridgehead 4a-methyl, and α to indicate the other side of the molecule.

(8) (a) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964); (b) H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 201 (1970).

ments,[9] even when the double bond is conjugated with a cyclopropane ring.[10] Consequently, hydroboration appears to possess real advantages to explore the steric requirements of reactions in flexible systems.

In the case of rigid bicyclic molecules, the direction of hydroboration can readily be interpreted in terms of the steric environment of the double bond.[8b] However, the situation is more complex in flexible cyclic systems, where ready interconversion of the ring system complicates the interpretation.[11] Fortunately, there are reasons for believing that hydroboration can minimize the ambiguities involved in interpreting the results realized with such systems.[12]

As was mentioned earlier, the hydroboration of olefins is a highly exothermic process. According to the Hammond postulate,[13] the transition state for such a reaction should resemble the reactants. Consequently, if the attack of the reagent occurs preferentially from the β side, this would indicate that the thujopsene moiety in the transition state exists preferentially in the steroidal conformation, and might imply that this steroidal conformation I is actually preferred in the ground state.[14]

It appeared appropriate therefore to establish the steric course of the hydroboration of thujopsene. In the course of this study we prepared and characterized all of the possible 3-thujopsanols and 3-thujopsanones.

Hydroboration of (−)-Thujopsene (1).—(−)-Thujopsene (1) on hydroboration, followed by alkaline hydrogen peroxide oxidation, gave only a single alcohol, confirmed by a detailed glpc examination and by a characteristic pmr spectrum, quite different from the spectra of the other three possible isomeric alcohols synthesized in the present study. Since the addition of diborane to the double bond is cis and the replacement of boron by hydroxyl in the oxidation proceeds with the retention of configuration,[15] the single alcohol obtained must be either 3-thujopsanol (2) or 3-isothujopsanol (4) depending upon whether the attack of diborane is from the β side or α side (Scheme I, a or b).[16]

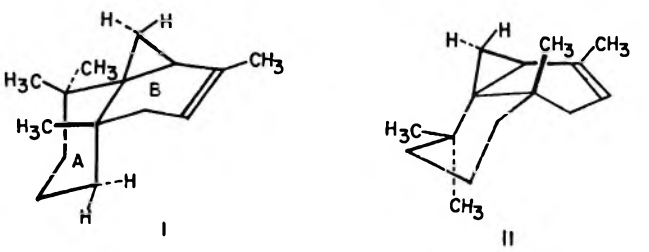
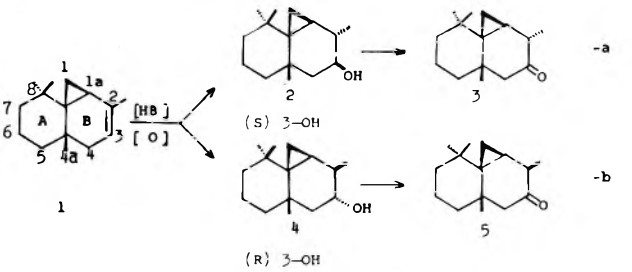


Figure 1.—Possible conformations of thujopsene.

SCHEME I
HYDROBORATION OF THUJOPSENE TO GIVE TWO POSSIBLE ALCOHOLS AND SUBSEQUENT OXIDATION TO TWO KETONES



Treatment of the alcohol with α-phenylbutyric anhydride left an excess of (−)-2-phenylbutyric acid behind, indicating the *S* configuration for the carbinol moiety in accordance with Horeau's rule.[17]

The absolute configuration of thujopsene has been firmly established[18,19] and is as shown in Scheme I. cis-Hydration of the double bond, a well established characteristic of hydroboration–oxidation, would require either the formation of 3-thujopsanol (2) with the *S* configuration, at the carbinol carbon atom, if the reaction had taken place from the β side, or the formation of 3-isothujopsanol (4) with the *R* configuration at the carbinol carbon atom, if the hydration had taken place from the α side. Horeau's method therefore indicates that the hydroboration–oxidation had taken place from the β side, and the hydroboration–oxidation alcohol is 3-thujopsanol (2).

It is interesting to note that, in our previous studies of the hydroboration of 2-carene,[19a] 3-carene[20] hydroboration had always taken place on the side away from the side of the cyclopropane ring, in contrast to the present case.

Oxidation of the alcohol by the chromic acid–ether procedure[21] gave only a single ketone. The ketone on reduction with lithium trimethoxyaluminum hydride afforded the isomeric alcohol, 3-neothujopsanol (11), and 3-thujopsanol in the ratio of 96:4 and with lithium

(9) E. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y. 1962.

(10) (a) S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, **89**, 1925 (1967); (b) S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa, and M. Itoh, *J. Org. Chem.*, **34**, 3015 (1969).

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

(12) J. Klein, E. Dunkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).

(13) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 3341 (1955).

(14) One of the referees objected strongly to this suggestion. He took the position that the Curtin–Hammett principle made it impossible to conclude which conformer of thujopsene is preferred in the ground state from the hydroboration results which reveal which conformer possesses the lower transition state. The Curtin–Hammett principle is not applicable to a situation where the energy of activation for the interconversion of conformers is larger than the activation energy for the reaction the system is undergoing.[11] Unfortunately, precise data are lacking for the present situation. However, we believe that a reasonable case may be made that this is indeed the case for the hydroboration of thujopsene and related interconverting olefins.

The activation energy for the interconversion of cyclohexane and its derivatives is of the order of 10–11 kcal/mol.[11] No data is available for thujopsene, but there appears to be no reason to anticipate that it will be much smaller than this, and it might even be higher.

The activation energies for bimolecular reactions which proceed at a reasonable rate at ordinary temperatures can be quite low. For example, the value for the reaction of methyl iodide and triethylamine in nitrobenzene solution is 9.7 kcal/mol [K. J. Laidler and C. N. Hinshelwood, *J. Chem. Soc.*, 858 (1938)]. The reaction of diborane with olefins in ether solvents is enormously fast. We early observed that the reaction was over in a matter of seconds at 0°, far too fast for us to measure.[9] Consequently, it is not unreasonable that the activation energy for the hydroboration step may be less than that for the interconversion stage. In any event, in the absence of contradictory data, it appears reasonable to consider this possibility. See also ref 12 and G. Zweifel and J. Plamondon, *J. Org. Chem.*, **35**, 898 (1970).

(15) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

(16) The numbering system followed is in accordance with the generic name for thujopsene, 1,1a,4,4a,5,6,7,8-octahydro-2,4a,8,8-tetramethylcyclopropa[*d*]naphthalene, as given in *Chem. Abstr.* However, the trivial name thujopsene is retained throughout this article for convenience. The prefix iso is used to indicate that the cyclopropyl and 2-methyl are cis to each other and neo is used to indicate that 3-hydroxy and 2-methyl are cis to each other. See discussion in ref 10b.

(17) A. Horeau and B. Kagen, *Tetradedron*, **20**, 2431 (1964).

(18) C. Enzell, *Acta Chem. Scand.*, **16**, 1553 (1962).

(19) W. G. Dauben and P. Oberhänsli, *J. Org. Chem.*, **30**, 3947 (1965).

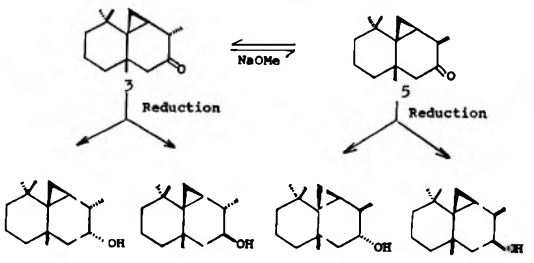
(20) H. C. Brown and A. Suzuki, *J. Amer. Chem. Soc.*, **89**, 1933 (1967).

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

aluminum hydride in the ratio 81:19 (Scheme II). There was no contamination of the product with 3-isothujopsanol (**4**) or 3-neoisothujopsanol (**8**), indicating the stereoselectivity of both the hydroboration and the oxidation stages.

SCHEME II

REDUCTION AND INTERCONVERSION OF 3-THUJOPSANONE AND 3-ISOTHUJOPSANONE



	11	2	4	8
$LiAlH_4$	81	19	65	35
$LiAl(OCH_3)_3H$	96	4	48	52

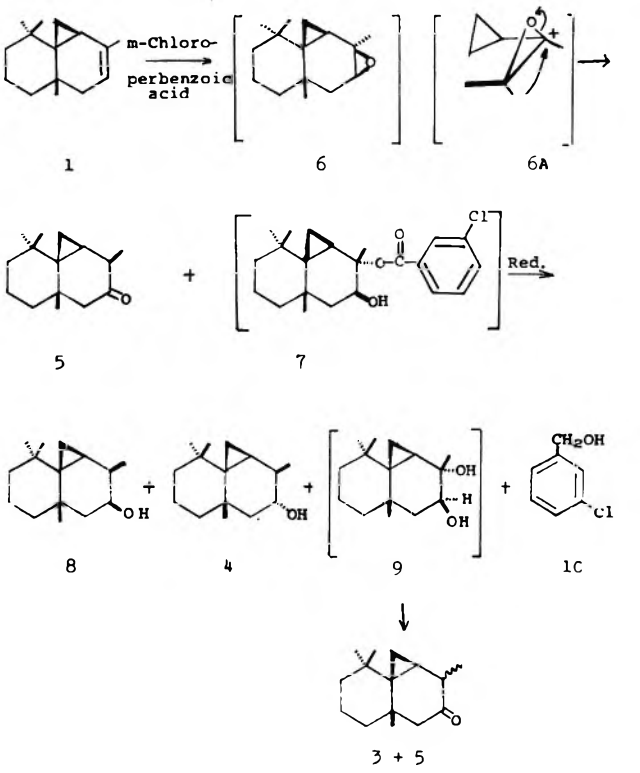
The ketone epimerized during glpc examination but was established to be essentially a single substance by the pmr spectrum. It also underwent epimerization to 3-isothujopsanone (**5**) in the presence of sodium methoxide in methanol to reach an about 50:50 equilibration of the two ketones by pmr analysis, indicating that the two ketones possess nearly equal ground state energies.

Epoxidation of (−)-Thujopsene (1).—The isomerization of epoxides to ketones with boron trifluoride etherate involves a stereospecific hydride shift.[22-24] Epoxidation, like hydroboration, appears also to involve an exothermic process proceeding through a cyclic transition state[25,26] with large steric requirements. Hence it would also be expected to take place on thujopsene from the β side to give a β-epoxide (**6**). We hoped to use the rearrangement of this epoxide with boron trifluoride etherate to obtain 3-isothujopsanone (Scheme III). Surprisingly, when thujopsene was epoxidized with *m*-chloroperbenzoic acid in chloroform at 25 or 0°, the β-epoxide (**6**) could not be obtained. Instead, 3-isothujopsanone (**5**) was realized directly in 72% yield, with 28% of another compound formed, probably 2-hydroxy-3-neoisothujopsanol 2-*m*-chlorobenzoate (**7**). All attempts to prepare the epoxide by modified procedures, such as epoxidation by perphthalic acid, or by benzonitrile–hydrogen peroxide in the presence of potassium bicarbonate,[27] failed. Likewise, all attempts to isolate pure 3-isothujopsanone (**5**) from the mixture of this ketone **5** and the benzoate **7** were futile because of the facile epimerization of the ketone. Hence the mixture was reduced with lithium aluminum hydride. The hydride uptake corresponded to a mixture containing 71% 3-isothujopsanone (**5**) and 29% benzoate (**7**). The reduced product contained 32% a mixture of *m*-chlorobenzyl alcohol (**10**), 3-thujopsanone (**3**), and 3-isothujopsanone (**5**), 44% 3-isothujopsanol (**4**), and 24% 3-neoisothujopsanol (**8**). These new alcohols were isolated as pure products by fractional distillation, followed by

(22) H. B. Henbest and T. T. Wrigley, *J. Chem. Soc.*, 4596 (1957).
(23) D. N. Kirk and V. Petrow, *ibid.*, 4657 (1960).
(24) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Org. Chem.*, **28**, 92 (1963).
(25) P. D. Bartlett, *Rec. Chem. Progr.*, **11**, 51 (1950).
(26) H. Kwart and D. M. Hofmann, *J. Org. Chem.*, **31**, 419 (1966).
(27) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

SCHEME III

EPOXIDATION OF THUJOPSENE WITH *m*-CHLOROPERBENZOIC ACID AND SUBSEQUENT REDUCTION OF THE PRODUCTS



preparative glpc. The presence of some ketone mixture **3** and **5** in the reaction product is presumably due to a secondary reaction of the diol (**9**) which is transformed into the ketones *via* ionization of the highly reactive tertiary hydroxyl group.

The mixture of **4** and **8** was oxidized by chromic acid–ether procedure[21] to obtain pure (−)-3-isothujopsanone (**5**). This ketone was reduced with lithium trimethoxyaluminohydride and with lithium aluminum hydride to establish the isomer distribution of 3-isothujopsanol (**4**) and 3-neoisothujopsanol (**8**) (Scheme II) formed in these reactions. All the four isomeric alcohols have been isolated in the pure state by preparative glpc. The melting points and the specific rotations of the two ketones, the four alcohols, and some of their corresponding *p*-nitrobenzoates are listed in Table I. Their pertinent pmr data are shown in Table II.

TABLE I

PROPERTIES OF 3-THUJOPSANONES AND 3-THUJOPSANOLS

Compd	Mp, °C	$[\alpha]_D$ (°C)	*c* (CCl_4)
(−)-3-Thujopsanone (**3**)	67–68	−85.5 (27)	13
(−)-3-Isothujopsanone (**5**)	45–46	−127.8 (25)	10
(+)-3-Neothujopsanol (**11**)	38–39	+64.41 (28)	10.9
(+)-3-Thujopsanol (**2**)	113.5–114	+14 (25)	13.4
p-Nitrobenzoate	118–119		
3-Isothujopsanol (**4**)	48–49	0 (26)	10
p-Nitrobenzoate	94–95		
(−)-3-Neoisothujopsanol (**8**)	106–107	−47.9 (26)	8.5
p-Nitrobenzoate	85–86		

It is known that the carbinyl proton of *cis*-2-methylcyclohexanols and of the corresponding steroids exhibits a chemical shift further downfield than that of the

TABLE II

PERTINENT PMR DATA[a] FOR THE 3-THUJOPSANONES AND 3-THUJOPSANOLS

Compd	2-H	2-CH_3	3-H	4-CH_2	*tert*-Methyls
3-Thujopsanone (**3**)	140[b]	70.5[e]		(α) 95,[l] (β) 127[l]	37, 66, 70.5
3-Isothujopsanone (**5**)	154[c]	65[e]		(α) 97,[m] (β) 120[n]	39, 68, 70
3-Thujopsanol (**2**)		68.5[f]	192[h]		31.5, 60, 66
3-Neothujopsanol (**11**)		64.5[e]	216[i]		41.5, 55, 64
3-Isothujopsanol (**4**)		62.5[e]	186.5[j]		46, 54, 64
3-Neoisothujopsanol (**8**)	141[d]	44.5[g]	231[k]		31.5, 59, 64

[a] All spectra were taken on a Varian A-60 or A-60A instrument. Chemical shift of the protons is expressed in terms of Hz from tetramethylsilane. [b] Quartet, $J \cong 7$ Hz. [c] Quintuet, $J = 7$ Hz. [d] Quartet, $J = 7.2$ Hz. [e] Doublet, $J = 7$ Hz. [f] Doublet, $J = 5$ Hz. [g] Doublet, $J = 7.2$ Hz. [h] Broad quartet, $J \cong 8$ Hz. [i] Doublet of triplet, $J = 8$ and 4 Hz. [j] Doublet of triplet, $J = 4.5$ and 8 Hz. [k] Doublet of doublet of doublet, $J = 12$, 8, and 4.5 Hz. [l] Doublet, $J = 14$ Hz. [m] Broad doublet, $J = 16$ Hz. [n] Doublet, $J = 16$ Hz.

trans-2-methyl isomers.[28,29] This can also be applied to the 3-thujopsanols, since the chemical shift of C-3 H of neothujopsanol is at 216 Hz and that of thujopsanol is at 192 Hz. The configurations of the two isomeric alcohols of the iso series were therefore assigned on the same basis. That is, the alcohol with a chemical shift of the carbinyl proton at 231 Hz is 3-neoisothujopsanol (**8**), and the one with this proton appearing at 186.5 Hz is the trans isomer, 3-isothujopsanol (**4**). The observed coupling constants of the carbinyl protons suggest that probably the hydroxy groups of all the four alcohols are equatorial if the B rings have half-chair conformations.

Conclusions

Both hydroboration and epoxidation of thujopsene evidently take place exclusively from the β side of the molecule. Both reactions are highly exothermic processes, suggesting that the transition states resemble the reactants.[13] It follows that the thujopsene moiety in the transition state must resemble the steroidal conformation of thujopsene I, rather than the nonsteroidal conformation II.

It is desirable to extend such studies to other exothermic processes involving reagents of large steric requirements. If the results exhibit a consistent pattern of behavior, predominant or exclusive reaction from the β side of the molecule, it would suggest that conformational preferences in the ground state are probably carried over into the transition state for reactions of this kind. Consequently, we may have a tool to explore for such flexible systems the conformational preferences in both the ground and the transition states.

Experimental Section

Materials.—(−)-Thujopsene, obtained from International Flavors and Fragrances, Inc., had $[\alpha]D$ −96.59° (neat) and was pure by glpc. The melting points are corrected and the boiling points are uncorrected. Ir spectra were taken on Perkin-Elmer 21, Serial No. 120. All pmr spectra were determined in carbon tetrachloride solution using tetramethylsilane as internal standard, added after the spectra was taken on a Varian A-60 or A-60A spectrometer. Optical rotations were determined at room temperature (25–30°) in carbon tetrachloride solutions on a Carl Zeiss polarimeter.

(+)-3-Thujopsanol (2).—The apparatus consisted of a round-bottom flask fitted with a side arm stoppered by a serum cap, a thermometer and a reflux condenser, containing at the top a nitrogen inlet and outlet connected to a gas flow meter. In this flask, previously flame dried and flushed with nitrogen, was placed 21.4 ml of (−)-thujopsene (20.4 g, 100 mmol) in 40 ml of THF. Diborane in THF (60.6 ml of 1.66 *M*, 100 mmol of BH_3) was added at 0° with stirring. The reaction mixture was stirred for 2 hr at 0° and 3 hr at 25°. The excess of hydride was decomposed with water (2 ml) in THF (10 ml). From the hydrogen evolved, 105 mmol of hydride had been utilized for the 100 mmol of thujopsene. Thus, the cyclopropane ring had not been attacked. Oxidation with sodium hydroxide (20 ml of 3 *M*) and hydrogen peroxide (20 ml of 30%) and subsequent isolation gave 21.4 g (96.3% yield) of the compound. It was purified by elution with pentane and ether on neutral alumina (200 g of grade II). The ether eluent gave only a single isomeric alcohol, as indicated by glpc examination with a 150 ft × 0.01 in. Carbowax 20M column on a Perkin-Elmer Model 226, and with a 10 ft column of 20% Carbowax 20M on Chromosorb W on an F & M Model 300 gas chromatograph. An analytical sample had mp 113–114°: $[\alpha]^{26}D$ +14° (*c* 13.45, CCl_4); ir 3401 (O—H), 1379 [$C(CH_3)_2$], and 1031 cm^{-1} (—OH or cyclopropane).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.02; H, 12.00.

3-Thujopsanol *p*-Nitrobenzoate.—The following procedure was used to prepare the *p*-nitrobenzoates. 3-Thujopsanol (0.055 g, 0.25 mmol) was placed in a previously flame-dried test tube flushed with nitrogen. Then 0.2 ml of THF, 0.16 ml of 1.60 *M* *n*-butyllithium (0.25 mmol), and 0.25 ml of a 1.60 *M* solution of *p*-nitrobenzoyl chloride in THF were added in succession at 0°; the mixture was kept for 2 hr at 25°. It was eluted on neutral alumina (0.5 g of grade II) with ether, giving 0.065 g of the compound, mp 118–119°.

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 70.75; H, 8.37. Found: C, 70.65; H, 8.42.

(−)-3-Thujopsanone (3).—The following procedure is representative of the two-phase oxidations which were carried out. In a 250-ml three neck flask, fitted with a mechanical stirrer, a dropping funnel, and a thermometer, was placed 100 ml of ether and 5.55 g of 3-thujopsanol (**2**) (25 mmol). To this vigorously stirred solution maintained at 0° was added over 10 min 25 ml of a chromic acid solution [prepared from 4 g of sodium dichromate dihydrate (13.5 mmol) and 5.4 g of sulfuric acid (55 mmol) and sufficient water to make 25 ml of the solution]. The solution was stirred for 30 min, and 25 ml of water, previously cooled to 0°, was added. The lower layer was transferred into another flask containing 25 ml of ether at 0°. The combined ether extracts were washed with cold water (2 × 10 ml), bicarbonate solution (5 × 5 ml), and brine (5 ml), and then dried and evaporated to give 4.9 g (85% yield) of 3-thujopsanone. The sample, purified by sublimation at 70° (1 mm), exhibited mp 67–68°: $[\alpha]^{27}D$ −85.5° (*c* 13, CCl_4); ir 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 81.76; H, 10.98. Found: C, 81.64; H, 11.06.

Equilibration of (−)-3-Thujopsanone (3).—(−)-3-Thujopsanone (2.2 g, 10 mmol) was added to a solution of 0.056 g of sodium methoxide (10 mmol) in 10 ml of methanol at 0° and maintained under nitrogen for 5 hr at 25°. The solution was then diluted with water, acidified with dilute phosphoric acid, saturated with sodium chloride, and extracted with pentane. The pentane extract was dried over magnesium sulfate and distilled, giving 2.03 g of the product, which on glpc examination (10 ft × 0.25 in. of 10% Carbowax 20M on Chromosorb W or on a 150 ft × 0.01 in Carbowax 20M column) showed a single peak. However, the pmr spectrum showed it to be a mixture of 50% 3-thujopsanone (**3**) and 50% isothujopsanone (**5**). The area by weight of the singlet at 41.5 Hz or the doublet at 128 Hz (J = 14 Hz) (**3**) and the singlet at 32.5 Hz or the doublet at 123 Hz

(28) E. L. Eliel, M. S. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962).

(29) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, **23**, 2339 (1967).

(J = 16 Hz for (5), all of which appear as single peaks, were used to establish the per cent of each ketone present in the product.

(+)-3-Neothujopsanol (11).—The reagent, lithium trimethoxyaluminohydride, was prepared in the usual manner by adding 3 mol of methanol to 1 mol of lithium aluminum hydride in THF.[30]

To such a solution containing an excess of reagent was added 0.44 g of 3-thujopsanone (3) (2 mmol), dissolved in 3 ml of THF, over 15 min at 0–5°. The excess of the reducing agent was destroyed by adding carefully 0.5 ml of water in 1 ml of THF. The thick white precipitate of aluminum hydroxide was treated with saturated solution of potassium sodium tartarate (15 ml), the upper THF layer separated, and the lower layer extracted with ether. The combined extract was washed with brine solution, dried over magnesium sulfate, and distilled, giving 0.418 g of the product, bp 140–145° (bath) (1.5 mm). Glpc analysis (10 ft × 0.25 in. column of 20% Carbowax 20M on Chromosorb W) indicated it to be a mixture containing 95.6% 3-neothujopsanol and 4.4% 3-thujopsanol. A pure sample of the alcohol was separated on the above column and sublimed: mp 38–39°; $[\alpha]^{28}D$ +64° (c 10.9, CCl_4); ir (CCl_4) 3425 (OH), 1375 [$C(CH_3)_2$] 1031 (—OH), and 958 cm^{-1} (cyclopropane).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.89; H, 11.94.

Epoxidation of (−)-Thujopsene (1).—To a vigorously stirred solution of 20.4 g of thujopsene (100 mmol) in 75 ml of chloroform was added 23.6 g of *m*-chloroperbenzoic acid (80% pure, 110 mmol) dissolved in 300 ml of chloroform over 25 min at 20–23°. The reaction mixture was followed by glpc. Thujopsene was absent as soon as the addition was over. The reaction mixture was cooled to −15° and filtered. The filtrate was washed with 5% sodium hydroxide (four 20-ml portions), brine (two 20-ml portions), and water, giving 25.5 g of thick turbid liquid. The pmr of the product indicated it to be a mixture of 3-isothujopsanone (5) (identified by its characteristic peaks at 32.5, 115, and 131 Hz) and of the *m*-chlorobenzoate of the alcohol (7) [identified by peaks at 449 and 480 Hz (multiplets) due to the aromatic protons and a broad quartet at 205 Hz (J = 7 Hz) due to HC(OH)]. The product is free from 3-thujopsanone, the ketone obtained by hydroboration–oxidation, as indicated by the absence of peaks at 41.5, 121, and 135 Hz. The integrated area of the aromatic protons due to *m*-chlorobenzoate (7) and that of the peaks appearing between 0–0.40 Hz due to methyl and cyclopropane protons of 3-isothujopsanone (5) gave the distribution 28% *m*-chlorobenzoate (7) and 72% ketone (5).

A number of attempts to separate 3-isothujopsanone (5) from the *m*-chlorobenzoate (7) failed. Distillation (even at 0.01 mm) decomposed the *m*-chlorobenzoate and epimerized 3-isothujopsanone to a 50:50 mixture with 3-thujopsanone. Sublimation at 60° (bath) (0.01 mm) also decomposed the ester and epimerized the ketone. Preparative glpc also gave the same mixture. Column chromatography over neutral alumina and elution with pentane gave a 50:50 mixture of the ketones which was completely free from the *m*-chlorobenzoate. A rapid filtration through alumina also gave the same mixture.

Reduction of the Mixture of 3-Isothujopsanone (5) and the *m*-Chlorobenzoate (7).—In a round-bottom flask fitted with a magnetic stirring bar, a reflux condenser, a nitrogen inlet, and a gas measuring meter, was placed 35 ml of 1.51 *M* lithium aluminum hydride in THF (212 mmol of hydride). The mixture of ketone and benzoate, 15 g, in 20 ml of THF was added in 2 hr to this excess of lithium aluminum hydride in THF and left overnight at 25°. The excess of hydride was destroyed with 50:50 water–THF. The hydrogen recovered revealed that the mixture had utilized 94 mmol of hydride, corresponding to the presence of 71% ketone (42.4 mmol) and 29% *m*-chlorobenzoate (17.2 mmol). This agrees with the pmr analysis 28% 7 as mentioned before. A saturated solution, 35 ml, of sodium potassium tartarate was added and the reaction mixture was worked up as described for 11, giving 13.9 g of the product. The glpc analysis on a 4 ft × 0.25 in. column of 20% Carbowax 20M on Chromosorb W indicated it to be a mixture of three components, namely, 32% A, 44% B, and 24% C. This mixture was distilled and separated into several fractions.

3-Isothujopsanol (4) and (−)-3-Neothujopsanol (8).—Fraction 5 was used to separate A and B which are, respectively, 4 and 8 by glpc at 200° on a 10 ft × 0.25 in. column of 20% Carbowax 20M on Chromosorb W. The separated components were recycled and purified by sublimation. 3-Isothujopsanol (4), component B, exhibited mp 48–49°, $[\alpha]^{26}D$ 0° (c 10, CCl_4); ir 3300 (O–H), 1379 [$C(CH_3)_2$] 1031 (–OH), and 1012 cm^{-1} (cyclopropane).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.87; H, 11.76.

3-Isothujopsanol *p*-nitrobenzoate had mp 94–95°.

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.86. Found: C, 70.94; H, 7.90.

(−)-3-Neoisothujopsanol (8) had mp 106–107°; $[\alpha]^{26}D$ −49.9° (c 8.5, CCl_4); ir 3356 (O–H), 1379 [$C(CH_3)_2$], 1036 (–OH), 1029 cm^{-1} (cyclopropane).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.62; H, 11.60.

3-Neoisothujopsanol *p*-nitrobenzoate had mp 85–86°.

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.86. Found: C, 71.34; H, 8.00.

(−)-3-Isothujopsanone (5).—Fraction 8 was chromatographed on alumina to separate A from the mixture of B and C. This mixture (0.271 g, 1.23 mmol) containing 60% 3-isothujopsanol (4) and 40% 3-neoisothujopsanol (8) was oxidized, as described earlier for 3, giving 0.24 g (88%) of 5. The ketone was purified by sublimation: mp 45–46°; $[\alpha]^{25}D$ −128° (c 10, CCl_4). The pmr spectrum indicated that it is free from 3-thujopsanone (3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.65; H, 10.88.

Reduction of (−)-3-Thujopsanone (3) and (−)-3-Isothujopsanone (5) with Lithium Trimethoxyaluminohydride.—(−)-3-Thujopsanone (3) (52 mg) or (−)-3-isothujopsanone (0.56 mg) were individually added to a solution of lithium aluminum hydride in THF (200 ml, 1.6 *M*) or a solution of lithium trimethoxyaluminohydride in THF (1 ml, 1.5 *M*) and left overnight. All four reaction mixtures were worked up as described previously and tested for the distribution of the isomeric alcohols. The results are summarized in Table III.

TABLE III

REDUCTION OF (−)-3-THUJOPSANONE (3) AND (−)-3-ISOTHUJOPSANONE (5) WITH $LiAlH_4$ AND $LiAl(OCH_3)_3H$

Ketone	Reducing agent	Composition[a] of 3-thujopsanols Neo-11[b]	3-2[b]	3-Iso-4[c]	3-Neo-iso-8[c]
3	$LiAlH_4$	81	19		
3	$LiAl(OCH_3)_3H$	96	4		
5	$LiAlH_4$			65	35
5	$LiAl(OCH_3)_3H$			48	52

[a] Glpc analysis on 20% Carbowax 20M on Chromosorb W (10 ft × 0.25 in.) at 225°. [b] From thujopsanone. [c] From isothujopsanone.

Epoxidation of Thujopsene by Other Methods.—Thujopsene (2.02 g, 10 mmol), was mixed with potassium bicarbonate (0.2 g, 10 mmol), benzonitrile (1.67 g, 12 mmol), and methanol (6 ml). Then 30% hydrogen peroxide (1.4 g, 12 mmol) was added at room temperature with stirring. Periodically the reaction mixture was tested for thujopsene by glpc. The time and percentage of thujopsene reacted were 5 min, 3%; 45 min, 8.6%; 1.74 hr, 26%; 2.74 hr, 38%; 6.75 hr, 45%. More 30% hydrogen peroxide (0.7 g, 6 mmol) was added. After 18 hr there was present only 22% of residual thujopsene. The reaction mixture was diluted with water and extracted with pentane. The pentane extract was dried, evaporated, and examined by pmr. The residue contained mostly isothujopsanone (5), and probably a small quantity of the Baeyer–Villiger oxidation product of the ketone, indicated by a singlet at 194 cps attributed to the –(O=)C—O—CH_2– grouping. The peaks characteristic of thujopsanone (3) were absent. Analysis by glpc showed it to be a mixture of three products and no further attempt was made to characterize these products.

Thujopsene (2.02 g, 10 mmol) was epoxidized with perphthalic acid (11 mmol) in ether. The pmr analysis of the reaction mixture, after work-up as described earlier, indicated it to contain 3-isothujopsanone (5) and probably the corresponding phthalate ester of the diol (9).

Absolute Configuration of 3-Thujopsanol.—To a solution of 0.444 g of 3-thujopsanol (2) (2 mmol) in 6 ml of dry pyridine was

(30) H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965).

added 2-phenylbutyric anhydride (4 mmol) and the mixture was maintained at room temperature for 18 hr. To this mixture was added 2 ml of water and 2 ml of benzene. After 1 hr, the excess of acid was titrated with 1.0 *M* sodium hydroxide (phenolphthalein). The results indicated that only 40% of esterification had occurred. The slightly alkaline solution was extracted with chloroform (four 15-ml portions) and the extracts were discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with benzene (three 20-ml portions). The benzene extract was washed twice with brine, dried, evaporated, and sublimed, providing (−)-2-phenylbutyric acid, $[\alpha]^{28}D$ −1.5° (c 25, CCl_4). (+)-2-Phenylbutyric acid, obtained by the hydrolysis of the 3-thujopsanol 2-phenylbutyrate with aqueous alcoholic potassium hydroxide for 24 hr at reflux, exhibited $[\alpha]^{28}D$ +3° (c 25, CCl_4).

Registry No.—**2**, 25966-77-2; **2** *p*-nitrobenzoate, 25966-78-3; **3**, 25966-79-4; **4**, 26039-33-8; **4** *p*-nitrobenzoate, 25966-80-7; **5**, 25966-81-8; **8**, 25966-82-9; **8** *p*-nitrobenzoate, 25966-83-0; **11**, 25966-84-1.

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Addition of Silicon Hydrides to Olefinic Double Bonds. XII. Use of Aminosilicon Hydrides and Silazane Hydrides

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The addition of aminosilicon hydrides and silazane hydrides to olefins and to dimethylaminodimethylvinylsilane in the presence of chloroplatinic acid was studied. *n*-Butylaminodimethylsilane and hexene-1 formed 2-*n*-butyl-1-*n*-hexyl-1,1,3,3-tetramethyldisilazane which diminished as the reaction proceeded to form *n*-butylaminohexyldimethylsilane. Dialkylaminodimethylsilanes and trisdimethylaminosilane reacted very little, if at all, with olefins. *sym*-Tetramethyldisilazane behaved much like *sym*-tetramethyldisiloxane in having similar reactivity and in forming *sec*-alkyl adducts from pentene-2. Dimethylaminodimethylsilane added to hexene-1 smoothly in the presence of *sym*-tetramethyldisilazane, but not in its absence. Methyl methacrylate, methyl acrylate, allyl chloride, methallyl chloride, or allyl acetate each gave complex mixtures of many products with *sym*-tetramethyldisilazane. Allylamine gave hydrogen. Trisdimethylsilylamine formed the dihexyl adduct, no trihexyl adduct, and products that indicated redistribution of methyl groups and hydrogen on the silicon atoms during the reaction. Poly-*N*-allylmethylsilazane reacted to form a polymer which degraded in methanol to form 2-(dimethoxymethylsilyl)propylamine.

More than 2000 examples of the addition of siloxane, and of halo- or alkoxy-, aryl-, and alkylsilicon hydrides to olefins with platinum catalysts have been described.[1] However, the only report of an aminosilicon hydride adding to an olefin is that of *sym*-tetramethyldisilazane adding to tertiary allyl amines.[2] Chemical and physical data indicate that Si–N bonds of disilazanes and trisilylamines are different from those of monosilylated amines.[3-5] We wished to determine the effect of structure among silicon hydrides that were aminosilanes, silazanes, and trisilylamines on their addition to olefins with chloroplatinic acid as a catalyst. To do this a series of hydrides was prepared. The series included *n*-butylaminodimethylsilane (*n*-BuNHSiMe$_2$H), anilinodimethylsilane (PhNHSiMe$_2$H), dialkylaminodimethylsilanes (R$_2$NMe$_2$SiH, R = Me, Et, *n*-Bu), trisdimethylaminosilane [(Me$_2$N)$_3$SiH], *sym*-tetramethyldisilazane [HN(SiMe$_2$H)$_2$], *sym*-diphenyldimethyldisilazane [HN(SiMePhH)$_2$], and trisdimethylsilyl amine [N(SiMe$_2$H)$_3$]. Chloroplatinic acid in propanol-2 was used as a catalyst with hexene-1 or pentene-1 and pentene-2 as typical olefins. Other unsaturated compounds were also used including poly-*N*-allylmethylsilazane $[CH_2{=}CHCH_2{-}\underset{|}{N}{-}\underset{|}{SiHMe}]_n$, allylamine, and other allyl or methallyl compounds.

(1) E. Y. Lukevits and M. G. Vorankov, "Organic Insertion Reactions of Group IV Elements," Consultants Bureau, New York, N. Y., 1966, and references cited therein.

(2) K. A. Andrianov, L. M. Khanenashvili, V. M. Kopylov, and T. V. Nesteroras, *Izv. Nauk Akad. USSR, Ser. Khim.*, **2**, 351 (1968).

(3) R. O. Sauer and R. H. Hasek, *J. Amer. Chem. Soc.*, **68**, 241 (1946).

(4) S. Sujishi and S. Witz, *ibid.*, **76**, 4631 (1954).

(5) K. Hedberg, *ibid.*, **77**, 6491 (1955).

Results and Discussion

n-Butylaminodimethylsilane with hexene-1 and chloroplatinic acid at 100° reacted smoothly but followed an unexpected course. After 1 hr the chief products were 2-*n*-butyl-1-hexyl-1,1,3,3-tetramethyldisilazane and butylamine. After 3 hr the disilazane had been largely converted to *n*-butylaminohexyldimethylsilane. Formation of these products probably occurred by a sequence of reactions as in the following reactions.

$$2n\text{-BuNHSiMe}_2\text{H} \rightleftharpoons n\text{-BuN(SiMe}_2\text{H)}_2 + n\text{-BuNH}_2$$

$$n\text{-BuN(SiMe}_2\text{H)}_2 \xrightarrow{\text{hexene-1}} n\text{-BuN(SiMe}_2\text{H)SiMe}_2\text{-}n\text{-Hex}$$

$$n\text{-BuN(SiMe}_2\text{H)SiMe}_2\text{-}n\text{-Hex} \xrightarrow{\text{hexene-1}} n\text{-BuN(SiMe}_2\text{-}n\text{-Hex)}_2$$

$$n\text{-BuN(SiMe}_2\text{-}n\text{-Hex)}_2 + \text{BuNH}_2 \longrightarrow 2n\text{-BuNHSiMe}_2\text{Hex}$$

Anilinodimethylsilane under the same conditions formed a 96% yield of anilinodimethylhexylsilane and no intermediate step in its formation was noted.

Dimethylaminodimethylsilane, diethylaminodimethylsilane, and di-*n*-butylaminodimethylsilane under the same conditions formed little or no adducts with hexene-1. However these silanes added very smoothly, although slowly, to hexene-1 if *sym*-tetramethyldisilazane was in the mixture of reagents.

This strange behavior was thought to be the likely consequence of an inability of dialkylaminodimethylsilanes to form a complex with platinum necessary for catalytic activity in such a system. The formation of di-*n*-butylaminohexyldimethylsilane then must have

occurred by an exchange such as in the following reactions.

$$HN(SiMe_2H)_2 + \text{hexene-1} \xrightarrow{Pt} HMe_2SiNHSiMe_2\text{-}n\text{-Hex}$$

$$HMe_2SiNHSiMe_2\text{-}n\text{-Hex} + n\text{-}Bu_2NMe_2SiH \xrightarrow{Pt} HN(SiMe_2H)_2 + n\text{-}Bu_2NMe_2Si\text{-}n\text{-Hex}$$

Di-*n*-hexyltetramethyldisilazane was mixed with octene-1 and dimethylaminodimethylsilane and the catalyst. Again, little or no reaction occurred. In the presence of 1-*n*-hexyl-1,1,3,3-tetramethyldisilazane, however, a complex mixture of products formed in excellent yields. The products included *n*-hexyldimethylaminodimethylsilane, which could result only by the exchange described above. The products also included dimethylaminodimethyloctylsilane, *sym*-dihexyltetramethyldisilazane, *sym*-dioctyltetramethyldisilazane, and 1-hexyl-3-octyltetramethyldisilazane. These products indicate that a reversible exchange of silyl groups between disilazanes and dimethylaminosilanes occurred in this system. Probably only the dimethylsilyl groups in disilazanes added to the olefins, but with the exchange going on all possible adducts were produced. In order to see if chloroplatinic acid was a catalyst for such exchange processes in the absence of an olefin, *n*-hexylmethylaminodimethylsilane and *sym*-tetramethyldisilazane were heated 20 hr at 100° with chloroplatinic acid. No exchange took place. This indicates that exchange required a platinum–olefin–silane complex. Dimethylaminosilanes are ineffective in making such a complex and are therefore not added to an olefin. Trisdimethylaminosilane was another example that did not add to hexene-1 with chloroplatinic acid nor with benzoyl peroxide.

Hexene-1, with *sym*-tetramethyldisilazane or with *sym*-diphenyldimethyldisilazane, gave the corresponding di-*n*-hexyl adducts in good yield. 3,3-Dimethoxypropene under similar conditions gave a 53% yield of *sym*-bis(3,3-dimethoxypropyl)tetramethyldisilazane. Under the same conditions pentene-2 reacted very slowly with *sym*-tetramethyldisilazane but formed a good yield of a mixture of *n*-pentyl and *sec*-pentyl adducts. This behavior of *sym*-tetramethyldisilazane with pentene-2 is closely analogous to the behavior of *sym*-tetramethyldisiloxane.[6]

sym-Tetramethyldisilazane and vinyldimethylaminodimethylsilane reacted smoothly to form *sym*-bis[2-(2-dimethylaminodimethylsilyl)ethyl]tetramethyldisilazane, $(Me_2NMe_2SiCH_2CH_2SiMe_2)_2NH$. This example is interesting chiefly because the large number of products were not observed that would have formed if silyl groups had exchanged extensively between the disilazane and dimethylaminosilane structures.

sym-Tetramethyldisilazane and allylamine made hydrogen and other products that were not identified. The formation of hydrogen from allylamine and silicon hydrides has been observed before.[7]

Allyl acetate, allyl chloride, methallyl chloride, methyl acrylate, and methyl methacrylate all gave numerous products which were not identified. Acrylonitrile did not seem to react with tetramethyldisilazane, but preferred to polymerize.

(6) H. M. Bank, J. C. Saam, and J. L. Speier, *J. Org. Chem.*, **29**, 792 (1964).

(7) J. C. Saam and J. L. Speier, *ibid.*, **24**, 119 (1959).

Trisdimethylsilylamine with hexene-1 formed at least five addition products detected by glc analysis. A large run was distilled to yield 41% bis(hexyldimethylsilyl)dimethylsilylamine. A mass spectrum of the products from a glc analysis indicated that the higher boiling products contained an unusual combination of hexyl and methyl groups and hydrogen on silicon. The lowest boiling peak had a *m/e* of 373 corresponding to bis(hexyldimethylsilyl)trimethylsilylamine. Three other peaks in the glc had a *m/e* of 429 suggesting trisilylamines each possessing five methyl groups, three hexyl groups, and one hydrogen, *e.g.*, bis(hexyldimethylsilyl)hexylmethylsilylamine.

These products were refluxed in ethanol for 10 days and after low boiling materials had been removed glc analysis indicated peaks with retention times of dihexylmethylethoxysilane, hexylmethylethoxysilane, and hexyldimethylethoxysilane.

Both trisdimethylsilylamine and tristrimethylsilylamine were refluxed in ethanol to corroborate the method of derivatizing the above products by ethanolysis. Tristrimethylsilylamine in 18 hr gave complete conversion to trimethylethoxysilane. Similarly trisdimethylsilylamine was converted to dimethylethoxysilane after 40 hr. These results were not to be expected in view of the reported stability of bis(methoxydimethylsilyl)trimethylsilylamine in refluxing methanol.[8]

No exchange of hydrogen and methyl groups on silicon in trisdimethylsilylamine occurred in the presence of chloroplatinic acid under the same conditions in the absence of the olefin.

The exchange of methyl groups and hydrogen from one silicon atom to another of trisdimethylsilylamine is without precedent during platinum-catalyzed addition of silicon hydrides to olefins. Methyl groups and trimethylsiloxy groups have exchanged during the addition of bistrimethylsiloxymethylsilane to hexene-2, but in that case no exchange of hydrogen was detected.[9]

A mixture of cyclo-*N*-allylmethylsilazanes, $(CH_2{=}CHCH_2NSiMeH)_n$, was added to refluxing toluene that contained chloroplatinic acid. A very high boiling product resulted. This product was refluxed in methanol for 64 hr and distilled to obtain about a 51% yield of 2-(methyldimethoxysilyl)propylamine. An isomer, thought to be 3-(methyldimethoxysilyl)propylamine was also present as an impurity to the extent of about 9%.

Experimental Section

Analyses.—Gas–liquid chromatographs (glc) were obtained with an 8 ft × 0.25 in. stainless steel column packed with 26% Dow Corning SGM-11 on Chromosorb W 80–100 mesh. Peaks were identified in most cases by injection of samples to which authentic compounds had been added. ^1H nmr spectra were obtained on a Varian Associates Model A-60 using CCl_4 as solvent and tetramethylsilane as an internal standard. Infrared spectra were obtained on a Perkin-Elmer 521 grating spectrometer. The mass spectra were obtained on an AEI-MS-12 mass spectrometer. Elemental analyses were determined by the Dow Corning Analytical Laboratory. The specific refractions of the compounds in this paper were calculated with the bond refraction values of Vogel, *et al.*[10]

(8) L. W. Breed and R. L. Elliot, *J. Organometal. Chem.*, **11**, 447 (1968).

(9) Marilyn R. Stober, M. C. Musolf, and J. L. Speier, *J. Org. Chem.*, **30**, 1651 (1965).

(10) A. I. Vogel, W. T. Creswell, and J. Lucester, *J. Phys. Chem.*, **58**, 174 (1954).

TABLE I

INTERMEDIATES

Compd	Registry no.	% yield	Bp, °C (mm)	$n^{25}D$	d^{25}_4	R_D Calcd	R_D Found	Neut equiv Calcd	Neut equiv Found
n-Pentyldimethylchlorosilane	25938-34-5	88	160 (atm)	1.4225				165	169
n-Hexyldimethylchlorosilane	3634-59-1	58	98–100 (50)	1.4269	0.8759	0.296	0.293	179	179
n-Octyldimethylchlorosilane[a]		79	90 (30)	1.4328				209	219
n-Hexylmethylchlorosilane	26015-61-2	34	172 (atm)						
n-Hexylmethylethoxysilane	25938-35-6	43	80 (25)	1.4136	0.8091	0.313	0.309	...[b]	
Di-*n*-hexylmethylsilane	1001-46-3	53	137 (20)	1.4365	0.7773	0.337	0.337	...[c]	
Di-*n*-hexylmethylethoxysilane	25938-37-8	81	157 (30)	1.4320				...[d]	
Dimethylaminodimethylvinylsilane[e]		42	108 (atm)	1.4169				129	133
n-Butylaminodimethylsilane	25938-38-9	49	88–91 (40)	1.4088	0.7591	0.318	0.318	131	135
Diethylaminodimethylsilane[f]		39	110 (atm)	1.4089					
Dimethylaminodimethylsilane[g]		28	68 (atm)	1.3889				103	105
Di-*n*-butylaminodimethylsilane	25938-39-0	39	70–71 (7)	1.4268	0.7916	0.328	0.325	187	186
sym-Dimethyldiphenyldisilazane	25938-40-3	53	120–121 (0.5)	1.5480	0.9998	0.321	0.318	257	255
Anilinodimethylsilane[h]			91 (12)	1.5312	0.9895	0.319	0.313	151	153
sym-Tetramethyldisilazane[i]		57	100 (atm)					133	134
Trisdimethylsilylamine[j]			150 (atm)	1.4222					
Dimethylamino-*n*-hexyldimethylsilane	25913-89-7	80	103–108 (30)	1.4278	0.9519	0.328	0.327	187	188
Diethylamino-*n*-hexyldimethylsilane	26015-62-3	75	72 (1.0)	1.4330	0.7976	0.320	0.326	215	217
N-Allylmethylcyclosilazanes		44.5	69–133 (0.1)	1.4791–1.5006	0.9322–0.9760	0.308	0.304–0.302	99	99–100

[a] R. H. Bunnell and D. A. Shirley, *J. Org. Chem.*, 17, 1545 (1952), report bp 222–225°. [b] *Anal.* Calcd for $SiC_9H_{22}O$: Si, 16.1; C, 62.0; H, 12.7. Found: Si, 15.7; C, 63.1; H, 12.6. [c] *Anal.* Calcd for $SiC_{13}H_{30}O$: Si, 13.1; C, 72.9; H, 14.1. Found: Si, 13.2; C, 72.8; H, 14.02. [d] *Anal.* Calcd for $SiC_{15}H_{34}O$: Si, 10.82; C, 69.4; H, 13.2. Found: Si, 10.98; C, 69.8; H, 13.6. [e] W. J. Patterson and N. Bilow, *J. Polym. Sci., Part A-1*, 7 (4), 1089 (1969), report bp 105–106° (760 mm). [f] K. A. Andrianov, T. K. Dzhashiashvili, V. V. Astakhin, and G. N. Shunakova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 12, 2229 (1966), report bp 112–112.5, $n^{20}D$ 1.8087. [g] W. J. Patterson and N. Bilow, *J. Polym. Sci., Part A-1*, 7 (4), 1089 (1969), report bp 65–66° (760 mm). [h] K. A. Andrianov, L. M. Khananashvili, V. M. Kopylou, and A. A. Vyaz'mitinova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 7, 1539 (1969), report bp 65° (8 mm). [i] H. Kriegsmann and G. Engelhardt, *Z. Anorg. Chem.*, 310, 100 (1961), report bp 99–100°. [j] R. P. Bush, N. C. Lloyd, and C. A. Pearce, *J. Chem. Soc. A*, 253 (1969), report bp 153° (760 mm).

The neutralization equivalents of the aminosilanes and disilazanes were determined by titration with 0.1 *N* perchloric acid in acetic acid to the blue methyl violet end point. The neutralization equivalents of the chlorosilanes were obtained by titration with 0.1 *N* sodium hydroxide in aqueous ethanol with phenophthalein as an indicator.

Reagents.—Chlorosilanes were products of the Dow Corning Corporation and, with the exception of dimethylchlorosilane, were >99% pure by glc analysis. Dimethylchlorosilane was approximately 75% pure.

Allylamine was obtained from the Shell Chemical Company >95% pure by glc analysis. Ammonia and dimethylamine were obtained from Matheson Company. Di-*n*-butylamine was obtained from Aldrich Chemical Company. Diethylamine, *n*-butylamine, and aniline were obtained from Fisher Scientific Company.

Synthesis of Intermediates.—Dimethylaminosilanes and disilazanes were prepared by bubbling an excess of dimethylamine or ammonia through a stirred solution of the appropriate chlorosilane in pentane at 0°. Other aminosilanes from liquid amines were prepared by adding chlorosilanes to a solution of the amine in pentane. Trisdimethylsilylamine was prepared from tetramethyldisilazane and dimethylchlorosilane with pyridine as a hydrogen chloride acceptor. The products were warmed to room temperature and filtered. The filtrates were then distilled to obtain the products shown in Table I.

n-Pentyl-, *n*-hexyl-, and *n*-octyldimethylchlorosilanes were prepared from pentene-1, hexene-1 or octene-1 and dimethylchlorosilane with chloroplatinic acid as the catalyst.[11]

Di-*n*-hexylmethylsilane was prepared from *n*-hexylmagnesium bromide in ether and *n*-hexylmethylchlorosilane.

Di-*n*-hexylmethylethoxysilane was prepared by the reaction of di-*n*-hexylmethylsilane and absolute ethanol in the presence of 5% palladium on charcoal.[12] Nmr spectral data are shown in Table II.

***n*-Butylaminodimethylsilane with Hexene-1.**—*n*-Butylaminodimethylsilane, 26.0 g (0.2 mol), was added to refluxing hexene-1, 16.8 g (0.2 mol), that contained 3 drops of 0.1 *M* H_2PtCl_6. The mixture was heated to about 100° during 1 hr and analyzed by glc. At this time it was mostly 2-*n*-butyl-1-*n*-hexyl-1,1,3,3-tetramethyldisilazane and butylamine. After 3 hr at 100° and a weekend at room temperature the product was distilled to give hexene, 7.0 g (42% of starting material), *n*-butylaminodimethylhexylsilane [17.5 g (0.086 mol, 74% based on unrecovered hexene); bp 52–54° (15 mm); $n^{25}D$ 1.4316; d^{25}_4 0.7893; R_D 0.328, calcd 0.327; neut equiv 214, calcd 215; ir (CCl_4) 3410 (NH), (CS_2) 1250 cm^{-1} (SiMe)], and 2-*n*-butyl-1-*n*-hexyl-1,1,3,3-tetramethyldisilazane [6.1 g (0.022 mol, 14.7% based on unrecovered hexene); bp 69° (0.1 mm); $n^{25}D$ 1.4410; d^{25}_4 0.8196; R_D 0.320, calcd 0.322; ir (CCl_4) 2130 (SiH), (CS_2), 1250 (SiMe), 900 cm^{-1} (Si–N)].

Anilinodimethylhexylsilane with Hexene-1.—Hexene-1, 4.2 g (0.05 mol), anilinodimethylsilane, 7.22 g (0.05 mol), and 0.01 ml of 0.1 *M* H_2PtCl_6 were sealed into a Pyrex tube and heated to 100° for 24 hr. Distillation gave 11.3 g (96%) of anilinohexyldimethylsilane: bp 122° (1.5 mm); $n^{25}D$ 1.5029; d^{25}_4 0.9010; R_D 0.328, (calcd 0.322); neut equiv 239, calcd 235; ir 3400 (N–H), 1500 and 1600 (Ph–N), 1253 cm^{-1} (Si–Me).

Dimethylaminodimethylsilane with Hexene-1.—A sealed tube containing 1.03 g (10 mmol) of dimethylaminodimethylsilane and 0.84 g (10 mmol) of hexene-1 containing 0.01 ml of 0.1 *M* chloroplatinic acid was heated at 100° for 20 hr. Analysis by glc indicated less than 10% of the mixture was higher boiling than the starting materials.

Diethylaminodimethylsilane with Hexene-1.—A sealed tube containing 1.31 g (10 mmol) of diethylaminodimethylsilane, 0.84 g (10 mmol) of hexene-1 and 0.01 ml of 0.1 *M* chloroplatinic acid was heated at 100° for 18 hr. A glc analysis of this mixture indicated less than 10% eluted after the starting materials.

Di-*n*-butylaminodimethylsilane with Hexene-1.—Di-*n*-butylaminodimethylsilane, 1.87 g (10 mmol), and 0.84 g (10 mmol) hexene-1 (0.84 g, 10 mmol) with 0.01 ml of 0.1 *M* chloroplatinic acid under conditions described above gave almost no reaction.

Dimethylaminodimethylsilane with Hexene-1 and *sym*-Tetramethyldisilazane.—A sealed tube containing 1.03 g (10 mmol) of dimethylaminodimethylsilane, 0.67 g (5 mmol) of *sym*-tetramethyldisilazane, 1.68 g (20 mmol) of hexene-1, and 0.01 ml of 0.1 *M* chloroplatinic acid was heated at 100° for 20 hr. A glc of the products indicated very small amounts of hexene-1 and dimethylaminodimethylsilane, no tetramethyldisilazane,

(11) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Amer. Chem. Soc.*, **79**, 974 (1957).

(12) L. H. Sommer and J. E. Lyons, *ibid.*, **91**, 7061 (1969).

TABLE II

NMR SPECTRAL DATA

Structure	Registry no.	τ	H's	Assignment	Type	Hz
$CH_3(CH_2)_3NSi(CH_3)_2H$ (H on N)	25938-38-9	9.93	6.3	$SiCH_3$	s	
		9.10	3.0	CCH_3	broad s	
		8.4–8.9	4.8	CH_2, NH	m	
		7.0–7.5	2.0	NCH_2	m	
		5.55	0.9	SiH	m	
$CH_3(CH_2)_5SiCH_3(OCH_2CH_3)H$	25938-35-6	9.87	3.0	$SiCH_3$	d	4
		8.3–9.6	18.5	alkyl H	m	
		6.36	2.0	OCH_2CH_3	q	7
		5.51	1.0	SiH	q	4
$[CH_3(CH_2)_5]_2SiCH_3H$	1001-46-3	9.97	3.0	$SiCH_3$	d	4
		8.3–9.7	26.0	alkyl H	m	
		6.25	1.0	SiH	q	4
$[CH_3(CH_2)_5]_2SiCH_3(OCH_2CH_3)$	25938-37-8	≈10.0	3.0	$SiCH_3$	s	
		8.7–9.7	29.0	alkyl H	m	
		6.41	2.0	OCH_2CH_3	q	7
$(\text{–}SiCH_3HNCH_2CH{=}CH_2)_x$		9.8–9.86	2.9	$SiCH_3$	m	
		6.55	2.0	NCH_2	m	
		4.8–5.4	3.0	SiH, $C{=}CH_2$	m	
		4.0–4.5	1.0	$-CH{=}CH_2$	m	
$CH_3(CH_2)_5Si(CH_3)_2N(CH_2)_3CH_3$ (H on N)	25942-76-1	10.04	6.0	$SiCH_3$	s	
		9.1–9.75	21.0	alkyl H	m	
		7.32	2.0	NCH_2	m	
$CH_3(CH_2)_5Si(CH_3)_2N[Si(CH_3)_2H][(CH_2)_3CH_3]$	25942-77-2	9.94	6.0	$SiCH_3$	s	
		9.89	6.0	$SiCH_3$	d	3
		8.7–9.5	20.0	alkyl H	m	
		7.3	2.0	NCH_2	m	
		5.58	1.0	SiH	m	3
$PhNSi(CH_3)_2(CH_2)_5CH_3$ (H on N)	25942-78-3	9.81	6.1	$SiCH_3$	s	
		9.13	3.0	CCH_3	d	
		6.84	0.9	NH	s	
		2.8–3.7	5.1	ArH	m	
$[CH_3(CH_2)_5Si(CH_3)_2]_2NH$	25942-79-4	9.98	12.0	$SiCH_3$	s	
		8.5–9.7	27.0	alkyl H, NH	m	
$CH_3(CH_2)_5Si(CH_3)_2NSi(CH_3)_2H$ (H on N)	25938-25-4	9.98	6.0	$SiCH_3$	s	
		9.89	6.0	$SiCH_3$	d	3
		9.12–9.7	14.0	alkyl H, NH	m	
		5.55	1.0	SiH	m	3
$CH_3(CH_2)_5Si(CH_3)_2NSi(CH_3)_2(CH_2)_7CH_3$ (H on N)	25938-26-5	10.0	12.0	$SiCH_3$	s	
		8.7–9.7	31.0	alkyl H, NH	m	
$CH_3(CH_2)_4Si(CH_3)_2NSi(CH_3)_2H$ (H on N)	25938-27-6	≈9.9	12.0	$SiCH_3$	m	
		8.5–8.8	12.0	alkyl CH_2	m	
		5.67	1.0	SiH	m	
$(CH_3)_2SiN[Si(CH_3)_2(CH_2)_5CH_3]_2$	25938-28-7	9.8	21.0	$SiCH_3$	m	
		8.4–9.6	16.0	alkyl H	m	

and large amounts of *sym*-dihexyltetramethyldisilazane and dimethylaminohexyldimethylsilane.

Diethylaminodimethylsilane with Hexene-1 and *sym*-Tetramethyldisilazane.—Hexene-1, 50.4 g (0.6 mol), was slowly added to a solution of 19.6 g (0.15 mol) of diethylaminodimethylsilane and 26.6 g (0.20 mol) of *sym*-tetramethyldisilazane with 0.1 ml of 0.1 *M* chloroplatinic acid was refluxed overnight. The products were distilled through a Vigreux column. All fractions containing dimethylamino-*n*-hexyldimethylsilane were combined and redistilled through a spinning-band column to give 15.2 g, 40%, of product: bp 75° (2 mm); $n^{25}D$ 1.4338; neut equiv 217, calcd 215.

Di-*n*-butylaminodimethylsilane, Hexene-1, and *sym*-Tetramethyldisilazane.—Hexene-1, 25.8 g (0.3 mol), was added slowly to di-*n*-butylaminodimethylsilane, 28.4 g (0.15 mol), and *sym*-tetramethyldisilazane, 10 g (0.075 mol), that contained 0.1 ml of 0.1 *M* H_2PtCl_6. The solution was refluxed 72 hr before analysis by glc indicated that the reagents had nearly completely reacted. Distillation did not separate di-*n*-butylaminodimethylhexylsilane and *sym*-dihexyltetramethyldisilazane although they

were distinguishable by glc analysis. One fraction contained 76 area per cent of the former, 23 area per cent of the latter and had a neut equiv of 281. Calcd (for such a mixture) 280.

sym-**Dihexyltetramethyldisilazane and** *sym*-**Tetramethyldisilazane.**—A sealed tube containing 1.87 g (10 mmol) of dimethylaminohexyldimethylsilane and 1.33 g (10 mmol) of *sym*-tetramethyldisilazane containing 0.01 ml of 0.1 *M* chloroplatinic acid was heated at 100° for 20 hr. A glc analysis indicated only starting materials.

Dimethylaminodimethylsilane with Octene-1 in the Presence of *sym*-**Dihexyltetramethyldisilazane.**—A sealed tube containing 1.5 g (5 mmol) of *sym*-di-*n*-hexyltetramethyldisilazane, 0.5 g (5 mmol) of dimethylaminodimethylsilane and 0.56 g (5 mmol) of octene-1 was heated for 72 hr at 110°. A glc analysis of the product mixture indicated no dimethylaminohexyldimethylsilane and the starting materials accounted for greater than 90% of the material present.

Dimethylaminodimethylsilane and 1-*n*-**Hexyl-1,1,3,3-tetramethyldisilazane with Octene-1.**—A sealed tube containing 0.87 g (4 mmol) of 1-*n*-hexyl-1,1,3,3-tetramethyldisilazane, 0.41 g (4 mmol) of dimethylaminodimethylsilane, and 0.45 g (4 mmol) of octene-1 was heated at 120° for 24 hr. A glc analysis of the mixture indicated the following compounds had formed: dimethylaminohexyldimethylsilane, 1-*n*-hexyl-1,1,3,3-tetramethyldisilazane, dimethylaminodimethyloctylsilane, *sym*-di-*n*-hexyltetramethyldisilazane, 1-*n*-hexyl-1,1,3,3-tetramethyloctyldisilazane, and a higher boiling material which probably was *sym*-tetramethyldioctyldisilazane, although no standard was available to identify it.

Trisdimethylaminosilane with Hexene-1 with Chloroplatinic Acid.—A sealed tube containing 1.6 g (10 mmol) of trisidmethylaminosilane and 0.84 g (10 mmol) of hexene-1 containing 0.01 ml of 0.1 *M* chloroplatinic acid was heated at 100° for 20 hr. A glc analysis indicated no reaction had taken place.

Trisdimethylaminosilane with Hexene-1 with Benzoyl Peroxide.—Benzoyl peroxide (50 mg) was added to a refluxing solution of 8.3 g (0.096 mol) of hexene-1 and 16.1 g (0.1 mol) of trisdimethylaminosilane. After 4 hr another 10 mg of benzoyl peroxide was added. After 22 hr 25 mg was added, and after 48 hr analysis by glc indicated no reaction had taken place.

sym-**Di-***n*-**hexyldimethyldiphenyldisilazane with Hexene-1.**—A sealed tube containing 2.6 g (10 mmol) of *sym*-diphenyldimethyldisilazane and 1.68 g (20 mmol) of hexene-1 with chloroplatinic acid was heated at 100° for 20 hr. Analysis by glc indicated one high boiling compound: $n^{25}D$ 1.5188; d^{25}_4 0.9477; R_D 0.320, calcd 0.322; neut equiv 417, calcd 426.

Bis[2-(dimethylaminodimethylsilyl)ethyldimethylsilyl]amine, $(Me_2NMe_2SiCH_2CH_2SiMe_2)_2NH$.—To 25.8 g (0.2 mol) of refluxing vinyldimethylaminodimethylsilane containing 0.3 ml of 0.1 *M* chloroplatinic acid was added slowly, 13.3 g (0.1 mol) of *sym*-tetramethyldisilazane. Distillation of the product gave 20.5 g, 53%: bp 120–125° (2 mm); $n^{25}D$ 1.4578; d^{25}_4 0.8752; R_D 0.312, calcd 0.314; neut equiv 134.3, calcd 130.3.

2-(**Methyldimethoxysilyl**)**propylamine.**—To a refluxing solution of 0.1 ml of 0.1 *M* chloroplatinic acid in 50 ml of toluene was slowly added 50 g (0.5 mol) of *N*-allylmethylcyclosilazane. The mixture was refluxed for 20 hr and cooled to 70°, and 50 ml of methanol was added. The mixture was then refluxed for 64 hr. A glc analysis revealed a small amount of methyltrimethoxysilane and a large amount of two products though to be isomers, methyldimethoxysilylpropylamines with one isomer predominating in a ratio of >9:1. The major isomer was isolated by distillation in 51% yield and identified as 2-(methyldimethoxysilyl)propylamine: bp 123–124° (130 mm); $n^{25}D$ 1.4258; d^{25}_4 0.9532; R_D 0.269, calcd 0.272; neut equiv 169, calcd 163; nmr τ 9.04 (d, $CHCH_3$, J = 1.5 Hz); ir 1384 cm^{-1} ($C-CH_3$).[13]

sym-**Tetramethyldisilazane with Hexene-1.**—*sym*-Tetramethyldisilazane, 13.3 g (0.1 mol), was added to refluxing hexene-1, 16.8 g (0.2 mol), that contained 0.03 ml of 0.1 *M* H_2PtCl_6. After 2 hr at 67–140° glc revealed only one product. Distillation gave 26.1 g (87%): bp 100° (0.8 mm); $n^{25}D$ 1.4419; d^{25}_4 0.8149; R_D 0.3244, calcd 0.3245; neut equiv 308, calcd 302; ir (CCl_4) 3375 NH (CS_2), 1245 (SiMe), 1180 (SiNHSi), 930 (SiN), 835 cm^{-1} ($SiMe_2$). *Anal.* Calcd for $Si_2C_{16}H_{39}N$: Si, 63.7; H, 13.1; N, 4.65. Found: Si, 63.7; H, 13.2; N, 4.64.

(13) A. D. Petrov, L. K. Freidlin, G. I. Kudryautsev, T. A. Sladkova, V. M. Vdovin, and T. I. Shein, *Chem. Zentralbl.*, 2947 (1961), report for 3-(methyldimethoxysilyl)propylamine bp 58–60° (4 mm), d^{20}_4 0.9430, $n^{20}D$ 1.4325.

1-Hexyl-1,1,3,3-tetramethyldisilazane.—In the same manner *sym*-tetramethyldisilazane, 34 g (0.25 mol), was heated with hexene-1, 21 g (0.25 mol). Distillation gave 24.3 g, 44.7%, of 1-*n*-hexyl-1,1,3,3-tetramethyldisilazane: bp 90° (6 mm); $n^{25}D$ 1.4280; d^{25}_4 0.8035; R_D 0.320, calcd 0.323; ir (CCl_4) 3385 (NH), 2115 (SiH) (CS_2), 1170 cm^{-1} (SiNSi).

sym-**Bis(3,3-dimethoxypropyl)tetramethyldisilazane.**—To 20.4 g (0.2 mol) of 3,3-dimethoxypropene containing 3 drops of 0.1 *M* chloroplatinic acid was slowly added with heating 13.4 g (0.1 mol) of *sym*-tetramethyldisilazane. The mixture was heated to 150° and then allowed to cool. A glc of the crude mixture indicated 78% of the diadduct and a mixture of at least six different lower boiling compounds. Distillation of a portion of this material gave *sym*-bis(3,3-dimethoxypropyl)tetramethyldisilazane: bp 121° (0.25 mm); $n^{25}D$ 1.4452; d^{25}_4 0.9501; R_D 0.280, calcd 0.282; ir (CCl_4) 3370 (NH), 2830 ($COCH_4$) (CS_2), 1253 ($SiCH_3$), 1175 (SiNSi), 1120 (COC), 930 cm^{-1} (SiN). *Anal.* Calcd for $Si_2C_{14}H_{35}NO_2$: Si, 16.7; C, 49.9; H, 10.5; N, 16.7. Found: Si, 16.8; C, 50.0; H, 10.5; N, 16.8. Treatment of this compound with acidic 2,4-dinitrophenylhydrazine solution gave the dihydrazone of tetramethyldisiloxane-1,3-dipropanal, mp 184–185°, mixture melting point undepressed.

1-Hexyl-1,1,3,3-tetramethyldisilazane with Octene-1.—To a refluxing solution of 0.03 ml of chloroplatinic acid in 11 g (0.1 mol) of octene-1 was slowly added 11 g (0.05 mol) of 1-hexyl-1,1,3,3-tetramethyldisilazane. The reaction was complete in 1 hr and distillation gave 13.7 g (83%) of 1-hexyl-1,1,3,3-tetramethyl-3-octyldisilazane: bp 138° (0.8 mm); $n^{25}D$ 1.4439; d^{25}_4 0.8240; R_D 0.323, calcd 0.325.

sym-**Tetramethyldisilazane with Pentene-2 at 100° for 40 Hr.**—A sealed tube containing 14.0 g (0.2 mol) of pentene-2 and 13.3 g (0.1 mol) of *sym*-tetramethyldisilazane with 0.1 ml of 0.1 *M* chloroplatinic acid solution was heated at 100° for 40 hr. Analysis by glc revealed that all of the starting disilazane had reacted, however, approximately one-half of the olefin was still present. The monoadduct was distilled to give 12.8 g (63%): bp 138–140° (140 mm); $n^{25}D$ 1.4340; d^{25}_4 0.8084; R_D 0.320, calcd 0.324; neut equiv 208, calcd 203; ir (CCl_4) 3380 (NH), 2115 (SiH) (CS_2), 1170 (SiNHSi), 840 cm^{-1} ($SiMe_2$). *Anal.* Calcd for $Si_2C_9H_{25}N$: Si-H, 0.49. Found: Si-H 0.535.

sym-**Tetramethyldisilazane with Pentene-2 at 110° for 48 Hr.**—Four sealed tubes containing 14.0 g (0.2 mol) of pentene-2 and 13.3 g (0.1 mol) of 1 with 0.03 ml of 0.1*M* chloroplatinic acid were heated at 110° for 48 hr. The contents of the sealed tubes were combined and distilled to give 55.5 g (68%) of monopentyladduct, bp 57° (2 mm), and 17 g (15.6%)of dipentyladduct: bp 84–86° (1 mm); $n^{25}D$ 1.4118; d^{25}_4 0.7570; R_D 0.324, calcd 0.329. This product 51 g (0.25 mol) in 50 ml of pentane was converted into chlorosilanes by a slow stream of dry hydrogen chloride during 6.5 hr. The solution was filtered and distilled. A fraction, bp 33–36°, was a mixture of pentane and dimethyldichlorosilane. No trimethylchlorosilane was detected by glc analyses. A fraction of pentyldimethylchlorosilane, 18.7 g (46%), bp 62–63° (20 mm), contained two peaks by glc analysis with similar retention times, one of them being *n*-pentyldimethylchlorosilane: ir (CCl_4) 1376 ($C-CH_3$) (CS_2), 1250 (SiMe), 510 cm^{-1} (SiCl); nmr τ 8.3–9.3 (11, alkyl CH) 9.63, 9.66 (6, $SiCH_3$). The $C-CH_3$ absorption in the infrared was greater than in the spectrum of *n*-pentyldimethylchlorosilane and two absorptions in the $SiCH_3$ region of the nmr spectrum indicate *sec*-pentyl derivatives.

sym-**Tetramethyldisilazane and Allylamine.**—A sealed tube containing 1.14 g (20 mmol) of allylamine, 1.33 g (10 mmol) of *sym*-tetramethyldisilazane, and 0.01 ml of 0.1 *M* chloroplatinic acid was heated at 100° for 20 hr. The tube at −80° exploded violently when it was opened.

sym-**Tetramethyldisilazane and Acrylonitrile.**—A sealed tube containing 1.06 g (20 mmol) of acrylonitrile, 1.33 g (10 mmol) of *sym*-tetramethyldisilazane, and 1 drop of 0.1 *M* chloroplatinic acid was heated at 100° for 20 hr. There was no evidence of addition by glc analysis. A similar experiment at 150° for 64 hr formed a large amount of solid polyacrylonitrile.

sym-**Tetramethyldisilazane with Other Compounds.**—*sym*-Tetramethyldisilazane was heated in sealed Pyrex tubes with H_2PtCl_6 and methyl methacrylate, methyl acrylate, allyl chloride, methallyl chloride, and allyl acetate. In each case the reagents were consumed to make a large number of products. These mixtures were not examined further.

Trisdimethylsilylamine with Hexene-1.—Five sealed tubes containing a total of 57.0 g (0.3 mol) of trisdimethylsilylamine

and 100.1 g (1.2 mol) of hexene-1 were heated at 115° for 72 hr. Each tube contained 0.03 ml of 0.1 *M* chloroplatinic acid. A glc analysis of the crude product revealed one major and four minor components. Distillation of 83 g of this material gave 23.3 g (41%) of bis(*n*-hexyldimethylsilyl)dimethylsilylamine: bp 110° (1 mm); $n^{25}D$ 1.4569; neut equiv 368, calcd 359; ir (CCl_4) 2130 (SiH) (CS_2), 900–920 cm^{-1} (SiN); nmr τ 9.87 (s, 12, $SiCH_3$), 9.74 (d, 6, $HSiCH_3$), 8.4–9.6 (26, alkyl-H) 5.44 (m, 0.8, SiH). One of the minor components was isolated from a separate experiment with trisdimethylsilylamine and hexene-1 and identified as bis(*n*-hexyldimethylsilyl)trimethylsilylamine: bp 115° (1 mm); $n^{25}D$ 1.4611; neut equiv 373, calcd 373; ir (CS_2) 1250–1260 (multiplet SiMe), 840 ($SiMe_3$), 910 cm^{-1} (SiN).

The residue from the distillation of the above 83 g of material was analyzed by a combination of glc and mass spectra. Three peaks in the glc had a *m/e* ratio of 429 for a molecular ion corresponding to $Si_3C_{23}H_{55}N$. This corresponds to $Hex_3Me_5HSi_3N$.

A solution of 17 g of this residue in 50 ml of ethanol with ≈100 mg of ammonium chloride was refluxed for 10 days. The volatiles were removed *in vacuo* and a glc of the resulting products had a large peak corresponding to hexyldimethylethoxysilane and smaller peaks for hexylmethylethoxysilane and dihexylmethylethoxysilane as indicated by coinjection with authentic samples.

Registry No.—Bis-[2-(dimethylaminodimethylsilyl)-ethyldimethylsilyl]amine, 25938-29-8; 2-(methyldimethoxysilyl)propylamine, 25938-30-1; *sym*-bis(3,3-dimethoxypropyl)tetramethyldisilazane, 26344-26-3; bis-(*n*-hexyldimethylsilyl)dimethylsilylamine, 25938-32-3; bis-(*n*-hexyldimethylsilyl)trimethylsilylamine, 25938-28-7.

A Novel Reaction of Saturated Aliphatic Acids with Aromatic Compounds in the Presence of Palladium(II) Chloride. The Formation of Cinnamic Acid Derivatives

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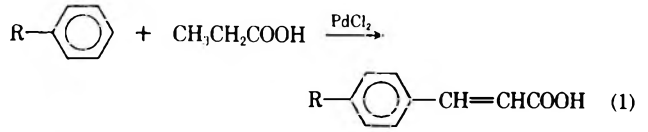
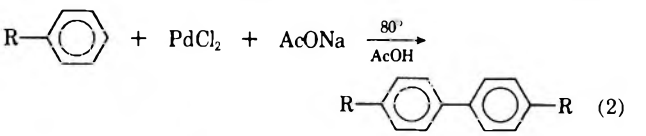
Saturated aliphatic acids with α and β hydrogens, such as propionic, *n*- and isobutyric acid, reacted with aromatic compounds and palladium(II) salts in the presence of alkali metal carboxylates to give cinnamic acid derivatives. The addition of some solvents, such as an acid anhydride, tetrachloroethylene, or acetonitrile, resulted in significant differences in products formed. A mechanism involving the formation of an intramolecular π complex of palladium acrylate (D) has been suggested for the dehydrogenation step.

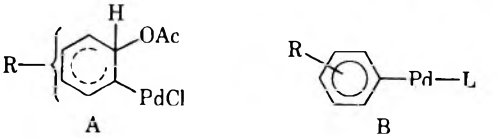
In a previous communication,[1] we reported on the novel carboxyvinylation of aromatic compounds by saturated aliphatic acids and palladium(II) chloride to give cinnamic acid derivatives.



As is well known, aromatic α,β-unsaturated acids can be synthesized by the reaction of aromatic aldehydes, ketones, or olefins with appropriate agents.[2] Also, with palladium(II) chloride, various cinnamates are successfully obtained from the reactions of unsaturated esters with benzenes.[3] However, our work is unique in that cinnamic acids are formed in one step from aromatic compounds and saturated aliphatic acids. This reaction is very interesting, since the formation of α,β-unsaturated aliphatic acids *via* dehydrogenation of saturated aliphatic acids by metal salts is unknown.

The reaction of aromatic compounds with palladium(II) chloride has been reported by van Helden and Verberg[4] to give biphenyl derivatives. They proposed that the reaction proceeds *via* dimerization of a π-cyclohexadienyl complex (A). Davidson and Triggs[5] suggested the presence of unstable phenylpalladium(II) complex (B) by analogy with the reaction of aromatic compounds with other metal acetates. Furthermore,





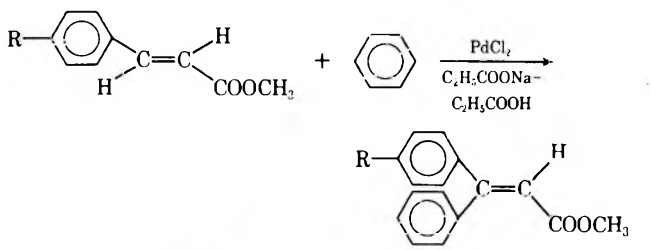
it was reported that some olefins reacted with aromatic compounds in the presence of palladium(II) acetate to give phenylated olefins.[6] That these reactions proceed *via* a similar phenylpalladium(II) complex (B) is supported by the reaction of *N*,*N*-dimethylbenzylamine–palladium complex with styrene to form a stilbene deriv-

* Author to whom correspondence should be addressed.

(1) S. Nishimura, T. Sakakibara, and Y. Odaira, *Chem. Commun.*, 313 (1969).

(2) (a) W. Perkin, *J. Chem. Soc.*, **21**, 53, 181 (1868); **31**, 388 (1877). (b) J. Johnson, *Org. React.*, **1**, 210 (1942). (c) E. Knoevenagel, *Chem. Ber.*, **31**, 2596 (1898); O. Doebner, *ibid.*, **33**, 2140 (1900). (d) S. Reformatsky, *ibid.*, **20**, 1210 (1887); R. Shriner, *Org. React.*, **1**, 1 (1942). (e) M. Kharasch, S. Kane, and H. Brown, *J. Amer. Chem. Soc.*, **64**, 333 (1942).

(3) Unpublished work. Various aromatic α,β-unsaturated esters were phenylated by palladium(II) chloride to give β-phenylcinnamates in 40–50% yields.



R = CH_3, OCH_3, H, Cl, NO_2

(4) R. van Helden and G. Verberg, *Recl. Trav. Chim. Pays-Bas*, **84**, 1263 (1965).

(5) J. Davidson and C. Triggs, *Chem. Ind. (London)*, 457 (1966).

(6) Y. Fujiwara, I. Moritani, M. Matsuda, and S. Teranishi, *Tetrahedron Lett.*, 633 (1968).

TABLE I

REACTION OF CARBOXYLATE IONS WITH AROMATIC COMPOUNDS IN THE PRESENCE OF Pd^{II} SALTS

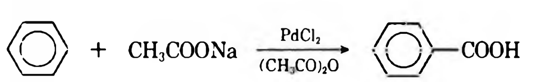
Pd^{II} salt	Reagents: Sodium carboxylate	Reagents: Aromatic compound	Reagents: Aliphatic acid	Solvent	Products, %[a]
$PdCl_2$	C_2H_5COONa	PhH	C_2H_5COOH	None	PhPh (11), $Ph_2C{=}CHCOOH$ (9.2), $Ph_2C{=}CH_2$ (2.5), $PhHC{=}CHCOOH$ (0.7), PhCOOH (0.2)
$PdCl_2$	C_2H_5COONa	PhH	C_2H_5COOH	$(C_2H_5CO)_2O$	$PhHC{=}CHCOOH$ (28), $PhHC{=}CHPh$ (3.2)
$Pd(OOCC_2H_5)_2$	None	PhH	C_2H_5COOH	None	PhPh (16), PhCOOH (2.1), $Ph_2C{=}CHCOOH$ (1.4)
$PdCl_2$	n-C_3H_7COONa	PhH	n-C_3H_7COOH	None	$CH_3(Ph)C{=}CHCOOH$ (12), PhCOOH (<1), $PhCH_2(Ph)C{=}C(Ph)COOH$ (2.5)
$PdCl_2$	n-C_3H_7COONa	PhH	n-C_3H_7COOH	$(n$-$C_3H_7CO)_2O$	PhCOOH (21), $CH_3(Ph)C{=}CHCOOH$ (<0.5)
$PdCl_2$	n-C_3H_7COONa	PhH	n-C_3H_7COOH	$Cl_2C{=}CCl_2$	PhCOOH (28), $CH_3(Ph)C{=}CHCOOH$ (9.2), PhPh (trace)
$Pd(n$-$OOCC_3H_7)_2$	n-C_3H_7COONa	PhH	n-C_3H_7COOH	None	PhPh (39), PhCOOH (7.9), $CH_3(Ph)C{=}CHCOOH$ (5.4)
$PdCl_2$	i-C_3H_7COONa	PhH	i-C_3H_7COOH	None	$PhHC{=}C(CH_2Ph)COOH$ (8.0), PhCOOH (0.8), $PhHC{=}C(CH_3)COOH$ (6.2)
$PdCl_2$	i-C_3H_7COONa	$PhCH_3$	i-C_3H_7COOH	None	$CH_3C_6H_4(H)C{=}C(CH_3)COOH$ (4.4), $CH_3C_6H_4(H)C{=}C(CH_2C_6H_4CH_3)COOH$ (0.8)
$PdCl_2$	i-C_3H_7COONa	PhH	i-C_3H_7COOH	$(i$-$C_3H_7CO)_2O$	PhCOOH (19), $PhHC{=}C(CH_3)COOH$ (<0.5), PhPh (trace)
$PdCl_2$	i-C_3H_7COONa	PhH	CH_3COOH	None	PhPh (75), $PhHC{=}C(CH_3)COOH$ (2.1), PhCOOH (1.4), $PhHC{=}C(CH_2Ph)COOH$ (0.9)
$PdCl_2$	i-C_3H_7COONa	PhH	CH_3COOH	CH_3CN	PhPh (55), PhCOOH (8.6), $PhHC{=}C(CH_3)COOH$ (0.7)
$Pd(i$-$OOCC_3H_7)_2$	i-C_3H_7COONa	PhH	i-C_3H_7COOH	None	$PhHC{=}C(CH_3)COOH$ (13), $PhHC{=}C(CH_2Ph)COOH$ (8.8)
$Pd(i$-$OOCC_3H_7)_2$	None	PhH	None	None	PhPh (98)

[a] Yield based on Pd^{II} salt charged (mol/mol).

ative.[7] Recently, it has been shown by Heck[8] that the complex (B) is an effective arylating agent of olefins. The reaction of palladium(II) chloride with aromatic compounds, therefore, has been generally considered to contain a complex (B) as a reactive intermediate.

$$PdCl_2 \xrightarrow{ArHgCl} B \xrightarrow{R{-}CH{=}CH_2} R{-}CH{=}CH{-}Ar \qquad (3)$$

As already reported by us,[9] some coordinative solvents had a significant influence on the reaction of aromatic compounds with palladium(II) chloride. For example, in the presence of acetic anhydride, benzene reacted with sodium acetate and palladium(II) chloride to yield benzoic acid.


(4)

In the present carboxyvinylation of aromatic compounds, an analogous solvent effect should be also expected. Accordingly, further investigation has been made of the solvent effect to establish the limitation and scope of this reaction.

Results and Discussion

In a typical carboxyvinylation experiment, the aromatic compound and sodium carboxylate were reacted in the presence of palladium(II) chloride and the corresponding carboxylic acid for several hours. During the reaction, palladium black precipitated, showing that Pd^{II} was reduced to Pd^0. The reaction was terminated when the precipitation of metallic palladium and gas evolution ceased. The results of product analyses in various systems are shown in Table I.

In the absence of aromatic compounds, the reaction of palladium(II) chloride with sodium propionate or butyrate in propionic acid or butyric acid and the corresponding acid anhydride, gave ethylene and propylene, respectively, in addition to carbon dioxide. The absence of ethane and propane suggests that the reaction does not proceed *via* the formation of alkyl radical as has been observed for other metal carboxylates.[10] It is well known that palladium has a strong affinity for hydrogen and that alkylpalladium–phosphine complexes with a β hydrogen in the alkyl group are easily decomposed *via* β-hydride abstraction by palladium to give olefin and Pd–H.[11] An analogous β-hydride abstraction by palladium may be involved in the above olefin-forming reaction *via* decarboxylation of carboxylate ion.

$$PdCl_2 + \underset{R_1}{CH_2}\underset{R_2}{CH}COONa \longrightarrow R_1CH{=}CHR_2 + CO_2 + Pd^0 + NaCl + HCl \qquad (5)$$

As shown in the carboxyvinylation in isobutyric acid, both palladium(II) chloride and palladium(II) isobutyrate gave cinnamic acid derivatives, in the presence of sodium isobutyrate. On the other hand, the reaction of palladium(II) isobutyrate with benzene, without isobutyrate ion, gave biphenyl almost quantitatively as the sole product (Table I). Similarly, the use of palladium(II) propionate without sodium propionate

(7) J. Tsuji, *Accounts Chem. Res.*, **2**, 144 (1969).

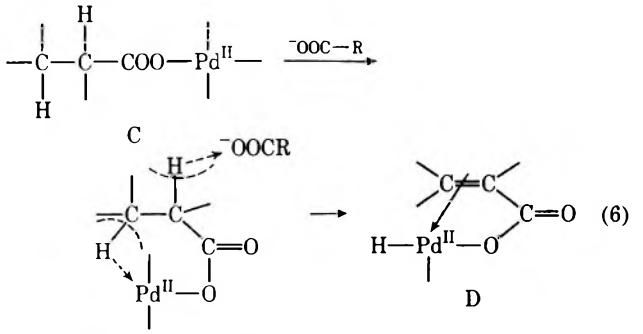
(8) R. Heck, *J. Amer. Chem. Soc.*, **90**, 5518 (1968).

(9) T. Sakakibara, S. Nishimura, and Y. Odaira, *Tetrahedron Lett.*, 1019 (1969).

(10) (a) J. Kochi, *J. Amer. Chem. Soc.*, **87**, 3609 (1965). (b) R. Sheldon and J. Kochi, *ibid.*, **90**, 6688 (1968). (c) J. Kochi and T. Betha, *J. Org. Chem.*, **33**, 75 (1968).

(11) G. Calvin and G. Coates, *J. Chem. Soc.*, 2008 (1960).

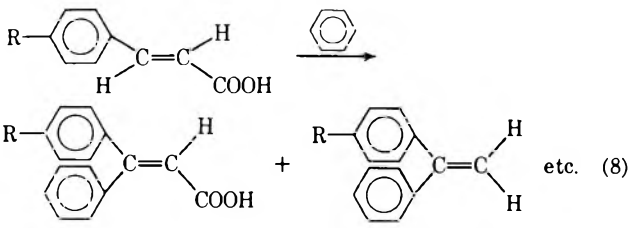
gave biphenyl rather than the olefinic acids. The presence of sodium carboxylate, therefore, is considered to be essential for carboxyvinylation. If hydride abstraction by palladium is involved in the formation of olefinic acids from saturated aliphatic acids, then an α hydrogen, activated by an adjacent carboxyl group, might be abstracted as proton by a nucleophile, such as carboxylate ion. Thus, a suggested mechanism for dehydrogenation is as follows.



(6)

The complex (D), possessing an unstable Pd–H bond, might rapidly decompose to unsaturated acid and Pd^0.

The reaction of acrylic acid with benzene gave cinnamic acid in the presence of palladium(II) chloride and sodium acetate in acetic acid solvent. The formation of di- or triphenylated acrylic acids may be explained as further arylation of cinnamic acids. As supporting evidence, cinnamic acid derivatives reacted with benzene in the presence of palladium(II) chloride and sodium propionate in propionic acid to give β-phenylcinnamic acids, along with decarboxylated products (Table II).



(8)

TABLE II

PHENYLATION OF CINNAMIC ACID DERIVATIVES[a]

R	Products, %[b]		
H	9.5	17.4	None
CH_3	11.6	5.8	6.8
CH_3O	12.8	7.2	7.7
Cl	23.9	6.9	9.2

[a] Cinnamic acid derivative (0.02 mol), benzene (0.5 mol), palladium(II) chloride (0.02 mol), and sodium propionate (0.1 mol) were reacted at 100° for 6 hr in propionic acid (110 ml). [b] Yield based on Pd^{II} chloride charged (mol/mol).

As shown in Table I, the addition of some solvents, such as acid anhydrides, tetrachloroethylene, or acetonitrile, remarkably influenced the distribution of products formed. For example, addition of butyric anhydride to the reaction of sodium butyrate and benzene with palladium(II) chloride accelerated carboxylation to give benzoic acid and propylene, while suppressing carboxyvinylation of aromatic compounds. Similarly, addition of propionic anhydride completely suppressed further arylation of cinnamic acids formed. Since tetrachloroethylene and acetonitrile had a similar effect, these solvents may coordinate strongly to palladium and thus promote elimination of olefin from the aliphatic acid–palladium complex (C) or suppress further arylation of cinnamic acids. Further study of the formation of unsaturated acids from saturated aliphatic acids is in progress.

Experimental Section

Materials.—Commercially available palladium(II) chloride (a guaranteed reagent by Tokyo Kasei Kogyo Co. Ltd.) was powdered and used without further purification. Carboxylic acids and anhydrides were distilled and dried by sodium sulfate before use. Thiophene-free aromatic compounds were used after drying by Na wire. Sodium and potassium propionate were dried under reduced pressure at 130°, and sodium butyrate at 50°, over phosphorus pentoxide overnight. Palladium(II) carboxylates were prepared according to the method of Stephenson, *et al.*[12]

All melting points are uncorrected. The ir spectra were recorded with a Japan Spectroscopic Model IR-G spectrophotometer; the nmr spectra with a Nippon Denshi Model JNM-3H60 spectrometer; the mass spectra with a Hitachi Model RMU-6E mass spectrometer.

Nmr spectral data for the various cinnamic acid derivatives isolated are given in Table III.

Reaction of Benzene with Sodium Propionate and Propionic Acid.—In a 200-ml four-necked flask, a stirred mixture of benzene (39.0 g, 0.5 mol), sodium propionate (9.6 g, 0.1 mol), palladium(II) chloride (3.5 g, 0.02 mol), and propionic acid (98.4 g, 1.33 mol) was heated at 100° for 6 hr under an atmosphere of dried nitrogen. The evolved gas was introduced to a manometric gas trap. The initial brown mixture gradually turned black as metallic palladium formed. After 4 hr, gas evolution almost stopped; 49 ml of gas was collected at the end of reaction. Metallic palladium was removed by filtration, and the solvent was removed under reduced pressure; 150 ml of 15% aqueous sodium carbonate was added to the residue and the mixture was extracted with five portions of diethyl ether (100 ml). The organic layer (K) was washed with water and dried by sodium sulfate overnight. The combined aqueous layer was acidified with concentrated hydrochloric acid and extracted again with diethyl ether, and the organic layer (L) was dried over sodium sulfate. The gaseous product was analyzed by gas chromatography, using a 3-m, 20% acetonylacetone on Neopac 1A column (0°, He carrier). Carbon dioxide was detected, but neither ethane nor ethylene. The ether layer (K): after a removal of ether, neutral products were isolated as solids (588 mg), which consisted of biphenyl (58%), 1,1-diphenylethylene (27%), and unidentified products (15%), by glc analysis using a 1.5-m, polyethylene glycohol 20M on Celite 545 column (250°) and a 1.5-m silicone DC550 on Celite 545 column (200°, H_2 carrier). The ether layer (L): after a removal of ether and propionic acid by distillation, acidic products were obtained as solids (439 mg). A portion was esterified by diazomethane and the products were identified as a mixture of methyl β-phenylcinnamate (94.3%), methyl cinnamate (4.5%), and methyl benzoate (1.2%) by glc analysis. Another part of the solid products was recrystallized twice from aqueous ethanol to yield β-phenylcinnamic acid, mp 156–157.5° (lit.[13] mp 162°); the amide gave mp 145–147° (lit.[14] mp 154°).

In the Presence of Propionic Anhydride.—Benzene (39 g, 0.5 mol), sodium propionate (9.6 g, 0.1 mol), palladium(II) chloride (3.5 g, 0.02 mol), and propionic acid (98.4 g, 1.3 mol) were re-

(12) T. Stephenson, S. Morehouse, A. Powell, J. Heffer, and G. Wilkinson, *J. Chem Soc.*, 3632 (1965).

(13) H. Rupe and E. Busolt, *Chem. Ber.*, **40**, 4539 (1907).

(14) S. Work, D. Bryant, and C. Hauser, *J. Amer. Chem. Soc.*, **86**, 872 (1964).

TABLE III
NMR SPECTRAL DATA FOR CINNAMIC ACID DERIVATIVES ISOLATED

Product	Registry no.	Solvent, %	Phenyl H	Vinyl H	Others H (-CH_3, -CH_2-, >CH-)
PhHC=CHCOOH	621-82-9	$CDCl_3$ (2.0)	2.55 (s, 5)	2.20 (d, 1) 3.55 (d, 1)	
Ph_2C=CHCOOH	606-84-8	$CDCl_3$ (4.5)	2.74 (s, 10)	3.71 (s, 1)	
CH_3(Ph)C=CHCOOH	1199-20-8	$CDCl_3$ (3.3)	2.66 (s, 5)	3.89 (s, 1)	7.42 (s, 3)
$PhCH_2$(Ph)C=C(Ph)COOH	25908-00-3 25860-60-6 (amide)	$CDCl_3$ (2.7)	2.71 (s, 5) 2.88 (s, 5) 3.20 (s, 5)		6.42 (s, 2)
PhHC=C(CH_3)COOH	1199-77-5	$CDCl_3$ (3.3)	2.57 (s, 5)	2.16 (s, 1)	7.81 (s, 3)
PhHC=C(CH_2Ph)COOH	4361-83-5	CCl_4	2.72 (s, 5) 2.85 (s, 5)	2.03 (s, 1)	6.10 (s, 2)
p-$CH_3C_6H_4$(H)C=C(CH_3)COOH	25860-59-7	$CDCl_3$ (3.0)	2.57-2.89 (q, 4)	2.22 (s, 1)	7.63 (s, 3) 7.83 (s, 3)

acted in propionic anhydride (90 ml) at 97° for 7.5 hr. Gaseous products (28 ml) were carbon dioxide and ethylene. After work-up as described above, a neutral ether solution (K) and an acidic ether solution (L) were obtained. Distillation of K under the reduced pressure (9 mm) gave white crystals (80 mg) as a sublimate on the neck of the Claisen flask, mp 121–122.5° (lit.[15] mp 124°), recrystallized from ethanol. A mixture melting point with a specimen of *trans*-stilbene was undepressed. The ir of the distillation residue showed characteristics of acid anhydride. The residue was hydrolyzed by potassium hydroxide in ethanol under reflux for 2 hr and, after usual treatment, white crystals (143 mg) were isolated; the melting point and ir and nmr spectra were identical with those of cinnamic acid. The acidic residue (480 mg) from L was recrystallized from water, after treatment with activated carbon to give white crystals, mp 130–131°; a mixture melting point with a specimen of cinnamic acid was undepressed. The amide gave mp 140–141° (lit.[16] mp 142°).

Reaction of Benzene with Sodium *n*-Butyrate and *n*-Butyric Acid.—A stirred mixture of benzene (117 g, 1.5 mol), sodium *n*-butyrate (33.2 g, 0.3 mol), palladium(II) chloride (3.5 g, 0.02 mol), and *n*-butyric acid (132 g, 1.5 mol) was heated under reflux (87.5°) for 8 hr. Evolved gas (22.5 ml) was carbon dioxide. The neutral residue (K) and the acidic residue (L) were isolated in yields of 446 mg and 362 mg, respectively. β-Methylcinnamic acid was isolated by recrystallization of L: leaflets from ligroin; mp 96–97° (lit.[17] mp 98°); ir 2500–2800, 1750, and 1225 (COOH), 1618 (C=C), 1575, 690–710, and 770 cm^{-1} (-Ph). After esterification of L with diazomethane, glc analysis showed the presence of methyl *n*-butyrate (1.5%), methyl benzoate (1.8%), methyl β-methylcinnamate (91%), and unidentified products (5.7%), which probably consisted of diphenylated olefinic acid methyl esters. α-Phenyl-β-benzylcinnamic acid was isolated from K, probably due to slow neutralization of the acid. The acid (151 mg) was separated as an insoluble substance with petroleum ether (bp 40–55°) from aromatic olefins, which mainly contained triphenylated propylene (by ir and mass analysis), and crystallized from acetonitrile as colorless crystals, whose further purification was made by sublimation: mp 196–197°; ir 2500–2800, 1670, and 1225 (COOH), 1580, 1560, 780, 760, 720, and 693 cm^{-1} (-Ph's); *m/e* 314 (M^+), 269 (M − 45); potassium permanganate solution was discolored under heating; the nmr data are shown in Table III.

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.86; H, 5.60.

Reaction of Benzene with Sodium Isobutyrate and Isobutyric Acid.—A mixture of benzene (117 g, 1.5 mol), sodium isobutyrate (33.2 g, 0.3 mol), palladium(II) chloride (3.6 g, 0.02 mol), and isobutyric acid (132 g, 1.5 mol) was heated under reflux for 7 hr. The evolved gas (53 ml) was carbon dioxide. An acidic residue (L) (675 mg) and a neutral residue (K) (233 mg) were obtained. Fractional crystallization of L gave α-benzylcinnamic acid: needles from ethanol, mp 155–156° (lit.[18] mp 158°); the amide gave mp 148–150°.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.38; H, 5.87.

Glc analysis of esterified L showed the presence of methyl α-benzylcinnamate (65%), methyl α-methylcinnamate (32%), and methyl benzoate (3%). Neutral products were mainly mono-, di-, or triphenylated propylene isomers, judging from the results of ir, glc, and mass analyses.

Phenylation of Cinnamic Acid Derivatives in Propionic Acid.—All products were identified by melting point and ir, nmr, and mass spectra. All new compounds were characterized by elementary analyses.

Registry No.—Palladium(II) chloride, 7647-10-1.

Acknowledgment.—The authors are indebted to Dr. E. Fujita and Mrs. M. Sakurai for the nmr measurements, to Miss J. Maenaka and Mrs. N. Ishii for the elemental analyses, and also to Mr. H. Moriguchi for the mass analyses.

(15) A. Michaelis and H. Lauge, *Chem. Ber.*, **8**, 1313 (1875).
(16) T. Poster, *ibid.*, **38**, 2320 (1905).
(17) R. Stoermer, F. Grimm, and E. Laage, *ibid.*, **50**, 968 (1917).
(18) A. Michael and E. Palmer, *J. Amer. Chem. Soc.*, **7**, 69 (1885).

Organometallic π Complexes. XXII. The Chemistry of π-Cyclopentadienyltetraphenylcyclobutadienecobalt and Related Compounds

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The reaction of π-cyclopentadienyldicarbonylcobalt and diphenylacetylene in refluxing xylene products π-cyclopentadienyltetraphenylcyclobutadienecobalt (**1**) and π-cyclopentadienyltetraphenylcyclopentadienonecobalt (**2**) in yields of 50 and 10%, respectively. This method has also been extended to the direct synthesis of the corresponding trimethylsilyl (**3**, **5**) and phenyl (**4**, **6**) derivatives, starting with trimethylsilyl- or phenylcyclopentadiene. The π-cyclopentadienyl ring in **1**, as in ferrocene, undergoes a number of electrophilic ring substitution reactions. Acetoxymercuration with a perchloric acid catalyst, followed by treatment with lithium chloride, produces a chloromercuri derivative **7** in 65% yield, together with a 1,2-bis(chloromercuri) derivative **8**. Complex **7** is readily converted into its iodo analog **9**. The transmetalation of **7** with *n*-butyllithium gives a lithium intermediate **10** which on treatment with acetyl chloride affords the acetyl derivative **11**. When **9** is heated with copper–bronze or with cuprous cyanide in *N*-methyl-2-pyrrolidone, the Ullmann product **12** and the cyano derivative **13** are obtained. Similar reactions with cupric acetate and cupric phthalimide produce acetate **14** and phthalimido **15** derivatives, respectively, which on hydrolysis give phenol **16** and amine **17**. The relative acidity and basicity of these products have been determined. Aminomethylation and Vilsmeier formylation give dimethylaminomethyl (**18**) and formyl (**20**) derivatives in yields of 74 and 8%, respectively. The conclusion is drawn that, while **1** participates in a variety of electrophilic substitution reactions, it is in general less reactive than is ferrocene.

Although the concept of aromaticity is still not well defined, ferrocene and related organometallic compounds are generally considered "aromatic" in that they resist ring-addition reactions and undergo ring-substitution reactions. Thus, ferrocene is known to undergo various electrophilic substitution reactions such as Friedel–Crafts acylation,[2] alkylation,[3,4] formylation,[5–7] sulfonation,[8–10] acetoxymercuration,[11,12] and aminomethylation.[13] Following these initial studies on ferrocene, various other organotransition metal compounds containing a π-cyclopentadienyl ring were found to exhibit similar chemical reactivities. Thus, ruthenocene,[14] osmocene,[14] cymantrene,[15–18] and its technitium[19] and rhenium[19,20] analogs, π-cyclopentadienyltetracarbonylvanadium,[21,22] and π-cyclopentadienyldicarbonylnitrosylchromium[23] all form acyl derivatives under Friedel–Crafts conditions. In addition, cymantrene has been shown to undergo many of the other ring-substitution reactions that are characteristic of ferrocene,[17] while π-cyclopentadienyltricarbonylrhenium can be mercurated and sulfonated,[24] and zirconocene dichloride has been reported to undergo sulfonation.[25] The aromatic-type reactivity of metallocenes has been the subject of several reviews.[26–29]

When our present program of research was undertaken, no examples of aromatic-type substitution reactions of cobalt-containing metallocenes had been described in the literature.[30,31] It appeared to us, however, that the organocobalt compound π-cyclopentadienyltetraphenylcyclobutadienecobalt (**1**), first prepared in 1961 by Nakamura and Hagihara,[32] and later by Wilkinson, *et al.*,[33] and by Maitlis, *et al.*,[34] possessed he necessary chemical stability and electronic configuration to undergo such substitution reactions without appreciable concurrent decomposition under the reaction conditions involved. Complex **1** is reported to be thermally stable to 360° under nitrogen and withstands external reagents such as hydrochloric acid, alcoholic potassium hydroxide, lithium aluminum hy-

(1) Alexander von Humboldt Research Fellow, 1969–1970. Author to whom correspondence should be addressed.

(2) R. B. Woodward, M. Rosenblum, and M. C. Whiting, *J. Amer. Chem. Soc.*, **74**, 3458 (1952); M. Rosenblum and R. B. Woodward, *ibid.*, **80**, 5443 (1958).

(3) A. N. Nesmeyanov and N. S. Kochetkova, *Dokl. Akad. Nauk SSSR*, **109**, 543 (1956).

(4) M. Vogel, M. D. Rausch, and H. Rosenberg, *J. Org. Chem.*, **22**, 1016 (1957).

(5) M. Rosenblum, *Chem. Ind. (London)*, 72 (1957).

(6) G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *ibid.*, 209 (1957); *J. Chem. Soc.*, 650 (1958).

(7) K. Schlögl, *Monatsh. Chem.*, **88**, 601 (1957).

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(10) G. R. Knox and P. L. Pauson, *J. Chem. Soc.*, 692 (1958).

(11) A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **97**, 459 (1954).

(12) M. D. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 900 (1957).

(13) C. R. Hauser and J. K. Lindsey, *ibid.*, **21**, 382 (1956).

(14) M. D. Rausch, E. D. Fischer, and H. Grubert, *Chem. Ind. (London)*, 756 (1958); *J. Amer. Chem. Soc.*, **82**, 76 (1960).

(15) E. O. Fischer and K. Plesske, *Chem. Ber.*, **91**, 1719 (1958).

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(17) J. Kozikowski, R. F. Maginn, and M. S. Klove, *J. Amer. Chem. Soc.*, **81**, 2995 (1959).

(18) R. Riemschneider and H. G. Kassahn, *Z. Naturforsch.*, **14b**, 348 (1959); *Chem. Ber.*, **92**, 3208 (1959).

(19) E. O. Fischer and W. Fellmann, *J. Organomental. Chem.*, **1**, 191 (1963).

(20) A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova, and L. I. Baryshnikov, *Dokl. Akad. Nauk SSSR*, **154**, 646 (1964).

(21) E. O. Fischer and K. Plesske, *Chem. Ber.*, **93**, 1006 (1960).

(22) R. Riemschneider, O. Goehring, and M. Kruger, *Monatsh. Chem.*, **91**, 305 (1960).

(23) E. O. Fischer and K. Plesske, *Chem. Ber.*, **94**, 93 (1961).

(24) A. N. Nesmeyanov, N. E. Kolobova, K. N. Anisimov, and L. T. Baryshnikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1135 (1964).

(25) R. Kh. Friedlina, E. M. Brainina, M. Kh. Minacheva, and A. N. Nesmeyanov, *ibid.*, 1417 (1964).

(26) K. Plesske, *Angew. Chem., Int. Ed. Engl.*, **1**, 312, 394 (1962).

(27) M. D. Rausch, *Can. J. Chem.*, **41**, 1289 (1963).

(28) W. F. Little, *Surv. Progr. Chem.*, **1**, 133 (1963).

(29) M. Rosenblum, "Chemistry of Iron-Group Metallocenes," Part 1, Wiley, New York, N. Y., 1965.

(30) Although it is claimed [J. Kozikowski, U. S. Patent 2,916,503 (Dec 8, 1959)], that the reaction of π-cyclopentadienyldicarbonylcobalt, benzoyl chloride, and aluminum chloride produced a corresponding benzoyl derivative, no experimental details were given.

(31) It has recently been reported [J. Lewis and A. W. Parkins, *J. Chem. Soc. A*, 1150 (1967)], that π-cyclopentadienylcycloocta-1,5-dienecobalt reacts with trityl fluorborate to give a product containing the trityl group on the π-cyclopentadienyl ring in 0.3% yield.

(32) A. Nakamura and N. Hagihara, *Bull. Chem. Soc. Jap.*, **34**, 452 (1961); *Nippon Kagaku Zasshi*, **84**, 339 (1963).

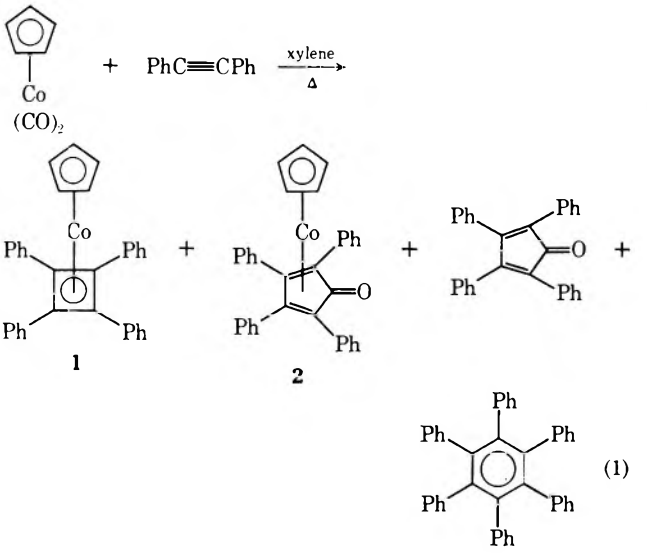
(33) J. L. Boston, D. W. Sharpe, and G. Wilkinson, *J. Chem. Soc.*, 3488 (1962).

(34) P. M. Maitlis and M. L. Games, *J. Amer. Chem. Soc.*, **85**, 1887 (1963); P. M. Maitlis, A. Efraty, and M. L. Games, *J. Organometal. Chem.*, **2**, 284 (1964); *J. Amer. Chem. Soc.*, **87**, 719 (1965).

dride, carbon monoxide under pressure, triphenylphosphine, dimethyl acetylenedicarboxylate, iodine, etc.[32] Further, **1** is isoelectronic with ferrocene and might be expected to have somewhat similar reactivity properties.

Our present article describes the reactions of **1** with various electrophilic reagents, and some chemistry of the resulting ring-substitution products.[35] It should be mentioned also that **1**,[35] like ferrocene,[36] is readily metalated by *n*-butyllithium–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine, and this nucleophilic-type substitution of **1** will be more fully described in a subsequent paper. When our reactivity studies on **1** were essentially completed, two other research groups reported the formation and properties of the parent complex of **1**, *viz.*, π-cyclopentadienylcyclobutadienecobalt.[37,38]

Direct Synthesis of π-Cyclopentadienyltetraphenylcyclobutadienecobalt Complexes.—Our studies concerning the aromatic-type reactivity of **1** have been greatly facilitated by the discovery of a new and convenient method for the synthesis of this compound. The method utilizes a reaction between diphenylacetylene and π-cyclopentadienyldicarbonylcobalt (eq 1).

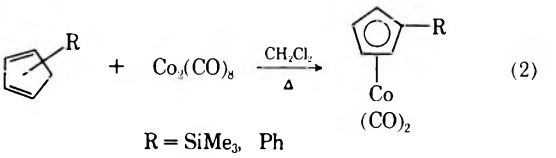


(1)

The latter has also been prepared by a new and improved method (90–95% yield) from a reaction between octacarbonyldicobalt and cyclopentadiene in methylene chloride solution at reflux. Complex **1** was thus obtained in ~50% yield compared to 15% overall yield from Nakamura's and Hagihara's method,[32] which first involved the reaction of π-cyclopentadienyldicarbonylcobalt with 1,5-cyclooctadiene and then treatment of the resulting diene complex with diphenylacetylene.

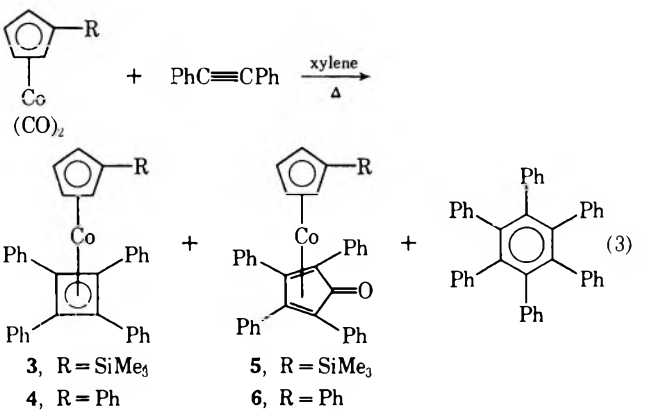
In addition to the major product **1**, a 10% yield of π-cyclopentadienyltetraphenylcyclopentadienonecobalt (**2**), a 15% yield of the cyclic trimerization product, hexaphenylbenzene, and a small amount of tetraphenylcyclopentadienone were obtained. Complex **2** could also be prepared directly from π-cyclopentadienyldicarbonylcobalt and tetraphenylcyclopentadienone. In contrast to our heat-promoted reaction between π-cyclopentadienyldicarbonylcobalt and diphenylacetylene (eq 1), it has previously been reported that these reactants gave an 80% yield of **2** when irradiated with sunlight for 2 weeks in benzene solution.[39]

In view of the successful synthesis of **1** as outlined in eq 1, it was of considerable interest to investigate the generality of the reaction. This has been done in two ways: (1) by utilizing substituted cyclopentadienes; (2) by utilizing acetylenes other than diphenylacetylene. The reactions of both phenyl- and trimethylsilylcyclopentadiene with octacarbonyldicobalt were successful and led to the corresponding substituted derivatives of π-cyclopentadienyldicarbonylcobalt (eq 2). Furthermore, both of the resulting carbonyls



(2)

reacted with diphenylacetylene to give trimethylsilyl and phenyl derivatives of **1** (**3** and **4**), as well as lesser amounts of the corresponding derivatives of **2** (**5** and **6**) (eq 3).



(3)

Thus, a useful and unequivocal route to π-cyclopentadienyl-substituted derivatives of **1** has been developed, and it seems probable that many other such derivatives could be prepared in an analogous manner. This route seems even more useful in view of a recent report by Altman and Wilkinson[40] that substituted π-cyclopentadienyldicarbonylcobalt complexes can be prepared from 6,6-dialkylfulvenes and octacarbonyldicobalt. The insertion of carbon monoxide to give tetraphenylcyclopentadienone complexes and the formation of hexaphenylbenzene also appear to be general reactions.

Two reactions of π-cyclopentadienyldicarbonylcobalt with acetylenes other than diphenylacetylene have been described in the literature. A reaction with 2-butyne in sunlight has been reported to give a tetramethylcyclopentadienone complex in 80% yield,[39]

(35) A preliminary account of this work has been published: M. D. Rausch and R. A. Genetti, *J. Amer. Chem. Soc.*, **89**, 5502 (1967).

(36) M. D. Rausch and D. J. Ciappenelli, *J. Organometal. Chem.*, **10**, 127 (1967).

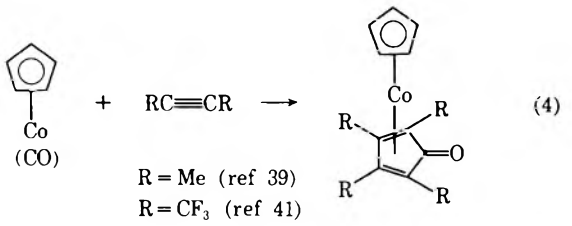
(37) R. G. Amiet and R. Pettit, *J. Amer. Chem. Soc.*, **90**, 1059 (1968).

(38) M. Rosenblum and B. North, *ibid.*, **90**, 1060 (1968).

(39) R. Markby, H. W. Sternberg, and I. Wender, *Chem. Ind.* (*London*), 1381 (1959).

(40) J. Altman and G. Wilkinson, *J. Chem. Soc.*, 5654 (1964).

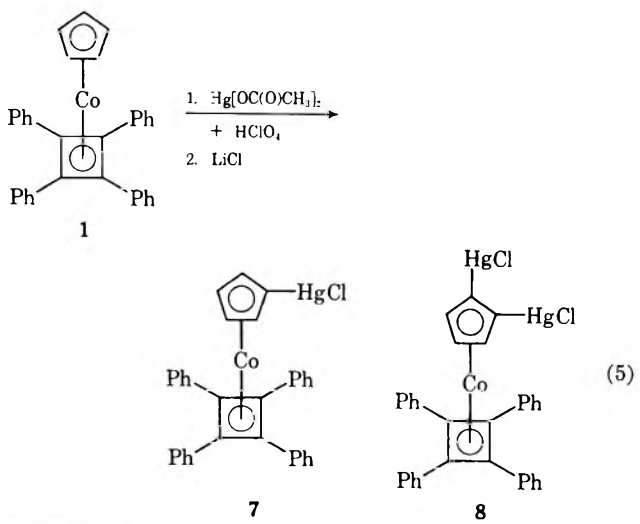
whereas a sealed tube reaction with hexafluoro-2-butyne at 110° resulted in the formation of a tetrakis(trifluoromethyl)cyclopentadienone analog[41] (eq 4).



(4)

The latter complex was originally formulated incorrectly as a cyclobutadiene complex.[42] Neither 2-butyne nor hexafluoro-2-butyne therefore gave a cyclobutadiene complex on reaction with π-cyclopentadienyldicarbonylcobalt, and attempts in our laboratory to prepare π-cyclopentadienyltetramethylcyclobutadienecobalt from 2-butyne have also been unsuccessful. However, the tetramethylcyclobutadiene complex has recently been prepared by Bruce and Maitlis[43] using an alternate procedure. Reactions of π-cyclopentadienyldicarbonylcobalt with a variety of other mono- and diarylacetylenes have been studied in detail[44] and will be described separately in a forthcoming paper.

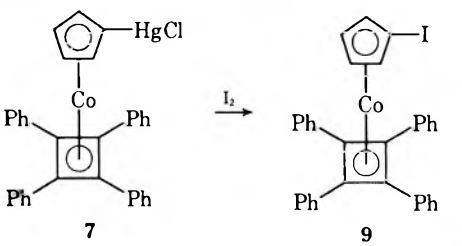
Ring-Substitution Reactions of π-Cyclopentadienyltetraphenylcyclobutadienecobalt (1).—Complex **1**, like ferrocene, has been found to undergo a variety of electrophilic substitution reactions on the π-cyclopentadienyl ring, and may thus be classified as a new aromatic organometallic system. The most important ring-substitution reaction of **1** in terms of developing the chemistry of this system has been acetoxymercuration. Treatment of **1** with mercuric acetate in methylene chloride solution containing perchloric acid, followed by the addition of lithium chloride, resulted in the formation of mono- and bis(chloromercuri) complexes **7** and **8** (eq 5). This mercuration reaction is a modification of a procedure described by Brown and coworkers.[45]



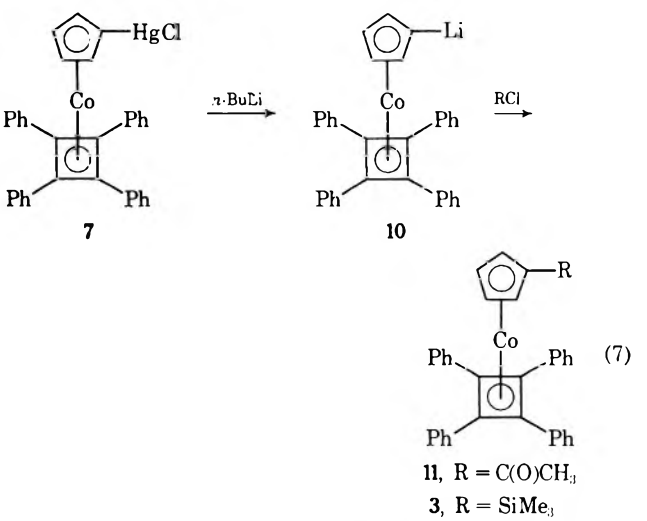
(5)

The isolation of **8** indicates that mercuration of **1** occurs very readily under these conditions. It was found advantageous to employ 3 equiv of **1** per equiv of mercuric acetate, in order to obtain **7** as the major product (65% yield). Even under these conditions small amounts of polymercurated products were occasionally observed; however, these were not investigated further. The assignment of **8** as the 1,2 isomer is based on nmr studies (*vide infra*). Mercuration could also be accomplished by treatment of **1** with mercuric acetate in methylene chloride–methanol in the absence of perchloric acid, as has been successfully demonstrated for the mercuration of ferrocene.[11,12] However, the perchloric acid modification provided generally higher yields of products, and product separation was considerably easier.

Chloromercuri complex **7** has proved to be a valuable derivative of **1**, since a large number of new organocobalt compounds have been derived from it. For example, iodo complex **9** is readily obtained in 83% yield from a reaction between **7** and iodine in chloroform solution (eq 6). Transmetalation of **7** with *n*-butyllithium resulted in rapid formation of the lithium intermediate **10**. This organolithium intermediate could be characterized by treatment with either acetyl chloride or trimethylchlorosilane to give acetyl derivative **11** or trimethylsilyl derivative **3**, respectively (eq 7). The latter was shown to be identical to **3** prepared directly.



(6)



(7)

Iodo complex **9**, like iodoferrocene, has led to a variety of interesting derivatives when treated with activated copper or copper salts. For example, **9** when heated with copper–bronze affords the Ullmann coupling product **12**, a novel organometallic system containing both fulvalene and tetraphenylcyclobutadiene ligands coordinated to cobalt.[46] Complex **9** undergoes

(41) R. S. Dickson and G. Wilkinson, *J. Chem. Soc.*, 2699 (1964); M. Gerlock and R. Mason, *Proc. Chem. Soc.*, 107 (1963); *Proc. Royal Soc. A*, **279**, 170 (1964).

(42) J. L. Boston, D. W. Sharpe, and G. Wilkinson, *J. Chem. Soc.*, 3488 (1962).

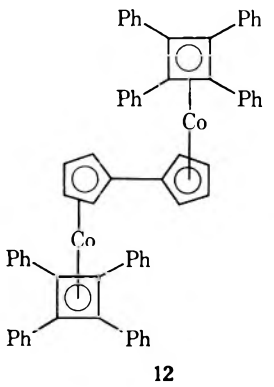
(43) R. Bruce and P. M. Maitlis, *Can. J. Chem.*, **45**, 2017 (1967).

(44) M. D. Rausch, R. A. Genetti, and F. Higbie, 157th National Meeting of the American Chemical Society, Division of Inorganic Chemistry, Minneapolis, Minn., April 1969.

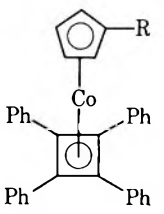
(45) A. J. Kresge, M. Dubeck, and H. C. Brown, *J. Org. Chem.*, **32**, 745, 752, 756 (1967).

(46) Fulvalene complexes of iron and manganese have previously been described: M. D. Rausch, R. F. Kovar, and C. S. Kraihanzel, *J. Amer. Chem. Soc.*, **91**, 1259 (1969).

the Rosenmund–von Braun reaction with cuprous cyanide in *N*-methyl-2-pyrrolidone[47] to give the cyano derivative **13** in 40% yield. Treatment of **9** with



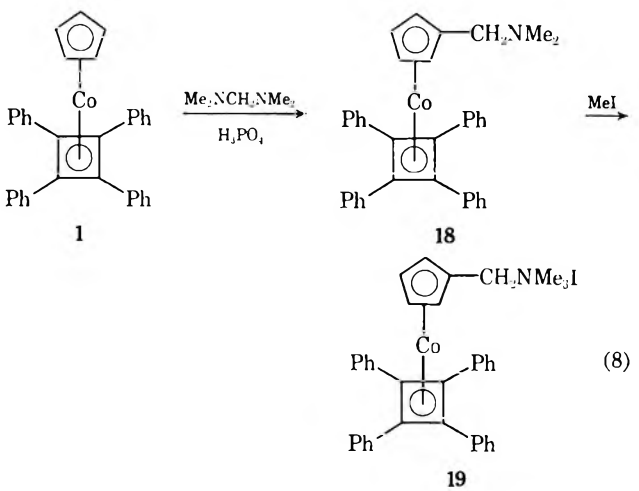
12



13, R = CN
14, R = $OC(O)CH_3$
15, R = $NC(O)C_6H_4C(O)$
16, R = OH
17, R = NH_2

cupric acetate or cupric phthalimide afforded acetoxy and phthalimido derivatives **14** and **15**, respectively. Acetoxy derivative **14** readily gave phenol **16** upon treatment with ethanolic potassium hydroxide solution. Phthalimido derivative **15** similarly produced amine **17** when hydrolyzed with aqueous ethanolic hydrazine solution. The ferrocene analogs of **13**–**17** have been previously prepared in a similar manner.[48]

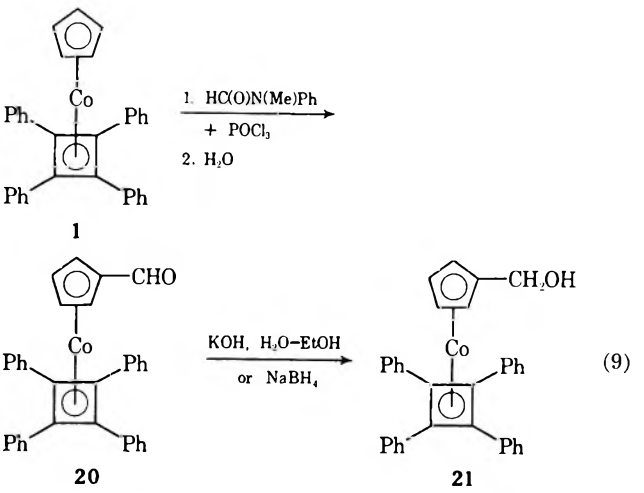
Another electrophilic substitution reaction which has been of widespread use in ferrocene chemistry is Mannich-type aminomethylation.[13] Cobalt complex **1** likewise readily undergoes this reaction to give the dimethylaminomethyl derivative **18** in 71% yield (eq 8). Amine **18** has also been characterized as the methiodide **19**.



(8)

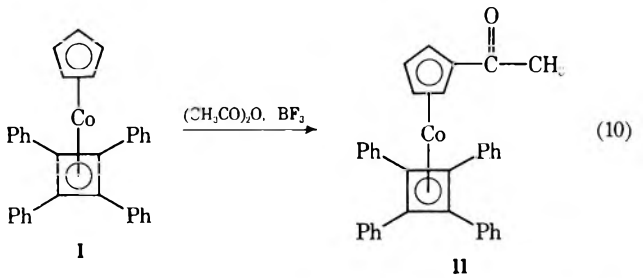
Vilsmeier formylation of **1** under conditions which have been used successfully for the formylation of ferrocene[6] gave the expected aldehyde derivative **20**, however, in only 8% yield (eq 9). Small amounts of several other products were obtained from this reaction, but were not further identified. Aldehyde **20** underwent a Cannizzaro reaction upon treatment with ethanolic potassium hydroxide solution. One of the products, hydroxymethyl derivative **21**, was also prepared by sodium borohydride reduction of **1**, as well as by treatment of methiodide **19** with strong base.

(47) M. S. Newman and H. Boden, *J. Org. Chem.*, **26**, 2525 (1961).
(48) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Dokl. Akad. Nauk SSSR*, **130**, 1030 (1960); *Chem. Ber.*, **93**, 2719 (1960).



(9)

Although a variety of metallocenes have been found to readily undergo Friedel–Crafts acylation, attempts to acylate cobalt complex **1** in a similar manner have been largely unsuccessful. Numerous reactions involving various acylating reagents and Lewis acid catalysts were examined, and acylated products were obtained in only a few instances, and even then in extremely low yield. Since a brown complex appears to form between Lewis acid catalysts and **1**, this complex formation may possibly deactivate the system toward electrophilic substitution. Thus, when an excess of catalyst was used, very little acylated products were produced, and most of the starting material **1** could be recovered after hydrolysis. When **1** was treated with acetic anhydride and boron trifluoride under conditions which have been successfully used to acetylate ferrocene,[49] a trace amount of the acetyl acetyl derivative **11** was obtained (eq 10). However, acetyl derivative **11** is more satisfactorily prepared by the transmetalation reaction involving **7**.



(10)

In another experiment involving benzoyl chloride and aluminum chloride in carbon disulfide solution, an acylated product was obtained in ~1% yield, in which substitution appeared to have occurred on a phenyl rather than the π-cyclopentadienyl ring. This conclusion was based on the appearance of a singlet for the π-cyclopentadienyl protons in the nmr spectrum of the product, and on the presence of a carbonyl stretching band in its infrared spectrum.

Spectra of π-Cyclopentadienyltetraphenylcyclobutadienecobalt Derivatives.—Proton nmr spectra of most of the organocobalt compounds prepared in this study are summarized in Table I. All monosubstituted derivatives of **1** in which the substituent is an electron-withdrawing group exhibit an A_2B_2 pattern, as is typical of

(49) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 482 (1957).

TABLE I

PROTON NMR SPECTRA OF SOME ORGANOCOBALT COMPOUNDS

Compd	Chemical shift and multiplicity[a-c] $H_{2,5}$	$H_{3,4}$	Ph	Other
$(\pi\text{-}C_5H_5)Co(C_4Ph_4)$ (1)	...[d]	...[d]	2.32–2.83 (m)	
$(\pi\text{-}C_5H_5)Co[C_4Ph_4C(O)]$ (2)	...[e]	...[e]	2.32–2.58 (m), 2.70–3.05 (m)	
$(\pi\text{-}C_5H_4SiMe_3)Co(C_4Ph_4)$ (3)	5.23 (t)[f]	5.33 (t)[f]	2.40–2.91 (m)	10.15 (s) (CH_3)
$(\pi\text{-}C_5H_4SiMe_3)Co[C_4Ph_4C(O)]$ (5)	4.90 (t)[f]	5.43 (t)[f]	2.10–2.30 (m), 2.62–2.96 (m)	10.03 (s) (CH_3)
$(\pi\text{-}C_5H_4Ph)Co(C_4Ph_4)$ (4)	5.00 (t)	5.31 (t)	2.52–3.18 (m)	
$(\pi\text{-}C_5H_4Ph)Co[C_4Ph_4C(O)]$ (6)	4.95 (t)	5.05 (t)	2.45–2.68 (m), 2.72–3.05 (m)	
$(\pi\text{-}C_5H_4HgCl)Co(C_4Ph_4)$ (7)	5.15 (t)	5.32 (t)	2.25–2.90 (m)	
$(\pi\text{-}C_5H_4I)Co(C_4Ph_4)$ (9)	5.24 (t)	5.45 (t)	2.40–2.92 (m)	
$(\pi\text{-}C_5H_3I_2)Co(C_4Ph_4)$ (22)	5.21 (d)[g]	5.49 (t)[h]	2.40–2.92 (m)	
$(\pi\text{-}C_5H_4CHO)Co(C_4Ph_4)$ (20)	4.77 (t)	5.13 (t)	2.42–2.88 (m)	0.65 (s) CHO)
$(\pi\text{-}C_5H_4CH_2OH)Co(C_4Ph_4)$ (21)	5.25 (t)[f]	5.37 (t)[f]	2.34–2.82 (m)	5.91 (s) (CH_2) 8.90 (s) (OH)
$[\pi\text{-}C_5H_4C(O)CH_3]Co(C_4Ph_4)$ (11)	4.71 (t)	5.15 (t)	2.30–2.79 (m)	8.32 (s) (CH_3)
$(\pi\text{-}C_5H_4CH_2NMe_2)Co(C_4Ph_4)$ (18)	5.37 (s)	5.37 (s)	2.35–2.90 (m)	7.29 (s) (CH_2) 7.96 (s) (CH_3)
$(\pi\text{-}C_5H_4CH_2NMe_3I)Co(C_4Ph_4)$ (19)	5.01 (t)	5.18 (t)	2.40–2.87 (m)	6.42 (s) (CH_2) 6.82 (s) (CH_3)
$(\pi\text{-}C_5H_4CN)Co(C_4Ph_4)$ (13)	4.98 (t)	5.23 (t)	2.35–2.80 (m)	
$[\pi\text{-}C_5H_4OC(O)CH_3]Co(C_4Ph_4)$ (14)	5.22 (t)	5.59 (t)	2.45–3.10 (m)	8.24 (d) (CH_3)
$[\pi\text{-}C_5H_4NC(O)C_6H_4C(O)]Co(C_4Ph_4)$ (15)	4.22 (t)	5.29 (t)	2.31–3.04 (m)	
$(\pi\text{-}C_5H_4NH_2)Co(C_4Ph_4)$ (17)	5.91 (t)[f]	5.66 (t)[f]	2.44–3.01 (m)	

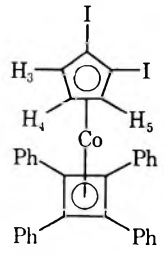
[a] Determined in dilute solutions in deuteriochloroform and given in τ, ppm, units. [b] s, singlet; d, doublet; t, triplet; m, multiplet. [c] Integrated intensities of resonances were consistent with the proposed structure. [d] Resonance for π-C_5H_5 ring protons occurs at τ 5.32 (s). [e] Resonance for π-C_5H_5 ring protons occurs at τ 5.16 (s). [f] Assignments are tentative and may be reversed. [g] Assigned to protons flanking adjacent iodine atoms ($H_{3,5}$). [h] Assigned to the proton β to both iodine atoms (H_4).

substituted cyclopentadienyl ring protons in many other metallocene derivatives.[50] The spectra consist of a pair of apparent triplets, and in each case the downfield triplet is assigned to the $H_{2,5}$ protons. Such an assignment is made on the basis that these protons are nearest the electron-withdrawing group, and thus would be expected to be deshielded to a greater extent than the protons $H_{3,4}$. Analogous assignments for monosubstituted ferrocenes have been unequivocally determined from the nmr spectra of 2,5-dideuterated ferrocene derivatives.[51] Assignment of the resonance peaks in the spectrum of amine **17** have been made in analogy to similar assignments in the spectrum of aminoferrocene.[52]

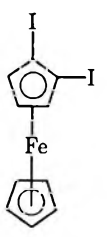
Our conclusion that the dimercurated complex **8** has a 1,2 rather than a 1,3 configuration has been made on the basis of the corresponding diiodo complex **22**. An nmr spectrum of the latter exhibits a low-field, two-proton doublet at τ 5.21, and a higher field, one-proton triplet[53] at τ 5.49. The protons ($H_{3,5}$) nearest the iodine substituents in **22** are assumed to be deshielded compared to proton H_4, by analogy to similar deshielding effects in iodobenzene and diiodobenzenes. In the iodobenzene derivatives, protons ortho to an iodine atom are substantially deshielded with respect to other ring protons.[54] Furthermore, the proton nmr spectrum of 1,2-diiodoferrocene (**23**) of known orientation exhibits a similar pattern for the ring-substituted protons.[55]

The proton nmr spectrum of the phthalimido derivative **15** is worthy of special comment. The downfield triplet for **15** occurs at ~30 Hz lower field than the corresponding triplets in all other monosubstituted derivatives of **1** examined thus far, while the upfield triplet appears in the normal region. Molecular models indicate that the $H_{2,5}$ protons in **15** reside in the deshielding region of the carbonyl groups, and this fact may possibly account for the enhanced deshielding of these protons. A similar enhanced deshielding is observed for the $H_{2,5}$ protons in the nmr spectrum of phthalimidoferrocene (**24**).[55]

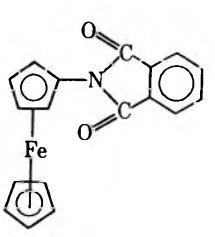
The proton nmr spectra of derivatives of **1** are of additional interest when compared to the spectra of analogous ferrocene derivatives. The resonances of protons on exocyclic carbon atoms in the former series invariably occur at significantly higher fields than do corresponding resonances in the ferrocene series. Some



22



23



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(50) M. D. Rausch and V. Mark, *J. Org. Chem.*, **28**, 3225 (1963); R. A. Benkeser, Y. Nagai, and J. Hooz, *Bull. Chem. Soc. Jap.*, **36**, 482 (1963); G. G. Dvoryantseva, S. L. Portnova, K. I. Grandberg, S. P. Gubin, and Yu. N. Sheinker, *Dokl. Akad. Nauk SSSR*, **160**, 1075 (1965).

(51) M. D. Rausch and A. Siegel, *J. Organometal. Chem.*, **17**, 117 (1969).

(52) D. W. Slocum, P. S. Shenkin, and T. R. Englemann, Abstracts, 4th International Conference on Organometallic Chemistry, Bristol, England, July 27–Aug 1, 1969, p G5.

(53) This resonance peak was incorrectly designated as a singlet in our earlier communication (ref 35).

(54) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961); M. Martin and B. P. Dailey, *ibid.*, **37**, 2594 (1962).

(55) P. V. Roling and M. D. Rausch, unpublished studies.

examples of this relationship are summarized in Table II. Molecular models indicate that a substantial

TABLE II
NMR COMPARISONS OF DERIVATIVES OF 1 AND DERIVATIVES OF FERROCENE

X	Fc-X,[a,b] τ ppm	R-X,[a] τ ppm
CH_2OH	5.65	5.91
$Si(CH_3)_3$	9.79	10.15
$CH_2N(CH_3)_2$	6.74	7.29
$CH_2N(CH_3)_2$	7.89	7.96
$CH_2N(CH_3)_3I$	5.00	6.42
$CH_2N(CH_3)_3I$	6.65	6.82
$C(O)CH_3$	7.62	8.32
CHO	0.05	0.65

[a] Fc-X represents ferrocene derivatives and R-X represents π-cyclopentadienyltetraphenylcyclobutadienecobalt (1) derivatives. [b] Reference 51 and unpublished studies by M. D. Rausch.

shielding effect may be imposed by the phenyl groups attached to the cyclobutadiene ring. This effect, together possibly with metal anisotropy differences between iron and cobalt, may account for the observed chemical shifts.

The infrared spectra of **1** and its derivatives can be interpreted by direct analogy to other metallocenes. Complex **1** exhibits absorbances at 1115 and 1005 cm^{-1}; such bands are well known to be characteristic of an unsubstituted cyclopentadienyl ring.[56] Both of these absorbances are absent in all derivatives of **1** examined, as is also the case for 1,1′-disubstituted ferrocenes.[56] Complex **1** and its derivatives also exhibit absorbances characteristic of a monosubstituted phenyl group. Each complex exhibited prominent absorptions in each of the following regions: 3080–3050, 1600, 1500, 1075–1065, and 1030–1020 cm^{-1}, as well as four bands between 815 and 690 cm^{-1}. The normal absorbances for functional groups such as –CN, –CHO, etc., were also observed in the appropriate derivatives and are listed in the Experimental Section.

Relative Acidity and Basicity Studies.—It was of interest to compare acidity and basicity constants of derivatives of **1** with similar constants in the ferrocene and benzene series. This was accomplished by determining the "pK" values of phenol **16** and amine **17**. It should be emphasized that the "pK" values reported are not authentic pK values, since they have been determined in nonaqueous systems. The "pK_A" values were determined in pyridine as the solvent by titrating with 0.1 N tetrabutylammonium hydroxide in benzene–methanol. The "pK_B" values were determined in acetonitrile as the solvent by titrating with 0.1 N perchloric acid in acetic acid. Both types of titrations were performed with an automatic recording titrimeter. The relative acidities and basicities presented in Tables III and IV are estimated to be accurate to within $\sim\pm0.1$ unit.

By this procedure, it was found that **16** is a slightly stronger acid than phenol (Table III), and that **17** has essentially the same base strength as aniline (Table IV). In contrast, Nesmeyanov and coworkers have reported that hydroxyferrocene is a weaker acid than phenol,[48] and that aminoferrocene is a stronger base than aniline.[57]

(56) Reference 29, p 38.

(57) E. G. Perevalova, K. I. Grandberg, N. A. Zharikova, S. P. Gubin, and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 832 (1966).

TABLE III
"pK_A" VALUES OF PHENOLS

Phenol	"pK_A" in pyridine, 23°	pK_A in water[a]
p-Chlorophenol	9.1	9.38
$(\pi\text{-}C_5H_4OH)Co(C_4Ph_4)$ (16)	9.4	
Phenol	10.0	9.99
o-Cresol	10.3	10.29
$(\pi\text{-}C_5H_4OH)Fe(\pi\text{-}C_5H_5)$	11.2	10.20[b]

[a] L. Meites, "Handbook of Analytical Chemistry," 1st ed, McGraw-Hill, New York, N. Y., 1963, pp 1–20. [b] Obtained in 5% ethanol (ref 48).

TABLE IV
"pK_B" VALUES OF AMINES

Amine	"pK_B" in acetonitrile, 23°	pK_B in water[a,b]
p-Toluidine	8.7	8.90
$(\pi\text{-}C_5H_4NH_2)Co(C_4Ph_4)$ (17)	9.4	
Aniline	9.4	9.40
p-Chloroaniline	10.5	10.01

[a] L. Meites, "Handbook of Analytical Chemistry," 1st ed, McGraw-Hill, New York, N. Y., 1963, pp 1–20. [b] The pK_B of aniline = 11.95 and the pK_B of aminoferrocene = 10.33 in 80% ethanol (ref 57).

Since the success of electrophilic substitution reactions in metallocenes depends in part on the availability of π-electrons in the π-cyclopentadienyl ring, it might be expected that **1**, which appears from the "pK" values to be electron-poor compared to ferrocene, would be less reactive than is ferrocene in these types of reactions. In general, this appears to be the case. However, a reliable comparison of reactivities can best be made on the basis of competition studies, and we intend to carry out such experiments in the near future.

Experimental Section

Melting points were determined using a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and were calibrated with polystyrene; all samples were prepared as potassium bromide pellets. Nmr spectra were recorded on a Varian A-60 spectrophotometer with tetramethylsilane as an internal standard. Microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Mr. Charles Meade of the Microanalytical Laboratory, Office of Research Services, University of Mass. Ethyl ether and tetrahydrofuran were dried over sodium and potassium hydroxide, respectively, and distilled from lithium aluminum hydride. Methylene chloride was dried by passing it through a short column of neutral alumina. Octacarbonyldicobalt was purchased from the Strem Chemical Co., Danvers, Mass., and *N*-methyl-2-pyrrolidone was obtained from the General Aniline and Film Co., New York, N. Y.

π-Cyclopentadienyldicarbonylcobalt.—Freshly distilled cyclopentadiene (31 ml, 0.38 mol), 60 ml of dried methylene chloride, and octacarbonyldicobalt (25 g, 0.073 mol) were placed in a 200-ml flask, which was fitted with a reflux condenser and a mercury check valve. The system was flushed with nitrogen and was covered with aluminum foil to exclude light. The contents were heated to reflux on a steam bath for 2 days, after which time the methylene chloride was distilled under water aspirator pressure. Continued distillation produced 24.6 g (93%) of product as a dark red liquid, bp 75–80° (22 mm) [lit.[58] bp 75° (22 mm)]. The product was stored under nitrogen at −20° in a covered flask.

π-Cyclopentadienyltetraphenylcyclobutadienecobalt (1) and π-Cyclopentadienyltetraphenylcyclopentadienonecobalt (2).—A 1-l. three-necked flask was fitted with a glass stopper, condenser, and a gas inlet tube which was used to maintain a nitrogen at-

(58) T. S. Piper, F. A. Cotton, and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **3**, 165 (1955).

mosphere during the reaction. A mixture of 19.7 g (0.11 mol) of diphenylacetylene, 10.0 g (0.055 mol) of π-cyclopentadienyldicarbonylcobalt, and 500 ml of *p*-xylene was placed in the flask. The latter was covered with aluminum foil and the solution heated to reflux. Soon after heating was begun, a definite but slow evolution of gas occurred. After 24 hr, the solution was allowed to cool to room temperature and the reaction mixture was filtered in air. The filtered solid was washed with cold benzene; the white residue remaining was identified as hexaphenylbenzene (2.8 g, 15%) on the basis of its melting point (454–455°) and a mixture melting point with an authentic sample.

The original xylene solution and the benzene extracts were chromatographed on separate columns of alumina, using benzene as the eluent. The orange cyclobutadiene complex **1** was eluted first as a dark orange band from both columns. A faint purple band, identified as a trace amount of tetraphenylcyclopentadienone by comparison with an authentic sample, was the second band to be eluted from the column containing the xylene solution. Finally, both columns gave the tetraphenylcyclopentadienone complex **2** as a red band when elution was made with chloroform.

The orange bands were combined and evaporated to dryness, and the product recrystallized from a mixture of benzene and heptane to give 12.0 g (46%) of **1**, mp 262–264° (lit.[32] mp 256°; lit.[33] mp 264°). Yields of **1** from other runs varied from 44 to 61%: ir 1115 and 1005 cm^{-1} (π-C_5H_5).

Anal. Calcd for $C_{33}H_{25}Co$: C, 82.49; H, 5.24; Co, 12.27; mol wt, 480. Found: C, 82.40; H, 5.31; Co, 12.31; mol wt (parent molecular ion), 480.

The red bands were combined and evaporated to dryness, and the product was recrystallized from a mixture of chloroform and heptane to give 2.65 g (9.5%) of **2**, mp 323–325° (lit.[39] mp 327–329°). An authentic sample of **2** was prepared by the reaction of tetraphenylcyclopentadienone with π-cyclopentadienyldicarbonylcobalt in refluxing xylene: mol wt (calcd) 508, mol wt (found, parent molecular ion) 508; ir 1590 cm^{-1} (C=O stretch).

(π-Chloromercuricyclopentadienyl)tetraphenylcyclobutadienecobalt (7) and [π-1,2-Bis(chloromercuri)cyclopentadienyl]tetraphenylcyclobutadienecobalt (8).—In a 250-ml erlenmeyer flask were placed 6.0 g (0.012 mol) of π-cyclopentadienyltetraphenylcyclobutadienecobalt, 150 ml of methylene chloride, and a magnetic stirring bar. To this solution was added 1.32 g (0.0042 mol) of mercuric acetate. Vigorous stirring was begun and 6 to 10 drops of perchloric acid were added dropwise over a 30-min period until most of the mercuric acetate had disappeared. Stirring was continued for 15 min and 1.0 g (0.024 mol) of lithium chloride was added, followed after an additional 15-min period by the addition of 3.0 g of sodium sodium bicarbonate. Finally, 4.0 g of sodium sulfate was added and the solution was allowed to dry. The dark orange methylene chloride solution was poured directly onto a short column of basic alumina (pH 9.5). The initial dark orange band, eluted with methylene chloride, gave 3.85 g of starting material **1**. The second band was eluted by adding 1–2% methanol to the methylene chloride. Upon evaporation of the solvent and recrystallization of the dark orange solid from a mixture of benzene and heptane, 1.93 g (65%) of **7**, mp 234–235°, was obtained.

Anal. Calcd for $C_{33}H_{24}ClCoHg$: C, 55.39; H, 3.39; Cl, 4.95; Co, 8.23. Found: C, 55.83; H, 3.72; Cl, 4.68; Co, 7.98.

In several runs, a third band was eluted which produced ~0.1 g (5%) of a dark orange solid (**8**) that was very sparingly soluble in most organic solvents. Since this product was difficult to purify because of its insolubility, it was treated with iodine to give an identifiable product as described below.

(π-Iodocyclopentadienyl)tetraphenylcyclobutadienecobalt (9) and (π-1,2(Diiodocyclopentadienyl)tetraphenylcyclobutadienecobalt (23).—A saturated solution of iodine in chloroform was slowly added with stirring to 3.0 g (0.0042 mol) of (π-chloromercuricyclopentadienyl)tetraphenylcyclobutadienecobalt dissolved in 75 ml of chloroform, until a definite darkening of the solution persisted for 30 sec. The solution was then immediately washed, twice with 100-ml portions of a 0.01 *M* solution of sodium thiosulfate, and once with water. The chloroform layer was dried over sodium sulfate and the solvent was removed. The solid residue was dissolved in a small amount of benzene and chromatographed on a short column of alumina to remove a small amount of polar material. The benzene was evaporated and the resulting yellow-orange residue was recrystallized from heptane to give 2.1 g (83%) of **9**, mp 191–192°.

Anal. Calcd for $C_{33}H_{24}CoI$: C, 65.36; H, 3.99; Co, 9.71; I, 20.93. Found: C, 65.16; H, 4.20; Co, 9.57; I, 21.19.

The bischloromercuri complex **8** was treated with iodine in the same manner to give **22**, mp 201–202°.

Anal. Calcd for $C_{33}H_{23}CoI_2$: C, 54.12; H, 3.18; Co, 8.05; I, 34.66. Found: C, 54.02; H, 3.31; Co, 8.14; I, 34.50.

(π-Formylcyclopentadienyl)tetraphenylcyclobutadienecobalt (20).—A three-necked 50-ml flask was fitted with a condenser, nitrogen inlet and syringe cap, and was flushed with nitrogen. To the flask was added 0.2 ml (0.002 mol) of phosphorus oxychloride, 0.3 ml (0.002 mol) of *N*-methylformanilide, and 1.0 g (0.002 mol) of π-cyclopentadienyltetraphenylcyclobutadienecobalt. The mixture was heated for 4 hr at 80° with occasional addition *via* a syringe of additional 0.1-ml portions of phosphorus oxychloride (0.5 ml extra added). The mixture turned from orange to red and finally to black during the reaction period. Hydrolysis was effected by stirring the reaction mixture with excess sodium acetate solution at room temperature. It was necessary to add a few ml of benzene to dissolve the tarry residue so that complete hydrolysis could occur. After 3 hr, additional benzene was added and the resulting solution was washed with 100 ml of water. The benzene layer was separated, dried over sodium sulfate, and chromatographed on Florisil using benzene as the eluent. The first band from the column contained 0.7 g of starting material **1**. The second band was collected, the solvent evaporated, and the solid residue was recrystallized from hexane to give 0.08 g (8%) of **20**, mp 189–190°, ir 1685 cm^{-1} (C=O stretch).

Anal. Calcd for $C_{34}H_{25}CoO$: C, 80.30; H, 4.96; Co, 11.58; O, 3.15. Found: C, 80.35; H, 4.90; Co, 11.46; O, 3.24.

When the benzene solution of the reaction mixture, shown to contain the desired aldehyde by tlc, was chromatographed on alumina rather than Florisil, an unidentified red compound, mp 203–204° (parent molecular ion 548), was obtained, and none of the aldehyde could be isolated. On the other hand, if a benzene solution of the purified aldehyde **20** was chromatographed on alumina, it was recovered unchanged.

(π-Hydroxymethylcyclopentadienyl)tetraphenylcyclobutadienecobalt (21).—A methanol solution of 0.1 g (0.2 mmol) of (π-formylcyclopentadienyl)tetraphenylcyclobutadienecobalt was prepared by warming the compound on a steam bath with 30 ml of methanol. After the solution had been allowed to cool slightly, 0.3 g (0.008 mol) of sodium borohydride in 4 ml of water was added. The color of the solution immediately changed from orange to yellow, however; the reaction mixture was allowed to stand overnight. The methanol solution was poured into 150 ml of water which was then extracted with methylene chloride. The organic layer was separated, washed with 100 ml of water, and was dried with sodium sulfate. Removal of the solvent left a solid residue which was recrystallized from a mixture of hexane and ethyl ether to give 0.08 g (80%) of **21** as fine light yellow crystals, mp 179–180°.

Anal. Calcd for $C_{34}H_{27}CoO$: C, 80.00; H, 5.33; Co, 11.54. Found: C, 80.15; H, 5.43; Co, 11.16.

Cannizzaro Reaction of (π-Formylcyclopentadienyl)tetraphenylcyclobutadienecobalt (20).—A suspension of 0.10 g (0.2 mmol) of (π-formylcyclopentadienyl)tetraphenylcyclobutadienecobalt in 20 ml of 50% potassium hydroxide in ethanol was refluxed for 4 hr. The reaction mixture was allowed to cool and water was added. The basic solution was extracted with chloroform and then acidified. The acidic portion was extracted with chloroform, and evaporation of the solvent produced several mg of a yellow acid. This was not characterized further due to the small amount available. The original chloroform extract of the basic solution was washed with water, dried with sodium sulfate, and evaporated. The solid residue was dissolved in benzene and chromatographed on alumina to give several poorly resolved bands. The major band (band 2) was subsequently further purified by preparative tlc to afford 0.014 g (28%) of **21**. The product was shown by tlc and nmr to be identical with **21** obtained from the sodium borohydride reduction of **20**.

(π-Dimethylaminomethylcyclopentadienyl)tetraphenylcyclobutadienecobalt (18).—To a 250-ml three-necked flask were added 100 ml of glacial acetic acid and 0.50 g (0.0010 mol) of π-cyclopentadienyltetraphenylcyclobutadienecobalt. The flask was equipped with a condenser, a nitrogen inlet, and a magnetic stirring bar. A heating mantel was used to heat the suspension, under nitrogen and with stirring, until reflux began. To the hot solution was added 0.90 ml (0.013 mol) of phosphoric acid followed by 4.5 ml (0.036 mol) of bis(dimethylamino)methane.

Refluxing and stirring were continued, and the solution became dark orange in color.

After 5 hr, the reaction mixture was cooled, 400 ml of water was added, and the resulting aqueous suspension was extracted several times with 75 ml portions of benzene. The combined extracts were washed twice with sodium bicarbonate solution, once with water, and were dried with sodium sulfate. After reducing the volume of the solution to 30 ml with an aspirator, the solution was chromatographed on basic alumina (pH 9.5) to produce, after evaporation, 0.38 g (71%) of **18** as the third (and major) band, when eluted with a 60:40 benzene–chloroform mixture. The first band gave 0.1 g of starting material. The amine **18** was recrystallized from a methanol-methylene chloride mixture, resulting in dark orange crystals, mp 189–190°.

Anal. Calcd for $C_{36}H_{32}CoN$: C, 80.43; H, 6.00; Co, 10.96; N, 2.61. Found: C, 80.36; H, 6.11; Co, 10.86; N, 2.61.

Amine **18** was insoluble in concentrated hydrochloric acid, but dissolved with decomposition in concentrated sulfuric acid.

The methiodide of **18** was prepared by heating a solution of 0.10 g (0.18 mmol) of the amine and 4.6 ml (80 mmol) of methyl iodide in 20 ml of methanol on a steam bath for 10 min. The solvent and excess methyl iodide were removed with an aspirator and the product was recrystallized from a mixture of benzene and methanol to give 0.11 g (89%) of **19**, mp 250°. The product was characterized by its nmr spectrum (Table I).

Treatment of 0.05 g (0.07 mmol) of the methiodide **19** with 10 g of potassium hydroxide and 30 ml of 95% ethanol at reflux for 44 hr, followed by the addition of water, extraction with benzene and chromatography of the extracts on alumina, produced four bands. The third band produced 8 mg (22%) of **21**; the latter was shown to be identical with carbinol **21** obtained from the sodium borohydride reduction of aldehyde **20**. The first two bands were present in only minor amount; these and the fourth band (26 mg) were not further identified.

Friedel–Crafts Acylation of π-Cyclopentadienyltetraphenylcyclobutadienecobalt (1).—Numerous attempts were made to carry out Friedel–Crafts reactions on **1**, using various combinations of acetic anhydride, benzoyl chloride, acetyl chloride, and methyl chlorothiolformate as acylating agent, aluminum chloride, phosphoric acid, tin tetrachloride, etc., as catalyst, and either methylene chloride or carbon disulfide as the reaction medium. All reactions were conducted under nitrogen and with dry solvents.

Of all the combinations, the procedure of Hauser and Lindsay[49] proved to be the most successful, employing acetic anhydride, a boron trifluoride solution in ethyl acetate, methylene chloride, and stirring for 30 min at 25°. The reaction mixture was hydrolyzed, the organic phase washed with sodium bicarbonate solution and with water, and was dried. Evaporation of the solvent and chromatography of the residue in benzene on alumina produced unreacted **1** followed by a very small second band which was not identified. Examination of the third band indicated that it contained **11**, on the basis of comparison with an authentic sample of **11** prepared from the chloromercuri complex **7**, as described below. The yield of **11**, however, was less than 1%.

Reaction of (π-Chloromercuricyclopentadienyl)tetraphenylcyclobutadienecobalt with *n*-Butyllithium.—To a 250-ml, three-necked flask, equipped with a nitrogen inlet tube, syringe cap, and condenser, were added under nitrogen 100 ml of dry hexane and 0.5 g (6.7 mmol) of (π-chloromercuricyclopentadienyl)tetraphenylcyclobutadienecobalt. The latter did not dissolve until 3 ml (7 mmol) of *n*-BuLi in hexane was added through the syringe cap. After stirring for 10 min, the clear orange solution of (π-lithiocyclopentadienyl)tetraphenylcyclobutadienecobalt (**10**) was poured into a cooled, stirred solution of 10 ml of acetyl chloride in dry hexane. A precipitate formed, and stirring was continued for 1 hr after which time the suspension was carefully poured over ice. After the ice had melted, the layers were separated, the organic layer was washed with sodium bicarbonate solution and with water, dried with sodium sulfate, and was chromatographed on alumina. The first band contained **1**; a very small second band was not collected. The third band contained starting material (**7**), while the fourth band produced 0.025 g (7%) of (π-acetylcyclopentadienyl)tetraphenylcyclobutadienecobalt (**11**), mp 175–176°, after recrystallization from heptane: ir, 1665 cm^{-1} (C=O stretch).

Anal. Calcd for $C_{35}H_{27}CoO$: C, 80.45; H, 5.21; Co, 11.28. Found: C, 80.40; H, 5.05; Co, 11.26.

The lithium intermediate **10** could also be characterized by reaction with trimethylchlorosilane in a similar manner. The compound was purified by preparative tlc and was shown to be identical by tlc and nmr with **3** prepared from trimethylsilylcyclopentadiene and octacarbonyldicobalt, as described below.

Fulvalene–bis(tetraphenylcyclobutadiene)dicobalt (12).—In a 50-ml Schlenk tube were combined under nitrogen 0.1 g (0.2 mmol) of (π-iodocyclopentadienyl)tetraphenylcyclobutadiene and 3.0 g of activated copper–bronze. A nitrogen atmosphere was maintained while the tube was heated at 250° for 14 hr in a bath of Wood's metal. The tube was cooled and the contents were extracted repeatedly with hot chloroform until the extracts were colorless. After filtration and concentration of the solvent, the products were separated by preparative tlc. The first band gave 0.05 g of **1**; no starting material **9** could be detected. The second band gave 0.020 g (21%) of **12**, mp 350–352° (sealed tube under nitrogen).

Anal. Calcd for $C_{66}H_{48}Co_2$: C, 82.66; H, 5.05; Co, 12.29; mol wt, 958. Found: C, 82.81; H, 5.08; Co, 12.07; mol wt (parent molecular ion), 958.

(π-Cyanocyclopentadienyl)tetraphenylcyclobutadienecobalt (13).—To a 50-ml flask equipped with a condenser and flushed with nitrogen were added 0.5 g (0.8 mmol) of (π-iodocyclopentadienyl)tetraphenylcyclobutadienecobalt, 1.0 g (0.011 mol) of cuprous cyanide, and 20 ml of *N*-methyl-2-pyrrolidone. The flask was heated in an oil bath at 210° for 2 hr. After cooling to room temperature, the reaction mixture was poured into a mixture of water and methylene chloride. The dark orange organic layer was separated, washed five times with 100-ml portions of water (to remove *N*-methyl-2-pyrrolidone), and dried over sodium sulfate. Removal of the methylene chloride left a solid which was dissolved in benzene and chromatographed on alumina. Elution with benzene produced a band containing **1**. Elution with 50% benzene–ethyl ether produced a second band, which after removal of the solvent gave an orange solid. Recrystallization of the latter from methylene chloride–heptane gave 0.16 g (~40%) of **13**, mp 198–199°, ir 2220 cm^{-1} (C≡N stretch).

Anal. Calcd for $C_{34}H_{24}CoN$: C, 80.78; H, 4.79; Co, 11.66. Found: C, 80.58; H, 4.81; Co, 11.56.

(π-Acetoxycyclopentadienyl)tetraphenylcyclobutadienecobalt (14).—(π-Iodocyclopentadienyl)tetraphenylcyclobutadienecobalt (0.5 g, 0.8 mmol), cupric acetate (0.3 g, 0.016 mol), and 10 ml of *N*-methyl-2-pyrrolidone were combined in a 50-ml flask which had been flushed with nitrogen. The cupric acetate had previously been dried by refluxing it in acetic anhydride for 24 hr, filtration, washing the solid with dry ethyl ether, and removal of the ether *in vacuo*. A condenser was added, and the reaction mixture was heated on an oil bath at 135–140° for 24 hr and then transferred to a separatory funnel where water and chloroform were added. Following separation of the layers, the chloroform layer was washed five times with 100-ml portions of water, dried with sodium sulfate, and was evaporated to give an orange residue. This solid was dissolved in benzene and chromatographed on a 2 by 22 cm column of Florisil using benzene as eluent. The first band gave a mixture containing 75% **9** and 25% **1**, as determined by nmr integration. The second band gave 0.070 g (16%) of **14** as an orange solid. Recrystallization of the product from methylene chloride–hexane produced orange-brown crystals: mp 192–193°; ir 1760 cm^{-1} (C=O stretch); 1210 cm^{-1} (C—O stretch).

Anal. Calcd for $C_{35}H_{27}CoO_2$: C, 78.07; H, 5.05; Co, 10.94; O, 5.94. Found: C, 78.40; H, 5.16; Co, 11.32; O, 5.12.

(π-Phthalimidocyclopentadienyl)tetraphenylcyclobutadienecobalt (15).—Cupric phthalimide was prepared in the following manner. To a solution of 9.08 g (0.05 mol) of cupric acetate, dissolved in 300 ml of water and stirred by means of a mechanical stirrer, was slowly added 18.5 g (0.01 mol) of potassium phthalimide dissolved in 125 ml of water. Cupric phthalimide precipitated as a light blue powder and was collected by suction filtration. The precipitate was washed thoroughly with three 300-ml portions of water, and was then dried overnight at 65° (22 mm).

In a 50-ml flask equipped with a condenser and flushed with nitrogen were combined 0.3 g (0.5 mmol) of (π-iodocyclopentadienyl)tetraphenylcyclobutadienecobalt, 0.4 g (0.001 mol) of cupric phthalimide, and 10 ml of *N*-methyl-2-pyrrolidone. The flask was heated under nitrogen in an oil bath at 160°. During the first 2-hr period, 0.4 g of additional cupric phthalimide was added (0.1 g every 0.5 hr). After heating for a total of 24 hr, the reaction mixture was allowed to cool and was poured into 150 ml of water contained in a separatory funnel. Chloroform (40 ml) was added and the funnel was shaken. After filtration

through Filter-Cel, the orange chloroform layer was separated, washed five times with 100-ml portions of water, and was dried over sodium sulfate. The chloroform solution was concentrated to 5 ml, and an equal volume of benzene was added to give a solution which was chromatographed on a 4 × 13 cm column of Florisil. Elution with benzene gave 0.17 g of **1**. Further elution with benzene and then with 10:1 benzene–chloroform produced a second band which on evaporation yielded 0.05 g (16%) of **15**. Recrystallization of the product from benzene–heptane resulted in orange-brown crystals, mp 183–185°: ir 1720 cm^{-1} (C=O stretch), 1480, 1360 cm^{-1}.

Anal. Calcd for $C_{41}H_{28}CoNO_2$: C, 78.72; H, 4.51; N, 2.24. Found C, 78.30; H, 4.43; N, 2.12.

(π-Hydroxycyclopentadienyl)tetraphenylcyclobutadienecobalt (16).—In a 50-ml flask equipped with a condenser were combined under nitrogen 0.05 g (0.1 mmol) of (π-acetoxycyclopentadienyl)-tetraphenylcyclobutadienecobalt, 0.6 g of potassium hydroxide in 5 ml of water, and 9 ml of 95% ethanol. The reaction mixture was heated for 45 min on a steam bath. The resulting orange solution was transferred to a separatory funnel containing water and ethyl ether. The transfer and the following purification procedure were conducted completely under nitrogen. The ether layer was separated, washed twice with 150-ml portions of water, dried over magnesium sulfate, and filtered. The filtrate was concentrated *via* a nitrogen stream and gentle heating to 15 ml, and was transferred to a tared glass vial. Hexane was added and the evaporation was continued until crystallization occurred. The shiny orange plates were dried with a nitrogen stream to give 0.04 g (78%) of **16**, mp 204–206° under nitrogen after softening at ~178°. The crystals were stable for only about 1 hr in air at room temperature, but for several days under nitrogen.

(π-Aminocyclopentadienyl)tetraphenylcyclobutadienecobalt (17).—(π-Phthalimidocyclopentadienyl)tetraphenylcyclobutadienecobalt (0.02 g, 0.03 mmol), 3 ml of 95% hydrazine in 1 ml of water, and 5 ml of ethanol were combined in a 50-ml flask equipped with a condenser. The suspension was refluxed until all the solid was dissolved and then poured into cold water. The resulting suspension was extracted with ethyl ether to give a yellow organic portion which was washed five times with 100-ml portions of water and dried with sodium sulfate. After the volume of solvent had been reduced to several milliliters *via* a stream of nitrogen, hexane was added and evaporation continued until orange crystals of **17** were obtained. The R_f of the amine **17** on tlc was 0.15 compared to 0.33 for **15** (elution with benzene).

Anal. Calcd for $C_{33}H_{26}CoN$: N, 2.83. Found: N, 3.00.

(π-Trimethylsilylcyclopentadienyl)tetraphenylcyclobutadienecobalt (3) and (π-Trimethylsilylcyclopentadienyl)tetraphenylcyclopentadienonecobalt (5).—In a 50-ml flask equipped with a condenser and flushed with nitrogen were combined 35 ml of dried methylene chloride, 20 g (0.15 mol) of trimethylsilylcyclopentadiene,[59] and 9.5 g (0.03 mol) of octacarbonyldicobalt. The flask was covered with aluminum foil to exclude light and was heated gently on a steam bath for 48 hr. Attempts at distillation succeeded in removing the starting material, trimethylsilylcyclopentadiene, but seemed to cause decomposition of the product. Therefore, the dark red liquid product (8.0 g, 53%), π-trimethylsilylcyclopentadienyldicarbonylcobalt, was used in the next step without additional purification.

To a 200-ml flask equipped with a condenser and flushed with nitrogen were added 6.8 g (0.038 mol) of diphenylacetylene, 4.7 g (0.019 mol) of π-trimethylsilylcyclopentadienyldicarbonylcobalt, and 75 ml of *p*-xylene. The reaction mixture was heated in an oil bath at 160° for 24 hr, cooled to room temperature, and allowed to stand for 1 hr. Filtration of the resulting precipitate gave 0.7 g of hexaphenylbenzene. The red filtrate was chromatographed on a 4 × 14 cm column of alumina Elution with benzene removed a broad orange-red band which contained starting material, as well as the desired product. After removal of the solvent, the residue was recrystallized from heptane to give 2.5 g (25%) of **3** as orange-red crystals, mp 178–179°.

Anal. Calcd for $C_{35}H_{33}CoSi$: C, 78.24; H, 6.02; Co, 10.66; mol wt, 552. Found: C, 78.00; H, 5.98; Co, 10.70; mol wt (parent molecular ion), 552.

A very small purple band was identified as tetraphenylcyclopentadienone.

A red third band, eluted with chloroform, gave 1.0 g (14%) of **5** as a brick red solid. After recrystallization of the product from heptane–carbon tetrachloride, the mp was 200–201° (softening at ~175°).

Anal. Calcd for $C_{37}H_{33}CoOSi$: C, 76.53; H, 5.73; O, 2.76; Co, 10.15; mol wt, 580. Found: C, 76.30; H, 5.72; O, 2.79; Co, 9.95; mol wt (parent molecular ion), 580.

(π-Phenylcyclopentadienyl)tetraphenylcyclobutadienecobalt (4) and (π-Phenylcyclopentadienyl)tetraphenylcyclopentadienonecobalt (6).—In a nitrogen-flushed Schlenk tube were combined 3.0 g (0.02 mol) of phenylcyclopentadiene (prepared from phenyllithium and 2-cyclopentenone-1 according to a literature method),[60] 1.7 g (0.005 mol) of octacarbonyldicobalt, and 10 ml of dried methylene chloride. The tube was covered with aluminum foil and was heated on a steam bath for 20 hr. The solvent was removed *via* an aspirator and the residue dissolved in hexane and chromatographed on alumina. The first band consisted of a small amount of octacarbonyldicobalt, while a second band produced, after removal of the solvent, 1.6 g (62%) of π-phenylcyclopentadienyldicarbonylcobalt as a dark red liquid.

In a 50-ml flask equipped with a condenser were combined under nitrogen 1.0 g (0.004 mol) of π-phenylcyclopentadienyldicarbonylcobalt, 1.4 g (0.008 mol) of diphenylacetylene, and 25 m of *p*-xylene. After heating for 24 hr in an oil bath maintained at 155°, the flask was cooled and allowed to stand at room temperature for 2 hr. Filtration gave 0.06 g of hexaphenylbenzene. The xylene filtrate was chromatographed on a 4 × 13 cm column of alumina. Elution with benzene produced an orange band which when evaporated gave 0.80 g (37%) of **4**. Recrystallization of the product from benzene–heptane gave orange-brown crystals, mp 209–210°.

Anal. Calcd for $C_{39}H_{29}Co$: C, 84.16; H, 5.25; Co, 10.59; mol wt, 556. Found: C, 83.80; H, 5.17; Co, 10.82; mol wt (parent molecular ion), 556.

A small red second band, eluted with chloroform, gave 0.10 g (4.5%) of **6**. The product had mp 250–251° when recrystallized from chloroform–heptane.

Anal. Calcd for $C_{40}H_{29}CoO$: C, 82.18; H, 5.00; Co, 10.08; O, 2.74; mol wt, 584. Found: C, 82.00; H, 4.97; Co, 9.94; O, 3.08; mol wt (parent molecular ion), 584.

Relative Acidity and Basicity Studies.—The most convenient way of measuring the relative acidities of phenol and basicities of amines is by obtaining an acid-base titration curve. The pK value can then be determined directly from the curve by calculating the pH at half-neutralization, since at this point pH = pK.[61a] For weak acids such as **16** and weak bases such as **17** it is necessary to use nonaqueous solvents to obtain a meaningful titration curve. In nonaqueous systems a true pK is not obtained, but the half-neutralization potential is proportional to pK.[61b]

The acidity and basicity values obtained experimentally from the half-neutralization potentials for phenol **16** and amine **17** were not conveniently comparable to literature pK values obtained under aqueous conditions. To make them comparable, it was necessary to adjust the values on the basis of a standard phenol (phenol was chosen) and a standard amine (aniline was chosen) which were run under analogous conditions. Each time that titrations of phenols or amines were run, the appropriate standards were also run. A fixed number was then added to the numerical value obtained at half-neutralization for each phenol or amine so that the new "pK" value for the standard corresponded to the literature pK value for the standard in aqueous solution. Titrations of each series of phenols or amines were made consecutively and under identical conditions. Duplicate series of runs made on different days showed that the relative values reported in Tables III and IV were completely reproducible.

In the acidity studies, 10- to 11-ml samples of 0.003 M solutions of **16** and various phenols in pyridine were used in each run; the temperature was 23°. Tetrabutylammonium hydroxide (0.1 N) in benzene–methanol, prepared as described in the literature,[62a] was used as the titrant in each case. Titrations were made on a Radiometer Titrigraph, Type SBR2c, Copenhagen, Denmark (U. S. Distributor, The London Co., Westlake, Ohio), coupled with a Radiometer Titrator 11 and pH meter 25 with a combination glass electrode. It was necessary to connect a ground wire from the chassis of the Titrigraph to that of the

(59) K. C. Frisch, *J. Amer. Chem. Soc.*, **75**, 6050 (1953).

(60) R. Riemschneider and R. Nevin, *Monatsh. Chem.*, **91**, 829 (1960).

(61) (a) W. Huber, "Titrations in Nonaqueous Solvents," Academic Press, New York, N. Y., 1967, p 18; (b) *ibid.*, p 10.

(62) (a) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," 3rd ed Wiley, New York, N. Y., 1963, p 45; (b) *ibid.*, p 432.

Titrator 11. The Titrigraph was coupled by its flexible drive shaft to a 0.5-ml syringe which delivered the titrant into the stirred sample.

Relative basicity studies were conducted in a similar manner, using 10- to 11-ml samples of 0.003 *M* solutions of 17 and various amines in acetonitrile; the temperature was 23°. The acetonitrile was purified by treatment with sulfuric acid and benzene (to azeotrope any water), and then distillation through a column of packed helicies; the fraction of bp 82° was collected and used. Perchloric acid (0.1 *N*) in glacial acetic acid was prepared as described in the literature,[62b] and was used as the titrant. Titrations were made on the instrument described above. Titration curves and calculations were made in a similar manner, except that values obtained were substracted from 14 to give "pK_B" values.

Registry No.—**1**, 1278-02-0; **2**, 12119-11-8; **3**, 12427-83-7; **4**, 12427-86-0; **5**, 12427-84-8; **6**, 12427-87-1; **7**, 12427-73-5; **9**, 12427-74-6; **11**, 12427-80-4; **12**, 12427-89-3; **13**, 12427-77-9; **14**, 12427-81-5; **15**, 12427-88-2; **16**, 12427-75-7; **17**, 12427-76-8; **18**, 12427-82-6; **19**, 12427-85-9; **20**, 12427-78-0; **21**, 12427-79-1; **22**, 12427-72-4.

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The Bis Adducts of Dimethyl Acetylenedicarboxylate and Certain Furans

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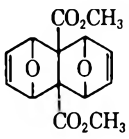
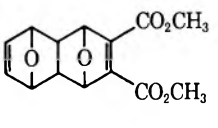
The structures of certain furan–dimethyl acetylenedicarboxylate bis-Diels–Alder adducts were determined by nmr spectroscopy. The reaction of furan with the acetylenic ester at room temperature led to the (exo–endo) bis adduct **4**, whereas 2,5-dimethylfuran did not form a bis adduct. At 100° furan reacted with the acetylenic ester to give (exo–exo) bis adduct **7**, (exo–endo) bis adduct **8**, and tris adduct **9**. Under similar conditions 2,5-dimethylfuran reacted with the acetylenic ester to give the (exo–endo) bis adduct **11**. The parent cyclic ether **17** of **11** was prepared and shown to have the (exo–endo) configuration. Selective hydrogenation of **11** led to dihydro adduct **22**. Acid treatment of **22** gave dimethyl 2,5-dimethylfuran-2,3-dicarboxylate and *p*-xylene while pyrolysis of **22** led to dimethyl 2,5-dimethylfuran-2,3-dicarboxylate, 2,5-dimethylfuran, and ethylene. The two (exo–endo) trimethyl bis adducts **19** and **21** were also prepared.

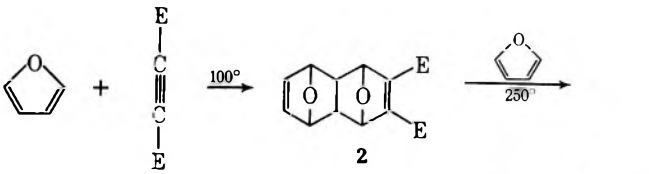
In 1931 Diels and Alder[2] isolated a furan–dimethyl acetylenedicarboxylate adduct with a mol ratio of 2:1. They suggested that adduct **1** was the product of this reaction; however they also noted that catalytic hydrogenation could be terminated after 1 equiv of hydrogen had reacted.



1



2



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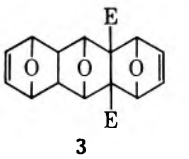


3

E = CO_2CH_3

Later Diels and Olsen characterized **1** by forming its dilactone.[3] This adduct was synthesized at relatively low temperature, whereas the previous adduct was prepared at elevated temperatures. This suggested that the first compound reported which was thought to be **1** may have been adduct **2**. In the same paper they reported the isolation of the tris adduct, **3**. Dimethyl acetylenedicarboxylate was allowed to react with excess furan for 17 hr at 100° and then allowed to react further at room temperature for 2 days. The isolation of **3** suggested that bis adduct **2** was formed at elevated temperatures, and then **2** reacted at room temperature to give **3**.

At the time these adducts were prepared it was difficult to make stereochemical assignments. Due to the development of nmr spectroscopy the configurations of these and other adducts could be investigated.

Results

When furan was allowed to react with acetylenic ester at room temperature (exo–endo) adduct **4** was formed along with approximately 6% of (exo–exo) adduct **5**.[4] The nmr spectrum of **4** revealed that the less symmetrical (exo–endo) adduct was the major product because the chemical shifts of the two pairs of vinyl hydrogens were different. They appeared as apparent triplets at δ 6.6 and 6.4.[5] The olefinic hydrogens of the symmet-

(1) (a) Taken from part of the Ph.D. Thesis of J. D. Slee, 1969. (b) To whom inquiries should be addressed.

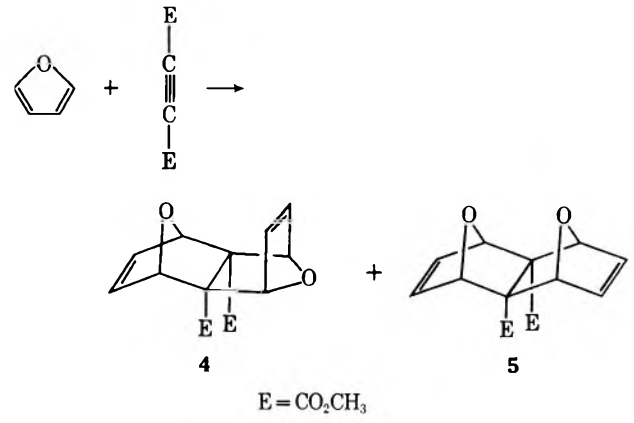
(2) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **490**, 143 (1931).

(3) O. Diels and S. Olsen, *J. Prakt. Chem.*, **156**, 284 (1940).

(4) J. Kallos and P. Deslongchamps, *Can. J. Chem.*, **44**, 1239 (1966).

(5) D. M. Grant and H. S. Gutowsky, *J. Chem. Phys.*, **34**, 699 (1961).

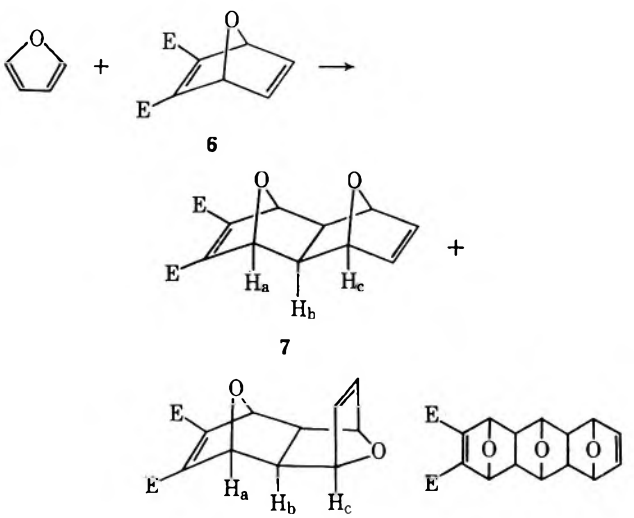
rical (exo–exo) and (endo–endo) structures, in contrast, would have identical chemical shifts.



4 5

E = CO_2CH_3

Reinvestigation of the reaction between excess furan and dimethyl acetylenedicarboxylate at 100° led to the isolation of three products.[2] Two bis adducts, **7** and **8**, along with tris adduct **9** were formed by addition to the less substituted double bond of the 1:1 furan–acetylenic ester adduct **6**. This is evident from the single, two proton resonance observed in the vinyl region of their nmr spectra.

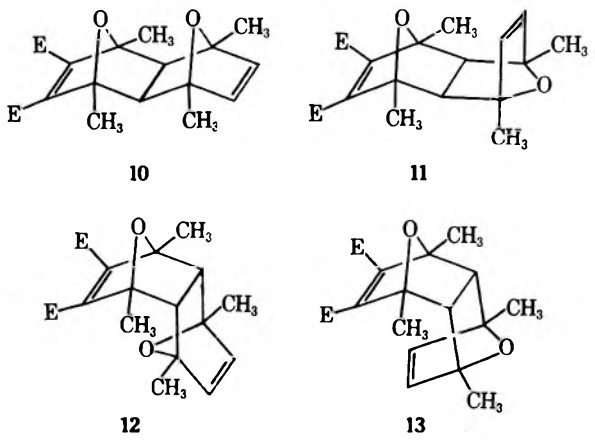


6 7 8 9

E = CO_2CH_3

The dihedral angles between H_a and H_b as well as between H_b and H_c of (exo–exo) adduct **7** are approximately 90° thus giving rise to coupling constants $J_{ab} \cong 0$ Hz and $J_{bc} \cong 0$ Hz.[6] The (exo–endo) adduct **8** has dihedral angles of approximately 90° between H_a and H_b, and 45° between H_b and H_c as indicated by the coupling constants $J_{ab} = 0$ Hz and $J_{bc} = 4.5$ Hz. The stereochemistry of the tris adduct was not determined.

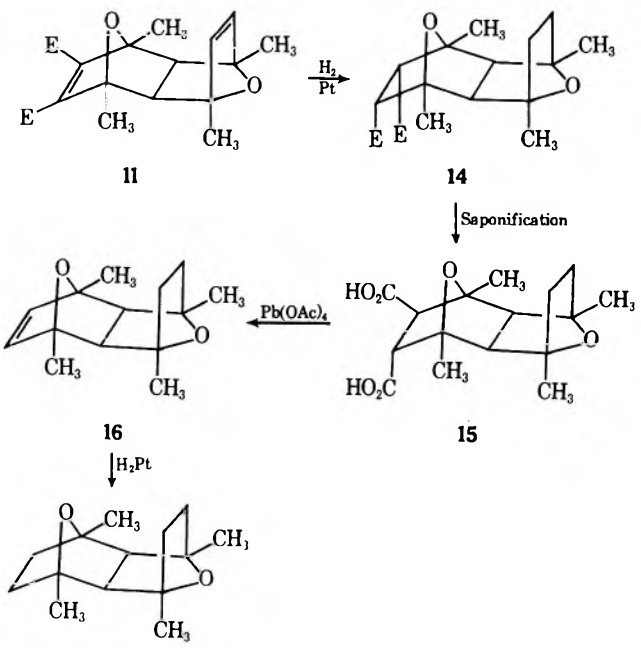
When excess 2,5-dimethylfuran was allowed to react with dimethyl acetylenedicarboxylate only a 1:1 adduct formed. Apparently steric hindrance prevents a second mole of furan from adding to the initially formed mono adduct.[7] However, the reaction of excess 2,5-dimethylfuran with the acetylenic ester at 100° gave rise to a single bis adduct. In this case addition of the second mole of 2,5-dimethylfuran occurred at the less substituted double bond. Four structural configurations are possible: (exo–exo) adduct **10**, (exo–endo) adduct **11**, (endo–exo) adduct **12**, and (endo–endo) adduct **13**.



10 11 12 13

E = CO_2CH_3

Evidence indicating that (exo–endo) bis adduct **11** is the most likely configuration was obtained by preparation of its parent compound. Catalytic hydrogenation of **11** gave *cis* diester **14**. Saponification led to *trans* diacid **15**, which in turn was bisdecarboxylated with lead tetraacetate[8] to olefin **16**. Hydrogenation of **16** produced the parent compound **17**.



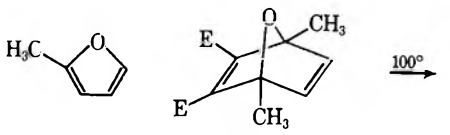
11 14 15 16 17

The nmr spectrum of **17** demonstrated that it possessed two nonequivalent pairs of methyl groups. Only (exo–endo) adduct **11** and (endo–exo) adduct **12** could give rise to **17**. Since endo addition to the initially formed 1:1 adduct is sterically unfavorable,[9] (exo–endo) adduct **11** is the proposed structure for the bis adduct.

Supporting evidence for the (exo–endo) configuration was obtained by synthesizing trimethyl bis adduct **19**. This adduct was prepared from monoadduct **18** and 2-methylfuran. The dihedral angle between H_a and H_b

(6) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(7) K. Alder and K. H. Backendort, *Justus Liebigs Ann. Chem.*, **535**, 101 (1938).
(8) J. Wolinsky and C. M. Dimarst, *J. Amer. Chem. Soc.*, **90**, 113 (1968).
(9) K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

was estimated to be 45° because J_{ab} = 5.2 Hz. As in the tetramethyl bis adduct endo addition is unlikely due to steric hindrance. For these reasons adduct **19** has been assigned the (exo–endo) configuration.



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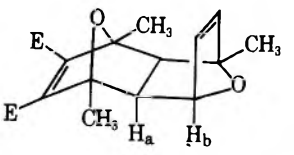
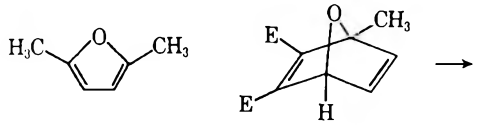
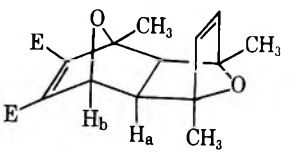


19

Synthesis of trimethyl bis adduct **21** from mono-adduct **20** and 2,5-dimethylfuran supports the postulate that exo addition to 7-oxabicyclo[2.2.1] systems are expected. Since $J_{ab} \cong 0$ Hz, the dihedral angle between H_a and H_b was estimated to be 90°. This result is consistent only with exo addition at the less substituted double bond of **21**. Adduct **21** most likely has the (exo–endo) configuration.



20



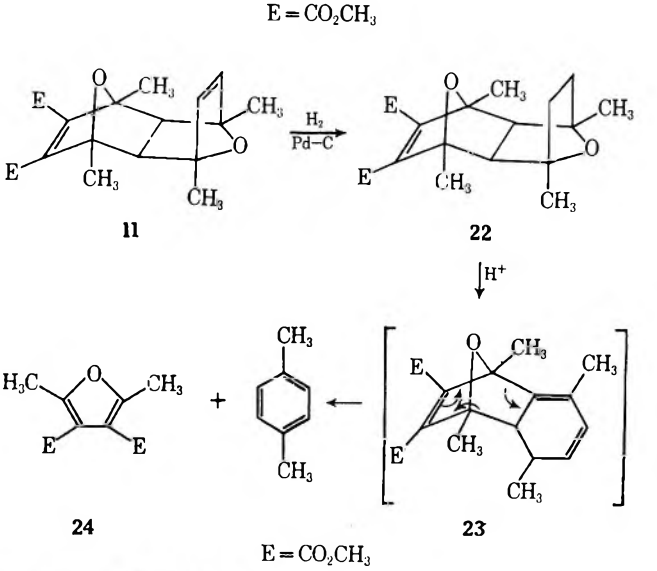
21

Taken together it is felt that the information presented concerning tetramethyl bis adduct **11**, trimethyl bis adduct **17**, and trimethyl bis adduct **21** is most consistent with the (exo–endo) configuration for this series of compounds.

Adduct **11** was selectively hydrogenated to its dihydro derivative **22**. Work of Alder and Rickert[10] suggested that treatment of this compound with a strong acid such as trifluoroacetic acid would give rise to a naphthalene derivative by an acid-catalyzed elimination of 2 equiv of water. Instead, dimethyl 2,5-dimethylfuran-2,3-dicarboxylate **24** and *p*-xylene formed. Elimination of 1 equiv of water probably led to intermediate **23** which readily underwent a retrograde Diels–Alder reaction. Since no trace of **23** was observed in the nmr spectra at any time during the course of the reaction, the retrograde step was probably very facile.

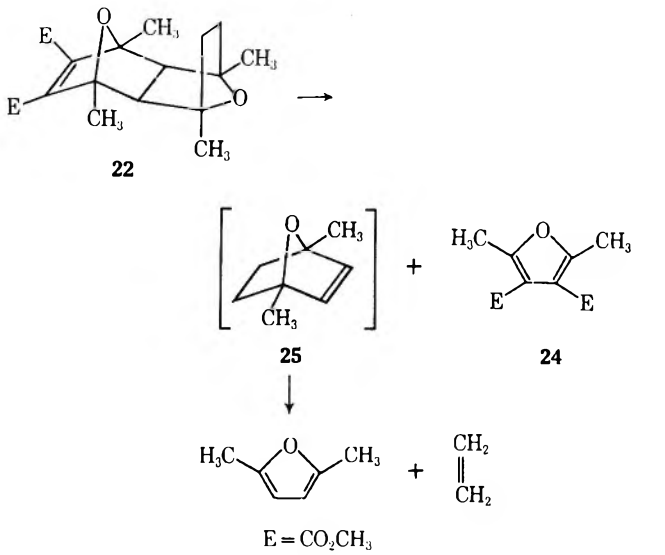
Pyrolysis of **22** produced dimethyl 2,5-dimethylfuran-2,3-dicarboxylate **24**, 2,5-dimethylfuran, and ethylene.[11] A retro-Diels–Alder reaction led to **24** and

(10) K. Alder and H. F. Rickert, *Chem. Ber.*, **70**, 1354 (1937).



11 **22** **24** **23**

to intermediate **25**. The latter compound underwent further degradation to 2,5-dimethylfuran and ethylene.



22 **25** **24**

Discussion

As in the earlier reports this series of reactions illustrates the temperature dependence of furan–dimethyl acetylenedicarboxylate bis adduct formation. At room temperature the kinetically controlled products were formed, whereas at elevated temperature products resulting from thermodynamic control were obtained. It is noteworthy that under kinetically controlled conditions the double bond substituted with carbomethoxy groups acted as a dienophile, whereas under thermodynamically controlled conditions equilibration led to addition at the less substituted double bond. This is not surprising since many furan Diels–Alder adducts are known to be thermally labile at relatively low temperatures.[12]

The formation of the (exo–endo) bis adduct **4** by the reaction of furan with dimethyl acetylenedicarboxylate at 25° is contrary to Alder's rule. The bulk of the methyl esters most likely caused this kinetically con-

(11) K. Alder and K. H. Backendorf, *Justus Liebigs Ann. Chem.*, **535**, 101 (1938).

(12) A. S. Onishchenko, "Diene Synthesis," Daniel Davey and Co., New York, N. Y., 1964, p 561.

trolled reaction to take a course which was not anticipated. In contrast, Kallos and Deslongchamps[4] demonstrated that acetylenedicarboxylic acid reacted at room temperature to give the expected (exo–exo) adduct.

In the cases of the tetramethyl and trimethyl adducts the products arise from thermodynamic control. Equilibration at the elevated temperatures led to the thermodynamically most stable products. Models reveal that the (exo–exo) and the (endo–endo) configurations have particularly severe 1,3-dimethyl nonbonding interactions. Since endo attack on the bicyclic systems are unlikely due to additional steric factors, the (exo–endo) adduct in which the nonbonding 1,3 dimethyl interactions were somewhat less was favored. The products resulting from thermodynamic control were, therefore, a result of stringent steric requirements.

Experimental Section

(Exo–Endo) Bis Adduct 4.—Furan, 14.5 g (0.21 mol), and dimethyl acetylenedicarboxylate, 14.2 g (0.1 mol), were placed in a screw-capped test tube and allowed to react at room temperature for 5 weeks. The entire reaction mixture crystallized. An nmr of the material indicated that it was primarily (90%) the (exo–endo) isomer **4**. The (exo–exo) isomer appeared to be present in approximately 6% (determined by the ratio of CO_2CH_3 resonances). Recrystallization (95% ethanol) gave adduct **4** as a white crystalline solid: mp 120–122°; ir ($CHCl_3$) 3000 (C–H), 2950 (C–H), 1735 (C=O), 1725 (C=O), 1430, and 1275 cm^{-1}; nmr ($CDCl_3$) δ 3.71 (s, 6, $-CO_2CH_3$), 4.50 (d, 2, J = 1 Hz, bridgehead), 5.13 (d, 2, J = 1 Hz, bridgehead), 6.49 (t, 2, J = 1 Hz, -CH=CH-, AA′ BB′ system), and 6.62 ppm (t, 2, J = 1 Hz, -CH=CH-, AA′ BB′ system).

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.08. Found: C, 60.24; H, 5.12.

(Exo–Exo) Bis Adduct 7, (Exo–Endo) Bis Adduct 8, and Tris Adduct 9.—In a 75-ml glass pressure tube fitted with a Teflon-lined pressure cap was placed 22.7 g (0.32 mol) of furan and 14.2 g (0.1 mol) of dimethyl acetylenedicarboxylate. The tube was heated to 100° for 18 hr. After cooling the reaction mixture was treated with 100 ml of chloroform. The insoluble materials were removed by filtration and the chloroform solution was concentrated. Column chromatography (silicic acid, chloroform) of the concentrate led to three products.

The first compound from the column was (exo–endo) bis adduct **8**: 7.5 g (35%); mp 120–122°; uv max (CH_3OH) 240 mμ (ϵ 4980); ir ($CHCl_3$) 2985 (C–H), 2945 (C–H), 1760 (C=O, 1720 (C=O), 1660 (C=C), and 1460 cm^{-1} (C=C); nmr ($CDCl_3$) δ 2.80 (d of d, 1, J = 3 and 1, J = 1.6 Hz, bridgehead protons between the dihydrofuran rings), 3.74 (s, 6, $-CO_2CH_3$), 4.70 (s, 2, bridgehead protons nearest the carbomethoxy groups), 4.78 (m, 2, bridgehead protons of the least substituted dihydrofuran ring), and 6.24 ppm (s, 2, -CH=CH-).

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.08. Found: C, 60.34; H, 5.06.

The second fraction contained 1.2 g (6%) of the white crystalline (exo–exo) bis adduct **7**: mp 157–159°; uv max (CH_3OH) 237 mμ (ϵ 4840); ir ($CHCl_3$) 3020 (C–H), 300 (C–H), 2950 (C–H), 1725 (C=O), 1630 (C=C), 1430 (C=C), and 1265 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (s, 2, bridgehead protons between the dihydrofuran rings), 3.77 (s, 6, $-CO_2CH_3$), 4.88 (s, 2, bridgehead protons of the least substituted dihydrofuran ring), 5.09 (s, 2, bridgehead protons nearest the carbomethoxy groups), and 6.40 (s, 2, -CH=CH-).

Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.08. Found: C, 60.34; H, 4.99.

The third fraction was eluted with a carbon tetrachloride–ethyl acetate (10:2) solution. Removal of the solvent gave 1.3 g (3.7%) of the white crystalline tris adduct **9**: mp 213–215°; uv max (CH_3OH) 239 mμ (ϵ 4310); ir ($CHCl_3$) 2990 (C–H), 2950 (C–H), 1740 (C=O), 1715 (C=O), 1640 (C=C), and 1440 cm^{-1}; nmr ($CDCl_3$) δ 2.65 (m, 4, bridgehead protons between rings), δ 3.80 (s, 6, $-CO_2CH_3$), 4.13 (m, 2, bridgehead protons on the least substituted dihydrofuran ring), 4.85 (m, 2, bridgehead protons on the tetrahydrofuran ring), 5.0 (s, 2, bridge head protons nearest the carbomethoxy groups), and 6.27 ppm (s, 2, -CH=CH-).

Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.19. Found: C, 62.22; H, 5.19.

(Exo–Endo) Bis Adduct 11.—A solution containing 11.1 g (0.078 mol) of adduct **18** and 25 g (0.26 mol) of 2,5-dimethylfuran was heated to 95° for 18 hr in a nitrogen atmosphere. Unreacted 2,5-dimethylfuran was removed by distillation at atmospheric pressure and adduct **18** was removed by vacuum distillation. The oily residue crystallized exothermically when treated with a small amount of pentane. Recrystallization from ether gave 2.6 g (10%) of the white crystalline adduct **11**: mp 107–108°; uv max (CH_3OH) 233 mμ (ϵ 4950); ir ($CHCl_3$) 2975 (C–H), 2950 (C–H), 1715 (C=O), and 1630 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.24 (s, 2, -CH=CH-), 3.76 (s, 6, $-CO_2CH_3$), 2.72 (s, 2, bridgehead), 1.54 (s, 6, $-CH_3$), and 1.48 ppm (s, 6, $-CH_3$).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.64; H, 6.63. Found: C, 64.75; H, 6.50.

Reduced Diester 14.—A suspension of platinum oxide (50 mg) in 10 ml of 95% ethanol was saturated with hydrogen. A solution of 173 mg (0.518 mmol) of adduct **11** in 15 ml of 95% ethanol was then added. Exhaustive hydrogenation at atmospheric pressure required 23.9 ml (1.06 mmol) of hydrogen at STP corresponding to the reduction of two double bonds (theoretical 1.04 mmol). The platinum was removed by filtration through a fiber glass filter. Removal of solvent followed by recrystallization (pentane) gave 0.160 g (92%) of the reduced adduct **14**: mp 154–156°; ir ($CHCl_3$) 2950 (C–H), and 1737 cm^{-1} (C=O); nmr (CF_3CO_2H) δ 3.82 (s, 6, $-CO_2CH_3$), 3.36 (s, 2, 2-$CHCO_2$–), 2.86 (s, 2, bridgehead), 2.4 (m, 2, 2-H of an A_2B_2 system), 1.72 (s, 7, 2-CH_3 plus 2-H of an, A_2B_2 system), and 1.58 ppm (s, 7, 2-H plus 1-H of an A_2B_2 system).

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.61; H, 7.69. Found: C, 63.89; H, 7.69.

Saponification of Diester 14.—Diester **14**, 7.3 g (0.021 mol), dissolved in a solution containing 40 ml of water, 20 ml of methanol, and 4 g of sodium hydroxide was heated to 80° for 12 hr. The cooled solution was extracted once with 40 ml of ether and then it was acidified with concentrated hydrochloric acid to a pH of 2. The aqueous layer was placed in a liquid–liquid extractor and extracted with ether for 8 hr. After drying ($MgSO_4$) and filtration, removal of the solvent gave 5.6 g (80%) of diacid **15** as a white powder: mp 255–257° dec; ir (KBr) 3150 (O–H), 2950 (C–H), 1715 (C=O) 1390, 1210, and 810 cm^{-1}; nmr (D_2O, Na_2CO_3; internal reference, sodium 2,2-dimethyl-2-silapentane-5-sulfonate) δ 2.91 (d, 1, J = 6.3 Hz, NaO C-CH-CH-CO Na, half of an AB quartet), 2.70 (d, 1, J = 6.3 Hz, NaO_2C-CH-CH-CO_2Na, half of an AB quartet), 2.20 (m, 4, bridgehead protons plus 2 protons from the AA′BB′ system of the tetrahydrofuran ring), δ 1.61 (s, 3, $-CH_3$), and 1.40 ppm (s, 11, 3, $-CH_3$, plus 2-H from the AA′BB′ tetrahydrofuran system).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.99; H, 7.15. Found: C, 61.67; H, 7.07.

Bisdecarboxylation of Diacid 15.—Into a 100-ml three-necked flask fitted with a mechanical stirrer, reflux condenser, and a gas inlet tube was placed 5.3 g (0.017 mol) of diacid **15** dissolved in 40 ml of dry pyridine. After saturation of the solution with oxygen, the gas inlet tube was removed and 11.4 g (0.256 mol) of lead tetraacetate (dried in a vacuum oven at 25°) was added directly to the solution. The flask containing the solution was then immersed in an oil bath preheated to 70°. After 5 min the stirred solution began to evolve carbon dioxide. As soon as the evolution of CO_2 ceased the reaction flask was cooled in an ice bath. The cooled solution was then treated with 50 ml of methylene chloride and extracted twice with 50 ml of 50% nitric acid (0°). The final traces of pyridine were removed by extraction with a 10% cadmium chloride solution followed by a final extraction with water. After drying the solution ($MgSO_4$), the methylene chloride was removed by careful distillation. The residue was treated with 15 ml of pentane and the insoluble material was removed by filtration. Removal of the pentane followed by sublimation (0.05 mm, 25°) of the oily residue gave 0.190 g (5.2%) of the white crystalline monoolefin **16**: mp 60–63°; ir ($CHCl_3$) 2970 (C–H), 2935 (C–H), 1460 (C=C), 1380, 1310, 1250, 1145, and 850 cm^{-1}; nmr (CCl_4) δ 2.17 (s, 1, 1-H of the A_2B_2 tetrahydrofuran system), 2.03 (s, 3, 2 bridgehead protons plus one proton from the A_2B_2 tetrahydrofuran system), 1.45 (s, 8, 2-CH_3, plus 2-H of the A_2B_2 tetrahydrofuran system), and 1.28 ppm (s, 2, $-CH_3$).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.43; H, 9.16. Found: C, 76.29; H, 9.26.

Reduction of Monoolefin 16.—A suspension of platinum oxide (20 mg) in 15 ml of methanol was saturated with hydrogen. A solution of 0.101 g (0.45 3 mmol) of alkene **16** in 15 ml of methanol was then added through a rubber septum. After the uptake of hydrogen had ceased, the methanol solution was filtered through a glass fiber filter and the methanol was removed. The reduced diether **17**, 0.090 g (90%), was purified by sublimation (0.05 mm, 25°): mp 54–55.5°; ir ($CHCl_3$) 2895 (C–H), 2885 (C–H), 2865 (C–H), 1460, 1380, 1140, 1080, and 850 cm^{-1}; nmr ($CDCl_3$) δ 2.24 (s, 1, 1 proton of an A_2B_2 tetrahydrofuran system), 2.09 (s, 3, 2 bridgehead protons plus 1-H from an A_2B_2 system), 1.51 (s, 5, $-CH_2CH_2-$ plus 1-H of an A_2B_2 system, 1.46 (s, 7, 2-CH_3 plus 1-H of an A_2B_2 system), and 1.42 ppm (s, 6, 2-CH_3).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.74; H, 9.99. Found: C, 75.66; H, 9.81.

Diels–Alder Adduct of Diester 18 and 2-Methylfuran.—A solution of 16.8 g (0.071 mol) of adduct **18** and 24.8 g (0.3 mol) of 2-methylfuran was refluxed in a nitrogen atmosphere for 24 hr. The excess 2-methylfuran was removed by distillation at atmospheric pressure and unreacted **18** was removed by vacuum distillation, bp 82–84° (0.3 mm).

Column chromatography (silicic acid, $CHCl_3$) gave 3 g (13%) of a light yellow oil which crystallized after standing several days. Recrystallization from pentane gave adduct **19** as a white crystalline solid: mp 90–92°; ir ($CHCl_3$) 2960 and 2940 (C–H), 1715 (C=O), 1360 (C=C), 1435, 1385, and 1310 cm^{-1}; nmr ($CDCl_3$) δ 6.42 (d, 1, J = 6.2 Hz, RCH-CHR′; each signal is split further into a doublet J = 1.8 Hz), 6.24 (d, 1, J = 6.2 Hz, RCH=CHR), 4.64 (d, 1, J = 5.2 Hz bridgehead on the dihydrofuran ring; each signal is split further into a doublet J = 3.8 Hz), 3.76 (s, 6, $-CO_2CH_3$), 3.08 (d, 1, J = 7.5 Hz bridgehead; each signal split further into a doublet J = 5.2 Hz), 2.54 (d, 1, J = 7.6 Hz, bridgehead), 1.57 (s, 3, $-CH_3$), 1.48 (s, 3, $-CH_3$), and 1.46 ppm (s, 3, $-CH_3$).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.29. Found: C, 63.87; H, 6.26.

Diels–Alder Adduct of Diester 20 and 2,5-Dimethylfuran.—A solution containing 10.5 g (0.047 mol) of adduct **20**, 9.0 g (0.094 mol) of 2,5-dimethylfuran, and 20 ml of toluene was heated to 96° for 18 hr in a nitrogen atmosphere. The toluene and unreacted 2,5-dimethylfuran were removed by distillation at atmospheric pressure and unreacted diester **20** was removed by vacuum distillation. Column chromatography (silicic acid, $CHCl_3$) of the residue gave a yellow oil which crystallized only after standing several days. Recrystallization (ether) gave 2 g, 13%, of adduct **21** as a white crystalline solid: mp 87–89°; ir ($CHCl_3$) 2580 and 2550 (C–H), 1715 (C=O), 1630 (C=C), 1430, and 1380 cm^{-1}; nmr ($CDCl_3$) δ 6.27 (d, 1, J = 6 Hz, R–CH=CH–R′), 6.18 (d, 1, J = 6 Hz R–CH=CH–R′), 4.58 (s, 1, bridgehead on furan ring) 3.81 (s, 3, $-CO_2CH_3$), 3.77 (s, 3, $-CO_2CH_3$), 2.65 (s, 2, bridgehead), 1.54 (s, 6, $-CH_3$), and 1.46 ppm (s, 3, $-CH_3$).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.29. Found: C, 63.78; H, 6.24.

Selective Reduction of Adduct 11.—A suspension of 10 mg of 10% palladium on powdered charcoal in 10 ml of methanol was saturated with hydrogen and adduct **11**, 0.973 g (2.41 mmol), dissolved in 15 ml of methanol was then introduced. The reduction was stopped after 1 mol (2.93 mmol) of hydrogen had been consumed. Filtration of the reaction mixture through a glass fiber filter followed by removal of the solvent and recrystallization (hexane) gave 0.830 g (86%) of compound **22**: mp 93–95°; ir ($CHCl_3$) 2960 and 2945 (C–H), 1710 (C=O), and 1635 cm^{-1}; nmr ($CDCl_3$) 3.80 (s, 6, $-COOCH_3$), 2.49 (s, 2, bridgehead) 2.21 (d, 2, J = 7.2 Hz, A_2B_2 system of furan ring), 1.65 (s, 8, 2-CH_3 plus 2 protons of an A_2B_2 system), and 1.43 ppm (s, 6, $-CH_3$).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.29; H, 7.14. Found: C, 64.44; H, 7.11.

Acid-Catalyzed Degradation of Monoolefin 22.—A solution containing 100 mg (0.30 mmol) of **22**, two drops of trifluoroacetic anhydride and 0.3 ml of trifluoroacetic acid was placed in an nmr tube at room temperature. An nmr taken immediately after mixing was consistent with the starting material: nmr (CF_3CO_2H) δ 3.95 (s, 6, CO_2CH_3), 2.79 (s, 2, bridgehead), 2.32 (d, 1, J = 5 Hz, part of an A_2B_2 system of the tetrahydrofuran ring), 1.83 (s, 8, $-CH_3$ plus 2 protons of an A_2B_2 system), and 1.62 ppm (s, 6, $-CH_3$).

After 12 hr the solution had turned black and the nmr spectrum had changed to (CF_3CO_2H) δ 7.03 (s, 4, aromatic), 4.26 (s, 6, $-CO_2CH_3$), 2.65 (s, 6, $-CH_3$), and 2.24 ppm (s, 6, $-CH_3$).

Pyrolysis of Monoolefin 22. Procedure A.—In a 4-ml side-arm distilling flask was placed 0.800 g (3.39 mmol) of monoolefin **22**. The compound was heated to 280° (sand bath) for 4 hr in a nitrogen atmosphere. 2,5-Dimethylfuran (110 mg, 36%) slowly distilled from the reaction mixture (ir was identical with that of a known sample). No attempt was made to trap the ethylene evolved during the pyrolysis.

When the sand bath temperature was increased to 350°, 244 mg (34%) of dimethyl 2,5-dimethylfuran-2,3-dicarboxylate (**24**) distilled from the reaction mixture: mp 58–61° (lit.[56] mp 58–61°); ir ($CHCl_3$) 3000 (C–H), 1750 (C=O), 1693 (C=C), 1445, 1320, and 1090 cm^{-1}; nmr ($CDCl_3$) δ 3.85 (s, 6, $-COOCH_3$) and 2.40 ppm (s, 6, $-CH_3$).

Procedure B.—A Pyrex tube, 1.5 cm in diameter, packed to a height of 22 cm with granular silicon carbide (10 mesh) was preheated in a vertical tube furnace to 380°. The tube was fitted with an addition funnel and a receiver consisting of a 100-ml three-necked flask fitted with a Dry Ice condenser. The collection flask was cooled in a Dry Ice–acetone bath. A slow stream of nitrogen was used as the carrier gas.

A solution of 0.952 g (2.85 mmol) of monoalkene **22** in 25 ml of benzene was slowly passed through the heated column. Removal of solvent (rotoevaporator) from the material collected in the receiver gave 450 mg (75%), of dimethyl 2,5-dimethylfuran-dicarboxylate, mp 58–61° (lit.[13] 58–61°).

Registry No.—**4**, 25860-27-9; **7**, 25860-28-0; **8**, 25860-29-1; **9**, 25860-30-4; **11**, 25860-31-5; **14**, 25860-32-6; **15**, 25860-33-7; **16**, 25860-34-8; **17**, 25860-35-9; **19**, 25860-36-0; **21**, 25860-37-1; **22**, 25860-38-2.

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(13) S. Kawai and S. Tanaka, *Bull. Chem. Soc. Jap.*, **33**, 674 (1960).

Synthesis and Pyrolysis of the Diels–Alder Adduct of Ditropyl and Dimethyl Acetylenedicarboxylate

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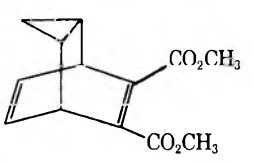
Dimethyl acetylenedicarboxylate (1) and ditropyl (3) react in a 2:1 mol ratio at 140° to produce a 24–42% yield of the Diels–Alder adduct 4. Adduct 4 was shown to possess two three-membered rings *formally* derivable from a bisnorcaradiene structure. Thermal decomposition of 4 proceeds in two stages, each of which produces dimethyl phthalate. Of the possible low-molecular-weight products only benzene was *tentatively* identified.

Cyclic conjugated trienes, when reacted with dieneophiles, generally produce Diels–Alder adducts in which considerable bond reorganization has taken place.[2] Thus the reaction of cycloheptatriene with dimethyl acetylenedicarboxylate (1) yields *mainly* dimethyl tricyclo[3.2.2.0^{2,4}]nona-6,8-diene-6,7-dicarboxylate[3,4] (2). Tetracyanoethylene produces an anal-



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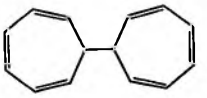


3

ogous product.[5,6] It is therefore of interest to establish the structure of the Diels–Alder adducts of ditropyl (biscycloheptatrienyl) (3)[7a] with one or more dieneophiles, with particular emphasis on the question whether bond reorganization remains intraannular or involves the interaction of one ring with the other.[7b]

Experimental Section[8]

Dimethyl Acetylenedicarboxylate (1).—1, Eastman Organic Chemicals (Cat. No. 7235), was distilled and the fraction collected at 66–73° (6–7 mm), possessing n^{20}D 1.4466, was used.

Ditropyl (7,7′-biscycloheptatriene) (3) was prepared in quantity according to the method of Harrison, *et al.*,[7a] from tropylium fluoroborate[9] and zinc dust. The material thus obtained proved quite unstable during short periods of storage in the dark. However, after chromatography on Merck Alumina (No. 71707) using pentane as eluent, a white solid, mp 60.0–61.5° (lit.[7a] 61.0°), was obtained which remained unchanged after several years.

Adduct 4.—A mixture of compound 3 (5.0 g, 27 mmol), ester 1 (9.7 g, 68 mmol), and redistilled xylene (10 ml) was refluxed under nitrogen for 5 hr. Evaporation at 1–5 mm and room temperature overnight produced a red, viscous gel which on trituration with methanol yielded an off-white solid. Recrystallization from methanol furnished 3.0 g (24%)[10] of white crystals, mp 173.2–175.8°. Further recrystallization from the same solvent gave small, white, fluffy needles: mp 175.2–176.3°; uv (EtOH) end absorption with a shoulder at 241–242 mμ (log ε 3.78); ir (CCl_4) 3060, 3030, 2993, 2950, 2900, 2840 (C–H), 1720 (conjugated ester C=O, broad, intense, and complex), 1632, 1596 (C=C), 1432, 1342 ($COOCH_3$), 1260, 1057 cm^{-1} (C–O); nmr data are summarized in Table I.

TABLE I

60-MHz NMR DATA OF 4[a]

Chemical shift (τ)	Relative area	Signal appearance	Assignment
9.08	1	Unresolved multiplet (5.0)[b]	H-3; H-3′
8.77	2	Unresolved multiplet (5.8)[c]	H-2, 4; H-2′,4′
6.23	6	Singlet	$-OCH_3$
5.95	2	Unresolved multiplet (10)[d]	H-1,5; H-1′,5′
4.00	2	"Triplet"[e]	H-8,9; H-8′,9′

[a] Data were obtained with a $CDCl_3$ solution containing internal TMS. No simplification of the spectrum was apparent at 100 MHz. A spectrum obtained at 100 MHz using a C_6H_6 solution of compound 4 exhibited only the expected upfield shift (0.1–0.3 ppm) of all signals with no attendant simplification of the spectrum. CCl_4 and C_5H_5N also failed to resolve the resonances. The numbers in parentheses refer to peak widths at half-height in Hz. [b] Irradiation of this signal produces no change in the other signals except the τ 8.77 resonance which then resembles the τ 5.95 signal. [c] Irradiation of this signal causes the τ 9.08 resonance to sharpen and the τ 5.95 resonance to mirror the τ 4.00 signal (AA′XX′). [d] Irradiation of this signal causes the τ 9.08 and 8.77 resonances to sharpen and the τ 4.00 signal to collapse to a singlet. [e] Irradiation of this signal causes the τ 5.95 resonance to approximately mirror the τ 8.77 signal.

Anal. Calcd for $C_{26}H_{36}O_8$ (assuming 2 mol of 1 per mol of 3): C, 67.0; H, 5.6; O, 27.4; mol wt, 466.5. Found: C, 67.0; H, 5.7; mol wt, 442 (cryoscopic camphor solvent).

Hydrogenation of the Adduct.—An ethyl acetate solution of the adduct 4 (0.844 g, 1.8 mmol), stirred at room temperature in contact with 5% Pd–C catalyst (0.235 g) absorbed 97% of the theoretical quantity of hydrogen (assuming four double bonds per molecule) in 1.5 hr. Chromatography on Alumina (Woelm, neutral, activity grade I, chloroform eluent) and recrystallization from ethyl acetate produced glistening white crystals of the octahydro adduct 5, mp 224–225°. The nmr data are given in Table II.

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.8; H, 7.2; O, 27.0; mol wt, 474.5. Found: C, 65.8; H, 7.5; mol wt, 459 (cryoscopic camphor solvent).

(1) (a) Partial support of this work from the North Carolina State University Engineering Foundation and Faculty Research and Professional Development Fund is acknowledged with pleasure. (b) Author to whom correspondence should be addressed. (c) Partial support by a grant from the Gulf Research and Development Co. is gratefully acknowledged.

(2) A. S. Onishchenko, "Diene Synthesis," L. Mandel, Translator, Daniel Davey and Co., New York, N. Y., 1964, pp 373–383.

(3) (a) K. Alder and G. Jacobs, *Chem. Ber.*, **86**, 1528 (1953); (b) M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Lett.*, 4413 (1965); (c) M. J. Goldstein and A. H. Gevirtz, *ibid.*, 4417 (1965).

(4) Systematic nomenclature graciously supplied by Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, Columbus, Ohio.

(5) N. W. Jordan and I. W. Elliott, *J. Org. Chem.*, **27**, 1445 (1962).

(6) G. H. Wahl, Jr., *ibid.*, **33**, 2158 (1968).

(7) (a) A. G. Harrison, L. R. Honnen, and H. J. Dauben, Jr., *J. Amer. Chem. Soc.*, **82**, 5598 (1960). (b) *E.g.*, R. S. Givens, *Tetrahedron Lett.*, 663 (1969). In a study of the photochemistry of 3, no product directly attributable to interannular reaction was isolated.

(8) All melting points are corrected. Ultraviolet spectra were obtained using a Beckmann DK-2 spectrophotometer. Infrared spectra were determined using a Perkin-Elmer 521 spectrophotometer. Elemental analyses were performed by Schwarzkopf Laboratories, Woodside, N. Y. Thermal analyses were obtained using DuPont 900 DTA and 950 TGA instruments. Nmr spectra were recorded with both Varian T-60 and HA-100 spectrometers.

(9) K. Conrow, *Org. Syn.*, **43**, 101 (1963).

(10) A yield of 42% was obtained by heating 0.5 g of compound 3 and 1.2 g of compound 1 at 140° for 2 hr under N_2 without solvent. *However, a similar reaction of 5.0 g of 3 and 12 g of 1 produced a violent explosion!*

TABLE II

100-MHz NMR DATA OF 5[a]

Chemical shift (τ)	Relative area	Signal appearance	Assignment
9.49	1	Unresolved multiplet (4.5)	H-3; H-3′
8.88	2	Unresolved multiplet (7.0)	H-2,4; H-2′,4′
8.78, 8.74	4	Two overlapping unresolved multiplets	H-$8_{ex,en}$,$9_{ex,en}$; H-$8'_{ex,en}$,$9'_{ex,en}$
7.72	2	Broad multiplet (9.5)	H-1,5; H-1′,5′
7.18	2	Singlet (3.5)	H-6,7; H-6′,7′
6.39	6	Singlet (3.5)	$-OCH_3$

[a] Data were obtained with a $CDCl_3$ solution containing internal TMS. The numbers in parentheses refer to peak width at half-height in Hz.

Saponification of the Adduct.—The adduct **4** (0.5 g) was refluxed for 5 hr with 25 ml of 20% aqueous KOH. Cooling, acidification with concentrated HCl, and stirring for 2 days produced a white solid which, after two recrystallizations from aqueous methanol furnished off-white crystals which do not melt, but turn brown and slowly decompose on heating above 100°.

Anal. Calcd for $C_{22}H_{18}O_8$: C, 64.4; H, 4.4; O, 31.2; neut equiv, 102.5. Found: C, 64.1; H, 4.3; neut equiv, 105.

Thermal Analysis of the Adduct 4.—A differential thermal analysis scan (10°/min, N_2 atmosphere) showed a sharp endotherm at the melting point and a broad exotherm beginning at 225° and peaking at about 265°. A shallow endotherm, peaking at about 290° was also noted.

A thermogravimetric scan (12.0 mg, 15°/min, N_2 atmosphere) indicated no weight loss until about 220°. These results are summarized in Table III.

TABLE III

THERMOGRAVIMETRIC ANALYSIS OF THE ADDUCT 4

Temperature °C	% wt loss
200	0
225	1.0
250	8.5
275	41.0
300	51.0
325	54.0
375	58.0
400	60.5
425	64.0
450	69.0
500	75.0

Decomposition of the Adduct 4. A. Under Nitrogen.—A flask containing 1.0 g of compound **4** which was connected to a trap at −78° was flushed with N_2 several times. It was then heated under an atmosphere of N_2 at 235–255° for 1 hr to produce a dark red, amorphous solid wet with a sweet-smelling liquid. Vacuum distillation followed by vpc and ir analyses clearly showed the volatile fraction to be predominantly (>90%) dimethyl phthalate (**6**). Approximately nine other minor products were detected by vpc. One of these products (~0.5%) is benzene as shown by vpc peak height enhancement experiments.

The solid product [ir (KBr) 1720, 1200 cm^{-1} (conjugated ester)] decomposes at about 280° without melting.

Anal. Calcd for $C_{16}H_{16}O_4$ (loss of 1 mol of **6** from **4**): C, 70.6; H, 5.9; O, 23.5. Found: C, 70.9; H, 6.2.

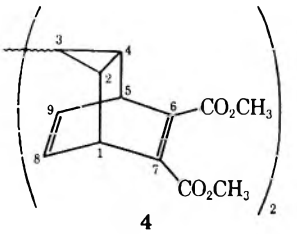
The 280° volatile decomposition product was also identified by ir and vpc as dimethyl phthalate (**6**). The nonvolatile product was a brittle, dark amorphous solid which was not further characterized.

B. In the Presence of Hydroquinone.—An experiment which differed from A only by the inclusion of 0.026 g of hydroquinone and by heating under vacuum gave essentially identical results.

C. Under High Vacuum.—An experiment similar to A, in which a vacuum of 10^{-4}–10^{-5} Torr was employed and in which the evacuated flask was immersed in a preheated oil bath at 240° for 1 hr produced a purer but lower yield of compound **6** and considerable sublimation of compound **4** into the tube connecting the flask to the receiver.

Discussion

Structure of the Adduct 4.—The elemental analysis and molecular weight data clearly indicate a 2:1 acetylenedicarboxylate–ditropyl addition product. The infrared absorption of the product and its saponification to a tetraacid further show that the ester grouping remains intact during the reaction. Finally, hydrogenation indicates the presence of only four double bonds per molecule. A centrosymmetric (C_{2h}) structure[11] of adduct **4** which is in accord with these results is given below.



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The nmr data (Table I) strongly confirm this assignment. Thus the presence of *only* five different types of hydrogens is evident. Furthermore, the low field, apparent triplet at τ 4.00 is strongly suggestive of a vinyl group in a symmetric bicyclic skelton. Its immediate environment is further established by the collapse of the signal to a singlet on irradiation of the τ 5.95 resonance. That this latter resonance is associated with bridgehead hydrogens is proven by its shape and location and by the decoupling experiments. The sharp resonance at τ 6.23 with relative area 6 is confidently assigned to the methyl hydrogens of the ester groups.

The two high-field resonances are completely consistent with a symmetrically substituted, cyclopropyl grouping. The lack of fine structure in these signals (in a variety of solvents) precluded a completely secure assignment of the relative configuration of H-3 with respect to H-2 and 4 (*i.e.*, cis or trans). However, the relatively small peak widths observed (5.0–5.8 Hz) argue strongly for a small (2–4 Hz) coupling constant ($^3J_{2,3}$). Thus the cyclopropyl hydrogens are most probably trans rather than cis since $^3J_{cis} > {}^3J_{trans}$.[12]

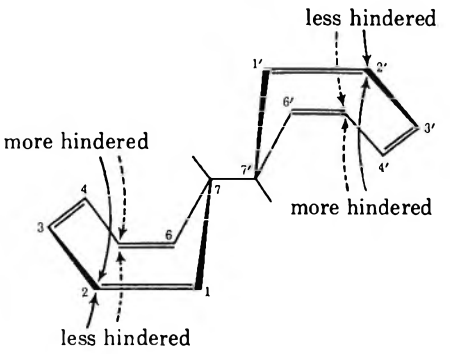
The sole remaining structural ambiguity concerns the orientation of the three-membered ring, *i.e.*, whether it is located over the substituted or over the unsubstituted double bond. Based on the steric control of approach argument which was originally proposed by Alder and Jacobs[3a] and confirmed by Goldstein and Gevirtz[3c] for the cycloheptatriene system, the most likely arrangement is as shown in **4**. Since **5** is very probably the most stable conformation of ditropyl (**3**),[13] approach of dieneophile **1** at carbons 2 and 5 (and at 2′ and 5′) to produce the adduct **4** will be substantially less hindered from the bottom of the "boat" than

(11) Systematic name:[4] Tetramethyl[3,3′-bitricyclo[3.2.2.$0^{2,4}$]nona-6,8-diene]-6,6′,7,7′-tetracarboxylate.

(12) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol 2, Pergamon Press, New York, N. Y., 1966. pp 692–695, and references cited therein.

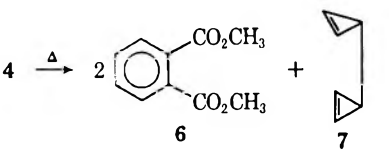
(13) Conformation **5** is used without comment in G. Vincow, H. J. Dauben, Jr., F. R. Hunter, and W. V. Volland, *J. Amer. Chem. Soc.*, **91**, 2823 (1969). Pertinent arguments concerning the conformations of seven-substituted cycloheptatrienes are given by R. W. Murray and M. L. Kaplan, *ibid.*, **88**, 3527 (1966), and by A. P. Ter Borg and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **82**, 741 (1963).

from the top (see **5**). It is encouraging to note that this mode of attack also predicts a trans orientation of the two types of cyclopropyl hydrogens.



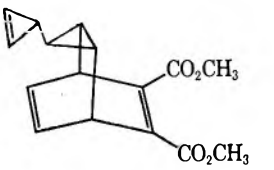
5

Pyrolysis of the Adduct 4.—Cope has demonstrated that cyclobutene may be produced by pyrolysis of the Diels–Alder adduct of 1,3,5-cyclooctatriene and compound **1**,[14] and Wiberg[15] has shown that the similar decomposition of compound **2** results in detectable quantities of cyclopropene. Consequently, we felt that pyrolysis of **4** might yield one or more isomers of C_6H_6. The *concerted* loss of two molecules of dimethyl phthalate from adduct **4** would produce 3,3′-biscyclopropene which *might* be transformed further into other C_6H_6 isomers by various intramolecular rearrangements.[16]



6 **7**

However, the thermal analysis data are not consistent with such a *concerted* decomposition. Apparently the loss of one molecule of ester **6** produces the reactive cyclopropene derivative **8** which polymerizes before a



8

second molecule of **6** is lost. This interpretation, which is consistent with the reactivity of cyclopropene observed by Wiberg and Bartley,[15] is supported by the analytical and spectral data for the nonvolatile pyrolysis product and, also, by the further production of ester **6** on pyrolysis of the polymer at a higher temperature.

Registry No.—**4**, 25967-00-4; **5**, 25967-01-5; **8**, 25967-02-6.

Acknowledgment.—We are grateful to Mr. Russell J. Miller for initial nmr measurements.

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Stable Carbonium Ions. CV.[1] Protonation of Sulfoxides and Sulfones in Fluorosulfuric Acid–Antimony Pentafluoride–Sulfuryl Chloride Fluoride Solution

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A series of sulfoxides and sulfones have been studied in HSO_3F–SbF_5 solution diluted with sulfuryl chloride fluoride. Protonation on sulfur was observed for sulfoxides by nmr spectroscopy. The site of protonation of sulfones is on oxygen. Protonated sulfoxides and sulfones in FSO_3H–SbF_5–SO_2ClF solution are stable up to 65° except protonated benzyl *tert*-butyl sulfone which cleaved to *tert*-butyl cation and phenylmethanesulfinic acid even at a temperature as low as −78°.

The interaction of sulfones and sulfoxides with Lewis acids has been studied by a number of investigations.[3–7] In some cases solid adducts could be obtained.[3,7] Cryoscopic studies of sulfoxides and sulfones in sulfuric acid solution have also been carried out.[8–11] Gillespie[8,10] showed that aryl sulfoxides are strong bases and aryl sulfones are weak bases in sulfuric acid. However, both cryoscopic and conductimetric measurements of Hall and Robinson[11] showed that diphenyl sulfone was a nonelectrolyte in sulfuric acid. These results do not agree with those of Gillespie.[8,10] Alkyl sulfones were found to behave as weak electrolytes in sulfuric acid.[11,12] It was also indicated that dimethyl sulfoxide has a cryoscopic *i* factor of slightly greater than two,[11] in agreement with complete protonation according to eq 1.

$$(CH_3)_2S{=}O + H_2SO_4 = (CH_3)_2\overset{+}{S}OH + HSO_4^- \qquad (1)$$

* To whom correspondence should be addressed.
(1) Part CIV: G. A. Olah and P. J. Szilagyi, *J. Org. Chem.*, in press.
(2) National Institutes of Health Predoctoral Research Investigator, 1970.
(3) T. Lindquist and P. Einarsson, *Acta Chem. Scand.*, **13**, 420 (1959).
(4) F. A. Cotton and R. Francis, *J. Amer. Chem. Soc.*, **82**, 2986 (1960).
(5) R. G. Laughlin, *J. Org. Chem.*, **25**, 864 (1960).
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(11) S. K. Hall and E. A. Robinson, *Can. J. Chem.*, **42**, 1113 (1964).
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TABLE I

PMR SPECTRAL PARAMETERS[a] OF PARENT AND PROTONATED SULFOXIDES

Compd	Registry no.	Temp, °C	Solvent	SH	α-CH_2	β-CH_2	γ-CH_2	CH_3	Aromatic H
$(CH_3)_2S{=}O$	67-68-5	−40	SO_2ClF					2.66	
$(CH_3)_2\overset{+}{S}(H){=}O$	26428-06-8	−80	FSO_3H–SbF_5 SO_2ClF	6.83				3.60	
$(CH_3CH_2)_2S{=}O$	70-29-1	−60	SO_2ClF		2.97 (q, 7.5)			1.47 (t, 7.5)	
$(CH_3CH_2)_2\overset{+}{S}(H){=}O$	26428-02-4	−80	FSO_3H–SbF_5 SO_2ClF	6.51	3.43 (q, 7.8)			1.53 (t, 7.8)	
$(CH_3CH_2CH_2)_2S{=}O$	4253-91-2	−60	SO_2ClF		2.61 (t, 7.0)	1.40 (m)		0.80 (t, 7.0)	
$(CH_3CH_2CH_2)_3\overset{+}{S}(H){=}O$	26428-07-9	−80	FSO_3H–SbF_5 SO_2ClF	6.49	3.30 (t, 7.0)	1.96 (m)		1.11 (t, 6.0)	
$(CH_3CH_2CH_2CH_2)_2S{=}O$	2168-93-6	−20	SO_2ClF		2.85 (t, 7.5)	1.80 (m)	1.80 (m)	1.11 (t, 6.5)	
$(CH_3CH_2CH_2CH_2)_2\overset{+}{S}(H){=}O$	26428-08-0	−80	FSO_3H–SbF_5 SO_2ClF	6.53	3.73 (m)	2.13 (m)	2.13 (m)	1.46 (t, 6.5)	
$(C_6H_5)_2S{=}O$	945-51-7	−60	SO_2ClF						7.53
$(C_6H_5)_2\overset{+}{S}(H){=}O$	26428-09-1	−80	HF–SbF_5 SO_2ClF	5.03					8.40–9.03

[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are given in parentheses following the multiplicities: t = triplet; m = multiplet; q = quartet.

Szmant and Brost[9] postulated that diphenyl sulfoxide ionizes in 100% sulfuric acid according to eq 2. Their

$$C_6H_5{-}\underset{\underset{O}{\downarrow}}{\ddot{S}}{-}C_6H_5 + 3H_2SO_4 = C_6H_5{-}\underset{\underset{\mathbf{1}}{\ddot{}}}{\overset{2+}{S}}{-}C_6H_5 + H_3O^+ + 3HSO_4^- \quad (2)$$

argument was based on their observations that the cryoscopic i factor was nearly five and that the original sulfoxide was recovered when the resulting green solution was diluted by water according to eq 3.

$$\mathbf{1} + 3H_2O = C_6H_5{-}\underset{\underset{O}{\downarrow}}{\ddot{S}}{-}C_6H_5 + 2H_3O^+ \quad (3)$$

To test the hypothesis of Szmant that the double positively charged ion **1** exists in sulfuric acid solution, Oae[13] and coworkers dissolved diphenyl sulfoxide in 97% sulfuric acid and diluted the solution with an excess of ^{18}O-enriched water. The original sulfoxide was recovered almost quantitatively but the recovered sulfoxide was found to have no incorporation of excess ^{18}O, contrary to what one would expect on the basis of Szmant's hypothesis. They extended the cryoscopic study on diphenyl sulfoxide, dimethyl sulfoxide, phenyl methyl sulfoxide, and other similar sulfoxides with 99.5–100% sulfuric acid, and found an i factor close to two. They concluded that all the compounds measured ionize according to eq 4.

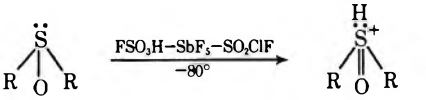
$$R{-}\underset{\underset{O}{|}}{\ddot{S}}{-}R' + H_2SO_4 = R{-}\underset{\underset{OH}{|}}{\overset{+}{S}}{-}R' + HSO_4^- \quad (4)$$

(i = 2.0)

Nuclear magnetic resonance spectroscopy in highly acidic solvent systems (superacids) offers a good possibility of directly observing protonated heteroorganic compounds. No such studies relating to protonation of sulfoxides and sulfones were so far reported in the literature.

Results and Discussion

Sulfoxides.—In the superacid system, FSO_3H–SbF_5 ("magic acid") diluted with SO_2ClF, all the sulfoxides studied were completely protonated. The pmr spectra of protonated sulfoxides in FSO_3H–SbF_5–SO_2ClF solution, recorded at −80°, showed a singlet in the S–H region at δ 5.03–7.10 indicating that sulfoxides are protonated on the sulfur atom (eq 5). These S–H



(5)

chemical shifts are in the region observed for that of protonated thiols and sulfides[14] studied previously.

The following sulfoxides were studied: methyl, ethyl, *n*-propyl, *n*-butyl, and phenyl sulfoxide. The chemical shifts and coupling constants of the parent and the protonated sulfoxides studied are summarized in Table I. The proton on the sulfur atom of protonated sulfoxides could be observed only at temperatures below −80°. At higher temperature proton exchange occurred. At −80° all the resonances are broad and

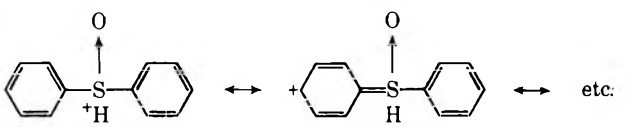
(13) S. Oae, T. Kitao, and Y. Kitaoka, *Chem. Ind. (London)*, 291 (1961).
(14) G. A. Olah, D. H. O'Brien, and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, **89**, 2996 (1967).

the coupling constants were generally evaluated from spectra recorded at −20°.

The pmr spectrum of protonated **dimethyl sulfoxide** in FSO_3H–SbF_5–SO_2ClF solution, recorded at −80°, showed the proton on sulfur as a singlet at δ 6.83 and the methyl singlet at δ 3.60 which shifted about 1 ppm downfield from that of the parent compound. This S–H resonance, although broad, showed no coupling between the methyl protons. In order to see if dimethyl sulfoxide could be recovered from the protonated species, a quenching of protonated dimethyl sulfoxide in methanol and sodium carbonate was carried out. Indeed, dimethyl sulfoxide was recovered in good yield (>85%).

Protonated **diethyl sulfoxide** in FSO_3H–SbF_5–SO_2ClF at −80° showed the proton on the sulfur atom at δ 6.50 and the ethyl triplet and quartet at δ 1.90 and 3.75. **Di-*n*-propyl** and **di-*n*-butyl sulfoxide** were also protonated on the sulfur atom.

In the case of **diphenyl sulfoxide** in FSO_3–SbF_5–SO_2ClF solution, sulfonation occurred in addition to protonation. However, diphenyl sulfoxide could be protonated in HF–SbF_5 solution diluted with SO_2ClF without sulfonation. The nmr spectrum of protonated diphenyl sulfoxide in HF–SbF_5–SO_2ClF solution showed the S–H proton at δ 5.03 and the phenyl protons at δ 8.40–9.03, substantially deshielded (about 1.2 ppm) from the parent compound (see Table I). Furthermore, the S–H proton of protonated diphenyl sulfoxide is considerably more shielded than those of protonated alkyl sulfoxides. We believe that this difference is attributed to resonance stabilization of protonated phenyl sulfoxide with contributing structures such as **2a** and **2b**. This also explains the deep green colored solution of protonated diphenyl sulfoxide. Upon quenching of the solution, the sulfoxide is recovered in >80% yield. It is, however, possible that some unidentified

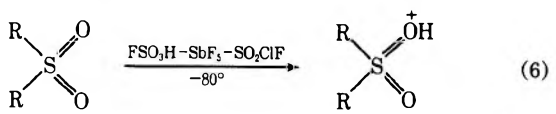


2a **2b**

decomposition product may contribute to the color of the solution.

In contrast to the observations of Chen and Yan,[15] and Kenney, Walsh, and Davenport,[16] protonated alkyl sulfoxides, investigated in this study in FSO_3H–SbF_5 solution diluted with SO_2ClF are very stable. No cleavage reaction occurred even when solutions were heated up to +65°. Protonated phenyl sulfoxide is stable up to −20°. At higher temperature the resonances broaden and decrease in intensity. The medium becomes viscous then solidifies to an unidentified dark solid.

Sulfones.—All sulfones studied in the extremely strong, FSO_3H–SbF_5 acid medium using SO_2ClF as diluent were protonated (eq 6).



(6)

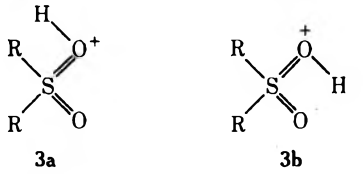
(15) C. T. Chen and S. J. Yan, *Tetrahedron Lett.*, 3855 (1969).

(16) W. J. Kenney, J. A. Walsh, and D. A. Davenport, *J. Amer. Chem. Soc.*, **83**, 4019 (1961).

No proton on oxygen (or on sulfur) could be observed in the FSO_3H–SbF_5 solution but it is assumed that protonation on oxygen occurred. As in the case of protonated sulfonic acids,[17] the S=$\overset{+}{O}$H peak could be obscured by, or exchange with the acid solvent peak at δ 11.9–12.6. The deshielding of the alkyl protons as compared to the parent sulfones clearly indicates that protonation indeed occurred. The alkyl protons of the protonated sulfones all show deshielding, with the methylene protons closest to the sulfur atom deshielded most (see Table II).

The following sulfones were protonated in FSO_3H–SbF_5–SO_2ClF solution at −80°: dimethyl, diethyl, di-*n*-propyl, di-*n*-butyl, benzyl *tert*-butyl, diphenyl, tetramethylene, sulfone (sulfolane), 3-sulfolene, 3-methyl-3-sulfolane. The chemical shifts and coupling constants of the parent and protonated sulfones are summarized in Table II.

The nmr spectrum of **protonated dimethyl sulfone** at −80° shows the methyl singlet at δ 3.96 and a small shoulder at δ 3.91. When SO_2 was used as diluent, the nmr spectrum shows two methyl singlets at δ 3.80 and 3.66, respectively, with a relative area ratio of 70:30. This indicates, as in the case of protonated methanesulfonic acid and protonated methyl methanesulfonate, that two isomeric species (**3a** and **3b**, where R = CH_3) are present. As the temperature increased to −20°, only the resonance of the major form is observed.



3a **3b**

No coupling was observed between the methyl protons and the proton on oxygen, hence no assignment of the two isomers could be made.

In the protonation of higher homologs, *e.g.*, **diethyl, di-*n*-propyl,** and **di-*n*-butyl sulfone,** only one isomer was found. Again, no couplings were observed between the proton on oxygen and the alkyl protons. Hence no structural assignment could be made based on the present pmr data.

Protonated alkyl sulfones in the FSO_3H–SbF_5–SO_2ClF solvent system are quite stable. The nmr spectra showed no significant change from −80° to room temperature.

Protonated **benzyl *tert*-butyl sulfone,** however, could not be observed even when sample was prepared and investigated at −78°. The pmr spectrum of benzyl *tert*-butyl sulfone in FSO_3H–SbF_5–SO_2ClF solution showed only that of the cleavage product, *tert*-butyl cation, at δ 4.20 and protonated phenyl methanesulfinic acid (aromatic protons centered at δ 8.10, $-CH_2-$ at 5.23, and $\overset{+}{S}O_2H_2$ at 9.16).

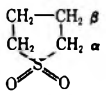
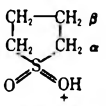
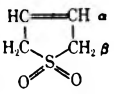
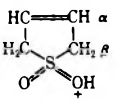
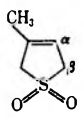
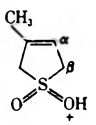
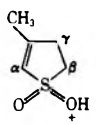
Phenyl sulfone in FSO_3H–SbF_5–SO_2ClF was also protonated and stable. The pmr spectrum showed the aromatic protons at δ 8.43–7.90 and the spectrum again showed no significant change from −80° to room temperature.

The pmr spectrum of **protonated tetramethylene sulfone** (sulfolane) showed the α-methylene protons at δ

(17) G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3908 (1970).

TABLE II

PMR SPECTRAL PARAMETERS[a] OF PARENT AND PROTONATED SULFONES

Compd	Registry no.	Temp, °C	Solvent	α-CH_2	β-CH_2	γ-CH_2	CH_3	Aromatic H
$(CH_3)_2SO_2$	67-71-0	−60	SO_2ClF				2.93	
$(CH_3)_2\overset{+}{S}O_2H$	26428-10-4	−80	FSO_3H–SbF_5 SO_2ClF				3.96 3.91	
$(CH_3CH_2)_2SO_2$	597-35-3	−60	SO_2ClF	2.93 (q, 7.5)			1.40 (t, 7.5)	
$(CH_3CH_2)_2\overset{+}{S}O_2H$	26428-11-5	−80	FSO_3H–SbF_5 SO_2ClF	4.17 (q, 7.20)			2.05 (t, 7.2)	
$(CH_3CH_2CH_2)_2SO_2$	598-03-8	−60	SO_2ClF	3.00 (t, 6.5)	1.96 (m)		1.27 (t, 7.0)	
$(CH_3CH_2CH_2)_2\overset{+}{S}O_2H$	26428-12-6	−80	FSO_3H–SbF_5 SO_2ClF	4.20 (m)	2.27 (m)		1.73 (t, 7.0)	
$(CH_3CH_2CH_2CH_2)_2SO_2$	598-04-9	−60	SO_2ClF	3.05 (m)	1.93 (m)		1.25 (t, 7.2)	
$(CH_3CH_2CH_2CH_2)_2\overset{+}{S}O_2H$	26428-13-7	−80	FSO_3H–SbF_5 SO_2ClF	4.17 (m)	2.23 (m)	2.23 (m)	1.50 (t, 7.0)	
$(C_6H_5)_2SO_2$	127-63-9	−30	SO_2					7.20–7.73
$(C_6H_5)_2\overset{+}{S}O_2H$	26428-14-8	−80	FSO_3H–SbF_5 SO_2ClF					8.43–7.90
	126-33-0	−60	SO_2ClF	3.26 (t, 7.0)	2.43 (m)			
	26428-15-9	−60	FSO_3H–SbF_5 SO_2ClF	4.41 (t, 7.0)	3.10 (m)			
	77-79-2	−60	SO_2ClF	6.37	3.85			
	26428-03-5	−80	FSO_3H–SbF_5 SO_2ClF	6.77	4.91			
	1193-10-8	−40	SO_2ClF	5.96	3.80	3.80	2.03	
	26428-04-6	−80	FSO_3H–SbF_5 SO_2ClF	6.35	4.86	4.81	2.30	
	26428-05-7	−30	FSO_3H–SbF_5 SO_2ClF	7.73 7.50	4.50 (t, 6.2) 4.90	3.68 (t, 6.2) 3.86	2.70 (90%) 2.83 (10%)	

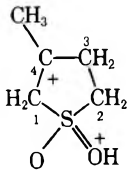
[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are given in parenthesis following the multiplicities: t = triplet; q = quartet; m = multiplet.

4.41 deshielded about 1.15 ppm from that of the parent sulfone in SO_2ClF at the same temperature. The β-methylene protons have a chemical shift centered at δ 3.10. Protonated sulfolane is stable and the nmr spectrum showed no significant change from −60° to room temperature.

3-Sulfolene (butadiene sulfone, 2,5-dihydrothiophene 1,1-dioxide) in FSO_3H–SbF_5–SO_2ClF is protonated only on the sulfonyl oxygen. No double bond protonation was observed even when the solution was warmed up to room temperature (see Table II).

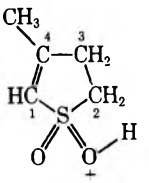
3-Methyl-3-sulfolene (isoprene sulfone) in FSO_3H–SbF_5 solution using SO_2ClF as diluent, at −80° gave an nmr spectrum similar to that of the parent sulfone in SO_2ClF except that the resonances are shifted to lower field. This indicates that 3-methyl-3-sulfolene is also protonated on the sulfonyl oxygen without attacking on the double bond. (The pmr chemical shifts are given in Table II.) When the temperature of the solution was increased to −60°, a slow change of the pmr spectrum is observed which can be accelerated by further raising the temperature. The pmr spectrum recorded

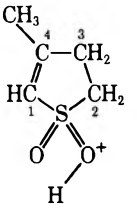
at −30° showed two triplets at δ 4.50 and 3.68, indicating two adjacent methylene groups formed. In addition to these two methylene groups, the nmr spectrum showed two singlets at δ 2.70 and 7.30. Diprotonation on the sulfonyl oxygen and the carbon–carbon double bond would presumably lead to the dication **4**. However, upon comparison of the pmr chemical shifts with that of 1-methylcyclopentyl cation **5**[18] ($CH_3-\overset{+}{C}<$) at δ 3.98) it appears that the methyl and methylene chemical shifts, except that of the methylene protons between the two positive centers, are at too high field to be considered as species **4**. Noteworthy is also that the long-range coupling (J_{HH} = 4.0 cps) of the methylene and methyl protons through the sp^2 hybridized center of ion **5** is absent. Furthermore, integration showed the relative area ratio of the resonances at δ 2.70, 3.68, 4.50, and 7.30 is 3:2:2:1 indicating that there is only one proton on carbon 1. This indicates that structure **6** is in accord with the nmr data. Thus as soon as ion **4** is formed, it undergoes deprotonation to form a double bond conjugated to the protonated sulfonyl group. At −60° the nmr spectrum shows a small singlet at δ 2.83, broad multiplets at δ 3.86, 4.90, and a weak resonance at δ 7.50 in addition to the major resonances. This probably indicates as in the case of protonated dimethyl sulfone, that two isomeric species of **6** are present.



4

5





6

(18) G. A. Olah, J. M. Bollinger, C. A. Cupas, and J. Lukas, *J. Amer. Chem. Soc.*, **89**, 2692 (1967).

Experimental Section

Materials.—All sulfoxides and sulfones were commercially available materials.

Nmr Spectra.—Varian Associates Model A-56/60A spectrometer with variable-temperature probe was used for all spectra.

Preparation of Protonated Sulfoxides and Sulfones.—The procedure used for the preparation of solutions of protonated sulfoxides and sulfones was identical with that described previously.[19]

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

(19) G. A. Olah, D. H. O'Brien, and A. M. White, *ibid.*, **89**, 5694 (1967).

Stable Carbonium Ions. CVI.[1] Protonation and Cleavage Reactions of Alkyl- and Arylsulfonic Acids and -sulfinic Acids and Alkyl Sulfonates and Sulfinates in Fluorosulfuric Acid–Antimony Pentafluoride Solution

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Received April 9, 1970

A series of sulfonic acids, sulfinic acids, and sulfonates were protonated in fluorosulfuric acid–antimony pentafluoride–sulfuryl chloride fluoride solution at low temperature (−60°). Two isomers were found for both protonated methanesulfonic acid and methyl methanesulfonate. At higher temperatures, protonated methane-, benzene-, and toluenesulfonic acid underwent dehydration to give the suggested sulfonylium ion which is not observed as it quickly picks up a fluoride ion from the acid system to form the corresponding sulfonyl fluoride. For protonated higher alkyl homologs, carbonium ions are the cleavage products. Protonated methyl methanesulfonate and methyl benzenesulfonate underwent alkoxy–sulfur cleavage whereas alkyl–oxygen cleavage was found for protonated ethyl and propyl methanesulfonate. Protonated sulfinic acids and methyl methanesulfinate are very stable; no cleavage reaction was observed.

Our recent investigations of protonated thiocarboxylic acids, *S*-alkyl esters,[3] dithiocarboxylic acids, thion esters, and dithio esters[4] lead us to study the protonation of a series of sulfonic acids, sulfinic acids, sulfonates, and sulfinates in the strong acid system, FSO_3H–SbF_5–SO_2ClF. No systematic studies relating to these systems in superacid solutions was previously reported.

Hantzsch[5] in 1908 studied the cryoscopic behavior of the sodium salts of benzene-, *m*-nitrobenzene-, and *p*-toluenesulfonic acids in sulfuric acid, and concluded that benzene- and *p*-nitrobenzenesulfonic acids behave as nonelectolytes in sulfuric acid while *p*-toluenesulfonic acid behaves as a weak base. Gillespie[6] carried out similar measurements on solutions of sodium benzenesulfonate and sodium *p*-toluenesulfonate in slightly aqueous sulfuric acid and concluded that these acids behave as weak bases. The conductimetric behavior of methanesulfonic acid in sulfuric acid studied by Gillespie and

* To whom correspondence should be addressed.

(1) Part CV: G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3904 (1970).

(2) National Institutes of Health Predoctoral Research Investigator, 1970.

(3) G. A. Olah, A. T. Ku, and A. M. White, *J. Org. Chem.*, **34**, 1827 (1969).

(4) G. A. Olah and A. T. Ku, *ibid.*, **35**, 331 (1970).

(5) R. Hantzsch, *Z. Phys. Chem.*, **65**, 41 (1908).

(6) R. J. Gillespie, *J. Chem. Soc.*, 2542 (1950).

TABLE I

PMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF THE PARENT AND PROTONATED SULFONIC ACIDS

Compd	Registry no.	Solvent	Temp, °C	OH	CH_3	α-CH_2	β-CH_2	γ-CH_2
CH_3SO_3H	75-75-2	SO_2[c]	−60	10.9 (s)	3.1 (s)			
	26428-16-0[d]	FSO_3H–SbF_5 SO_2ClF	−60		4.07 (s) 4.15 (s)			
$CH_3CH_2SO_3H$	594-45-6	SO_2ClF	−40	12.2 (s)	1.58 (t, 7.0)[b]	3.43 (q, 7.0)		
	26428-17-1[d]	FSO_3H–SbF_5 SO_2ClF	−60		2.18 (t, 7.0)	4.50 (q, 7.0)		
$CH_3CH_2CH_2SO_3H$	5284-66-2	SO_2ClF	−10	11.8	1.27 (t, 7.5)	3.51 (t, 7.5)	2.13 (m)	
	26428-18-2[d]	FSO_3H–SbF_5 SO_2ClF	−60		1.58 (t, 7.0)	4.26	2.53 (m)	
$CH_3CH_2CH_2CH_2SO_3H$	2386-47-2	SO_2ClF	−40	12.7	1.17 (t, 7.0)	3.43	1.85 (m)	1.60 (m)
	26428-19-3[d]	FSO_3H–SbF_5 SO_2ClF	−60		1.53 (t, 7.0)	4.46	2.50 (m)	2.10 (m)

[a] In parts per million from external TMS. [b] The coupling constants are indicated in hertz next to the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. [c] Methanesulfonic acid does not dissolve in SO_2ClF. [d] Protonated.

coworkers[7] was interpreted in terms of its behavior as either a nonelectrolyte or as a very weakly ionized base. Hall and Robinson[8] studied the cryoscopic behavior of sodium *p*-toluenesulfonate and sodium 2,4-dinitrobenzenesulfonate in sulfuric acid and found that the ionization goes according to the following example.

$$p\text{-}CH_3C_6H_4SO_3Na + H_2SO_4 = CH_3C_6H_4SO_3H + Na^+ + HSO_4^-$$

Thus they concluded that these arylsulfonates behave as nonelectrolytes in sulfuric acid.

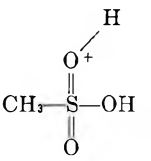
Results and Discussion

Sulfonic Acids.—In the superacid system, FSO_3H–SbF_5, all the sulfonic acids studied were protonated.

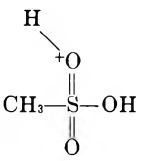
$$RSO_3H \xrightarrow[-60°]{FSO_3H\text{-}SbF_5\text{-}SO_2ClF} R\overset{+}{S}O_3H_2$$

The protonation is evident by the deshielded nmr chemical shifts of the alkyl protons of the protonated species as compared to those of the parent compounds in SO_2ClF (see Table I). It is presumed that the protonation occurred on sulfonyl oxygen. The S–OH protons of protonated sulfonic acids could not be seen in the nmr spectra but their chemical shift might be expected to be similar to that of the acid solvent system (δ 11–12.8). Assignments of derived chemical shifts and coupling constants of the parent and protonated sulfonic acids studied: methane-, ethane-, propane-, and butanesulfonic acid are summarized in Table I.

Protonated methanesulfonic acid at −60° shows two sharp singlets at δ 4.15 and 4.07 with a relative area ratio of 60:40 for the methyl protons. This indicates the existence of two isomeric species possibly Ia and Ib due to hindered rotation about the S—O bond and further indicates that the initial protonation is on sulfonyl oxygen. No coupling was observed between the methyl protons and the protons on oxygen. Therefore,



Ia



Ib

no structural assignments of protonated methanesulfonic acid could be made based on the present data.

The nmr spectrum of **protonated ethanesulfonic acid** showed only one set of triplet and quartet at δ 2.18 and 4.50, respectively, indicating that only one isomer exists, or at least the concentration of the other is so low that it is not observed under the experimental condition.

In the protonation of higher homologs, again only one isomer is observed (presumably there is one sterically favored isomer, although based on available data no assignment of structure can be made).

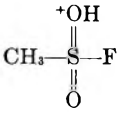
Cleavage Reactions of Protonated Sulfonic Acids.—Protonated methanesulfonic acid is stable up to +10°. At higher temperature, cleavage reactions occurred. At +20°, the pmr spectrum shows a doublet at δ 4.50 (J = 7.0 Hz) similar to that found in the methanesulfonyl fluoride–antimony pentafluoride complex in SbF_5–SO_2ClF solution and also similar to that of protonated methanesulfonyl fluoride in FSO_3H–SbF_5–SO_2ClF solution. The ^{19}F nmr spectrum of this cleavage product shows the fluorine resonance as a quartet at ϕ 58.6 downfield from $CFCl_3$ with a coupling constant of 7.0 Hz. These data indicate that methanesulfonyl fluoride indeed is formed in the cleavage reaction. In addition, the pmr spectrum of the solution also displays a very strong intense H_3O^+ peak indicating that dehydration had occurred.

It is evident that, if the methylsulfonylium ion is formed by dehydration during the cleavage reaction, it appears to react immediately with fluoride ion (from its gegenion or the solvent system) to form methanesulfonyl fluoride which in turn gives the methanesulfonyl fluoride–antimony pentafluoride donor:acceptor complex. In "magic acid," FSO_3H–SbF_5 solution, the

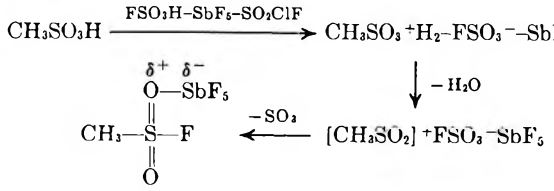
(7) J. Barr, R. J. Gillespie, and E. A. Robinson, *Can. J. Chem.*, **39**, 1266 (1961).

(8) S. K. Hall and E. A. Robinson, *ibid.*, **42**, 1113 (1964).

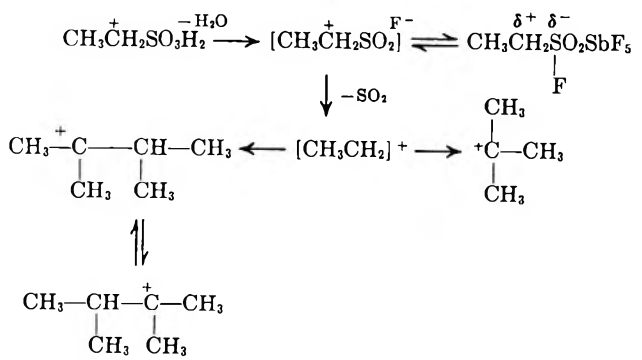
methanesulfonyl fluoride formed could also possibly be in the protonated form



We have found, however, that methanesulfonyl fluoride in FSO_3H–SbF_5 solution diluted with SO_2ClF, gave two protonated species, whereas only one isomer of the donor:acceptor complex[9] was found for methanesulfonyl fluoride in SbF_5–SO_2ClF solution. The obvious explanation can be a steric effect, due to the bulkiness of SbF_5. In the cleavage reaction of protonated methanesulfonic acid thus obviously the donor:acceptor complex of the sulfonyl fluoride–antimony pentafluoride is formed.



Protonated ethanesulfonic acid at room temperature also undergoes dehydration. After the solution of protonated ethanesulfonic acid in FSO_3H–SbF_5–SO_2ClF has stood at room temperature for about 15 min, the nmr spectrum shows in addition to the resonances of protonated ethanesulfonic acid, a methyl triplet at δ 2.23 and a methylene quartet at δ 4.60 assignable to the donor:acceptor complex, $CH_3CH_2\overset{\delta+}{S}O_2F\overset{\delta-}{S}bF_5$. When the solution was allowed to stand at room temperature for a longer period of time, alkyl–sulfur cleavage occurs to give the ethyl cation[10] which is not stable in the medium and immediately reacts further to the stable *tert*-butyl and *tert*-hexyl cations.



Protonated *n*-propane- and **isopropanesulfonic acid** at room temperature undergo cleavage reaction to give *tert*-hexyl cations. Similarly, **protonated butanesulfonic acid** at room temperature gives the *tert*-butyl cation. The protonated acids first are assumed to undergo dehydration (indicated by the intense H_3O^+ peak at δ 10.2) to give the corresponding alkyl sulfonyl cations which undergo alkyl–sulfur cleavage to give the related alkyl cations (*n*-propyl, isopropyl and *n*-butyl cation). The primary and secondary cations are not observed, since they are not stable under the reaction conditions and immediately rearrange to the stable *tert*-hexyl and *tert*-butyl cations, respectively.

Protonated **benzenesulfonic acid** could not be observed in FSO_3H–SbF_5–SO_2ClF solution even at −60°. The nmr spectrum of benzenesulfonic acid in FSO_3H–SbF_5–SO_2ClF at −60° showed a strong H_3O^+ peak indicating that dehydration occurred. The aromatic protons centered at δ 8.43, similar to that of benzenesulfonyl fluoride–antimony pentafluoride complex (δ 8.49). It, therefore, is indicated that benzenesulfonic acid is first protonated in FSO_3H–SbF_5–SO_2ClF solution, followed by dehydration to give the benzenesulfonylium ion which then quickly abstracts fluoride ion from the gegenion or solvent to form the benzenesulfonyl fluoride–antimony pentafluoride complex.

Protonated *p*-toluenesulfonic acid could not be observed either. *p*-Toluenesulfonic acid in FSO_3H–SbF_5–SO_2ClF solution, just as in the case of benzenesulfonic acid, gave the donor:acceptor complex of p-$CH_3C_6H_4\overset{\delta+}{S}O_2(F)\overset{\delta-}{S}bF_5$ (ArH, δ 8.33; CH_3, δ 3.00).

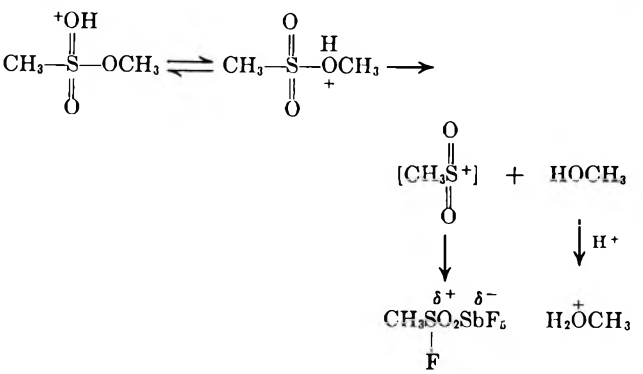
Alkyl Sulfonates.—Alkyl sulfonates in FSO_3H–SbF_5–SO_2ClF solution are protonated on the sulfonyl oxygen. Again, as in the case of protonated sulfonic acids, the S–OH protons of the protonated sulfonates cannot be directly observed. The protonation is evident by the deshielding of the alkyl proton chemical shifts of the protonated sulfonates as compared to those of the corresponding parent sulfonates in SO_2ClF (see summary of data in Table II).

The nmr spectrum of **methyl methanesulfonate** in FSO_3H–SbF_5–SO_2ClF solution at −60° shows two singlets at δ 4.80 and 4.03 for the OCH_3 and $-CH_3$ protons, respectively. Two shoulders at δ 4.70 and 3.93 are also observed indicating, as in the case of protonated methanesulfonic acid, that two isomeric species (IIa and IIb) are present.

IIa IIb

No coupling was observed between the proton on oxygen and the methyl protons. Therefore, no differentiation and assignment of the structures could be made. At −30°, only the singlets at δ 4.80 and 4.03 for the major isomer were observed. (The observation of the lower temperature spectrum is, however, reversible.)

Protonated methyl methanesulfonate is stable up to +20°. At room temperature it undergoes alkoxy–sulfur cleavage and reacts with the acid solvent system to



(9) G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3925 (1970).

(10) The reversibility of this cleavage was found by reacting the C_2H_5F → SbF_5 complex with SO_2 to give ethanesulfonyl fluoride (G. A. Olah, J. R. DeMember, and R. H. Schlosberg, unpublished work).

TABLE II

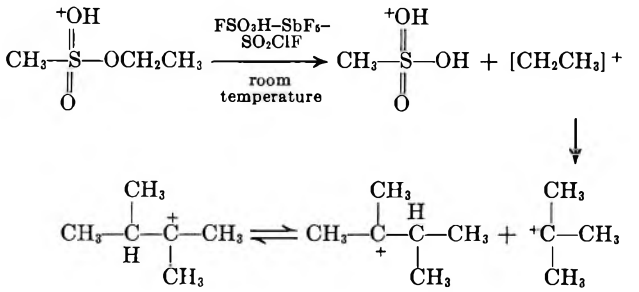
PMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS (IN HERTZ)[b] OF THE PARENT AND PROTONATED SULFONATES

Compd	Registry no.	Solvent	Temp, °C	CH_3–S	α-CH_2	β-CH_2	–CH_3	Aromatic H
$CH_3SO_2OCH_3$	66-27-3	SO_2ClF	−60	3.03 (s)			3.96 (s)	
	26428-20-6[b]	FSO_3H–SbF_5 SO_2ClF	−60	4.03 (s) 3.93 (s)			4.80 (s) 4.70 (s)	
$CH_3SO_2OCH_2CH_3$	62-50-0	SO_2ClF	−60	3.11 (s)	4.47 (q, 7.5)		1.55 (t, 7.5)	
	26428-21-7[b]	FSO_3H–SbF_5 SO_2ClF	−60	4.21 (s)	5.80 (q, 7.0)		2.18 (t, 7.0)	
$C_6H_5SO_2OCH_3$	80-18-2	SO_2ClF	−60				3.80 (s)	7.90
	26428-22-8[b]	FSO_3H–SbF_5 SO_2ClF	−60				4.80 (s)	8.36

[a] Same as that of Table I. [b] Protonated.

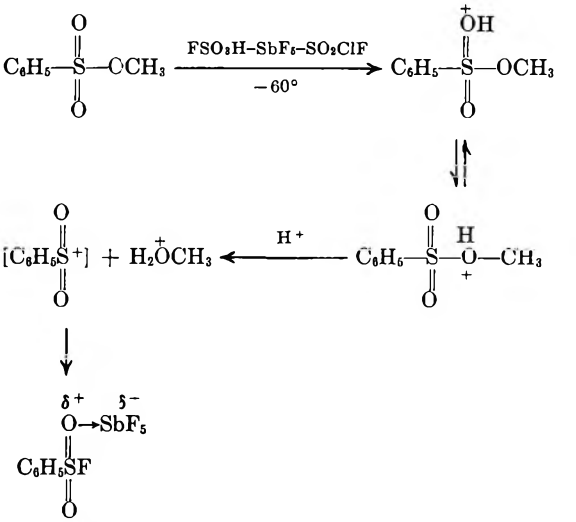
give the methanesulfonyl fluoride–antimony pentafluoride complex.

Ethyl methanesulfonate is protonated in FSO_3H–SbF_5–SO_2 solution (chemical shifts and coupling constants are given in Table II). The protonated species is stable up to +10°. After the sample stood at room temperature for about 10 min, the nmr spectrum shows resonances characteristic for the *tert*-butyl cation, the *tert*-hexyl cations, and protonated methanesulfonic acid in addition to those of protonated ethyl methanesulfonate. This indicates as shown in the following equation that alkyl oxygen cleavage occurred to give ethyl cation which then forms the stable *tert*-butyl and *tert*-hexyl cations.



Protonated propyl methanesulfonate in FSO_3H–SbF_5–SO_2ClF solution could not be observed even at a temperature as low as −80°. The nmr spectrum showed only the *tert*-hexyl cations and protonated methanesulfonic acid, indicating complete cleavage by the time spectra were obtained. **Butyl methanesulfonate** under similar conditions gave the *tert*-butyl cation and protonated methanesulfonic acid.

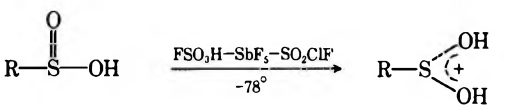
The nmr spectrum of protonated **methyl benzenesulfonate** recorded at −80° showed the methyl singlet at δ 4.86 and the ring protons centered at δ 8.43. At room temperature protonated methyl benzenesulfonate undergoes alkoxy–sulfur cleavage to give protonated methanol (CH_3 at δ 4.80 and $\overset{+}{O}H_2$ at 9.42 at −60°) and the benzenesulfonyl fluoride–antimony pentafluoride complex with a chemical shift of δ 8.46 for the aromatic protons. The cleavage reaction again can be represented as in the following reactions.



Sulfinic Acids and Sulfinates.—No direct investigation relating to the protonation of alkyl- or arylsulfinic acids and sulfinates in superacid system have been reported so far in the literature. Sulfination of aromatics by sulfur dioxide[11] and the reactions of benzenonium ions with sulfur dioxide is known[12,13] and was studied also in strong acid media to yield protonated arylsulfinic acids.[14]

In continuation of our study of the protonation of sulfonic acids, we considered it of interest to extend our investigation to the protonation of sulfinic acids and sulfinates in the extremely strong acid system.

Methane-, benzene-, and toluenesulfinic acid studied were all protonated on the sulfinyl oxygen at low temperature. The nmr spectrum showed the S–OH protons as a singlet at δ 9.12 to 9.40. The pmr chemical



(11) G. A. Olah, "Friedel–Crafts and Related Reactions," Vol. I, Wiley-Interscience, New York, N. Y., 1963, Chapter 2.

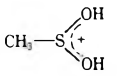
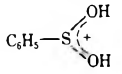
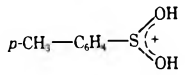
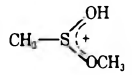
(12) G. A. Olah, C. U. Pittman, Jr., E. Namanworth, and M. B. Comisarow, *J. Amer. Chem. Soc.*, **88**, 5571 (1966).

(13) M. Brookhart, F. A. L. Anet, and S. Winstein, *ibid.*, **88**, 5657 (1966).

(14) G. A. Olah, R. H. Schlosberg, D. P. Kelly, and Gh. D. Mateescu, *ibid.*, **92**, 2546 (1970).

TABLE III

PMR CHEMICAL SHIFTS[a] OF PROTONATED SULFINIC ACIDS AND METHYL METHANESULFONATE IN FSO_3H–SbF_5–SO_2ClF SOLUTION

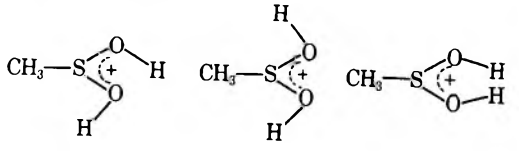
Compd	Registry no.	Temp, °C	S–OH	CH_3	OCH_3	Aromatic H
	26428-23-9	−60	9.40 (s)	3.93 (s)		
	26428-24-0	−80	9.30 (s)			8.05 to 8.56
	26428-25-1	−80	9.12 (s)	2.78		8.00
	26428-26-2		8.93 (s)	3.70 (s)	4.66 (s)	

[a] Same as that of Table I.

shifts and coupling constants of protonated sulfinic acids are summarized in Table III.

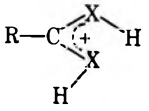
Protonated **methanesulfinic acid,** at −60° gave an nmr spectrum having a methyl singlet at δ 3.93 and one S–OH singlet at δ 9.40 with a relative area ratio of 2:3. These resonances, although broad, showed no couplings.

As in the case of protonated simple carboxylic acids,[10] thiocarboxylic acids,[3] and dithiocarboxylic acids,[4] one would expect that two or even three possible isomers (IIIa, IIIb, IIIc) would exist for protonated methanesulfinic acid. However, the nmr spectrum of proton-



IIIa IIIb IIIc

ated methanesulfinic acid at −80° indicated that only one isomer exists. An attempt was made in order to see if the S–OH resonances could be resolved into two singlets, as in the case of the predominant isomers of protonated carboxylic acids[10] (IV) and protonated dithiocarboxylic acids[4] (IV). Unfortunately, at temper-



IV

X = O,S

atures lower than −80°, the solution became very viscous and the resonance became broad. Therefore, the structure of the protonated sulfinic acid could not be assigned.

Benzene- and *p*-toluenesulfinic acid in FSO_3H–SbF_5–SO_2ClF solution are also protonated on the sulfinyl oxygen. The pmr chemical shifts are summarized in Table III.

The protonated sulfinic acids studied are extremely stable. No cleavage reactions could be observed even when the solutions were heated up to +65°.

The only sulfinate we studied in the present work was **methyl methanesulfinate.** The nmr spectrum of methyl methanesulfinate in FSO_3H–SbF_5 solution diluted with SO_2ClF showed a singlet in the S–OH region at δ 8.93 indicating that it is also protonated on the sulfinyl oxygen. The pmr chemical shifts of the parent and protonated methyl methanesulfinate are given in Table III.

No couplings were observed between the S–OH protons and the two methyl protons. Hence, the structure of protonated methyl methanesulfinate could not be assigned.

Protonated methyl methanesulfinate is very stable. No cleavage reaction occurred even when the solution was standing at room temperature for days.

Experimental Section

Materials.—All the compounds used in this study were commercial available reagents except methanesulfinic acid and methyl methanesulfinate.

Methanesulfinic acid were prepared by the method described by Cram and coworkers[15] by the reaction of distilled water and methanesulfinyl chloride at −30° under dry nitrogen. The methanesulfinyl chloride was prepared following the method of Douglass and coworkers[16] by the reaction of chlorine and methyl disulfide in glacial acetic acid at low temperature. Methyl methanesulfinate was also prepared by the method described by Douglass[17] by the reaction of methanesulfinyl chloride and methanol at −30°.

Nmr Spectra.—Varian Associates Model A-56/60A with variable-temperature probes was used for all spectra.

Preparation of Solutions.—The procedure used for the preparation of solutions of the protonated sulfonic acids, sulfonates, sulfinic acid, and methyl methanesulfinate was identical with that described previously.[18]

Acknowledgment.—Support of our work by a grant from the National Institutes of Health is gratefully acknowledged.

(15) F. Wudl, D. A. Lightner, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 4099 (1967).

(16) I. B. Douglass, B. S. Farah, and E. G. Thomas, *J. Org. Chem.*, **26**, 1996 (1961).

(17) I. B. Douglass, *ibid.*, **30**, 633 (1965).

(18) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).

Stable Carbonium Ions. CVII. Diprotonated Hydroxycarboxylic Acids and Their Cleavage in Fluorosulfuric Acid–Antimony Pentafluoride Solution[1]

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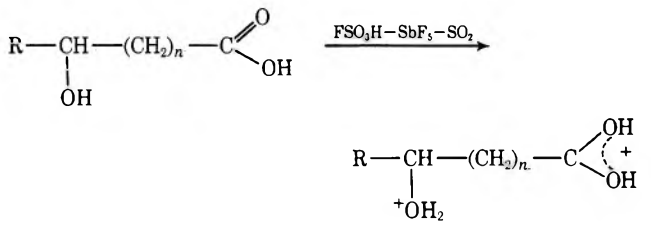
Received April 9, 1970

A series of hydroxycarboxylic acids were protonated in fluorosulfuric acid–antimony pentafluoride–sulfur dioxide solution at low temperature. Oxygen diprotonation was observed for all the hydroxy acids studied. At higher temperature, α-hydroxycarboxylic acids undergo dehydration to give the corresponding lactides. Protonated 3-hydroxybutyric acid undergoes dehydration to give protonated crotonic acid at 0°. Lactone formation was observed for protonated 4-hydroxybutyric acid at room temperature.

We have previously reported the observation of protonated aldehydes,[3] ketones,[4] alcohols,[5,6] carboxylic acids,[7] thiocarboxylic acids,[8] and ketocarboxylic acids[9] in superacid solutions by nmr spectroscopy. In continuation of our studies we wish now to report the protonation of hydroxycarboxylic acids and their cleavage reactions in fluorosulfuric acid–antimony pentafluoride solution.

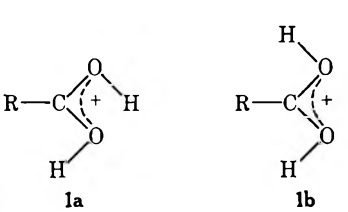
In FSO_3H–SbF_5–SO_2 solution, all the aliphatic hydroxycarboxylic acids studied were completely diprotonated. Studying the temperature dependence of these systems we were able to observe, depending on the relative position of the OH and CO_2H group, dehydration of protonated α-, β-, and γ-hydroxycarboxylic acid to form the corresponding lactide, α,β-unsaturated carboxylic acid and lactone, respectively.



$n = 0, 1, 2$

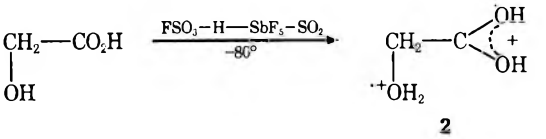
The following aliphatic hydroxycarboxylic acids were examined in FSO_3H–SbF_5–SO_2 solution: **glycolic, lactic, 3-hydroxypropionic, 3-hydroxybutyric** and **4-hydroxybutyric acid.** The derived pmr parameters of protonated hydroxycarboxylic acids are summarized in Table I.

It has been shown that two isomeric species (**1a** and **1b**) are found for protonated formic and acetic acid in superacid systems.[7,10,11] Isomer **1a** is the predominant species for both protonated formic and acetic acid, and in the protonation of higher homologs isomer **1b** is not observed. The two OH protons of the predominant species, **1a**, are in different environment and hence give different chemical shifts at low temperature. The same observations were made for protonated thiocarboxylic acids[8] and dithiocarboxylic acids.[12] The OH protons of protonated glycolic, lactic, 3-hydroxypropionic and 3-hydroxybutyric acid, however, could not be resolved even at a temperature as low as −80°. This observation is in accord with that of protonated ketocarboxylic acids[9] and dicarboxylic acids[13] in which, when the two functional groups are too close together, only a singlet absorption was observed for the $-CO_2H_2^+$ protons. As the two functional groups are separated further, such as in the case of protonated γ-hydroxybutyric acid, the two OH protons of the $CO_2H_2^+$ group at low temperature gave two singlets.



1a **1b**

The nmr spectrum of **protonated glycolic acid** (2) in FSO_3H–SbF_5–SO_2 solution at −80° showed two low field singlets in the OH region at δ 14.2 (broad) and 13.5 (sharp) and another two singlets for the methylene protons at δ 6.10 and 5.96. The relative area ratio of the resonance at δ 6.10 and 5.96 is dependent on the acid concentration in SO_2. When the superacid concentration was increased in the sample, absorptions at lower field were increased at the expense of the higher field resonance. Furthermore, the OH protons at δ 14.2 are much more deshielded than those of protonated acetic acid. Hence we assign the absorptions at δ 14.2 and 6.10 to the protons on carboxylic oxygen and the methylene protons of the diprotonated species **2.**



2

The $^+OH_2$ protons of the diprotonated species are not observed and are probably covered by the acid solvent peak at δ 10.9 to 12.0, or exchanging. By studying further hydroxycarboxylic acids, such as **lactic acid** and **2-hydroxy-2-methylbutyric acid** (see Discussion), it is indicated that the absorptions at δ 13.5 and 5.90 are due

* To whom correspondence should be addressed.

(1) Part CVI: G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3908 (1970).

(2) National Institutes of Health Predoctoral Research Investigator, 1970.

(3) G. A. Olah, D. H. O'Brien, and M. Calin, *J. Amer. Chem. Soc.*, **89**, 3582 (1967).

(4) G. A. Olah, M. Calin, and D. H. O'Brien, *ibid.*, **89**, 3586 (1967).

(5) G. A. Olah and E. Namanworth, *ibid.*, **88**, 5327 (1966).

(6) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, **89**, 3576 (1967).

(7) G. A. Olah and A. M. White, *ibid.*, **89**, 3591 (1967).

(8) G. A. Olah, A. T. Ku, and A. M. White, *J. Org. Chem.*, **34**, 1827 (1969).

(9) G. A. Olah, A. T. Ku, and J. Sommer, *ibid.*, **35**, 2159 (1970).

(10) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **43**, 1045 (1965).

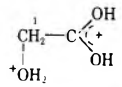
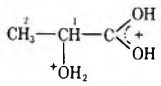
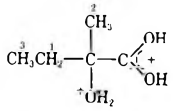
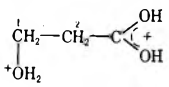
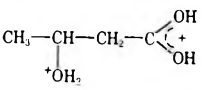
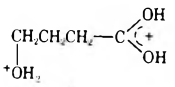
(11) H. Hogeveen, A. F. Bickel, C. W. Hilbers, E. L. Mackor, and C. Maclean, *Chem. Commun.*, 898 (1966).

(12) G. A. Olah and A. Ku, *J. Org. Chem.*, **35**, 331 (1970).

(13) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 4752 (1967).

TABLE I

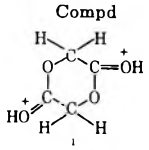
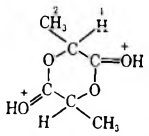
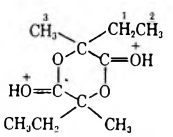
PMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF HYDROXYCARBOXYLIC ACIDS IN FSO_3H–SbF_5 SOLUTION DILUTED WITH SO_2

Compd	Registry no.	°C	$^{+}CO_2H_2$	$^{+}OH_2$	H_1	H_2	H_3
	25951-46-6	−80	14.2[c]		6.10		
	25951-47-7	−60	14.1[d]		6.06	2.23 (d, 7.5)[e]	
	25951-48-8	−60	14.5[f]		2.55 (q, 7.5)	2.25	1.30 (t, 7.5)
	25951-49-9	−80 −30	13.5 13.4	 10.8 (t, 4.0)	5.43 5.46 (m)	4.10 4.10 (t, 5.0)	
	25951-50-2	−60	13.1	10.4 (d, 3.8)	5.66 (m)	3.78 (d, 4.7) 3.80 (d, 6.5)	1.88 (d, 6.5)
	25951-51-3	−60	12.7	9.93 (t, 3.5)	5.03 (m)	3.48 (t, 7.0)	2.66 (qi, 7.0)

[a] In parts per million referred to external TMS. [b] In hertz as indicated following the multiplicity in the parenthesis. [c] Observed only below −70°. [d] Observed below −90°. [e] Multiplicity: d, doublet; t, triplet; q, quartet; qi, quintet; m, multiplet. [f] Observed only below −80°.

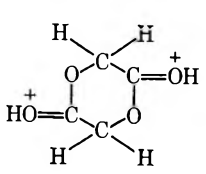
TABLE II

PMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS[b] OF PROTONATED LACTIDES FORMED FROM THE CORRESPONDING PROTONATED α-HYDROXYCARBOXYLIC ACIDS IN FSO_3H–SbF_5–SO_2ClF SOLUTIONS

Compd	Registry no.	°C	OH	H_1	H_2	H_3
	25966-55-6	−70	13.5	5.90		
	26039-36-1	−60	13.3	6.06 (m)	2.06 (d, 7.2)[c]	
	25966-56-7	−30	13.3	2.50 (q, 7.0)	1.21 (t, 7.0)	2.20 (s)

[a] In parts per million referred to external TMS. [b] In hertz as indicated following multiplicity in the parenthesis. [c] Observed only below −70°.

to the protons on oxygen and methylene protons of protonated 2,5-dioxo-1,4-dioxane (**3**) at −70°. Isolation

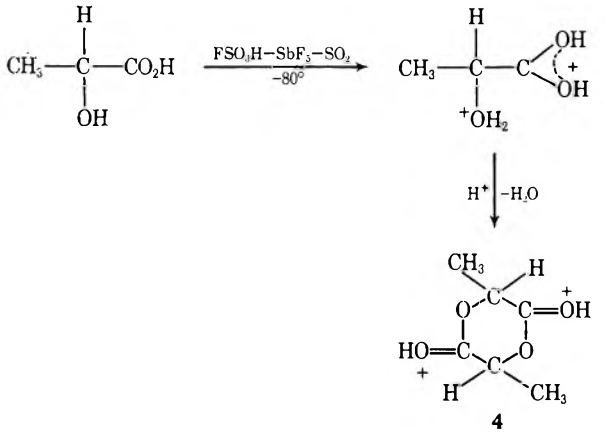


3

of lactides from the superacid solutions is difficult because they cannot be treated with water or hydroxylic solvents without solvolysis. The identity of the protonated lactides was, however, confirmed when authentic lactides were dissolved in FSO_3H–SbF_5–SO_2 solution −70° and gave identical pmr spectra (nmr data of protonated lactides are summarized in Table II).

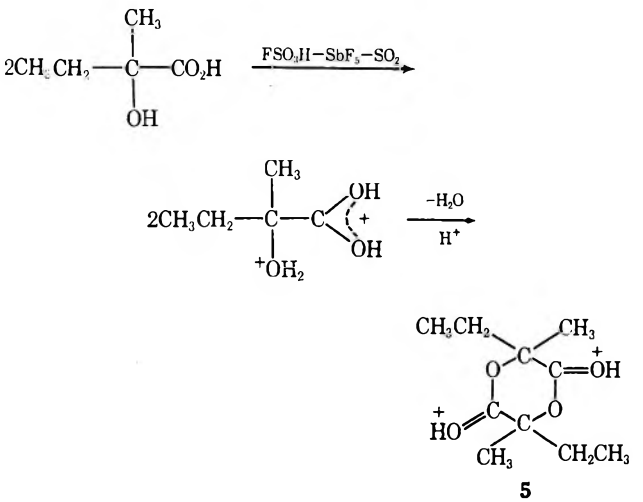
Protonated lactic acid (added as the lithium salt) in FSO_3H–SbF_5 solution diluted with SO_2 at −80°, gave an nmr spectrum having the methyl doublet at δ 2.33, methine multiplet at δ 6.20 and a low field peak at δ 14.1. The resonance at δ 14.1 is assigned to the $-CO_2H_2^+$ protons and is much more deshielded than that of the OH protons of protonated propionic acid (δ 12.73)[7] indicating that lactic acid is diprotonated. The $^{+}OH_2$ protons again are not observed and are possibly overlapped by, or exchanging with, the acid solvent peak. As the temperature of the solution was increased to −60°, new peaks at higher field of each absorption appeared, which we believed to be due to the formation of protonated lactide **4**. The nmr spectrum at −60° showed the $C{=}\overset{+}{O}H$ singlet, methyl doublets, and the methine multiplets of protonated lactide **4** at δ 13.3,

2.06, and 6.06, respectively. At −30°, the rate of the formation of the protonated lactide is increased and readily goes to completion.



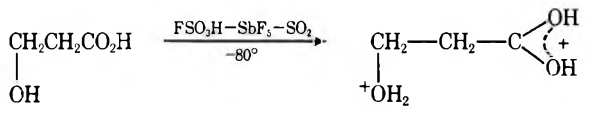
4

2-Hydroxy-2-methylbutyric acid in 1:1 FSO_3H–SbF_5–SO_2 solution is also diprotonated. At −80° the nmr spectrum showed a broad low field peak at δ 14.5 which is assigned to the $CO_2H_2^+$ protons. The $^+OH_2$ absorptions could be overlapped by or exchanging with the acid solvent peak at δ 11.4∼12.3 is not observed. The methyl triplet appeared at δ 1.30, ethyl quartet at δ 2.55, and the methyl singlet at δ 2.25. As the temperature of the solution increased to −30°, a new methyl triplet at δ 1.31, ethyl quartet at δ 2.50, and methyl singlet at δ 2.20 appeared, and all appeared at a higher field than those of protonated 2-hydroxy-2-methylbutyric acid. In addition, the nmr spectrum also showed a sharp singlet at δ 13.3, indicating that protonated 2-hydroxy-2-methylbutyric acid at −30° undergoes dehydration to give the 2,5-ethyl-2,5-methyl-3,6-oxo-1,4-dioxane (**5**). Conversion of protonated 2-hydroxy-2-methylbutyric acid to **5** goes to completion when the sample is kept at −30°.



5

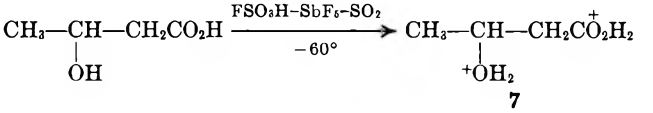
3-Hydroxypropionic acid (**6**) is diprotonated in FSO_3H–SbF_5 solution diluted with SO_2 at −80°. The $-CO_2H_2^+$ protons appear as a singlet at δ 13.5. The



6

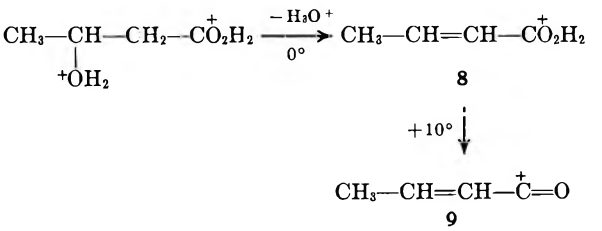
resonance of $^+OH_2$ is overlapping with the acid solvent peak at δ 10.7–11.2 at −80°. At −30°, as the acid solvent peak shifted to δ 11.0–11.3, the $^+OH_2$ absorption appeared as a triplet with a coupling constant of 4.0 Hz at δ 10.8. The chemical shifts and coupling constants of the methylene protons are summarized in Table I. Diprotonated 3-hydroxypropionic acid in FSO_3H–SbF_5–SO_2 solution is stable. The nmr spectrum showed no significant change from −80° to room temperature.

3-Hydroxybutyric acid in FSO_3H–SbF_5 solution with SO_2 as diluent, is also diprotonated (**7**). The $\overset{+}{C}O_2H_2$

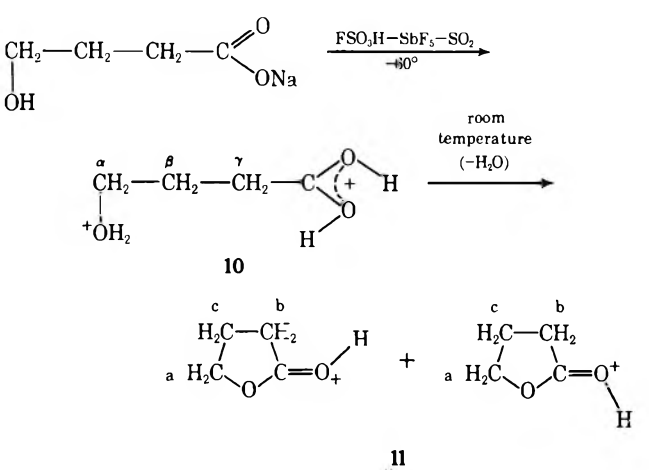


7

protons appear as a singlet at δ 13.3 which could not be resolved even at a temperature as low as −100°. The $^+OH_2$ protons appear as a doublet with a coupling constant of 3.8 Hz at δ 10.5. The methine proton appeared as a multiplet at δ 5.9 and the two methylene protons appeared at δ 3.96 (doublet, J = 5.0 Hz) and δ 4.0 (doublet, J = 6.5 Hz). The methyl protons appeared as a doublet at δ 2.1. Protonated 3-hydroxybutyric acid is stable up to 0°. At higher temperature dehydration occurred (indicated by the strong intense H_3O^+ absorption at δ 10.25) to form protonated crotonic acid **8** which at +10° undergoes further dehydration to give the corresponding α,β-unsaturated oxocarbonium ion **9**.



In "magic acid," **4-hydroxybutyric acid** (added as sodium salt) also undergoes diprotonation to give ion **10**. The nmr spectrum of **10** recorded at −60° showed



11

the $-CO_2H_2^+$ and $^+OH_2$ protons at δ 2.17 and 9.93, respectively. The latter is a triplet with a coupling constant of 3.5 Hz, the former is resolved to two singlets at −70° indicating, as in the case of protonated simple carboxylic acids, that the two protons of $^+CO_2H_2$ are

magnetically nonequivalent. The α-methylene protons appeared as multiplet at δ 5.03, the γ-methylene protons as a triplet at δ 3.48, and the β-methylene protons centered at δ 2.66.

At room temperature, protonated 4-hydroxybutyric acid rearranged slowly to the corresponding protonated γ-butyrolactone **11**. The nmr spectrum of this solution cooled back to −80° showed the $\overset{+}{C}=\overset{+}{O}H$ proton at δ 12.25 and 12.03 with a relative area ratio of 75:25%, indicating that two isomeric species of protonated lactone **11** are formed. The three methylene groups a, b, and c of the protonated lactone appeared as triplets and quintet at δ 5.45 3.53, and 2.75, respectively. It is noted that the nmr spectrum showed no $-\overset{+}{O}H_2$ absorptions and of course the coupling between $-\overset{+}{O}H_2$ and the methylene protons is absent. The nmr spectrum is identical with that of the protonated authentical γ-butyrolactone.

Experimental Section

Materials.—All hydroxycarboxylic acids used in this study were commercially available materials.

Nmr Spectra.—Varian Associates Model A-56/60A spectrometer with variable temperature probe was used for all spectra.

Preparation of Protonated Hydroxycarboxylic. Acids.—The procedure used for the preparation of solutions of protonated hydroxycarboxylic acids was identical with that described previously.[14]

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

(14) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).

Stable Carbonium Ions. CVIII. Protonated Lactones and Their Cleavage Reactions in Fluorosulfuric Acid–Antimony Pentafluoride Solution[1]

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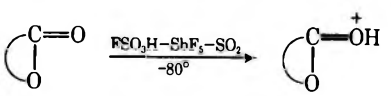
A series of lactones were protonated in fluorosulfuric acid–antimony pentafluoride solution at low temperature. With the exception of protonated δ-valerolactone, α-acetyl-γ-butyrolactone, coumarin, dihydrocoumarin, and 4-hydroxycoumarin, two isomeric species were found for all the protonated lactones studied. Structure assignments for these two isomers are proposed. Protonated lactones in FSO_3H–SbF_5–SO_2 solution are stable except protonated β-butyrolactone which undergoes alkyl–oxygen cleavage and deprotonation to give protonated crotonic acid at −40°. Protonated α-angelicalactone at −60° undergoes acyl–oxygen cleavage to give the corresponding protonated ketooxocarbonium ion.

In continuation of our preceding study of the protonation of hydroxycarboxylic acids,[1] we felt it of interest to study the protonation and cleavage reactions of lactones in FSO_3H–SbF_5–SO_2 solution.

Extensive kinetic studies were carried out on the hydrolysis of β-lactones.[3] With the exception of Hogeveen's recent report[4] of the behavior of α,α-dimethyl-β-propiolactone in hydrogen fluoride–boron trifluoride solution, no study of lactones in superacid media has been reported. We wish now to report such a systematic study of the protonation and cleavage reactions of lactones in superacid media.

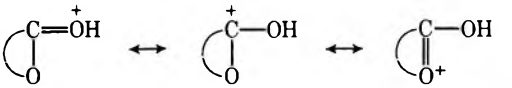
Results and Discussion

In FSO_3H–SbF_5 solution diluted with SO_2 generally at −80°, all the lactones studied, *e.g.*, β-propiolactone, β-butyrolactone, γ-butyrolactone, γ-valerolactone, α-bromo-γ-butyrolactone, α-bromo-γ-valerolactone, α-acetyl-γ-butyrolactone, δ-valerolactone, α-angelicalactone, coumarin, dihydrocoumarin, and 4-hydroxycoumarin, were protonated on the carbonyl oxygen atom.



The protonated lactones give well resolved pmr spectra. Assignments of the pmr chemical shifts and coupling constants of the parent and protonated lactones are summarized in Table I.

The proton on oxygen of protonated lactones occurs at lower field than those in protonated alcohols[5,6] and ethers[7] but are more shielded than those in protonated aliphatic ketones[8] and aldehydes,[9] similar to those in protonated alkylcarboxylic acids[10] and esters.[11] This is consistent with the partial double bond character in the protonated lactones.



With the exception of protonated δ-valerolactone, α-acetyl-γ-butyrolactone, coumarin, dihydrocoumarin, and 4-hydroxycoumarin, all the lactones studied gave two low field peaks in the $C=\overset{+}{O}H$ region at low temperature. This indicates the existence of hindered rotation about the C—O bond. In all cases no coupling was

* To whom correspondence should be addressed.

(1) Part CVII: G. A. Olah and A. T. Ku, *J. Org. Chem.*, **35**, 3913 (1970).

(2) National Institutes of Health Predoctoral Research Investigator, 1970.

(3) For references, see A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1965, Chapter 12.

(4) H. Hogeveen, *Recl. Trav. Chim. Pays-Bas*, **87**, 1303 (1968).

(5) G. A. Olah and E. Namanworth, *J. Amer. Chem. Soc.*, **88**, 5327 (1966).

(6) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, **89**, 3576 (1967).

(7) G. A. Olah and D. H. O'Brien, *ibid.*, **89**, 1725 (1967).

(8) G. A. Olah, M. Calin, and D. H. O'Brien, *ibid.*, **89**, 3586 (1967).

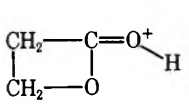
(9) G. A. Olah, D. H. O'Brien, and M. Calin, *ibid.*, **89**, 3582 (1967).

(10) G. A. Olah and A. M. White, *ibid.*, **89**, 3591 (1967).

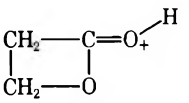
(11) G. A. Olah, D. H. O'Brien, and A. M. White, *ibid.*, **89**, 5694 (1967).

observed between the proton on oxygen and the α-alkyl protons. At higher temperatures, in some of the cases, only the major C=OH resonance is observed.

Protonated β-propiolactone in 1:1 FSO_3H–SbF_5–SO_2 solution at −80° showed two low field absorptions in the C=OH region at δ 14.2 and 14.4 with relative area ratio of 60:40, respectively, indicating that two isomeric species (**1a** and **1b**) are present. The two



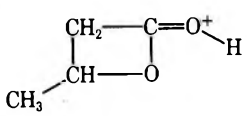
1a



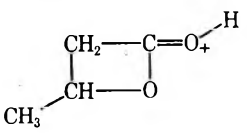
1b

methylene groups appeared as broad peaks at δ 5.50 and 4.13. At higher temperatures, such as −40°, the lower field C=OH peak begins to broaden, owing to exchange with the acid solvent system, and finally disappears. At −20°, the methylene protons appear as two well resolved triplets with a coupling constant of 6.0 Hz.

The pmr sectrum of **protonated β-butyrolactone** in FSO_3H–SbF_5–SO_2 solution, recorded at −60°, showed the C=OH proton as two singlets at δ 12.9 and 13.0 with relative area ratio of 52:48, indicating two forms (**2a** and **2b**) are present. It should be noted that the



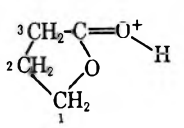
2a



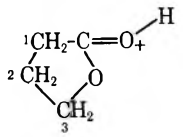
2b

relative area ratio of the higher field C=OH resonance with the lower field one is less than that of protonated β-propiolactone. The methylene doublet of protonated β-butyrolactone appears at δ 3.51, methine multiplet at δ 5.66, and the methyl doublet at δ 1.75.

Protonated γ-butyrolactone, 3a and **3b,** in the same solvent system at −80°, showed the proton on oxygen as two singlets with relative area ratio of 75:25 at δ 12.30 and 12.51. The resonance at δ 12.51 begins to broaden as temperature increases, and at −60° only the major resonance at δ 12.30 is observed. The α- and γ-methylene triplets appear at δ 3.60 and 5.50, respectively, and the β-methylene protons appear as quintet at δ 2.80.

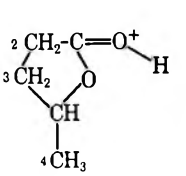


3a

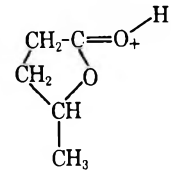


3b

The nmr spectrum of **protonated γ-valerolactone, 4a** and **4b,** at −80° showed the two C=OH resonances



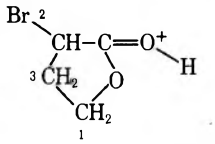
4a



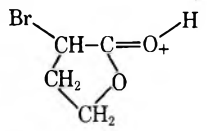
4b

at δ 11.8 and 12.1 with relative area ratio of 75:25. At −70° only the singlet at δ 11.8 is observed. The chemical shifts and coupling constants of the alkyl protons are summarized in Table I.

Protonated α-bromo-γ-butyrolactone (**5a** and **5b**) at −60° showed the C=OH proton at δ 12.93 and 13.2 with a relative area ratio of 85:15 which is larger than that of protonated γ-butyrolactone. The two C=OH singlets are temperature independent and could be seen even at a temperature as high as −40°, indicating that proton exchange remained slow.

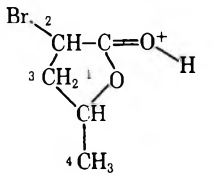


5a

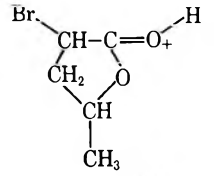


5b

Again two forms (**6a** and **6b**) are observed for **protonated α-bromo-γ-valerolactone** with relative ratio of 65:35 at δ 12.5 and 12.65, respectively. The isomer ratio is lower than that of protonated α-bromo-γ-butyrolactone, and the C=OH resonances are also sharp singlets even at a temperature as high as −40°.

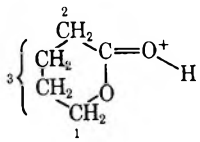


6a



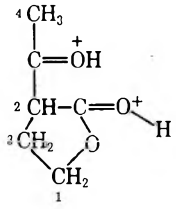
6b

The nmr spectrum of **protonated δ-valerolactone** (**7**) at −70° gave only one singlet for the C=OH proton at 11.3. No other C=OH resonance could be observed even when the temperature of the solution was lowered to −100°. This indicates that only one protonated form was observed.

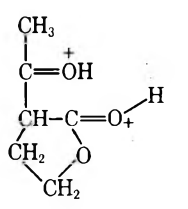


7

α-Acetyl-γ-butyrolactone in FSO_3H–SbF_5–SO_2 solution is diprotonated (**8a**). The pmr spectrum recorded



8a

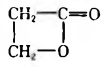
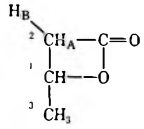
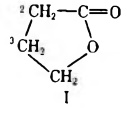
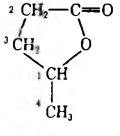
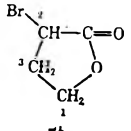
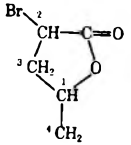


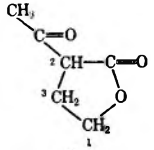
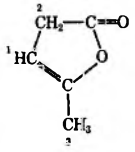
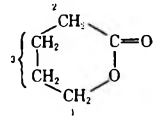
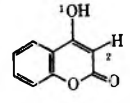
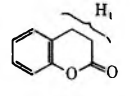
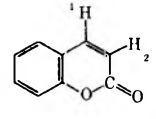
8b

at −90° showed two sharp singlets at δ 16.6 and 14.03 which are assigned to the protons on the acetyl oxygen and the lactone carbonyl oxygen, respectively. No coupling was observed between the proton on oxygen and the α protons.

Table I

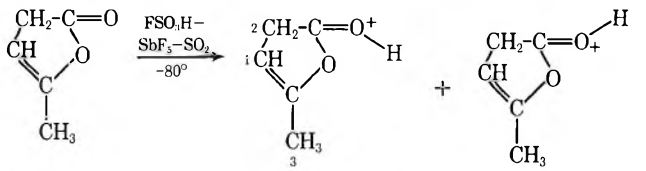
Pmr Spectral Parameters[a] of Parent and Protonated Lactones

Compd	Registry no.	Solvent	°C	$C{=}O^{+}H$	H_1	H_2	H_3	H_4	Aromatic H
	57-57-8	SO_2	−60		4.20 (t, 5.7)	3.40 (t, 5.7)			
1[b]	25966-30-7	FSO_3H–SbF_5, SO_2	−80	14.4 14.2	5.50 (t, 6.0)	4.13 (t, 6.0)			
	3068-88-0	SO_2	−60		4.61 (m)	H_A 3.40 (q) H_B 2.86 (q) J_{AB} = 17.0 J_{AC} = 6.0 J_{BC} = 4.8	1.31 (d, 6.1)		
2[b]	25966-32-9	FSO_3H–SbF_5, SO_2	−60	13.0 12.9	5.66 (m)	3.51 (d, 6.2)	1.75 (d, 6.2)		
 I	96-48-0	SO_2	−60		4.20 (t, 7.0)	2.25 (m)	2.13 (t, 7.0)		
3[b]	25966-34-1	FSO_3H–SbF_5, SO_2	−80	12.51 12.30	5.50 (t, 8.0)	3.60 (t, 8.0)	2.80 (qi, 8.0)		
	108-29-2	SO_2	−70		4.60 (m)	2.31 (m)	1.93 (m)	1.21 (d, 6.2)	
4[b]	25966-36-3	FSO_3H–SbF_5, SO_2	−80	12.1 11.8	5.95 (m)	3.58 (m)	2.66 (m)	1.65 (d, 6.2)	
	5061-21-2	SO_2	−60		4.30 (m)	4.26 (m)	2.45 (m)		
5[b]	25966-38-5	FSO_3H–SbF_5	−60	12.9 13.2	5.88 (m)	5.63 (m)	3.50 (m)		
	25966-39-6	SO_2	−60		4.81 (m)	4.50 (m)	2.50 (m)	1.40 (d, 6.0)	
6[b]	25966-40-9	FSO_3H–SbF_5, SO_2	−70	12.65 12.5	6.06 (m)	5.43 (m)	3.03 (m)	1.86 (d, 6.2)	

	517-23-7	SO_2	−60		4.13 (t, 7.2)	3.60 (q, J_{AC} = 9.5) J_{BC} = 8.0)	2.23 (m)	2.10 (s)	
8[b]	26039-35-0	FSO_3H–SbF_5, SO_2	−70	16.3 14.3	5.65 (m)	5.65 (m)	3.60 (m)	3.65 (s)	
	591-12-8	SO_2	−50		5.05 (m)	2.86 (m)	1.78 (m)		
9[b]	25966-43-2	FSO_3H–SbF_5, SO_2	−80	12.9 12.6	6.01 (m)	4.23 (m)	2.28 (m)		
	542-28-9	SO_2	−60		4.15 (m)	2.31 (m)	1.66 (m)		
7[b]	25966-45-4	FSO_3H–SbF_5, SO_2	−70	11.3	5.20 (t, 5.0)	3.19 (t, 5.0)	2.15 (m)		
	91-64-5	SO_2	−40		7.65 (d, 9.5)	6.15 (d, 9.5)			7.0–7.5
10[b]	25966-47-6	FSO_3H–SbF_5, SO_2	−70		9.36 (d, 9.2)	7.61 (d, 9.2)			Centered at 8.33
	119-84-6	SO_2	−60		2.63 (m)				Centered at 7.13
12[b]	25966-49-8	FSO_3H–SbF_5, SO_2	−80	12.8 (18%) 12.5 (82%)	3.55 (m)				7.47 (s)
	1076-38-6	DMSO-d_6 $CDCl_3$	−40		12.5 (s)	5.70 (s)			7.16–7.96
11[b]	25966-51-2	FSO_3H–SbF_5, SO_2	−80			6.66 (s)			7.66–8.46

[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are given in parenthesis following the multiplicities: d = doublet; t = triplet; q = quartet; m = multiplet; qi = quintet. [b] See text for structure.

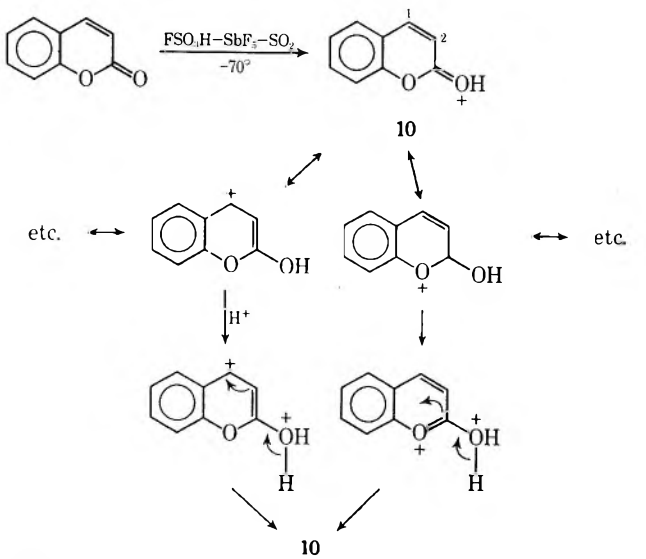
Protonated α-angelicalactone (9a and 9b) in FSO_3H–SbF_5 solution diluted with SO_2 at −80° gave an nmr spectrum similar to that of the parent compound in SO_2 except it showed additional C=$\overset{+}{O}$H resonances at δ 12.6 and 12.9 (60:40) and the deshielding of the alkyl protons (see Table I). The nmr spectrum also showed additional small resonances at δ 3.53 and 4.80 which can be attributed to the methyl and methylene protons of the cleavage product (see later discussion) and are due to local heating during sample preparation. The in-



9a 9b

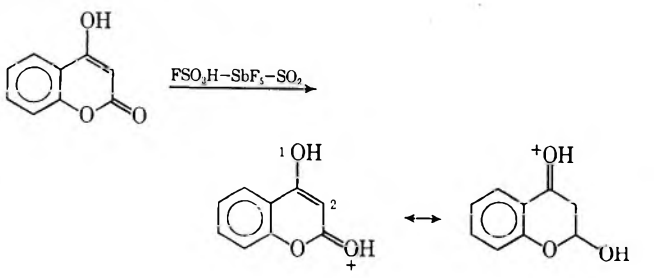
tensities of the resonances of the cleavage product did not increase with time at −80°.

The pmr spectrum of **protonated coumarin (10)** in FSO_3H–SbF_5 solution diluted with SO_2 at −70° showed the two −CH=CH− doublets at δ 9.36 (J = 9.2 Hz) and 7.63, and the aromatic resonance centered at δ 8.33. The spectrum showed no C=$\overset{+}{O}$H resonance. This is due to the fact that in protonated coumarin the –OH proton is probably in a keto–enol equilibrating form, and proton exchange occurred.



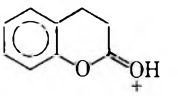
10

The same reason is suggested for not being able to observe the C=$\overset{+}{O}$H resonance for **protonated 4-hydroxy coumarin, 11.** Comparison of the chemical shifts of =CH and the aromatic protons with those of protonated coumarin **10** indicated that **11** probably was only monoprotonated.



11

Dihydrocoumarin was protonated (**12**) on the carbonyl oxygen and showed only one C=$\overset{+}{O}$H resonance at δ 12.6 at −60° which is consistent with the observation of protonated δ-valerolactone.



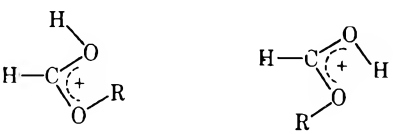
12

Structure of Protonated Lactones.—Protonated lactones with the exceptions of protonated δ-valerolactone, coumarin, 4-hydroxycoumarin, α-acetyl-γ-butyrolactone, and dihydrocoumarin, all showed two C=$\overset{+}{O}$H resonances. The partial double bond character of the carbon–oxygen bonds and the observation of two OH resonances for the proton on oxygen imply the presence of two isomers (**13a** and **13b**) in protonated lactones.

13a 13b

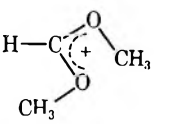
Similar isomers have been observed in the case of other protonated carbonyl compounds.[8-11] No coupling of the proton on oxygen with the α-alkyl protons was observed for protonated lactones. Therefore, no structural assignments could be made on this basis.

It has been shown, however, that protonated alkyl formates have two isomeric forms (**14** and **15**)[11-13] in



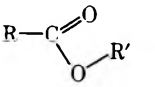
14 15

which the OH proton, the methine proton, and the alkyl group were in a cis–trans relationship. It was also reported[14] that the isomer observed for dimethoxy carbonium ion had the cis–trans structure **16**. In addition,



16

it has been shown that the preferred conformation of esters[15] is the one in which the alkyl group is coplanar and cis to the carbonyl oxygen (**17**) thus minimizing the interaction between the lone pairs on oxygen.[16]

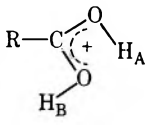


17

(12) A. M. White and G. A. Olah, *J. Amer. Chem. Soc.*, **91**, 2943 (1969).
(13) H. Hogeveen, *Recl. Trav. Chim. Pays-Bas*, **86**, 816 (1967).
(14) R. F. Borsch, *J. Amer. Chem. Soc.*, **90**, 5303 (1968).
(15) G. J. Karabatsos, N. Asi, and C. E. Orzch, Jr., *Tetrahedron Lett.*, 4639 (1966), and references cited therein.
(16) N. L. Owen and N. Sheppard, *Proc. Chem. Soc. (London)*, 264 (1963).

In protonated lactones the orientation of the *O*-alkyl group is fixed trans to the OH proton. Thus in order to minimize the lone pair interactions of the two oxygens, the orientation of the $C{=}\overset{+}{O}H$ proton has to be cis to the ether oxygen. Thus we suggest that the predominant species in protonated lactones is that of structure **13a**, in which the $C{=}\overset{+}{O}H$ proton is cis to the ether oxygen. The minor species would then be structure **13b**.

A number of additional facts are consistent with this assignment. The $C{=}\overset{+}{O}H$ absorption of the major isomer of protonated lactones is assumed to be more shielded than that of the minor isomers. This is in agreement with the C^{13} nmr study of protonated carboxylic acids which indicated[17] that proton H_A of **18** has a



18

more shielded chemical shift than that of H_B. In addition, the inner methyl protons of dimethoxy carbonium ion[12,14] **16**, and the inner OH proton of protonated alkyl formates **15**, also have more shielded chemical shifts than those of the corresponding outer ones.

Some hydrogen bonding interaction between the OH proton and the neighboring oxygen in spite of the resultant unfavorable four-membered ring is possible and could add to the preponderance of isomer **13a** over **13b**. In addition, if this is the case, the hydrogen bonded proton should be in the shielding zone of the carbonyl. Hence the $C{=}\overset{+}{O}H$ proton of **13a** should be more shielded than that of **13b**, in agreement with our structural assignment.

It should be noted that the relative isomer ratio of **13a**:**13b** of protonated lactones is found to be increased as the ring size is increased. This is due to the fact that the lone pair interaction of six-membered ring lactones is much larger than that of the four-membered ring lactones. This may be the reason why only one isomer, presumably the major isomer **13a**, is observed for protonated δ-valerolactone and protonated dihydrocoumarin.

Steric effects should also play a role in the isomer distributions of protonated lactones. Substituents at the position α to the carbonyl should tend to increase the amount of the major isomer, while the substituents α to the ether oxygen should decrease the amount of the major isomer. This indeed is in accordance with our observations (see Table II). In the case of protonated α-acetyl-γ-butyrolactone, only one $C{=}\overset{+}{O}H$ resonance for the proton on the lactone carbonyl oxygen was observed, and was assigned to **8a**. It is believed that sterically and electronically isomer **8a** should be favored than **8b**. Thus, the observed data are indeed in accordance with our structural assignment.

Cleavage of Protonated Lactones.—In general, protonated lactones in FSO_3H–SbF_5SO_2 solution are stable. No cleavage was observed for protonated five- and six-membered ring lactones (except protonated α-angelicalactone) even when solutions were heated up to +65°.

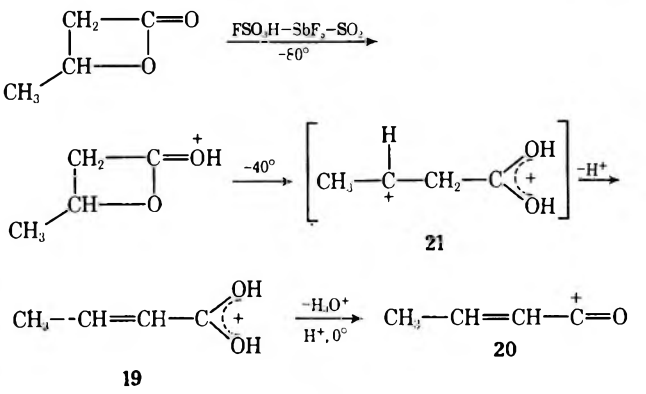
TABLE II

PER CENT ISOMER DISTRIBUTIONS OF PROTONATED LACTONES IN FSO_3H–SbF_5–SO_2 SOLUTION AT −80°

Compd	% isomer 13a	% isomer 13b
1	60	40
2	52	48
3	75	25
4	75	25
5	85	15
6	65	35
9	60	40
8	100	
7	100	

Protonated β-propiolactone (**1a** and **1b**) in FSO_3H–SbF_5–SO_2 solution, in contrast to Hogeveen's study on α,α-dimethyl-β-propiolactone[4] and kinetic studies in weaker acidic systems, is stable and the nmr spectrum showed no significant change from −80° to room temperature.

Protonated β-butyrolactone (**2a** and **2b**) is stable up to −50°. At higher temperature cleavage occurred. At 0°, the nmr spectrum showed the absorptions for protonated crotonic acid (**19**) which has been studied previously,[18] and the absorptions for the propenyloxocarbonium ion(**20**). This indicates that alkyl–oxygen cleavage occurred to form the secondary carbonium ion (**21**) which is not stable and is deprotonated to give the protonated crotonic acid (**19**) which in turn undergoes further dehydration to give the corresponding oxocarbonium ion **20**. The nmr spectrum, recorded at 0°,



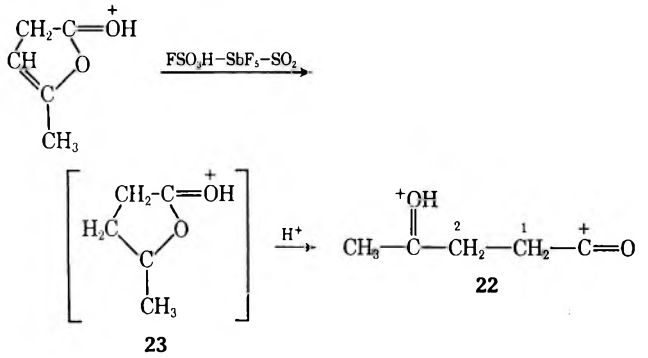
also shows a singlet at δ 3.53 and some multiplets at δ 4.3–5.1 which are not understood at the present time.

Protonated α-angelicalactone in excess FSO_3H–SbF_5 solution at −60° underwent acyl–oxygen cleavage to give the corresponding protonated ketooxocarbonium ion **22**. The nmr spectrum recorded at −60° showed methylene protons at δ 4.30 (broad), the methyl singlet at δ 3.53, and the proton on oxygen at δ 16.2 which is more deshielded than that of protonated simple ketones[8] and is similar to that of protonated ketooxocarbonium ion studied previously.[19] The two resonances of the two methylene groups (1 and 2) of ion **22** are well separated on a HA 100 nmr spectrum and having chemical shifts of δ 4.96 and 4.71, respectively.

(17) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 7072 (1967).

(18) G. A. Olah and M. Calin, *ibid.*, **90**, 405 (1968).

(19) G. A. Olah, A. T. Ku, and J. Sommer, *J. Org. Chem.*, **35**, 2159 (1970).



23 22

It should be mentioned that ion **22** was not formed by dehydration of protonated acetylpropionic acid which was studied previously.[19] Obviously, the double bond in α-angelicalactone does assist the formation of ion **22**. It is possible that the diprotonated species (**23**) could be the intermediate for the formation of ion **22**. In excess FSO_3H–SbF_5 solution, ion **23** is not observed.

Experimental Section

Materials.—All lactones were commercially available materials. Liquid lactones were redistilled before use.

Nmr Spectra.—Varian Associates Model A-56/60A and HA 100 spectrometers with variable temperature probes were used for all spectra.

Preparation of Protonated Lactones.—The procedure used for the preparation of solutions of protonated lactones was identical with that described previously.[11]

Registry No.—Fluorosulfuric acid, 7789-21-1; antimony pentafluoride, 7783-70-2.

Acknowledgment.—Support of the work by a grant of the National Institutes of Health is gratefully acknowledged.

Stable Carbonium Ions. CIX. Protonation of Hydroxy Ketones in Fluorosulfuric Acid–Antimony Pentafluoride–Sulfur Dioxide Solution and the Study of Hydroxy Ketone–Antimony Pentafluoride Complexes[1]

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Received April 9, 1970

Protonation of hydroxy ketones was studied in FSO_3H–SbF_5–SO_2 solution. Oxygen diprotonation was observed for all the hydroxy ketones. For comparison, hydroxy ketone–antimony pentafluoride complexes were also studied in sulfuryl chloride fluoride solution.

We have previously reported the observation of protonated ketones,[3] ketocarboxylic acids,[4] hydroxycarboxylic acids,[5] and lactones.[1] No investigation relating to protonation of hydroxy ketones has been reported so far in the literature. In continuation of our work of protonation of heteroorganic compounds, we considered it of interest to extend our investigation to the protonation of hydroxy ketones in the fluorosulfuric acid–antimony pentafluoride superacid system.

Results and Discussion

Protonated Hydroxy Ketones.—The pmr parameters of protonated hydroxyketones have been measured in FSO_3H–SbF_5–SO_2 solution at −80°. It was found that 1-hydroxy-2-propanone (acetol, hydroxyacetone), 3-hydroxy-2-butanone (acetoin), 3-hydroxy-3-methyl-2-butanone, and 4-hydroxy-3-methyl-2-butanone are diprotonated in excess 1:1 *M* FSO_3H–SbF_5 solution diluted with SO_2. In the case of hydroxyacetone the monoprotonated form was also observed. In all cases there is no indication of resolvable fine structure in the OH resonance. The peaks are broad indicating exchange of the proton on oxygen with the solvent acid system. The pmr parameters of both the parent and the protonated hydroxy ketones are summarized in Table I.

The pmr spectrum of **diprotonated hydroxyacetone** (acetol, **1**) in excess 1:1 FSO_3H–SbF_5–SO_2 solution at −80° showed two low field absorption peaks at δ 12.5 and 16.8 with a relative area ratio of 2:1. These two absorptions are assigned to the proton on the alcohol and ketone oxygen atom, respectively. The protons on oxygen of protonated hydroxyacetone are much more deshielded than those of protonated methanol[6,7] and acetone.[3] The effect of the double positive charge is considered to be responsible for this strong deshielding. The nmr spectrum shows two singlets for the methyl protons at δ 3.88 and 3.63, and two sets of methylene resonance at δ 7.16 and 6.46. The higher field methyl and methylene protons tend to increase with decreasing acid concentration. We consequently assign the lower field methylene (δ 7.16) and methyl (δ 3.88) absorptions to the diprotonated species (**1a**) and the higher field resonances to the monoprotonated species (**1b**). The protons on oxygen for **1b** are not observed probably owing to proton exchange. The proton on oxygen for **1a** could only be observed at temperatures below −80°. At these low temperatures the absorptions are broad and show no resolvable coupling with the α protons. Hence no structural assignment could be made.

* To whom correspondence should be addressed.

(1) Part CVIII: G. A. Olah and A. T. Ku, *J. Org. Chem.*, **35**, 3916 (1970).

(2) National Institutes of Health Predoctoral Research Investigator, 1967–1970.

(3) G. A. Olah, M. Calin, and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 3586 (1967).

(4) G. A. Olah, A. T. Ku, and J. Sommer, *J. Org. Chem.*, **35**, 2159 (1970).

(5) G. A. Olah and A. T. Ku, *ibid.*, **35**, 3913 (1970).

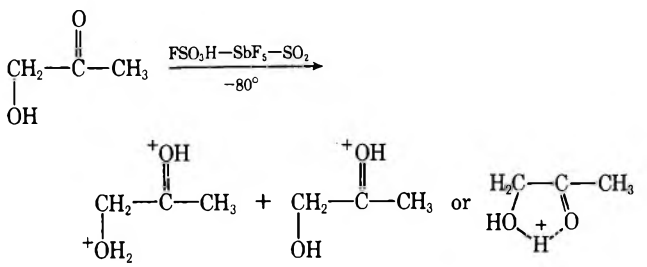
(6) G. A. Olah and E. Namanworth, *J. Amer. Chem. Soc.*, **88**, 5327 (1966).

(7) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, **89**, 3576 (1967).

TABLE I
PMR SPECTRAL PARAMETERS[a] OF PARENT AND PROTONATED HYDROXY KETONES

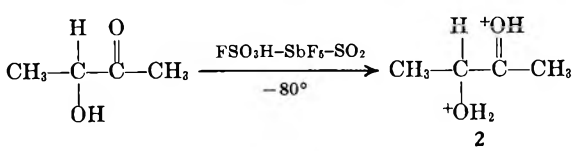
Compd	Registry no.	Solvent	°C	^{+}OH ‖ C	$^{+}OH_2$	OH	H_1	H_2	H_3	H_4
$CH_2(OH)-C(=O)-CH_3$	116-09-6	SO_2	−60			3.58	3.95	1.90		
		FSO_3H–SbF_5–SO_2	−80	16.8	12.5		7.16 6.46	3.88 3.63		
$CH_3-CH(OH)-C(=O)-CH_3$	513-86-0	SO_2	−60			4.47	4.11 (q, 7.0)	2.00	1.17 (d, 7.0)	
		FSO_3H–SbF_5	−80	16.87	12.16		6.57	3.50	2.53	
$H_3C-C(OH)(CH_3O)-C(=O)-CH_3$	115-22-0	SO_2	−60			4.00	2.03	1.17		
		FSO_3–SbF_5–SO_2	−80	17.03	12.0		3.66	2.20		
$CH_2(OH)-CH(CH_3)-C(=O)-CH_3$	3393-64-4	SO_2	−60				3.40 (d, 7.0)	2.58	1.96	0.83
						3.50	3.36 (d, 5.0)	(m)		(d, 7.2)
		FSO_3H–SbF_5–SO_2	−50	15.5 (q, 1)	10.6 (t, 3.5)	5.20 (m)	4.26 (m)	3.45 (d, 1)	1.75 (d, 7.2)	

[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are in parenthesis following the multiplicities: d = doublet; t = triplet; q = quartet; m = multiplet.



1a 1b

3-Hydroxy-2-butanone (acetoin) in FSO_3H–SbF_5–SO_2 solution is also O-diprotonated **2.** The pmr spectrum of **2** at −80° showed the $^{+}HO{=}C$ proton at δ 16.9 and the $^{+}OH_2$ protons at δ 12.16. At −80°, the resonances are broad. The methyl protons appeared at δ

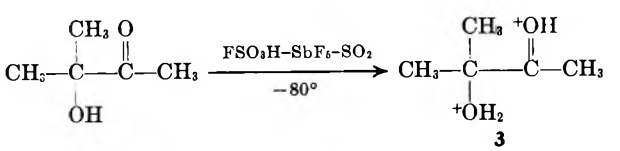


2

2.53, the acetyl methyl protons at δ 3.50, and the methine proton at δ 6.57. As the absorptions of the protons on oxygen are again broad with no resolvable couplings, no structural assignment could be made.

At −40°, protonated acetoin starts to undergo cleavage reactions. The solution gives a complicated nmr spectrum with so far unidentified products.

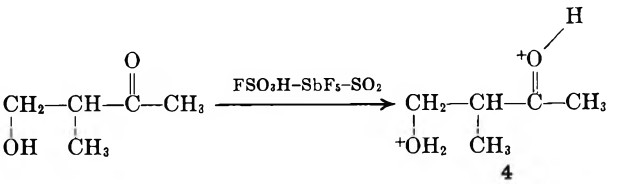
3-Hydroxy-3-methyl-2-butanone in FSO_3H–SbF_5–SO_2 is also diprotonated **3.** The proton on the acetyl



3

oxygen appears at δ 17.05. The $-\overset{+}{O}H_2$ protons are not observed in 1:1 *M* FSO_3H–SbF_5–SO_2 solution. They are obscured by the acid solvent peak at δ 12.0. However, both the $-C{=}\overset{+}{O}H$ and $\overset{+}{O}H_2$ protons could be observed when the hydroxy ketone is protonated in 4:1 *M* FSO_3H–SbF_5–SO_2 solution diluted with SO_2 at −100° and are observed at δ 17.1 and 12.0, respectively. The chemical shifts and coupling constants of the alkyl protons are summarized in Table I. The nmr spectrum of **3** in FSO_3H–SbF_5–SO_2 solution showed no significant change from −80 to 0°.

1-Hydroxy-2-methyl-3-butanone is also diprotonated in FSO_3H–SbF_5 solution diluted with SO_2. The nmr

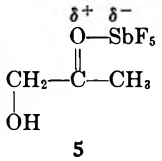


4

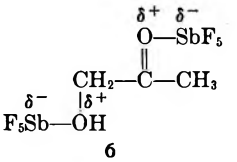
spectrum, recorded at −60°, showed the $\overset{+}{O}H_2$ and $-C{=}\overset{+}{O}H$ proton at δ 10.8 and 15.7, respectively. At higher temperature, such as −50°, the $\overset{+}{O}H_2$ resonance is shown to be a sharp triplet with a coupling constant of 3.5 Hz, and the absorption at δ 15.5 ($^{+}OH{=}C$) is also a well resolved quartet with a coupling constant of about 1 Hz, indicating that this proton is coupled with the acetyl methyl protons. The acetyl methyl absorption at δ 3.46 is accordingly a doublet having a coupling constant of 1 Hz. Comparison of the 1-Hz coupling constant with that of protonated simple ketones[3] indicates that the proton on the keto oxygen and the acetyl methyl group are in a cis relation. Thus protonated 1-hydroxy-2-methyl-3-butanone has the shown structure **4.** Solutions of **4** are stable and the

pmr spectra showed no significant changes up to room temperature.

Hydroxy Ketone–Antimony Pentafluoride Complexes. Nuclear Magnetic Resonance Studies.—The nmr spectrum of **hydroxyacetone** in SbF_5 diluted with SO_2ClF at −60° showed the absorptions for the methyl and methylene protons at δ 3.65 and 6.15, respectively. These absorptions, having a chemical shift close to those of the monoprotonated species **1b**, are assigned to the donor:acceptor complex **5**. The OH proton resonance is not observed and is probably due to the proton exchange. Two very weak absorptions at δ 7.16 and 3.96 with chemical shifts similar to those observed for diprotonated hydroxyacetone **1a** are also observed, and are assigned to the methylene and methyl protons of the dicomplexed species **6.**



5

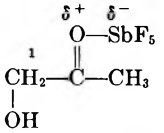
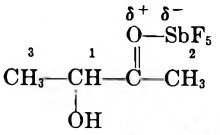
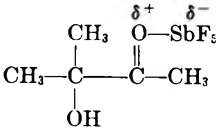
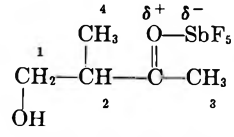


6

Donor:acceptor complexes with antimony pentafluoride are also observed for **3-hydroxy-2-butanone** (acetoin), **3-hydroxy-3-methyl-2-butanone,** and **4-hydroxy-3-methyl-2-butanone** in SO_2ClF solution. The chemical shifts and coupling constants of these hydroxyketone–antimony pentafluoride complexes are summarized in Table II. The pmr spectra showed only the absorptions due to the monodonor:acceptor complexes, with complexing on the carbonyl oxygen atoms.

TABLE II

PMR CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS OF HYDROXY KETONE–ANTIMONY PENTAFLUORIDE COMPLEXES IN SO_2ClF SOLUTION AT −60°

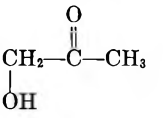
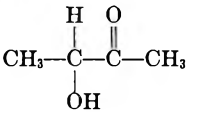
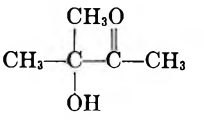
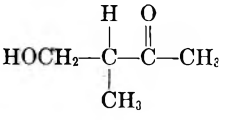
Compd	H_1	H_2	H_3	H_4
	6.15 (s)	3.65 (s)		
	6.16 (m)	3.40 (s)	2.26 (d, 6.0)	
	3.46 (s)	2.40 (s)		
	4.81 (m)	3.93 (m)	3.11 (s)	1.60 (d, 7.0)

[a] Same as that in Table I.

Infrared Spectroscopic Studies.—Solutions of the hydroxy ketone complexes in antimony pentafluoride (with small amount of SO_2ClF) were pressed between Irtran plates, all operations being carried out in a drybox, as the compounds are sensitive to moisture. Infrared spectra were obtained on a Beckman IR-10 infrared spectrophotometer. The main characteristic data obtained are summarized in Table III.

TABLE III

INFRARED C=O STRETCHING FREQUENCIES (CM^{-1}) OF HYDROXY KETONE–ANTIMONY PENTAFLUORIDE COMPLEXES

Compd	$\nu_{C=O}$, hydroxy ketone	$\nu_{C=O}$, hydroxy ketone–SbF_5 complex	$\Delta\nu_{CO}$
	1715	1615	100
	1721	1605	116
	1716	1601	115
	1709	1630	79

All the investigated hydroxy ketone–antimony pentafluoride complexes show significantly shifted carbonyl stretching frequencies at 1601 to 1630 cm^{-1} indicative of donor:acceptor complex nature. Thus the hydroxy ketone–antimony pentafluoride complexes are clearly formed by carbonyl oxygen coordination.

Experimental Section

Materials.—All of the hydroxy ketones used were commercially available.

Nmr Spectra.—A Varian Associates Model A-56/60A spectrometer with variable temperature probe was used for all spectra. Chemical shifts are reported in ppm (δ) from external (capillary) tetramethylsilane.

Preparation of Superacid Solutions.—The procedure used for the preparation of FSO_3H–SbF_5–$SO_2(SO_2ClF)$ solutions of the protonated hydroxy ketones was identical with that described previously.[8]

Solutions of the hydroxy ketone–antimony pentafluoride complexes were obtained by preparing saturated solution of antimony-pentafluoride in sulfuryl chloride fluoride at −20°. Portions (2 ml) of this solution were cooled to −78°, causing some antimony-pentafluoride to crystallize from solution. To this suspension was added dropwise with efficient stirring, approximately 0.3 g of the appropriate hydroxy ketone in ~0.5 ml of sulfuryl chloride fluoride.

Acknowledgment.—Support of our work by a grant of National Institutes of Health is gratefully acknowledged.

(8) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).

Stable Carbonium Ions. CXVI.[1] Sulfonyl Halide–Antimony Pentafluoride Complexes and Study of Protonation and Cleavage of Sulfonyl Halides in Fluorosulfuric Acid–Antimony Pentafluoride–Sulfuryl Chloride Fluoride Solution

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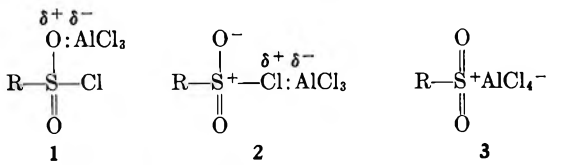
Received May 8, 1970

Sulfonyl chlorides and fluorides form oxygen coordinated complexes with antimony pentafluoride. In "magic acid," FSO_3H–SbF_5 solution, diluted with SO_2ClF, sulfonyl halides are protonated on sulfonyl oxygen. Two isomeric forms were observed for protonated methanesulfonyl chloride and fluoride. For higher protonated homologs, only one isomer was found. No long-lived sulfonyl cations could be observed in any of the systems studied.

The reaction of acyl halides with aromatic compounds or olefins in the presence of Friedel–Crafts catalysts is one of the most commonly used reaction in organic chemistry. The mechanism of Friedel–Crafts acylation[3] was extensively studied and many intermediate acyl cations (oxocarbonium ions) were isolated and investigated by various methods, ir, nmr, etc.

The sulfonylation reaction can be regarded as a modification of the acylation reaction in which a sulfonyl group is substituted for a carbonyl group and the product is a sulfone instead of a ketone.[4] Olivier[5] was the first to study the mechanism of the sulfonylation reaction and the structure of addition complex between aluminum chloride and benzenesulfonyl chloride in the acid chloride as solvent. The existence of 1:1 addition complex was demonstrated. There has been no determination of the structure of the complex, but according to Jensen and Goldman[4] the following structures **1**, **2**, and **3** are possible. Brown and Jensen studied in detail the mechanism of the sulfonylation reaction[4] and based primarily on kinetic evidence, considered **1** and **3** to be present in equilibrium, with **3** being the effective sulfonylating agent.



1 **2** **3**

Burton and Hopkins[6] claimed the use of sulfonylium perchlorates as reagents in sulfonylation reactions. It should be pointed out, however, that in the metathetic reactions of chlorides with silver perchlorate the elimination of silver chloride does not necessarily prove the formation of an ionic complex, as covalent perchlorates can also be formed.

$$RSO_2Cl + AgClO_4 = AgCl + RSO_2{}^+ClO_4{}^- \text{ or } RSO_2OClO_3$$

Klages and Malecki[7] subsequently studied "tosyl perchlorate" in the interaction of *p*-toluenesulfonyl chloride (bromide) with silver perchlorate in nitromethane solution. They concluded that sulfonyl cations in contrast to acyl cations are very electrophilic and react even with weakly nucleophilic anions to give sulfonyl halides. Thus, *p*-toluenesulfonyl bromide with anhydrous silver tetrafluoroborate gave only the sulfonyl fluoride and no aryl sulfone was formed. Toluene with *p*-toluenesulfonyl chloride and silver perchlorate, on the other hand, gave 4,4′-dimethyldiphenyl sulfone. As no direct physical observation of tosyl perchlorate was made, no conclusion can be reached whether it should be considered as the covalent ester p-$CH_3C_6H_4SO_2OClO_3$ or the ionic complex p-$CH_3C_6H_4SO_2{}^+ClO_4{}^-$.

Lindner and Weber claimed[8] the formation of the *p*-*N*,*N*-dimethylaminobenzenesulfonylium ion by the reaction of *p*-*N*,*N*-dimethylaminobenzenesulfonyl chloride with silver hexafluoroantimonate in sulfur dioxide solution.

$$p\text{-}(CH_3)_2N\text{—}C_6H_4SO_2Cl + Ag[MF_6] \xrightarrow[SO_2]{-25^\circ} [p\text{-}(CH_3)_2N\text{—}C_6H_4SO_2][MF_6] + AgCl$$

With the exception of Lindner and Weber's study,[8] no direct observation of the intermediate complexes was reported.[9] We wish now to report the antimony pentafluoride complexes of sulfonyl halides and the behavior of sulfonyl halides in the superacid system, FSO_3H–SbF_5.

Results and Discussion

We have extended our previous investigations of acyl halide–antimony pentafluoride complexes[10] to the study of sulfonyl halide complexes and also studied the behavior of sulfonyl halides in the superacid system, FSO_3H–SbF_5–SO_2ClF.

Preparation of the sulfonyl halide–antimony pentafluoride complexes was carried out according to our previously reported method for obtaining acyl halide complexes using excess antimony pentafluoride.[10]

The antimony pentafluoride complexes of sulfonyl halides and protonated sulfonyl halides were studied by nmr spectroscopy. Table I summarizes the pmr data obtained.

The following sulfonyl fluorides and chlorides were studied in both SbF_5–SO_2ClF and FSO_3H–SbF_5–SO_2ClF

* To whom correspondence should be sent.

(1) Part CXV: G. Olah and R. D. Porter, *J. Amer. Chem. Soc.*, in press.

(2) National Institutes of Health Predoctoral Research Investigator, 1970.

(3) For summary, see F. R. Jensen and G. Goldman, in "Friedel–Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Wiley–Interscience, New York, N. Y., 1963–1964, p 1003.

(4) F. R. Jensen and G. Goldman, ref 3, p 1319.

(5) M. S. C. J. Olivier, *Recl. Trav. Chim. Pays-Bas*, **35**, 166 (1915).

(6) H. Burton and H. B. Hopkins, *J. Chem. Soc.*, 4457 (1952).

(7) F. Klages and F. E. Malecki, *Justus Liebigs Ann. Chem.*, **691**, 15 (1966); *Chem. Ber.*, **96**, 2054 (1963).

(8) E. Lindner and H. Weber, *ibid.*, **101**, 2832 (1968).

(9) After conclusion of our work, P. A. W. Dean and R. J. Gillespie, [*J. Amer. Chem. Soc.*, **91**, 7260 (1969)] reported the ^{19}F nmr spectrum of a single donor:acceptor complex:the methanesulfonyl fluoride–antimony pentafluoride complex.

(10) (a) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *ibid.*, **84**, 2733 (1962); (b) G. A. Olah, *Rev. Chim. Acad. Raumain*, **7**, 1139 (1962); (c) G. A. Olah and M. B. Comisarow, *J. Amer. Chem. Soc.*, **88**, 3313 (1966).

TABLE I

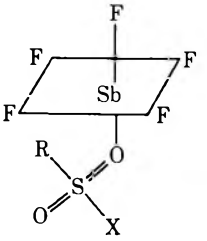
PMR SPECTRAL PARAMETERS[a] OF THE PARENT AND PROTONATED SULFONYL HALIDES AND SULFONYL HALIDE–ANTIMONY PENTAFLUORIDE COMPLEXES AT −60°

Compd	Registry no.	Solvent[b]	H_1	H_2	H_3	H_4	C_6H_5
CH_3SO_2F	558-25-8	A	3.35 (d, 6.0)				
		B	4.40 (d, 7.0)				
			4.26 (d, 7.0)				
		C	4.36 (d, 6.8)				
CH_3SO_2Cl	124-63-0	A	3.70				
		B	4.73				
			4.60				
		C	4.70				
$CH_3CH_2SO_2F$	754-03-0	D	3.71 (m)	1.70 (t, 7.0)			
		B	4.66 (m)	2.20 (t, 7.0)			
		C	4.65 (m)	2.20 (t, 7.2)			
$CH_3CH_2SO_2Cl$	594-44-5	A	3.63 (q, 7.0)	1.63 (t, 7.0)			
		B	4.71 (q, 7.0)	2.23 (t, 7.0)			
		C	4.63 (q, 7.0)	2.10 (t, 7.0)			
$CH_3CH_2CH_2SO_2F$	762-69-6	A	3.50 (m)	2.10 (m)	1.26 (t, 7.5)		
		B	4.50 (m)	2.65 (m)	1.70 (t, 7.0)		
		C	4.61 (m)	2.66 (m)	1.70 (t, 7.5)		
$CH_3CH_2CH_2SO_2Cl$	10147-36-1	A, −30°	3.81 (t, 7.5)	2.23 (m)	1.30 (t, 7.5)		
		B, −40°	4.71 (t, 7.0)	2.63 (m)	1.63 (t, 7.0)		
		C	4.63 (m)	2.55 (m)	1.57 (t, 7.0)		
$CH_3CH_2CH_2CH_2SO_2F$	660-12-8	A	3.60	1.96 (m)	1.63 (m)	1.15 (t, 7.2)	
		B	4.50 (m)	2.53 (m)	2.03 (m)	1.46 (t, 6.5)	
		C	4.56 (m)	2.47 (m)	2.00 (m)	1.45 (t, 6.5)	
$CH_3CH_2CH_2CH_2SO_2Cl$	2386-60-9	A	3.81 (m)	2.10 (m)	1.66 (m)	1.20 (t, 6.0)	
		B	4.73 (m)	2.53 (m)	2.00 (m)	1.65 (t, 7.0)	
		C	4.66 (m)	2.50 (m)	2.00 (m)	1.46 (t, 6.0)	
$C_6H_5SO_2F$	368-43-4	A					7.78
		B					8.42
		C					8.60
$C_6H_5SO_2Cl$	98-09-9	A					7.90
		B					8.56
		C					8.50
p-$CH_3C_6H_4SO_2F$	455-16-3	A	2.57				7.76
		B	2.93				8.25
		C	3.05				8.36
p-$CH_3C_6H_4SO_2Cl$	98-59-9	A	2.57				7.73
		B	2.93				8.23
		C	3.12				8.40

[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are given in parenthesis following the multiplicities: d = doublet; t = triplet; q = quartet; m = multiplet. [b] A = SO_2ClF; B = FSO_3H–SbF_5–SO_2ClF; C = SbF_5–SO_2ClF; D = SO_2.

solutions: methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, benzenesulfonyl fluoride and chloride and toluenesulfonyl fluoride and chloride.

Sulfonyl Halide–Antimony Pentafluoride Complexes.—The pmr spectrum of **methanesulfonyl fluoride,** CH_3SO_2F, in SO_2ClF solution at −60°, showed a doublet at δ 3.35 with a coupling constant of 6.0 Hz. The ^{19}F spectrum consisted of a quartet at ϕ 59.0 (from external CCl_3F). Attempted ionization of methanesulfonyl fluoride in SbF_5–SO_2ClF solution to obtain the corresponding sulfonylium ion was unsuccessful. The pmr spectrum recorded at −80° showed a methyl doublet at δ 4.41 with a H–^{19}F coupling of 6.8 Hz. The ^{19}F nmr spectrum showed the corresponding quartet at ϕ 58.6, further indicating that the fluorine atom is still bonded to sulfur and is further shielded by complex formation on sulfonyl oxygen atom with SbF_5. Thus, we conclude, as also indicated by Dean and Gillespie's ^{19}F study,[9] that the oxygen bonded donor:acceptor complex **1** is formed.



1, R = CH_3; X = F or Cl

Methanesulfonyl chloride in excess SbF_5 diluted with SO_2ClF at −80° showed a singlet at δ 4.56 deshielded about 0.86 ppm from that of the parent compound, indicating again the oxygen coordinated complex **1.**

Ethanesulfonyl fluoride in antimony pentafluoride–SO_2ClF solution showed the deshielded CH_2 multiplets at δ 4.77 and the methyl triplet at δ 2.23. The CH_2–F coupling (7.0 Hz) observed indicates that the oxygen coordinated donor:acceptor complex is formed.

The nmr spectrum of **ethanesulfonyl chloride** in antimony pentafluoride diluted with SO_2ClF similarly showed the methylene quartet at δ 4.63 and the methyl triplet at δ 2.10.

***n*-Propanesulfonyl chloride, *n*-propanesulfonyl fluoride, *n*-butanesulfonyl chloride** and ***n*-butanesulfonyl fluoride** in SbF_5–SO_2ClF solution also gave the sulfonyl oxygen coordinated donor:acceptor complexes. The pmr chemicals shifts and coupling constants are summarized in Table I, together with those of the parent sulfonyl halides. The H–^{19}F coupling observed in the complexes of propanesulfonyl fluoride and butanesulfonyl fluoride indicates that fluoride atoms are still bonded to sulfur and no sulfonylium ions are formed.

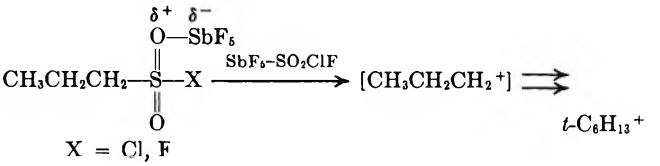
Benzenesulfonyl chloride and **fluoride** in SbF_5–SO_2ClF also form the donor:acceptor complexes with the aromatic protons centered at δ 8.50 and 8.60, respectively (about 0.6 ppm deshielded from the parent compounds in SO_2ClF).

The nmr spectrum of ***p*-toluenesulfonyl fluoride** and **chloride** in SbF_5–SO_2ClF showed the aromatic AB quartets at δ 8.36 and 8.40 (about 0.6 ppm deshielded from those of the parent compounds) and the methyl protons at δ 3.05 and 3.12, respectively, indicating that the donor:acceptor complexes are again formed. Furthermore, a ^{19}F spectrum of *p*-toluenesulfonyl fluoride–antimony pentafluoride complex showed a fluorine resonance in the $-SO_2F$ region at ϕ 64.8, implying that the fluoride atom is still bonded to the sulfur atom.

Cleavage Reactions of the Sulfonyl Halide–Antimony Pentafluoride Complexes.—The **methanesulfonyl fluoride–antimony pentafluoride** complex is thermally stable; the nmr spectrum showed no significant change from −80 to +65°. **Methanesulfonyl chloride–antimony pentafluoride** complex at +20° undergoes chlorine–fluoride exchange to give the methanesulfonyl fluoride–antimony pentafluoride complex, but it is not cleaved or decomposed.

Ethanesulfonyl chloride–antimony pentafluoride complex at +20° undergoes both chlorine–fluorine exchange and alkyl–sulfur cleavage, to give ethyl cation which rearranges to the more stable *tert*-butyl and *tert*-hexyl cations.[11] The same behavior was also observed in the case of the **ethanesulfonyl fluoride–antimony pentafluoride** complex.[12]

Both **propanesulfonyl fluoride–antimony pentafluoride** complex and **propanesulfonyl chloride–antimony pentafluoride** complex at +15° undergo alkyl–sulfur cleavage to give the (propyl cation) which is not observed as such and is immediately rearranged to the more stable *tert*-hexyl cations.



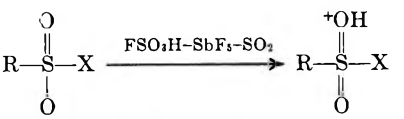
X = Cl, F

The **butanesulfonyl fluoride–antimony pentafluoride** and **butanesulfonyl chloride–antimony pentafluoride** complexes are stable up to −10°. At higher temperatures, alkyl–sulfur cleavage occurs to give the *tert*-butyl cation, as shown by a sharp singlet in the pmr spectra of the system at δ 4.10.

The donor:acceptor complex of **benzenesulfonyl fluoride** and **chloride** and **toluenesulfonyl fluoride** and **chloride** are stable. The nmr spectra showed no significant change from −60° to room temperature.

Our system is not well adaptable to study *p*-*N*,*N*-dimethylaminobenzenesulfonyl halides, as complexing on nitrogen cannot be avoided. We therefore have no data on the claimed highly stabilized p-$(CH_3)_2NC_6H_4SO_2^+$ ion.[8] As metathetic reactions with silver salts frequently run into serious difficulties, we await with interest further data, including nmr studies, on this reported system which presently seems to be the only claimed example of a stable sulfonylium ion.

Prontonated Sulfonyl Halides.—All the alkylsulfonyl halides studied are protonated in FSO_3H–SbF_5–SO_2 superacid system on sulfonyl oxygen. Although the proton on oxygen is not directly observed, yet the protonation is evident by the deshielding of the alkyl pro-



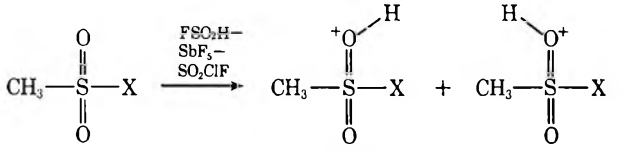
X = F, Cl; R = CH_3–, CH_3CH_2–, $CH_3CH_2CH_2$–, $CH_3CH_2CH_2CH_2$–, C_6H_5–, p-$CH_3C_6H_4$–

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

(12) The reversibility of the reaction was recently observed in the reaction of the ethyl fluoride–antimony pentafluoride complex with sulfur dioxide: G. A. Olah and J. R. DeMember, unpublished work.

ton nmr chemical shifts and the proton–fluorine coupling observable in protonated sulfonyl fluorides (see Table I).

The pmr spectrum of **protonated methanesulfonyl fluoride** in FSO_3H–SbF_5–SO_2ClF solution at −60° showed two doublets at δ 4.40 and 4.26 (J_{HF} = 7.0 Hz) with a relative area ratio of 30:70. This indicates, as in the case of the previously observed protonated methyl sulfone,[13] that two isomeric species (**2a** and **2b**, where X = F) are present.

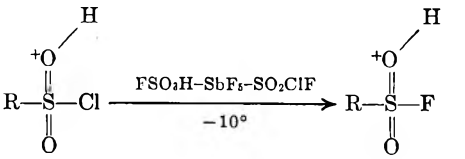


The coupling (7.0 Hz) between CH_3 and F indicates that the fluorine atom is still bonded to the sulfur atom and is not rapidly exchanging. It is interesting to note that only one isomeric form was observed for the methanesulfonyl fluoride–antimony pentafluoride complex. This is believed to be due to the steric effect of antimony pentafluoride which is much larger than the proton and sterically favors one form.

For **protonated methanesulfonyl chloride,** two forms (**2a** and **2b**, where X = Cl) are again observed. The pmr spectrum recorded at −60° showed the two methyl singlets at δ 4.75 and 4.60 with a relative area ratio of 60:40.

For protonated higher homologs of sulfonyl halides only one isomeric form is observed. No observable coupling was found between the proton on oxygen and the α-alkyl protons; hence no structural assignments could be made. Chemical shifts and coupling constants are summarized in Table I.

Cleavage Reactions of Protonated Sulfonyl Halides.—Protonated alkylsulfonyl chlorides in FSO_3H–SbF_5–SO_2ClF solution undergo chlorine–fluorine exchange at −10° to give the corresponding protonated sulfonyl fluoride. **Protonated methanesulfonyl fluoride** is stable with no indication of cleavage even when the solution was heated up to +65°. **Protonated ethanesulfonyl fluoride** is also stable. The pmr spectrum showed no significant change from −60° to room temperature. On further heating to +40°, the solution



R = CH_3–, CH_3CH_2–, $CH_3CH_2CH_2$–, $CH_3CH_2CH_2CH_2$–

turned dark and solidified. **Protonated propanesulfonyl fluoride** at +10° undergoes alkyl–sulfur cleavage to give, through alkylative dimerization of the propyl cation, *tert*-hexyl cations. **Protonated *n*-butanesulfonyl fluoride** also undergoes alkyl–sulfur cleavage to give the *tert*-butyl cation at −10°. **Protonated benzenesulfonyl fluoride** and **chloride** and ***p*-toluenesulfonylfluoride** and **chloride** are stable. The nmr spectrum showed no significant change from −60° to room temperature.

Experimental Section

Materials.—All the alkylsulfonyl chlorides and methanesulfonyl fluoride were commercially available materials. Ethane-, propane-, and butanesulfonyl fluoride were prepared by the method of Davis and Dick[14] by heating the corresponding sulfonyl chloride with 70% KF solution on a water bath for 20 min followed by distillation and extraction with ether.

Nmr Spectra.—Varian Associates Model A-56/60A spectrometer, equipped with a variable temperature probe, was used for all spectra. Chemical shifts are reported in ppm (δ) from external (capillary) tetramethylsilane or ppm (ϕ) from capillary $CFCl_3$.

Preparation of Solutions.—The procedures used for the preparation of solutions of the protonated sulfonyl halides and the sulfonyl halide–antimony pentafluoride complexes were identical with those described previously.[15,16]

Acknowledgment.—Support of our work by a grant from the National Institutes of Health is gratefully acknowledged.

(13) G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, in press.

(14) W. Davis and J. H. Dick, *J. Chem. Soc.*, 483 (1932).

(15) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).

(16) G. A. Olah and A. T. Ku, *J. Org. Chem.*, **35**, 331, 2159 (1970).

Stable Carbonium Ions. CXVII.[1] Protonation of Sulfites and Sulfates and Their Cleavage Reactions in Fluorosulfuric Acid–Antimony Pentafluoride Solution

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Protonation of a series of alkyl sulfites and sulfates was examined in FSO_3H–SbF_5 solution. Protonated sulfites could not be directly observed even at −60° as sulfur–oxygen cleavage occurred with ease to give the corresponding protonated alcohols and subsequently stable carbonium ions. Protonated dialkyl sulfates were observed in the case of dimethyl and diethyl sulfate, each showing two isomeric forms. Higher homologs undergo fast carbon–oxygen cleavage to yield the corresponding alkylcarbonium ions.

No study of sulfites and sulfates in superacid media was reported so far in the literature. In continuation of our study of the protonation of organic sulfur compounds like sulfonyl halides,[1] sulfonic acids, sulfinic acids, alkyl sulfonates, alkyl sulfinates,[3] sulfoxides, and sulfones[4] we felt it of interest to study the protonation and cleavage reactions of alkyl sulfites and sulfates in FSO_3H–SbF_5 solution.

Results and Discussion

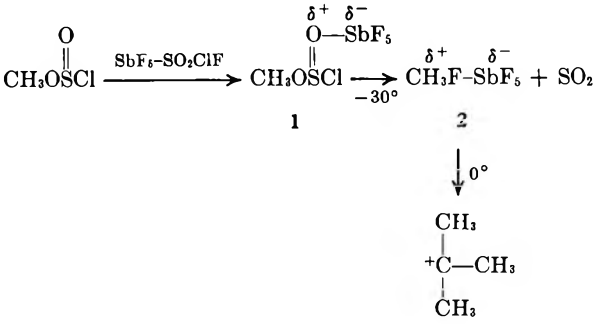
Sulfides.—The following sulfites were studied in FSO_3H–SbF_5–SO_2 solution at low temperature: dimethyl, diethyl, di-*n*-propyl, diisopropyl, di-*n*-butyl, diisobutyl, and dineopentyl sulfite.

Protonated sulfites could not be observed in FSO_3H–SbF_5 solution diluted with SO_2 even when the solutions were prepared and examined at −78°. Cleavage reactions had occurred.

The nmr spectrum of **dimethyl sulfite** in FSO_3H–SbF_5–SO_2 solution at −80° showed a sharp singlet at δ 5.63, a triplet at δ 4.66, and a quartet at δ 9.60. The latter two chemical shifts, assignable to protonated methanol, were reported previously.[5,6] This indicates that dimethyl sulfite in "magic acid" undergoes sulfur–oxygen cleavage to give protonated methanol and another species which gives a chemical shift of δ 5.63. At −40°, the resonance at δ 5.63 decreases and a new resonance appears at δ 4.40 which is assigned to the *tert*-butyl cation. Upon further raising the temperature, the nmr spectrum showed only the resonances for *tert*-butyl cation and protonated methanol.

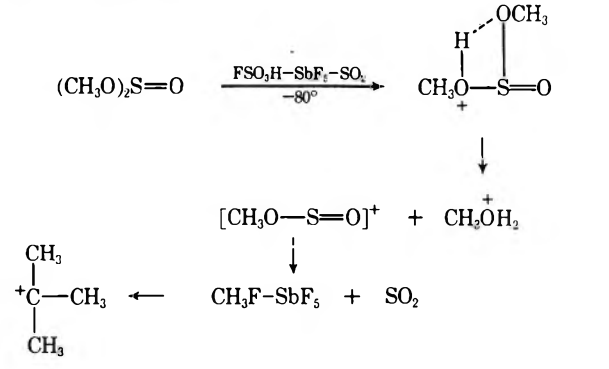
Methyl chlorosulfinate, CH_3O–S(=O)Cl, dissolved in antimony pentafluoride diluted with SO_2ClF, gave two sharp nmr singlets at δ 5.60 and 4.85. At −30°, the resonance at δ 5.60 increases at the expense of that at δ 4.85, which eventually disappeared completely. On further warming at 0°, a new peak which is assigned to the *tert*-butyl cation appeared at δ 4.50, and the resonance at δ 5.60 decreased with time. Finally, the nmr spectrum showed only one *tert*-butyl cation singlet at δ 4.50.

The resonance absorption at δ 5.60 is due to that of methyl fluoride–antimony pentafluoride complex. This assignment is made based on the fact that it not only has the same ^1H chemical shift as an authentic sample of methyl fluoride–antimony pentafluoride complex, but also has the same ^{13}C chemical shift (found at 119 ppm).[7] The resonance at δ 4.85 is in all probability due to that of the donor:acceptor complex **1**. At



−30°, **1** loses SO_2 to give methyl fluoride–antimony pentafluoride complex **2**. It is known that complex **2** goes to *tert*-butyl cation at higher temperature.

Data obtained indicate that the cleavage pathway for dimethyl sulfite in the superacid solution is as shown. The resonance absorption at δ 5.63 is due to the methyl fluoride–antimony pentafluoride complex which at higher temperature decomposes to the *tert*-butyl cation.



The site of protonation of sulfites cannot be directly detected based on the present data. There is indication in the low temperature (−100°) spectra of an nmr absorption at δ ~6.5 which could evolve at S protonation similar to that observed in the case of dimethyl sulfoxide. It is assumed, based on the ease of cleavage reactions, that protonation involves, at least in equilib-

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(1) Part CXVI: G. A. Olah, A. T. Ku, and J. O. Olah, *J. Org. Chem.*, **35**, 3925 (1970).

(2) National Institutes of Health Predoctoral Research Investigator, 1970.

(3) G. A. Olah, A. T. Ku, and J. A. Olah, *J. Org. Chem.*, **35**, 3908 (1970).

(4) G. A. Olah, A. T. Ku, and J. A. Olah, *ibid.*, **35**, 3904 (1970).

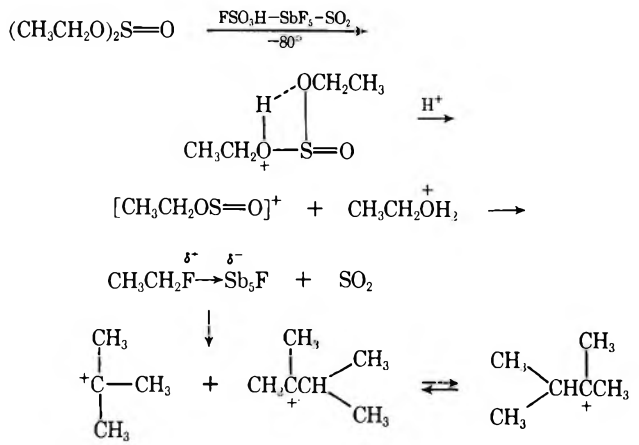
(5) G. A. Olah, J. Sommer, and E. Namanworth, *J. Amer. Chem. Soc.*, **89**, 3576 (1967).

(6) G. A. Olah and E. Namanworth, *ibid.*, **88**, 5327 (1966).

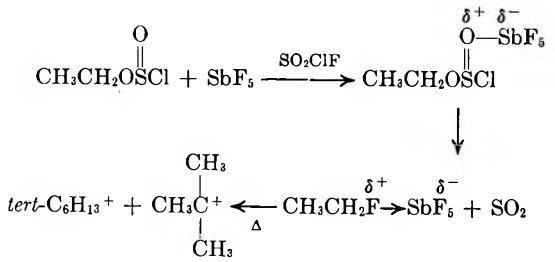
(7) G. A. Olah, J. R. DeMember, and R. H. Schlosberg, *ibid.*, **91**, 2112 (1969).

rium, the alkyl oxygen. The cleavage reaction (see subsequent discussion) is clearly O–S cleavage.

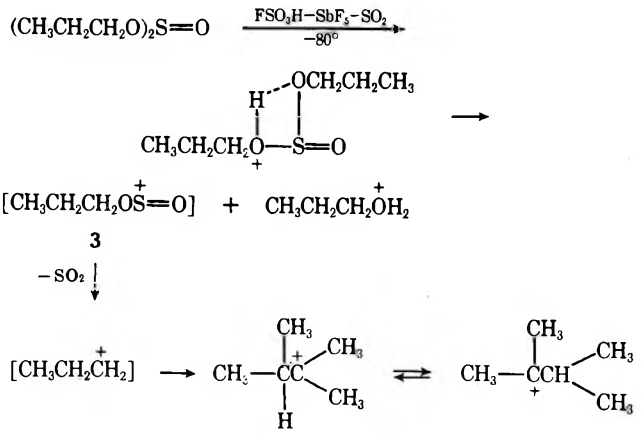
The nmr spectrum of **diethyl sulfite** in "magic acid," FSO_3H–SbF_5–SO_2, solution at −80° showed also that of the cleavage product protonated ethanol (CH_3 triplet at δ 1.56, $-CH_2-$ multiplet at 4.80 and $\overset{+}{O}H_2$ triplet at 9.20)[5,6] and the ethyl fluoride–antimony pentafluoride complex with CH_3 triplet at δ 1.93 and $-CH_2-$ quartet at 6.20. At higher temperature further cleavage reaction occurred and the nmr spectrum showed resonances for *tert*-butyl and *tert*-hexyl cations in addition to that of protonated ethanol. Thus the cleavage reaction of diethyl sulfite in "magic acid" is the same as that observed for dimethyl sulfite.



Ethyl chlorosulfinate in SbF_5–SO_2ClF at −80°, as in the case of methyl chlorosulfinate, gives the donor:acceptor complex (CH_2 quartet at δ 5.20, CH_3 triplet at 2.23). In addition, the nmr spectrum also showed a quartet at δ 6.40 which we believe to be due to the $-CH_2$ of the ethyl fluoride–antimony pentafluoride complex. The chemical shift of the CH_3 protons of the complex is overlapped by that of the donor:acceptor complex at δ 2.23. On warming, decomposition of ethyl fluoride–antimony pentafluoride complex to *tert*-butyl and *tert*-hexyl cations occurred. These data further proved the cleavage pathway of diethyl sulfite in "magic acid." The nmr spectrum of *di-n-propyl* sulfite in FSO_3H–SbF_5 solution diluted with SO_2 at −80° showed the absorptions for protonated propanol and that of *tert*-hexyl cations, indicating that both sulfur–oxygen and alkyl–oxygen cleavage had occurred. It is believed that di-*n*-propyl sulfite, as in the case of dimethyl sulfite, was first protonated and then underwent sulfur–oxygen cleavage to give protonated propanol and



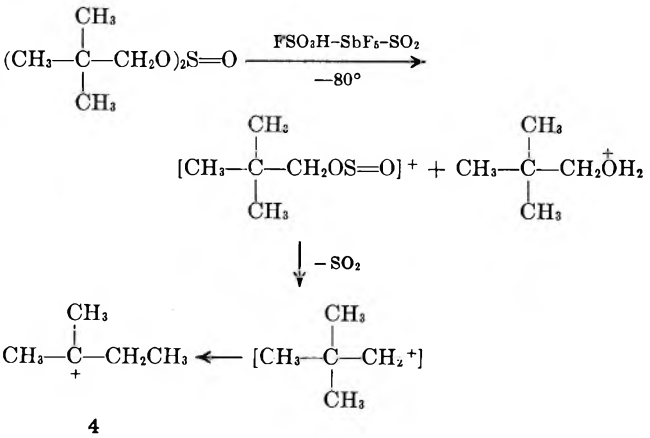
3 which is not observed and undergoes further cleavage to give the *n*-propyl cation which in turn rearranges to the more stable *tert*-hexyl cation.



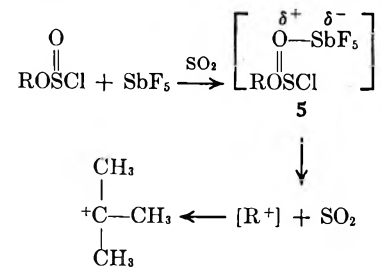
Diisopropyl sulfite, again, in FSO_3H–SbF_5–SO_2 solution undergoes both sulfur–oxygen and alkyl–oxygen cleavage to give the protonated isopropyl alcohol and *tert*-hexyl cation. The cleavage pathway is believed to be the same as that of di-*n*-propyl sulfite.

Accordingly, **di-*n*-butyl** and **diisobutyl sulfite** in FSO_3H–SbF_5–SO_2 solution undergo cleavages to give the corresponding protonated alcohol and *tert*-butyl cation.

The nmr spectrum of **neopentyl sulfite** in FSO_3H–SbF_5–SO_2 solution at −80° again showed no absorptions corresponding to the protonated species, but only that of the cleavage product, protonated neopentyl alcohol, and that of the *tert*-amyl cation (**4**). The cleavage is believed to be similar to that of di-*n*-propyl sulfite as shown in the following.



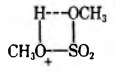
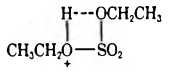
Ionization of isomeric **butyl chlorosulfinates**[8] in antimony pentafluoride–sulfur dioxide gave only the *tert*-butyl cation. In order to achieve the cleavage, warming of the samples to −10° was needed. Again, we feel that the reaction proceeds through intermediate **5**, although it was not directly observed.



(8) Work done with J. M. Bollinger and previously unpublished.

TABLE I

PMR SPECTRAL PARAMETERS[a] OF THE PARENT AND PROTONATED SULFATES AT −60°

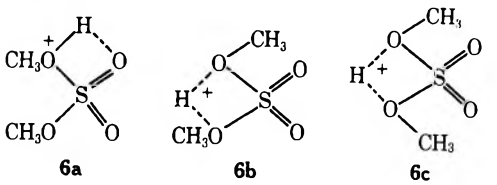
Compd	Registry no.	Solvent	CH_2	CH_3
$(CH_3O)_2SO_2$	77-78-1	SO_2		3.73
	26402-44-8	FSO_3H–SbF_5		4.86
		SO_2ClF		4.70
$(CH_3CH_2O)_2SO_2$	64-67-5	SO_2	4.10 (q, 7.0)	1.15 (t, 7.0)
	26402-45-9	FSO_3H–SbF_5	5.53 (q, 7.0)	1.95 (t, 7.0)
		SO_2ClF	5.33 (q, 7.0)	

[a] Chemical shifts are in parts per million from external TMS. Coupling constants in hertz are given in parentheses following the multiplicities: t = triplet, q = quartet.

It is of interest to mention that the conversion of alcohols into chlorosulfites or haloformates and their subsequent cleavage in SbF_5–SO_2/SO_2ClF represents a useful fragmentation method to generate carbonium ions.[9] It is also of interest to note that the chlorosulfite cleavage reactions provide further proof for the mechanism of the conversion of alcohols into chlorides by thionyl chloride.[10]

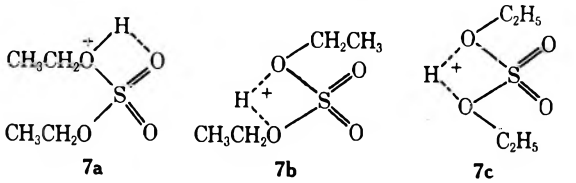
Sulfates.—The following sulfates were studied in FSO_3H–SbF_5–SO_2ClF solution at low temperature: dimethyl, diethyl, di-*n*-propyl, and di-*n*-butyl sulfate.

The nmr spectrum of **dimethyl sulfate** in FSO_3H–SbF_5–SO_2ClF solution at −80° showed a strong singlet at δ 4.85 and a small peak (*ca.* 1/5th of that at δ 4.85) at δ 4.66. These chemical shifts are much more downfield than those of the parent compound in SO_2 (see Table I), indicating that dimethyl sulfate is protonated presumably on alkyl oxygen although no proton on oxygen could be directly observed due to obvious fast exchange. These two singlets could be assigned to the methyl protons of any or all possible isomers **6a**, **b**, and **c**, of protonated dimethyl sulfate. No coupling was observed between the proton on oxygen and the methyl



6a **6b** **6c**

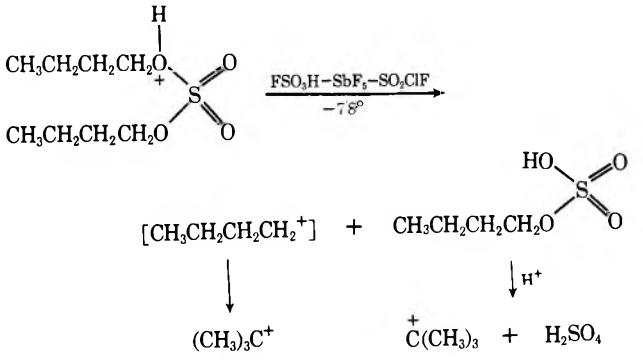
protons; hence no structural assignment could be made. The absence of coupling indicates rapid exchange which could not be frozen even at the lowest temperatures observable, −120°. The dotted lines used in the formulas are intended to denote oxygen sites between which proton equilibration can take place and not distinct species (of course, intramolecular exchange with the solvent also must be considered). Similar observations were also made for protonated diethyl sulfate in the same acid solvent system. Again, no proton on oxygen and no coupling was observed between the proton on oxygen and the α-alkyl protons, and no structural assignment could be made. The chemical shifts and coupling constants of the parent and protonated dimethyl and diethyl sulfates are given in Table I.



7a **7b** **7c**

The nmr spectrum of both protonated dimethyl and diethyl sulfate in FSO_3H–SbF_5–SO_2ClF showed no significant change from −80° to room temperature.

However, **protonated di-*n*-propyl** and **di-*n*-butyl** sulfate could not be observed. The nmr spectrum of di-*n*-propyl and di-*n*-butyl sulfate in FSO_3H–SbF_5–SO_2ClF showed only the resonances of the most stable cation, *tert*-hexyl and *tert*-butyl cation, respectively. This indicates that alkyl oxygen cleavage occurred, for example



The difference in the superacid protolytic cleavage reactions of dialkyl sulfites and sulfates can be found in the fact that the former undergo oxygen–sulfur cleavage (in good accordance with available data on acid-catalyzed hydrolysis of dialkyl sulfites)[11] whereas the latter only undergo carbon–oxygen cleavage (again in accordance with hydrolysis behavior of dialkyl sulfates).[12] Primary alkyl groups, particularly methyl and ethyl, are poor leaving groups in the alkyl–oxygen cleavage reaction, thus the stability of dimethyl and diethyl sulfate, as compared to their sulfites.

(9) G. A. Olah, *Chem. Eng. News*, **45**, 77 (1967).

(10) E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.*, **74**, 308 (1952), and references cited therein.

(11) For a summary, see H. F. Van Woerden, *Chem. Rev.*, **63**, 562 (1963), and references given therein.

(12) E. T. Kaiser, M. Ranar, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 602 (1963); E. T. Kaiser, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1959; R. E. Robertson and S. E. Sugamori, *Can. J. Chem.*, **44**, 1728 (1966).

Experimental Section

Materials.—*n*-Propyl, isopropyl, *n*-butyl, isobutyl, *n*-pentyl, and neopentyl sulfite were prepared by the reaction of the corresponding alcohol with thionyl chloride.[13] Dimethyl and diethyl sulfite were commercially available. Alkyl chlorosulfinates were prepared by the reaction of alcohols with excess thionyl chloride.[14]

Di-*n*-propyl and di-*n*-butyl sulfate were prepared by the reaction of the corresponding sulfite with sulfuryl chloride. Dimethyl and diethyl sulfate were commercially available materials.

(13) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, Wiley, New York, N. Y., 1943, p 112; p 111.

(14) P. D. Bartlett and H. F. Herbrandson, *J. Amer. Chem. Soc.*, **74**, 5971 (1952).

Nmr Spectra.—Varian Associates Model A-56/60A spectrometer, equipped with a variable temperature probe, was used for all spectra. Chemical shifts are reported in ppm (δ) from external (capillary) tetramethylsilane, as in previous publications in this series.

Preparation of Solutions.—The procedure used for the preparation of solutions of the protonated sulfites and sulfates was identical with that described previously.[15]

Acknowledgment.—Support of our work by a grant from the National Institutes of Health is gratefully acknowledged.

(15) G. A. Olah, D. H. O'Brien, and A. M. White, *ibid.*, **89**, 5694 (1967)

The Synthesis of 1,8-Di-*tert*-butylnaphthalenes

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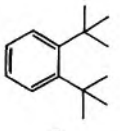
Received June 26, 1970

A direct synthetic route to *peri*-di-*tert*-butylnaphthalenes, **23**, **24**, and **25**, is described. A key step involves Diels–Alder reaction of a benzene with *tert*-butylfurans. Reaction of the naphthalenes with acid serve to demonstrate behavior that is different from the di-*tert*-butylbenzene case. Thus, crowding in **23** results in diminished reactivity at the peri position due to hindrance rather than increased reactivity resulting from relief of strain. Similarly, **25** is 1–2 orders of magnitude less reactive than **21** under identical acid conditions. Extreme structural perturbation is also detected *via* nmr and uv spectroscopy.

One approach to the study of van der Waals repulsion effects has been to synthesize aromatic hydrocarbons where the geometric requirements for π orbital overlap force crowding of bulky substituents located on the aromatic ring. The resulting balance between relief of strain and distortion of the planar aromatic framework has been examined by both physical and chemical probes. Examples of structures that have been studied are *o*-di-*tert*-butylbenzene (**1**)[2] and 1,12-dimethylbenzo[*c*]phenanthrene (**2**),[3] as well as related



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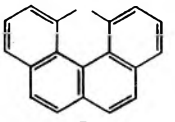
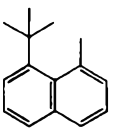


2

systems such as *o*-di-*tert*-butylquinoxaline[4] and β,β'-dihydroxy-2,3-di-*tert*-butylnaphthalene.[5] The present work on *peri*-*tert*-butylnaphthalenes developed from the principle stated by Newman to estimate qualitatively the steric effects of ortho substituents in aromatic compounds:[6] (1) a fused aromatic ring is equivalent to a methyl group, and (2) either (a) a fused aromatic ring containing a methyl group in the adjacent peri position, or (b) two continuously angularly fused aromatic rings is equivalent to a *tert*-butyl group. Thus it was our estimate that a 1-*tert*-butyl-8-methylnaphthalene (**3**) is comparable in its crowding to *o*-di-*tert*-butylbenzene (**1**) and that a 1,8-di-*tert*-butylnaphthalene (**4**) is more crowded than **1** or **3**. A strain energy of 22 kcal/mol has been determined for 1,[2a] and using a value of 6–7 kcal/mol for the strain in *o*-*tert*-butyltoluene, one can assign a 15–16 kcal/mol increment for the replacement of methyl by *tert*-butyl.[7] Thus we can estimate that the substitution of the methyl in **3** by *tert*-butyl in **4** would result in a strain energy of 37–38 kcal/mol.



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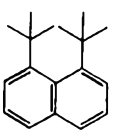


4

Syntheses of 1-*tert*-butylnaphthalene have been reviewed recently.[8] Our experience with the use of a *tert*-butylbenzyne–furan reaction followed by aromatization to afford 1,4-di-*tert*-butylnaphthalene led us to extend the method to the peri-crowded series.[9] The sequence shown below was developed for the preparation of a *tert*-butylbenzyne **8**, with the critical step being the aprotic diazotization and decarboxylative elimination of the anthranilic acid (**7**).[10]

Two results of some interest, although not germane to the naphthalene problem have been obtained with **7** and **8**. When acid **7** was treated with dicyclohexylcarbodiimide, the benzoxazine **9** (20% yield) was

* To whom correspondence should be addressed.

(1) (a) Portions of this work have been previously reported: R. W. Franck and E. G. Leser, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, ORGN 167; R. W. Franck and E. G. Leser, *J. Amer. Chem. Soc*, **91**, 1577 (1969). (b) This paper is based on the Ph.D. Thesis of E. G. L., Fordham University, 1970. (c) This research was supported in part by Fordham University funds, NSF Grant GP 7754, and an NSF Traineeship for E. G. L.

(2) (a) E. M. Arnett, J. C. Sanda, J. M. Bollinger, and M. Barber, *J. Amer. Chem. Soc.*, **89**, 5389 (1967); (b) A. W. Burgstahler, P. Chien, and M. O. Abdel-Rahman, *ibid.*, **86**, 5281 (1964).

(3) M. A. Frisch, C. Barker, J. L. Margrave, and M. S. Newman, *ibid.*, **85**, 2356 (1963).

(4) G. J. Visser, A. Vos, A. deGroot, and H. Wynberg, *ibid.*, **90**, 3253 (1968).

(5) L. R. C. Barclay, G. R. Nixon, H. M. Foote, and S. L. Barclay, *Can. J. Chem.*, **47**, 4313 (1969).

(6) M. S. Newman and W. H. Powell, *J. Org. Chem.*, **26**, 812 (1961).

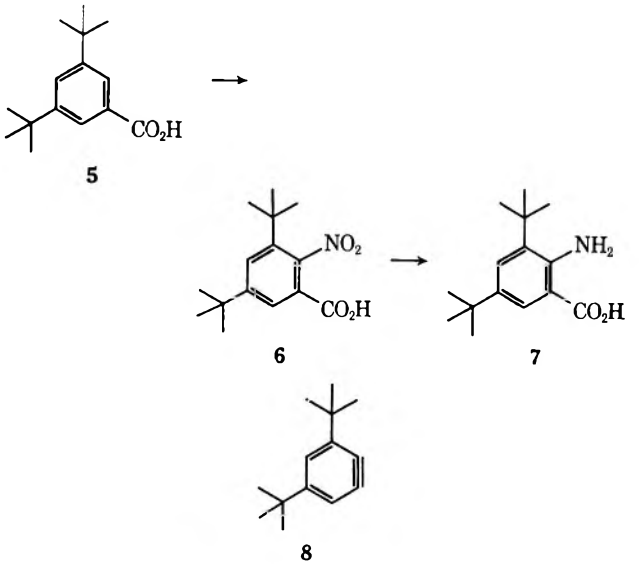
(7) H. C. Brown, *J. Chem. Soc.*, 1248 (1956); (b) J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, **80**, 905 (1958); (c) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955).

(8) H. Van Bekkum, T. J. Nieuwstad, J. Van Barneveld, P. Klapwijk, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas.*, **88**, 1028 (1969).

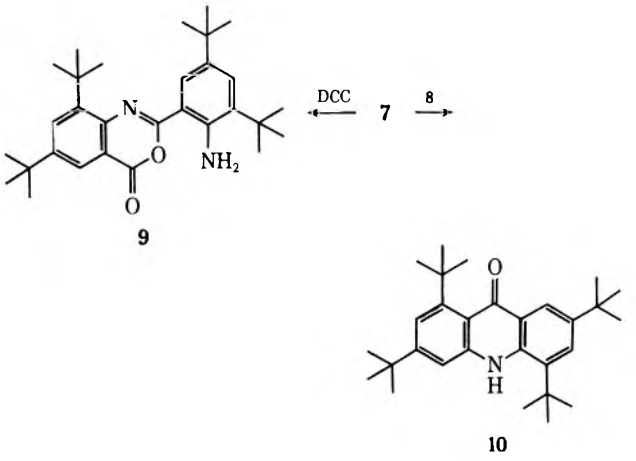
(9) R. W. Franck and K. Yanagi, *J. Org. Chem.*, **33**, 811 (1968).

(10) L. Friedman and F. M. Logullo, *ibid.*, **34**, 3089 (1969).

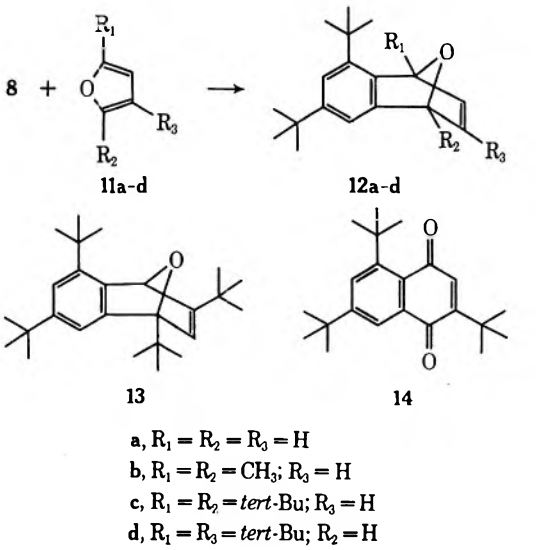
formed.[11] When no diene was present in the diazotization–elimination step to form **8**, leaving **7** as the only



benzyne trap, there was formed the acridone **10**.[12] The proof that **10** was the C_s isomer rather than the C_{2v} possibility required an nmr solvent shift study (see Experimental Section).

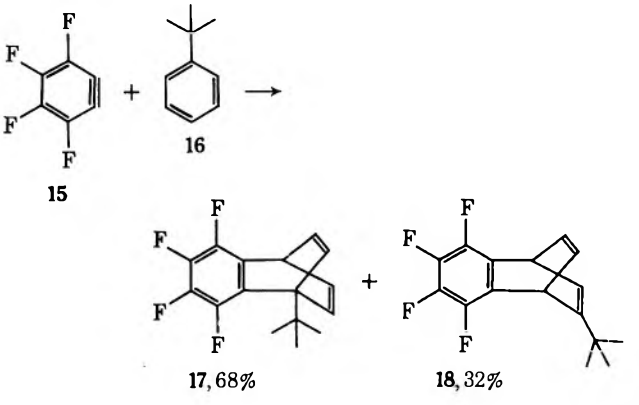


Generation of the benzyne **8** in the presence of furans **11a–c** afforded Diels–Alder adducts **12a–c** in yields of 94, 89, and 9%, respectively. The reaction with di-*tert*-butylfuran **11c** was sensitive to time and concentration. The acridone **10** was formed in moderate yield (23%) in some cases. We postulated that the *tert*-butyl *vs. tert*-butyl repulsion in the transition state for **12c** formation prevented the attainment of optimal overlap and that side reactions became competitive. Thus when furan **11d** was reacted with benzyne **8**, the expected product was the uncrowded adduct **13**. The adduct isolated (34–37%), however, proved to be **12d** (as shown conclusively by later conversions). The crude reaction mixture was shown (glpc) to consist of **12d** (six parts), and unknown substance [not conclusively **13** (three parts)], and quinone **14** (one part). A simple explanation for the formation of **12d** in good yield is that the transition state for this Diels–Alder



a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = CH_3$; $R_3 = H$
c, $R_1 = R_2 =$ *tert*-Bu; $R_3 = H$
d, $R_1 = R_3 =$ *tert*-Bu; $R_2 = H$

reaction does not have both new bonds formed to the same extent. Even though 4 + 2 cycloadditions of benzyne have been predicted to be concerted[13] and demonstrated to be stereospecific,[14] the present case may be an example of nonsimultaneity in bond formation. The unhindered benzyne and furan termini with no steric repulsions could develop more bonding earlier in the reaction coordinate than the more hindered termini. A similar argument may be adduced for the observed ratios of adducts obtained in the reaction of tetrafluorobenzyne (**15**) with *tert*-butylbenzene (**16**).[15] The change in reactivity of arylisobenzofurans toward



vinylene carbonate has been rationalized in a similar manner.[16] The appearance of quinone **14** in the reaction mixture was rationalized as coming from **12d** *via* a reaction sequence involving acid-catalyzed ring opening, de-*tert*-butylation, and air oxidation. When a sample of **12d** was treated with ethanolic HCl for several minutes in the absence of air, a phenolic substance could be detected by ir spectroscopy. Exposure of the presumed phenol to air resulted in the appearance of carbonyl bands, and a sample of quinone **14** could be isolated.

(11) G. Schroeter, *Justus Liebigs Ann. Chem.*, **367**, 129, 153 (1909).
(12) (a) S. F. Dyke, A. R. Marshall, and J. P. Watson, *Tetrahedron*, **22**, 2515 (1966); (b) R. Howe, *J. Chem. Soc. C*, 478 (1966).
(13) R. Hoffman A. Inamura, and W. J. Hehre, *J. Amer. Chem. Soc.*, **90**, 1499 (1968).
(14) (a) M. Jones, Jr., and R. H. Levin, *ibid.*, **91**, 6411 (1969); (b) R. W. Atkin and C. W. Rees, *Chem. Commun.*, 152 (1969).
(15) J. P. N. Brewer, I. F. Eckhard, H. Heaney, and B. A. Marples, *J. Chem. Soc. C*, 664 (1968).
(16) M. Newman, *J. Org. Chem.*, **26**, 2630 (1961).

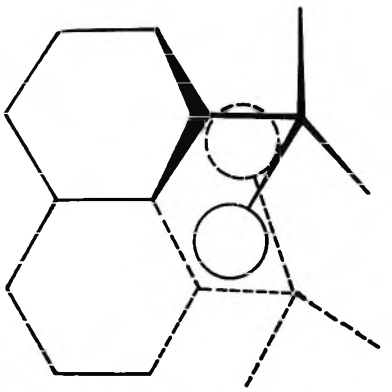
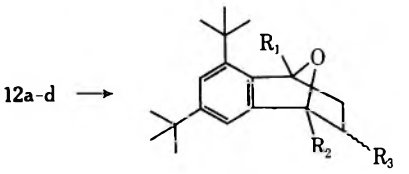


Figure 1.—The steric shielding of a peri carbon by a neighboring *tert*-butyl group.

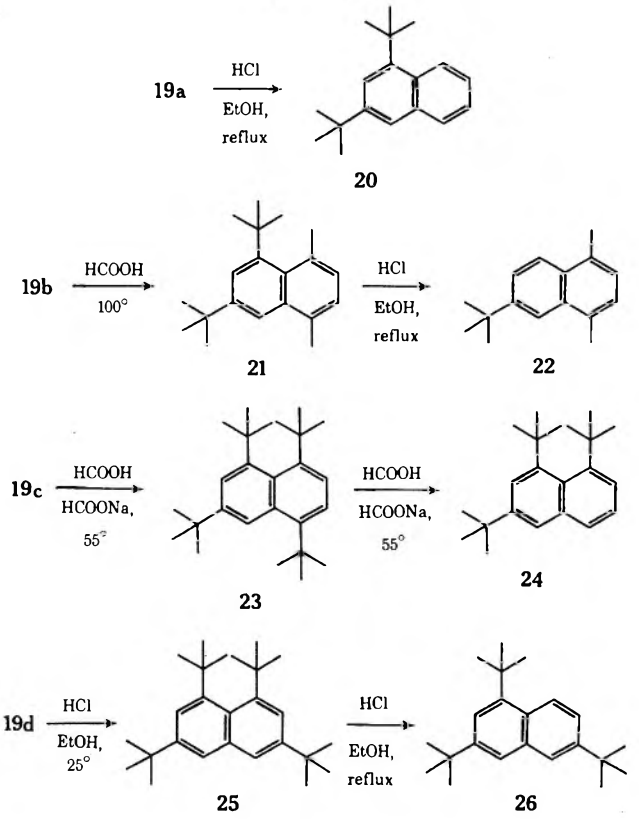
Catalytic hydrogenation of the adducts **12a–d** proceeded in high yield to form the saturated endoxides **19a–d**. This series of compounds was then subjected



19a–d

to acid-catalyzed dehydration conditions to form the naphthalenes as depicted in the scheme below (Scheme I). Whereas naphthalene **20** was stable toward re-

SCHEME I



fluxing ethanol saturated with HCl, the *o*-di-*tert*-butylbenzene analog **21** readily lost (half-life 0.05 hr) the crowded 1-*tert*-butyl group to yield **22**. This facile dealkylation to relieve steric repulsion is similar to that in the benzene series, except that in the latter case, a stronger Lewis acid was required to protonate the unactivated ring.[2] The exclusive formation of naphthalene **23** without further acid-catalyzed de-*tert*-butylation to produce **24** was not achieved. The Experimental Section summarizes a wide variety of experiments conducted in search of proper conditions of acidity. That the less hindered *tert*-butyl group in **23** was lost was demonstrated by nmr data (*vide infra*) which are quite unique for each possible *tert*-butyl environment. The unexpected dealkylation under mild conditions deserves further comment. One possible distortion to relieve crowding by the *peri*-di-*tert*-butyl groups could be a twisting of the naphthalene framework so that the stability of the aromatic nucleus would be reduced and would be susceptible to protonation by weak acids. The greatest relief of crowding would occur if one of the peri-disubstituted positions were protonated. Model studies show that there is extra steric shielding of one peri carbon by the adjacent *tert*-butyl (if the naphthalene ring is indeed twisted), thus preventing the approach of the protonating solvent from the lateral direction that would allow σ complex formation[17] (Figure 1). Thus, the less hindered carbon is protonated and the *tert*-butyl is lost because of the relief of the 6–7 kcal/mol of *o*-*tert*-butyltoluene strain. The observed stability of 1-*tert*-butylnaphthalene to H_3PO_4–BF_3 acid conditions[18] can be explained by noting that these conditions are known to be nonrearranging and perhaps insufficient to protonate 1-*tert*-butylnaphthalene. Alternately, one could argue that the 5-*tert*-butyl in **23** is more strained than a simple 1-*tert*-butyl group because of the buttressing effect of the 3-*tert*-butyl on the peri H at C_4. The HCl-catalyzed dealkylation of **25** to form **26** has a half-life of 1.8 hr, an order of magnitude greater than the corresponding dealkylation of **21**. Although the greater relief of strain to be achieved in the de-*tert*-butylation of **25** would account for *a priori* a faster rate of protonation and dealkylation than for **21**, one can rationalize the observed slower rate by reinvoking the argument of steric hindrance to lateral approach of acid that was developed for **23**.

Nmr Spectra.—Molecular interactions in peri-substituted naphthalenes have been investigated by nmr methods, including the effect of peri substituents which cause significant deshielding of the neighboring peri proton.[8,9] This magnetic deshielding of protons due to intramolecular steric interactions has been the subject of a recent analysis by Cheney.[19] It was pointed out that the degree of deshielding observed for a compressed proton H is dependent upon the conformational geometry existing between the C–H bond and the interacting proton H′. The magnitude of the steric shift was shown to depend upon the component of the nonbonded proton–proton repulsive force along the C–H bond axis. Using our earlier work on 1,4-di-*tert*-butylnaphthalenes as a precedent, assignments of resonances were made as listed in Table I. It will be observed that β-*tert*-butyl resonances serve as an excellent internal standard and that the downfield shifts for peri H's compressed by *tert*-butyls are consistent with previous work. It can be seen in the cases of naphthalenes

(17) E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964).
(18) H. M. Friedman and A. L. Nelson, *ibid.*, **34**, 3211 (1969).
(19) B. V. Cheney, *J. Amer. Chem. Soc.*, **90**, 5386 (1968).

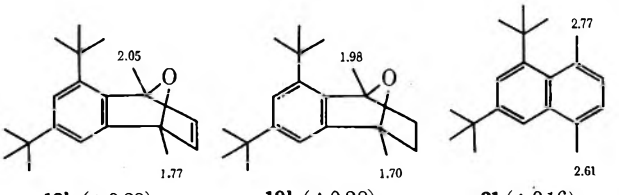
TABLE I

NMR DATA FOR *tert*-BUTYLNAPHTHALENES

Compd	β	α	peri	Other resonances[a]
20	1.40	1.64		7.17-7.82 (m, 3), 7.50 (s, 2), 8.30 (m, 1, H_8)
21	1.42	1.59		2.61 (s, 3, C-5 CH_3), 2.77 (s, 3, C-8 CH_3), 6.99 (s, 2, H_6 and H_7), 7.66 (d, 1, J_{24} = 2 Hz, H_2), 7.72 (d, 1, J_{42} = 2 Hz, H_4).
22	1.40			2.58 (s, 3), 2.62 (s, 3), 7.03 (s, 2, H_2 and H_3), 7.46 (dd, 1, J_{78} = 9 Hz and J_{75} = 2 Hz, H_7), 7.83 (d, 1, J_{87} = 9 Hz, H_8), 7.83 (d, 1, J_{57} = 2 Hz, H_5).
23	1.42	1.57	1.22 1.24	7.10 (d, J = 8 Hz), 7.28 (d, 1, J = 8 Hz), 7.43 (d, 1, J = 1.8 Hz, H_2), 7.90 (d, 1, J = 1.8 Hz, H_4).
23	1.40		1.27 1.28	7.1-7.6 (m, 5).
25	1.40		1.30	7.22 (d, 2, J = 1.7 Hz, H_2 and H_7), 7.48 (d, 2, J = 1.7 Hz, H_4 and H_5).
26	1.43	1.65		7.48 (dd, 1, J_{78} = 9.2 Hz and J_{75} = 2 Hz, H_7), 7.57 (d—overlapping with part of H_7 absorption, 2, J_{42} = J_{57} = 2 Hz, H_2 and H_5), 7.78 (d, 1, J_{24} = 2 Hz, H_4), 8.34 (d, 1, J_{87} = 9.2 Hz, H_8).

[a] Chemical shifts are in parts per million (ppm) relative to TMS as an internal standard, CCl_4 solvent.

24 and **25**, which were not the expected products, that the nmr data obtained would not be consistent with that predicted for the isomeric compounds originally expected. The J_{78} in naphthalene **26** is supportive evidence for the recently proposed theory of J_{HH} coupling in conjugated carbocyclic molecules.[20] The introduction of a *peri*-*tert*-butyl increases *J ortho* from 8.30 to 8.88 Hz. In benzene, a *tert*-butyl increases *J* by 0.32 Hz. Thus, the expected *J ortho* in **26** is (8.30 + 0.58 + 0.32) = 9.2 Hz, in good agreement with experiment. It is informative to compare the chemical shifts of the crowded and uncrowded methyl groups in the series **12b**, **19b**, **21**. A simple assumption of a direct relationship between the degree of crowding and the magnitude of the compression shift *is not* correct. The peri methyl in **21**, compared to the internal standard of the other methyl, is more compressed than in the precursors **12b** and **19b**, yet it is deshielded to a lesser extent; and in fact, the shift is approximately the same as that observed in 1,3,5,8-tetramethylnaphthalene (0.18 ppm).[21] In *o*-di-*tert*-butylbenzenes, the resonances of the *tert*-butyls have been deshielded by about 0.2 ppm from that of uncrowded *tert*-butyls. In our peri-crowded *tert*-butyls in **23**, **24**, and **25**, an upfield shift is observed. This information can be rationalized using the same twisting argument (*vide supra*) that explained the observed chemical inertness of the peri positions. If the framework is twisted so that the *tert*-butyls lie above and below the mean plane of the ring, the protons will be out of the zone of maximum deshielding of the aromatic system. Hence, their resonance would occur upfield from "normal" expectation. Also, models of this twisted naphthalene indicate that the *tert*-butyls would be free to rotate, thus explaining the nonobservance of line broadening or signal multiplicity.[15] The assumption of a twisted naphthalene framework has a corollary requirement that the naphthalenes be chiral. An nmr method of detecting chirality without resolution is to use a chiral solvent so as to form diastereoisomeric solvates and induce a doubling of nmr peaks.[22] When the spectrum of naphthalene **25** was examined in l-carvone, the 1,8-*tert*-butyl resonance, at 60 MHz, was broadened relative to the 3,6-*tert*-butyl band. However, at 220 MHz, the line widths and peak heights of the two bands were identical.[23] Since increasing the field strength in the nmr determination did not enhance the apparent broadening which might have been the beginnings of peak doubling, the results are best explained by relaxation arguments. Relaxation of spin is directly proportional to solvent viscosity (and carvone is viscous), while it is inversely proportional to the square of the field strength (that contribution to relaxation from anisotropic shielding).[24] Thus the viscosity effect observed at 60 MHz is countered by a field strength effect at 220 MHz.



12b (Δ 0.28) **19b** (Δ 0.28) **21** (Δ 0.16)

Uv Spectra.—Dale has studied the variation in uv spectra as a function of group size in benzenes.[25] The *o*-di-*tert*-butyl interaction causes a slight loss of intensity and fine structure compared to the less crowded homologs. A large bathochromic shift is observed when three *tert*-butyl groups are on adjacent benzene ring positions.[26] For a comparison of the uv spectra of the naphthalenes prepared in this research with the analogous methylnaphthalene spectra in the literature, solvent differences and substituent differences must be accounted for. In fact, solvent variation effects in naphthalene uv spectra are nonexistent. Good examples for this rest in comparison of the spectra of 1,2,5- and 1,2,7-trimethylnaphthalenes taken in petroleum ether[27] and ethanol[28] which are identical, respectively. The nearly identical spectra of 1,3,6-trimethylnaphthalene (in petroleum ether) and 1,3,6-tri-*tert*-butylnaphthalene (**26**) (in ethanol) are compared in Figure 2. There is neither a solvent effect or a substituent effect in replacing methyl with *tert*-butyl. The comparison (Figure 3) of the uv of 1,3,8-trimethylnaphthalene (petroleum ether) and that of the

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(22) W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, **91**, 5150 (1969).

(23) We thank Professor W. Gibbons of Rockefeller University for this spectrum.

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(25) J. Dale, *Chem. Ber.*, **94**, 2821 (1961).

(26) E. M. Arnett and J. M. Bollinger, *Tetrahedron Lett.*, 3803 (1964).

(27) M. J. Kamlet, Ed., "Organic Electronic Spectral Data," Vol. I, Interscience, New York, N. Y., 1960, p 522.

(28) H. E. Ungnade, Ed., *ibid.*, Vol. II, p 363.

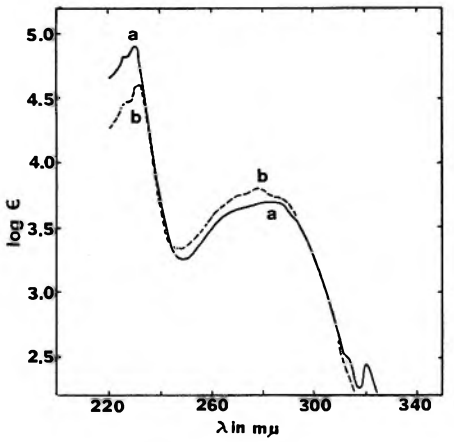

Figure 2.—Uv spectra of 1,3,6-trialkylnaphthalenes: a, 1,3,6-trimethylnaphthalene [E. Heilbronner, U. Fröhlicher, and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949)]; b, 1,3,6-tri-*tert*-butylnaphthalene (**26**).

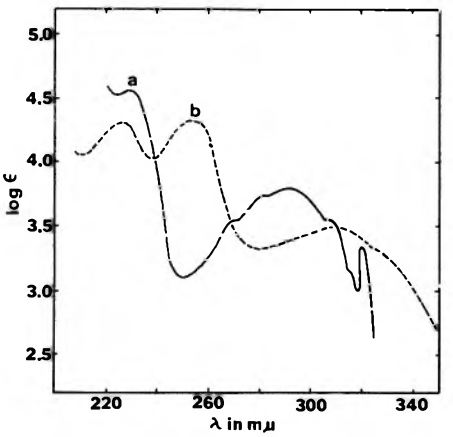

Figure 3.—Uv spectra of 1,3,8-trialkylnaphthalenes: a, 1,3,8-trimethylnaphthalene [E. Heilbronner, U. Fröhlicher, and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949)]; b, 1,3,8-tri-*tert*-butylnaphthalene (**24**).

peri-crowded 1,3,8-tri-*tert*-butylnaphthalene **24** (ethanol) shows the four effects of distortion due to the 1,8-*tert*-butyl interaction. Bathochromism of maxima (≈20 mμ), the appearance of a new band which is probably the result of a shift of a maximum in the 200 mμ range, reduction in intensity, and loss of fine structure are observed. Similar perturbations are seen in the comparison of spectra of 1,3,6,8-tetramethylnaphthalene (ethanol) and the homologous tetra-*tert*-butyl compound **25** (ethanol) in Figure 4. The spectra in ethanol of three 1,3,5,8-tetraalkylnaphthalenes are compared in Figure 5. The spectrum of **21**, the *o*-di-*tert*-butylbenzene homorph, shows the expected slight spectral differences from the model 1,3,5,8-tetramethylnaphthalene. Larger structural perturbation due to 1,8-*tert*-butyl interaction in **23** is evidenced again by the four effects listed above. The observed bathochromic shifts in our series correspond well with that observed for 1,2,3,5-tri-*tert*-butylbenzene.[26] In the development of synthetic methods for the *peri*-di-*tert*-butylnaphthalene system, we have already discovered chemistry that is not a logical extension of *o*-di-*tert*-butylbenzene studies. With a reasonable synthetic route in hand, further physical and chemical probing of this new system can be undertaken.

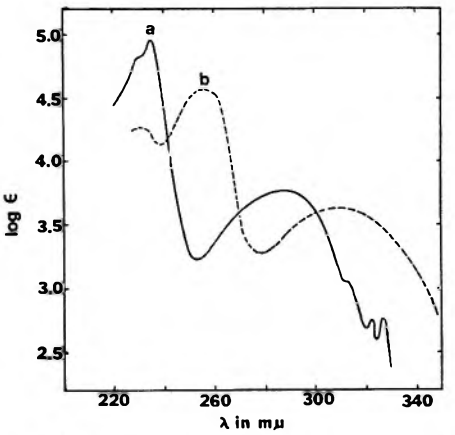

Figure 4.—Uv spectra of 1,3,6,8-tetraalkylnaphthalenes: a, 1,3,6,8-tetramethylnaphthalene [P. Canonne and A. Regnault, *Can. J. Chem.*, **45**, 1267 (1967); we thank Professor Cannone for a gift of this naphthalene]; b, 1,3,6,8-tetra-*tert*-butylnaphthalene (**25**).

Experimental Section[29]

3,5-Di-*tert*-butylbenzoic Acid (5).—Following the procedure of Wepster,[30] 88.0 g (0.432 mol) of 3,5-di-*tert*-butyltoluene[31] was converted to 80.1 g (79%) of acid **5**: mp 177–178° (lit.[27] mp 172–173°); ir (CCl_4) 3.1–3.4 (acid OH), 3.44 (*tert*-butyl), 3.7–4.0 (several weak bands), 5.79 (monomeric C=O), 5.95 (dimeric C=O), and 8.00 μ.

2-Nitro-3,5-di-*tert*-butylbenzoic Acid (6).—Employing a salt–ice bath, 81 ml of fuming nitric acid (sp gr 1.59–1.60) was cooled to below 10°. This temperature was maintained throughout the *slow* addition of 27.5 g (0.118 mol) of 3,5-di-*tert*-butylbenzoic acid to the rapidly stirred nitric acid. After addition was completed, the solution was stirred at this temperature (5°) for 15 min and then at room temperature for 30 min. The product comes out of solution during the addition of the benzoic acid.

The reaction mixture was poured into ice–water, and the precipitate was filtered, washed acid free, and air-dried. Recrystallization of the crude material from ethanol gave 26.8 g (82%) of pure **6**: mp 206–208°; ir ($CHCl_3$) 3.1–3.4 (acid OH), 3.7–4.0 (several weak bands), 5.76 (monomeric C=O) 5.90 (dimeric C=O), 6.55 (NO_2), and 7.32 μ (NO_2); nmr ($CDCl_3$) δ 1.38 (s, 9), 1.45 (s, 9), 7.98 (d, 1, J = 2 Hz), 8.13 (d, 1, J = 2 Hz), and 10.22 ppm (s, 1).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.39; H, 7.59; N, 5.07.

3,5-Di-*tert*-butylanthranilic Acid (7).—To 10 ml of absolute ethanol was added 1.85 g (6.62 mmol) of 2-nitro-3,5-di-*tert*-butyl benzoic acid with stirring. After the nitro compound was dissolved, 5.4 ml of 85% hydrazine hydrate and 0.040 g of 10% palladium-on-carbon catalyst were added. The mixture was refluxed for 2 hr, after which it was cooled and the catalyst was *carefully* filtered and washed with ethanol. The ethanol solution was evaporated and the residue refluxed with 50 ml of 10% sodium hydroxide solution for 3.5 hr. This alkaline solution was

(29) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were recorded on Perkin-Elmer Model 137 and 337 spectrophotometers. Ultraviolet spectra were recorded on a Cary 15 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60A instrument, probe temperature 38°, with signals reported relative to internal tetramethylsilane. Eastman practical grade isopentyl nitrite was purified by washing with saturated sodium bicarbonate solution and saturated sodium chloride solution, drying with anhydrous sodium sulfate, and distillation. Thin layer chromatography was done using Merck silica gel G on precleaned microslides. Florisil (Fisher, 60–100 mesh) was used as the adsorbant for separations by column chromatography. Gas–liquid partition chromatography (glpc) was performed on a F & M Model 810 instrument equipped with thermal conductivity detectors. One or both of the following columns were used throughout this work: column A (6 ft × 0.25 in., 10% silicon gum rubber SE-30 (methyl) on 80–100 mesh Chromosorb W, carrier gas flow 90 ml/min); column B (6 ft × 0.25 in., 10% polyphenyl ether (6 ring) on 60–80 mesh Chromosorb W, carrier gas flow 80 ml/min).

(30) W. Van Hartingsveldt, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **75**, 349 (1956).

(31) J. Geuse, C. Ruinard, J. Soeterbroek, P. E. Verkade, and B. M. Wepster, *ibid.*, **75**, 301 (1956).

TABLE II

PHYSICAL PROPERTY OF DIELS–ALDER ADDUCTS

Compd	% yield	Mp, °C	Formula	% calcd C	% calcd H	% found C	% found H	Infrared, μ (CCl_4)	Nmr spectrum, ppm (TMS, CCl_4)
12a	94	95–96	$C_{18}H_{24}O$	84.32	9.44	84.42	9.41	3.43, 6.81, 6.90, 7.22, 7.39, 11.35, 11.54	1.30 (9 H, s), 1.36 (9 H, s), 5.45 (1 H, s-broad), 5.95 (1 H, s-broad), 6.88 (3 H, s-broad), 7.07 (1 H, d, J = 2 Hz)
12b	89	76–78	$C_{20}H_{28}O$	84.45	9.92	84.52	9.86	3.43, 6.81, 6.91, 7.21, 7.30, 7.39, 8.63, 11.46, 11.53	1.30 (9 H, s), 1.38 (9 H, s), 1.77 (3 H, s), 2.05 (3 H, s), 6.63 (2 H, AB quartet, J_{AB} = 5 Hz), 6.91 (2 H, AB quartet, J_{AB} = 2 Hz).
12c	9.2	149–150	$C_{26}H_{40}O$	84.72	10.94	84.60	10.87	3.40, 6.79, 7.33, 8.03, 9.13, 11.58	1.25 (9 H, s), 1.28 (9 H, s), 1.35 (9 H, s), 1.38 (9 H, s), 6.81 (2 H, s), 6.93 (1 H, d, J_{AB} = 2 cps), 7.18 (1 H, d, J_{AB} = 2 Hz)
12d	34	135–137	$C_{26}H_{40}O$	84.72	10.94	84.89	11.09	3.42, 6.82, 6.90. 7.23, 7.39, 11.35	1.00 (9 H, s), 1.29 (9 H, s), 1.34 (9 H, s), 1.40 (9 H, s), 5.25 (1 H, s), 6.18 (1 H, s), 6.98 (2 H, s)

cooled, acidified with concentrated hydrochloric acid, and extracted with ether. Ether evaporation gave a pale yellow solid which upon recrystallization from ethanol–water afforded 1.28 g (77.8%) of the desired product: mp 256–258°; ir ($CHCl_3$) 2.90 (NH_2), 3.05 (NH_2), 3.1–3.4 (acid OH), 3.7–3.9 (several weak bands), 5.96 (monomeric C=O), and 6.07 μ (dimeric C=O); nmr [$(CD_3)_2CO$] δ 1.32 (s, 9), 1.48 (s, 9), 7.69 (d, 1, J = 2 Hz), and 8.07 ppm (d, 1, J = 2 Hz).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.09; H, 9.21; N, 5.55.

2-(2′-Amino-3′,5′-di-*tert*-butylphenyl)-6,8-di-*tert*-butyl-4-one-4*H*-3,1-benzoxazine (9).—To a stirred solution of 0.498 g (2.42 mmol) of dicyclohexylcarbodiimide dissolved in 15 ml of acetone at room temperature was added (2 mmol) of anthranilic acid **7**. After five min, precipitation of dicyclohexylurea began. Stirring was continued for 20 min, after which the formed dicyclohexylurea was filtered, mp 223–225° (lit.[32] 229–230°), and the acetone solution evaporated. The crude material was shown to consist of unreacted anthranilic acid and a single product by tlc analysis.

The product was isolated by chromatography of the crude material on 10 g of Florisil, eluting with 1% ether–hexane. Recrystallization from ethanol gave 0.090 g (20%) of yellow crystals of pure **9**: mp 174–176°; uv max (95% C_2H_5OH) 239 mμ (log ϵ 4.48), 292 (4.04), 305 (4.04), and 396 (3.87); ir (CCl_4) 2.84 (NH_2), 3.06 (NH_2), 3.41 (*tert*-butyl), and 5.07 μ (an α-pyrone C=O); nmr (CCl_4) δ 1.37 (s, 9), 1.42 (s, 9), 1.52 (s, 9), 1.64 (s, 9), 6.73 (br s, $W_{1/2}$ = 5 Hz, 2, NH_2, exchangeable with deuterium), 7.42 (d, 1, J = 2 Hz), 7.81 (d, 1, J = 2 Hz), and 8.08 ppm (t, 2, J = 2 Hz, two overlapping doublets); mass spectrum (70 eV) *m/e* (rel intensity) 462 (71.2), 447 (100), 231 (3.9), 216 (37.2).

Anal. Calcd for $C_{30}H_{42}N_2O_2$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.97; H, 9.21; N, 6.00.

Diels–Alder Adducts 12a–d.—The details are given for the reactions forming **12c** and **d**. The physical data for the compounds in this series are tabulated in Table II.

1,4,5,7-Tetra-*tert*-butyl-1,4-dihydronaphthalene 1,4-Endoxide (**12c**).—To a refluxing solution of 1.124 g (9.6 mmol) of isopentyl nitrite and 0.865 g (4.8 mmol) of 2,5-di-*tert*-butylfuran[33] in 20 ml of methylene chloride was added over a period of 1.5 hr a solution of 0.600 g (2.4 mmol) of 3,5-di-*tert*-butylanthranilic acid in 20 ml of acetone. The resulting solution was refluxed an additional hour after the initial addition period. The reaction mixture was evaporated in a base-washed vessel, and the residue chromatographed on 20 g of Florisil using hexane as the eluent. Unreacted 2,5-di-*tert*-butylfuran was separated from the lead fractions under vacuum (0.05 mm, room temperature), and collected in the Dry Ice trap of the pump. The amount of starting furan recovered in this manner varied over several experiments. The solid residue from the chromatographic fractions was recrystallized from methanol and then dried under vacuum to give 0.055 g (6.2%) of pure **12c**, mp 149–150°.

In another experiment, employing the reagent quantities given above, the anthranilic acid solution was added over 1 hr to the refluxing solution of the other reactants. The resulting solution was refluxed an addition 15 min after the addition period was over. Evaporation of this solution, followed by extraction of the residue with pentane, afforded 0.230 g (22.8%) of pentane insoluble material which was shown to be 1,3,5,7-tetra-*tert*-butylacridone (**10**), mp 293–295°. The pentane filtrate was chromatographed as described above, the starting furan removed, and the crude adduct recrystallized to give 0.081 g (9.2%) of pure **12c**, mp 149–150°.

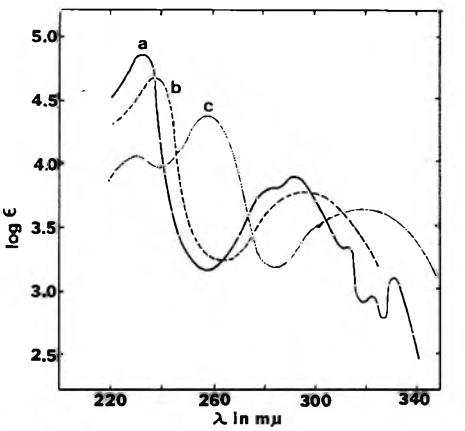

Figure 5.—Uv spectra of 1,3,5,8-tetraalkylnaphthalenes: a, 1,3,5,8-tetramethylnaphthalene [W. L. Mosby, *J. Amer. Chem. Soc.*, **75**, 3348 (1953)]; b, 1,3-di-*tert*-butyl-5,8-dimethylnaphthalene (**21**); c, 1,3,5,8-tetra-*tert*-butylnaphthalene (**23**).

1,3,6,8-Tetra-*tert*-butyl-1,4-dihydronaphthalene 1,4-Endoxide (**12d**).—A solution of 0.600 g (2.4 mmol) of anthranilic acid **7** in 20 ml of acetone was added over 1.5 hr to a refluxing solution of 0.865 g (4.8 mmol) of 2,4-di-*tert*-butylfuran[34] and 1.124 g (9.6 mmol) of isopentyl nitrite in 20 ml of methylene chloride. The solution was refluxed for an additional 15 min after the addition period was over. Evaporation of the reaction mixture, chromatography of the residue over 20 g of Florisil employing hexane as the eluent, followed by removal of starting furan from the lead fractions (0.05 mm, room temperature) gave the crude material. Two recrystallizations from pentane afforded 0.300 g (34%) of pure **12d**, mp 135–137°.

In another experiment, employing the same reagent and solvent ratios given above, the anthranilic acid solution was added over 4 hr to the refluxing solution of the other reactants. The resulting solution was refluxed for an additional 1.5 hr after the addition period was over and was then evaporated at room temperature under vacuum. The residue was dissolved in hexane, extracted several times with saturated sodium bicarbonate solution, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate.

Analysis of this reaction mixture by glpc (column A, isothermal at 240°) showed that it consisted approximately of 60% **12d**, 30% of a substance which might be isomeric to **12d**, and a very small amount of a compound later identified as 2,5,7-tri-*tert*-butyl-1,4-

(32) A. Skita and H. Rolfes, *Chem. Ber.*, **53**, 1248 (1920).

(33) A. Ramasseul and A. Rassat, *Bull. Soc. Chim. Fr.*, 2214 (1963).

(34) E. E. Van Tamelen and T. H. Whitesides, *J. Amer. Chem. Soc.*, **90**, 3895 (1968).

naphthoquinone (14). In addition, a number of impurities were revealed, most of them low boiling components. Evaporation of the above hexane solution afforded the crude product, which after two recrystallizations from pentane gave 0.515 g (37%) of pure 12d, mp 134–136°.

1,3,5,7-Tetra-*tert*-butylacridone (10).—To a stirred, refluxing solution of 0.422 g (3.6 mmol) of isopentyl nitrite in 20 ml of methylene chloride was added, over a period of 1 hr, a solution of 0.600 g (2.4 mmol) of 3,5-di-*tert*-butylanthranilic acid in 20 ml of acetone. The solution was refluxed an additional 1.5 hr after the addition period was over. Evaporation of the solvent and washing the crystalline residue with pentane gave 0.208 g (41.3%) of the pale yellow acridone 10, mp 297–299°. Benzene recrystallization afforded an analytical sample: mp 300–302°; uv max (95% C_2H_5OH) mμ 220 (log ε 4.30), 265 (4.67), 298 (3.58), and 390 (3.83); ir ($CHCl_3$) 2.87 (NH), 3.35 (*tert*-butyl), 6.10, 6.18, and 6.24 μ; nmr (summarized in Table III).

TABLE III

NMR DATA FOR 1,3,5,7-TETRA-*tert*-BUTYLACRIDONE (10)

Solvent	Resonances (δ, relative to TMS)
CH_2Cl_2	1.42 (s, 18), 1.65 (s, 18), 7.10 (d, 1, J = 2 Hz), 7.49 (d, 1, J = 2 Hz), 7.76 (d, 1, J = 2 Hz), 8.21 (broad, 1, exchangeable), 8.35 (d, 1, J = 2 Hz)
$CDCl_3$	1.42 (s, 18), 1.63 (s, 9), 1.69 (s, 9), 7.02 (d, 1, J = 2 Hz), 7.48 (d, 1, J = 2 Hz), 7.72 (d, 1, J = 2 Hz), 8.18 (broad, 1, exchangeable), 8.43 (d, 1, J = 2 Hz).
Benzene	1.29 (s, 9), 1.33 (s, 9), 1.35 (s, 9), 1.97 (s, 9).

Anal. Calcd for $C_{29}H_{41}NO$: C, 83.00; H, 9.85; N, 3.34. Found: C, 82.71; H, 9.88; N, 3.29.

A sample of acridone 10 was dissolved in $CDCl_3$ in an nmr tube, a few drops of NaOD and D_2O were added, and the mixture was heated in the steam bath for 15 min and then let stand overnight. The NH absorption in the nmr was removed. The compound was reisolated: mp 296–298°; ir ($CHCl_3$) 3.92 μ (ND).

2,5,7-Tri-*tert*-butyl-1,4-naphthoquinone (14).—The Diels–Alder adduct 12d (0.050 g, 0.136 mmol) was dissolved in 1 ml of absolute ethanol, the solution cooled, and hydrogen chloride gas bubbled into it for 15 min. The alcohol was removed under reduced pressure and the residue was exposed to the atmosphere for 4 days. Glpc analysis (column A, isothermal at 240°) of this material showed that approximately 66% of 14 and 34% of a presumed precursor were present. To complete the conversion to 14, the material was dissolved in hexane and oxygen was bubbled through the solution for 1 hr. This material was then chromatographed twice over 1 g of silica gel (Fisher, 100–200 mesh) employing hexane–benzene (2:1) as the eluent. A yellow material separated first and upon solvent removal crystallized to give 0.020 g (45%) of 14. Trituration with ethanol gave the analytical sample: mp 96–98°; uv max (95% C_2H_5OH) 255 mμ (log ε 4.80), and 352 (4.09); ir (CCl_4) 3.42 (*tert*-butyl), 6.04 (extended quinone C=O), 7.38, and 8.11 μ; nmr (CCl_4) δ 1.37 (s, 9), 1.42 (s, 9), 1.50 (s, 9), 6.75 (s, 1, H_3), 7.91 (d, 1, J = 2 Hz, H_6), and 8.17 ppm (d, 1, J = 2 Hz, H_8); mass spectrum (70 eV) m/e 326.

Anal. Calcd for $C_{22}H_{30}O_2 \cdot C_2H_5OH$: C, 77.38; H, 9.74. Found: C, 77.93; H, 9.22. Duplicate determination. C, 78.08; H, 9.17.

Hydrogenation of Endoxides.—A semimicro hydrogenation apparatus, consisting of a gas buret and a vacuum outlet system, was used so that the uptake of hydrogen by small sample quantities could be accurately measured. The adduct to be hydrogenated was dissolved in absolute ethanol and added to the prereduced catalyst in ethanol contained in the reaction flask *via* a pressure equalizing addition funnel. All of the adducts were hydrogenated using the above apparatus and technique at atmospheric pressure and room temperature. The crude saturated endoxides were isolated by evaporation of the ethanol solvent after the hydrogenation catalyst had been first separated by filtration. The physical data for the compounds in this series (19a–d) are tabulated in Table IV.

Naphthalenes. 1,3-Di-*tert*-butylnaphthalene (20).—To a stirred 25-ml solution of absolute ethanol saturated with hydrogen chloride was added 0.515 g (1.99 mmol) of saturated endoxide 19a. The resulting solution was refluxed 6 hr, after which the solvent was evaporated and the residue recrystallized from absolute ethanol to yield 0.436 g (91%) of pure 20: mp 67–68°; uv max (95% C_2H_5OH) 228 mμ (log ε 4.99), 260 sh (3.58), 271 (3.72), 278 (3.77), and 287 (3.68); ir (CCl_4) 3.31 (aromatic CH shoulder), and 3.43 μ (*tert*-butyl CH).

Anal. Calcd for $C_{18}H_{24}$: C, 89.94; H, 10.06. Found: C, 90.04; H, 10.04.

1,3-Di-*tert*-butyl-5,8-dimethylnaphthalene (21).—A mixture of 0.690 g (2.40 mmol) of 19b in 14 ml of 100% formic acid was immersed in a steam bath with rapid swirling for 20 min. The resulting solution was poured into ice–water and extracted with ether and the ether layer washed with saturated sodium bicarbonate solution until gas evolution ceased. The ether layer was then washed with saturated sodium chloride solution, dried with sodium sulfate, and evaporated to yield an essentially pure (by glpc analysis on column A, isothermal at 250°) yellow-white oil. Passage of this oil through 1.0 g of Florisil using hexane as the solvent gave 0.257 g (40%, the yield was not maximized) of pure 21: bp 68° (0.03 mm); uv max (95% C_2H_5OH) 238 mμ (log ε 4.67), and 298 (3.78); ir (CCl_4) 3.40 and 3.48 μ.

Anal. Calcd for $C_{20}H_{28}$: C, 89.49; H, 10.51. Found: C, 89.25; H, 10.46.

6-*tert*-Butyl-1,4-dimethylnaphthalene (22). A. From Dihydroendoxide 19b.—To a stirred 25-ml solution of absolute ethanol saturated with hydrogen chloride was added 0.516 g (1.80 mmol) of 19b. The resulting solution was refluxed overnight. Evaporation of the solvent gave a light brown oil which was extracted with pentane and separated from pentane insoluble material on the centrifuge. Concentration of this pentane extract and cooling gave 0.328 g (86%) of pure 22: mp 30–31°; uv max (95% C_2H_5OH) 232 mμ (log ε 4.69), 278 (3.64), 288 (3.70), 293 sh (3.63), and 323 (2.69); ir (CCl_4) 3.30 and 3.42 μ.

Anal. Calcd for $C_{16}H_{20}$: C, 90.51; H, 9.49. Found: C, 90.43; H, 9.46.

B. From Naphthalene 21.—A mixture of 0.003 g of naphthalene 21 in 1 ml of the ethanol–hydrogen chloride reagent was refluxed for 0.5 hr. Evaporation of the solvent, followed by examination of the pentane extract of the residue by glpc (column A, isothermal at 250°) showed that the conversion to naphthalene 22 had been quantitative in this time period. Naphthalene 22 was identified by glpc peak enhancement with an authentic sample.

1,3,5,8-Tetra-*tert*-butylnaphthalene (23) and 1,3,8-Tri-*tert*-butylnaphthalene (24).—A mixture of 6.60 g of sodium formate, 132 ml of 97+% formic acid (Aldrich), and 0.330 g (0.89 mmol) of dihydroendoxide 19c was stirred at a constant temperature of 60° for 169 hr. The dehydration was followed by glpc analyses (column A, isothermal at 250°) of reaction mixture aliquots taken at various times. Such analysis showed that after 48 hr, 80% of tetra-*tert*-butylnaphthalene 23 was present in the mixture. After 169 hr the reaction mixture was poured into water and extracted with hexane. The hexane extract was washed with water, saturated sodium bicarbonate solution, dried with sodium sulfate, and evaporated to give 0.256 g of a light yellow oil. Analysis of this oil showed the following approximate percentages of components: 26% tri-*tert*-butylnaphthalene 24 (retention time 2.5 min), 60% tetra-*tert*-butylnaphthalene 23 (3.0 min), and 14% dihydroendoxide 19c (3.5 min). Separation of these three components proved to be ineffective on tlc and on a variety of columns (*e.g.*, alumina, silica gel, Florisil). The mixture was successfully separated by preparative gas chromatography. A Perkin-Elmer Model F21 instrument equipped with a 12 ft × 0.50 in. column of 18% QF 1 on 60–80 mesh Chromosorb W (AW-DMCS) was employed.

In this manner, 0.024 g (0.068 mmol) of 1,3,5,8-tetra-*tert*-butylnaphthalene (23) was isolated as a white, crystalline solid, mp 78–82°. One recrystallization from methanol gave the analytical sample: mp 83–86°; uv max (95% C_2H_5OH) 230 mμ (log ε 4.04), 258 (4.38), and 320 (3.63); ir (CCl_4) 3.31, 3.40, 6.80, 6.88, 7.20 and 7.36 μ.

Anal. Calcd for $C_{26}H_{40}$: C, 88.57; H, 11.43. Found: C, 88.56; H, 11.53.

In like manner, 0.015 g (0.050 mmol) of 1,3,8-tri-*tert*-butylnaphthalene (24) was isolated as a colorless liquid. Passage through 1.0 g of Florisil employing pentane as the solvent gave analytical sample: mp ~10°; uv max (95% C_2H_5OH) 223 mμ sh (log ε 4.28), 228 (4.31), 253 (4.32), and 310 (3.49); ir (CCl_4) 3.30, 3.40, 5.78, 6.84, 7.16, 7.25, and 7.32 μ.

Anal. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88. Found: C, 88.86; H, 11.04.

TABLE IV

PHYSICAL PROPERTIES OF SATURATED ADDUCTS

Compd	% yield	Mp, °C	Formula	% calcd C	% calcd H	% found C	% found H	Infrared, μ (CCl_4)	Nmr spectrum, ppm (TMS, CCl_4)
19a	83	56–58	$C_{18}H_{26}O$	83.67	10.14	83.73	10.10	3.46, 6.82, 6.91, 7.23, 7.4, 10.61, 11.52	1.30 (9 H, s), 1.36 (9 H, s), 1.90 (4 H, m), 5.12 (1 H, m), 5.58 (1 H, m), 7.04 (2 H, AB quartet, J_{AB} = 2 Hz)
19b	100	86–88	$C_{20}H_{30}O$	83.86	10.56	83.68	10.54	3.45, 6.82, 6.91, 7.24, 7.32, 7.41 11.00, 11.57	1.30 (9 H, s), 1.42 (9 H, s), 1.67 (4 H, m), 1.70 (3 H, s), 1.98 (3 H, s), 6.88 (1 H, d, J_{AB} = 2 Hz), 7.14 (1 H, d, J_{AB} = 2 Hz)
19c	92	94–96	$C_{26}H_{42}O$	84.26	11.42	84.49	11.43	3.44, 6.82, 6.90, 7.23, 7.38, 8.49, 9.34, 11.30, 11.45	1.22 (9 H, s), 1.32 (18 H, s), 1.45 (9 H, s), 1.75 (4 H, m), 7.16 (2 H, s)
19d	88	129–131	$C_{26}H_{42}O$	84.26	11.42	84.31	11.47	3.40, 6.80, 7.22, 7.37, 11.63	0.49 (9 H, s), 1.27 (9 H, s), 1.29 (1 H, buried), 1.31 (9 H, s), 1.46 (9 H, s), 1.8–2.3 (2 H, m), 4.85 (1 H, d, J = 4 Hz), 7.00 (1 H, d, J = 2 Hz), 7.21 (1 H, d, J = 2 Hz)

TABLE V

DEHYDRATION OF 1,4,5,7-TETRA-*tert*-BUTYL-1,2,3,4-TETRAHYDRONAPHTHALENE 1,4-ENDOXIDE (**19c**)

Reaction conditions[a]	Yield,[b] % **19c**	**23**	**24**
100% HCOOH, 100°, 0.5[c]	27	64	9
100% HCOOH, 100°, 1	10	60	30
100% HCOOH, 100°, 3		50	50
Excess $(C_2H_5)_3O^+BF_4^-$, 25°, 26	60	9	31
Benzoic acid–nitrobenzene, 120°, 15	100		
CH_3COOH–$(CH_3CO)_2O$, 100°, 23	100		
CH_3COOH–HCOOH (1:1), 100°, 3		40	60
CH_3COOH–HCOOH (1:1), 100°, 12		20	70
HCOONa–HCOOH, 55°, 144	4	94	2
HCOONa–HCOOH, 60°,[d] 48	17	80	3
HCOONa–HCOOH, 60°,[d] 169	14	60	26

[a] The dehydrating reagent, the temperature, and the time (hr) are listed. [b] Reaction mixture composition was determined by glpc analysis on column A, isothermal at 250°. [c] The components of this reaction mixture were separated by glpc and were shown not to interconvert on the analysis column. [d] A constant temperature oil bath was used.

Table V lists the studies made to determine optimum acidity for this reaction.

1,3,6,8-Tetra-*tert*-butylnaphthalene (25). A.—To 10 ml of absolute ethanol saturated with anhydrous hydrogen chloride was added 0.095 g (0.256 mmol) of saturated endoxide **19d**. The mixture was refluxed for 10 min, the solvent boiled off, and the residue extracted with pentane. Evaporation of the pentane gave the crude product which upon recrystallization from methanol afforded 0.058 g (64.5%) of pure tetra-*tert*-butylnaphthalene **25**, mp 125–127°. Another recrystallization from methanol gave the analysis sample: mp 127–128°; uv max (95% C_2H_5OH) 231 mμ (log ε 4.26), 256 (4.57), and 310 (3.63); ir (CCl_4) 3.29, 3.37, 6.76, 6.85, 7.17, 7.34, and 11.28 μ.

Anal. Calcd for $C_{26}H_{40}$: C, 88.57; H, 11.43. Found: C, 88.61; H, 11.50.

B.—The conversion of dihydronaphthalene endoxide **19d** to naphthalene **25** at room temperature was found to proceed quickly and quantitatively with no further reaction of **25** occurring employing the following procedure.

To 0.002 g of **19d** dissolved in a few drops of absolute ethanol was added a cooled 0.5-ml solution of absolute ethanol saturated with hydrogen chloride. This mixture was swirled 2 min and then extracted with pentane. Analysis of the pentane extract by glpc on column A (isothermal at 260°) showed that no starting material **19d** remained; analysis on column B (isothermal at 260°) showed that only tetra-*tert*-butylnaphthalene **25** had formed and no tri-*tert*-butylnaphthalene **26** could be detected.

C.—The stability of tetra-*tert*-butylnaphthalene **25** toward ethanol–hydrogen chloride was demonstrated in the following experiments.

When the naphthalene **25** (0.002 g) was dissolved in ethanol–hydrogen chloride (0.5 ml) by warming on the steam bath for about 3 min, some conversion to **26** had taken place as evidenced by glpc analysis (column B, isothermal at 260°) of the pentane extract of the ethanol solution. Similarly, when **25** was dissolved in absolute ethanol and the resulting solution saturated with hydrogen chloride, glpc analysis again showed that **26** had started to form.

The naphthalene **25** was shown to be stable toward the ethanol–hydrogen chloride reagent at room temperature at least for short time periods. Naphthalene **25** (0.002 g) was dissolved in a few drops of absolute ethanol, the solution cooled, and to this was added a cooled solution (0.5 ml) of ethanol–hydrogen chloride. This mixture was swirled from 1 to 3 min, extracted with pentane, and analyzed by glpc (column B, isothermal at 260°). Only pure **25** was indicated.

1,3,6-Tri-*tert*-butylnaphthalene (26). A. From the Mother Liquors of 1,3,6,8-Tetra-*tert*-butylnaphthalene (25).—In the reaction of dihydroendoxide **19d** with refluxing hydrogen chloride–ethanol, a 64.5% yield of **25** was obtained. The remaining mother liquors upon glpc analysis with column A (isothermal at 260°) showed that no starting material **19d** remained and that only "one" product had formed. Examination of these same mother liquors on column B (isothermal at 260°) clearly showed that about 35% **25** and 65% **26** were present.

In one experiment, 0.160 g of the mother liquors of the above composition in 10 ml of the ethanol–hydrogen chloride reagent was refluxed 3 hr. Evaporation of the ethanol, followed by recrystallization of the product from methanol gave 0.109 g of pure **26**. Analysis (glpc column B, isothermal at 260°) of the remaining filtrate (0.050 g) showed that it consisted of about 35% **25** and 65% **26**. The physical properties of **26** are: mp 106–108°; uv max (95% C_2H_5OH) 227 sh mμ (log ε 4.47), 232 (4.61), 271 sh (3.75), 278 (3.80), and 286 sh (3.72); ir (CCl_4) 3.25 (sharp) and 3.30 (shoulder, both aromatic CH), 3.41 (*tert*-butyl), 6.82, 6.88, 7.22, 7.37, 11.07, and 11.26 μ.

Anal. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88. Found: C, 89.15; H, 10.94.

B. From Pure Tetra-*tert*-butylnaphthalene 25.—In order to determine the approximate time for complete conversion of tetra-*tert*-butylnaphthalene **25** to tri-*tert*-butylnaphthalene **26**, the following glpc experiment was carried out. An analytically pure sample (0.005 g) of **25** was combined with 2.5 ml of the ethanol–hydrogen chloride reagent and refluxed for 12.5 hr. After removal of the solvent and extraction of the residue with pentane, glpc analysis on column B (isothermal at 260°) showed that the conversion of **25** to **26** was essentially complete (1% **25**, 99% **26**).

Registry No.—**6**, 26157-22-2; **7**, 26157-23-3; **9**, 26157-24-4; **10**, 26157-25-5; **12a**, 22495-81-4; **12b**, 22495-82-5; **12c**, 22495-83-6; **12d**, 22495-84-7; **14**, 26157-30-2; **19a**, 26157-31-3; **19b**, 26157-32-4; **19c**, 26157-33-5; **19d**, 26157-34-6; **20**, 22495-85-8; **21**, 22495-87-0; **22**, 22495-88-1; **23**, 22550-43-2; **24**, 22495-89-2; **25**, 22495-86-9; **26**, 26157-41-5.

Base-Catalyzed Condensations of *o*-Phthalaldehyde with Primary Amides. Synthesis and Characterization of Some Isoindoline and Phthalan Derivatives

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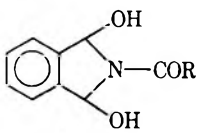
Aliphatic primary amides [$RCONH_2$ (R = H, CH_3, C_2H_5, n-C_3H_7, CH_3OCH_2, or CH_3NH)] react with *o*-phthaladehyde in aqueous sodium hydroxide at room temperature to yield *N*-acyl-1,3-dihydroxyisoindolines (**1a**-f). Under the same reaction conditions, primary amides of structure $ArCONH_2$ (Ar = C_6H_5, p-ClC_6H_4, or p-$CH_3OC_6H_4$) and trimethylacetamide give 1-hydroxy-3-amidylphthalans (**2b–e**). The method employing ethanolic sodium ethoxide previously used for preparation of **1b** was found to be applicable to synthesis of **1c** and **1d**. Its use with benzamide resulted in formation of 1-ethoxy-3-benzamidylphthalan (**2a**). Production of phthalans rather than isoindolines is considered to be primarily the result of steric factors. All products were characterized physically *via* ir and nmr spectra. Chemical characterization included an examination of hydrolytic and oxidative behavior.

In a previous paper[1] we reported the preparation of *N*-acetyl-1,3-dihydroxyisoindoline (**1b**) from *o*-phthalaldehyde and acetamide in the presence of ethanolic sodium ethoxide. Reactions of this type, in which the same atom of an attacking nucleophile reacts with both formyl groups of *o*-phthalaldehyde, are still relatively rare, and further investigation of base-catalyzed condensations of *o*-phthalaldehyde with amides seemed warranted.

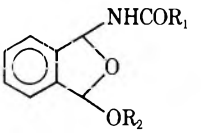


1a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = n-C_3H_7
e, R = CH_3OCH_2
f, R = CH_3NH

The previously reported method was successfully applied to synthesis of *N*-*n*-propionyl- and *N*-*n*-butyryl-1,3-dihydroxyisoindolines (**1c** and **1d**); however, yields were only fair (averaging 50%). More satisfactory results were obtained when aqueous suspensions of appropriate amides and *o*-phthalaldehyde were treated with aqueous sodium hydroxide and stirred for a few hours at room temperature. Slow dissolution of reactants was followed by gradual precipitation of products in nearly pure form and in high yield.

Use of the sodium ethoxide–ethanol system in condensation of benzamide with *o*-phthalaldehyde resulted in formation of 1-ethoxy-3-benzamidylphthalan (**2a**). The yields (averaging 50%) and the difficulty experienced in product isolation led us to abandon this system in favor of aqueous sodium hydroxide. Again reactions proceeded smoothly; the products isolated were the phthalan derivatives, **2b–e**.

Structural assignments for all compounds of structures **1** and **2** were based on spectral evidence as well as chemical reactivity. Solid state infrared spectra of all compounds were consistent with structural assignments (see Experimental Section). The only significant differences in the spectra **1** and **2** were in the NH and OH stretching regions. Since bonded OH absorption bands are often quite broad and the NH bands in **2c–e** appeared as shoulders, the infrared spectra must be considered as supporting evidence only.[2]



2a, $R_1 = C_6H_5$; $R_2 = C_2H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = p$-ClC_6H_4; $R_2 = H$
d, $R_1 = p$-$CH_3OC_6H_4$; $R_2 = H$
e, $R_1 = (CH_3)_3C$; $R_2 = H$

Nuclear magnetic resonance spectra (Table I) provided strong support for both the isoindoline and phthalan structures. All compounds showed similar absorption behavior in the CHOH region; relative areas of these sets of signals corresponded to four protons in the isoindoline series and to two protons in the phthalan derivatives. In the aromatic region all of the isoindoline derivatives showed a four proton singlet, normal for benzene derivatives bearing identical ortho substituents which do not interact strongly with the ring.[3] More complexity would, of course, be expected for aromatic proton absorption in **2a–d**, but even **2e** shows complex multiplicity in this area.

Chemical shifts and multiplicities of signals for all other protons of general structure, **1**, were normal with one exception. The methylene protons of **1e** absorbed as two broad singlets suggesting that the singlets were really doublets. This apparent anomaly might be explained by postulating intramolecular hydrogen bonding between the ether oxygen and hydrogen of either OH group resulting in rigidity of the methylene group and consequent magnetic nonequivalence of the two protons.

In compounds of the general structure **2**, signals for NH and CHN were quite distinct, and coupling constants could be measured in most cases. It is of interest to note that the CHN signal for **2a** is split not only by the neighboring NH but also by the proton on C-1.

Chemically, all the isoindolines behaved in a manner analogous to that previously reported for **1b**.[1] Base-

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(1) R. D. Reynolds and R. J. Conboy, *J. Org. Chem.*, **30**, 2251 (1965).

(2) Definite assignments for the amide II bonds of **2** could not be made because of the complexity of the spectra.

(3) J. Martin and B. P. Daily, *J. Chem. Phys.*, **37**, 2594 (1962).

TABLE I

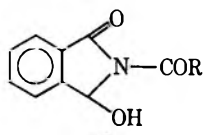
NMR SPECTRA OF *N*-ACYL-1,3-DIHYDROXYISOINDOLINES AND 1-HYDROXY- (OR -ETHOXY-) 3-AMIDYLPHTHALANS[a]

Compd	ArH	CHOH[b]	CHN	NH	Other
1a	2.54, s	3.63, q			CHO, 1.35, s
1b	2.47, s	3.72, m			CH_3, 7.78, s
1c	2.57, s	3.74, m			CH_3, 8.93, t (7)
					CH_2, 2.5, q[c]
1d	2.58, s	3.80, m			$CH_3CH_2CH_2$,
					0.8–3.0, m
1e	2.54, s	3.60, q			CH_3, 6.62, s
					CH_2, 5.67, s
					6.10, s
1f	2.60, s	3.90, m		~3.9[d]	CH_3, d (7)
2a	2.50, m	3.65, d (2)[e]	2.90, 2 d's	0.72, d (9)	CH_3, 8.84, t (7)
	2.05, m		(2) (9)		CH_2, 6.32, q (7)
2b	2.53, m	3.47, q[f]	2.92, d (9)[f]	0.89, d (9)[f]	
	2.05, m				
2c	2.53, s[g]	3.63, q	3.05, q[h]	2.27, q[h]	
	2.47[i]				
	2.05[i]				
2d	2.98, d (9)	3.65, q	3.11, d (7)[j]	1.13, d (7)	OCH_3, 6.17, s
	2.05, d (9)				
	2.52, s				
2e	2.60, m	...[k]	...[k]	2.09, d (9)[l]	CH_3, 8.88, s
				1.82, d (9)	

[a] Chemical shifts are given in τ from TMS in DMSO-d_6; relative areas all were as expected; when possible, J values (hertz) are given in parentheses. [b] Because the quartets expected were badly deformed in some cases and showed further multiplicity in others, specific assignments for CH and OH were not made. [c] Superimposed on residual DMSO absorption. [d] Superimposed on CHOH absorption. [e] CHOC; coupling is with CHN as noted. [f] Multiplicity nearly collapses upon heating to 80°. [g] Relative area of highest field peak = 4; sum of relative areas of lower field peaks = 4. [h] Probably two doublets with J = 9 Hz. [i] Signals for protons of para-substituted ring; consisted of 4 sets of 2 pairs, J = 9 and 2 Hz. The highest field pair is superimposed on the signal for the protons of the ortho-substituted ring. [j] Superimposed on upfield aromatic proton signal. [k] Splitting pattern was too complex to allow assignments. [l] Two doublets are possibly due to rotamers. Overall area = 1 proton.

catalyzed hydrolysis led to formation of α-hydroxy-*o*-toluic acid as expected. Acid-catalyzed hydrolysis was not particularly useful in structural assignments. Apparently, complex decomposition and recombination occur; this problem will be discussed in a later paper.

Oxidation to the corresponding *N*-acyl-3-hydroxyphthalimidines (**3**) and *N*-acylphthalimides (**4**) was possible in some cases. It was found that such oxidations



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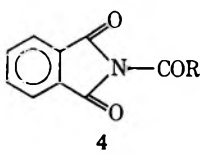

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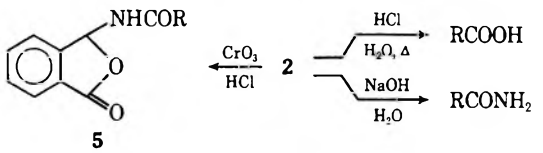
take place more cleanly and effectively with a chromic anhydride–hydrochloric or sulfuric acid system than with the previously used acid dichromate reagents.[1] It was possible, by the former method, to obtain from compounds **1b–d** and **1f** the corresponding oxidation products, **3b–d** and **3f** as well as **4b**, **4c**, and **4f**. All except **3b** and **4b** were previously unknown compounds and were identified from their typical infrared spectra, elemental analyses, and, in some cases, nmr spectra (see Experimental Section) Oxidation of **1a** and **1e** resulted in formation of phthalimide only under all conditions used.

Base-catalyzed hydrolysis of **2b–e** led to formation of the starting amides, $RCONH_2$; with **2a** no identified products were isolated. After acid-catalyzed hydrolysis at reflux, the corresponding carboxylic acids, RCOOH, were isolated. Oxidation with the chromic anhydride–hydrochloric acid system led to the corresponding phthalides (**5**) (Scheme I). These phthalides, previously unknown, were identified from their infrared

SCHEME I



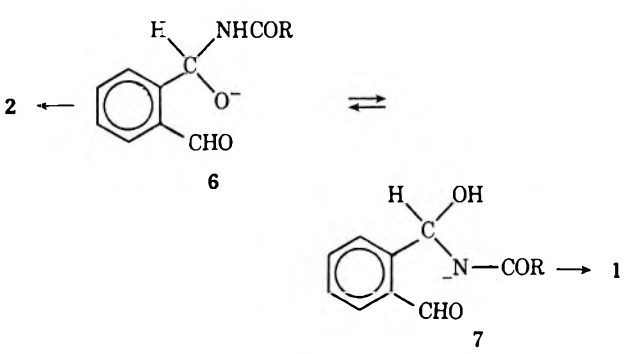
5

and nuclear magnetic resonance spectra and elemental analyses (See Experimental Section).

Conversion of **2b** to **2a** was easily effected. When an ethanolic solution of **2b** was acidified and allowed to stand overnight at room temperature, the product was **2a** in high yield.

It seems clear, then, that under the conditions used, condensations of *o*-phthalaldehyde with primary amides proceeded to yield two different product types. A reasonable first step in both reactions would involve attack by the anion of the amide on a carbonyl group of *o*-phthalaldehyde to yield the intermediate, **6**, which could well exist in equilibrium with **7** (Scheme II).

SCHEME II



Ring closures would result in the observed products. Normally one would expect the more stable intermediate, **7**, to predominate; hence, **2** should form only if formation or ring closure of **7** were difficult.

Attempted explanations of the different courses of reaction based on resonance and/or inductive effects lead to predicted results which are the opposite of those observed. Therefore, it is postulated that product composition is controlled by steric factors. Fisher–Hirschfelder models of the intermediates, **6** and **7**, support this explanation. When R is any group sufficiently small or elongated, there is no steric interference with attack of either oxygen or nitrogen on the formyl group; hence, reaction proceeds through the more stable intermediate, **7**, and isoindolines are the products. However, when R is aromatic or the *tert*-butyl group, there is steric interference to attack by nitrogen. Oxygen attack appears not particularly hindered, and phthalans can then be formed in high yields.

The extreme experimental simplicity of the syntheses reported here renders production of these new compounds a very easy matter and invites further investigation.

Experimental Section[4]

Materials.—Amides and *o*-phthalaldehyde were purchased from Aldrich Chemical Co., Milwaukee, Wis., and purified by standard methods.

***N*-Acyl-1,3-dihydroxyisoindolines (1).**—*o*-Phthalaldehyde (3.0 g, 0.0224 mol) and the appropriate amide (0.0224 mol) were suspended in distilled water in an erlenmeyer flask. Maximal yields were obtained with various amides by varying the amounts of distilled water as follows: for syntheses of **1e**, 30 ml; **1a** and **1d**, 50 ml; **1b**, **1c**, and **1f**, 200 ml. Aqueous NaOH (5 ml, 2.5% by weight) was added dropwise over a period of 15 min to the magnetically stirred suspension. Dissolution of reactants took place during this period and was followed shortly by gradual precipitation of products. Total reaction times were varied from 1.25–30 hr with little effect on yields. Products were suction filtered and, except for **1a**, recrystallized from acetonitrile; water was used as recrystallizing solvent for **1a**. All compounds were obtained as white crystals.

Yields and melting points were obtained: **1a**, 70%, 164–165°; **1b**, 78%, 157–158°; **1c**, 65%, 176–177°; **1d**, 73%, 150–152°; **1e**, 80%, 114–116; **1f**, 78%, 178.5–180°. Ir (cm^{-1}): bonded OH, **1a** (3230), **1b** (3247), **1c** (3225), **1d** (3250), **1e**, (3300), **1f** (3370); amide I C=O, **1a** (1645), **1b** (1621), **1c** (1610), **1d** (1610), **1e** (1630), **1f** (1640); CH out-of-plane deformation, **1a** (752), **1b** (750), **1c** (750), **1d** (755), **1e** (760), **1f** (758).

Anal.[5] Calcd for $C_9H_9NO_3$ (**1a**): C, 60.28; H, 5.58; N, 7.82. Found: C, 60.28; H, 5.45; N, 7.73. Calcd for $C_{11}H_{13}NO_3$ (**1c**): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.26; N, 6.76. Calcd for $C_{12}H_{15}NO_3$ (**1d**): C, 65.10; H, 6.84; N, 6.33. Found: C, 64.92; H, 6.86; N, 6.26. Calcd for $C_{11}H_{13}NO_4$ (**1e**): C, 59.19; H, 5.83; N, 6.28. Found: C, 59.21; H, 5.90; N, 6.22. Calcd for $C_{10}H_{12}N_2O_3$ (**1f**): C, 57.64; H, 5.76; N, 13.45. Found: 57.72; H, 5.72; N, 13.39.

1-Hydroxy-3-amidylphthalans (2b–e).—The preparative procedure was identical with that used for preparation of the *N*-acyl-1,3-dihydroxyisoindolines. Best yields were obtained using the following amounts of distilled water: **2b**, **2c**, and **2e**, 200 ml; **2d**, 100 ml. Reactions to produce **2b–d** were allowed to proceed for 1.5 hr; that to produce **2e** was much slower and was carried on for 24 hr. Recrystallization was effected from acetonitrile; all compounds existed as white crystals.

Yields and melting points were obtained: **2b**, 69%, 135–136°; **2c**, 38%, 148–149°; **2d**, 74%, 139–140°; **2e**, 62%, 140–141°. Ir (cm^{-1}): bonded OH, **2b** (3400), **2c** (3300, sh), **2d** (3380, sh), **2e** (3405, sh); NH, **2b** (3245), **2c** (3280), **2d** (3300), **2e** (3375); amide I C=O, **2b** (1620), **2c** (1600), **2d** (1600), **2e** (1610); CH out-of-plane deformation, **2b** (758, 690–720, 3 peaks), **2c** (752, 845, **2d** (752, 840), **2e** (755).

Anal. Calcd for $C_{15}H_{13}NO_3$ (**2b**): C, 70.60; H, 5.13, N, 5.48. Found: C, 70.49; H, 5.12; N, 5.43. Calcd for $C_{15}H_{12}NO_3Cl$ (**2c**): C, 62.07; H, 4.13; N, 4.83; Cl, 12.24. Found: C, 62.27; H, 3.98; N, 4.74; Cl, 12.04. Calcd for $C_{16}H_{15}NO_4$ (**2d**): C, 67.35; H, 5.29; N, 4.90. Found: C, 67.35; H, 5.23; N, 4.94. Calcd for $C_{13}H_{17}NO_3$ (**2e**): C, 66.36; H, 7.28; N, 5.95. Found: 66.45; H, 7.30; N, 5.92.

1-Ethoxy-3-benzamidylphthalan (2a).—This compound was prepared using a modification of the method previously described for preparation of **1b**.[1] Reaction was carried out at reflux, and, after rotary evaporation of the reaction mixture, water was added to effect precipitation. Recrystallization from acetonitrile yielded **2a** in 53% yield: mp 189–190°; ir (cm^{-1}), 3280 (NH), 1620 (amide I C=O), 758, 700, 735 (CH out-of-plane deformation.)

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.12; H, 6.01; N, 4.99.

***N*-Acyl-3-hydroxyphthalimidines (3) and *N*-Acylphthalimides (4). Oxidation of *N*-Acyl-1,3-dihydroxyisoindolines. General Procedure.**—The isoindoline derivative, 1 (0.002 mol), was added to 5 ml of acetone contained in a 50-ml erlenmeyer flask. The oxidizing mixture (1.03 g, 0.01 mol of chromium trioxide, 3 ml of distilled water, and 0.9 mol of concentrated HCl) was added dropwise to the magnetically stirred acetone solution over a period of 1.5 hr. Stirring was allowed to proceed for another 0.5 hr after which 30 ml of distilled water was added. The mixture was filtered following another 0.5-hr stirring period. The residue was washed with distilled water and recrystallized. Yields of oxidized products ranged from 50–60%.

Oxidation of 1a and 1e.—The above procedure, as well as many modifications of that procedure (temperature variation: ice bath, room temperature, reflux; acid variation: HCl, H_2SO_4, HOAc; variation in molar quantities), led only to formation of phthalimide identified by comparison of its infrared spectrum with that of an authentic sample.

Oxidation of 1c.—Use of the general procedure at reflux led to phthalimide formation; at room temperature or under ice bath conditions, the half-oxidized product, **3c**, was formed. It was recrystallized from water: mp 144–145°; ir 3450 (OH), 1724 (imide C=O), 1666 (amide I C=O), 752 (CH out-of-plane deformation).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.38; H, 5.37; N, 6.71.

The fully oxidized product was obtained when **1c** was treated as noted in the general procedure at room temperature except that concentrated H_2SO_4 was used instead of concentrated HCl. Recrystallization from ether yielded white crystals of **4c**: mp 129–132°; ir 1720 (imide C=O), 1650 (amide I C=O), 725 (CH out-of-plane deformation).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.30; H, 4.41; N, 6.70.

Oxidation of 1d.—Use of the general procedure under ice bath conditions resulted in formation of **3d**, white crystals from acetonitrile: mp 78–79°; ir 3440 (OH), 1724 (imide C=O), 1660 (amide I C=O), 752 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 9.07 (t, 3, J = 9 Hz, CH_3), 7.1–8.7 (m's, 4, CH_2CH_2), 3.30 (q, 4, J = 7 Hz, CHOH), 2.20 (m, 4, ArH).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.68; H, 5.92; N, 6.38. Found: C, 65.82; H, 5.89; N, 6.43.

At room temperature and at reflux, only phthalimide was formed by oxidation of **1d**.

Oxidation of 1f.—Ice bath conditions and the general procedure followed by recrystallization from acetonitrile resulted in formation of **3f**: mp 182–183°; ir 3400 (OH), 3333 (NH), 1700 (imide C=O), 1670 (amide I C=O), 740–760 (3 strong peaks); nmr τ 7.18 (d, 3, J = 5 Hz, CH_3), 3.35 (q, 4, J = 7 Hz, CHOH), 2.31 (m, 4, ArH), 1.85 (broad absorption, 1, NH).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.19; H, 4.84; N, 13.57. Found: C, 58.27; H, 4.85; N, 13.63.

At room temperature, and with concentrated H_2SO_4 instead of concentrated HCl, **4f**, white crystals from acetonitrile, was formed: mp 185–186°; ir 3311 (NH), 1720 (imide C=O), 1666 (amide I C=O), 760 (CH out-of-plane deformation); nmr τ 7.18 (d, 3, J = 5 Hz, CH_3), 2.06 (s, 4, ArH), 1.75 (broad absorption, 1, NH).

(4) Melting points were taken on a Büchi melting point apparatus previously calibrated against standard substances. Infrared spectra were determined on a Beckman IR8 spectrophotometer in KBr pellets (0.5 mg sample/50 mg KBr). A Varian A60A spectrometer was used for nmr spectra. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(5) Analysis for **1b** and its oxidation products are in ref 1.

Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.76; H, 3.91; N, 13.71. Found: C, 58.84; H, 3.97; N, 13.59.

3-Amidylphthalides (5). Oxidation of 1-Hydroxy-3-amidylphthalans.—All oxidations were carried out using the procedure described above for oxidation of compounds of structure **1**. Ice bath conditions were employed. Products were recrystallized from acetonitrile. Yields ranged from 50–60%.

Oxidation of 2a and 2b.—The product in both cases was **5b**: mp 175–176°; ir (cm^{-1}) 3257 (NH), 1748 (phthalide C=O), 1626 (amide C=O), 755, 688, 745 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 2.68 (d, 1, J = 9 Hz, CHN), 1.90–2.08 (2 m's, 9, ArH), 0.42 (d, 1, J = 9 Hz, NH).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.34; N, 5.53. Found: C, 71.02; H, 4.40; N, 5.58.

Oxidation of 2c.—The product, **5c**, had mp 162–163°; ir (cm^{-1}) 3250 (NH), 1755 (phthalide C=O), 1630 (amide I CO), 750, 840 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 7.1–8.1 (m's, 9, ArH, CHN), 0.15 (d, 1, J = 9 Hz, NH).

Anal. Calcd for $C_{15}H_{10}NO_3Cl$: C, 62.50; H, 3.47; N, 4.86. Found: C, 62.25; H, 3.66; N, 4.81.

Oxidation of 2d.—Use of the general procedure with **2d** led to formation of **5d**, mp 180–182° from acetonitrile: ir (cm^{-1}) 3257 (NH), 1757 (phthalide C=O), 1630 (amide I C=O), 747 840, (CH out-of-plane deformation); nmr (DMSO-d_6) τ 6.16 (s, 3, OCH_3), 2.68 (d, 1, J = 10 Hz, CHN), 2.95 and 2.06 (2 d's, 4, J = 9 Hz, ArH on *para*-substituted ring), 2.50–2.00 (m, partially superimposed on down field ArH of para-substituted ring, 4, ArH in ortho-substituted ring), 0.48 (d, 1, J = 10 Hz, NH).

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95. Found: C, 67.84; H, 4.59; N, 4.90.

Oxidation of 2e.—The product of this oxidation was **5e**: mp 179–180°; ir (cm^{-1}) 3256 (NH), 2959 (CH_3), 1754 (phthalide C=O), 1653 (amide I C=O), 745 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 8.85 (s, 9, CH_3), 2.94 (d, 1, J = 9 Hz, CHN), 2.30 (m, 4, ArH), 1.25 (d, 1, J = 9 Hz, NH).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.05; H, 6.40; N, 5.95.

Acid-Catalyzed Hydrolysis of 2.—Acid-catalyzed hydrolysis of the phthalans *via* the method described in ref 1 led to formation of benzoic acid from **2a** and **2b**, *p*-chlorobenzoic acid from **2c**, *p*-methoxybenzoic acid from **2d**, and trimethylacetic acid from **2e**. Products were identified *via* undepressed mixture melting points when applicable and ir spectra which were identical with those of authentic samples

Base-Catalyzed Hydrolysis of 2.—The procedure used for base-catalyzed hydrolysis of the phthalans was that described in ref 1; however, all reactions except one were carried out at room temperature. Such reactions resulted in formation of benzamide from **2b**, *p*-chlorobenzamide from **2c**, *p*-methoxybenzamide from **2d**, and trimethylacetamide from **2e**. No identified products were isolated from base-catalyzed hydrolysis of **2a**.

All products isolated were identified by undepressed mixture melting points and infrared spectra which were identical with those of authentic samples.

Conversion of 2b to 2a.—Compound **2b** (0.51 g, 0.002 mol) was dissolved in 20 ml of absolute ethanol; 1 ml of 1 *M* HCl was added, and the mixture was allowed to stir overnight. Removal of solvent on the rotary evaporator and recrystallization from acetonitrile yielded 0.46 g (80%) of **2a** identical with that prepared by reaction of *o*-phthalaldehyde with benzamide in ethanolic sodium ethoxide.

Registry No.—**1a**, 26268-85-9; **1b**, 1968-04-3; **1c**, 26268-87-1; **1d**, 26268-88-2; **1e**, 26268-89-3; **1f**, 26268-90-6; **2a**, 26268-91-7; **2b**, 26322-33-8; **2c**, 26268-92-8; **2d**, 26268-93-9; **2e**, 26322-34-9; **3c**, 26268-94-0; **3d**, 26322-35-0; **3f**, 26322-36-1; **4c**, 26268-95-1; **4f**, 26268-96-2; **5b**, 26268-97-3; **5c**, 26322-37-2; **5d**, 26322-38-3; **5e**, 26268-98-4.

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Rate and Equilibrium in Carbanion Formation[1a] by Bis(methylsulfonyl)methane

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Bis(methylsulfonyl)methane has been found to have a pK_a of 12.54 in water at 25°. The rate constant for exchange of its methylene hydrogen atoms in deuterium oxide at 25° is (8 ± 2) × 10^{-4} sec^{-1} per hydrogen atom, and the Arrhenius activation energy is 8 ± 3 kcal/mol. Between one tenth and one half of the ion pairs formed by donation of a proton from the sulfone to water are estimated to recombine with exchange instead of dissociating.

A number of studies of the kinetics and stereochemistry of the formation of carbanions stabilized by α-sulfone substituents have been made.[2] Several of these studies provide evidence that the pyramidal form of the carbanion is not as unstable relative to the planar form as is the case for carbanions stabilized by α-carbonyl, α-aryl, and certain other substituents, and it is not even clear that the most stable form of α-sulfonyl carbanions is necessarily the planar one. According to the principle of least motion,[3,4] if α-sulfonyl carbanions are not preferentially planar or if the difference in stabilities between their planar and pyramidal forms is particularly small, then, other things being equal, they should be formed more rapidly than equally basic carbanions whose planar forms are much more stable than their pyramidal forms.

The data available in 1953 were sufficient to convince Pearson and Dillon that "sulfones are characterized by high rates of ionization for a given acid strength."[5] However, these data included only five observations on sulfones, and there was no sulfone for which both the rate and equilibrium constants for carbanion formation had been determined. We therefore decided to make such a determination, using bis (methylsulfonyl) methane, a sulfone for which both constants seemed likely to be measurable.

The pK_a of this bissulfone was found by potentio-

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metric titration to be 12.54, in good agreement with the value 12.5 reported without experimental details[6] and in moderate agreement with the admittedly rough value 14.[7]

Although $(MeSO_2)_2CD_2$ was easily prepared from the bissulfone and deuterium oxide, its deuterium exchange with protium oxide could not be studied conveniently because the proton magnetic resonance (pmr) peak due to the methylene group is so near the protium oxide peak. Therefore, the reaction studied kinetically was the exchange between deuterium oxide and the protiated bissulfone. When the bissulfone was dissolved in pure deuterium oxide, the peak due to the methylene group had disappeared before the pmr spectrum could be run. In view of the possibility that this exchange reaction was catalyzed largely by the deuterioxide ions in the solution, the experiment was repeated using acidified deuterium oxide. The methylene peak was then found to disappear at an observable rate, the half-life of the reaction being about 7 min at 42°. The reaction kinetics had to be studied at bissulfone concentrations of only a few hundredths molar, because the solubility of the bissulfone in water is low and the rapidity of exchange made it impractical to take the time to saturate the water with bissulfone. In these solutions the methylene peak is so small that peak area measurements are not very reproducible. In our rate constant determination we tried to compensate somewhat for this poor reproducibility by making a large number of measurements.

From the results shown in Table I, it is seen that

TABLE I

RATE CONSTANTS FOR DEPROTONATION OF THE METHYLENE GROUP OF BIS(METHYLSULFONYL)-METHANE IN DEUTERIUM OXIDE SOLUTION

[Acid][a]	Temp, °C	No. of runs	$10^4\,k$,[b] sec^{-1}	Mean correln coefficient
0.108	25	5	8.7 ± 3.5	0.93
0.0108	25	5	7.7 ± 1.2	0.93
0.0011	25	5	9.5 ± 1.1	0.95
0.108	42	9	16.5 ± 3.2	0.96
0.0108	42	6	17.2 ± 2.7	0.95
0.0011	42	3	20.7 ± 1.4	0.94

[a] Hydrochloric acid. [b] Means and standard deviations.

rate constants obtained in the presence of 0.108, 0.0108, and 0.0011 M hydrochloric acid are all within the experimental uncertainty of each other. From this and the fact that α-hydrogen exchange by sulfones has not been found to be acid catalyzed, it was concluded that the proton removal was being accomplished by solvent molecules, possibly by mechanism 1 (eq 1). The

$$(MeSO_2)_2CH_2 + D_2O \xrightarrow{k_1} (MeSO_2)_2CH^- + D_2OH^+$$
$$(MeSO_2)_2CH^- + D_3O^+ \longrightarrow (MeSO_2)_2CHD + D_2O \qquad (1)$$

method of calculating rate constants employed, in which the removal of all the equivalent protons is treated as a single reaction, gives the rate constant *per* proton, *i.e.*, the statistically corrected rate constant,[8] which in the present case is equal to one half the rate constant for carbanion formation. Since those carbon acids that have been studied (nitromethane[9] and 3-methyl-2,4-pentanedione[10]) ionize 37–69% faster in protium oxide than in deuterium oxide solution, the first-order rate constant for the ionization of bis(methylsulfonyl)methane in protium oxide at 25° is estimated to be (2.6 ± 0.6) × 10^{-3} sec^{-1}, assuming that mechanism 1 is the only reaction path. From this value and the ionization constant, the value (9 ± 3) × 10^9 M^{-1} sec^{-1} may be calculated for k_p, the rate constant for protonation of bis(methylsulfonyl)methide ions by hydrogen ions in water at 25°. This value is so near the rate constant (k_d) that would be expected for the diffusion of the two ions together[11] as to suggest that a significant fraction of the ion pairs formed by diffusion together undergo proton transfer. This fraction, which will be denoted f, may be expressed in terms of rate constants that are known or can be rather reliably estimated, by the following derivation. The rate constant k_1 for exchange *via* the formation of dissociated ions must equal $(1 - f)k_c$, where k_c is the rate constant for the formation of carbanions involved in exchange, including those carbanions that are formed only as part of ion pairs that collapse without dissociation. The value for k_p stated above was calculated from k_c, but it should have been calculated from k_1. It follows that k_p is really equal to $(1 - f)(9 \pm 3) \times 10^9\ M^{-1}\ sec^{-1}$. It may also be seen that k_p must be equal to the rate constant k_d for formation of ion pairs from the dissociated ions multiplied by the fraction of those ion pairs that undergo proton transfer. If these two expressions for k_p are equated, eq 2 results,

$$k_d f = (1 - f)(9 \pm 3) \times 10^9\ M^{-1}\ sec^{-1} \qquad (2)$$
$$f = \frac{(9 \pm 3) \times 10^9\ M^{-1}\ sec^{-1}}{k_d + (9 \pm 3) \times 10^9\ M^{-1}\ sec^{-1}}$$

which may be solved for f with the result shown. Since k_d may be estimated[12] to be in the range 1–4 × 10^{10} $M^{-1}sec^{-1}$, f is probably between 0.1 and 0.5.

From the kinetics of exchange at 42°, an Arrhenius activation energy of 8 ± 3 kcal/mol may be calculated.

When the acid concentration was decreased further to 8 × 10^{-4}, 4 × 10^{-4}, and 2 × 10^{-4} M, the rate constants observed for exchange at 25°, (11.8 ± 1.2) × 10^{-4}, (61 ± 22) × 10^{-4}, and (300 ± 40) × 10^{-4} sec^{-1}, respectively, seemed to increase more rapidly than $1/[D^+]$. We have no explanation for this observation, which was not investigated thoroughly, but it cannot arise simply from attack of deuterioxide ions on the bissulfone. An upper limit on the rate constant for attack of deuterioxide ions on the bissulfone may be obtained from the data in Table I. It seems assured that this reaction is contributing less than 4 × 10^{-4} sec^{-1} to the total rate constant obtained in the presence of 0.0011 M acid. Since the deuterioxide ion concentration in this solution was about 1.4 × 10^{-12} M, the second-order rate constant for attack by OD^- is less than 3 × 10^8 M^{-1} sec^{-1}. Thus, when bis(methylsulfonyl)methane is involved in a proton-transfer reaction in which the equilibrium constant is considerably smaller than in the protonation of the bis(methylsulfonyl)methide ion, the rate constant in the exergonic direction falls short of the

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diffusion-controlled rate constant by at least two powers of ten. In contrast, glucose and guanidinium ions [each of which has an acidity constant within a factor of two of that for bis(methylsulfonyl)methane] are deprotonated by hydroxide ions with rate constants larger than $10^{10}\ M^{-1}\ \text{sec}^{-1}$.[11] Thus, although Pearson and Dillon's generalization is supported by the present work, the proton-transfer reactions of bis(methylsulfonyl)methane are slower than those of an oxygen or nitrogen acid (in which the acidic proton is not internally hydrogen bonded) of the same strength.

Experimental Section

Reagents.—The method of Backer[12] was used for the preparation of bis(methylsulfonyl)methane: mp 147–148.5° (lit.[12] mp 148°); pmr (CD_3SOCD_3) τ 4.58 (m, 2, J = 0.6 Hz, CH_2) and 6.78 ppm (t, 6, J = 0.6 Hz, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 172 (14), 94 (100), 79 (54), 78 (33), 63 (86).

When bis(methylsulfonyl)methane was recrystallized from deuterium oxide solution, the product was bis(methylsulfonyl)-methane-d_2: mass spectrum (70 eV) *m/e* (rel intensity) 174 (10), 96 (65), 80 (25), 79 (55), 63 (100).

Solvent solutions for kinetic runs were prepared by dissolving gaseous hydrogen chloride in 99.8% deuterium oxide, titrating, diluting with deuterium oxide, and retitrating. In the most concentrated solutions used (0.1 M), this increased the protium content of the solvent by 50%.

Determination of pK_a.—A Radiometer automatic titrator (ABU1, PHM26c, SBR2c, and type C electrode) was used manually to titrate 25-ml samples of 0.00653 and 0.02317 M bis(methylsulfonyl)methane with 0.1326 M sodium hydroxide solution at 25°. From the pH values recorded at intervals of about 0.2 ml from 0.4–2.5 ml of added base, values of the ionization constant were calculated from the equation

$$K_a = \frac{[H^+]^2 + [H^+][Na^+] - K_w}{[(MeSO_2)_2CH_2]_t + (K_w/[H^+]) - [H^+] - [Na^+]}$$

where $[(MeSO_2)_2CH_2]_t$ is the "total" concentration of bissulfone (including its conjugate base), pH was assumed to be equal to $-\log [H^+]$, and K_w is the value for the autoprotolysis constant of water calculated (by averaging several determinations) from the pH measured when the given volume of sodium hydroxide solution was added to pure water in the absence of sulfone. This method of calculation may be considered to be a way of calibrating the system at the high pH's encountered in the titration. The reliability of the method is supported by the values of pK_w obtained, ranging from 13.90 to 13.98, none of which differed by more than 0.02 from the value at the given ionic strength that may be obtained from a plot of the data listed by Harned and Owen.[13] The runs using 0.00653 M bissulfone gave pK_a values around 12.6, but these were based on measured pH values that differed from those in the absence of sulfone by only about 0.05. The values obtained using 0.02317 M bissulfone, where the pH differed by about 0.18 from that observed using no sulfone, are believed to be more reliable. Application of the Debye–Hückel limiting law to 11 observations between ionic strengths 0.0021 and 0.0120 M gave the average value 12.536 ± 0.008 for pK_a at infinite dilution.

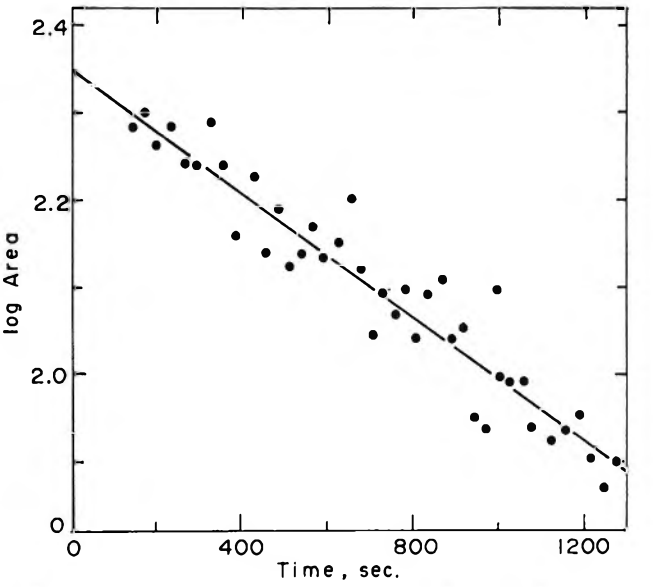

Figure 1.—Kinetic plot for the deuteration of bis(methylsulfonyl)methane in deuterium oxide containing 0.0108 M hydrochloric acid.

Kinetics of Deuterium Exchange.—In a typical run, about 1 ml of a solution of hydrochloric acid in deuterium oxide was added to more finely powdered bis(methylsulfonyl)methane than would readily dissolve, and the mixture was shaken vigorously for about 30 sec and filtered through a disposable pipet containing glass wool into a nmr tube. The nmr tube was inserted into the Varian A60-A nmr spectrometer, which had already been tuned for a solution of the bissulfone in deuterium oxide, taking care that no spinning side bands from the nearby peak due to the residual protons in the deuterium oxide fell too near the methylene peak of the bissulfone. The methylene peak was scanned repeatedly (the solution was too dilute for reliable results to be obtained from the integrator on the spectrometer) and the time noted at the midpoint of each scan. The peak areas were measured, some by planimetry and some by cutting out and weighing, before the method of counting squares was settled on. Rate constants were calculated from the slopes of the best lines, determined by the method of least squares, through plots of the logarithm of the area of the peaks *vs.* time. In a few runs the area of the methyl peaks was used as an internal standard and log (A_{CH_2}/A_{CH_3}) was plotted against time, but it was not clear that this resulted in any more reliable rate constants. Correlation coefficients for the plots ranged from 0.83 to 1.00 with a median of 0.95. The runs were followed to about 75% completion. Some of the runs were carried out at 42 ± 1°, the temperature attained when the variable temperature controller was not used, and some at 25 ± 1°. The average number of points taken was 37 at 25° and 17 at 42°. A kinetic plot for a typical run (correlation coefficient 0.95) is shown in Figure 1. The rate constants obtained are summarized in Table I.

Registry No.—Bis(methylsulfonyl)methane, 1750-62-5.

(12) H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **65**, 53 (1946).

(13) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, pp 752–754.

Protonation of the Isopropenylcyclopentadienyl Anion[1a]

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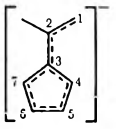
The reaction of isopropenylcyclopentadienylpotassium with aqueous acid gives a mixture containing, in order of decreasing yield, the linearly conjugated product 1-isopropenyl-1,3-cyclopentadiene (**4**), the cross-conjugated product 2-isopropenyl-1,3-cyclopentadiene (**5**), and 6,6-dimethylfulvene (**2**) under conditions where the smallest amount of subsequent isomerization of initially formed products is believed to have occurred. The equilibrium mixture of these isomers at room temperature contains about 98% **2**, 1.4% **4**, and 0.6% **5**. It is possible that the deconjugated product 5-isopropenyl-1,3-cyclopentadiene (**3**), believed to be the least stable of the four possible isomers, was also formed in significant amounts in the protonation reaction but that it rearranged before the product mixture was analyzed.

In an earlier paper[2] certain data on the protonation of resonance-stabilized carbanions were rationalized in terms of the principle of least motion.[3] In this connection the protonation of the isopropenylcyclopentadienyl anion (1) is of interest. Protonation at carbon 1 gives



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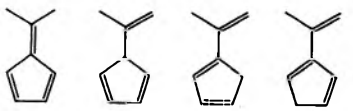
the most stable product. Protonation at carbon 3 would be accompanied by the smallest changes in bond lengths and essentially the same changes in bond angles as in the other cases. According to an HMO calculation, carbons 4 and 7 have the greatest electron density; hence their protonation might be expected to be accompanied by the least change in electronic configuration.

Results

Simple protonation of carbanion **1** can give dimethylfulvene (2), the deconjugated product 5-isopropenyl-1,3-cyclopentadiene (**3**), the linearly conjugated product 1-isopropenyl-1,3-cyclopentadiene (**4**), or the cross-conjugated product 2-isopropenyl-1,3-cyclopentadiene (**5**). Treatment of a heterogeneous slurry of potassium



2 3 4 5

tert-butoxide in bis(2-methoxyethyl) ether (diglyme) with 1 equiv of dimethylfulvene (containing a small amount of dicyclopentadiene as a reference compound) gave a homogeneous brown-red solution presumed to contain carbanion **1**. This solution was added to aqueous acid in the presence of a separate layer of organic solvent at various temperatures. The resultant yellow organic layer was washed and analyzed by gas–liquid partition chromatography (glpc), sometimes before and sometimes after the solvent was removed to give an amber liquid whose properties changed significantly if it was allowed to remain at room temperature for as long as 30 min. The glpc analysis usually showed only peaks for dicyclopentadiene, dimethylfulvene, and a third component with a somewhat shorter retention time, which is believed to be due to isomers of dimethylfulvene. In some cases the dicyclopentadiene content of these products was essentially the same as that of the reactant, showing that probably no significant amounts of other products were formed. The area of the isomer peak ranged from somewhat less than that of the dimethylfulvene peak to 7.5 times as large. There was no clear difference between the results obtained using the different protonation procedures.

The isomer peak was separated from the amber liquid by preparative glpc. Its mass spectrum was identical with that of dimethylfulvene at 70 eV but not at 12.5 eV. These observations, including the parent peak at mass 106, give strong evidence that one or more of the isomers **3**, **4**, and **5** were present. This interpretation is supported by the infrared spectrum, which contained a strong peak at 895 cm^{-1} and a weak peak at 1780 cm^{-1}, characteristic of $-C{=}CH_2$ groups.[5]

The 100-MHz proton magnetic resonance spectrum of the "isomer mixture" showed absorption in four regions, τ 3.20–3.80, 4.75–5.30, 6.85–7.05, and 7.95–8.10 ppm, with relative areas of 3.1:2.07:2.07:3.00, which were assigned to hydrogen atoms attached to unsaturated ring carbon atoms, exocyclic vinyl hydrogen atoms, ring methylene hydrogen atoms, and methyl hydrogen atoms, respectively. The assignments are supported by analogy to the unsaturated ring hydrogen atoms of the methylcyclopentadienes[6] (τ 3.6–4.0 ppm), the terminal unsaturated hydrogen atoms of 1,3-butadiene and 2,3-dimethyl-1,3-butadiene[7] (τ 4.8–5.0 ppm), the ring methylene hydrogen atoms of 1- and 2-methylcyclopentadiene[6] (τ ~7.2 ppm), and the methyl groups of 2,3-dimethyl-1,3-butadiene[7] (τ ~8.0 ppm), respectively. The relative areas of the four regions of absorption are as expected for compounds **4** and **5** but not for **3**. Since the methinyl hydrogen atoms of 5-methylcyclopentadiene absorb at τ 6.97 ppm and replacing the methyl by a vinyl group would be expected to shift the absorption 0.5–1.0 ppm lower, compound **3** should absorb in the range 6.0–6.5 ppm. No absorption in this range was observed. For these reasons and the fact that we can explain essentially the entire spectrum

(1) (a) This investigation was supported in part by Grant GP-4445 from the National Science Foundation. (b) The Ohio State University. (c) The University of North Carolina at Greensboro.

(2) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966).

(3) "Those elementary reactions will be favored that involve the least change in atomic position and electronic configuration." [4]

(4) F. O. Rice and E. Teller, *J. Chem. Phys.*, **6**, 489 (1938).

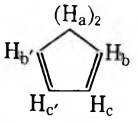
(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, pp 26, 50.

(6) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2313 (1965).

(7) R. Hobgood and J. H. Goldstein, *J. Mol. Spectrosc.*, **12**, 76 (1964).

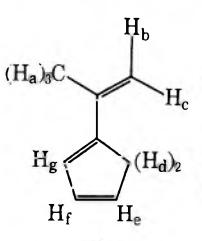
without it, we believe that no appreciable amount of **3** is in the separated isomer mixture. The methyl region consisted of two slightly overlapping multiplets at τ 8.05 and 8.01 ppm with relative areas of about 68:32. The methylene region consisted of a doublet of doublets at τ 6.89 and a broad peak at 6.96 ppm, with relative areas of about 71:29. The exocyclic vinyl hydrogen region contained a pair of larger and a pair of smaller broad peaks with relative areas about 73:27. Decoupling experiments showed that the larger peaks in one region were in the same molecule as the larger peaks in another region. These observations suggest that the material is a mixture containing about 70% of one component and 30% of another. The composition of this mixture remained relatively constant from run to run even though the amount of dimethylfulvene formed varied considerably.

The unsaturated ring hydrogen region contained, with relative areas of about 1:1.64:0.22, a multiplet at τ 3.73, a multiplet at 3.59, and, at 3.26 ppm, a doublet (J = 5 Hz) of quartets (J = 1.5 Hz) that became a doublet (J = 5 Hz) of doublets (J = 1.5 Hz) upon irradiation at τ 6.96 ppm. These observations require that the unsaturated ring hydrogen atoms of the less abundant component absorb at τ 3.26, about 3.59, and about 3.73 ppm, and that those of the more abundant component absorb at about 3.59, 3.59, and 3.73 ppm. From the following analysis of the pmr spectrum of cyclopentadiene by Manatt[8] and similar data, we concluded that the hydrogen atoms at the ends of π sys-



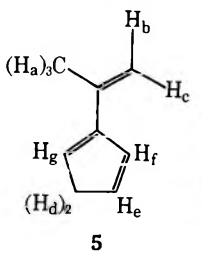
	τ, ppm	Hertz	
H_a	7.21	J_{ab}	= 1.2
H_b	3.67	J_{ac}	= −1.3
H_c	3.53	J_{bc}	= 5.06
		$J_{cc'}$	= 1.94
		$J_{b'c}$	= 1.09
		$J_{bb'}$	= 1.94

tems in our compounds absorbed at higher field than those attached to the interior carbon atoms. These considerations and additional apparent coupling constants, largely from decoupled spectra, led to the following assignments for the pmr spectra of **4** and **5**. The



4

	τ, ppm	Hertz	
H_a	8.05	J_{ab}	= 1.3
H_b	5.23	J_{ac}	= 0.75
H_c	4.93	J_{de}	= 1.5
H_d	6.89	J_{df}	= 1.5
H_e	~3.73	J_{dg}	= 1.5
H_f	~3.59	J_{ef}	= 5.0
H_g	~3.59	J_{eg}	= 1.5
		J_{fg}	= 1.9*



5

	τ, ppm	Hertz	
H_a	8.01	J_{ab}	= 1.25
H_b	5.04	J_{ac}	= 0.75
H_c	4.80	J_{de}	= 1.5
H_d	6.96	J_{df}	= 1.5
H_e	~3.73	J_{dg}	= 1.5
H_f	3.26	J_{ef}	= 5.0
H_g	~3.59	J_{eg}	= 1.5
		J_{fg}	= 1.9*

peaks at τ 3.59 and 3.73 ppm were never clearly separated and therefore the chemical shifts so listed are more uncertain than the others. The starred coupling constant (J_{fg}) was not derived from any of our measurements but was assumed by analogy to cyclopentadiene. The coupling constants listed are all plausible (the best models for the last six being those in cyclopentadiene), but they would also be if the assignments for the two compounds were reversed. Hence, the two compounds were distinguished on the basis of chemical shifts.

The carbon skeletons of compounds **4** and **5** would be expected to be nearly coplanar in order to maximize overlap between the π systems of the rings and those of the isopropenyl groups. Therefore the ring protons will be deshielded by the isopropenyl group, and the methylene protons in **4** will be more deshielded than the more distant methylene protons in **5**.[9] Conversely, the protons of the isopropenyl group will be more deshielded by the double bond to which H_e and H_f are attached in **5** than in **4**. Thus the major component of the mixture, whose methylene protons absorb at lower field and whose isopropenyl protons absorb at higher field than those of the minor component, must be **4**. The fact that the methylene protons are not in the plane of the carbon skeleton probably makes the difference in chemical shifts for these protons smaller than it would otherwise be. This is partly true for the methyl protons, but the fact that these protons in **4** and **5** have so nearly the same chemical shift also suggests that the isopropenyl group is oriented as shown in the formulas, with its double bond trans to the ring double bond with which it is conjugated.

As the product mixture stood, new pmr peaks appeared and grew at the expense of those due to **2**, **4**, and **5**. The fraction of the absorption appearing above τ 6.0 ppm increased from about 54% initially to 63% after 4 hr at 37°, when at least 58% of the **4** and about 38% of the **5** had disappeared. After 280 hr, when all the **4** and **5** and about half the dimethylfulvene were gone, 68% of the absorption was above τ 6.0 ppm.

In order to learn more about the relative stabilities of compounds **2**–**5**, samples of dimethylfulvene were treated with small amounts of base in 85:15 diglyme–*tert*-butyl alcohol and in *tert*-butyl alcohol. Equilibrium seemed to have been reached when about 98.8% dimethylfulvene and 1.2% of material with the retention time of **4** and **5** were present. Equilibrium was approached from the other side by use of a mixture containing about 40% dimethylfulvene and 60% **4** and **5**, which was treated in the same way. Equilibrium seemed to be near when 96.5% dimethylfulvene and 3.5% of material with the retention time of **4** and **5** were present, but slow side reactions made it impossible to wait indefinitely for the establishment of equilibrium. A small amount of the minor component of the equilibrium mixture obtained starting with dimethylfulvene was separated by glpc and found to have an ultraviolet spectrum (maxima at 212 and 288 mμ with shoulders at 214 and 216 mμ) almost identical with that of the major glpc fraction from the protonation of carbanion **1** and quite different from that of dimethylfulvene (maxima at 266, 271, and 354 mμ). Taking the position of equilibrium as intermediate between that attained starting from the two different sides, we estimate

(8) S. L. Manatt, Jet Propulsion Laboratory, California Institute of Technology, personal communication, 1967.

(9) Somewhat similar effects may be seen in the pmr spectra of 6-phenylfulvene[10] and 6-vinylfulvene.[11]

(10) M. L. Heffernan and A. J. Jones, *Aust. J. Chem.*, **19**, 1813 (1966).

(11) J. M. Neuenschwander, D. Meuche, and H. Schaltegger, *Helv. Chim. Acta*, **47**, 1022 (1964).

that the equilibrium mixture of isomers contains about 98% dimethylfulvene, 1.4% **4**, 0.6% **5**, and too little **3** to detect.

In view of the possibility that some isomerization may have occurred during the glpc separation (at 115°), the products of protonation of **1** were not separated in several runs. In one run in which the product mixture had been distilled (at room temperature and reduced pressure), the ultraviolet spectrum was found to contain all the absorbance peaks characteristic of dimethylfulvene and the mixture of **4** and **5**, separated by glpc, except that the 288 mμ peak became a shifted shoulder on the stronger dimethylfulvene peak at 271 mμ. In addition, there was an unexplained peak at 253 mμ. The pmr spectrum of material that had been extracted but not distilled showed all the peaks found in the two fractions obtained when glpc separation was used. Integration of these peaks showed that about 20% dimethylfulvene, 55% **4**, 20% **5**, and 5% of the material that forms on standing was present.

When deuterium acetate in deuterium oxide was used as the quenching solution, the reaction product was found by mass spectral measurements to be about 66% monodeuterated and 12% dideuterated. The combined yield of **4** and **5** in this run was 4.4 times that of dimethylfulvene.

Discussion

We may use dimethylfulvene as a standard and define the stabilities of the isomers in terms of ΔG°_{chem}[12] for their formation from dimethylfulvene. From our equilibrium measurements and the symmetry numbers of dimethylfulvene (18), **4** (3), and **5** (3), values of 0, 3.6, and 4.1 kcal/mol may be calculated for the respective ΔG°_{chem} values at room temperature. Simple HMO calculations give the same delocalization energies for **2**, **3**, **4**, and **5** as for fulvene (1.466 β), 1,3-butadiene (0.472 β), 1,3,5-hexatriene (0.988 β), and 3-methylene-1,4-pentadiene (0.899 β), respectively.[13a] A plot of the three known values of ΔG°_{chem} *vs.* the corresponding delocalization energies gives a surprisingly good straight line of slope −7.2 kcal/β, in satisfactory agreement with −6 kcal/β, the average value for polyenes.[13b] This correlation supports the structural assignments **4** and **5** made for the more and less stable components of the isomer mixture. Extrapolation of the plot gives a ΔG°_{chem} value of 7.3 kcal/mol for **3**, from which **3** may be estimated to comprise less than 0.001% of the equilibrium mixture of isomers.

The starting dimethylfulvene not accounted for in our glpc analyses may have been lost partly because of its significant volatility and solubility in aqueous diglyme. However, reactions to give products of higher molecular weight, perhaps *via* Diels–Alder reactions, probably also contributed. The variation in yields of dimethylfulvene may be due to isomerization of the kinetically controlled product mixture by a carbanion mechanism, perhaps partly because of local excesses of base present during the protonation reaction. Since there would certainly be no significant net rearrangement of dimethylfulvene to the other isomers, the fraction of dimethylfulvene present in the original kinetically controlled product mixture should be as low as, or lower than, that obtained in any run (since dimethylfulvene gives higher molecular weight products more slowly than do **4** and **5**). The presence of dideuterated products in the reaction mixture obtained using deuterium acetate shows that some carbanion formation by **4** and **5**, and hence some isomerization to dimethylfulvene, have occurred (in a run in which about 18% dimethylfulvene was formed).[14] Thus, it is not clear that protonation of carbanion **1** to give the most stable of the possible products occurs to a greater than random extent (16 2/3%), and it may occur to a considerably smaller extent.

Further interpretation of our results is limited by our ignorance of whether **3** is formed or not. If **3** were formed from **1** and then rearranged *via* reversion to **1** (perhaps during the work-up), the *relative* yields of the other three isomers would not be affected. However, the isomerization of **3** by a sigmatropic migration of hydrogen should give **4** specifically. The fact that the ratio of **4** to **5** appears to move away from the equilibrium ratio as the compounds are transformed to higher molecular weight products on standing at 37° suggests that **4** and **5** are not interconverted very rapidly. It therefore appears that the **4** observed may be the sum of that formed directly by protonation of **1** and that formed indirectly *via* rearrangement of **3**.

We believe that the following facts are relevant to consideration of the relative rates of protonation of the various carbon atoms of carbanion **1**. A simple estimate of the magnitude of the least nuclear motion effect, the sums of the squares of the changes in bond numbers that accompany the reactions,[2] gives the values 0.89, 1.22, 1.55, and 2.22 for the formation of **3**, **5**, **4**, and **2**. A semiquantitative method of estimating the least nuclear motion effect from force constants and changes in bond length[2] gives the same sequence, except that the values for **4** and **5** are close to each other and become essentially equal when certain methods of estimating molecular geometry are used. An HMO calculation gives charge densities of −0.187, −0.182, −0.162, and −0.116 at the carbon atoms whose protonation gives **4**, **5**, **3**, and **2**, respectively, but calculation by an SCF MO method[15] gives the greatest negative charge density at the carbon atom whose protonation gives **2**.[16] More detailed application of these least nuclear motion effects and charge densities to the problem of the protonation of **1** is probably not warranted until a larger fraction of the dimethylfulvene used can be unambiguously accounted for, subsequent isomerization of initially formed products can be consistantly minimized, and it can be learned whether **3** is formed or not.

(12) S. W. Benson, *J. Amer. Chem. Soc.*, **80**, 5151 (1958).

(13) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, (a) pp 43, 44, 95, or calculated by the methods given; (b) p 242.

(14) The oxygen-bound hydrogen atoms in the deuterium acetate quenching mixture contained about 6% protium, largely from the *tert*-butyl alcohol formed in the generation of carbanion **1**. The observed formation of about 22% undeuterated products might be due to a kinetic isotope effect, but much of the product may have been formed before the local excesses of protium that initially surrounded the carbanions had been dispersed by mixing. It seems unlikely that the reaction of the carbanion was complicated by the presence of a two-phase system. Diglyme and water are completely miscible and a second phase does not appear when the reaction mixture is poured into an aqueous solution until after the isomer mixture has been formed and its molecules had a chance to agglomerate. When the quenching experiments were carried out in the presence of a lower layer of carbon tetrachloride, the reaction was probably essentially complete before contact with the carbon tetrachloride.

(15) O. W. Adams and R. L. Miller, *Theor. Chim. Acta*, **12**, 151 (1968).

(16) R. L. Miller, University of North Carolina at Greensboro, personal communication, 1969.

Experimental Section[17]

Dimethylfulvene.—The method of Freiesleben[18] was used to obtain dimethylfulvene (5-isopropylidene-1,3-cyclopentadiene), which was found to contain about 10% dicyclopentadiene. Fractional freezing was used to reduce the dicyclopentadiene content to about 5%, at which level it was used as a reference in glpc analysis of the reaction products. Pure dimethylfulvene was obtained by preparative glpc: mass spectrum (12.5 eV) *m/e* (rel intensity) 107 (9.0), 106 (100), 105 (0.6), 91 (4.6), 66 (1.2).

Reaction of 1-Isopropenyl-2,4-cyclopentadienylpotassium with Acid.—In a typical run a slurry of 11.0 g (98 mmol) of potassium *tert*-butoxide in 20 ml of diglyme (distilled over sodium and stored over Molecular Sieves) was prepared under nitrogen in the 500-ml flask of a flame-dried glass system. A solution of 10.4 g (94 mmol of the principal component) of dimethylfulvene containing 4.4% dicyclopentadiene in 5 ml of diglyme was added with stirring to the slurry, which had been cooled to 3°. The resulting red-brown solution was homogeneous at 20° but cloudy at 5°, at which temperature it was added rapidly to a separatory funnel containing 10 g of glacial acetic acid, 700 ml of water, and 200 ml of light petroleum ether, all at about 0°. After vigorous shaking a yellow-orange organic layer was present, which was washed twice with 700 ml of ice-cold water. The solvent was removed from the organic layer at reduced pressure and a temperature below 0° to give an amber liquid. Analysis *via* glpc on a 6-ft Apiezon L column at 100° showed 77.6% of the isomer–mixture peak at 8.0 min, 16.9% of dimethylfulvene at 11.75 min, and 5.3% of dicyclopentadiene at 21.5 min. The increase in dicyclopentadiene content shows that about 17% or more of the starting dimethylfulvene is unaccounted for, probably largely because of loss during removal of the solvent. In some runs in which the organic extract was analyzed without removing the solvent the dicyclopentadiene content was within the experimental uncertainty (~10%) of its original value. In other runs there was up to twice as much dicyclopentadiene in the products as in the reactant. In some of these cases the reaction mixtures had spent 1 hr or more at room temperature before analysis and in others the quenching solution had contained methanol (as an antifreeze agent), which may have retained more of the products, but in some cases the loss of product is not understood.

Reaction temperatures ranging from those obtained by Dry Ice cooling to room temperature were used, both hydrochloric and acetic acids were used, and diethyl ether and carbon tetrachloride were used instead of petroleum ether. Since the variation in yield of isomer mixture with reaction temperature seemed to be no larger than the variations observed at a given temperature, most of the later runs were carried out at room temperature using acetic acid rather than hydrochloric acid, which gave a smaller yield of isomers in the few cases in which it was used. The products obtained were stored at 0° or below. In several runs in which no significant loss of dimethylfulvene occurred, glpc analysis of the unconcentrated extracts showed a ratio of isomer mixture to dimethylfulvene of greater than 5:1, but in none of these cases was it possible to run 100-MHz pmr spectra on the products within a reasonable time after they were formed.

Sodium hydride and metallic sodium as the reagents and diethyl ether, dimethyl sulfoxide, and tetrahydrofuran as the solvents for preparing a salt of dimethylfulvene usually gave darker colored reaction mixtures that reacted with acid to give little of the isomers of dimethylfulvene (and often little dimethylfulvene). Poor yields of the isomers were also usually obtained in quenching the carbanion with acetic acid in nonaqueous solvents.

The amber liquid product was separated by preparative glpc into dimethylfulvene and the light yellow isomer mixture: uv max (hexane) 211 mμ (ε 6490), 288 (6760); ir (neat) (in order of decreasing intensity) 895, 665, 1360, 2975, 2950, 2930, 880, 3090, 860, 2900, 1615, 1440, 1435, 1255, 2875, 955, 680, 705, 3050, 815, 1575, 780, 765, 925, 985, 1015, 625, 1230, 595, 575, 1315, 1000, 1105, 1280, 1125, 1090, 1780, and 2745 cm^{-1}; mass spectrum (12.5 eV) *m/e* (rel intensity) 107 (8.6), 106 (100), 105 (1.8), 92 (1.3), 91 (16), 80 (0.4), 78 (0.4), 66 (0.6).

Reaction of 1-Isopropenyl-2,4-cyclohexadienylpotassium with Deuterium Acetate.—In the deuteration experiment, the solution of 1 from 12.7 g (113 mmol) of potassium *tert*-butoxide and 11.9 g (108 mmol) of 95% dimethylfulvene–5% dicyclopentadiene in 35 ml of diglyme was divided into three equal portions. One was added to 5 g of acetic acid-d_4, 15 ml of 99.8% deuterium oxide, and 30 ml of carbon tetrachloride and then worked up in the usual way, with product being vacuum distilled. A second portion was quenched and worked up in the usual way using carbon tetrachloride and "light" water and acetic acid. Both products were analyzed by mass spectrometry at 9.0 eV where the only observed peaks for the protium product were at *m/e* 107, 106, and 66. The *m/e* 107 peak was 9.2% as large as the 106 peak, in good agreement with the value 8.8% calculated from 1.1% natural abundance of ^{13}C. The assumption that every parent peak was accompanied by a parent + 1 peak 9.2% as large led to the values 22, 66, and 12% for the amounts of C_8H_{10}, C_8H_9D, and $C_8H_8D_2$ in the product formed using deuterium acetate.

Equilibration of Dimethylfulvene and Its Isomers.—When pure dimethylfulvene was heated to 100° for 23 hr, an intractable black sludge was formed. The same treatment in the presence of 5 mol % diphenylamine led to the recovery of 35% of the dimethylfulvene, but no isomers were detected. Solutions of dimethylfulvene in about 85% diglyme–15% *tert*-butyl alcohol containing less than 1 mol % potassium *tert*-butoxide were added to water–petroleum ether after various lengths of time at room temperature and the organic layer analyzed by glpc. After the content of isomer mixture reached 1–1.5%, the composition of the mixture no longer changed significantly. More isomer mixture was obtained from refluxing solutions and perhaps when stronger solutions of potassium *tert*-butoxide were used, but about the same results were obtained using triethylamine in *tert*-butyl alcohol. When a mixture of about 40% dimethylfulvene and 60% isomer mixture (4 and 5) was used as the starting material, changes in composition of the mixture had become slow when 3.5 ± 1% isomer mixture was left, but the glpc peaks were not clearly resolved as they were when dimethylfulvene was the starting material.

Registry No.—**4**, 26385-00-2; **5**, 26385-01-3.

Acknowledgment.—We are indebted to Dr. Wendel Lim for having checked certain of our experimental results, to Mr. William Jankowski of Varian Associates for running the 100-MHz pmr spectra, to Dr. S. L. Manatt for his interpretation of the pmr spectrum of cyclopentadiene, and to Dr. R. L. Miller for information on SCF MO calculations.

(17) Perkin-Elmer Model 337 and Cary Model 14 spectrophotometers were used to obtain infrared and ultraviolet spectra, respectively. Mass spectra were determined with an AEI MS-9 instrument and pmr spectra with Varian A-60 and A-100 spectrometers.

(18) W. Freiesleben, *Angew. Chem.*, **75**, 576 (1963).

Reactions of Aziridines. II. The Acid-Catalyzed Formation of 1,4-Dialkylpiperazines from 1-Alkylaziridines

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It has been demonstrated that hydrohalic acids in 2-propanone or 2-butanone will catalyze the conversion of certain 1-alkylaziridines to the corresponding 1,4-dialkylpiperazines in yields as high as 95%. The rates of piperazine formation were effected in the order HI > HBr > HCl. Perchloric acid and *p*-toluenesulfonic acid resulted in the formation of poly(1-alkylaziridines) rather than piperazines. The major products formed in a water solvent were poly(1-alkylaziridines) with 1,4-dialkylpiperazines being formed in maximum yields of 27% in the case of a hydriodic acid catalyst.

The formation of 1,1,4-trialkylpiperazinium halides from alkyl halides and 1-alkylaziridines was discussed in the first paper of this series.[1] The proposed mechanism involved the initial reaction of an alkylating agent with a 1-alkylaziridine to produce a 1,1-dialkylaziridinium salt which lead to the formation of either the piperazinium halide or a polymer. It was also demonstrated that the presence of a halide ion was necessary for piperazine formation. A further test of the proposed mechanism has now been carried out by replacing the alkylating agents with acids under the same conditions as previously reported. In the presence of acids the expected products would be either polymer or 1,4-dialkyl piperazines and their acid salts.

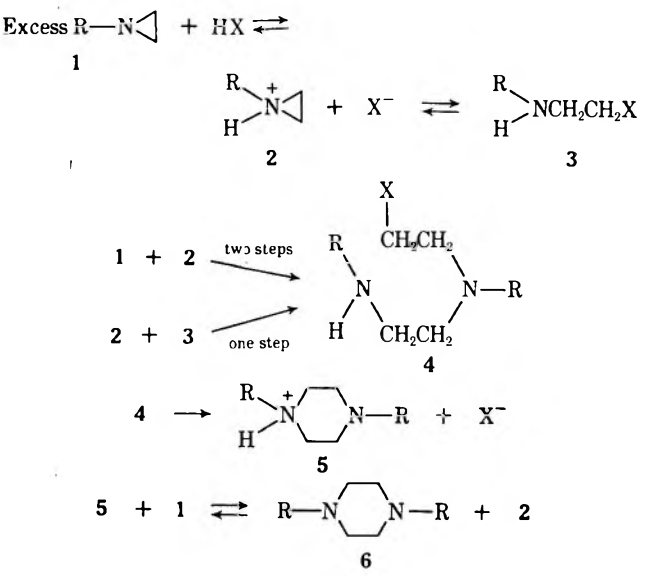
From a consideration of the data in Table I it is apparent that halogen acids are required (reactions 1–6, 9, 10, 11) for piperazine formation and that the order of catalyst effectiveness is HI > HBr ≫ HCl. Replacement of the halides by ions of low nucleophilicity such as perchlorate (reaction 7) and *p*-toluenesulfonate (reaction 8) resulted in polymer formation. The effect of solvent polarity on product distribution can be ascertained by comparing the yields of 1,4-diethylpiperazine in acetone (reactions 1, 6) with those achieved in acetone–water mixtures (reactions 11, 12). It is apparent that a solvent of low polarity and solvating power favors piperazine formation. The general results concerning the effects of anions and solvent polarity are in complete agreement with those results reported for alkylating agents.[1]

A predictable difference between alkylating agents and acids was noted when it was found that several moles of 1,4-diethylpiperazine were produced for each equivalent of hydrohalic acid charged thereby demonstrating that the acids were functioning as catalyst. Thus the formation of 1,4-dialkylpiperazines using an acid catalyst can best be formulated according to Scheme I.

Through a series of steps the monomer **1** is ultimately converted to **4** which cyclizes to form the 1,4-dialkylpiperizinium halide (**5**). The transfer of a proton from **5** to **1** results in the formation of the 1,4-dialkylpiperazine (**6**) plus **2** which completes the catalyst cycle. It is worth noting that as the reaction progresses the position of the equilibrium **5** + **1** ⇄ **6** + **2** will favor **5** at the expense of **2**. Thus the rate of conversion and the total conversion achievable within some practical time limit will be dependent on the initial monomer to acid catalyst ratio (reactions 1–4).

In order to further demonstrate that halide ions are

SCHEME I



involved in the product determining step of piperazine formation, a series of rate measurements was made and is depicted by the adjoining graph. It is evident that the rate of diethylpiperazine formation is dependent on the particular halide ion involved, $I^- > Br^- > Cl^-$, and that the reaction rate closely approaches zero at low aziridine conversions in the case of hydrochloric acid catalyst. The perchloric acid curve depicts a typical acid catalyzed polymerization, *i.e.*, a very rapid consumption of monomer followed by an equally rapid cessation of the reaction (Figure 1).

As was previously noted,[1] not all 1-alkylaziridines will form the corresponding piperazines even under the most favorable conditions. The ethylaziridine, 1-*n*-butyl aziridine, 1-phenethylaziridine, and 1-allylaziridine were all converted to the corresponding piperazines in good yields with hydriodic acid and sodium iodide in acetone. However, 1-(2-hydroxyethyl)aziridine and 1-cyanoethylaziridine did not form piperazines even in the presence of the added sodium iodide.

Further consideration of the data in Table I revealed that all of the aziridine converted is not forming 1,4-diethylpiperazine. Runs 1–4 demonstrate that higher acid–aziridine ratios result in lower yields, or alternatively, that higher conversions of aziridines result in lower yields of 1,4-diethylpiperazine. Runs 1 and 5 were completely devolatilized to determine if the loss in product was due to polymer formation. The residues were subjected to infrared analysis and were

(1) C. R. Dick, *J. Org. Chem.*, **32**, 72 (1967).

Table I

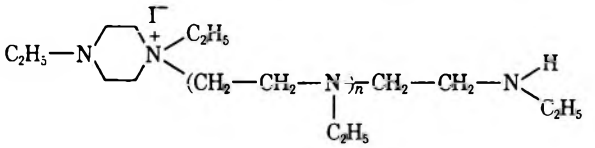
Reaction of 1-Ethylaziridine with Acids in Acetone

Run no.	Acid, equiv/equiv aziridine	Aziridine conversion, %[a]	Diethylpiperazine % yield by glpc	Diethylpiperazine % yield by ir	Nonvolatile residue, g	Piperazine rings in residue, %[c]
1	HI, 0.116	96	73	76	1.75	52
2	HI, 0.058	81	87	90		
3	HI, 0.035	65	93	95		
4	HI, 0.012	28	93	93		
5	HBr, 0.116	78	80	83	1.4	23
6	HCl, 0.116	31	48	48	1.0	<1.0
7	$HClO_4$, 0.116	77	0	<0.4	3.3[d]	<1.0
8	*p*-Toluenesulfonic, 0.116	79	0	<0.4	3.5[d]	<1.0
9	HI, 0.116, plus 0.006 mol of NaI	98	81	83		
10	HCl, 0.116, plus 0.006 mol of NaI	97	72	76		
11	HI, 0.116, 50% water–acetone	99+	27			
12	HCl, 0.116, 50% water–acetone	97	<1		3.1[d]	

[a] 24-hr reaction time. [b] After stirring reaction solution with excess potassium carbonate to ensure all acid was neutralized; yields calculated on basis of converted aziridine. [c] 1,1,4-Triethylpiperazinium bromine used infrared standard. [d] Poly(1-ethylaziridine).

found to contain significant quantities of nonvolatile monoquaternary piperazines.

In order to prepare a large quantity of the piperazine containing residue, reaction 1 was repeated on a larger scale from which 27.6 g of residue were isolated. This residue was separated into a 21-g diethyl ether insoluble fraction I which contained all of the piperazine moieties and a 5.2-g fraction II which was poly(1-ethylaziridine), completely free of piperazine rings as determined by infrared analysis. In addition to the aforementioned monoquaternary piperazines, the infrared spectra of fraction I was also found to contain bands characteristic of a significant concentration of acyclic, secondary amino nitrogen. Based on the infrared data, elemental analysis, molecular weight determination, and secondary and primary amine analysis, it was concluded that fraction I was a mixture of quaternary piperazines best represented by structure **7**. For an M_n of 380, the average value of n is 0.7.



7

The formation of a quaternary nitrogen demonstrates the existence of an acid catalyst consuming reaction; therefore, reaction 1 was repeated and allowed to stand for 7 days at which time no further reaction could be detected by glpc. Additional 1-ethylaziridine was then added to the reaction mixture and the concentration of 1,4-diethylpiperazine was noted to increase approximately 50% thereby demonstrating that these reactions seem to stop at high conversions not only because of quaternary piperazine formation but due to amine salt formation other than the aziridinium salts (2).

Experimental Section[2]

Preparation of 1,4-Diethylpiperazine (Table I).—A series of four-ounce bottles containing 100.0 ml of 0.52 *M* 1-ethylaziridine in acetone or acetone–water were placed in a 25.0° bath. Sodium iodide (0.77 g, 0.006 mol) was added to the appropriate bottles. The indicated amount of acid was added as a 6.0 *N* aqueous solution to each bottle which was shaken and returned to the bath. After 24 hr, 15 g of anhydrous potassium carbonate was added in order to neutralize the acid and the bottles were shaken for 4 hr. After allowing the solids to settle, the contents of each bottle were analyzed for 1,4-diethylpiperazine and unconverted 1-ethylaziridine by standard glpc and infrared techniques.

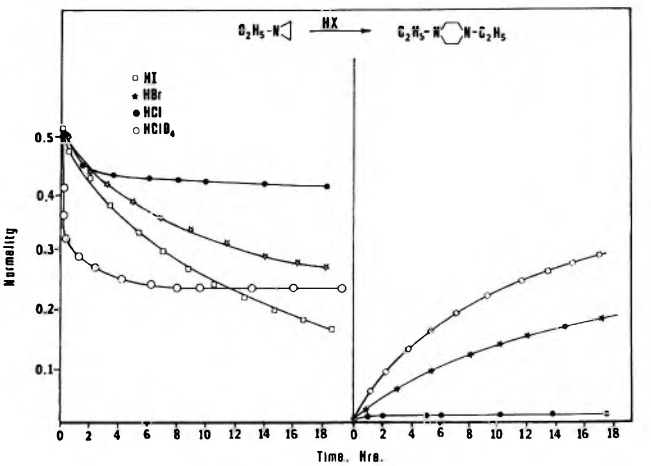


Figure 1.—Rate of acid-catalyzed formation of 1,4-diethylpiperazine.

The glpc column was 9 ft × 0.25 in. stainless steel packed with 15% Carbowax 20M plus 5% potassium hydroxide on 60–80 mesh Chromosorb W. For infrared analysis, the band at 955 cm^{-1} was used for diethylpiperazine and at 730 cm^{-1} for 1-ethylaziridine. The data is reported in Table I.

Preparation and Identification of Residue from Hydriodic Acid Catalyzed Reactions.—To a well-stirred mixture of 1425 ml of acetone and 80 g (1.11 mol) of 1-ethylaziridine maintained at 25–30° was added dropwise (1 hr) 30 ml of concentrated hydriodic acid. The mixture was stirred an additional 3 hr at 25–30°, was transferred to a stoppered bottle, and was stored in the dark. After 5 days, 150 g of anhydrous potassium carbonate was added and the mixture was stirred for 12 hr. The solution was filtered and devolatilized in a rotary evaporator. The residue was taken up in 100 ml of tetrahydrofuran, filtered to remove traces of potassium carbonate, and again devolatilized. The product, 27.6 g, was shown to be free of 1,4-diethylpiperazine by glpc analysis.

The product was fractionated by dissolving in 300 ml of tetrahydrofuran and adding three 40-ml aliquots of diethyl ether. After each addition a gummy phase separated which was removed. The three fractions and the mother liquor were freed of solvent. Product isolated from the mother liquor, 5.2 g, was shown to be poly(1-ethylaziridine) by comparison of its infrared spectra with that of an authentic sample. Fractions 1, 2, and 3

(2) All melting points are uncorrected. Infrared spectra were taken on a Beckman IR-9. Glpc data were taken on an F & M 810.

were combined, 21 g, since they had nearly identical infrared spectra. The spectra of the composite indicated the presence of high concentrations of a 1,1,4-trisubstituted piperazinium salt (1210–1220 cm^{-1}), $(-CH_2-)_3N$ (1060, 2860 cm^{-1}) characteristic of poly(1-ethylaziridine), and $(-CH_2-)_2NH$ (1110, 2810 cm^{-1}). Since poly(1-ethylaziridine) is soluble in diethyl ether, the composite was thoroughly washed with ether and dried, and its spectra remained unchanged. The ether washed was found to contain no polymer. Analysis of the residue is reported below.

Anal. Found: N, 12.85; C, 42.20; H, 8.78; I, 33.19; >NH, 3.4; $-NH_2$, <0.1; mol wt, 340 (ebulliometrically in 2-butanone) [Calcd: mol wt, 383 (based on iodide), 378 (based on secondary amine)].

Procedure for Rate Determinations.—Into a 100-ml volumetric flask were weighed 2.00 g of phenetole and 3.70 g of 1-ethylaziridine. The flasks were filled with 2-butanone and placed in a 25.0° water bath. To each flask was added 0.50 ml of 6.0 *N* acid and the contents were thoroughly mixed. At predetermined time intervals the reaction mixtures were analyzed by standard glpc techniques using the phenetole as an internal standard. The glpc column previously mentioned was used for these analyses. All runs were made in duplicate.

Preparation of 1,4-Disubstituted Piperazines for Glpc and Infrared Standards.—The diethyl-, di-*n*-butyl-, and diallylpiperazines were prepared by mixing 0.12 mol of the corresponding aziridine and 10 g (0.078 mol) of sodium iodide in 150 ml of 2-butanone followed by the addition of 3.2 g of concentrated hydriodic acid. After remaining at room temperature (24–26°) for 48 hr, the mixtures were shaken for 4 hr with 50 g potassium carbonate and filtered, and the solvent was removed by distillation at atmospheric pressure. The piperazines were isolated from the distillation residues by preparative scale glpc using the aforementioned Carbowax column.

Anal. Calcd for 1,4-diethylpiperazine: N, 19.72. Found: 19.82; $n^{25}D$ 1.4530 (lit.[3] 1.4520).

Anal. Calcd for 1,4-di-*n*-butylpiperazine: N, 14.1. Found: 19.82; $n^{25}D$ 1.4540 (lit.[3] 1.4542).

Anal. Calcd for 1,4-diallylpiperazine: N, 16.87. Found: 16.68; $n^{25}D$ 1.4754 (lit.[4] 1.4761).

The preparation of 1,4-diphenethylpiperazine was the same as above; however the product was isolated by devolatalizing the filtered reaction mixture, washing the residue with water to remove the soluble salts, and recrystallizing the crude product from an acetone–water mixture, mp 79.5–80.5°.

Anal. Calcd: N, 9.52. Found: 9.44.

Attempted Preparation of 1,4-Disubstituted Piperazines Other Than 1,4-Diethylpiperazine.—Using the preceeding procedure, 1-cyanoethylaziridine, 1-(2-hydroxyethylaziridine), 1-allylaziridine, 1-phenethylaziridine, and 1-*n*-butylarizidine were treated with hydriodic acid and sodium iodide in 2-butanone at 25°. After filtering the reaction mixtures in order to remove the potassium salts, the concentrations of the reacted aziridines and of the corresponding piperazines were determined by infrared analysis. The conversions of the aziridines were 99+% in each case.

Anal. % yield for 1,4-substituted piperazine: 1,4-bis(cyanoethyl), <1.0; 1,4-bis(2-hydroxyethyl), <10; 1,4-diallyl, 46; 1,4-diphenethyl, 73; 1,4-di-*n*-butyl, 83.

Registry No.—1-Ethylaziridine, 1072-45-3; 1-*n*-butylaziridine, 1120-85-0; 1-phenethylaziridine, 3164-46-3; 1-allylaziridine, 5536-99-2.

Acknowledgment.—The author gratefully acknowledges the contributions of H. L. Spell who obtained and interpreted the infrared spectra.

(3) J. I. G. Cadogan, *J. Chem. Soc.*, 2971 (1955).

(4) G. B. Butler, and R. L. Bunch, *J. Amer. Chem. Soc.*, **71**, 3120 (1949).

Reactions of Nucleophiles with 1-*tert*-Butyl-3-chloroazetidine and 1-*tert*-Butyl-2-chloromethylaziridine[1]

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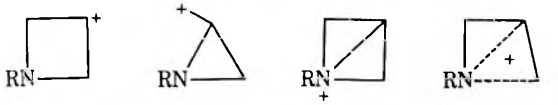
These small heterocycles, **1** and **2**, are exceptionally unreactive β-aminoalkyl chlorides. With nucleophiles under vigorous conditions **1** and **2** reacted by simple displacement (mercaptides, alkoxides, and uncatalyzed amines), partial (hydrolysis) or complete (cyanide) ring expansion of **2** to form azetidines, or ring cleavage, recyclization, and reopening (acetic acid, acid-catalyzed amines). Isomerization, **1** ⇄ **2**, occurred with mechanistic duality. Equilibria involving the 1-*tert*-butylazabicyclobutonium and 1-*tert*-butyl-2-aziridinylcarbinyl cations are proposed. Cyclization of β-aminoalkyl mesylates was a versatile route to aziridines carrying functional groups.

A problem of current interest in the chemistry of small heterocycles concerns the nature of nucleophilic substitution of azetidines bearing exophiles in the 3 position. A possible intermediate is the simple carbonium ion (I). The formal relationship of I to the



I II III IV

cyclobutyl–cyclopropylcarbinyl nonclassical cation system[2] suggested a parallel investigation of aziridinylcarbinyl derivatives, perhaps leading to cation II. Nitrogen participation in either case would lead to the strained quaternary 1-azabicyclobutonium ion (III), while the possibility of nonclassical hybridization implies intermediates such as IV.

We recently presented preliminary evidence to support nitrogen assistance in the ionization of the chlorides corresponding to ions I and II (R, *tert*-Bu) and suggested that a common intermediate (such as III alone) could not rationalize the results.[1] Independently Deyrup and Moyer proposed III as an intermediate in solvolysis of the tosylate of 1-*tert*-butyl-3-azetidinol, but they considered unclear the mechanism by which the aziridinylcarbinyl tosylate reacted.[3] The present paper concerns expanded evi-

(1) Preliminary account: V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968). Presented in part at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968; Abstracts, ORGN 1.

(2) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959). Review: R. Breslow, in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 233–294. J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, **90**, 4303 (1968), gave a recent summary. See, however, R. E. Davis and A. Ohno, *Tetrahedron*, 2063 (1968), for the view that cyclobutyl cation is classical.

(3) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968). We are grateful to Professor Deyrup for initiating an exchange of results with the writer.

dence on reactions of the chlorides and a mechanism consistent with the data on such systems.

Ring expansion and cleavage have been noted in pertinent studies of strained heterocycles. 2-Chloromethylthiirane and 3-chlorothietane were said to ionize with sulfur assistance to give a classical bicyclic sulfonium ion

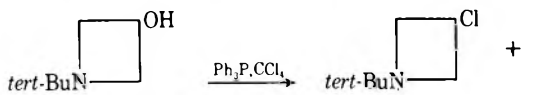
which yielded only 3-substituted thietanes by cross-ring bond cleavage.[4]

In the nitrogen series, the 1-benzenesulfonyl-2-aziridinylmethyl cation expanded to the -2-azetidinyl ion or a nonclassical intermediate, as shown by isotopic tagging, in the Friedel–Crafts alkylation of benzene.[5] Evidence involving ring expansion in tosylate solvolysis has been given recently for the 1-oxabicyclobutonium cation.[6]

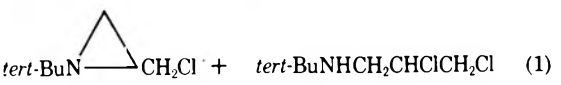
Results

Synthesis of Azetidines and Aziridines.—The chlorides, 1-*tert*-butyl-3-chloroazetidine (**1**) and 1-*tert*-butyl-2-chloromethylaziridine (**2**), were chosen for study. Their stabilities were expected to permit more vigorous reaction conditions, and thus yield more varied, revealing results than might the tosylates,[3,7] for example.

The conversion of 3-azetidinols[8] to 3-chloroazetidines called for mild neutral conditions to avoid ring cleavage or autodehydrochlorination and these requirements were met by the triphenylphosphine–carbon tetrachloride reagent.[9] Although the reaction of 1-*tert*-butyl-3-azetidinol (**3**) was very sluggish (3 days at 76° compared to 10 min for unstrained alcohols[9]), good yields (**1**, 69–72%) were realized. The reaction was unexpectedly complex, two minor products being formed (eq 1). An isomer of **1** formed in 1–4% yield



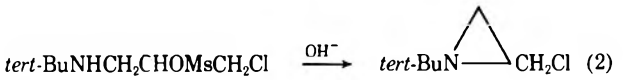
3 **1**



2 **4** (1)

was identified as chloromethylaziridine (**2**), and an unstable dichloro amine proved to be *tert*-butyl-2,3-dichloropropylamine (**4**). These secondary products are considered below. 3-Chloro-1-cyclohexylazetidine was prepared similarly. Functionally 3-substituted azetidines were obtainable by displacements on the tosylate[7,3] or, with precautions to be described, from the chloride.

A preparative method for 1-*tert*-butyl-2-chloromethylaziridine (**2**) began with *O*-mesylation of crude 1-*tert*-butylamino-3-chloro-2-propanol.[10] Cyclization[11] of the unstable mesylate (**5**) gave **2** in 55% yield, based on *tert*-butylamine (eq 2). By comparison,

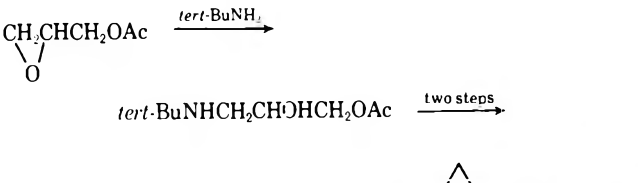


5 **2** (2)

cyclization of the *O*-sulfuric acid (Wenker aziridine synthesis) gave only a 3% yield of **2**. 1-Cyclohexyl-2-chloromethylaziridine was also prepared.

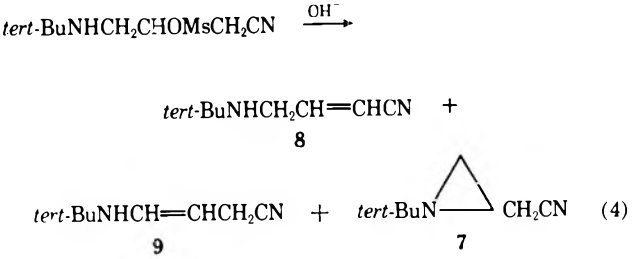
The method is a useful and apparently fairly general synthesis of aziridines. Since either aminochloropropanols or glycidyl derivatives condense with nucleophiles to form 3-substituted aminopropanols,[12,13] it is potentially quite versatile. The preparation of two reference compounds for this work illustrates the probable scope.

1-*tert*-Butyl-2-acetoxymethylaziridine (**6**) was prepared directly, despite its ease of hydrolysis, from glycidyl acetate (eq 3).



6 (3)

The synthesis of 1-*tert*-butyl-2-cyanomethylaziridine (**7**) involved an unstable mesylate which was sensitive to elimination.[14] 4-*tert*-Butylamino-3-hydroxybutyronitrile, prepared from the aminochloropropanol[10] and cyanide (alkali), was mesylated and cyclized. A mixture of three isomers was isolated (eq 4). The



8

9 **7** (4)

two major products were thermally unstable and resinified rapidly in air. The nmr spectra of several mixtures were consistent with 4-*tert*-butylamino-2- (**8**) and -3-butenonitriles (**9**). The third isomer, the

(4) J. C. Martin and D. J. Anderson, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, p 0–31. See also, E. P. Adams, K. N. Ayad, F. P. Doyle, D. O. Holland, W. H. Hunter, J. H. C. Nayler, and A. Queen, *J. Chem. Soc.*, 2665 (1960); M. Sander, *Monatsh. Chem.*, **96**, 896 (1965).

(5) W. J. Gensler and W. R. Koehler, *J. Org. Chem.*, **27**, 2754 (1962).

(6) H. G. Richey, Jr., and D. V. Kinsman, *Tetrahedron Lett.*, 2505 (1969).

(7) T. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **40**, 2401 (1967), described 1-*tert*-butyl-3-tosyloxyazetidine and the normal displacement by cyanide. Our work on tosylates was discontinued when we became aware of this study and of the work of Deyrup and Moyer,[3] who also prepared chlorides **1** and **2** by displacements on the tosylates.

(8) V. R. Gaertner, *J. Org. Chem.*, **32**, 2972 (1967); *Tetrahedron Lett.*, 4691 (1966).

(9) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1966).

(10) V. R. Gaertner, *ibid.*, **23**, 2123 (1967).

(11) J. Smrt, J. Beránek, and J. Sicher, U. S. Patent Patent 2,958,691 (1960), and K. Okawa, T. Kinutani, and K. Sakai, *Bull. Chem. Soc. Jap.*, **41**, 1353 (1968), described cyclization of sulfonate esters of serine and threonine to aziridine derivatives.

(12) V. R. Gaertner, *J. Org. Chem.*, **33**, 523 (1968).

(13) V. R. Gaertner, *J. Heterocycl. Chem.*, **6**, 273 (1969).

(14) I. Photaki, *J. Amer. Chem Soc.*, **85**, 1123 (1963), described mesyloxyamino acid elimination.

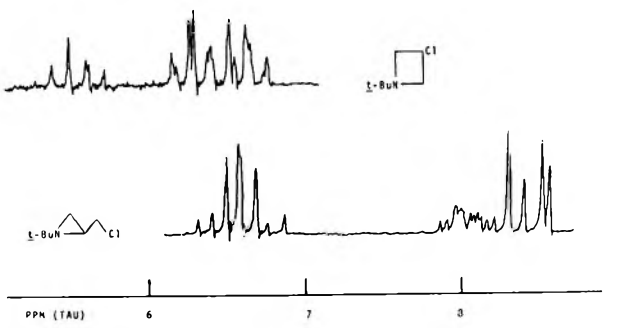


Figure 1.—60-MHz nmr spectra for 1-*tert*-butyl-3-chloroazetidine (**1**) and 1-*tert*-butyl-2-chloromethylaziridine (**2**), in deuteriochloroform.

desired aziridine (**7**), was easily isolated by distillation after thermal resinification of the butenonitriles.

Isomeric azetidines and aziridines were characterized definitively by nmr spectra. Figure 1 illustrates typical features. In addition to the *tert*-butyl singlet at about τ 9 or other usual *N*-alkyl peaks, the 3-substituted azetidines showed two broad triplets (often with further minor splitting) due to the ring methylene protons and downfield a broad pentuplet from the 3 proton. The chemical shifts were little different from those in related strainless heterocycles.

However, aziridine ring-proton multiplets appeared at much higher field (τ 8–9). Also, the substituted methyl protons appeared downfield (τ 5–7) as double AB quartets or collapsed equivalents. Analysis of mixtures involved nmr and vpc methods. Double titration in acetic acid with anhydrous hydrogen bromide and with perchloric acid gave a good estimate of the aziridines present in mixtures. The difference between the 2 titers was due to aziridine cleavage by HBr; azetidines are not cleaved. Aziridines opened more slowly than epoxides.

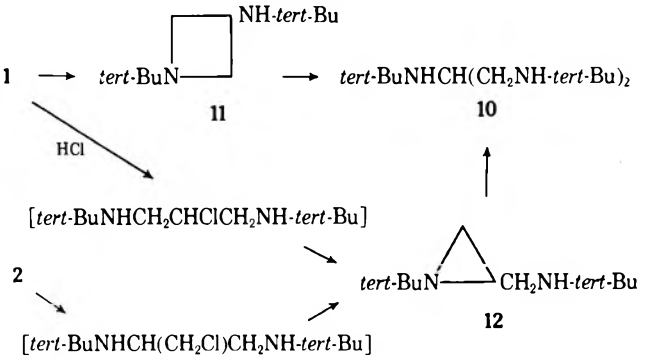
Nucleophilic Displacement Reactions.—The behavior of chlorides **1** and **2** provided evidence for reaction paths ranging from tightly bound SN2 complexes to relatively free rearranging cations. The complication of ring cleavage was foreseeable in displacements with aziridines,[15] but the unexpected ease of azetidine opening was the subject of a parallel investigation.[13]

Simple displacements occurred when both chlorides were treated with good ionic nucleophiles under alkaline conditions. This result was observed with sodium methoxide in methanol, sodium *tert*-butylmercaptide in methanol, potassium *tert*-butoxide in butanol, and *tert*-butylamine in aqueous alkali. The structure of the product corresponded exclusively to that of the starting chloride, ring cleavage being negligible. It is noteworthy that the three bulky reagents, intended as probes for an ionic equilibrium which could be shifted by a large steric requirement of the nucleophile, revealed no such effect.

Initially, *tert*-butylamine in excess gave the same compound from either the chloroazetidine or the chloromethylaziridine. The nmr spectrum and other data indicated that the product was the acyclic triamine **10**. The first cleavage products (Scheme I, in brackets) were undoubtedly chlorodiamines which could not be

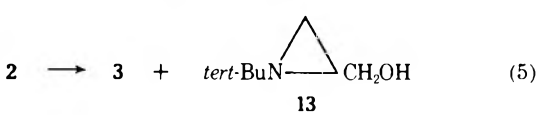
(15) D. H. Powers, Jr., V. B. Schatz, and L. B. Clapp, *J. Amer. Soc.*, **78**, 907 (1956).

SCHEME I



detected in the reaction mixture because both recyclized to the aziridine amine **12**, which was in turn reopened to form **10**. In the presence of anhydrous sodium carbonate, the expected azetidine amine **11** was formed along with **10**; under these conditions **2** gave only **10**. However, when the reaction was conducted in a horizontally rotated bomb with a rolling bar to crush the sodium carbonate and continuously neutralize the hydrogen chloride of reaction, **1** *gave exclusively diamine* **11**, and no triamine, *i.e.*, exclusively chloride displacement and no azetidine ring opening. Similarly, **2** gave diamine **12** by displacement, but aziridine ring cleavage was not completely suppressed and triamine formed slowly from diamine **12**. These reaction conditions were employed to assure the absence of ring opening in azetidine isomerization studies (*vide infra*).

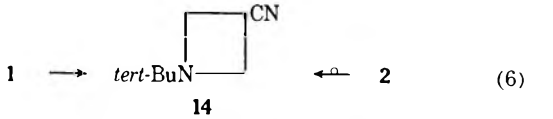
Hydrolysis of β-aminoalkyl chlorides is typically SN1 and may give rearranged products *via* aziridinium cations. Chloroazetidine **1** hydrolyzed to the 3-azetidinol (**3**) as the only monomeric product found, and chloromethylaziridine (**2**) gave both 3-azetidinol and the aziridinylcarbinol (**13**) in a 3:1 ratio (eq 5).



(5)

Kinetics of chloride solvolyses in 50% aqueous ethanol were complex, but specific rate constants could be estimated from the first 10–25% of reaction with adequate accuracy to support qualitative conclusions on relative reactivities. The values for the chloroazetidine were 0.14 hr^{-1} at 35.0° and 0.50 hr^{-1} at 50.0°, and for the chloromethylaziridine about 0.016 hr^{-1} at 70.0°. These data and those of Deyrup and Moyer[3] for the tosylates are consistent, but the order of reactivity is the reverse of comparable data for cyclobutyl and cyclopropylcarbinyl chlorides.[16] Indeed **1** and, especially, **2** are apparently at most a few orders of magnitude more reactive than acyclic secondary and primary alkyl chlorides, respectively.

Cyanide ion gave the same nitrile, 1-*tert*-butyl-3-cyanoazetidine[7] (**14**), from either **1** or **2** (eq 6), the



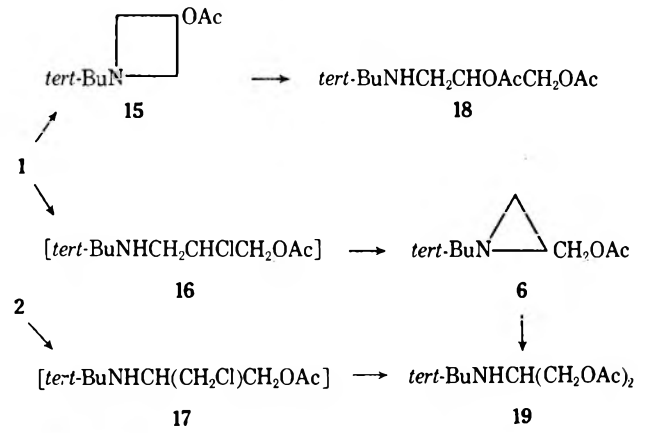
(6)

(16) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509 (1951). At 50°, data for the chlorides were: cyclobutyl, 0.017; cyclopropylcarbinyl, 0.45; allylcarbinyl, >0.0005 hr^{-1}.

second example of ring expansion. The purified nitrile from **2** contained an unstable isomer (probably elimination products **8** and **9**) but no cyanomethylaziridine (**7**).

The acetolysis of chlorides **1** and **2** did not involve ionic intermediates importantly, because acid-catalyzed ring opening intervened. The major reaction paths are summarized in Scheme II.

SCHEME II



Direct displacement on **1** gave the azetidinyl acetate **15**, after incomplete reaction, along with the unstable chloro acetate **16**, isolated as the impure free amine. Exhaustive reaction produced only 1,2 and 1,3 diacetates **18** and **19**, in a 1:1 ratio, from cleavage of **15**[13] and **6**, respectively. The latter conversion was confirmed separately, a small amount of 1,2 diacetate also being formed.

The reaction of chloromethylaziridine (**2**) involved ring opening[17] to chloro acetate **17** (also isolated, as an impure hydrochloride), which cyclized to **6** more rapidly than did chloro acetate **16**.

Isomerization.—The presence of chloromethylaziridine (**2**) in chloroazetidine (**1**) suggested that partial isomerization occurred either during displacement or by isomerization. The amount of **2** increased with extended reaction times, at the expense of **1**. Isomerization of **1** proceeded in either carbon tetrachloride or acetonitrile even in the absence of triphenylphosphine. The conversion of **3** to **1** and the isomerization of either **1** or **2** were accompanied by formation of a third unstable compound shown to be dichloro amine **4** (eq 7).

$$\text{1 or 2} \longrightarrow \underset{\mathbf{4}}{\textit{tert}\text{-BuNHCH}_2\text{CHClCH}_2\text{Cl}} \xrightarrow{\text{DEIPA}} \mathbf{2} + \mathbf{1} \quad (7)$$

Experiments indicated that **4** was formed from either **1** or **2** by addition of hydrogen chloride. An added acid scavenger, such as diethylisopropylamine (DEIPA), partially cyclized **4** to a mixture of **2** and **1** in a 10:1 ratio. Aziridine **2** was more stable but slowly isomerized to **1**. Similar equilibrium mixtures were obtained by heating either 3-chloro-1-cyclohexylazetidine or 2-chloromethyl-1-cyclohexylaziridine in acetonitrile. Clearly these "equilibria" were attained at least in part by a reversible series of ring cleavage and reclosure sequences initiated by hydrogen chloride from the autodehydrochlorination of the starting chloride.

To determine whether cations I and II (for example) participated in ionic isomerization concomitantly with the above cleavage–recyclization, we employed the conditions under which no ring opening occurred with **1**, even with the powerfully nucleophilic amines in excess. Chloroazetidine (**1**) still slowly isomerized to chloromethylaziridine (**2**). Although **2** did not generate **1** under these conditions, catalysis by potassium iodide in acetonitrile did promote the reverse reaction, giving up to 0.7% of **1**. No dichloro amine or any other product of cleavage was detected. True reversibility was not attained.

Discussion

Clearly 1-*tert*-butyl-3-chloroazetidine (**1**) and, especially, 1-*tert*-butyl-2-chloromethylaziridine (**2**) are among the least reactive β-aminoalkyl chlorides known. Their chemistry contains contradictory elements which a successful formulation of cationic intermediates must reconcile.

Qualitatively, preferential formation of azetidines from both chlorides in nucleophilic displacements is understandable in terms of aziridine ring strain relief. On the other hand, the more strained aziridine ionized the more slowly. Thus, ionization is not appreciably concerted with strain relief.

Both ring contraction and expansion were observed in ionic isomerization. Similar reactions occur in relatively strainless systems,[18] but the present case is exceptional in that contraction increases ring strain. This is apparently the first instance of azetidine isomerization to an aziridine.

The simple 3-azetidinyl carbonium ion (I) cannot explain the rate data for **1**. A nonclassical carbonium ion of the cyclobutyl type[2] might rationalize the reactivity of **1** to a degree, but this idea does not fit the sluggishness of the more strained **2**. The aziridine ring-strain energy (14 kcal/mol;[19] cyclopropane, 25 kcal) is clearly too small to give rise to nonclassical ions, and the unknown azetidine ring strain energy is surely even smaller.

Steric activation of the chlorine at C-3 in **1** may be considered. Steric interaction between N and 3 substituents across the puckered azetidinium ring has been invoked to explain increasingly negative entropies of cyclization.[12] However, *tert*-butyl and chloro groups were not bulky enough to exhibit the effect.

The intermediacy of the 1-*tert*-butyl-1-azabicyclobutonium[20] ion (III) accounts satisfactorily for the reactivity of **1** (or the tosylate[3]). Anchimeric assistance of ionization by the nitrogen lone pair is favored, in the most probable conformational isomer (**1a**, Scheme III) with a puckered ring,[21] by a shortened N–C-3 distance, a very basic and presumably strongly

(17) This cleavage was originally overlooked[1] and the specific rate constant for appearance of chloride ion was erroneously assigned to solvolysis of **2**. The acetolysis constant given for **1** is also incorrect because **1** gave **6** by ring opening and recyclization, not by direct rearrangement. Acetolysis and recyclization of **16** simulated simple first-order kinetics.

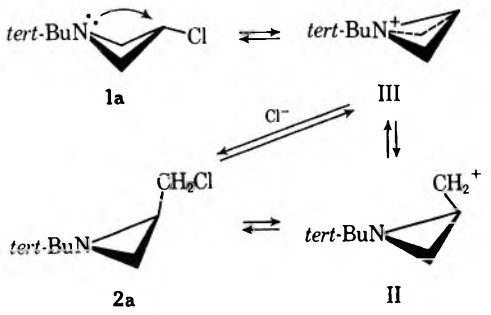
(18) (a) J. F. Kerwin, G. E. Ullyot, R. C. Fuson, and C. L. Zirkle, *J. Amer. Chem. Soc.*, **69**, 2961 (1947); E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948); R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948). (b) See E. M. Fry, *J. Org. Chem.*, **30**, 2058 (1965), and references therein.

(19) R. A. Nelson and R. S. Jessup, *J. Res. Nat. Bur. Stand., A*, **48**, 206 (1952).

(20) A. G. Hortmann and D. A. Robertson, *J. Amer. Chem. Soc.*, **89**, 5974 (1967), synthesized an example of the uncharged ring system.

(21) R. L. VanEtten, personal communication, X-ray crystallographic results on L-azetidine-2-carboxylic acid.

SCHEME III



nucleophilic nitrogen,[22] and a relatively exophilic secondary chlorine. Cation III would be expected, as observed, to add nucleophiles at C-3 by cleavage of the long weak cross-ring bond, on the basis of both heterocyclic[4,6] and bicyclobutane[23a] chemistries.

The simplest pathway for the ring-expanding reactions of chloromethylaziridine 2 involves ionization–rearrangement to III. The relative sluggishness of 2 suggests that ionization to III, if it occurs directly, gains little driving force from rearrangement, however. This may be a result of a long N–CH_2 distance in 2a and of the facts that aziridine nitrogen is less basic[22] and primary exophiles are less easily displaced.

Isomerization of 1 *via* III requires nucleophilic attack at C-2 of III. The closest precedent for this step in heterocyclic chemistry involves openings of the 1-azoniabicyclo[3.1.0]hexane system[18b] in which attack may occur at both the more- and the less-substituted carbon atoms. This system falls far short of III in ring strain energy, however.

A second possibility which avoids C-2 attack on III is ionization of 2 to II, the primary carbonium ion.[23b] Rapid ionic isomerization, II $\rightleftarrows$ III, and recombination of either cation would account for interconversion, 2 $\rightleftarrows$ 1, and for the rearrangements of 2. Cation II, although it should presumably be less stable thermodynamically than III, might be more stable than a simple primary carbonium ion by reason of "internal solvation." In this view, II carries partial single bond character between nitrogen and the exocyclic carbonium carbon atom similar to, and possibly stronger than, that of a polar ionizing solvent.

Experimentally, formation of chloromethylaziridine (2) from 1, counter to ring strain, is undoubtedly detectable only because, under these isomerization conditions, 2 is the more stable thermally and ionizes the more slowly. Many ionization–recombination cycles, each leading to a trace of 2, yield measurable amounts of 2. It is not surprising that 2 did not give 1 detectably; 1 resinified preferentially under these conditions. The stabilities of 1 and 2 were reversed in the presence of potassium iodide, and the formation of 1 from 2 became observable, but 1 did not appear to yield 2, for the same reasons.

(22) Reviews: (azetidines) J. A. Moore, in "Heterocyclic Compounds with Three- and Four-Membered Rings," A. Weissberger, Ed., Part Two, Interscience, New York, N. Y., 1964, pp 885–977; (aziridines) P. E. Fanta, *ibid.*, Part 1, pp 524–575.

(23) (a) Review: K. B. Wiberg, *Rec. Chem. Progr.*, **26**, 143 (1965). (b) In addition to the generally accepted delocalized benzyl, allyl, and cyclopropylcarbinyl primary carbonium ions, support has also been advanced for simple unstabilized examples; see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 254.

The present evidence does not permit a conclusive choice between C-2 attack on III and the stabilized II in equilibrium with III.

Experimental Section[24]

1-*tert*-Butyl-3-chloroazetidine (1).—1-*tert*-Butyl-3-azetidinol,[8] (3, 37.0 g), and 84 g of triphenylphosphine in 700 ml of carbon tetrachloride was stirred and heated under reflux for 3 days as a solid separated. The cooled mixture was filtered, and the filtrates were extracted with excess dilute sulfuric acid, and then washed with water. The combined aqueous extracts were cooled with ice, made strongly alkaline with 50% sodium hydroxide solution, and extracted with ether. Drying ($MgSO_4$) and distillation gave 29.3 g (69%) of chloroazetidine (1): bp 63–64° (25 mm); 45–46° (10 mm); $n^{25}D$ 1.4475; nmr (see Figure 1) except τ 9.0 (s, *tert*-Bu); ir (neat) 3.37 i, 3.50 i, 6.80 m, 7.12 w, 7.36 i, 7.65 w, 7.96 i, 8.13 i, 8.22 i, sh, 9.1 m, 9.24 m, 10.18 m, 11.52 m, 12.53 w, 15.4 i μ.[25]

Anal. Calcd for $C_7H_{14}ClN$: C, 56.94; H, 9.56; Cl, 24.02; N, 9.49; amine neut equiv, 148. Found: C, 56.73; H, 9.35; Cl, 24.25; N, 9.62; amine neut equiv 148.

This product contained usually about 1% of chloromethylaziridine (2), which could be removed by heating with an equal volume of acetic acid at 50° overnight and reisolating pure 1 (vpc, column C, 130°); constants were unchanged.

Longer heating (6 days) gave another higher boiling unstable oil (vpc, column B, 130°, decomposing to 2) which was isolated in up to 11% yields by basifying the iced acidic extracts with aqueous sodium carbonate solution. Distillation gave, after collecting 1 containing up to 4% 2, *tert*-butyl-2,3-dichloropropylamine (4): bp 51° (2 mm); $n^{26}D$ 1.4567; nmr τ 8.9 (s, *tert*-bu), 6.9–7.1 (m, CH_2N), 5.6–6.2 (m, $CHClCH_2Cl$). It could not be obtained completely free of 2; crystals separated upon standing.

Anal. Calcd for $C_7H_{15}Cl_2N$: C, 45.66; H, 8.21; Cl, 38.52; N, 7.61; amine neut equiv, 184. Found: C, 46.40; H, 8.25; Cl, 37.41; N, 7.44; amine neut equiv, 187.

Dichloro amine 4 (0.79 g) was also obtained from 5.9 g of 2 by heating with 0.2 g of triphenylphosphine in 10 ml of carbon tetrachloride at 80° for 8 days. The complex multiplets were identical for samples from the two sources.

3-Chloro-1-cyclohexylazetidine.—From 1-cyclohexyl-3-azetidinol[8] (12.0 g) was similarly obtained 6.6 g (49%) of the chloride: bp 62–63° (1 mm); $n^{25}D$ 1.4837; nmr τ 7.7–9.1 (m, cyclohexyl), 6.7–7.0, 6.1–6.4 (basically triplets further split, ring CH_2), 5.4–5.7 (pentuplet, CHCl). A trace of the chloromethylaziridine (below) was detected (vpc, column B, 150°).

Anal. Calcd for $C_9H_{16}ClN$: C, 62.24; H, 9.29; Cl, 20.33; N, 8.07. Found: C, 62.02; H, 9.25; Cl, 20.62; N, 7.91.

1-*tert*-Butyl-2-chloromethylaziridine (2).—Crude 1-*tert*-butylamino-3-chloro-2-propanol[10] (79.1 g from 0.5 mol each of *tert*-butylamine and epichlorohydrin), which had been freshly prepared and carefully freed of starting materials by rotary evaporation at 20° (2 mm), was dissolved in 250 ml of ethanol-free chloroform. The solution was cooled to 0–10° and treated successively with 71 g of anhydrous pyridine, 36.0 g of methanesulfonic acid (75% of theory for salt formation), and then dropwise with 57.3 g of methanesulfonyl chloride. After being stirred as the ice bath melted overnight, the slurry was poured into excess ice and water. The mixture was shaken and treated with 10% sodium carbonate solution in small portions until the pH was about 8, in the presence of ice. All solids dissolved. The cold chloroform layer was dried ($MgSO_4$) in a 10° water bath. The aqueous layer was again extracted with chloroform and the extracts were added to the drying solution.

(24) Melting and boiling points are uncorrected. Three vpc columns used routinely: A, 2 m × 0.25 in., 10% SE-52 on 60–80 mesh Diatoport S; B, 2 m × 0.25 in., 10% neopentyl glycol succinate on 30–60 mesh acid-washed Chromosorb W; C, 28 ft × 1/16 in., 1% silver nitrate and 18% Carbowax 20M on 30–60 mesh Chromosorb W. Toluene or xylene was the vpc standard; areas were measured by a disk-integrated recorder on a F & M Model 700 chromatograph (thermal conductivity detector, helium carrier). Nmr spectra were run in deuteriochloroform with internal tetramethylsilane as reference on the Varian A-60 and T-60 spectrometers. Integrations supported the assignments. Pressure reactions were conducted in 100- or 20-ml stainless steel or glass vessels. Some data are based on composites of several experiments. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.

(25) Infrared spectra were of little value in distinguishing isomers. Data for 1 and 2 are presented: i, intense; m, medium; w, weak; sh, shoulder.

The cold filtered chloroform layer was concentrated below 15° (2 mm); the crude mesylate was unstable at 25°, warming spontaneously and lowering the yield. The cool mesylate was promptly added to a stirred cold solution of 53 g of Na_2CO_3 and 10 g of diethylenetriamine (a scavenger for epoxide impurities) in 400 ml of water in an ice bath. Stirring was continued overnight as the ice melted. Ether extraction, drying ($MgSO_4$), and distillation (persistent foaming) gave isomerically pure (vpc, column C, 130°) chloromethylaziridine (2): bp 47–48° (10 mm); 40.6 g (55%); $n^{26}D$ 1.4454; nmr (see Figure 1) except τ 9.0 (s, *tert*-bu); ir (neat) 3.38 i, 3.49 m, sh, 6.82 m, 6.90 m, sh, 6.94 m, 7.00 m, 7.22 m, 7.36 i, 7.93 i, 8.12 i, 8.32 i, 9.1–9.2 w, 9.78 m, 9.97 w, 10.16 m, 10.73 w, 11.40 w, 12.19 m, 12.3–12.5 w, 13.8 m, 15.02 i. μ [25]

Anal. Calcd for $C_7H_{14}ClN$: C, 56.94; H, 9.56; Cl, 24.02; N, 9.49. Found: C, 57.11; H, 9.50; Cl, 24.06; N, 9.46.

The amine neutralization equivalent was satisfactory (Calcd: 148. Found: 150.) when measured with perchloric acid in acetic acid, but was halved when determined with anhydrous hydrogen bromide in acetic acid (Found: 76.), due to the ring opening by HBr. To avoid overheating the sample can be added to frozen glacial acetic acid, treated with excess HBr in HOAc, allowed to stand 15 min to complete the cleavage, and back-titrated with standard NaOAc in HOAc. The aziridines of this work, and aziridine itself, reacted similarly. The present aziridines were stable to dissolution in 10% aqueous HCl. Crystal violet was a convenient indicator for titrations in acetic acid. Azetidines were not cleaved by HBr at 25°.

1-*tert*-Butylamino-3-chloro-2-propylsulfuric Acid Inner Salt.—Distilled 1-*tert*-butylamino-3-chloro-2-propanol[10] (78.3 g) in 800 ml of carbon tetrachloride was stirred and treated dropwise below 10° with 31.7 ml of chlorosulfonic acid. The gum which separated slowly crystallized and was stirred overnight. Evolution of HCl was completed by heating at 40° for 6 hr. Cooling, filtration, and drying *in vacuo* gave 116 g (99%) of colorless salt. Several recrystallizations from 80:20 ethanol–water gave the pure salt, mp 232–233° dec (placed in bath at 220°).

Anal. Calcd for $C_7H_{16}ClNO_4S$: N, 5.70; S, 13.05. Found: N, 5.70; S, 13.45.

Cyclization with aqueous KOH[26] gave only a 3% yield (vpc) of impure *tert*-butylcdloromethylaziridine (2).

2-Chloromethyl-1-cyclohexylaziridine.—From 41.2 g of 1-chloro-3-cyclohexylamino-2-propanol[27] was obtained similarly 20.1 g (54%) of the aziridine: bp 66–67° (2 mm); $n^{25}D$ 1.4814; nmr τ 8.0–8.9 (m, all ring protons), 4.2–4.9 (m, CH_2Cl).

Anal. Calcd for $C_9H_{16}ClN$: C, 62.24; H, 9.29; Cl, 20.41; N, 8.07; amine neut equiv, 174. Found: C, 62.00; H, 9.28; Cl, 20.33; N, 8.18; amine neut equiv, 177.

The modified Wenker synthesis, *via* amine hydrochloride,[26] gave a 3% yield (vpc, column B, 140°) of this aziridine.

2-Acetoxymethyl-1-*tert*-butylaziridine (6).—1-Acetoxy-3-*tert*-butylamino-2-propanol,[13] 19.9 g, was mesylated and cyclized overnight at 0–10° to give 5.7 g (32%): bp 45–46° (1 mm); $n^{25}D$ 1.4306; nmr τ 9.0 (s, *tert*-bu), 8.4–8.6 (4 lines, CH_2N), 7.9–8.3 (m, NCH), 7.95 (s, CH_3CO), 5.7–6.4 (overlapping quartets, CH_2OAc).

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.12; H, 10.01; N, 8.18; amine neut equiv, 171. Found: C, 63.03; H, 9.93; N, 8.31; amine neut equiv, 176.

1-*tert*-Butyl-2-hydroxymethylaziridine (13).—The acetate, 6, was hydrolyzed and the distilled carbinol [bp 46–47° (2 mm)] solidified: mp 31–32°; nmr τ 9.0 (s, *tert*-bu), 8.4–8.6 (3 lines, CH_2N), 7.8–8.3 (m, CHN), 6.3–6.6 (t, CH_2OH).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.92; H, 11.63; N, 10.82.

4-*tert*-Butylamino-3-hydroxybutyronitrile.—A solution of 150.5 g of crude *tert*-butylaminochloropropanol[10] (from 1.00 mol of amine and epichlorohydrin) in 100 ml of ethanol was added with stirring during 2 hr to a solution of 97.5 g of potassium cyanide in 250 ml of water and 300 ml of ethanol. After stirring another 5 hr, the mixture was treated with 50 ml of 50% NaOH solution, extracted with ether, dried (K_2CO_3), and concentrated. The residual oil crystallized from ethanol: 44.3 g (28%); mp 75–76°; nmr τ 8.9 (s, *tert*-bu), 7.2–7.5 (m, $CH_2CHOHCH_2CN$), 5.9–6.3 (m, CHOH).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32; N, 17.93. Found: C, 61.37; H, 10.75; N, 17.73.

1-*tert*-Butyl-2-cyanomethylaziridine (7).—The above nitrile (20.2 g) was mesylated as described for the preparation of 2, and the crude mesylate was isolated below 10° and added to iced carbonate–diethylenetriamine solution and stirred to 20° overnight. A mixture of three isomers was isolated and kept in a nitrogen atmosphere, 7.6 g (42%), bp 65–72° (2 mm). The cuts ranged from 76 to 87 area % of the unstable overlapping major peaks (column B, 150°). They resinified rapidly in air. Analysis of the last cut and the nmr spectrum were consistent with 50 mol % **4-*tert*-butylamino-2-** and 40 mol % **-3-butenonitrile** containing 13 area % of the cyanomethylaziridine 7 (10 mol %): nmr τ 9.0, 8.9, 8.4 (3 s, *tert*-bu), 8.3–8.6 (m, CH_2N), 6.6–6.8 (4 main lines, CH_2CN), 4.0–4.6, 3.0–3.7 (m, CH=CH).

Anal. Calcd for $C_8H_{14}N_2$: C, 69.45; H, 10.21; N, 20.27. Found: C, 69.39; H, 9.98; N, 20.15.

Further, 24.0 g of hydroxynitrile was mesylated (7% excess methanesulfonic acid, 60% excess mesyl chloride, etc.), and the crude mesylate cyclized as usual. The crude product mixture was heated for 2 days at 70° and distilled and 1.40 g (7%) of 7 collected: bp 59° (2 mm); nmr τ 9.0 (s, *tert*-bu), 8.3–8.6 (4 lines, CH_2N), 7.9–8.3 (m, CHN), 7.5–7.7 (4 lines, CH_2CN).

Anal. Calcd for $C_8H_{14}N_2$: C, 69.45; H, 10.21; N, 20.27. Found: C, 69.55; H, 10.22; N, 20.01.

1-*tert*-Butyl-2-*tert*-butylaminomethylaziridine (12).—1,3-Di-*tert*-butylamino-2-propanol,[10] 28.2 g, was mesylated and cyclized as usual: 14.5 g (52%); bp 59–60° (4 mm); nmr τ 9.0 (s, *tert*-buN), 8.9 (s, *tert*-buNH), 7.9–8.8 (m, 3 ring protons), 7.3–7.5 (two broad peaks, CH_2NH).

Anal. Calcd for $C_{11}H_{24}N_2$: C, 71.68; H, 13.12; N, 15.20. Found: C, 71.72; H, 13.14; N, 15.11.

Reactions of Chlorides 1 and 2 with Nucleophiles. 1. Hydrolysis.—The chloride (3.00 g) was heated and rotated in a 90° oven for 6 days with equimolar 10% aqueous sodium carbonate solution. The isolated product mixture was analyzed on columns A and B. The best results, with least tailing, were obtained on column A at 100° using the trimethylsilyl ethers prepared on the 5–10-mg scale with TRI-SIL (Pierce Chemical Co., Rockford, Ill.). From chloroazetidine (1) only 1-*tert*-butyl-3-azetidinol (3) was obtained in 16% yield. Three minor high boiling impurities were present but no aziridinylcarbinol.

Chloroaziridine (2) gave both the azetidinol (11% yield) and 1-*tert*-butyl-2-aziridinylcarbinol (4.4%). The vpc analyses were confirmed by nmr.

In 50:50 v/v aqueous ethanol, specific rate constants were determined by titration of aliquots with 0.1 *N* silver nitrate (HNO_3). For the chloroazetidine (1), $k_1^{35.0°}$ was 0.135, 0.146, and 0.130 hr^{-1} in three runs, but the first-order plots were linear through only 11–15% reaction. A 50.0°, the constant was 0.50 hr^{-1} and addition of 1 vol % of triethylamine gave a value of 0.79. (Deyrup and Moyer found no effect on the tosylate hydrolysis rates with triethylamine addition.[3]) 3-Chloro-1-cyclohexylazetidine gave rates of 0.087 and 0.086 hr^{-1} at 35.0°.

The chloromethylaziridine (2) hydrolyzed too slowly to measure accurately by the above method but the initial constant at 70.0° was about 0.016 hr^{-1}; the plots were linear up to about 10% reaction.

2. Potassium Cyanide.—The chloroazetidine (1, 1.56 g) and 6.5 g of KCN in 10 ml of acetonitrile were heated in the bomb at 100° for 18 hr, when no 1 remained (vpc). 1-*tert*-Butyl-3-cyanoazetidine (0.68 g) was isolated in 42% yield, bp 66–68° (4 mm). After 6 days at 100° chloromethylaziridine (2) gave the same nitrile in 27% conversion and 79% yield (vpc). The nmr and ir spectra were identical with those of the compound prepared from the tosylate as described by Ohta *et al.*[7] No aziridine was detected in either mixture. Similar but inferior results were obtained in methanol. A second product, previously identified as chloroazetidine (1),[1] has now been shown by vpc on another column (C, 130°) and by nmr to be 1-*tert*-butyl-2-methoxymethylaziridine (below).

3. Sodium *tert*-Butylmercaptide.—Chloroazetidine (1), 1.49 g, in 4 ml of methanol containing 4.86 meq of sodium methoxide was treated with 0.90 g of *tert*-butyl mercaptan and heated in the bomb at 100° for 18 hr, giving **1-*tert*-butyl-3-*tert*-butylthioazetidine**: bp 68–69° (2 mm); 1.42 g (71%); nmr τ 9.0 (s, *tert*-buN), 8.7 (s, *tert*-buS), 6.2–7.0 (m, ring protons). Two minor impurities persisted (vpc, column B, 150°), but neither was the aziridine.

Anal. Calcd for $C_{11}H_{23}NS$: C, 65.61; H, 11.45; N, 6.96; S, 15.92. Found: C, 64.89; H, 11.49; N, 7.33; S, 16.55.

(26) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949).
(27) J. B. McKelvey, B. G. Webre, and E. Klein, *ibid.*, **24**, 614 (1959).

Pure **1-*tert*-butyl-2-*tert*-butylthiomethylaziridine** was formed from **2** in 73% yield: bp 52–54° (1 mm); nmr τ 9.0 (s, *tert*-buN), 8.7 (s, *tert*-buS), 8.0–8.6 (m, ring protons), 7.3–7.6 (m, CH_2S).

Anal. Calcd for $C_{11}H_{23}NS$: C, 65.61; H, 11.45; N, 6.96; S, 15.92. Found: C, 65.57; H, 11.46: H, 7.03; S, 16.17.

4. Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.—In a nitrogen-filled glove bag, 5.9 g of **1** in 10 ml of anhydrous *tert*-butyl alcohol and 4.2 g of *tert*-buOK (MSA Research Corp., Evans City, Pa.) were sealed in a 20-ml bomb. After being rotated in a 70° oven for 11 days, water and ether were added. After a forerun containing unchanged **1** (0.6 g, column C, 130°), 4.7 g (64%) of **1-*tert*-butyl-3-*tert*-butoxyazetidine** was collected: bp 56–58° (4 mm); nmr τ 9.0 (s, *tert*-buN), 8.8 (s, *tert*-buO), 6.5–7.1 (m, ring protons), 5.7 (pentuplet, CHO).

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.27; H, 12.50; N, 7.60. Found: C, 71.22; H, 12.68; N, 7.64.

Similarly (6 days, 70°) **2** gave 49% yield of isomer-free (vpc, column C, 150°) **1-*tert*-butyl-2-*tert*-butoxymethylaziridine**: bp 35–36° (1 mm partial decomposition); nmr τ 9.0 (*tert*-buN), 8.8 (s, *tert*-buO), 8.0–8.7 (m, ring protons), 6.3–7.1 (m, CH_2O).

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.27; H, 12.50; N, 7.60. Found: C, 70.42; H, 12.38; N, 8.29.

5. Sodium Methoxide in Methanol.—A solution of 3.00 g of **1** in 6 g of methanol containing 20 mequiv of sodium methoxide was heated at 100° for 6 days. Pure **1-*tert*-butyl-3-methoxyazetidine** (2.04 g, 71%) was isolated: bp 45–46° (10 mm); vpc, column B, 90°; nmr τ 9.0 (s, *tert*-bu), 6.7 (s, CH_3O), 6.4–7.1 (m, ring CH_2), 5.7–6.2 (m, $CHOCH_3$).

Anal. Calcd for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 67.40; H, 11.88; N, 9.70.

From chloroaziridine (**2**), after 4 days at 70°, **1-*tert*-butyl-2-methoxymethylaziridine** (88%) was obtained: bp 41–42° (10 mm); nmr τ 9.0 (s, *tert*-bu), 8.3–8.8 (5 lines, ring CH_2), 7.9–8.3 (m, ring CH), 6.3–6.8 (m, CH_2O), 6.7 (s, CH_3O). An impurity persisted (vpc, column B, 90°); it was not an azetidine.

Anal. Calcd for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 66.04; H, 11.70; N, 9.61.

6. *tert*-Butylamine.—Either of the chlorides gave the same triamine when heated at 100° for 24 hr with 100% excess amine, 0.01 mol of chloride, 5 ml of acetonitrile, and 1.5 g of potassium carbonate. The carbonate became caked during the reaction. **1,2,3-Tris-(*tert*-butylamino)propane** (**10**), bp 71–72° (1 mm), 55–57% yield, was a viscous oil: nmr τ 8.9, 8.8 (uot resolved, 2 s, *tert*-bu), 7.3–7.5 [two broad peaks, $(NCH_2)_2CHN$].

Anal. Calcd for $C_{15}H_{35}N_3$: C, 69.98; H, 13.70; N, 16.32; amine neut equiv, 86; mol wt, 257. Found: C, 69.92; H, 13.81; N, 16.40; amine neut equiv, 88; mol wt, 269 (osmometric, in benzene).

Under milder conditions the above method gave a forerun containing a diamine, along with the triamine. It was the sole monomeric product when a similar mixture was heated at 70° in a horizontally rotated bomb containing a Teflon-coated magnetic stirring bar which continually crushed the carbonate and maintained it in a finely divided suspension. After 10 days, 24% of the chloride remained (**1**) and a 39% yield of **1-*tert*-butyl-3-*tert*-butylaminoazetidine** (**11**) was isolated but no triamine was detected. The diamine had bp 59–60° (2 mm); nmr τ 9.0 (s, *tert*-bu), 8.9 (s, *tert*-buNH), 7.0–7.3 (m, ring CH_2); 6.2–6.7 (m, ring CH_2, CHNH).

Anal. Calcd for $C_{11}H_{24}N_2$: C, 71.68; H, 13.12; N, 15.20; amine neut equiv, 92; mol wt, 184. Found: C, 71.44; H, 13.26; N, 15.28; amine neut equiv, 94; mol wt, 199 (benzene).

Similarly, chloromethylaziridine (**2**) without the rolling bar gave only the triamine **10**. When the bar was used with **2**, after 12 days at 70°, analysis (vpc, column C, 130°) indicated that 13% of **2** remained, and 1.08 g (23%) of a diamine (**12**) was isolated, along with 1.37 g (21%) of triamine. The diamine was identical (nmr and ir spectra, vpc, and constants) with **12** prepared from di-*tert*-butylaminopropanol and analyzed correctly.

1-*tert*-Butyl-3-methylaminoazetidine.—Using sodium carbonate with a rolling bar, chloroazetidine (**1**) and excess anhydrous methylamine at 75° for 4 days gave the diamine (66% yield): bp 62–64° (10 mm); nmr τ 9.0 (s, *tert*-buN), 7.6 (s, CH_3NH), 6.3–7.2 (m, 5 ring protons).

Anal. Calcd for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.69. Found: C, 67.18; H, 12.88; N, 19.76.

1-*tert*-Butyl-3-dimethylaminoazetidine.[28]—Chloroazetidine (**1**) did not react appreciably with dimethylamine at 75° in 18 hr. A solution of 3.7 g of **1** and 5.1 g of silver tetrafluoroborate (Ozark-Mahoning Co., Tulsa, Okla.) in 10 ml of acetonitrile was cooled and treated with 19 g of dimethylamine, then sealed in the bomb and heated at 75° for 20 hr. Evaporation and dissolution in water, filtration, addition of excess 50% alkali and filtration, ether extraction, drying over NaOH pellets, and concentration gave the crude amine. It was precipitated from acetic acid as the **diperchlorate** salt, which did not melt, but decomposed at 210–225°.

Anal. Calcd for $C_9H_{22}Cl_2N_2O_8$: C, 30.26; H, 6.21; Cl, 19.85; N, 7.84. Found: C, 30.43; H, 6.27; Cl, 19.73; N, 7.84.

The free amine was obtained with alkali: bp 62° (10 mm); $n^{25}D$ 1.4384; nmr and ir spectra were identical with those of Ohta, *et al.*,[28] *via* the tosylate.

7. Acetolysis.—A mixture of 7.4 g of chloroazetidine (**1**) and 9.8 g of anhydrous potassium acetate in 40 ml of glacial acetic acid heated at 100° in a bomb for 4 days gave *tert*-butyldiacetoxypropylamines (7.9 g, 68%), bp 85–87° (1 mm), $n^{25}D$ 1.4355.

Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.31; H, 9.22; N, 6.02.

The nmr and ir spectra were additive combinations for the ***tert*-butyl-1,3-diacetoxy-2-propyl- and -2,3-diacetoxy-1-propylamines.**[13] The aminodiols obtained by alkaline hydrolysis were present in equal amounts as indicated by nmr integration of the two *tert*-butyl singlets. This was confirmed by vpc analysis of the trimethylsilylated diols (TRI-SIL, Pierce Chemical Co., Rockford, Ill.) separated on column B at 125°.

The 1,3-diacetate was separated by heating the mixed amines with equimolar acetic anhydride at 80° overnight. Distillation gave ***tert*-butyl-1,3-diacetoxypropylamine** (**19**): bp 89–90° (1 mm); $n^{26}D$ 1.4372; nmr τ 8.9 (s, *tert*-bu), 8.0 (s, CH_3CO), 6.7–7.1 (pentuplet, CHN), 5.9–6.1 (2 d, $2CH_2OAc$).

Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.10; H, 9.64; N, 5.89.

Hydrolysis of the diester gave **2-*tert*-butylamino-1,3-propanediol**, crystallized from ethanol–hexane: mp 107–108°; nmr τ 8.9 (s, *tert*-bu), 6.9–7.3 (m, NCH), 6.4, 6.5 (broad lines, $2CH_2OH$).

Anal. Calcd for $C_7H_{17}NO_2$: C, 57.11; H, 11.64; O, 21.74. Found: C, 57.25; H, 11.72; O, 22.00.

A partial acetolysis run (3.00 g of **1**, 60°, 20 days) was quickly worked up with iced carbonate solution and extracted with ether. Rapid distillation gave 0.39 g of an unstable oil, bp 63–66° (1 mm). It contained (vpc, column B, 100–150°) 3-acetoxy-1-*tert*-butylazetidine,[8] the diacetoxyamines **18** and **19**, and a new chlorine-containing compound (75 area %) decomposing on the column to 2-acetoxymethyl-1-*tert*-butylaziridine (**6**). It was impure (80 mol %) **3-*tert*-butylamino-2-chloro-1-propyl acetate** (**16**): nmr τ 8.9 (s, *tert*-bu), 7.9 (s, CH_3CO), 7.0–7.4 (m, NCH_2), 5.8–6.1 (m, CHCl), 5.5–5.7 (m, CH_2OAc).

Anal. Calcd for $C_9H_{18}ClNO_2$: Cl, 17.07. Found: Cl, 13.77.

The impure amine (**16**, 75 area %, 82 mg) and 65 mg of diisopropylethylamine in 2 ml of acetonitrile was heated at 60° for 18 hr. Analysis (column A) indicated 38% conversion to acetoxymethyl-*tert*-butylaziridine (**6**).

Acetolysis of chloroaziridine **2** (90°, 18 hr) gave only the 1,3- and 1,2-diacetoxyamines, **19** and **18**, in a 95:5 ratio, determined by nmr and confirmed by selective acetylation and acid extraction.

Solutions of **2** made by adding it to partially frozen glacial acetic acid were unstable at 20°. A solution, which initially required 1.98 mequiv of HBr–HOAc/mmole, after 18 hr used only 1.12 mequiv/mmol, but potentiometric titration with silver perchlorate (0.1 *M* in HOAc) indicated only 3.9% ionization of chloride. A similar solution after 3 days was iced, quickly basified with carbonate and extracted, and an oil isolated below 20°. The oil was too unstable to distil (giving only acetoxymethyl-*tert*-butylaziridine **6**) and contained **6**, diacetoxyamine **19**, and an unstable peak (column A, 100–130°) decomposing to **6**. The oil deposited a white salt, which was purified by dissolution in chloroform and reprecipitation by ether, mp 157–159°. It was ***tert*-butyl-1,3-diacetoxypropylamine (19) hydrochloride**, as shown by regeneration of the free amine and charcterization by nmr and vpc.

(28) T. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **41**, 712 (1968).

Acetolysis of 1.5 g of **2** in 10 ml of acetic acid, for 16 hr at 20°, was followed by titration to the crystal violet endpoint with 1.6 *M* hydrogen chloride in HOAc. Evaporation of the solvent at 20° left a gum which crystallized partially after several precipitations from chloroform with ether. It was impure **1-*tert*-butylamino-3-chloro-2-propyl acetate (17) hydrochloride**, 0.30 g.

Anal. Calcd for $C_9H_{19}Cl_2NO_2$: C, 44.27; H, 7.84; Cl, 29.04. Found: C, 46.81; H, 7.53; Cl, 25.09.

1-*tert*-Butyl-3-tosyloxyazetidine[7] (5.67 g) was heated in buffered acetic acid 4 days at 60°; under these conditions 1-*tert*-butyl-3-acetoxyazetidine[8] did not react detectably. Basification with iced carbonate and ether extraction gave an oil from which 2.9 g of the unchanged tosylate was recovered by Dry Ice cooling of the solution in *n*-pentane. The purity of the tosylate was confirmed by nmr. The remaining oil (0.79 g) contained only 1-*tert*-butyl-3-acetoxyazetidine and *tert*-butyl-1,3-diacetoxypropylamine (**19**) in a mole ratio of 91:9, determined by nmr. Although it may be inferred that ionization and ring contraction were followed by formation of acetoxymethylaziridine (**6**) which was then cleaved to give **19**, it is possible that opening by acetic acid occurred first; then the acetoxy tosylate, *tert*-$BuNHCH_2CHOTsCH_2OAc$, may have cyclized to **6**.

1,3-Diacetoxypropyldimethylamine.—1,3-Benzylideneglycerol[29] was prepared and converted to the tosylate[30] and to the mesylate, **5-mesyloxy-2-phenyl-1,3-dioxane** (66% yield), mp 132–133°, from methanol.

Anal. Calcd for $C_{11}H_{14}O_5S$: C, 51.15; H, 5.46; S, 12.41. Found: C, 51.22; H, 5.59; S, 12.55.

Neither the mesylate nor the tosylate reacted with *tert*-butylamine at 100° in acetonitrile, but the tosylate with excess dimethylamine in acetonitrile at 130° in a bomb gave **5-dimethylamino-2-phenyl-1,3-dioxane** (46% yield): bp 103–104° (1 mm); $n^{26}D$ 1.5320; nmr τ 7.8 [s, $(CH_3)_2N$], 7.2–7.6 (m, CHOMs), 6.1–6.6 (*m*, 2CHO), 5.5–5.8 (m, 2CHO), 4.7 (s, $O_2CHC_6H_5$), 2.4–2.8 (m, C_6H_5).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; amine neut equiv, 207. Found: C, 69.90; H, 8.15; amine neut equiv, 207.

The dioxane was hydrolyzed with dilute sulfuric acid at 60–70°; the aminodiol was prepared by alkali, dried, and acetylated with acetic anhydride to give **1,3-diacetoxy-2-propyldimethylamine**: bp 73–74° (1 mm); $n^{26}D$ 1.4467; nmr τ 8.0 (s, $2CH_3CO_2$), 7.7 [s, $(CH_3)_2N$], 7.3–6.9 (m, NCH), 5.7–5.9 (2 d, $2CH_2OAc$).

Anal. Calcd for $C_9H_{17}NO_4$: C, 53.18; H, 8.43; N, 6.89. Found: C, 53.33; H, 8.41; N, 7.00.

The nmr and ir spectra showed the expected resemblances to data for *tert*-butyl-1,3-diacetoxy-2-propylamine (**19**).

Isomerization.—The two chlorides isomerized under a variety of conditions. When subjected to vpc on a 10 ft × 0.25 in. column packed with 1% mercuric chloride and 20% Carbowax 20M on Gas Chrom (60–80 mesh), chloroazetidine **1**, programmed at 7.5°/min from 75 to 220°, eluted at about 166° and was followed by chloromethylaziridine **2** (22% from **1**) at 177°. Under these conditions, **2** was stable.

A series of runs was carried out in bombs and glass pressure vessels. The contents were analyzed periodically by vpc (toluene standard, column C, 130°). The isomer ratios were not self-consistent but in a few runs were essentially stable for several days. For the following runs are listed starting chloride, solvent-catalyst, days at temperature, total isomeric chlorides based on starting chloride, and ratio of **1**:**2**: (1) **1**, CCl_4–4% Ph_3P based on **1**, 8–90°, 76%, 41:59; (2) **1**, CH_3CN–, 2.7–90°, 41%, 62:38; (3) **1**, CCl_4–1% Ph_3P, 5–90°, 16%, 78:22; (4) **1**, CH_3CN–, 7 to 16–90°, 49–21%, 54 46 (stable 8 d); (5) **1**, CH_3CN–10% $HgCl_2$, 1–80°, 18%, 98:2; (6) **2**, CH_3CN–, 3–90°, 77%, 5:95; (7) **2**, CCl_4–4% Ph_3P, 4–90°, less than 1% **1**; (8) 3-chloro-1-cyclohexylazetidine, CH_3CN–, 2–90°, 44%, 33:67 azetidine:aziridine; (9) 2-chloromethyl-1-cyclohexylaziridine, CH_3CN–17–90°, 7%, 30:70 (stable for several days).

(29) H. S. Hill, M. S. Whelen, and H. Hibbert, *J. Amer. Chem. Soc.*, **50**, 2235 (1928).

(30) N. K. Matheson and S. J. Angyal, *J. Chem. Soc.*, 1133 (1952).

In runs 1–4 above, up to 15 mol % of *tert*-butyl-2,3-dichloropropylamine (**4**), based on **1**, was detected. It was also isolated from **2** in a run similar to run 8. An equimolar mixture of **4** and diisopropylethylamine in acetonitrile after 4 hr at 80° gave in 80% conversion a mixture of **1** and **2** in a 9:91 ratio.

Runs were conducted in acetonitrile using **1** and an equal weight of anhydrous sodium carbonate with a Teflon-covered stirring bar in a horizontally rotated bomb at 80°. Under these conditions *no* ring opening of **1** by excess *tert*-butylamine or even methylamine was observed. During 6 days, the 1:2 ratio gradually reached 93.5:6.5 while the total of the two isomers slowly dropped to 53.4% of **1** charged; no **4** was detected but poorly resolved higher boiling by-products (eluted at 200° from column C) were formed.

Similar runs with **2** showed it to be more stable, decreasing only a few per cent per day, but no trace of **1** or **4** was detected. The results do not exclude formation of **1** but reflect its poorer stability toward resinification. This was shown by rotating a solution of 1.61 g of **2**, 0.154 g of **1**, and 2.5 g of anhydrous Na_2CO_3 in 5 ml of acetonitrile with a bar at 70°. After 2 days, for instance, analysis indicated that 88.9% **2** and 86.3% **1** remained. Thus the initial loss of **1** was over 20% greater for **1** than for **2**.

Catalysis by potassium iodide (0.20 g and 1.5 g of **1** or **2**) in the presence of sodium carbonate and acetonitrile was studied at 75°. After 18 hr, **2** gave 0.71% **1** and 66% of the original **2** was found. In 2 days, **1** remained constant, but **2** decreased to 56%. No other volatile products were detected. With KI, **1** did not isomerize to **2** detectably, but it was shown that **2** was less stable than **1** under these conditions. A third compound, eluting between xylene and **1**, was probably an elimination product.

1-*tert*-Butyl-3-azetidinol (**3**) was not opened detectably with diethylamine in 10 days at 100° in the presence of carbonate and a rolling bar, although this reaction did occur at 150° in the absence of carbonate.[13]

Registry No.—**1**, 21452-71-1; **2**, 21452-72-2; **4**, 17027-01-9; **6**, 26146-47-4; **7**, 26146-48-5; **10**, 26146-49-6; **11**, 26146-50-9; **12**, 26146-51-0; **13**, 25665-28-5; **16**, 26146-53-2; **18**, 22741-50-0; **19**, 26146-54-3; **19** HCl, 26146-55-4; 3-chloro-1-cyclohexylazetidine, 26146-56-5; 1-*tert*-butylamino-3-chloro-2-propylsulfuric acid inner salt, 26146-57-6; 2-chloromethyl-1-cyclohexylaziridine, 26146-58-7; 4-*tert*-butylamino-3-hydroxybutyronitrile, 26146-59-8; 1-*tert*-butyl-3-*tert*-butylthioazetidine, 26146-60-1; 1-*tert*-butyl-2-*tert*-butylthiomethylaziridine, 26146-61-2; 1-*tert*-butyl-3-*tert*-butoxyazetidine, 26146-62-3; 1-*tert*-butyl-2-*tert*-butoxymethylaziridine, 26146-63-4; 1-*tert*-butyl-3-methoxyazetidine, 26146-64-5; 1-*tert*-butyl-2-methoxymethylaziridine, 25662-25-3; 1-*tert*-butyl-3-methylaminoazetidine, 26146-66-7; 1-*tert*-butyl-3-dimethylaminoazetidine, 18713-65-0; 1-*tert*-butyl-3-dimethylaminoazetidine diperchlorate, 26146-68-9; 2-*tert*-butylamino-1,3-propanediol, 26146-70-3; 5-mesyloxy-2-phenyl-1,3-dioxane, 26146-71-4; 5-dimethylamino-2-phenyl-1,3-dioxane, 26146-72-5; 1,3-diacetoxy-2-propyldimethylamine, 26146-73-6.

Acknowledgments.—The writer thanks Professor Nelson J. Leonard for discussions and suggestions. The assistance of Research Center colleagues with some of the spectra and preliminary instrumental work were appreciated. In particular, vpc–rapid scan mass spectral analyses by Mr. Donald A. Wallace provided early clues to complex reactions.

Crystal Structure of Hydroxypelenolide *p*-Bromobenzoate

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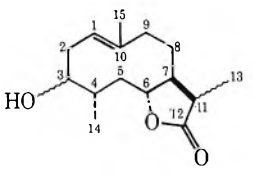
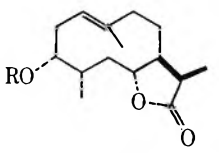
Received April 7, 1970

A crystal structure analysis of the title compound has verified the partial structures previously forwarded for hydroxypelenolide and ketopelenolide a and shows the complete structures to be IIa and III, respectively. Ketopelenolide b is presumably IV. The trans double bond in the ten-membered ring in the crystal is twisted 20°, presumably to relieve nonbonded steric interactions across the ring.

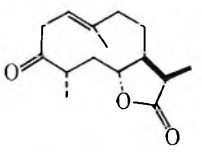
Partial formula I has been proposed for hydroxypelenolide, one of three chemically interrelated sesquiterpene lactones isolated from *Artemisia absinthium* L.[1] To test this proposed formula and to establish the remaining stereochemical features of these substances, the title compound was prepared and subjected to an X-ray study.[2]



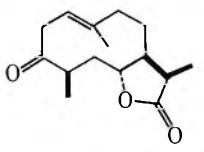
I



IIa, R = H
b, R = *p*-COC_6H_4Br



III



IV

Experimental Section

Crystals suitable for X-ray analysis were kindly prepared by Drs. M. Suchý and V. Herout. After 12 hr, a mixture of hydroxypelenolide (60 mg), *p*-bromobenzoyl chloride (1 ml), and pyridine (2 ml) was poured onto ice water. Recrystallation from methanol gave needles, mp 123–124°. *Anal.* Calcd for $C_{22}H_{27}O_4Br$: C, 60.82; H, 6.23. Found: C, 60.58; H, 6.77. The preliminary X-ray data shown in Table I were obtained from

TABLE I

a, Å	9.72
b, Å	9.82
c, Å	11.05
β	98.8°
Space group	$P2_1$
Molecules per unit cell	2
Measured *d*, g/ml	1.33
Calcd *d*, g/ml	1.33
Observed reflections	837

oscillation and Weissenberg photographs around *b*, the needle axis. The intensities were measured around the *b* axis of a 0.1 × 0.1 × 0.3 mm crystal with a Supper automatic diffractometer using Ni-filtered Cu radiation. A 3° scan at 2°/min and 45 sec background counts were used. Reflections were accepted if the intensity was at least twice the square root of the sum of the scan and background counts.[3] No absorption corrections were made.

The bromine atom was readily located on a Patterson map, and a Fourier map was calculated. After several trials, the aromatic ring and attached COO group were properly placed, and the next Fourier map revealed the remaining nonhydrogen atoms. Anisotropic refinement lowered R to 8.5,[4] and, in spite of the small number of reflections, most of the hydrogens could be located on a difference map, and all except those on carbons 11, 13, 15, and 19 were successfully refined to give a final R of 7.8. Hydrogens were given the same temperature factors as the carbons to which they were attached, and hydrogen temperature factors were not refined. Bond lengths and angles calculated using ORFFE[5] are given on an ORTEP[6] plot in Figure 1.

Discussion

This X-ray study verifies the partial structure I forwarded[1] for hydroxypelenolide. In addition, it shows the configurations at C-3, C-11, and of the double bond to be as shown in IIa. Ketopelenolide a, obtained by mild oxidation of hydroxypelenolide, can now be assigned structure III, and ketopelenolide b, obtained from III by mild base treatment, is presumably IV. No attempt was made to verify the *absolute* configurations crystallographically.

During attempts to refine the hydrogens, it was noted that the hydrogen on C-11 kept moving to a position 1.5 Å from C-11, and it was suspected that a small amount of the C-11 epimer of the major structure might be present as an impurity. Accordingly, C-13 and the suspected carbon were assigned normal temperature factors and their multipliers were refined. The multiplier for C-13 dropped to 0.91 and that for the new carbon settled at 0.08. This is in accord with the view that about 8% of the epimer is present, as is the finding of the poorest bond length (C-11–C-13) in this part of the molecule.

The ten-membered-ring conformation approximates a chair–boat with C-3 at the boat apex and C-8 at the chair apex. The ring is considerably more open than a Dreiding model would indicate, presumably due to cross-ring nonbonded steric interactions. The most

(1) M. Suchý, Z. Samek, V. Herout, R. B. Bates, G. Snatzke, and F. Šorm, *Collect. Czech. Chem. Commun.*, **32**, 3917 (1967).

(2) Previous X-ray studies of derivatives of sesquiterpenoids with ten-membered rings: Elephantol *p*-bromobenzoate [S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **88**, 3675 (1966)], and germacratriene silver nitrate complex [F. H. Allen and D. Rogers, *Chem. Commun.*, 588 (1967)].

(3) 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, American Chemical Society Publications, 1155 16th St. N.W., Washington D. C. 20036. Remit $3.00 for photocopy or $2.00 for microfiche.

(4) Refinements were by full matrix least squares with the ORFLS program of W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-305, Oak Ridge National Laboratory, 1962. Unit weights were used. Form factors were obtained by graphical interpolation of those in the International Tables for X-ray Crystallography, Vol. III, Table 3.3.1A, except for hydrogen, for which the form factors of R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965), were used.

(5) W. R. Busing, K. O. Martin, and H. A. Levy, ORNL-TM-306, Oak Ridge National Laboratory, 1964.

(6) C. K. Johnson, ORNL-3794.

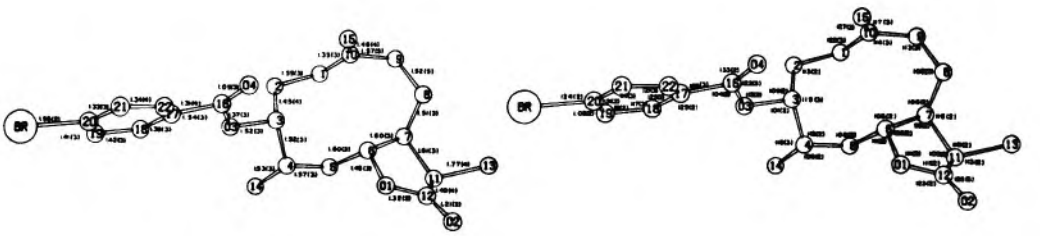


Figure 1.—Left and right eye views of a hydroxypelenolide *p*-bromobenzoate molecule. Bond distances and their standard deviations in angstroms are given on the left eye view, and bond angles on the right eye view.

striking feature of this opening is the angle between the planes formed by C-2–C-1–C-10 and C-1–C-10–C-9, which would be very close to 0° in a simple alkene but is in this case 20°.

Registry No.—IIa, 17909-94-3; IIb, 25975-82-0; III, 17909-92-1.

Acknowledgments.—We thank the Oak Ridge National Laboratory for programs, S. H. Jay for assistance with programming, the University of Arizona Computer Center for computer time, and the PHS (GM-12447), the NSF (postdoctoral support for C. J. C., URP support for T. C. S.), and the Sloan Foundation (Fellowship to R. B. B.) for financial assistance.

Notes

Reaction of Nitric Oxide with 1-Pentyne

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Received March 5, 1970

In contrast to reactions involving the addition of tetrafluorohydrazine to olefins in the presence of nitric oxide which gave predominately difluoramine-N′-fluorodiimide N-oxides,[1] we have found that with acetylenic compounds the reaction takes an alternate course to give in low-yield products devoid of carbon–nitrogen bonding. It was further established that tetrafluorohydrazine does not enter into the transformation, nor was it necessary for the interaction of nitric oxide with 1-pentyne. In the reaction with 1-pentyne, the products obtained were 1-pentyn-3-ol, 1-pentyn-3-one, and 1-pentyn-3-nitrate.

$$CH_3CH_2CH_2C{\equiv}CH + NO \longrightarrow CH_3CH_2CH(OH)C{\equiv}CH + CH_3CH_2\overset{O}{\overset{\|}{C}}C{\equiv}CH + CH_3CH_2CH(ONO_2)C{\equiv}CH$$

These reactions were conducted in an evacuated system at ambient temperature by first introducing 1-pentyne with or without solvent ($HCCl_3$) into a reaction flask which was attached to a glass vacuum system and deaerated by alternate freeze–thaw cycles. The system was then charged with nitric oxide to 500–600 mm of pressure, and the mixture was warmed to reaction temperature for periods of 20–24 hr. Visibly, there was little indication of any reaction except for a slight decrease in pressure. In all instances, 15–55% of the nitric oxide reacted with the formation of nitrogen, and 1-pentyne was converted to products in low conversions followed by termination of the reaction. This behavior was common to both lighted and covered reaction flask.

Gas chromatography was employed to analyze the product mixtures which showed the presence of three products separated in sufficient quantities on a preparative column for proton nmr spectral analysis. 1-Pentyn-3-ol displayed a triplet (J = 7 cps) centered at τ 9.01 (CH_3), a quintet (J = 7 cps) at τ 8.20 (CH_2), a doublet (J = 2 cps) at τ 7.63 (HC≡), a triplet (J = 7 cps) of doublets at τ 5.74 (HC—O), and a singlet at τ 6.46 (OH). A triplet (J = 7 cps) at τ 8.88 (CH_3), a quadruplet (J = 7 cps) at τ 7.43 (CH_2), and a singlet at τ 6.80 (HC≡) were exhibited in the spectrum of 1-pentyn-3-one. The nitrate ester of 1-pentyn-3-ol show absorption as a triplet (J = 7 cps) at τ 8.90 (CH_3), a quintet (J = 7 cps) at τ 8.11 (CH_2), a doublet (J = 2 cps) at τ 7.48 (HC≡), and a triplet (J = 7 cps) of doublets (J = 2 cps) at τ 4.68 (HC—O). All peak areas were in the appropriate ratio, and the spectra and glc retention times were identical with those of authentic samples of the three compounds.

Treatment of 1-pentyn-3-ol with nitric oxide under the same conditions gave the ketone and nitrate ester in low yields, and again, the reaction stopped at low conversions. Similarly, when 1-hexyne was treated with nitric oxide the corresponding alcohol, ketone and nitrate ester were formed with low conversion of 1-hexyne to products.

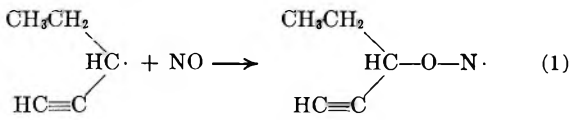
The preliminary results point to a free-radical process; however, nitric oxide while known[2] to be very efficient at trapping hydrocarbon radicals is not par-

(1) S. F. Reed, Jr., *J. Org. Chem.* **32**, 3869 (1967).

(2) J. F. Brown, Jr., *J. Amer. Chem. Soc.*, **79**, 2480 (1957).

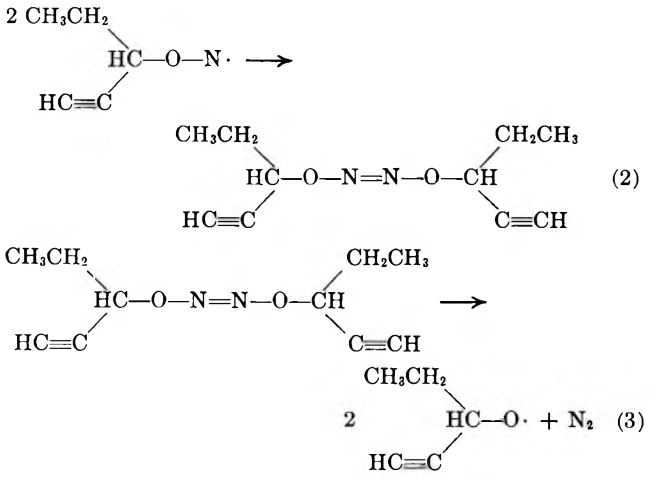
ticularly effective at initiating radical reactions, and in most instances must depend on initiation by other radical species. In many reactions of nitric oxide with neutral molecules, nitrogen dioxide is considered to be the initiating species and arises through air oxidation of nitric oxide. Under our experimental conditions no special attempt was made to scrupulously exclude oxygen from the system; however, it is thought that air was removed from the reaction zone and, hence, did not serve as a reagent for the formation of nitrogen dioxide, because of the absence of reddish-brown coloration in the gas phase and of products containing carbon–nitrogen bonding.[3]

It is proposed that initiation in the 1-pentyne–nitric oxide reaction is spontaneous making alkyl free radicals available for interaction with nitric oxide. Such spontaneous initiation by reactions between molecules has been suggested in a number of reactions.[4] The action of nitric oxide with the radical intermediate is suggested to occur through the formation of a nitroxymethane derivative (eq 1) which rapidly associates yielding an



(1)

organic ester of hyponitrous acid (eq 2). This ester being unstable decomposes with the formation of alkoxy radicals and nitrogen (eq 3). These reactions are in ac-



(2)

(3)

cord with the known chemistry of inorganic nitroxy compounds[5] and hyponitrous esters,[6] and this type of mechanism has been employed to explain the formation of products from the reaction of nitric oxide with pentaphenylethane.[7] This latter study represents the only known instance where alkyl radicals react with nitric oxide to give dialkylmethane nitroxy compounds.

Further known reactions of alkoxy radicals can explain the formation of the observed products, 1-pentyn-3-ol and 1-pentyn-3-one. Nitration of the alcohol by nitric oxide yields the nitrate ester. This series of reactions constitutes a plausible mechanism which is consistent with the available experimental results and with the established properties of analogous compounds.

(3) J. P. Freeman and W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 1712 (1957).

(4) M. L. Poutsma, *ibid.*, **87**, 2161 (1965), and references cited therein.

(5) "Gmelins Handbuck der Anorganischen Chemie," 8th ed, Verlag Chemie, Berlin, 1963, System-Nummer 4, p 855.

(6) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, New York, N. Y., 1937, pp 1–2.

(7) H. Sonneborn, III, and F. Y. Wiselogle, *J. Amer. Chem. Soc.*, **64**, 860 (1942).

Experimental Section

To a 100-ml round-bottom flask fitted with magnetic stirrer was introduced 15.0 g (0.22 mol) of 1-pentyne and the flask connected to a vacuum manifold containing a 2-l. expansion bulb through a Dry Ice–Acetone condenser. The total system was dearated by passing through three freeze–thaw cycles while under vacuum. Nitric oxide (3.78 g, 0.26 mol) was charged into the system and the mixture allowed to come to ambient temperature. The initial pressure was 565 mm; after stirring for 28 hr the pressure was 525 mm. A mass spectral analysis of the gaseous materials showed the presence of nitric oxide and nitrogen. A total of 2.24 g (0.075 mol) of nitric oxide was recovered (40.7% consumed). The contents of the reaction flask were examined by glc and found to consist of 1-pentyne and three major products identified as 1-pentyn-3-ol, 1-pentyn-3-one, and 1-pentyn-3-nitrate.

In a similar reaction with 1-hexyne (8.2 g, 0.1 mol), 1.5 gm (0.05 mol) of nitric oxide was consumed (41%) and the corresponding alcohol, ketone and nitrate ester found.

When 15.0 g (0.18 mol) of 1-pentyn-3-ol was treated with 3.78 g (0.126 mol) of nitric oxide, a total of 2.0 g (0.066 mol) nitric oxide was consumed (52.9%) and the reaction products were 1-pentyn-3-one and 1-pentyn-3-nitrate.

Registry No.—Nitric oxide, 10102-43-9; 1-pentyne, 627-19-0.

Acknowledgment.—This work was conducted under the sponsorship of the Advanced Research Projects Agency under Army Ordnance Contract DA-01-021 ORD 11909. The technical assistance of Mr. James O. Woods and Mrs. Carolyn Haney is appreciated.

Novel cis-Hydroxylation with Nitrous acid

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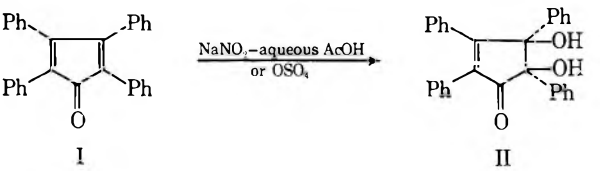
Received April 1, 1970

We report a unique high yield cis-hydroxylation with sodium nitrite–aqueous acetic acid. A benzene solution of tetraphenylcyclopentadienone (I, tetracyclone) when reacted with sodium nitrite in aqueous acetic acid at 0°, conditions generally employed for diazotization, gave after work-up a white crystalline compound, mp 191°, in 85% yield which was subsequently identified as *cis*-2,3-dihydroxy-2,3,4,5-tetraphenylcyclopent-4-en-1-one (II) on the basis of ir, nmr, analysis, and by direct comparison with an authentic sample.[1]

The stereochemical assignment was confirmed to be cis through preparation of II by treatment of tetra-



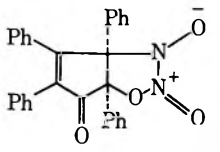
I II

* Author to whom correspondence should be addressed.

(1) P. Yates and G. H. Stout, *J. Amer. Chem. Soc.*, **76**, 5110 (1954).

cyclone with osmium tetroxide. The reaction of $NaNO_2$–H^+ with olefins has been extensively studied;[2-8] however, no cis-hydroxylation has been reported with this reagent.

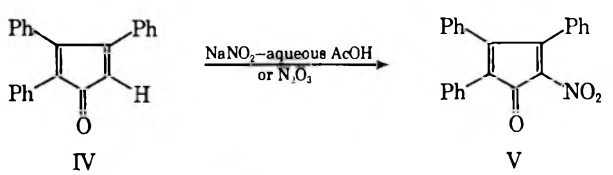
Since, at low temperatures dinitrogen trioxide has been recognized as the reactive species involved in sodium nitrite–aqueous acetic acid reactions, it was considered probable that this reagent could bring about transformation leading to II. Following this reasoning, an ice-cooled dry benzene solution of I was treated in drops, with a dry benzene solution of dinitrogen trioxide until the intense pink color of I was completely discharged. The reaction is extremely rapid and takes only few minutes for completion. Removal of benzene under anhydrous conditions gave a colorless foamy material which has been tentatively assigned the structure III.[9] The compound III was tremendously sensi-



III

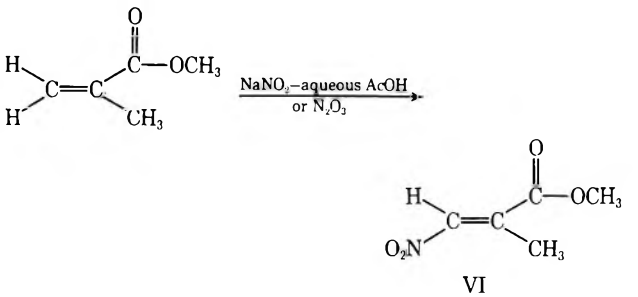
tive to moisture and on keeping, even under best possible "dry" conditions, was converted to the dihydroxy compound II. Compound III could be transformed exclusively to II by treatment with water, aqueous acetic acid, and aqueous dioxane.[10]

With a view to further understand the hydroxylation reaction the action of sodium nitrite–aqueous acetic acid and also dinitrogen trioxide on the closely related 3,4,5-triphenylcyclopentadien-1-one (IV, tricyclone) was carried out. Surprisingly, both these reagents gave as the sole isolable product the orange-brown 2-nitro-3,4,5-triphenylcyclopentadien-1-one (V). Structure V is based on ir, nmr, and analysis.



IV V

Similarly methyl methacrylate under conditions employed in the I → II change gave the nitro olefin (VI) (structural assignment supported by ir, nmr, and analysis[5]).



VI

Compounds V and VI are products expected on basis of known pathways involved in dinitrogen trioxide initiated reactions.[4,5] In these cases the possibility present for the elimination of HNO, which is not possible in the case of I, gives direction to the overall reaction.[11]

The formation of II from either I or III could be rationalized on basis of several pathways and this facet of the transformation is currently being examined in detail.

Experimental Section[12]

Preparation of *cis*-2,3-Dihydroxy-2,3,4,5-tetraphenylcyclopent-4-en-1-one (II). A. From I and Sodium Nitrite in Acetic Acid–Water–Benzene.—A stirred benzene solution of tetracyclone (0.5 g, 1.3 mmol, 10 ml) was treated with acetic acid–water (3:2, 5 ml), and the mixture was cooled to 0°. Solid sodium nitrite (0.5 g, 7 mmol) was gradually introduced over a period of 15 min while maintaining the temperature below 5°. The colorless reaction mixture was stirred for an additional 30 min. The layers were separated; the organic layer was washed several times with water, dried ($MgSO_4$), and evaporated. The residue on crystallization from benzene gave 0.46 g (85%) of II: mp 190–191° dec; this melting point was not depressed by admixture with an authentic sample,[1] mp 190–191°; ir [λ_{max}^{KBr} 2.9 (OH), 5.9 (>C=O) μ]; nmr [δ_{CDCl_3} 7.2 (aromatic protons)].

Anal. Calcd for $C_{29}H_{22}O_3$: C, 83.25; H, 5.26. Found: C, 83.52; H, 4.98.

B.—From I and Dinitrogen Trioxide in Acetic Acid–Water–Benzene.—A stirred benzene solution of tetracyclone (0.2 g, 0.52 mmol, 5 ml) was treated with acetic acid–water (3:2, 5 ml) and the mixture was cooled to 0°. A dilute dry benzene solution of dinitrogen trioxide[13] was added dropwise until decolorization was complete (~10 ml). The clear solution was stirred for additional 30 min, the layers separated, and the organic layer was washed several times with water, dried ($MgSO_4$), and evaporated. The residue on crystallization from benzene gave 0.182 g (85%) of II, mp 192–193° dec.

C.—From I and Sodium Nitrite in Sulfuric Acid–Water–Benzene.—A stirred benzene solution of tetracyclone (0.5 g, 1.3 mmol, 10 ml) was treated with sulfuric acid:water (3:2, 5 ml) and the mixture was cooled to 0°. Solid sodium nitrite (0.5 g, 7 mmol) was gradually introduced over a period of 25 min while maintaining the temperature below 5°. The colorless reaction mixture was stirred for an additional 30 min. The layers were separated and the organic layer was washed several times with water, dried ($MgSO_4$), and evaporated. The residue on crystallization from benzene gave 0.378 g (70%) of II, mp 190–191° dec.

D.—From I and Osmium Tetroxide.—An ice-cooled dry ether solution of tetracyclone (0.5 g, 1.3 mmol, 20 ml) was treated

(2) T. R. Govindachari, B. R. Pai, N. Arumugan, and K. Nagarajan, *Chem. Ind. (London)*, 757 (1954); T. R. Govindachari and B. R. Pai, *J. Org. Chem.*, **18**, 1253 (1953); T. R. Govindachari, K. Nagarajan, and V. N. Sundarajan, *Tetrahedron*, **15**, 60 (1961).

(3) N. Levy, C. W. Scaife, and A. E. Wilder-Smith, *J. Chem. Soc.*, 52 (1948); A. Michael and G. H. Carlson, *J. Org. Chem.*, **4**, 169 (1939); H. O. Larson in "The Chemistry of the nitro and Nitroso Groups," Part 1, Henry Feuer, Ed., Interscience, New York, N. Y., 1969, p 320.

(4) J. L. Riebsomer, *Chem. Rev.*, **45**, 157 (1945).

(5) H. Shechter and D. E. Ley, *Chem. Ind. (London)*, 535 (1955).

(6) H. Shechter, *Rec. Chem. Progr.*, **25**, 55 (1964).

(7) A. S. Onishchenko, *Chem. Abstr.*, **31**, 5340 (1937).

(8) J. R. Park and D. L. H. Williams, *Chem. Commun.*, 332 (1969).

(9) Initially we preferred an open nitro nitroso dimer structure for III. Subsequently a referee suggested the cyclic structure and provided persuasive arguments in favor of this structure [J. R. Park and D. L. H. Williams, *Chem. Commun.*, 332 (1969), and unpublished work]. We are grateful to this referee for the valuable suggestion.

(10) Reaction of the adduct III with excess dry methanol lead to *instant* appearance of the characteristic pink color of tetracyclone and tlc of the reaction mixture taken immediately indicated reversal to I. This unexpected observation has no precedence and is being currently examined.

(11) The more promising examples, 2,3-dihydrotetracyclone and *trans*-dibenzoylethylene, were not affected under conditions of I → II change; however, 2,3-diphenyl-glyoxalone, gave the *cis*-diol in 50% yield [H. Biltz, *Justus Liebigs Ann. Chem.*, **368**, 156 (1909), and ref 1].

(12) All melting points and boiling points are uncorrected. Ir spectra were taken on Perkin-Elmer Model 521 spectrometer. Nmr spectra were obtained on a Varian A-60 spectrometer using TMS as an internal reference. Microanalyses were done in the microanalytical laboratory of the Department of Chemistry, I. I. T., Kanpur.

(13) G. Brauer, "Preparativen Anorganishen Chemie," Vol. I, Ferdinand Enke Verlag, Stuttgart, 1960, p 438.

with osmium tetroxide (0.33 g, 1.3 mmol) and pyridine (1 ml) and the mixture was stirred at room temperature for 72 hr. The insoluble complex was decomposed with mannitol (5 g) in 10% aqueous potassium hydroxide (20 ml) and stirring continued for 12 hr. The reaction mixture was extracted with methylene chloride, the organic layer washed with water and dried ($MgSO_4$), and solvents were evaporated. The residue on crystallization from benzene gave 0.34 g (63%) of II, mp 190–191° dec. This melting point was not depressed by admixture with an authentic sample,[1] mp 190–191° dec.

Reaction of I with Dinitrogen Trioxide in Benzene. Preparation of III.—A stirred and ice-cooled dry benzene solution of tetracyclone (0.5 g, 1.3 mmol, 10 ml) was treated dropwise with a dry benzene solution of dinitrogen trioxide until decolorization was complete (~10 ml). The solvent was removed *in vacuo* and without heating under rigorously dry conditions to give III as a noncrystalline solid: mp 95° dec; ir [λ_{max}^{KBr} 5.7 (>C=O), 6.5, 7.5 μ; also present 2.85 (OH) 5.9 (>C=O) μ due to decomposition to II].

Anal. Calcd for $C_{29}H_{20}N_2O_4$: N, 6.08. Found: N, 6.01.

Reactions of III. A. With Aqueous THF.—Aqueous THF (3:2, 5 ml) was added to 0.1 g of III. The solution became pink owing to the formation of some I. The color disappeared on standing. The colorless reaction mixture was extracted with benzene and dried ($MgSO_4$), and solvent evaporated to yield II, mp 191–192° dec.

B. With Aqueous Acetic Acid.—Aqueous acetic acid (3:2, 5 ml) was added to 0.1 g of III. The pinkish color due to the formation of some I, disappeared immediately. The colorless reaction mixture was extracted with benzene, the organic layer was washed with water and dried ($MgSO_4$), and solvents were evaporated to yield II, mp 190–191° dec.

C. With Anhydrous Methanol.—Absolute methanol (5 ml) was added to 0.1 g of III. The solution instantly became pink owing to the formation of I. The color did not fade on long standing. Evaporation of solvents gave pure I, mp 223°.

Preparation of 3,4,5-Triphenylcyclopentadien-1-one IV (Tricyclone).—The blue tricyclone was prepared by the condensation of benzil with phenylacetone,[14] mp 292–293° dec (lit.[14] mp 292–294°).

Reactions of Tricyclone. A. With Sodium Nitrite Acetic Acid–Water–Benzene.—A stirred benzene solution of tricyclone (0.5 g, 1.62 mmol, 10 ml) was treated with acetic acid:water (3:2, 5 ml) and cooled to 0°. Solid sodium nitrite (0.5 g 7 mmol) was gradually introduced over a period of 15 min while maintaining the temperature below 5°. The brown reaction mixture was stirred for additional 30 min. The layers were separated, the organic layer was washed several times with water and dried ($MgSO_4$), and solvents were evaporated. The residue on crystallization from benzene–hexane mixture gave 0.45 g (79%) of V: mp 158–160° dec; ir [λ_{max}^{KBr} 5.8 (>C=O), 6.5 ($-NO_2$, asymmetric), 7.3 ($-NO_2$, symmetric) μ]; nmr [δ_{CDCl_3} 7.2 (aromatic protons)].

Anal. Calcd for $C_{23}H_{15}NO_3$: C, 78.18; H, 4.24; N, 3.96. Found: C, 78.08; H, 4.6; N, 3.63.

B. With Dinitrogen Trioxide under Anhydrous Conditions and Treatment with Absolute Methanol.—A stirred and ice-cooled dry benzene solution of tricyclone (0.5 g, 1.62 mmol, 10 ml) was treated dropwise with a dry benzene solution of dinitrogen trioxide (10 ml). Tricyclone color disappeared rapidly and the solution became chocolate brown. Solvents were removed *in vacuo* without heating and under rigorously dry conditions. Absolute methanol (10 ml) was added. No tricyclone color reappeared even on standing. Solvents were removed and the residue on crystallization from benzene–hexane mixture gave 0.46 g (80%) of V, mp 159–160° dec.

Reaction of Methyl Methacrylate with Sodium Nitrite Acetic Acid–Water–Benzene.—A stirred benzene solution of methyl methacrylate (5 g, 50 mmol, 10 ml) was treated with acetic acid:water (3:2, 20 ml) and the mixture was cooled to 0°. Solid sodium nitrite (5 g, 70 mmol) was gradually introduced over a period of 15 min while maintining the temperature below 5°. The reaction mixture was stirred for additional 6 hr. The layers were separated, the organic layer was washed several times with water and dried ($MgSO_4$), and solvents were evaporated. The residue on distillation gave 3.6 g (45%) of VI: bp 90° (4 mm);[5] ir [$\lambda_{max}^{CHCl_3}$ 5.78 (>C=O), 6.1 (C=C), 6.5 ($-NO_2$, asymmetric), 7.4 ($-NO_2$, symmetric) μ]; nmr [δ_{CCl_4} 2.2 (d, $-CH_3$), 3.8 (s, $-OCH_3$) 7.6 (q, H)].

Anal. Calcd for $C_5H_7NO_4$: C, 41.37; H, 4.82; N, 9.64. Found: C, 41.4; H, 4.9; N, 9.4.

(14) C. F. Koelsch and T. A. Geissman, *J. Org. Chem.*, **3**, 480 (1939); P. L. Pauson and B. J. Williams, *J. Chem. Soc.*, 4162 (1961).

Registry No.—Nitrous acid, 7782-77-6; II, 25716-03-4; III, 25662-49-1; V, 25665-22-9; VI, 25662-50-4.

Acknowledgments.—We thank Dr. Nitya Nand, CDRI, Lucknow, for providing nmr facilities. Financial assistance by way of a Lady Tata Memorial Trust Scholarship (SKK) is gratefully acknowledged.

Preparation of Optically Pure Diastereomeric 2-Methyl-2,3-dihydrobenzothiophene 1-Oxides and Comments on the Mechanism of Reduction of Cyclic Sulfones[1]

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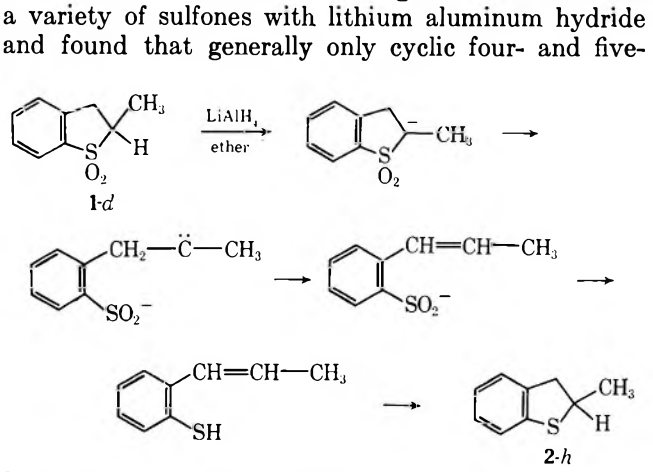
Contribution No. 2564 from the Department of Chemistry, University of California, Los Angeles, California 90024

Received April 3, 1970

As a part of the study of electrophilic substitution at saturated carbon,[3] the title compounds were prepared as follows. Optically pure 2-methyl-2,3-dihydrobenzothiophene-2-*d* (or -2-*h*) 1-dioxide [*e.g.*, (+)-1-*h*] was reduced with lithium aluminum hydride to (−)-2-*h*, which was oxidized under controlled conditions to give a mixture of optically pure diastereomers (+)-3-*h* and (−)-3-*h*, separable by column chromatography. Although the 2,3-dihydrobenzothiophene 1-oxide system was found to be unstable toward *tert*-butyl alcohol–potassium *tert*-butoxide (thus precluding study of the stereochemistry of electrophilic substitutions), the reactions involved in the preparation of the compounds provide insight into the mechanism of the reduction of cyclic five-membered ring sulfones to sulfides.

Bordwell and McKellin[4] investigated the behavior of a variety of sulfones with lithium aluminum hydride and found that generally only cyclic four- and five-



* Author to whom correspondence should be addressed.

(1) This investigation was supported by the U. S. Public Health Service Research Grant No. GM 12640-04 from the Department of Health, Education and Welfare.

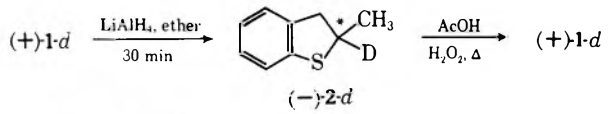
(2) National Science Foundation Predoctoral Fellow, 1962–1966.

(3) D. J. Cram and T. A. Whitney, *J. Amer. Chem. Soc.*, **89**, 4651 (1967). See also, F. A. L. Anet, L. M. Sweeting, T. A. Whitney, and D. J. Cram, *Tetrahedron Lett.*, **22**, 2617 (1968).

(4) F. G Bordwell and W H. McKellin, *J. Amer. Chem. Soc.*, **73**, 2251 (1951).

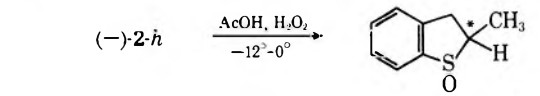
membered ring sulfones are readily reduced. The reduction of 2,3-dihydrobenzothiophene 1-dioxide went easily. These authors[4] suggested the mechanism involved nucleophilic attack of a donated hydride on sulfur to displace oxygen as the critical stage of the reaction. More recently, Meyers[5] suggested the mechanism (as applied to 1-*h*) as indicated.

The results reported here are inconsistent with the Meyers, but consistent with the Bordwell–McKellin mechanism. Optically pure 1-*d* was reduced by lithium aluminum hydride to optically active 2-*d* *without* loss of label. Reoxidation[3] of 2-*d* with an excess of hydrogen peroxide in acetic acid gave 1-*d* having the same rotation and deuterium content as starting material. These results are consistent with the suggestion of Bordwell and McKellin that reduction occurs by displacement of oxygen from sulfur by hydride forming sulfide, aluminum oxide, and hydrogen gas, the evolution of which was noted previously and during the present investigation.

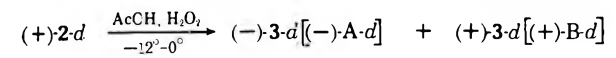


(−)-2-*d*

Partial oxidation of (−)-2-*h* gave nearly a quantitative yield of a mixture of diastereomers (+)-3-*h* and (−)-3-*h* [configurations (+)-A and (−)-B, respectively], which were separated chromatographically. From (−)-2-*d* of maximum rotation, the corresponding (−)-3-*d* [(−)-A-*d*)] and (+)-3-*d* [(+)-B-*d*)] were isolated.[6]



(+)-3-*h* [(+)-A-*h*]
(−)-3-*h* [(−)-B-*h*]



Experimental Section[7]

(−)-2-Methyl-2,3-dihydrobenzothiophene [(−)-2-*h*].—To a rapidly stirred suspension of 4.0 g of lithium aluminum hydride in 135 ml of anhydrous ethyl ether was added dropwise a solution of 8.14 g of (+)-1-*h*[3], $[\alpha]^{25}_{546}$ +23.7° (*c* 3.92), in 300 ml of 50:50 ethyl ether–benzene, and the reaction mixture was stirred at 25° for 30 min after addition of the sulfone was complete.[4] Hydrolysis was effected by dropwise addition of 100 ml of 10% aqueous hydrochloric acid. The layers were separated and the aqueous phase was extracted with two 80-ml portions of ethyl ether. The combined organic phase was dried and evaporated to a colorless oil, wt 6.53 g, $[\alpha]^{25}_{546}$ −165° (*c* 5.00). A 0.50-g portion of the product, [(−)-2-*h*], was chromatographed on a 2 × 30 cm column of silica gel with 5% ether–85% pentane as developer. The remainder of the sample was not purified, but was used directly in the next step.

Anal. Calcd for $C_9H_{10}S$: C, 72.00; H, 6.64; S, 21.34. Found: C, 72.15; H, 6.73; S, 21.37.

Stability of the 2,3-Dihydrobenzothiophene Ring System under Conditions of Reduction with Lithium Aluminum Hydride and Oxidation with Hydrogen Peroxide.—A 0.30-g portion of sulfone (−)-2-*d*, $[\alpha]^{25}_{543}$ −13.30° (*c* 3.94), was dissolved in 10 ml of 50:50 benzene–ether. The solution was added dropwise to a stirred suspension of 0.3 g of lithium aluminum hydride in 7 ml of anhydrous ether. After 30 min, the product sulfide was isolated, as detailed above, wt 0.210 g (85%), $[\alpha]^{25}_{546}$ +87.0° (*c* 4.03). This sulfide [(+)-2-*d*] was oxidized in 2 ml of glacial acetic acid with 0.5-ml portions of 30% hydrogen peroxide being added every 10 min for 1.5 hr on a steam bath. The oxidation reaction mixture was cooled, and 10 ml of ice water was added. The sulfone (−)-1-*d* was isolated as described for the sulfoxides and evaporation of solvent left a white solid having absolutely no sulfide odor. The total sample was sublimed, wt 0.220 g, $[\alpha]^{25}_{546}$ −13.23° (*c* 4.44). This product sulfone [(−)-1-*d*] was found to have 0.970 atom of deuterium per molecule. The starting sulfone contained 0.977 atom of deuterium per molecule.

Diastereomers of 2-Methyl-2,3-dihydrobenzothiophene 1-Oxide [(+)-A-*h* and (−)-B-*h*].—The crude sulfide, (−)-2-*h*, wt 6.50 g, $[\alpha]^{25}_{546}$ −165° (*c* 5.00), as prepared above, was dissolved in 33 ml of glacial acetic acid. The solution was cooled in an ice–salt bath until it partially froze and 6.9 g of 30% hydrogen peroxide was added to 0.5-ml portions with constant swirling and continued cooling in the freezing mixture. When addition of hydrogen peroxide was complete, a homogeneous solution resulted which was kept at −12° for 30 min, warmed to −5°, and allowed to stand at −5–0° for 16.5 hr. The reaction mixture was poured into 175 ml of ice water, and the solution was extracted with three 100-ml portions of dichloromethane. The combined dichloromethane extracts were washed with 175 ml of water, 100 ml of cold ferrous sulfate solution, 75 ml of saturated sodium bicarbonate solution, and 175 ml of water, in that order. The dichloromethane solution of the product was dried and evaporated under reduced pressure, yielding the crude sulfoxides as an oil, wt 6.82 g. This product was purified by chromatography on a 7 × 100 cm column packed with Baker silica gel powder. Developer was 96% ethyl ether–4% anhydrous methanol. Eluate was collected in 250 ml fractions. Fractions 1–8 were empty, fractions 9–13 contained a very small amount of sulfide, fractions 14–19 contained sulfone (wt 0.113 g), and fractions 20–34 were empty. The sulfoxides were eluted in fractions 35–72. Fractions 35–45 contained only diastereomer A (wt 1.96 g), fractions 46–48 contained both diastereomers (wt 0.610 g), and the remaining fractions contained only diastereomer B (wt 3.43 g), as determined by thin layer chromatography on silica gel with 7% methanol–93% ethyl ether as developer. Diastereomer A gave $[\alpha]^{25}_{546}$ +148° (c 4.40), whereas diastereomer B displayed $[\alpha]^{25}_{546}$ −241° (*c* 4.01); both were oils.

Anal. Calcd for $C_9H_{10}SO$ (A): C, 65.06; H, 6.02; S, 19.30. Found: C, 65.23; H, 6.19; S, 19.09.

Anal. Calcd for $C_9H_{10}SO$ (B): C, 65.06; H, 6.02; S, 19.30. Found: C, 65.13; H, 6.21; S, 19.42.

Diastereomer A from the column had an R_f value of 0.43, while diastereomer B had an R_f value of 0.35 when both were spotted separately on silica gel and the plate was developed with 93% ethyl ether–7% methanol.

When both diastereomers were spotted together as a 50:50 mixture, the R_f values were 0.44 and 0.38, respectively. Separate experiments demonstrated that 5% by weight of one diastereomer could be detected in a mixture with the other. Such was the case, regardless of which diastereomer predominated. Thus, each diastereomer was at least 95% free of contamination by the other.

Diastereomers of 2-*d*-2-Methyl-2,3-dihydrobenzothiophene 1-Oxide [(−)-A-*d* and (+)-B-*d*].—Reduction of 8.70 g of (−)-1-*d*[3], $[\alpha]^{25}_{546}$ −24.1° (*c* 3.86), as described above, with lithium aluminum hydride yielded 6.68 g of crude (+)-2-*d*, $[\alpha]^{25}_{546}$ +170° (*c* 4.57). The sulfide was not purified, but was oxidized in 34 ml of glacial acetic acid with 7.0 g of 30% hydrogen peroxide, as described above, and 6.96 g (94.5%) of crude sulfoxides were obtained. The two diastereomeric sulfoxides were separated *via* chromatography on silica gel by the same method utilized above to give 2.16 g of (−)-A-*d*, $[\alpha]^{25}_{546}$ −150° (*c* 4.26), and 3.92 g of (+)-B-*d*, $[\alpha]^{25}_{546}$ +248° (*c* 5.36). The nmr spectrum of diastereomer (−)-A-*d* showed the following absorptions: aromatic protons (m, 4.0 protons), τ 2.05–2.83; benzyl protons (s, 1.96 protons), τ 6.67; methyl protons (s, 2.90 protons), τ 8.50. Diastereomer (+)-B-*d* showed the following spectrum: aromatic protons (m, 4.0 protons), τ 2.10–2.81; benzyl protons (AB quartet, J_{AB} = 16 cps, ν_{AB} = 55.9 cps, 2.09 protons), centered at τ 6.64; methyl protons (s, 2.98 protons), τ 8.62.

(5) C. Y. Meyers, Abstracts, 144th National Meeting of the American Chemical Society, Los Angles, Calif., April 1963, p 4M.

(6) Determination of the absolute configurations of A and B is in progress (W. H. Pirkle, T. A. Whitney, and S. D. Beare).

(7) Rotations were taken with a Perkin-Elmer Model 141 polarimeter with chloroform as solvent. Nmr spectra were taken with a Varian A-60 spectrometer. Deuterium analyses were performed by Dr. J. Nemeth of Urbana, Ill., using the combustion and falling drop method.

By nmr, the degree of separation achieved between the two diastereomeric deuteriosulfoxides was found to be 98 ± 1% (area of the methylene singlet for diastereomer A *vs.* area of the methylene AB quartet for diastereomer B). Thin layer chromatograpy was employed to determine which fractions contained both deuteriodiastereomers in exactly the same manner as in the above separation. The degree of separation of the individual protiodiastereomers was probably 98 ± 1% also.

Registry No.—(−)-**2**-*h*, 25662-51-5; (+)-**3**-*h*, 25662-52-6; (−)-**3**-*h*, 25662-53-7; (+)-**3**-*d*, 20550-30-5; (−)-**3**-*d*, 20550-31-6.

The Reformatsky Reaction at Room Temperature and in the Presence of Trimethyl Borate. Improved Procedures for the Preparation of β-Hydroxy Esters

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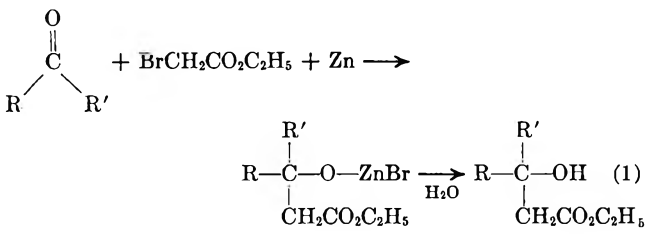
Michigan State University, East Lansing, Michigan 48823

Received March 31, 1970

The Reformatsky reaction (eq 1) is normally conducted at reflux temperatures in benzene or benzene–ether solvents. Using such procedures, the yields of β-hydroxy esters from a wide variety of aldehydes and ketones lie in the range of 25–65%.[1] It is likely that a major factor responsible for such low yields is base-catalyzed side reactions of the starting materials.[2] This should be especially critical at the elevated temperatures utilized in the normal procedures.



(1)

It occurred to us that trimethyl borate would provide a mildly acidic medium for conducting the Reformatsky reaction, possibly allowing the reaction to proceed as usual, but neutralizing the basic alkoxide products. In addition, we considered the possibility of conducting the reaction at room temperature. Accordingly we carried out a brief study of the Reformatsky reaction of acetaldehyde and ethyl bromoacetate, varying both solvent and temperature. The results were applied to a representative number of aldehydes and ketones.

Results

Reaction of acetaldehyde with 1 equiv of zinc and ethyl bromoacetate in refluxing benzene is complete in 2 hr and gives a 22% yield of ethyl 3-hydroxybutanoate. The same reaction conducted at 25° is complete in 4 hr and gives a 65% yield of product. Reactions with ethyl ether or tetrahydrofuran as solvent proceed faster but give somewhat lower yields, 56 and 35%, respectively.

Attempts to use trimethyl borate or trimethyl borate–benzene mixtures as solvent were unsuccessful; no reaction occurs over a period of 2 days at 25°. However, a solvent mixture of trimethyl borate and tetrahydrofuran gives complete reaction in 2 hr at 25° and the yield of β-hydroxy ester is 95%. These results are summarized in Table I.

TABLE I
REACTION OF ACETALDEHYDE WITH ETHYL BROMOACETATE AND ZINC UNDER VARIOUS CONDITIONS[a]

Solvent	Temp, °C	Time for complete reaction, hr[b]	Yield, %[c]
Benzene	75	2	22
Benzene	25	4	65
Ethyl ether	25	2	56
Tetrahydrofuran	25	1	35
Tetrahydrofuran–trimethyl borate	25	2	95

[a] 20.0 mmol of each reactant and 10.0 ml of each solvent. [b] Judged by the disappearance of zinc metal. [c] Glpc analysis for ethyl 3-hydroxybutanoate.

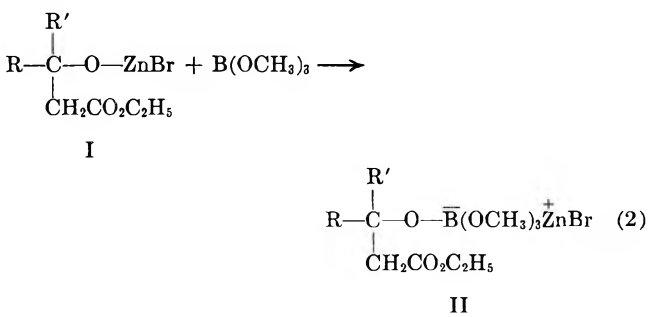
The reaction mixture in tetrahydrofuran remains homogeneous. However, in the presence of trimethyl borate a white precipitate which contains boron is formed during the reaction. Hydrolysis of the precipitate following completion of the reaction gives methanol as the sole organic product while hydrolysis of the clear supernatent gives the β-hydroxy ester.

The procedure using trimethyl borate–tetrahydrofuran as solvent at room temperature was applied to a variety of aldehydes and ketones with the results shown in Table II. For comparison, our results using benzene as solvent at room temperature are also presented, together with the yields previously reported in the literature.

Discussion

Our results show that the Reformatsky reaction proceeds readily at 25° in benzene solution and that higher yields are obtained at this temperature than at the usual reflux temperature. More important, the yields are nearly quantitative when a solvent mixture containing trimethyl borate is used.

It is likely that the function of trimethyl borate is to neutralize the zinc alkoxides, I, formed in the reaction, as illustrated in eq 2. The tetraalkylborate salt, II, is



(2)

I II

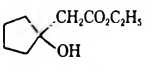
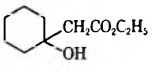
* Author to whom correspondence should be addressed.

(1) R. L. Shriner, "Organic Reactions," Vol. I, Wiley, New York, N. Y., 1942, p 20.

(2) Allen S. Hussey and Melvin S. Newman, *J. Amer. Chem. Soc.*, **70**, 3024 (1948).

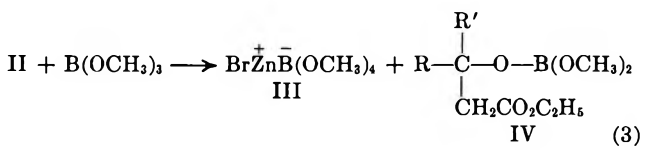
TABLE II

REACTION OF CARBONYL COMPOUNDS WITH ZINC AND ETHYL BROMOACETATE AT 25°

Carbonyl compd	Product	Yield, %[b] Tetrahydrofuran–trimethyl borate	Benzene	Lit.[c]
Acetaldehyde	$CH_3CHOHCH_2CO_2C_2H_5$	95	65	
Butyraldehyde	$CH_3(CH_2)_2CHOHCH_2CO_2C_2H_5$	97 (90)	80	25
Isobutyraldehyde	$(CH_3)_2CHCHOHCH_2CO_2C_2H_5$	98 (89)	95	35
Crotonaldehyde	$CH_3CH{=}CHCHOHCH_2CO_2C_2H_5$	98 (90)	89	60
Benzaldehyde	$C_6H_5CHOHCH_2CO_2C_2H_5$	(95)	(84)	61
Phenylacetaldehyde	$C_6H_5CH_2CHOHCH_2CO_2C_2H_5$	90	70	
Acetone	$(CH_3)_2COHCH_2CO_2C_2H_5$	90 (85)	90	
Cyclopentanone		93 (87)	50	40[d]
Cyclohexanone		85 (80)	80	56

[a] All products gave analytical data and spectra in accordance with the assigned structures. [b] Glpc yields. Isolated yields in parentheses. [c] Reference 1 unless otherwise noted. [d] V. N. Ipatieff, J. E. Germain, and H. Pines, *Bull. Soc. Chem. Fr.*, 259 (1951).

not isolated. Instead a precipitate assumed to be the zinc salt III is formed, presumably by reaction of II with excess trimethyl borate (eq 3). Hydrolysis of the



(3)

boron ester IV during work-up then gives the β-hydroxy ester.

As expected, the advantage of using trimethyl borate is most apparent when the carbonyl compound is especially susceptible to base-catalyzed condensations. Thus the reactive aldehydes, acetaldehyde and phenylacetaldehyde, and the reactive ketone, cyclopentanone, give clearly increased yields with the trimethyl borate procedure. With less reactive carbonyl compounds, the procedure utilizing benzene at 25° gives comparable yields. With either procedure, the yields are much higher than those obtained at reflux temperatures.

Experimental Section

All experiments were conducted using unactivated 20 mesh zinc metal. Ethyl bromoacetate was distilled under reduced pressure and stored under a nitrogen atmosphere. Trimethyl borate was distilled from calcium hydride and stored under nitrogen. All carbonyl compounds were distilled shortly before use. Tetrahydrofuran and benzene, reagent grades, were used directly. Glpc analyses were performed on a SE-30 silicon oil column using appropriate internal standards.

Reactions Using Tetrahydrofuran–Trimethyl Borate Solvent.—The following procedure for the conversion of benzaldehyde into ethyl 3-phenyl-3-hydroxypropionate is representative. Zinc metal (6.54 g, 100 mg-atoms) was put in a 250-ml round-bottom flask equipped with septum inlet and magnetic stirring bar and maintained under a static nitrogen pressure. The flask was immersed in a water bath at 25° and a solution of 10.6 g (100 mmol) of benzaldehyde in 25 ml of tetrahydrofuran and 25 ml of trimethylborate was injected. Stirring was initiated and 11.1 ml (100 mmol) of ethyl bromoacetate was injected all at once. The reaction mixture was stirred for 12 hr at which time all of the zinc was consumed (with the other aldehydes and ketones studied, complete reaction was achieved in 5 hr or less). The reaction mixture was hydrolyzed by the addition of a solution containing 25 ml of concentrated ammonium hydroxide (to dissolve zinc salts) and 25 ml of glycerine (to dissolve boric acid). The organic phase was separated and the aqueous layer extracted with three 25-ml portions of ether. The combined organic extracts were dried and subjected to vacuum distillation to obtain 18.5 g (95% yield) of ethyl 3-phenyl-3-hydroxypropionate, bp 105° (0.2 mm).

Reactions Using Benzene as Solvent.—An identical procedure was utilized except an equal volume of benzene was substituted for the tetrahydrofuran–trimethyl borate solvent.

Registry No.—Trimethyl borate, 121-43-7; acetaldehyde, 75-07-0; ethyl bromoacetate, 105-36-2; tetrahydrofuran, 109-99-9.

Acknowledgment.—Support of this work by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Cyanuric Chloride. A Novel Laboratory Hydrochlorinating Reagent for Alcohols

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This note reports on the investigation of cyanuric chloride with alcohols with the aim of extending the SNi type of reaction, already well known. In an attempt to prepare 2,4,6-trimethyl-*s*-triazine by the reaction of a methanolic solution of sodium methoxide with cyanuric chloride, methyl chloride was unexpectedly obtained in 92% yield along with a 100% yield of cyanuric acid.

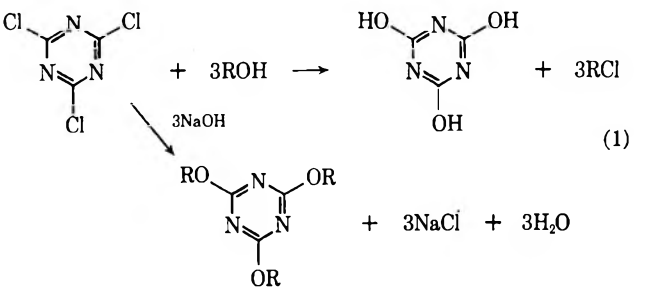
A search of the literature revealed that only two earlier reports in 1834[1] and 1886[2] had briefly mentioned the occurrence of a similar reaction in the absence of sodium methoxide or other bases, but they gave no experimental details. More recent investigators[3] reporting the preparation of trialkyl-*s*-triazines by similar methods

(1) J. Liebig, *Ann. Pharm.*, **10**, 1 (1834).
(2) P. Klason, *J. Prakt. Chem.*, **34**, 152 (1886).
(3) (a) J. R. Dudley, J. T. Thurston, F. C. Schaefer, D. H. Hansen, C. J. Hull, and P. Adams, *J. Amer. Chem. Soc.*, **73**, 2986 (1951); (b) J. R. Dudley, J. T. Thurston, F. C. Schaefer, C. J. Hull, D. H. Hansen, and P. Adams, *ibid.*, **73**, 2999 (1951); (c) J. R. Dudley, U. S. Patent 2,510,564 (1950); (d) A. J. Matuszko and M. S. Chang, *J. Org. Chem.*, **27**, 677 (1962).

TABLE I
HYDROCHLORINATION OF PRIMARY, SECONDARY, AND TERTIARY ALCOHOLS WITH CYANURIC CHLORIDE[a,b]

Alcohol (mol)	Cyanuric chloride (mol)	Base (mol)	% yield, RCl
CH_3OH		$NaOCH_3$	
2.5	0.5	0.5	92
3.0	0.5		72
C_2H_5OH			
5.4	0.5		70
n-C_3H_7OH			
4.2	0.5		65
n-C_4H_9OH			
3.4	0.5		41
		NaOBu	
2.5	0.5	0.5	34
t-C_4H_9OH			
3.4	0.5		56
Allyl alcohol			
7.8	0.5		43
n-$C_5H_{11}OH$			
4.0	0.5		44
2-$C_5H_{11}OH$			
1.7	0.73		29
3.4	0.50		57
3-$C_5H_{11}OH$			
0.85	0.49		38
$C_6H_5CH_2OH$			
3.0	0.5		71

[a] The reaction temperature is the boiling point of the alcohol and the reaction time is 1–1.5 hr. [b] The chlorides were identified by their ir and nmr spectra.



(1)

lides as seen for the case of methanol and n-butyl alcohol in Table I. The results of Table I also indicate that cyanuric chloride can be conveniently used to hydrochlorinate primary, secondary, and tertiary alcohols. 2- and 3-pentanol are hydrohalogenated to their respective chlorides without isomerization as is not true for zinc chloride–HCl hydrochlorination (Table II). Thionyl chloride–pyridine[4] also gives no isomerization as shown for 2-pentanol in Table II.

Experimental Section

A typical preparation involves heating the alcohol (2–20 mol) to 10–20° below its boiling point and then slowly adding powdered cyanuric chloride (1 mol). A Dry Ice trap should be connected *via* a rubber tube to the top of the reflux condenser in order to trap the low boiling chlorides. After the addition (*ca.* 1–1.5 hr), the reaction mixture is cooled, filtered, and distilled. If complete conversion to the chloride is desired, excess cyanuric chloride should be added. See Table I for molar quantities used.

TABLE II
HYDROCHLORINATION OF 2-PENTANOL USING VARIED METHODS

ROH (Mol)	Cyanuric chloride (Mol)	$ZnCl_2$ (Mol)	HCl (concd) (Mol)	$SOCl_2$ (Mol)	Pyridine (Mol)	Temp, °C	Time, hr	% yield	Isomer, % 2-Chloro	Isomer, % 3-Chloro
2-Pentanol										
3.4	0.5					117	1	57	100	
1.0		2.0	2.0			78	1–2	68	38	62
0.547				0.848	0.552	5–10	1	48	100	
0.25			0.50			86–95	1–2	27	76	24

completely ignored the hydrochlorination reaction of the alcohols.

The results of the investigation indicate that cyanuric chloride under the appropriate conditions can be used as a convenient hydrochlorinating reagent for alcohols giving no isomerization as is also true with other SNi reagents.[4–9] Cyanuric chloride has the advantage that it can be conveniently handled and requires no added base such as sodium alkoxide or pyridine.[4–6] The alcohol can be completely converted to the chloride by using an excess of cyanuric chloride under anhydrous conditions. The crude chloride is simply isolated by filtration and then purified by distillation. The presence of sodium hydroxide changes the reaction so that trialkylcyanurates are produced.[3] The presence of sodium alkoxide has little effect on the reaction to give alkyl ha-

(4) F. C. Whitmore and F. A. Karnatz, *J. Amer. Chem. Soc.*, **60**, 2536 (1938).
(5) E. S. Lewis and C. E. Boozer, *ibid.*, **74**, 308 (1952).
(6) L. H. Sommer, H. D. Blankman, and P. C. Miller, *ibid.*, **76**, 803 (1954).
(7) K. L. Oliver and W. G. Young, *ibid.*, **81**, 5811 (1959).
(8) K. B. Wiberg and T. N. Shryne, *ibid.*, **77**, 2774 (1955).
(9) S. J. Rhoads and R. E. Michel, *ibid.*, **85**, 585 (1963).

Registry No.—Cyanuric chloride, 108-77-0; 2-pentanol, 6032-29-7.

Base-Induced α-Sulfonylation of Aryl Alkanesulfonates

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In the course of our investigations utilizing sulfur-stabilized carbanions for synthetic purposes,[1] it has been

(1) (a) W. E. Truce and F. E. Roberts, *J. Org. Chem.*, **28**, 961 (1963); (b) W. E. Truce and L. W. Christensen, *Tetrahedron*, **25**, 181 (1969); (c) W. E. Truce and D. J. Vrencur, *J. Org. Chem.*, **35**, 1226 (1970); (d) H. Fukuda, F. F. Frank, and W. E. Truce, *ibid.*, **28**, 1420 (1963).

TABLE I
$RCH(SO_2CH_2R)SO_3Ar$

Compd no.	Compd R	Compd Ar	Mp, °C	Yield,[a] %	Calcd, % C	Calcd, % H	Calcd, % S	Found, % C	Found, % H	Found, % S
3	C_6H_5	C_6H_5	174–175	69	59.70	4.52	15.94	59.59	4.55	15.74
4	C_6H_5	p-C_7H_7	160–160.5	60	60.60	4.84	15.40	60.86	5.10	15.13
5	C_6H_5	p-BrC_6H_4	155–156	59[b]	49.98	3.56	13.35	49.70	3.68	13.20
6	p-ClC_6H_4	C_6H_5	154–155	62[c]	51.00	3.50	13.60	51.22	3.71	13.35
7	p-C_7H_7	C_6H_5	160–161	52	61.40	5.14	14.90	61.20	5.22	14.67

[a] Isolated, purified material, yield not optimized. [b] Br analyses: calcd, 16.58; found, 16.29. [c] Cl analyses: calcd, 15.02; found, 15.00.

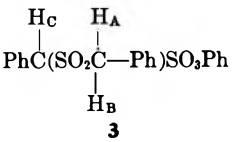
found that when aryl alkanesulfonates (**1**) are treated with potassium *tert*-butoxide in tetrahydrofuran, α-sulfonylation of the sulfonic esters occurs to give **2** in good yield (Table I). This transformation bears a formal

$$\underset{\mathbf{1}}{RCH_2SO_3Ar} + KO\text{-}t\text{-}Bu \xrightarrow[5°]{THF} \underset{\mathbf{2}}{RCH(SO_2CH_2R)SO_3Ar}$$

resemblance to the Claisen condensation of carboxylic esters. Also, there seemingly is only one other reported preparation of an α-alkylsulfonylsulfonate.[2] The latter preparative method, which proceeds through a sulfene dimer, could not be extended to esters of α-toluenesulfonic acids; hence, these two procedures complement one another for the preparation of this novel class of α-sulfonylated sulfonic esters.

The large steric requirements of potassium *tert*-butoxide minimize transesterification.[3] In addition, tetrahydrofuran alone is a desirable solvent; when *tert*-butyl alcohol–tetrahydrofuran was used as a mixed solvent system the yield of condensation product was markedly decreased.[4] It has been suggested that the observed increased reactivity of anions in tetrahydrofuran is due to preferential solvation of the cation.[5] The superiority of phenolic esters in this condensation is illustrated by the substantial recovery of starting material when neopentyl α-toluenesulfonate is subjected to the reaction conditions.

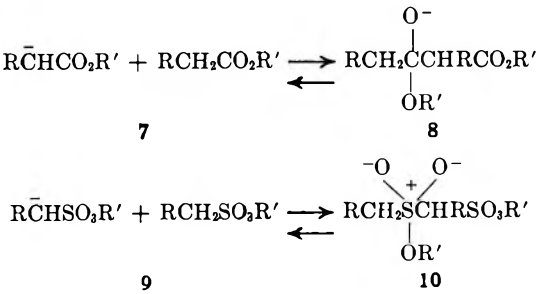
Characterization of the condensation products is based on chemical properties, elemental analyses, molecular weight determinations, infrared spectra and well-defined proton magnetic resonance spectra. The nmr spectrum is especially noteworthy. For compound **3** in



3

deuteriochloroform the methylene protons, H_A and H_B, give rise to a four-line AB pattern centered at δ 4.68 with J_{AB} = 13.8 cps, and the methyne proton, H_C, gives a singlet at δ 5.40. In contrast, the spectrum of **3** in acetone-d_6 consists of a singlet for the methylene protons at δ 4.82 and a singlet at δ 6.41 for the methyne proton. [The solvent dependence of the splitting of the methylene protons (H_A and H_B) may be due to a preferred conformation of the sulfonylsulfonate, which allows intramolecular hydrogen bonding in $CDCl_3$, while in acetone, a better hydrogen-bonding solvent, intermolecular hydrogen bonding negates this conformational preference.] The same nmr solvent dependency was found for the other α-sulfonylsulfonates.

Although this sulfonylation reaction constitutes a sulfonic ester analog of the Claisen condensation, the mechanistic sequences may be different. With carboxylic esters an intermediate such as **8** has experimental support.[6] However, available data relating to similar displacements on sulfonate esters would make a pentacoordinated intermediate, such as **10**, somewhat unlikely.[7] One alternative mechanism would be simple S_N2 displacement by **9** on an unionized ester molecule to afford the product directly. Other mechanisms may also be postulated,[8] however, at this time there is little data available to support such speculation.



7 **8**

9 **10**

Experimental Section

All melting points are uncorrected. The nmr spectra were obtained in $CDCl_3$ or acetone-d_6 using a Varian A-60 spectrometer with TMS = 0. Microanalyses and molecular weight determinations were performed by Dr. C. S. Yeh and staff. Potassium *tert*-butoxide was purchased from MSA Corporation and purified by sublimation. Reagent grade THF was distilled from LAH prior to use. The para-substituted α-toluenesulfonyl chlorides were prepared by known methods and the phenols were used as commercially obtained.

General Procedure for the Preparation of Aryl α-Toluenesulfonates.—To a solution of 0.10 mol of triethylamine (Matheson Coleman and Bell reagent) and 0.10 mol of phenol in 200 ml of benzene under nitrogen at 5–10° was slowly added with cooling and stirring a solution of 0.10 mol of α-toluenesulfonyl chloride in 50 ml of tetrahydrofuran. The mixture was stirred for an additional hour, and the precipitated triethylamine hydrochloride was filtered. The filtrate was washed several times with dilute hydrochloric acid, dried over sodium sulfate, and then

(2) G. Opitz, M. Kleeman, D. Bucher, G. Walz, and K. Rieth, *Angew. Chem., Int. Ed. Engl.*, **5**, 594 (1966). Following completion of our work, a related system was reported by Y. Shirota, T. Nagai, and N. Tokura, *Tetrahedron*, **25**, 3193 (1969).

(3) L. A. Paquette and L. S. Wittenbrook, *J. Amer. Chem. Soc.*, **89**, 4483 (1967).

(4) For example, the yield of product **4** was 60% in THF as compared to 4% in *tert*-BuOH–THF (90:10).

(5) H. Feuer and B. F. Vincent, Jr., *J. Org. Chem.*, **29**, 939 (1964), and references cited therein.

(6) C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, **1**, 266 (1942).

(7) (a) C. A. Bunton and Y. F. Frei, *J. Chem. Soc., London*, 1872 (1951); (b) R. V. Vizgert, *Usp. Khim.*, **32**, 3 (1963); (c) E. T. Kaiser and O. R. Zaborsky, *J. Amer. Chem. Soc.*, **90**, 4626 (1968).

(8) Sulfene ($PhCHSO_2^+$) formation accompanied by its novel trapping *via* the precursory carbanion ($PhCHSO_2Ar$) can be envisioned.

evaporated under reduced pressure. The resulting solid was recrystallized from 95% ethanol to afford white crystalline product.

Phenyl α-Toluenesulfonate.—α-Toluenesulfonyl chloride (19.06 g, 0.10 mol) gave 16.8 g (68%) of phenyl α-toluenesulfonate, mp 84.5–85.5°.

Anal. Calcd for $C_{13}H_{12}O_3S$: C, 62.90; H, 4.85; S, 12.05. Found: C, 62.98; H, 4.98; S, 12.16.

p-Tolyl α-Toluenesulfonate.—α-Toluenesulfonyl chloride (15.0 g, 0.079 mol) afforded 16.2 g (78%) of *p*-tolyl α-toluenesulfonate, mp 87–88°.

p-Bromophenyl α-Toluenesulfonate.—α-Toluenesulfonyl chloride (15.0 g, 0.079 mol) gave 19.3 g (75%) of *p*-bromophenyl α-toluenesulfonate, mp 84–85°.

Phenyl p-Methyl-α-toluenesulfonate.—*p*-Methyl-α-toluenesulfonyl chloride (10.0 g, 0.049 mol) gave 10.5 g (83%) of phenyl *p*-methyl-α-toluenesulfonate, mp 98–99°.

Phenyl p-Chloro-α-toluenesulfonate.—*p*-Chloro-α-toluenesulfonyl chloride (20.2 g, 0.09 mol) afforded 16.0 g (67%) of phenyl *p*-chloro-α-toluenesulfonate, mp 81–82.5°.

General Procedure for the Preparation of α-Sulfonylsulfonates.—To 150 ml of THF under nitrogen at 5–10° was added 0.030 mol of sublimed KO-*t*-Bu. This mixture was allowed to stir for 15 min after which 0.028 mol of the sulfonate ester in 50 ml of THF was added dropwise. After stirring for 8 hr at room temperature, 0.030 mol of glacial acetic acid was added and the mixture filtered. The solid was washed with four 50-ml portions of THF; the combined filtrates were evaporated *in vacuo*. The resulting solid was taken up in chloroform and the chloroform solution washed with three 50-ml portions of water and with 50 ml of a saturated sodium chloride solution and dried over Na_2SO_4 and the chloroform evaporated *in vacuo* leaving a white solid, which was recrystallized from absolute ethanol.

Phenyl α-(Benzylsulfonyl)-α-toluenesulfonate (3).—Phenyl α-toluenesulfonate (7.45 g, 0.030 mol) afforded 4.45 g (69%) of **3** (Table I): nmr (acetone d_6) δ 4.85 (s, 2), 6.40 (s, 1), 7.48 (m, 15); mol wt, calcd, 408; found, 405.

p-Tolyl α-(Benzylsulfonyl)-α-toluenesulfonate (4).—*p*-Tolyl α-toluenesulfonate (10.0 g, 0.039 mol) gave 4.85 g (60%) of **4** (Table I): nmr (acetone-d_6) δ 2.32 (s, 3), 4.77 (s, 2), 6.30 (s, 1), 7.35 (m, 14); mol wt, calcd, 416; found, 422.

p-Bromophenyl α-(Benzylsulfonyl)-α-toluenesulfonate (5).—*p*-Bromophenyl α-toluenesulfonate (10.0 g, 0.0306 mol) gave 4.32 g (59%) of **5** (Table I): nmr (acetone-d_6), δ 4.75 (s, 2), 6.38 (s, 1), 7.45 (m, 14); mol wt, calcd, 487; found, 477.

Phenyl α-(p-Chlorobenzylsulfonyl)-p-chloro-α-toluenesulfonate (6).—Phenyl *p*-chloro-α-toluenesulfonate (7.94 g, 0.028 mol) yielded 4.09 g (62%) of **6** (Table I): nmr ($CDCl_3$) δ 4.75 (q, 2), 5.30 (s, 1), 7.50 (m, 13); mol wt, calcd, 471; found, 475.

Phenyl α-(p-Methylbenzylsulfonyl)-p-methyl-α-methyl-α-toluenesulfonate (7).—Phenyl *p*-methyl-α-toluenesulfonate (6.0 g, 0.23 mol) gave 2.10 g (52%) of **7** (Table I): nmr (acetone-d_6) δ 2.40 (d, 6), 4.75 (s, 2), 6.30 (s, 1), 7.33 (m, 13); mol wt, calcd, 430; found, 428. A small amount of phenyl *p*-methyl-α-toluenesulfonate, 1.00 g (17%), was also recovered.

Attempted Reaction of Potassium *tert*-Butoxide with Neopentyl α-Toluenesulfonate.—Neopentyl α-toluenesulfonate (5.09 g, 0.021 mol) and KO-*t*-Bu (2.80 g, 0.025 mol) were stirred in 100 ml of dry THF under nitrogen at 5° for 14 hr. After careful acidification of the reaction mixture with glacial acetic acid (1.50 g, 0.025 mol), the solution was filtered, the solid was washed with three 50-ml portions of THF and the combined filtrates were evaporated *in vacuo*. The resulting white solid was recrystallized from 95% EtOH to afford 3.86 g (76%) recovery of starting ester.

Registry No.—**3**, 17074-71-4; **4**, 25894-34-2; **5**, 25894-35-3; **6**, 25894-36-4; **7**, 25957-56-6; phenyl α-toluenesulfonate, 10271-81-5; *p*-tolyl α-toluenesulfonate, 25894-38-6; *p*-bromophenyl α-toluenesulfonate, 25894-39-7; phenyl *p*-methyl-α-toluenesulfonate, 25894-40-0; phenyl *p*-chloro-α-toluenesulfonate, 25894-41-1.

Acknowledgment.—Financial support by the Public Health Service under Research Grant No. CA-04536-11 from the National Cancer Institute is gratefully acknowledged.

Formation of an α-Chlorovinylamine and Its Interconversion to a Ketenimmonium Salt

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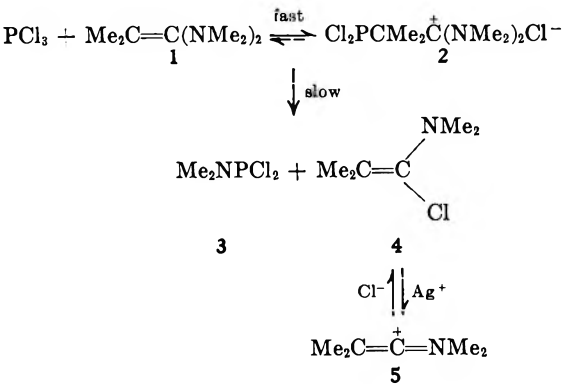
While studying the reactions of enamines with inorganic halides,[1] we observed a reaction that should be of interest to organic chemists. Phosphorus trichloride reacts with 2-methylpropenylidenebisdimethylamine (**1**) to form first a one-to-one complex which we believe to have structure **2** (see Scheme I). The proton nmr of

SCHEME I



2 displays a broadened singlet at τ 6.50 consistent with amidinium *N*-methyl protons and a broadened doublet at τ 7.98 (J = 8.6 Hz) consistent with *C*-methyl protons coupled to phosphorus. Compound **2** was not isolated and is known only by its nmr. This spectrum disappears in 24–72 hr depending on temperature and concentration, and new resonances, a doublet[2] at τ 7.15 (J = 12.5 Hz) and sharp singlets at τ 7.63 and 8.22 in the ratio 1:1:1, are generated. This secondary reaction mixture was separated by preparative vpc into components **3** corresponding to the doublet above and **4** corresponding to the two sharp singlets. Compound **3** was shown to be dichloro(dimethylamino)phosphine by vpc and proton nmr comparison with an authentic sample prepared by equilibrating phosphorus trichloride with tris(dimethylamino)phosphine[3]. Compound **4**, a colorless, distillable, thermally unstable liquid was prepared more conveniently by reaction of **1** with dichlorophenylphosphine. Although the reaction was slower, the products, chloro(dimethylamino)-phenylphosphine and **4**, have sufficiently different volatilities to allow separation *via* simple fractional distillation.

Subtracting the elements of the phosphorus containing products from those of the starting materials permits only a limited number of alternatives for the structure of **4**. Furthermore, hydrolysis of **4** yields *N*,*N*-dimethylisobutyramide which seemed to exclude most reasonable possibilities except the structure shown

(1) H. Weingarten and J. S. Wager, *Chem. Commun.*, 854 (1970).

(2) Demonstrated by decoupling experiments on a Varian Model HA-100 spectrometer.

(3) J. R. Van Wazer and L. Maier, *J. Amer. Chem. Soc.*, **86**, 811 (1964).

in Scheme I, but the observed nmr spectrum of two sharp singlets seemed inconsistent with this structure, which apparently requires three lines. However, if **4** were shown to be ionizing rapidly and reversibly to structure **5** the nmr spectrum could be rationalized.

Low temperature nmr in chloroform showed substantial broadening of the peak at τ 8.22 consistent with the ionization hypothesis. It was subsequently observed that when the nmr of **4** was examined in nonpolar solvents the peak attributed to the *C*-methyl protons was split into the expected pair of quartets, even at normal probe temperatures, confirming structure **4**.[4]

Finally, it was of interest to know if **5**, previously proposed as a reaction intermediate,[5] could be observed directly. To this end a 5% solution of **4** in acetonitrile-d_3 was treated with increasing amounts of $AgPF_6$. Silver chloride was precipitated and the nmr peaks of **4** were broadened and displaced downfield, the peak attributed to the *N*-methyl protons being the most influenced. In the presence of excess silver ion, two new sharp singlets appear at τ 6.48 and 8.02 in agreement with structure **5**. Compound **5**, which has a half-life of *ca.* 10 min under the experimental conditions, can be reconverted to **4** by addition of anhydrous tetrabutylammonium chloride.

It is not known if **3** and **4** arise *via* rearrangement of **2** or direct reaction of starting materials, although the latter appears more attractive.

Experimental Section

General.—Proton nmr spectra were obtained from a Varian Model T60 or A-56/60 spectrometer, the latter equipped with a variable temperature probe. Elemental analyses were performed in the Physical Sciences Center, Central Research Department, Monsanto Co. All reactions were carried out in an atmosphere of dry nitrogen.

Preparation of 1-Chloro-*N*,*N*,2-trimethylpropenylamine (4).—To a solution of 2.7 g (0.015 mol) of dichlorophenylphosphine in 10 ml of chloroform was slowly added a solution of 2.0 g (0.014 mol) of **1** in 5 ml of chloroform. The resulting solution was allowed to stand at room temperature for 14 days, while monitoring the progress of the reaction by proton nmr. At the end of this period the solvent was removed and the more volatile portion of the residue was distilled into a Dry Ice trap, yielding 1.4 g (75%) of **4**: bp 40° (25 mm); nmr ($DCCl_3$) τ 7.63 (s, 1), 8.22 (s, 1).

Anal. Calcd for $C_6H_{12}NCl$: C, 53.9; H, 9.1; N, 10.5; mol wt, 133. Found: C, 53.7; H, 9.3; N, 10.2; mol wt, 133 (mass spectrum).

When a solution of **4** in acetonitrile-d_3 was treated with a small amount of water, the nmr spectrum immediately changed to that of *N*,*N*-dimethylisobutyramide.[6]

Proton Nmr Study of 1-Chloro-*N*,*N*,2-trimethylpropenylamine (4).—An nmr spectrum of **4** (5% in chloroform) changed in the following way as the temperature was decreased. The width at half height changed, in going from +36° to −75°; for the tetramethylsilane resonance from 0.38 Hz to 0.44 Hz; for the resonance at τ 8.22 (CH_3-C) from 0.46 Hz to 2.60 Hz; and for the resonance at τ 7.63 (CH_3-N) from 0.42 Hz to 1.00 Hz.

In toluene-d_8 or benzene, the *C*-methyl resonance becomes two quartets[7] centered at τ 8.29 and 8.31 (*J ca.* 0.4 Hz) at normal probe temperature.

Registry No.—4, 26189-59-3; **5,** 26189-60-6.

(4) Several α-chloroenamines have been reported: see A. J. Speziale and R. C. Freeman, *ibid.*, **82**, 903 (1960); E. Ott, G. Dittus, and H. Weisenburger, *Chem. Ber.*, **76**, 84 (1943).

(5) C. F. Hobbs and H. Weingarten, *J. Org. Chem.*, **33**, 2385 (1968).

(6) The nmr spectrum of *N*,*N*-dimethylisobutyramide in acetonitrile-d_3 is sensitive to acid concentration.

(7) The spectra are sensitive to tetramethylsilane concentration and the values reported are for 10% tetramethylsilane solutions.

A Simple Preparation of "Active" Manganese Dioxide from "Activated" Carbon

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In view of the usefulness[1] of "active" manganese dioxide as an oxidant in organic chemistry, it is unfortunate that current methods of preparing or "activating" this material are experimentally so tedious. By accident we noted that ordinary decolorizing carbon discharges the purple color of aqueous permanganate solutions with the precipitation of a brown-black powder, presumably manganese dioxide, on the excess carbon.[2] Whether because of the nature of the material precipitated in this way or the presence of excess carbon, the powder can be filtered rapidly and washed with ease in a few minutes on an ordinary Büchner funnel.[3] We have used this mixture routinely for several years in the oxidation of a variety of hydrazine derivatives (hydrazones, hydrazo compounds, 1,1-disubstituted hydrazines) and find it to be as effective for such purposes as the MnO_2 oxidants previously described.[6] Drying the oxidant mixture in an oven at 105–110° for 8–24 hr increases its activity to the point where its effectiveness in the oxidation of allylic and benzylic alcohols appears comparable with that of the material described by Attenburrow and coworkers. Some results are listed in Table I. Since we have not

TABLE I

OXIDATION OF CINNAMYL ALCOHOL[a]

Oxidant	% cinnamaldehyde after 30 min
MnO_2–C, BP, air-dried[b]	30–35
MnO_2–C, BP, oven-dried[b]	46–51
MnO_2–C, RT, air-dried[c]	48–54
MnO_2–C, RT, oven-dried[c]	82–91

[a] Test oxidations were carried out by stirring, at room temperature, a solution containing 0.5 g of cinnamyl alcohol in 5.5 g of benzene and 19 g of ligroin (bp 30–60°) with 5.0 g of the oxidant. Extent of conversion to the aldehyde was determined by infrared analysis according to the method of R. J. Gritter and T. J. Wallace, *J. Org. Chem.*, **24**, 1051 (1959). [b] Precipitated at the boiling point of the solution (method A). [c] Precipitated at room temperature (method B). The increased activity of the oxidant mixture obtained by precipitation at room temperature is at the expense of slightly reduced ease of filtration.

(1) For pertinent reviews see (a) O. Meth-Cohn and H. Suschitzky, *Chem. Ind. (London)*, 443 (1969); (b) S. P. Korshunov and L. I. Vereshchagin, *Russ. Chem. Rev.*, **35**, 942 (1966); (c) R. M. Evans, *Quart. Rev. (London)*, **13**, 61 (1959).

(2) We have no evidence as to the exact composition of the material precipitated but assume it to be a mixture of MnO_2 and unoxidized carbon. Elemental analysis of an air-dried sample of the oxidant obtained on the scale given in method A showed the presence of about 20% carbon.

(3) In the most common procedure[4] for the preparation of active manganese dioxide, a thick paste is obtained which is most easily collected and washed by repeated centrifugation. Activation by azeotropic removal of water through distillation of a suspension in benzene has recently been recommended.[5]

(4) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(5) I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).

(6) Details regarding the oxidation of benzalhydrazone to phenyldiazomethane (50–70%), 1,1-disubstituted hydrazines to hydrocarbon products, and hydrazo compounds to azo compounds will be described separately.

directly compared our oxidant with previous preparations, except in the case of the nitrogen compounds mentioned above, it remains for interested investigators to determine its suitability for various specific purposes.

Experimental Section

A.—A solution of 20 g of potassium permanganate in 250 ml of water contained in a 600-ml beaker was heated to the boiling point, removed from the source of heat, and treated portionwise over 5–7 min with 6.25 g of activated carbon.[7] The frothing was allowed to subside between additions. After complete addition of the carbon the mixture was boiled for 2–4 min until the purple color was completely discharged, allowed to stand at room temperature for 10–15 min and filtered on a Büchner funnel. The precipitate was washed four times with 50-ml portions of water and spread out to dry in the air. The air-dried material amounted to 22.2 g. After drying in an oven at 105–110° for 8–24 hr, the weight dropped to 18.7 g. After either air- or oven-drying, the oxidant was obtained as a fine powder which could be used directly without grinding.

B.—A solution of 20 g of potassium permanganate in 250 ml of water was stirred at room temperature with 10 g of activated carbon for 16 hr. Filtration and drying as in A gave 26.5 g of the air-dried or 22.2 g of the oven-dried oxidant.

Registry No.—Manganese dioxide, 1313-13-9; carbon 7440-44-0.

Acknowledgment.—This work was carried out under the support of the National Science Foundation under Grants GP-4283 and 10152.

(7) Since it was on the shelf at the time this work was initiated, we have generally used activated carbon supplied by the J. T. Baker Co., Phillipsburg, N. J. Unfortunately this material, which proved to be the most active of all the carbon samples tested, was subsequently removed from the market. Some commercial samples of activated carbon were completely unreactive toward permanganate under the conditions studied. Of the various carbons tested to date, Nuchar C-190N appeared to give the best results, nearly comparable to those obtained with the J. T. Baker material. In general the "fluffy" carbons are effective whereas the dense ones are not. Effective, although yielding an oxidant less active than that obtained from J. T. Baker or Nuchar C-190N (possibly an advantage in the oxidation of some nitrogen compounds), were the following: Darco G-60 and Mallinckrodt USP. Ineffective were Fisher C-263 and Norit-neutral.

On the Thermal and Free-Radical Reactions of Pyruvyl Chloride and Benzoylformyl Chloride

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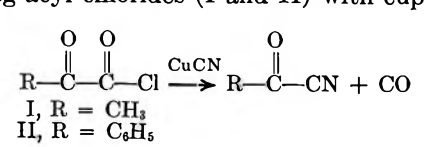
During the attempted synthesis of pyruvyl cyanide and benzoyl formyl cyanide from the reaction of the corresponding acyl chlorides (I and II) with cuprous cyanide, a reaction purported to be successful with other acid halides,[2a-c] it was found that only acetyl cyanide or benzoyl cyanide could be obtained. Since both benzoyl chloride and acetyl chloride will form acyl cyanides under these conditions,[2] the fragmentation of the corresponding keto acyl chlorides to form their acid chlorides was investigated.



I, R = CH_3
II, R = C_6H_5

Carbon tetrachloride solutions (0.2 *M*) of I were shown to undergo a free-radical chain fragmentation to yield acetyl chloride. The fragmentation could be initiated thermally (140°), or, under conditions where the keto acid chloride was stable, I could be converted to its acid chloride by photolysis (40°), by trace initiation with benzoyl peroxide (5%, 98°), or with AIBN (3%, 40°).

On the basis of its initiation by light and by benzoyl peroxide or AIBN the fragmentation reaction can be postulated as a chain sequence[3] (Scheme I).

SCHEME I

$$In\cdot + CH_3COCOCl \longrightarrow CH_3COCO\cdot + InCl$$
$$CH_3COCO\cdot \longrightarrow CH_3CO\cdot + CO$$
$$CH_3CO\cdot + CH_3COCOCl \longrightarrow CH_3COCl + CH_3COCO\cdot$$

In cyclohexane the reaction took a somewhat different course; not only was acetyl chloride produced but also a series of radical displacement reactions on I yielded as products cyclohexanecarboxylic acid chloride, cyclohexyl methyl ketone, and cyclohexyl chloride (see Table I). In addition to the products listed in Table I, a significant quantity of gaseous material was produced during the reaction. These products could be fractionated by standard vacuum line procedures. Analysis of the gaseous products obtained from the photoinduced reaction of a solution of pyruvyl chloride (1.00 mmol) in cyclohexane (see Table I) showed hydrogen chloride (0.10 mmol), methane (0.41 mmol), and carbon monoxide (1.00 mmol). A combination of the yields of both the gaseous and nongaseous products constituted, within experimental limits, a quantitative material balance for the initial pyruvyl chloride.

TABLE I

PRODUCTS FROM THE INITIATED REACTION OF PYRUVYL CHLORIDE (0.2 *M*) IN CYCLOHEXANE

		Products, %			
Initiator	Temp, °C	CH_3COCl	$C_6H_{11}COCH_3$	$C_6H_{11}COCl$	$C_6H_{11}Cl$
Benzoyl peroxide (5%)	98	50.3	10.0	39.5	3.0
Light	40	54.3	10.2	35.5	5.0
AIBN (8%)	40	75	3	17	Trace

On the basis of the products, the excellent material balance obtained, and the trace initiation observed, and by analogy to the reactions in cyclohexane of this system with those of oxalyl chloride[4] and biacetyl,[5] the following chain propagating steps are proposed to rationalize the observed reactions (see Scheme II). The inclusion in the mechanism of the propagation steps contained in Scheme I with those of Scheme II constitutes a plausible explanation for the initiated reactions of pyruvyl chloride in cyclohexane.

The competitive attack of the cyclohexyl radical on the carbonyl adjacent to the electron-donating methyl

* Author to whom correspondence should be addressed.

(1) Postdoctoral Fellow, University of Alberta, 1968–1969.

(2) (a) T. S. Oakwood and C. A. Weisgerber, "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 112; (b) H. Sutter, *Justus Liebigs Ann. Chem.*, **499**, 47 (1932); (c) L. Claisen, *Ber.*, **31**, 1023 (1898).

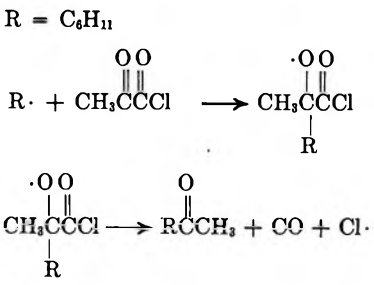
(3) The possible inclusion of a chain transfer sequence with solvent has been suggested by the referee to account for the smooth conversion of I to acetyl chloride.

(4) M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **64**, 329 (1942).

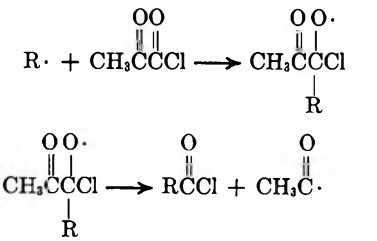
(5) W. G. Bentrude and K. R. Darnall, *ibid.*, **90**, 3588 (1968).

SCHEME II

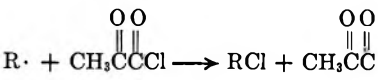
Step a



Step b



Step c



group or upon the one adjacent to the electron-withdrawing chlorine, is reflected, if one assumes that the addition of the cyclohexyl radical to either carbonyl is irreversible, in the ratio of carbonyl substituted cyclohexanes found. The preference for the addition of the alkyl radical to the electron deficient carbonyl is evident from the 1:3.8 ratio of cyclohexyl methyl ketone–cyclohexyl carboxylic acid chloride, the products obtained from the β-scisson of the corresponding radicals.[6]

Solutions of benzoylformyl chloride (0.2 M) in chlorobenzene at 120° were quantitatively converted to benzoyl chloride and carbon monoxide. This reaction could not be inhibited with iodine (5%), 1,3,5-trinitrobenzene (5%), or with molecular oxygen. Under conditions where the keto acid chloride (II) was found to be stable, 80°, in oxygen-free solutions of carbon tetrachloride or chlorobenzene, neither photolysis nor small amounts of benzoyl peroxide (5%) or AIBN (5%) initiated the fragmentation. In degassed solutions of cyclohexane, benzoylformyl chloride (0.2 M) could be initiated with 20% benzoyl peroxide to give low yields of cyclohexyl chloride (10%), cyclohexylcarbonyl chloride (5%), and benzoyl chloride (10–15%) as the only identifiable volatile products other than the unreacted keto acid chloride. Prolonged photolysis (5 days, 40°) of the same solutions yielded almost identical results.

Contrary to the results obtained with pyruvyl chloride, attempts to initiate the radical chain fragmentation of II either chemically or photochemically were unsuccessful, and the thermal fragmentation was not inhibited by several common inhibitors. These results suggest that the thermal fragmentation of II may not be a free-radical chain reaction but may be a molecular decomposition, although only negative evidence supports this proposal.

It was instructive to note that the initiated reactions of II in cyclohexane, although definitely not long-chain processes, did produce cyclohexylcarbonyl chloride resulting, presumably, from attack of a cyclohexyl radical on II at the carbonyl adjacent to the electron-withdrawing chloride. This behavior is consistent with the observed preference for attack of the cyclohexyl radical at the more electron-deficient carbonyl group of I. The lack of product, cyclohexyl phenyl ketone, resulting from an attack of the radical on the carbonyl adjacent to the phenyl group is likewise in keeping with the absence of a similar type of radical addition β scission reported for the attempted initiated reaction of benzil with cyclohexane.[5]

(6) An investigation is now in progress on the electronic effects operative in similar carbonyl addition reactions: private communication from Professor W. G. Bentrude.

Experimental Section

Materials.—Cyclohexane (Philips research grade) was used without further purification. Carbon tetrachloride, reagent grade, was distilled before use. All reagents were checked for purity by glpc using a 10 ft × 0.25 in. stainless steel column packed with 10% SE-30 on Chromosorb W. All of the analyses in this study were carried out with this column.

Pyruvyl Chloride (I).—To a cold, 0° mixture of anhydrous sodium carbonate (10.6 g, 0.1 mol), anhydrous dimethylformamide (0.1 ml), and pyruvic acid (17.6 g, 0.2 mol) in 125 ml of dry ether was slowly added (2 hr), a solution of oxalyl chloride (25.4 g, 0.2 mol) in 25 ml of dry ether. This reaction mixture was then allowed to warm to room temperature and was stirred for 24 hr. The reaction mixture was filtered and the filtrate was fractionated using a teflon annular spinning-band column. The fraction boiling at 75–80° (lit.[7] bp 75–80°) was pyruvyl chloride (5.30 g, 25%). The material was shown to be free of starting material and to be one compound by glpc analysis. The ir showed only two carbonyl absorptions at 5.60 and 5.70 μ.

Benzoylformyl Chloride.—Benzoylformic acid (15.0 g, 0.1 mol) and oxalyl chloride (51.0 g, 0.4 mol) were heated to reflux for 6 hr. The excess oxalyl chloride was removed by distillation at atmospheric pressure and the benzoylformyl chloride was distilled under reduced pressure, 90–92° (10 mm) [lit.[4] bp 91° (9.5 mm)], yield 12.8 g (78%).

The product was shown to be free of starting materials by glpc analysis and showed only one peak on its glpc chromatogram. The ir showed only two carbonyl absorptions at 5.65 and 5.90 μ.

Reactions of Pyruvyl Chloride (I).—Solutions of I (0.2 M) and chlorobenzene (0.2 M) in carbon tetrachloride or cyclohexane were sealed in degassed Pyrex ampoules or break-seals with the desired initiator or inhibitor and the reaction mixtures were subjected to the appropriate reaction conditions.

The fragmentation reactions carried out in carbon tetrachloride could be followed by the disappearance of the carbonyl absorptions of I at 5.60 and 5.70 μ, and the appearance of the spectrum of acetyl chloride (C=O, 5.50 μ). The reactions could also be monitored by glpc analysis. Both methods were consistent within experimental error.

The decompositions carried out in solvent cyclohexane were monitored and quantitated by glpc analysis. The liquid products were identified by a comparison of their glpc retention times and ir spectra with those of authentic samples.

In order to analyze the gaseous products, the reactions were carried out in break-seals (0.02 M, 5 ml). After the completion of the reactions, the break-seals were opened to a vacuum line and the gases were distilled through a −80° trap to collect the hydrogen chloride gas. The methane and carbon monoxide were collected and measured using a Toepler pump. The HCl was absorbed in standard aqueous base and determined by back titrating. Methane and carbon monoxide were found by glpc retention time (6 ft-column of molecular sieve 5A) to be the only two noncondensable gases. The ratio of methane and carbon monoxide was determined by quantitative mass spectrometry (AEI, Model MS-9 spectrometer).

Reactions of Benzoylformyl Chloride (II).—The reactions of II (0.2 M) in chlorobenzene or cyclohexane were carried out and monitored as were those of I. The ir method of analysis utilized the ability to follow the disappearance of the carbonyl absorption frequencies of II (C=O, 5.90, 5.65) and the appearance of

(7) Pierre-Carré and P. Jullien, *C. R. Acad. Sci., Ser. C*, **202**, 1521 (1936).

the spectrum of benzoyl chloride (C=O, 5.60). The decomposition products of II were analyzed and characterized as were those of I.

Registry No.—I, 5704-66-5; II, 25726-04-9.

Acknowledgments.—The authors wish to thank the National Research Council of Canada and the University of Alberta for their generous support of this work.

The Alumina-Catalyzed Condensation of 9-Carbazolylacetaldehyde[1]

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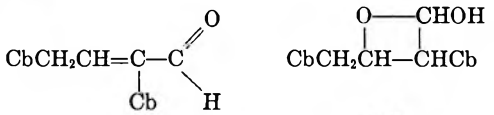
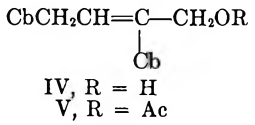
The literature contains few examples of the condensation of aldehydes or ketones catalyzed by alumina.[3] During a study of the decarbonylation of 9-carbazolylacetaldehyde[4] (I), we found that, when this aldehyde is passed through a chromatographic column prepared with neutral alumina (activity grade I), it undergoes facile conversion to 2,4-dicarbazol-9-yl-2-butenal (II) (20%) and to an alcohol III (7%), which was assigned the novel structure III, along with considerable polymeric solid.



II III

(Cb = 9-carbazolyl)

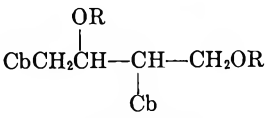
Structure II was assigned on the basis of information obtained from its mass, infrared, and nmr spectra and by conversion to derivatives which were characterized by similar techniques (see Table I). Reduction of II with sodium borohydride in 80% aqueous dioxane gave an alcohol IV (76%) which when treated with pyridine–acetic anhydride gave the monoacetate V (76%).



IV, R = H
V, R = Ac

The elucidation of the structure of III was difficult owing to its very low solubility in conventional solvents. Its structure is based in part on spectroscopic data and the properties of its derivatives given in Table I. Purified III gave one spot by tlc, a correct analysis for $C_{28}H_{22}N_2O_2$, and an ir spectrum which is consistent with the proposed structure. In addition, mass spectroscopy gave a molecular weight of 418 and a fragmentation pattern similar to that of the dehydrated form II. The reaction of III with base yielded, on neutralization, carbazole (27%), a small amount of II, and considerable amorphous solid. The isolation of II from these hydrolyses confirms the conclusions reached from the mass spectral data and establishes the presence of the carbon skeleton of II as part of structure III. Evidently, the reaction of III with base causes the oxetane ring to open with the simultaneous formation of an aldehyde group which activates the carbazole bearing 2 position toward nucleophilic attack.

This possibility was supported when the hydrolysis of III was carried out under reducing conditions with sodium borohydride. Under these conditions the aldehyde group was reduced as it formed yielding the diol VI (90%) which gave a negative periodic acid test as expected. The diacetate VII was prepared as usual with pyridine and acetic anhydride.



VI, R = H
VII, R = Ac

The amorphous solid obtained in the column reaction could not be separated into components by either chromatography, sublimation, or attempted recrystallization. Its infrared spectrum was identical with that of the polymeric material obtained by the acid-catalyzed condensation of I.

When III was acetylated, an acetate (VIII) formed (67%) which had a saponification equivalent consistent with the monoacetate of III and showed a single acetate carbonyl peak in the ir spectrum and one acetate peak in the nmr spectrum. The saponification yielded the same products as did the treatment of III with base.

The mass spectrum of VIII had a fragmentation pattern very similar to that of III except for the parent peak of III at *m/e* 418 and a peak at *m/e* 669 (8.1%). We have not yet identified the latter peak but it seems reasonable to assume that it is due to some decomposition product which could have formed at the near decomposition temperature (about 300°) required to vaporize this sample.[5]

In an effort to obtain further confirmation of the molecular weight of III, cryoscopic and ebullioscopic molecular weight determinations were attempted. Unfortunately, these attempts were not successful due to the low solubility of III and its low stability. In hot solvent (about 90°) nmr showed extensive decomposition in a matter of minutes; at room temperature under dry nitrogen, degradation became apparent by elemental analysis after a few weeks.

The mechanism of this reaction appears to be an acid-catalyzed aldol condensation which must occur in this system because of high attraction of the carbazole nucleus for the activated alumina surface[6] and the increased stability of the enol form of the aldehyde due to its conjugation with the heteroaromatic ring system. In strongly acidic solutions the condensation proceeds rapidly to produce an insoluble material even at temper-

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(1) Presented in part at the Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 14, 1968.

(2) American Hoechst Fellow, 1967–1968.

(3) For room temperature reactions, see A. M. Kuliev, A. M. Levshina, and A. G. Zul'fugarova, *Azerb. Khim. Zh.*, No. 5, 29 (1959); *Chem. Abstr.*, **59**, 2638*a* (1963); also, K. Tanabe and Y. Morisowa, *Chem. Pharm. Bull.* **11**, 536 (1963).

(4) Synthesis reported in B. M. Vittimberga and M. L. Herz, *J. Org. Chem.*, **35**, 3694 (1970).

(5) We had also considered the dimer of structure III as a possibility for III, but this seems unlikely because of the absence of a complicated fragmentation pattern above *m/e* 400.

(6) E. Funakubo, T. Nagai, and J. Moritani, *Kogyo Kaguku Zasshi*, **65**, 782 (1962); *Chem. Abstr.*, **59**, 1445*g* (1963). Also, E. Funakubo, T. Nagai, and G. Kon, *Kogyo Kagaku Zasshi*, **66**, 33 (1963); *Chem. Abstr.*, **59**, 12145*f* (1963).

TABLE I
PHYSICAL PROPERTIES[a]

Compd	Formula	Mp, °C	M	Ir, cm⁻¹	Nmr, τ
I	$C_{14}H_{11}NO$	140.5–141.5	209[b]	2850 (ald C—H) 1730 (C—O)	0.37 (t, 1, J = 4.0 Hz), 2.5 (m, 8) 5.24 (d, 2, J = 4.0 Hz) ($CDCl_3$)
II	$C_{28}H_{20}N_2O$	172–174	400[b]	2820, 2730 (ald C—H) 1690 (C=O) 1640 (C=C)	0.42 (s, CH=O), 2.50 (m, Cb protons), 3.10 (t, J = 6.6 Hz, CH=) 5.06 (d, J = 6.6 Hz, CH_2) (acetone-d_6)
III	$C_{28}N_{22}N_2O_2$	221–226	418[b]	3535 (OH) 1220, 1150, 1115 (C—O)	2.5 (m, Cb protons). broad unresolved bands between 6.6 and 3.1, 8.0 (s, weak, OH) (nitrobenzene-d_5)
IV	$C_{28}H_{22}N_2O$	164–165		3270 (O—H) 1675 (C=C) 1060 (C—O)	2.5 (m, 16), 3.59 (t, 1, J = 6.0 Hz, CH=), 5.24 (d, 2, J = 6.0 Hz), 5.5 (s, 2), 8.39 (s, 1, OH) ($CDCl_3$)
V	$C_{30}H_{24}N_2O_2$	145.5–146.5	441.5[c]	1745 (C=O) 1665 (C=C) 1215, 1025 (C—O)	2.5 (m, 16), 3.59 (t, 1, J = 6.4 Hz), 4.09 (s, 2), 5.31 (d, 2, J = 6.4 Hz), 8.20 (s, 3)($CDCl_3$)
VI	$C_{28}H_{24}N_2O_2$	218–220		3400 (OH) 1150, 1110 (C—O)	Complex splitting between 6.6 and 3.0 (6 protons), 2.5 (m, 16), 8.01 (s, 2, OH) ($CDCl_3$)
VII	$C_{32}H_{28}N_2O_4$	192.5–194.5		1745 (d, C=O) 1230, 1050 (C—O)	Two regions of complex splitting at 6.65–4.65 (m, 5) and 4.0–1.7 (m, 17), acetate protons at 8.43 (s, 3), 8.30 (s, 3) ($CDCl_3$)
VIII	$C_{30}H_{24}N_2O_3$	295 dec	462[c,d]	1750 (C=O) 1225, 1120 (C—O)	2.5 (m, Cb protons), broad unresolved bands between 8.4 and 3.6, 8.73 (s, strong) (pyridine-d_5, 100 Mc)

[a] All spectra were taken in KBr. New compounds gave elemental analyses that were within 0.30% of the theoretical value for C, H, and N except for II and V which after many recrystallizations analyzed correctly for N but were off 0.5% in C and H. [b] By mass spectroscopy. [c] By saponification equivalent. [d] No resolution of parent peak.

atures about 10°. In contrast to this, the aldehyde I was recovered unchanged after 3 days at reflux in alcoholic potassium hydroxide solution. These facts support a mechanism involving acid catalysis.

The column appears to have two functions: (1) it catalyzes the reaction, and (2) it prevents the complete conversion of the aldehyde to polymeric materials. The alumina, in effect, dilutes the aldehyde by allowing reaction to occur only at separated active sites, thereby causing a localized dimerization reaction. The aldol, which could not be isolated, must dehydrate to II or react to form III. Though structure III seems energetically unlikely, it might be the result of distortion in the molecule caused by the steric repulsion of the large carbazolyl groups. A study of the mechanism of this reaction with aromatic systems is in progress and will be reported subsequently.

Experimental Section

All melting points are corrected and were determined on a Thomas–Hoover melting point apparatus. The nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 spectrometer at 60 Mc unless otherwise indicated using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide on either a Beckman IR-8 or a Perkin-Elmer Model 521 spectrophotometer. The microanalyses were performed by Micro-Analysis, Inc., Wilmington, Del.

The Reaction of I with Alumina.—The 9-carbazolylacetaldehyde (5.0 g, 0.24 mol) was passed over 60 g of aluminum oxide (Woelm neutral, activity I, pH 7.5) using eluents of increasing polarity from benzene to methanol. The earlier fractions contained II (~20%) and III (~7%) while in the later fractions these were mixed with a red amorphous solid. These compounds were separated by fractional recrystallization from ethanol. The amorphous solid formed in this reaction gave an ir spectrum which is essentially the same as that for the solid formed by acid-catalyzed polymerization (*vide infra*) of 9-carbazolylacetaldehyde. Its nmr spectrum (in acetone-d_6) showed strong carbazole type aromatic proton resonance (τ 2.5) with broad unresolved absorption between τ 4.1 and 7.1, and three weak peaks about τ 8.9. The acetate, VIII, was prepared by heating III (100 mg, 2.4×10^{-4} mol) in 5.0 ml of pyridine (dried over sodium hydroxide) and 3.0 ml (3.24 g, 0.032 mol) of acetic anhydride on a steam bath for 1.5 hr to give a precipitate. The mixture was poured over crushed ice and solids were removed by suction filtration, washed with 2% hydrochloric acid, and finally washed thoroughly with water. The acetate was recrystallized from 2-butanone to give white crystals (0.074 g, 1.6×10^{-4} mol, 67%). The saponification of this acetate or the treatment of III (100 mg) with base followed by neutralization produced a precipitate in ~100% yields. The precipitate was resolved on a silica column to yield 30 mg of carbazole, 10 mg of II, and amorphous solid.

The Reduction of II by Sodium Borohydride.—To a stirred solution of 0.350 g (8.7×10^{-4} mol) of II in 25 ml of 80% aqueous dioxane at 0° was added 0.050 g (1.3×10^{-3} mol) of sodium borohydride. This was followed immediately by 6 drops of 20% sodium hydroxide solution and the resulting solution was stirred for 1 hr. Then it was allowed to warm to room temperature at which point it was made slightly acid to litmus with 20% acetic acid and was poured into 200 ml of water. Stirring produced a curdy precipitate which was separated by filtration and washed thoroughly with water. The crude material was recrystallized from carbon tetrachloride to yield 0.265 g of IV (6.6×10^{-4} mol, 76%).

The monoacetate V was prepared by the procedure used to produce the acetate of III (76% yield).

Reduction of III by Sodium Borohydride.—The hemiacetal, III, was reduced as was described above for the reduction of II to yield, after repeated recrystallization from ethanol, VI (37%). The diacetate VII was prepared in 95% yield by the procedure described above for the esterification of III.

The Acid-Catalyzed Condensation of I.—The aldehyde (1.0 g, 4.8×10^{-3} mol) was dissolved in a stirred, cooled solution of 25 ml of acetic acid and 0.77 ml (1.4 g, 1.4×10^{-2} mol) of sulfuric acid. The starting material was completely converted over a period of 24 hr to a highly insoluble grayish precipitate. The product was repeatedly extracted with carbon tetrachloride

to give a green material which decomposed at ~375°: ir 3410 (O—H), 1750 (C—O), 1205, 1150, and 1120 cm^{-1} (C—O).

Registry No.—I, 25557-77-1; II, 25894-27-3; III, 25894-28-4; IV, 25894-29-5; V, 25894-30-8; VI, 25894-31-9; VII, 25894-32-0; VIII, 25894-33-1.

Acknowledgments.—We thank Dr. Charles Merritt, Jr., and his group at the U. S. Army Natick Laboratories, Natick, Mass., and Mr. Donald L. Travis of Varian Associates for the mass spectra determinations.

Cyclohexadienyl Cations. II. Evidence for a Protonated Cyclohexadienone during the Dienone–Phenol Rearrangement[1,2]

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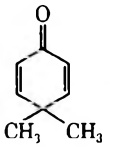
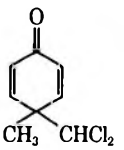
In an earlier paper[1] we suggested that the oxygen-protonated cyclohexadienone formed from 4-dichloromethyl-4-methylcyclohexadienone (2) in concentrated acid could be considered a good model for the first intermediate in the dienone–phenol rearrangement.[4] The structure of this ion as well as its equilibrium acidity dependence in concentrated acid solution was firmly established.[1,5] While this suggestion seemed entirely reasonable, it lacked force because of the demonstrated reluctance of 2 to undergo the dienone–phenol rearrangement. Thus, even at 60° in 80% sulfuric acid, 2 rearranges only slowly (half-life ~ 24 hr) to afford a mixture of two rather unusual products.[6]

In this paper, we would like to report the results of a similar investigation on a closely related system, 4,4-dimethylcyclohexadienone (1). This substrate does undergo the dienone–phenol rearrangement rapidly at 25° in 70% perchloric acid to form a single major product, 3,4-dimethylphenol, in >90% yield. Thus, we reasoned that the detection of a protonated cyclohexadienone during the isomerization of this substrate would not suffer from the deficiencies noted above for 2.



1



2

Results and Discussion

1 was prepared in a straightforward manner by condensation of the pyrrolidine enamine of isobutyraldehyde with methyl vinyl ketone.[7,8] The resulting 4,4-dimethylcyclohexenone was oxidized to the corresponding dienone using 2,3 dichloro-5,6-dicyanobenzoquinone in refluxing carbon tetrachloride.

The uv spectrum of 1 in water is characteristic of a $\Delta^{2,5}$-cyclohexadienone.[9] However, in concentrated sulfuric or perchloric acid solution the spectrum is completely different and nearly identical with that produced by dissolving 2 in concentrated sulfuric acid. These results are summarized in Table I.

TABLE I
ULTRAVIOLET SPECTRAL PROPERTIES OF NEUTRAL AND PROTONATED CYCLOHEXADIENONES

Dienone	Solvent	λ_{max} (nm)	Log ϵ
1	H_2O	235	4.17
2[a]	H_2O	238	4.15
1	71.0% $HClO_4$	260, 295	4.12, 3.57
2[a]	90.5% H_2SO_4	262, 294	4.12, 3.56

[a] Data from ref 1.

The long wavelength band of the species formed by protonation of 1 can be used to monitor its concentration as a function of acid concentration. The results of such an investigation for solutions of 1 in both sulfuric and perchloric acids are reported in Tables II and III.

TABLE II
EQUILIBRIUM PROTONATION DATA FOR 1 IN $HClO_4$ AT 25.3°

Absorbance[a]	Wt % of $HClO_4$	$[DH^+]/[D]$[b]	$-H_0$[c]
0.215	41.03	0.157	2.26
0.355	44.35	0.292	2.81
0.573	47.61	0.576	3.18
0.812	50.50	1.076	3.55
1.058	53.55	2.07	4.00
1.200	56.44	3.26	4.47
1.395	59.03	8.08	5.02
1.605	64.16		6.26
1.538	68.83		7.45
1.542	70.95		8.01

[a] At 295 nm, concentration 4.12×10^{-4} M, cell path 1 cm. [b] Ratio of concentrations of protonated $[DH^+]$ to neutral [D] species. [c] H_0 values from K. Yates and H. Wai, *Can. J. Chem.*, **43**, 2131 (1965).

TABLE III
EQUILIBRIUM PROTONATION DATA FOR 1 IN H_2SO_4 AT 25.3°

Absorbance[a]	Wt % of H_2SO_4	$[DH^+]/[D]$[b]	$-H_0$[c]
0.149	36.28	0.102	2.15
0.276	42.10	0.200	2.57
0.445	46.57	0.383	3.01
0.668	51.75	0.712	3.56
0.842	54.34	1.100	3.84
1.188	60.07	2.83	4.46
1.402	65.02	6.82	5.09
1.633	94.70		9.79
1.583	94.70		9.79

[a] At 295 nm, concentration 4.12×10^{-4} M, cell path 1 cm. [b] Ratio of concentrations of protonated $[DH^+]$ to neutral [D] species. [c] H_0 values from M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963).

(1) Part I: V. P. Vitullo, *J. Org. Chem.*, **34**, 224 (1969).

(2) Presented in part at the 157th National Meeting of the American Chemical Society, April 1969, Minneapolis, Minn., Abstract ORGN 163.

(3) Address all correspondence to Department of Chemistry, University of Maryland, Baltimore, Md. 21228.

(4) For a discussion of possible mechanisms of the dienone–phenol rearrangement, see A. J. Waring, *Advan. Alicycl. Chem.*, **1**, 207 (1966), and references contained therein.

(5) E. C. Friedrich, *J. Org. Chem.*, **33**, 412 (1968).

(6) T. G. Miller, *ibid.*, **27**, 1549 (1962).

(7) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(8) G. A. Smith, B. J. L. Hiff, W. H. Powers, III, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967).

(9) Reference 4, p 188.

A conventional indicator plot of these data (Figure 1) was linear and adequately represented by eq 1.

$$\log [DH^+]/[D] = (0.62 \pm 0.02)[(-3.66 \pm 0.13) - H_0] \quad (1)$$

The slope and intercept of this type of plot completely characterizes the acidity dependence of any equilibrium protonation reaction.[10] *E.g.*, if upon protonation two substrates produce conjugate acids of very similar structure (with regard to charge distribution and solvation), their indicator slopes should be essentially identical. In general, the intercepts of these plots will vary considerably from substrate to substrate and will reflect the intrinsic basicity of a particular substrate.

The slope observed in this work for **1** is identical with that reported[1] for the equilibrium protonation of **2** in sulfuric acid (0.62). This adds confirmatory evidence that very similar species, namely protonated cyclohexadienones, are produced from **1** and **2** in concentrated acid solution. The intercepts, on the other hand, are quite different, −3.66 for **1** and −5.52 for **2**. This difference corresponds to a difference in basicity of about a factor of 70, with **1** being the stronger base. This is consistent with the well-known electron-withdrawing tendency of a $CHCl_2$ group (σ^* 1.94)[11] relative to a methyl (σ^* 0.00). Thus, inductive withdrawal of electron density by a $CHCl_2$ group from the protonated form of **2** reduces the basicity of the parent cyclohexadienone.

We believe that the results detailed in this report provide conclusive evidence for the existence of a cyclohexadienyl cation during the isomerization of **1** to 3,4-dimethylphenol. Furthermore, it seems intuitively reasonable that this species is an intermediate which lies directly on the reaction path.

Experimental Section

1-Pyrrolidino-2-methylpropene.[7]—In a 250-ml round-bottom flask equipped with a Dean–Stark separator, dropping funnel, and a magnetic stirring bar was placed 83.6 ml (71.1 g, 1.0 mol) of pyrrolidine. The flask was cooled in an ice bath and 109 ml (86.5 g, 1.2 mol) of isobutyraldehyde was added with stirring. After the addition was complete, the mixture was heated at reflux for 6 hr. A total of 19.5 ml (108%) of water was collected. A further 22 ml of aldehyde was then collected and the residue distilled under reduced pressure. A middle cut had the following properties: 67.6 g (54.2%); bp 63–65° (28 mm) [lit.[7] 70–71° (38 mm)].

4,4-Dimethylcyclohexenone.[8]—In a 500-ml round-bottom flask equipped with a condenser, dropping funnel, and a nitrogen inlet tube was placed 52 ml (45 g, 0.36 mol) of 1-pyrrolidino-2-methylpropene. The system was flushed with nitrogen and cooled in an ice bath. At this point, 29.3 ml (25.2 g, 0.36 mol) of methyl vinyl ketone was added dropwise over a period of 0.5 hr. The mixture was allowed to stir under nitrogen for 24 hr. A 350-ml portion of 15% HCl was then added and the mixture allowed to stir for an additional 24 hr. The dark brown reaction mixture was heated on a steam bath for 45 min and allowed to cool. The organic phase was separated from the aqueous layer which was saturated with NaCl and extracted with three 100-ml portions of ether. The ether solution was combined with the organic layer and dried over Na_2SO_4. Removal of the ether afforded 28.3 g (64%) of impure product. Distillation under reduced pressure furnished 18.2 g (41%) of slightly yellow 4,4-dimethylcyclohexenone, bp 89–90° (28 mm) [lit.[8] 81–84° (21 mm)], exhibiting concordant nmr and ir spectra.

4,4-Dimethylcyclohexadienone (1).—In a 500-ml round-bottom flask equipped with an overhead stirring motor, a nitrogen inlet tube, and a condenser was placed 200 ml of CCl_4. To this was added 25 g (0.11 mol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and 7.5 ml (7.0 g, 0.058 mol) of 4,4-dimethylcyclohexenone in 25 ml of CCl_4. The reaction mixture was allowed to reflux on a steam bath with vigorous stirring for 24 hr, cooled to room temperature, and filtered. A 100-ml portion of ether was added and the solution was washed with two 100-ml portions of 10% KOH solution, dried over Na_2SO_4 and the ether removed on a steam bath. There remained 2.89 g (42%) of impure product which was distilled to afford 1.99 g (30%) of water-white **1**: bp 60–61° (3 mm) [lit.[12] 90° (15 mm)]; $\nu_{C=O}$ (CCl_4) 1670 cm^{-1}.

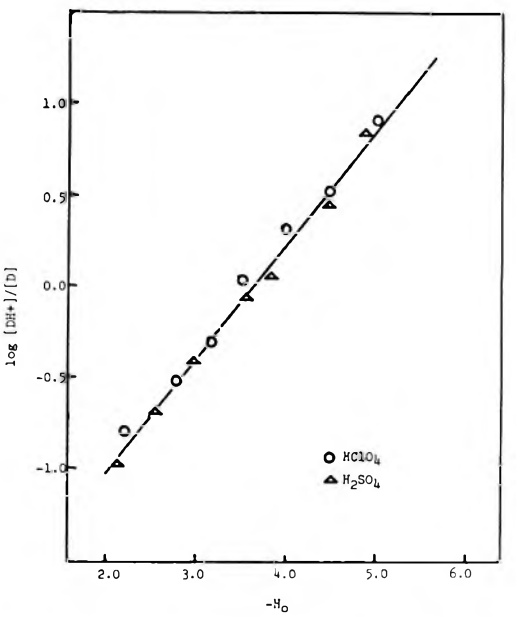


Figure 1.—Plot of log $[DH^+]/[D]$ *vs.* $-H_0$ for the protonation of 4,4-dimethylcyclohexadienone in $HClO_4$ and H_2SO_4.

Product Study.—A 183.0-mg sample of **1** was treated at 25° with 3.0 ml of 72% $HClO_4$. After 30 min (ten half-lives), the mixture was poured onto ice and extracted with three 30-ml portions of ether. The ether solution was dried over Na_2SO_4 and removed on a steam bath leaving 175 mg (96%) of 3,4-dimethylphenol. After one recrystallization from hexane, the slightly purplish product had mp 59–61°. Authentic 3,4-dimethylphenol, recrystallized once from hexane, had mp 62.5–65°.

In a separate experiment 74.9 mg of **1** was treated at room temperature with 1.0 ml of 72% $HClO_4$ for 5–6 half-lives. Work-up of the reaction mixture in the way described above afforded 74.8 mg (100%) of an oil. The ir spectrum of the crude product revealed the presence of unreacted dienone and 3,4-dimethylphenol exclusively. Gas chromatographic analysis demonstrated the presence of a single major product which was collected and shown to be 3,4-dimethylphenol by a comparison of its ir with that of authentic material.

The quantitative conversion of **1** to 3,4-dimethylphenol is further substantiated by uv spectroscopy. These results are summarized in Table IV. As can be seen from the results in Table IV the phenol product is not stable in sulfuric acid but is rapidly sulfonated, presumably to a mixture of sulfonic acids.

TABLE IV

UV PRODUCT STUDY FOR 1

Substrate	Solvent, %	λ_{max} (nm)	Log ϵ
1[a]	$HClO_4$, 71.0	207, 271	3.07, 3.86
3,4-Dimethylphenol[b]	$HClO_4$, 71.0	207, 271	3.01, 3.81
1[a]	H_2SO_4, 94.7	302	1.49
3,4-Dimethylphenol[b]	H_2SO_4, 94.7	303	1.53

[a] After 10 half-lives at 25.3°. [b] Aldrich Chemical Co., recrystallized from hexane.

(10) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

(11) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions." Wiley, New York, N. Y., 1963, p 222.

(12) F. G. Bordwell and K. Wellman, *J. Org. Chem.*, **28**, 1347 (1963).

Equilibrium Protonation Studies.—A wholly aqueous solution of 1 (0.0618 *M*, 20 μl) was placed in a clean, dry cuvette. To this was added 3.00 ml of an acid solution of the desired strength previously equilibrated at 25.3°. The contents of the cuvette were thoroughly mixed by several rapid inversions and placed in the thermostated cell compartment of the Cary 16 spectrophotometer. The absorbance was monitored as a function of time and the initial absorbance obtained by a back extrapolation to the time of mixing. Acid concentrations were determined by mixing carefully weighed amounts of standardized acid and distilled water.

Registry No.—1, 1073-14-9; 2, 6611-78-5.

Acknowledgment.—The author wishes to acknowledge with gratitude the hospitality shown him by the Department of Chemistry, University of Kansas, during his tenure as a Visiting Instructor for the academic year, 1968–1969. Special thanks are also due Professor R. L. Schowen for many helpful and stimulating discussions throughout the course of this work. Thanks are also due Professor J. Swenton for experimental details for the synthesis of **1**.

Alkylation of 5-Substituted Tetrazoles with α-Chlorocarbonyl Compounds

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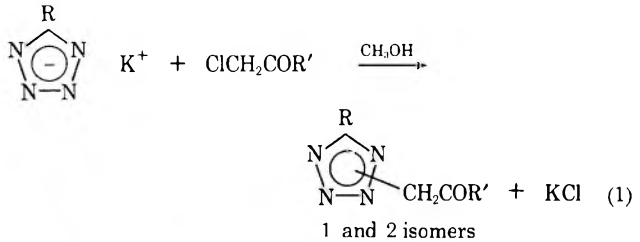
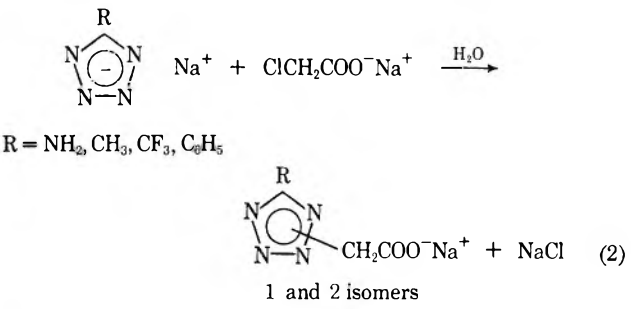
As part of a study on the preparation of polyfunctional tetrazoles, we have alkylated 5-substituted tetrazoles with α-chlorocarbonyl compounds to prepare 1- and 2-carbonyl substituted isomers. Substitutions of 5-substituted tetrazoles with α-haloacetates and triethylamine in acetone have recently been reported.[1] 5-Substituted 1-carboalkoxymethyltetrazoles were previously prepared by an indirect method involving ring closure to form the tetrazole ring.[2] The alkylation of tetrazoles with alkyl halides, dialkyl sulfates, and diazomethane also has been reported.[3] Our work[4] has included several chlorocarbonyl compounds other than chloroacetate, and the reactions were conducted in methanolic potassium hydroxide except that with chloroacetic acid, the reactions also were carried out in aqueous sodium hydroxide. The substitution reactions in methanolic potassium hydroxide (eq 1) and in aqueous sodium hydroxide (eq 2) were as follows.



1 and 2 isomers

(1)

R = NH_2; R′ = OH, OCH_3, OC_2H_5, CH_3, C_6H_5, NH_2 and
R = CH_3, CF_3, C_6H_5, *p*-$NO_2C_6H_5$; R′ = OCH_3



1 and 2 isomers

(2)

The reaction of potassium 5-aminotetrazolate with α-chlorocarbonyl compounds (eq 1) in methyl alcohol gave mostly 1-substituted products and minor products substituted in the 2 position. The yield of 2-substituted isomer varied from 0 to *ca.* 21% (Table I). The chlorocarbonyl compounds evidently exerted some influence in directing substitution on the tetrazole ring in addition to the strong inductive effect of the 5-substituent group. Substitution on the 1- and 2-ring positions of different tetrazoles with chloroacetate in methyl alcohol or chloroacetic acid in water clearly demonstrated the inductive effect of the 5 substituents. Electron-donating groups favored 1 substitution and electron-withdrawing groups favored 2 substitution. This inductive effect also was demonstrated in the work reported by Raap[1] and in prior work[3] on the alkylation of 5-substituted tetrazoles. In the reactions with chlorocarbonyl compounds in methanolic potassium hydroxide or in aqueous sodium hydroxide, neutralization of the strong base by formation of the salts of the tetrazoles and of chloroacetic acid prevented hydrolysis of the chlorocarbonyl compounds. With chloroacetic acid 2 mol of base per mol of tetrazole were required to give an appreciable yield of substitution product. Apparently, substitution on the ring occurred only in reaction with the tetrazolate anion which formed after all or most of the chloroacetic acid was converted to salt. Decreased yields were obtained with excess base owing to hydrolytic reaction with chloroacetic acid or ester.

The 1- and 2-carbomethoxymethyl-5-aminotetrazole isomers were readily acetylated with acetic anhydride to stable diacetyl derivatives (Table I). The acetylated 2-substituted isomer could be distilled at low pressure at 180–190° without decomposition. 1-Acetonyl-5-aminotetrazole also was acetylated to a diacetyl derivative, but it was hydrolyzed rapidly in boiling water to monoacetyl derivative.

The strong acidity (see Table II) of 1- and 2-carboxymethyl-5-aminotetrazole and of 2-carboxymethyl-5-trifluoromethyltetrazole manifests the strong electron-withdrawing effect of the tetrazole ring.[5] Rapid hydrolysis of the tetrazolyl acetate esters in cold aqueous alkali also demonstrated the same electron-withdrawing effect. This is in accord with the known fact that strong electron-withdrawing groups substituted in the α position of acetates greatly accelerate hydrolysis.[5] The 5-substituent group apparently has only a weak

(1) R. Raap and J. Howard, *Can. J. Chem.*, **47**, 813 (1969).
(2) C. R. Jacobson and E. D. Amstutz, *J. Org. Chem.*, **21**, 311 (1956).
(3) Robert C. Elderfield, "Heterocyclic Compounds," Vol. 8, Frederick R. Benson, Ed., Wiley, New York, N. Y., 1961, Chapter 1. Section on alkylation of tetrazoles and references there.
(4) F. Einberg, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, p ORGN, 173.
(5) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehard and Winston, New York, N. Y., 1959.

TABLE I
CARBONYL SUBSTITUTED TETRAZOLES

Substituted[a] tetrazole	Registry no.	Yield,[b] %	Mp or bp (mm), °C	Recrystallization solvent	—Nmr, chemical shifts, δ (ppm)— Solvent	NH_2	CH_2
1-CH_2COOH-5-NH_2	21743-62-4[c]	53.1	212–213 dec	Water	$(CD_3)_2S{=}O$	6.78	5.04
2-CH_2COOH-5-NH_2	21743-72-6		211–212 dec	Water	$(CD_3)_2S{=}O$	5.97	5.28
1-CH_2COOCH_3-5-NH_2	21744-59-2	43	185–186 dec	Alcohol	$(CD_3)_2S{=}O$	6.82	5.17
2-CH_2COOCH_3-5-NH_2	25828-03-9	14	133–134	Benzene	$(CH_3)_2S{=}O$[d]	6.01	5.43
1-$CH_2COOC_2H_5$-5-NH_2	21744-57-0	50	147–148	Alcohol			
2-$CH_2COOC_2H_5$-NH_2	21744-50-3	21	106–107	Benzene			
1-CH_2COCH_3-5-NH_2	25828-06-2	53	204.5–205.5 dec	Alcohol	$(CD_3)_2S{=}O$	6.70	5.21
2-CH_2COCH_3-5-NH_2	25876-96-4	14	105.0–105.5	Benzene	$(CH_3)_2S{=}O$[e]	5.96	5.50
1-$CH_2COC_6H_5$-5-NH_2	25828-07-3	49	214.0–214.5 dec	Alcohol			
2-$CH_2COC_6H_5$-5-NH_2	25876-97-5	7	124–125.0	Benzene			
1-CH_2CONH_2-5-NH_2	25828-08-4	84	208.0–208.5 dec	Water			
1-CH_2COOCH_3-5-$N(COCH_3)_2$	25828-09-5		137.5–138.5	Alcohol	$CDCl_3$		5.10
2-CH_2COOCH_3-5-$N(COCH_3)_2$	25828-10-8		71–73, 180 (0.1)	Alcohol			
1-CH_2COCH_3-5-$NHCOCH_3$	25828-11-9		114.0–114.5	Alcohol			
1-CH_2COOCH_3-5-CH_3	25828-12-0	48	67–68	Benzene	$CDCl_3$		5.03
2-CH_2COOCH_3-5-CH_3	25828-28-8	33	70–71 (0.8)		CCl_4		5.30
2-CH_2COOCH_3-5-CF_3	25876-98-6	11.5	55–56 (0.1)		CCl_4		5.52
2-$CH_2COOC_2H_5$-5-CF_3	25876-99-7	25.4	68–69 (0.6)				
2-CH_2COOCH_3-5-C_6H_5	25828-29-9	60[b]	93–94, 130 (0.1)		CCl_4		5.38
2-CH_2COOCH_3-5-*p*-$NO_2C_6H_5$	25828-30-2	92	136.5–137.5	Alcohol	$CHCl_3$		5.54

[a] Satisfactory analytical values (±0.35 for C, H, and N) were reported for all compounds except for 1-$CH_2CO_2C_2H_5$-5-NH_2 tetrazole (Calcd: H, 5.26. Found: 5.79.) and 2-$CH_2CO_2C_2H_5$-5-NH_2 (Calcd: H, 5.26. Found: 6.02.): Ed. [b] From reaction of chlorocarbonyl compounds with potassium tetrazolate in methanol. [c] Pyridine salt, registry no. 25828-00-6. [d] In $(CD_3)_2C{=}O$, overlap of amino and methylene protons at 5.37. In CF_3COOH, NH_2, 5.65, CH_2, 5.53. [e] In $(CD_3)C{=}O$, overlap of amino and methylene protons at 5.47. In CF_3COOH, NH_2, 5.77, CH_2, 5.68.

TABLE II
CARBOXYMETHYL SUBSTITUTED TETRAZOLES

Substituted tetrazole	Yield,[a] %	Mp, °C	Recrystallization solvent	pK_a[c]
1-CH_2COOH-5-NH_2	53.1	212–213 dec (lit.[1] 202–203 dec)	Water	2.7
2-CH_2COOH-5-NH_2	23.8	211–212 dec (lit.[1] 185–186 dec)	Water	2.6
1-CH_2COOH-5-CH_3	32.5	193–194 dec (lit.[1] 184–186 dec)	Water	
2-CH_2COOH-5-CH_3	18.3	153–155 dec (lit.[1] 155–156 dec)	Acetonitrile	
1-CH_2COOH-5-C_6H_5	18.6	146–148 dec (lit.[1] 148–150 dec)	Acetonitrile	
2-CH_2COOH-5-C_6H_5	56.9	186–187 dec[b] (lit.[1] 182–184 dec)	Water	
2-CH_2COOH-5-CF_3	65.3	Oil, did not distil at 150° (0.15 mm), began to decompose		2.5

[a] From reaction with chloroacetic acid and aqueous sodium hydroxide. [b] Melting point sample from hydrolysis of methyl ester. Note reversal of usual lower melting point for 2 isomer. [c] Determined from pH at half-neutralization

effect on the electron-withdrawing capacity of the tetrazole ring since a strong electron donor and a strong electron-withdrawing group produce only a small difference in the acid strength of the substituted acetic acids (Table II).

1 and 2 ring substitution of 5-aminotetrazole with methyl and ethyl chloroacetate and chloroacetone was established based on their diacetylation, neutrality, and infrared and nmr spectra. However, assignment of the 1- and 2-substituted structures to the isomers was based on the known greater solubility of the 1-substituted isomers in polar solvents and of the 2-substituted isomers in nonpolar solvents and of the higher melting points of the 1-substituted isomers compared with the 2-substituted isomers.

There was a significant difference in nmr chemical shift for the amino and methylene protons of the 1- and 2-acetate and acetonyl-substituted 5-aminotetrazole isomers, Table I ($\Delta\delta$ for amino protons, 0.7–0.8 ppm, and for methylene protons, 0.26–0.31 ppm). This difference in chemical shift has been shown previously for tetrazolyl acetates[1] and acetic acids and also has been shown for alkyl 1- and 2-substituted isomers.[6,7] The chemical shifts for the methylene protons of different 5-substituted tetrazolyl methyl acetates also showed a similar increase in δ vs. for 2 vs. 1 substitution (Table I). The highly electronegative trifluoromethyl and *p*-nitrophenyl groups in the 5 position apparently decrease the electronic shielding of the acetate methylene protons by exerting an electron-withdrawing effect through the tetrazole ring (Table I). This is indicated by the smaller δ values for methylene absorptions with amino, methyl, and phenyl compared with trifluoromethyl and *p*-nitrophenyl groups in the 5 position.

Experimental Section

The chlorocarbonyl compounds were the purest commercially available grade and were used as received. 5-Aminotetrazole monohydrate obtained commercially was dehydrated at 90–100° for about 24 hr in a vacuum oven evacuated with a vacuum pump. Other reagents were the purest commercially available grade. Infrared spectra were obtained in Nujol mulls with a Perkin-Elmer Model 21 instrument. Nmr spectra were obtained at the Temple University Chemistry Department and at the Sadtler Research Laboratories, Inc., with Varian A-60

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instruments using tetramethylsilane as internal reference. Melting points were uncorrected and were obtained with a Hoover–Thomas capillary melting point apparatus. Analyses were done at this laboratory and at the Schwarzkopf Microanalytical Laboratory.

5-Methyltetrazole,[8] 5-trifluoromethyltetrazole,[8] and 5-phenyltetrazole[9] were prepared according to the methods described in the literature.

General Procedure for the Reaction of Chlorocarbonyl Compounds with Potassium Tetrazolate in Methanol (Products Listed in Table I).—The 5-substituted tetrazole (1 mol) was added to a solution of potassium hydroxide (1 mol) in methanol, followed by the addition of chlorocarbonyl compound (1 mol). With chloroacetic acid, 2 mol of potassium hydroxide was used (see procedure below for reaction with 5-aminotetrazole). The mixture was refluxed 18–24 hr, cooled in a refrigerator several hours or overnight, and the crystalline precipitate of crude 1-substituted isomer was collected on a filter, extracted with benzene and recrystallized. The methanolic filtrate was evaporated to dryness and the solid residue was extracted with benzene. The benzene solutions were combined and evaporated to dryness, and the crude 2-substituted isomer was recrystallized.

General Procedure for the Reaction of Chloroacetic Acid with Sodium Tetrazolate in Water (Products Listed in Table II).—The 5-substituted tetrazole (1 mol) dissolved in an aqueous solution of sodium hydroxide (2 mol) and chloroacetic acid (1 mol) was refluxed 18–24 hr. The mixture was cooled and made strongly acidic with concentrated hydrochloric acid (pH less than 2). The precipitate which formed was collected and recrystallized. The filtrate or the acidified reaction mixture was evaporated to dryness and the residue was extracted with solvent used for recrystallization. The residual sodium chloride was discarded and the extracted solid was recrystallized. Typical preparations are described below.

1- and 2-Carboxymethyl-5-aminotetrazole (I and II). Method 1.—Chloroacetic acid (47.3 g, 0.5 mol), 5-aminotetrazole (42.5 g, 0.5 mol), and potassium hydroxide (56.2 g, 1.0 mol) in 1 l of methyl alcohol was refluxed 24 hr, cooled to room temperature, and filtered. The collected solid (74.8 g) was dissolved in water (200 ml) and the pH of the solution (~6) was reduced to less than 2 with concentrated hydrochloric acid (30 ml). The mixture was cooled overnight in a refrigerator and filtered to give 37.9 g of I, 53.0% yield, mp 209–210° dec. The presence of II in the residue from the water filtrate was indicated by its ir spectrum. However, it could not be readily purified. Using a mole ratio of 2:1:3, respectively, and the same procedure, a 52.9% yield of I based on the moles of 5-aminotetrazole, but no disubstituted product was obtained. Using a 1:1:1 mol ratio, no substitution product was obtained. After twice recrystallizing I from water, the melting point was 209–210° dec.

Method 2.—Chloroacetic acid (9.4 g, 0.1 mol), 5-aminotetrazole monohydrate (10.3 g, 0.1 mol), and sodium hydroxide (8.0 g, 0.2 mol) in 100 ml of water was refluxed 20 hr, cooled, and made strongly acidic with concentrated hydrochloric acid. The mixture was cooled overnight and filtered to give 7.6 g of I, 53.1% yield, mp 212–213° dec (high purity without recrystallization). The filtrate was evaporated to a low volume and 3.4 g of solid, 23.8% yield, mp 203–205° dec, was collected on a filter. The ir spectrum of the solid showed it to be mostly II.

Pyridine Salt of I.—I was dissolved in hot pyridine and the pyridine salt came out of the cooled solution. Recrystallization from pyridine gave a crystalline solid: mp 185–186° dec; ir 3460, 3300 (NH), 1640, 1610 (C=O), 1550 (C=N), 1087, 1013 cm^{-1} (ring).

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.50; N, 37.84. Found: C, 42.93; H, 4.37; N, 37.61.

1- and 2-Carbomethoxymethyl-5-aminotetrazole (III and IV).—Methyl chloroacetate (54.2 g, 0.5 mol), 5-aminotetrazole and potassium hydroxide (28.0 g, 0.5 mol) in 500 ml of anhydrous methyl alcohol was refluxed 24 hr with stirring. The methyl alcohol was removed under reduced pressure and the dry solid was extracted in a Soxhlet extractor for 24 hr with benzene. The solid insoluble in benzene was extracted with alcohol and the alcohol filtrate was evaporated to dryness yielding 33.7 g, 42.9% of III, mp 177–178° dec. After further extraction for 24 hr in a Soxhlet extractor with benzene and crystallization from alcohol gave mp 185–186° dec: ir 3300, 3120 (NH), 1740 (C=O), 1668, 1640, 1590, 1495 (C=N), 1010 cm^{-1} (ring).

Evaporation of the benzene solution yielded 10.9 g, 13.9% of IV, mp 128–130°. After recrystallization from benzene the melting point was 132–133°: ir 3450, 3320, 3230, 3170 (NH), 1740 (C=O), 1650, 1627 (C=N), 1087, 1015 cm^{-1} (ring).

Hydrolysis of III and IV.—Compounds III and IV were refluxed 2 and 1.5 hr, respectively, in excess 5% sodium hydroxide and the solutions made strongly acidic with hydrochloric acid. After recrystallization of I (hydrolyzed III) from water the melting point was 212–213° dec. After recrystallization of hydrolyzed IV from water, the melting point was 211–212° dec: neut equiv (I) (calcd 143.0); neut equiv 142.5, 142.2, (II) 143.5; ir (I) 3380, 3330, 3260, 3200 (NH), 1700 (C=O), 1645, 1598 (C=N), 1090, 1053 cm^{-1} (ring); ir (II) 3460, 3340 (NH), 1730 (C=O), 1645 (C=N), 1023 cm^{-1} (ring).

1- and 2-Carbomethoxymethyl-5-*N*,*N*-diacetylaminotetrazole (V and VI).—Compound III (3.14 g, 0.02 mol) and 50 ml of acetic anhydride was refluxed 1.5 hr. The acetic anhydride then was removed on a rotating film evaporator and a light tan solid slurried and washed with ether was collected on a filter. The solid was treated with decolorizing carbon and crystallized from alcohol to give 2.3 g of shiny, white crystals, V: mp 137.5–138.5°; ir (V) 1770, 1755, 1735 (C=O), 1540 (C=N), 1042, 1031, 1005 cm^{-1} (ring).

Compound IV was acetylated as above, the acetic anhydride removed, and the residue dissolved in a minimum of hot benzene. The solution was cooled and unreacted IV was collected on a filter. The benzene was evaporated and the liquid residue was distilled in a short-path distillation apparatus at approximately 180° and 0.1 mm pressure. The distillate was a crystalline solid: mp 71–73°; ir (VI) 1760, 1740, 1725 (C=O), 1510 (C=N), 1040, 1020 cm^{-1} (ring).

1- and 2-Acetonyl-5-aminotetrazole (VII and VIII).—Chloropropanone (18.5 g, 0.2 mol), anhydrous 5-aminotetrazole (17.0 g, 0.2 mol), and potassium hydroxide (11.2 g, 0.2 mol) in 200 ml of methyl alcohol was refluxed 24 hr with stirring. The mixture then was allowed to stand overnight at room temperature and filtered. The solid, 15.0 g, 53.2% yield of VII, mp 204.5–205.5° dec, was collected. Recrystallization from alcohol or water gave shiny, white platelets: mp 204.5–205.5° dec; ir (VII) 3300, 3150 (NH), 1725 (C=O), 1645, 1485 (C=N), 1045 cm^{-1} (ring).

The methyl alcohol filtrate from the reaction mixture was evaporated to dryness and the solid was extracted with boiling benzene. Evaporation of the benzene solution gave 4.0 g, 14.2% yield of VIII as a yellowish solid, mp 103–105°. Treatment with decolorizing carbon in boiling benzene and crystallization from benzene gave fluffy white needles: mp 105.0–105.5°; ir (VIII) 3430, 3320 (NH), 1725 (C=O), 1630, 1550 (C=N), 1085, 1040, 1010 cm^{-1} (ring).

1-Acetonyl-5-*N*-acetylaminotetrazole (IX).—1-acetonyl-5-aminotetrazole (2.8 g, 0.02 mol) and 50 ml of acetic anhydride was refluxed 1 hr. The mixture turned a dark reddish-amber color. The acetic anhydride was evaporated under reduced pressure and a crystalline solid was collected on a filter and washed with hot alcohol. The solid (1.5 g) had mp 208–209° dec. A small portion rapidly recrystallized from hot water melted at 210.0–210.5° dec. The remaining solid was dissolved in boiling water from which it did not crystallize even on evaporation to a low volume. The water then was completely evaporated and the solid was crystallized from alcohol. The solid, 0.6 g, mp 114.0–114.5°, was analyzed for monoacetylated 1-acetonyl-5-aminotetrazole (X): ir (X) 3340, 3230 (NH), 1725 (C=O), 1603, 1550 (C=N), 1045, 1015 cm^{-1} (ring).

Apparently, the initial product isolated was diacetylated and hydrolyzed rapidly in boiling water to monoacetylated product.

Acknowledgment.—The author wishes to express his appreciation for initial samples of 5-methyltetrazole, sodium-5-trifluoromethyltetrazole, and *p*-nitrophenyltetrazole kindly furnished by Dr. R. A. Henry. He also wishes to thank Dr. Charles W. Jefford, formerly of the Temple University Chemistry Department, and Mr. William Peterson of this laboratory for assistance in obtaining nmr spectra.

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Selective *N*-Methylations of Heterocycles with Dimethyloxosulfonium Methylide

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Studies in this laboratory on methyltransferases[2] and nonenzymatic methylations of nucleotides[3] have shown the need for model systems capable of preferential or selective methylation. Thus, dimethyloxosulfonium methylide[4] is known to react with acidic NH or OH groups to give the corresponding methylation compounds[5] and also methylates aromatic hydrocarbons, such as anthracene and nitrobenzene.[6]

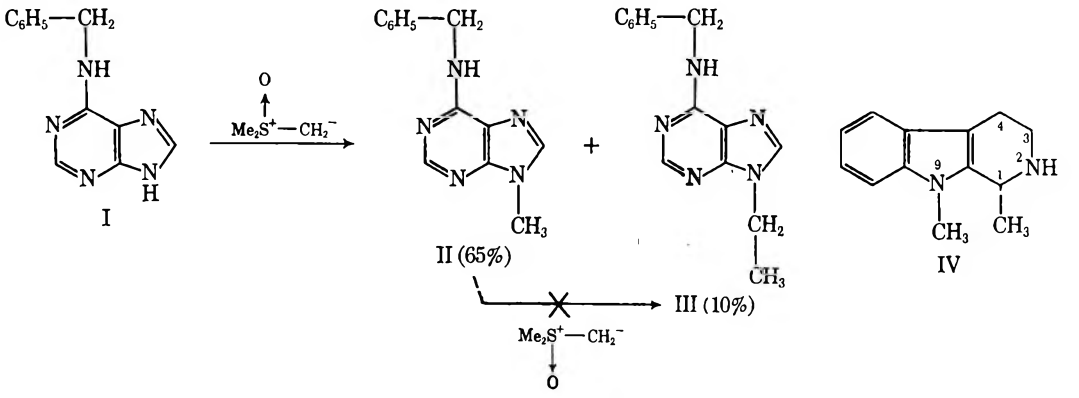
We have extended these observations to *N*-methylation of heterocycles, such as pyrimidines, imidazoles, and pyrroles. In connection with the preparation of cyclothymine nucleosides,[7] we reported that the dimethyloxosulfonium ylide smoothly methylates uracil derivatives at the 1 or 3 positions to give 1-methyluracil or 3-methyluridine, and, in one special case, the sugar hydroxyls were also methylated.[8]

As a model compound for building stones of nucleic acids, 6-benzyladenine (I) reacted with 3 mol of ylide in tetrahydrofuran to give 9-methyl-6-benzyladenine (II), mp 127°, *m/e* 239 (M), in 63% yield, whose structure was confirmed by direct comparison with that of an authentic sample prepared from benzylamine and 6-chloro-9-methylpurine ($\delta_8 - \delta_2 = 9$ Hz in DMSO).[9]

By-product, mp 144°, *m/e* 253 (M), obtained in 10% yield, was identified as 6-benzyl-9-ethyladenine (III) on the basis of nmr, uv, and ir spectra. This ethylation to III indicates alkylation by the rearranged ylide, dimethyloxosulfonium ethylide, since direct treatment of II with excess ylide did not afford the ethyl compound III.

Similarly, benzimidazole was converted to the 1-methyl derivative in 80% yield. In the cases of indole and 1,2,3,4-tetrahydroharman only the pyrrole ring was methylated to give 1-methylindole and 9-methyltetrahydroharman (IV) in almost 90% yield (corrected). This provides a convenient method for *N*-methylation of indole derivatives.[10] Oxindole underwent both *N*- and competitive *C*-alkylation.[11] With an equimolar amount of ylide 1-methyloxindole was obtained (66% yield), while 3 mol of ylide gave 1,3,3-trimethyloxindole (69% yield) in addition to traces of mono- and dimethyl derivatives. By contrast *N*-phenethylbenzamide was completely unreactive.

While *N*-methylase from rabbit lung converts adenine to 3-methyladenine,[12] the ylide reagent leads to 9-methyladenine derivatives. In analogy to the *in vivo* methylation of tRNA from yeast to a 1-methyladenine-containing species by an enzyme from rat tissue,[13] we recently found a methylating model that converts adenosine to 1-methyladenosine and very little 3-methyladenine with concomitant loss of the ribose moiety.[14]



Experimental Section

Melting points are uncorrected. Nmr and mass spectra were determined on a Varian A-60 and a Hitachi RMU-6D instrument, respectively. Chemical shifts and *J* values are given in τ and hertz, respectively.

General Procedure of Methylation.—Dimethyloxosulfonium methylide was prepared by gently refluxing a suspension of sodium hydride and trimethyloxosulfonium chloride in THF for 2–2.5 hr under N_2.[4] The heterocyclic compounds were added as solids and the mixture was kept boiling gently overnight. After filtration, the solution was evaporated *in vacuo*, and the residue was taken up in organic solvent and washed with H_2O. The products were purified by chromatography on silica gel or by recrystallization.

6-Benzyl-9-methyladenine (II) and 6-Benzyl-9-ethyladenine

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(III).—6-Benzyladenine (I, 1.0 g) was reacted with the ylide prepared from NaH (0.7 g) and trimethyloxosulfonium chloride (4.2 g) in THF. The two main products were obtained pure by chromatography on silica gel (acetone). The minor product (150 mg) eluted faster and was recrystallized from benzene–ligroin to give 9-ethyl-6-benzyladenine III (110 mg) as colorless prisms, mp 141–144°. The nmr spectrum ($CDCl_3$) showed peaks at 8.53 (t, J = 7.5, CH_3), 5.81 (q, J = 7.5, CH_2), 5.07 (d, J = 7.0, benzylic methylene), 2.68 (aromatic), 2.52 (s, H_2), and 1.57 (s, H_8); mass spectrum m/e 253 (M^+); uv λ_{max}^{MeOH} 270 nm.

Anal. Calcd for $C_{14}H_{15}N_5$: C, 66.40; H, 5.93; N, 27.67. Found: C, 66.12; H, 5.98; N, 27.86.

Recrystallization of the major product (670 mg) from benzene–ligroin gave 6-benzyl-9-methyladenine (II) as colorless needles: mp 127–128°; nmr ($CDCl_3$) 6.27 (s, CH_3), 5.09 (d, J = 6.0, $ArCH_2$), 2.70 (aromatic), 2.60 (s, H_2), 1.60 (s, H_8); nmr (DMSO-d_6) 1.90 (s, H_2), 1.76 (s, H_8); mass spectrum m/e 239 (M^+); uv λ_{max}^{MeOH} 270 nm.

Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.27; H, 5.44; N, 29.29. Found: C, 65.28; H, 5.23; N, 28.96.

This product was identical with an authentic sample (mp 128°, nmr, ir, and uv spectra), which was prepared by boiling 6-chloro-9-methylpurine and benzylamine in methyl Cellosolve.

1-Methylbenzimidazole.—Benzimidazole (0.8 g) was reacted with the ylide prepared from NaH (0.8 g) and sulfonium chloride (4.8 g) in THF. 1-Methylbenzimidazole was obtained as an oil (0.74 g), which showed singlet peaks at 6.61 (NCH_3) and 2.33 (H_2) in addition to aromatic protons in the nmr spectrum ($CDCl_3$). The picrate formed in ether was recrystallized from EtOH as yellow needles, mp 250–251°.

Anal. Calcd for $C_8H_8N_2 \cdot C_6H_3N_3O_7$: C, 46.54; H, 3.07; N, 19.38. Found: C, 46.80; H, 3.13; N, 19.21.

1-Methylindole.—Indole (1.17 g) was allowed to react with the ylide prepared from NaH (0.7 g) and sulfonium chloride (4.5 g). The product obtained as a reddish yellow oil was purified by chromatography on silica gel (hexane–benzene). The product obtained as a pale yellow liquid was identical with authentic 1-methylindole with regard to ir and nmr spectra. The nmr spectrum showed peaks at 6.47 (s, NCH_3), 3.60 (d, J = 3.0, 3 H), and 3.16 (d, J = 3.0, 2 H).

9-Methyl-1,2,3,4-tetrahydroharman.—1,2,3,4-Tetrahydroharman (1.0 g) was treated with the ylide prepared from NaH (0.75 g) and sulfonium chloride (4.5 g). The nmr spectrum of the crude products showed a mixture of starting material and 9-methylharman in a ratio of 2:3. The unchanged compound was removed as a solid by treatment with benzene–ligroin. Evaporation of the mother liquor gave the pure N-methylation product (0.6 g) whose nmr spectrum ($CDCl_3$) showed peaks at 8.75 (d, J = 7.0, CCH_3) and 6.77 (s, NCH_3). The picrate was obtained from EtOH–ether as reddish yellow prisms, mp 243–245° dec (lit.[6] 242°).

Anal. Calcd for $C_{13}H_{16}N_2 \cdot C_6H_3O_7N_3$: C, 53.15; H, 4.43; N, 16.32. Found: C, 53.39; H, 4.36; N, 16.37.

1-Methyloxindole.—Oxindole (2.6 g) was reacted with the ylide prepared from NaH (0.5 g) and sulfonium chloride (3.2 g). The crude products were chromatographed on silica gel (benzene–acetone) to give two main products.

An oily product, which eluted faster, was identified as 1,3-dimethyloxindole by the nmr spectrum ($CDCl_3$) which showed signals at 8.57 (d, J = 8.0, C-CH_3), 6.85 (s, NCH_3), and 6.67 (q, J = 8.0, 3 H).

The subsequently eluted product (1.9 g) was obtained as colorless needles from ligroin, mp 89–90° (lit.[6] 88°). The nmr spectrum ($CDCl_3$) showed peaks at 6.80 (s, N-CH_3), 6.51 (s, CH_2), and around 3.0 (m, aromatic).

1,3,3-Trimethyloxindole.—Oxindole (0.9 g) was treated with the ylide prepared from NaH (0.5 g) and sulfonium chloride (3.0 g). A major product obtained by chromatography on silica gel ($CHCl_3$) was further purified by distillation at 0.5 mm (120°) to give trimethyloxindole (0.8 g) as a slightly yellow oil. The nmr spectrum ($CDCl_3$) showed singlet peaks at 8.64 (6 H) and 6.80 (3 H), mass spectrum m/e 175 (M^+). The uv and ir spectral data were identical with those reported.

Registry No.—II, 5440-16-4; III, 25870-60-4; dimethyloxosulfonium methylide, 5367-24-8; 1-methylbenzimidazole picrate, 25870-61-5.

Reaction of Aliphatic Nitro Compounds with Carbon Monoxide. A New Route to Trialkylpyridines

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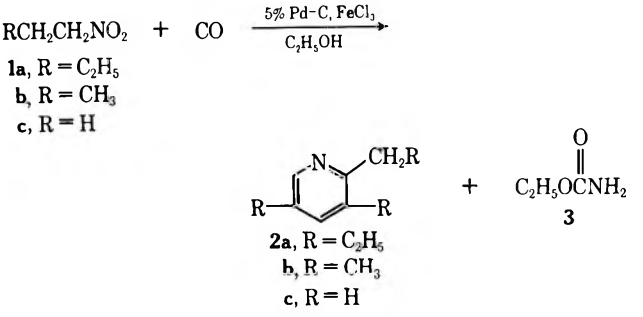
Recently, Bennett, Hardy, and coworkers[1] reported that carbon monoxide reacts with aromatic nitro, nitroso, azo, and azoxy compounds in the presence of a noble metal and ferric chloride to yield the corresponding isocyanates. In a patent issued to Mountfield[2] it is stated that urethans may be produced from the reaction of carbon monoxide, aromatic or aliphatic nitro compounds, and alcohols in the presence of a metal carbonyl catalyst system. We have found that certain primary aliphatic nitro compounds yield trisubstituted pyridines when treated with carbon monoxide under pressure using a noble metal–ferric chloride catalyst system. For example, treatment of an ethanol solution of 1-nitrobutane (**1a**) with carbon monoxide in the presence of palladium on carbon and ferric chloride yields 2-propyl-3,5-diethylpyridine (**2a**) and ethyl carbamate (**3**). Likewise, 1-nitropropane (**1b**) gives rise to 2-ethyl-3,5-dimethylpyridine (**2b**) and **3**. The pyridines were



identified by spectral methods (nmr, uv, and mass spectra), from their picrate derivatives and by comparison of their nmr spectra with the spectra of the authentic samples prepared by Falbe.[3,4] It is apparent from the structure of the pyridines that this reaction must involve a trimerization process wherein three molecules combine in a specific fashion to form the heterocyclic ring. The pyridine formation is markedly dependent upon the structure of the nitro compound as indicated by the results summarized in Table I. Although the reaction of aromatic nitro compounds under these conditions gives high yields of the corresponding N-arylurethans,[5] N-alkylurethans are probably not involved in the cyclization since N-1-butylurethan was recovered

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TABLE I
EFFECT OF STRUCTURE ON CO REACTION PRODUCTS

Nitro compd	Products[a] (yield, %)	
1a	3 (39)	2a (24)
1b	3 (30)	2b (52)
1c	3 (18)	
2-Nitrobutane	3 (89)	2-Butanone[b] (58)
Nitrocyclohexane	3 (37)	N-Cyclohexylurethan (trace)
2-Methyl-2-nitropropane		Recovered unchanged

[a] Significant quantities of volatile by-products such as ammonia are formed in most of these reactions. [b] Isolated as the 2,4-dinitrophenylhydrazone.

unchanged after being subjected to the reaction conditions.

Ethanol is the preferred solvent for this reaction, but benzene has been employed successfully (reaction is much slower in benzene). Temperatures have been varied from 125 to 200° and pressures from 2000 to 5000 psig with no significant changes in product distributions. Rhodium is equally as effective as palladium for the noble metal portion of the catalyst while carbon or alumina supports appear to be equivalent. All the components of the reaction system (noble metal, ferric chloride, and carbon monoxide) were found to be necessary; if any one is omitted, none of the pyridine product is observed.

Falbe[3] has reported that *n*-butyraldoxime reacts with 1:1 hydrogen–carbon monoxide in the presence of a cobalt carbonyl catalyst to yield **2a** (24%) and butyramide (38%). Treatment of this oxime under our conditions also gave 2a (33%) suggesting that oxime intermediates may be involved in the pyridine formation. The 2-butanone isolated from the reaction of 2-nitrobutane could be derived from the corresponding oxime.

These results as well as those previously reported[1-3,5] suggest that nitro compounds can react with carbon monoxide to yield a number of different products depending on catalyst and solvent as well as the structure of the nitro compounds.

Experimental Section[6]

2-Propyl-3,5-diethylpyridine (2a).—Into a glass-lined autoclave were charged 16.9 g (0.162 mol) of 1-nitrobutane, 2.11 g (0.013 mol) of anhydrous ferric chloride, 4.2 g of 5% palladium on carbon,[7] and 100 ml of anhydrous ethanol. The autoclave was pressurized to 5,000 psig with carbon monoxide[8] and heated for 2 hr at 190°. After cooling and venting, the product mixture was filtered to remove the catalyst. Analysis of the filtrate (vpc, silicone rubber column) indicated **2a** and **3** were present in approximately equal amounts. After evaporation of the solvent, the products were distilled, bp 45–70° (0.1 mm), affording 12.3 g of a solid–liquid mixture. Washing of this mixture with petroleum ether left 5.7 g (39%) of **3**, which after purification melted at 46–48° and was identical with that of an authentic sample (vpc, ir, mixture melting point). The pyridine **2a**, 2.3 g (24%), was recovered from the washings by evaporation and acid extraction. The amine was further purified by preparative vpc: uv max (C_2H_5OH), 270 mμ (ε 4400), (HCl, C_2H_5OH), 277 (1800); nmr ($CDCl_3$) δ 8.28 (d, 1, J = 2 Hz, py-**H**), 7.28 (d, 1, J = 2 Hz, py-**H**), 2.65 (m, 6, py-CH_2–), 1.75 (m, 3, $-CH_2-CH_2-CH_3$), and 1.20–0.99 ppm (overlapping t, 9, $-CH_3$); mass spectrum (70 eV) *m/e* 177 (M), 162, 148, 134, 129, 91; picrate mp 121–122° (lit.[9] mp 122°).

Anal. Calcd for $C_{18}H_{22}N_4O_7$: C, 53.20; H, 5.46; N, 13.79. Found: C, 53.18; H, 5.52; N, 13.84.

The nmr spectrum of **2a** was identical with the spectrum of the authentic material.[3]

n-Butyraldoxime was substituted for **1a** in the above experiment and **2a** was isolated in 33% yield. No **3** was evident in the product mixture, but the ir spectrum of the ethanol solution showed a strong absorption band at about 2000 cm^{-1} suggesting the presence of iron pentacarbonyl.

2-Ethyl-3,5-dimethylpyridine (2b).—1-Nitropropane was treated with carbon monoxide under the conditions described above for **1a**. The yield of **3** was 30% and **2b**, 52%. The structure of **2b** was established from the following data: uv max (C_2H_5OH) 270 mμ (ε 3400), (HCl, C_2H_5OH), 274 (5800); nmr ($CDCl_3$) δ 8.19 (broad s, 1, py-**H**), 7.20 (broad s, 1, py-**H**), 2.76 (q, 2, J = 7 Hz, py-CH_2CH_3), 2.23 (s, 6, py-CH_3), and 1.25 ppm (t, 3, J = 8 Hz, CH_2-CH_3); mass spectrum (70 eV) *m/e* 135 (M), 134, 120, 107, 91, 79, 77; picrate mp 154–155° (lit.[10] mp 156–157°).

Anal. Calcd for $C_{16}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.20; H, 4.18; N, 15.42.

The nmr spectrum of **2b** was identical with the spectrum of the authentic material.[3]

Registry No.—Carbon monoxide, 630-08-0; 2a, 4808-75-7; 2b, 1123-96-2.

Acknowledgments.—The author wishes to thank Dr. Jessie Gove for nmr spectra, Mr. Tom Mead and coworkers for mass spectra, Mr. John Kobliska for elemental analyses, and Drs. Robert P. Bennett and Richard K. Madison for many helpful discussions.

(6) Melting points were determined on a Mel-Temp block and are uncorrected. Vpc, nmr, uv, and mass spectral measurements were carried out on an F & M Model 500 chromatograph, a Varian A-60, a Beckman DU and a CEC Model 110, respectively.

(7) Obtained from Engelhard Industries in the unreduced form and dried at 350° under nitrogen just prior to use.

(8) Obtained from Air Products and Chemicals, Inc., CP grade.

(9) T. M. Patrick, *J. Amer. Chem. Soc.*, **74**, 2984 (1952).

(10) A. E. Chichibabin and M. P. Oparina, *J. Prakt. Chem.*, **107**, 146 (1924).

Rearrangement of Aromatic *N*-Oxides. IV. The Reaction of Acridine *N*-Oxide with Acetyl Sulfide[1]

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Previous reports from this laboratory have involved mechanistic studies of the rearrangement of aromatic *N*-oxides in acetic anhydride.[3] From a detailed kinetic analysis of such a reaction with acridine *N*-oxide (**1**), it was concluded that the key step involved an intramolecular rearrangement of the *N*-acetoxyacridinium ion (**2**).[4] This was somewhat surprising since in the analogous reaction with pyridine *N*-oxide (**3**) kinetic[5] and oxygen-18[6] studies established that the pathway

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(1) Part III: J. H. Markgraf and C. G. Carson, III, *J. Org. Chem.*, **29**, 2806 (1964).

(2) Based on the Honors theses, Williams College, of M.-K. Ahn, 1963, C. G. Carson, III 1964, and G. A. Lee, 1967.

(3) For general reviews, see (a) E. Ochiai, "Aromatic *N*-Oxides," Elsevier, Amsterdam, 1967, pp 290–302, 310–325; (b) V. J. Traynelis, "Mechanisms of Molecular Migration," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1969, Chapter 1.

(4) J. H. Markgraf and M.-K. Ahn, *J. Amer. Chem. Soc.*, **86**, 2699 (1964).

(5) J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *ibid.*, **85**, 958 (1963).

(6) S. Oae and S. Kozuka, *Tetrahedron*, **21**, 1971 (1965).

was intermolecular. These data, therefore, corresponded to the correlation that rearrangement of **3** proceeded to the α position *via* an intermolecular process while **1** was converted to the γ derivative *via* an intramolecular process. In order to corroborate our mechanistic inferences from the kinetic study, we directed our attention to the reaction of **1** with the corresponding thioanhydride, acetyl sulfide (Ac_2S). On the assumption that the reactants initially generate **2** and thioacetate ions, alternate pathways can subsequently afford either acridone (**4**) or thioacridone (**5**) *via* intra- or intermolecular processes, respectively. Although the comparison of the thioanhydride with acetic anhydride introduced a more competitive nucleophile (thioacetate *vs.* acetate), it was felt that a combined product–kinetic investigation would offer additional insight into this rearrangement. No previous studies have included thioanhydrides; our work was in progress when the reaction of **1** with oxygen-18 labeled acetic anhydride was reported.[7] The latter study confirmed the intramolecularity of the rearrangement.

Results and Discussion

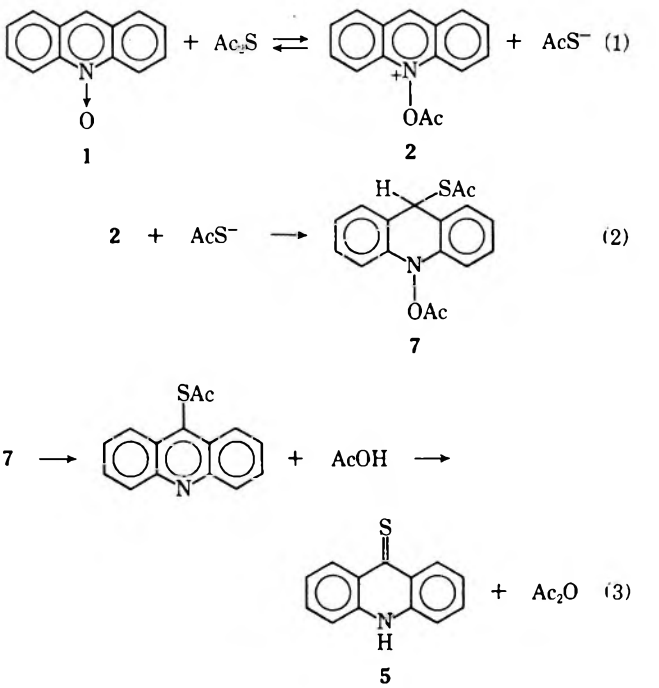
The development of a suitable analytical scheme proved more difficult than anticipated. The previous techniques of spectrophotometric[4,5] and conductometric[4] methods were unsatisfactory in the present case: the slower rate of hydrolysis of Ac_2S introduced inaccuracies in the quenching of aliquots and the variation of resistance with time showed only a further slight decrease during the course of the reaction (following the initial large change upon addition of **1**). The process finally used involved monitoring the ultraviolet visible spectrum of a solution of **1** in a thermostated cell.

The results of such runs were quite different from those of the earlier studies in acetic anhydride (Ac_2O). The product was not acridone (**4**, λ_{max} 392 mμ), but thioacridone (**5**, λ_{max} 481 mμ). It was established by control experiments that **4** was completely stable in Ac_2S and was not converted to **5**. Unfortunately, **5** was not indefinitely stable in the reaction medium and the initial increase in absorbance at 481 mμ was accompanied by a slow decrease. The rearrangement of **1** in Ac_2S was considerably slower than in Ac_2O and, over the longer time periods required, the complex variation in the absorbance at 481 mμ rendered quantitative kinetic data unreliable. The spectrum of the initial solution of **1** in Ac_2S, however, exhibited absorbance at 367 mμ which decreased with time. This peak undoubtedly corresponded to species **2**, since the identical spectrum was observed for a solution of *N*-acetoxyacridinium perchlorate (**6**) in Ac_2S. Observation of this peak in a run that was initially 3.84×10^{-4} *M* **1** in Ac_2S at 49.0° indicated 11% rearrangement after 5.5 hr. This reaction rate was strikingly slower than the half-life of 0.3 hr for **1** in Ac_2O at 25°.

The rearrangement of acridine *N*-oxide in acetyl sulfide produced thioacridone. This fact established that an intermolecular pathway was operative. Our original objective would have required at this point determination of the thermodynamic activation parameters. By such data the intermolecular process for the **1**–Ac_2S system could then have been contrasted with the intramolecular process for the **1**–Ac_2O system. The results of Oae's study of oxygen-18 labeling appeared during this time,[7] and further attempts to obtain quantitative kinetic data were abandoned.

There still existed the opportunity to test the presumed intermediacy of the *N*-acetoxyacridinium ion (**2**) and attention was focused on that species. Preparation of the previously unknown salt **6** was accomplished and its above-mentioned spectrum confirmed that a solution of **1** in Ac_2S rapidly generated **2**. A kinetic run of **6** (3.67×10^{-4} *M*) in Ac_2S at 49.0° indicated 40% rearrangement after only 3.0 hr. Identical runs to which were added trace amounts of thioacetic acid or tetra-*n*-butylammonium thioacetate showed further enhancement of the rate of appearance of **5**.

All of these data are consistent with the following mechanistic scheme. Establishment of an initial



equilibrium (eq 1) in such systems is well documented.[3] The rate-determining step is considered to be the intermolecular attack by thioacetate ion at C-9 to give **7** (eq 2). Subsequent loss of acetic acid with concomitant aromatization followed by transacetylation to give thioacridone and acetic anhydride (eq 3) are inferred to be rapid and irreversible from the analogous steps observed in the **1**–Ac_2O system.[4] The generation of Ac_2O during the course of the rearrangement accounts for the observed conductometric behavior. The failure to detect acridone vitiates any intramolecular process, a pathway known to occur in acetic anhydride. The present observations with acetyl sulfide, therefore, are consistent with a change in mechanism. This result can be attributed to the enhanced nucleophilicity of thioacetate.

The facile conversion of **6** to **5** in Ac_2S without added thioacetate species was unexpected. This reaction corresponds formally to eq 4. The nucleophile is most

$$6 + Ac_2S \longrightarrow 5 + Ac_2O + AcClO_4 \quad (4)$$

(7) S. Oae, S. Kozuka, Y. Sakaguchi, and K. Hiramatsu, *Tetrahedron.*, **22**, 3143 (1966).

likely acetyl sulfide. Following attack at C-9, transacetylation can occur to give 7 and acetyl perchlorate. Solutions of the latter compound in acetic anhydride are well documented.[8]

Experimental Section

Melting points (Kofler apparatus) and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer, Model 237B spectrophotometer calibrated with a polystyrene film. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Materials.—Acridine *N*-oxide,[1] acridone,[4] and acetyl sulfide[9] were prepared as previously described. Thioacridone was prepared by the method of Edinger and Arnold[10] and chromatographed on alumina by elution with tetrahydrofuran. Thioacetic acid was refluxed over phosphorus pentoxide and distilled; the product was redistilled through a 24-in. spinning-band column: bp 86.0–86.4° (748 mm), n^{25}D 1.4620.

***N*-Acetoxyacridinium Perchlorate (6).**—The general method of Muth and Darlak[11] was followed. A 0.5-ml aliquot of an ice-cold solution of 70% perchloric acid (1.3 g) in acetic anhydride (5 ml) was added dropwise to a stirred, ice-cold solution of 1 (0.15 g, 0.00076 mol) in acetic acid (1 ml) and acetic anhydride (2 ml). After 2 hr at 0°, reddish-brown crystals were collected under a nitrogen atmosphere, washed three times with cold anhydrous diethyl ether, and dried *in vacuo* over phosphorus pentoxide to give 0.060 g (33%) of 6: mp 186° dec; ir (KBr) 1821 cm^{-1}.

Anal. Calcd for $C_{15}H_{12}ClNO_6$: C, 52.35; H, 3.58; N, 4.15. Found: C, 53.26; H, 3.72; N, 4.40.

Tetra-*n*-butylammonium Thioacetate.—A 25% solution of tetra-*n*-butylammonium hydroxide in methanol was treated with a slight excess of thioacetic acid, concentrated on a rotary evaporator at reduced pressure, and refrigerated under an inert atmosphere. The residual oil crystallized and was dried *in vacuo* at 80° over phosphorus pentoxide to give a product (69%) of mp 74.6–77.6°.

Anal. Calcd for $C_{18}H_{39}NOS$: C, 68.08; H, 12.38; N, 4.41; S, 10.10. Found: C, 67.98; H, 12.49; N, 4.34; S, 10.26.

Product Identification.—A solution of 1 (0.10 g) in acetyl sulfide (50 ml) was allowed to remain at room temperature 16 hr and then evaporated to dryness at reduced pressure. The solid residue was chromatographed on alumina in tetrahydrofuran and recrystallized from methanol to give 0.064 g (58%) of 5, mp 259–261°; a mixture melting point showed no depression.

In another experiment a solution of 1 (33 mg) in acetyl sulfide (30 ml) was maintained at 15° for 40 hr, hydrolyzed with excess sodium hydroxide solution, and extracted with chloroform. The combined extract was washed with water and concentrated on a rotary evaporator to give a solid residue (35 mg) which by its ultraviolet visible spectrum (in acetonitrile) and by thin layer chromatography (in chloroform on alumina) was identical with thioacridone. By these same criteria, 1 was not present.

Rate Measurement.—Conductometric studies were carried out as previously described.[4] At 15° the resistance of pure acetyl sulfide was 206,400 ohms, compared to 45,000 ohms for acetic anhydride.[4]

Spectrophotometric studies were conducted in a jacketed, 10-mm cell fitted with a Teflon stopper containing a glass probe thermistor, which was connected to a thermometric bridge and galvanometer. Water was circulated through the cell jacket from an external constant temperature bath; temperatures of the reaction solution were maintained at 48.95 ± 0.05°. All apparatus was flushed with nitrogen and all transfers of solutions were conducted under a nitrogen atmosphere.

Registry No.—1, 10399-73-2; 6, 25876-95-3; acetyl sulfide, 3232-39-1; tetra-*n*-butylammonium thioacetate, 25827-89-8.

(8) (a) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 2034 (1950). (b) G. Jander and H. Surawski, *Z. Electrochem.*, **65**, 469 (1961). (c) G. N. Dorofeenko, Z. N. Nazarova, and V. N. Novikov, *Zh. Obshch. Khim.*, **34**, 3918 (1964); *Chem. Abstr.*, **62**, 9099c (1965).

(9) J. H. Markgraf, G. A. Lee, and J. F. Skinner, *J. Phys. Chem.*, **72**, 2276 (1968).

(10) A. Edinger and W. Arnold, *J. Prakt. Chem.*, **64**, 182 (1901).

(11) C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).

Acknowledgments.—We are indebted to Professor E. G. Taylor of this department for assistance with the conductance measurements. We thank Dr. R. C. Petersen (Sprague Electric Co.) for helpful discussions.

Novel Synthesis of a Dihydrotetrazapentalene from Trifluoroacetonitrile and Sodium Cyanide

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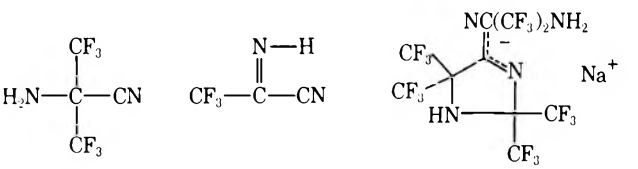
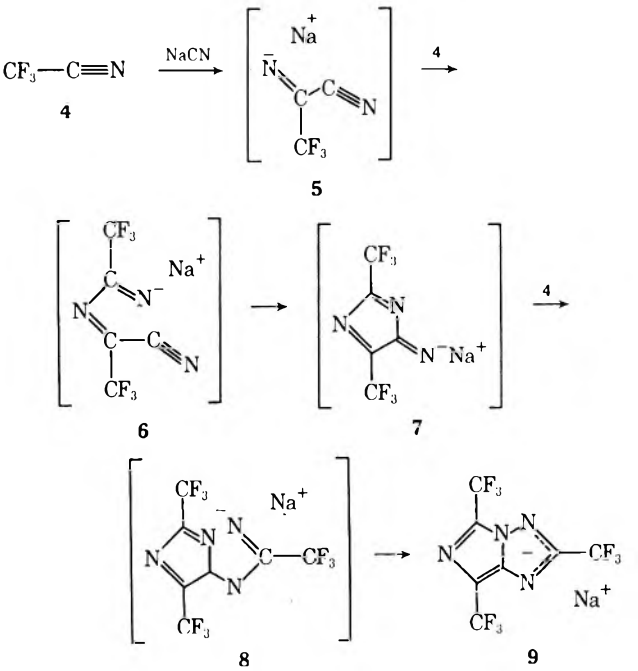
The carbon-to-nitrogen multiple bond in perfluoroalkyl imines and nitriles is extremely reactive in the addition of nucleophilic agents. Both hexafluoroacetone imine and trifluoroacetonitrile (**4**) combined with hydrogen cyanide under the influence of basic catalyst to give 1:1 adducts (**1** and **2**, respectively).[1,2] Re-



1 2 3

cently, it was reported[3] that 1 equiv of sodium cyanide reacts with 3 equiv of hexafluoroacetone imine to form a 1:3 adduct (**3**). This addition cannot be stopped at a 1:1 or a 1:2 adduct stage, presumably because these intermediate adducts are stronger nucleophiles than the cyanide ion.

We have found that trifluoroacetonitrile also reacts with sodium cyanide in a polar solvent to form a 1:3 adduct. The structure of this adduct was determined to be a salt of a dihydrotetrazapentalene (**9**).



4 5 6 7 8 9

* To whom correspondence should be addressed.

(1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

(2) W. J. Middleton and C. G. Krespan, *ibid.*, **33**, 3625 (1968).

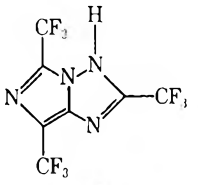
(3) W. J. Middleton and C. G. Krespan, *ibid.*, **35**, 1480 (1970).

The reaction is believed to proceed stepwise to give first the intermediate adduct **5**, which adds to another nitrile unit to give **6**. This intermediate (**6**) then cyclizes to give the 1:2 adduct **7** which adds still another nitrile unit to give intermediate **8**. The final step is the cyclization of **8** to **9**. This last step is unusual in that a nitrogen-to-nitrogen bond is formed by the addition of a nitrogen anion to a carbon-to-nitrogen double bond in a direction opposite to that normally observed. A driving force for this final step could be the formation of a resonance-stabilized salt (**9**), the anion of which is an aromatic structure. A 1:1 and 1:2 adduct of sodium cyanide with trifluoroacetonitrile (**5** and **7**) could not be isolated, presumably because these adducts are stronger nucleophiles than cyanide ion and react preferentially with the trifluoroacetonitrile.

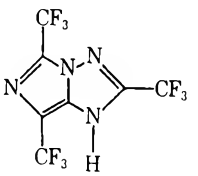
This addition of sodium cyanide to 3 equiv of trifluoroacetonitrile closely parallels the known addition of potassium cyanide to 3 equiv of cyanogen to give an analogous dihydrotetrazapentalene that contains cyano groups in place of the trifluoromethyl groups.[4]

The dihydrotetrazapentalene structure of the anion of **9** was supported by the spectral data. The ^{19}F nmr spectrum, which was obtained on the readily purified tetramethylammonium salt, indicated three different trifluoromethyl groups. The two lower field signals, probably due to the CF_3 groups at the 4 and 6 positions, were split to quartets by a spin–spin coupling of 2.1 Hz. The ultraviolet spectrum of the tetramethylammonium salt showed maxima at 268 and 245 mμ, indicating aromaticity.

Acidification of the water-soluble sodium salt **9** gives a water-insoluble acidic product (**10**). Two tautomeric structures (**10a** and **10b**) for this product are theoretically possible. Because of the acidic nature of **10** (pK_a = 2.75 in 40% ethanol), the position of the lone hydrogen is difficult to ascertain. To determine which of the two tautomeric structures (**10a** and **10b**) best represents **10**, a sample containing a ^{15}N label at the 3 position was prepared from ^{15}N-labeled sodium cyanide and unlabeled trifluoroacetonitrile.



10a

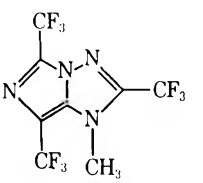


10b

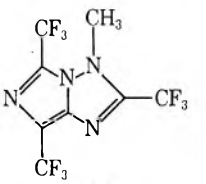
If the proton were bonded directly to the labeled nitrogen (as in **10b**), a large spin–spin coupling between the ^{15}N and ^{1}H would be expected in the proton nmr spectrum,[5] unless hydrogen exchange were very rapid. Also, the signal band width should be much less than that observed in the spectrum of the unlabeled material, since ^{15}N has no quadrupole.

The actual proton nmr spectrum of the labeled sample of **10** was essentially the same as that of the unlabeled sample in the temperature range from −120 to 30°. Since coupling to ^{15}N was not observed, and signal narrowing due to loss of quadrupole interaction was not observed, the proton is not tightly bound to the ^{15}N. Rapid proton exchange (at least, in the nmr time scale) appears unlikely, since low temperatures, which should slow the exchange, did not change the width of the signal. Also, an equilibrating mixture containing appreciable amounts of both tautomers (**10a** and **10b**) appears unlikely, since the ^{19}F nmr spectrum of **10** in acetone shows well-resolved quartets for the two lower field absorptions. The evidence thus indicates that **10** exists primarily in only one tautomeric form, **10a**, and that protonation of the anion of **9** occurs at the 1 position (on the unlabeled nitrogen).

When **10** was treated with diazomethane in ether, the crude methylated product apparently consisted of a 93:7 mixture of two isomeric monomethyl derivatives (**11** and **12**). The major product was purified by recrystallization. Its ^{19}F and ^{1}H nmr spectra indicate that the protons on the methyl group are spin–spin coupled to the fluorines on two of the CF_3 groups (J_{FH} ~ 0.6 Hz). One of the coupled CF_3 groups is at the highest field position and is probably the group at the 2 position since it is not coupled to the other two CF_3 groups. The other CF_3 group coupled to the methyl is at the lowest field position, and is likely at the 4 position, since it has been observed that CF_3 groups attached to a carbon atom flanked by two nitrogen atoms absorb at a higher field position than CF_3 groups in otherwise similar situations attached to a carbon atom flanked by one nitrogen atom and one carbon atom[6] If these assignments are correct, then it appears that the major methyl isomer is **11**, since coupling of the methyl with the CF_3 groups at the 2 and 4 positions is more likely in this isomer than in structure **12**.



11



12

Experimental Section

2,4,6-Tris(trifluoromethyl)-1,6a-dihydro-1,3,5,6a-tetrazapentalene (10).—Trifluoroacetonitrile, 85.5 g (0.9 mol), was distilled into stirred suspension of 25 g (0.5 mol) of sodium cyanide in 250 ml of dimethylformamide. The rate of addition was adjusted so that the temperature did not rise above 40°. The mixture was stirred for 1 hr and then poured into 300 ml of 10% hydrochloric acid. The oil that separated was washed with successive portions of water until it solidified. The solid was filtered off, washed with water, and dried in a desiccator over P_2O_5 to give 65.5 g (70%) of crude **10** as a light-yellow powder. A colorless sample, mp 180–195° dec, was obtained by recrystallization from benzene: uv (ethanol) λ_{max} 266 mμ (ε 5400), 246 (4250), and 228 (3750); ^{19}F nmr (acetone), CCl_3F std, δ 59.8 ppm (q, J = 0.9 Hz, 3 F), 62.9 (q, J = 0.9 Hz, 3 F), and 64.9 (s, 3 F); ^{1}H nmr (acetone) τ −3.3; ir (KBr) 6.00, 6.37, 6.53, and 6.66 μ.

Anal. Calcd for $C_7HF_9N_4$: C, 26.94; H, 0.32; F, 54.79; N, 17.95; neut equiv, 312. Found: C, 27.07; H, 0.36; F, 54.86; N, 17.69; neut equiv, 312.

Tetramethylammonium Salt of 10.—A solution of 1.0 g of tetramethylammonium chloride in 10 ml of water was mixed with a solution prepared by dissolving 1.0 g of **10** in 10 ml of 5% sodium bicarbonate. The precipitate that formed was filtered off, washed with water, and recrystallized from alcohol–ether to give 0.6 g of the tetramethylammonium salt of **10** as colorless crystals: mp 284–285° dec; uv (ethanol) λ_{max} 268 mμ

(4) O. W. Webster, U. S. Patent 3,093,653 (1963).

(5) G. Binsch, J. B. Lambert, B. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 5564 (1964).

(6) See ref 3 for leading references.

(ε 7100) and 245 (5800); ir (KBr) 6.28, 6.55, 6.69 μ; ^{1}H nmr (acetone-d_6) τ 6.53 (t, J_{NH} = 0.5 Hz); ^{19}F nmr (acetone), CCl_3F std, δ 57.2 ppm (q, J = 2.1 Hz, 3 F), 60.9 (q, J = 2.1 Hz, 3 F), and 64.2 (s, 3 F). An analytical sample was prepared by a second recrystallization from alcohol–ether.

Anal. Calcd for $C_{11}H_{12}F_9N_5$: C, 34.29; H, 3.14; F, 44.39; N, 18.18. Found: C, 34.41; H, 3.30; F, 44.14; N, 17.84.

3-Methyl-2,4,6-tris(trifluoromethyl)-3,6a-dihydro-1,3,5,6a-tetrazapentalene (11).—A 3% solution of diazomethane in ether was added dropwise to a solution of 1.0 g of **10** in 5 ml of ether until no further evolution of nitrogen was evident. The solution was evaporated to dryness. The ^{1}H nmr spectrum of the crude product showed two signals at 5.65 (7%) and 6.08 (93%). Two recrystallizations from pentane gave 0.75 g of 11 as long needles: mp 43–45.5°; uv (ethanol) λ_{max} 266 mμ (ε 3800), 226 (5500); ir (KBr) 6.12, 6.42, 6.49, and 6.63 μ; ^{1}H nmr (acetone-d_6) τ 6.08 (poorly resolved multiplet, probably two overlapping quartets, $J_{HF} \sim 0.6$ Hz); ^{19}F nmr (acetone), CCl_3F std, δ 57.5 ppm (m, probably two overlapping quartets with J_{FF} = 1.0 and J_{FH} = 0.6 Hz), 62.2 (q, J = 1.0 Hz), and 64.1 (q, J = 0.6 Hz). An analytical sample was prepared by a third recrystallization from pentane.

Anal. Calcd for $C_8H_3F_9N_4$: C, 29.46; H, 0.93; F, 52.43; N, 17.18. Found: C, 29.26; H, 0.87; F, 52.48; N, 16.90.

Registry No.—**10a**, 25894-19-3; tetramethylammonium salt of **10a**, 25894-20-6; **11**, 25894-21-7.

Structures of Alleged 1,4-Dihydropyrazines

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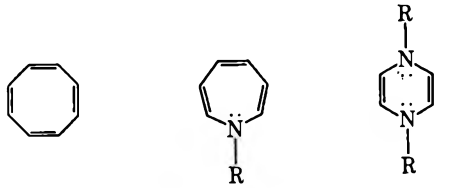
Received April 16, 1970

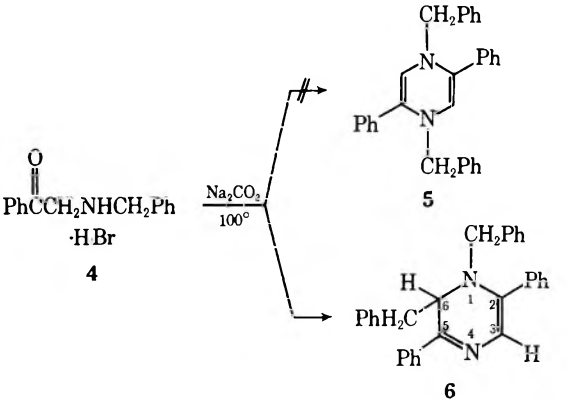
The 1,4-dihydropyrazine ring system is an interesting conjugated cyclic structure containing 8 π electrons. It is electronically analogous to cyclooctatetraene and 1*H*-azepine, both of which have in recent years displayed some fascinating chemistry.[1] Since the 1,4-



1 2 3

dihydropyrazine ring system is generally thought to be a known structure[2] and has been used to demonstrate the nonaromatic character of 8-π-electron compounds[3] we are prompted to report the following results. We have repeated the work in the most frequently quoted reference[4] and find the original structural assignments to be in error.

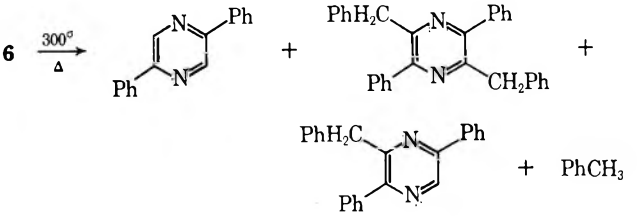
Mason[4] has reported that the base-catalyzed cyclodehydration of *N*-phenacylbenzylamine hydrobromide (**4**) gives 1,4-dihydropyrazine (**5**). The nmr spectrum



4 5 6

of the product from this reaction showed in the nonaromatic region two doublets at τ 5.17 and 5.30 (1 H, J = 5.0 Hz), a quartet (AB), centered at 6.15 (2 H, J = 15.0 Hz), and a complex multiplet at 6.83–7.62 (2 H). This spectrum is clearly inconsistent with **5**. However, structure **6** is in agreement with the available data. The two proton multiplet at τ 6.83–7.62 and the one proton doublets at 5.17 and 5.30 are assigned to the AB and the X portions of an ABX spectrum. These absorptions represent the benzyl hydrogens of the benzyl group at C_6 and methine hydrogen at C_6. Irradiation of the τ 6.83–7.62 multiplet caused the doublets at 5.17 and 5.30 to collapse into a singlet confirming the coupling between these two groups of hydrogens. The AB quartet centered at τ 6.15 is assigned to the benzyl hydrogens adjacent to the nitrogen atom. The nonequivalence of the hydrogens on both benzyl substituents is attributable to the presence of the asymmetric carbon atom (C_6) in dihydropyrazine **6**. Similar effects have been observed in related systems.[5]

Pyrolysis of **6** gave a mixture of pyrazines which further supports the postulated dihydropyrazine structure for **6**.



The reaction of diphenacylbenzylamine hydrobromide with benzylamine is also reported to give the 1,4-dihydropyrazine ring system,[4] **7**. The nmr spectrum of the reaction product, which is similar to **6**, is inconsistent with structure **7**. The methine hydrogen at C_6 occurs as two doublets (τ 5.17 and 5.32, J = 5 Hz) further split by the vinyl hydrogen (τ 3.42, d, J = 1 Hz) at C_2. The benzyl hydrogens of the benzyl group (τ 6.87–7.70) at C_6 occur as a complex multiplet. Irradiation of the τ 6.87–7.70 multiplet caused the doublets at τ 5.17–5.32 to collapse into a singlet thus confirming the coupling between these groups of hydrogens. The benzyl hydrogens adjacent to the nitrogen occur as an AB quartet centered at τ 6.32 (J = 15 Hz).

* Author to whom correspondence should be addressed.

(1) For leading references, see (a) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and L. M. Leichter, *J. Org. Chem.*, **34**, 2888 (1969); (b) G. Schroder, "Cyclooctatetraene," Verlag Chemie, Weinheim/Bergstr., Germany, 1956.

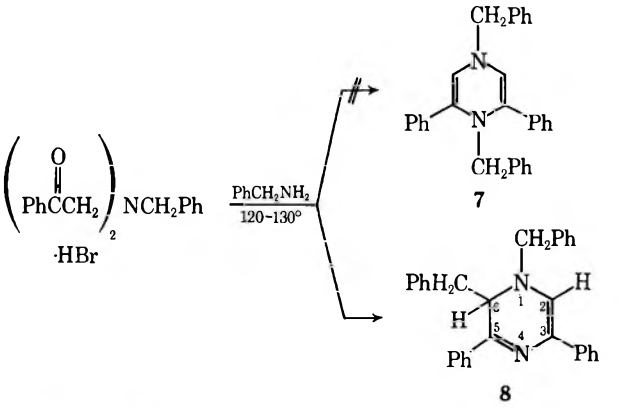
(2) Y. T. Pratt and R. C. Elderfield, *Heterocycl. Compounds*, **6**, 414 (1957).

(3) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 276.

(4) A. T. Mason and G. R. Winder, *J. Chem. Soc.*, **63**, 1355 (1893).

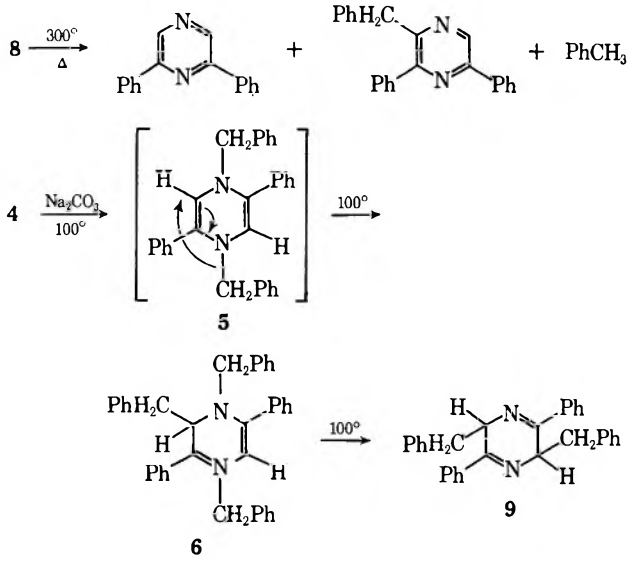
(5) J. C. Randall, J. J. McLeskey, III, P. Smith, and M. E. Hobbs, *J. Amer. Chem. Soc.*, **86**, 3229 (1964).

An attempt was made to isolate the 1,4-dihydropyrazine **7** by carrying out the reaction at lower tempera-



ture in refluxing benzene and azeotropically removing the water produced. Only the dihydropyrazine **8** could be isolated.

Pyrolysis of **8** gave a mixture of 3,5-diphenylpyrazine and 3,5-diphenyl-2-benzylpyrazine.



The formation of both **6** and **8** can be rationalized as initially proceeding through the 1,4-dihydropyrazine which undergoes a 1,3 shift of a *N*-benzyl substituent.[6] 1,3-Sigmatropic reactions are rare, occurring only under very favorable thermodynamic conditions.[7] The apparent ease at which the group migrates in this case could be due to the migratory aptitude of the benzyl group and/or the instability of the enamine compared to the imine. Since **6** is also an enamine containing a *N*-benzyl substituent its nonrearrangement to **9** under the reaction conditions indicates there is probably additional instability associated with enamine **5**.

Instability of **5** compared to a normal enamine would not be unexpected since *N*-alkyl derivatives of the isoelectronic azepines are also known to be very unstable, a fact which can be attributed to the antiaromatic character of 8-π-electron systems.[8]

(6) Alternatively, as suggested by a referee, the reaction may not be concerted but could involve a diradical intermediate.

(7) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 114.

(8) (a) R. Breslow, J. Brown, and J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967); (b) R. Breslow, *Angew. Chem., Int. Ed. Engl.*, **7**, 565 (1968).

Benzyl migration of **6** to give **9** probably does occur at higher temperatures and **9** is most likely the intermediate leading to 2,5-diphenyl-3,6-dibenzylpyrazine in the pyrrolysis experiment. We are continuing our efforts toward an unambiguous synthesis of the 1,4-dihydropyrazine ring system.

Experimental Section[9]

1,6-Dibenzyl-2,5-diphenyl-1,6-dihydropyrazine (6).—To 4.00 g of phenacylbenzylamine hydrobromide was added 20 ml of a saturated Na_2CO_3 solution. The reaction mixture was stirred magnetically and refluxed for 1 hr. The red oil obtained was washed with hot water and then dissolved in ethanol. On standing overnight 0.55 g of yellow crystals precipitated, mp 150–155°. Recrystallization from ethanol gave the analytical sample: mp 153–157°; nmr ($CDCl_3$) τ 1.83–3.35 (m, 18 H, aromatics), 5.17 and 5.30 (two doublets, J = 5.0 Hz, 1 H), 6.15 (center of AB, J = 15 Hz, 2 H), and 6.83–7.62 (m, 2 H); ir ($CHCl_3$) 1602, 1495, 1445, 1347, and 694 cm^{-1}.

Anal. Calcd for $C_{30}H_{26}N_2$: C, 86.95; H, 6.28; N, 6.76. Found: C, 87.08; H, 6.40; N, 6.69.

Pyrolysis of 6.—To a 25.0 × 1.0 cm tube was added 372 mg of **6**. The tube was sealed under vacuum (10^{-5} Torr) and heated to 300° for 40 min. The nmr spectrum of the crude pyrolysate showed the presence of 2,5-diphenyl-6-benzylpyrazine (relative ratio 3:1:3) and toluene. The toluene was removed *in vacuo* and recrystallization of the residue gave 2,5-diphenylpyrazine: mp 194–196° (lit.[10] 195–196); nmr ($CDCl_3$) τ 0.95 (s, 2 H) and 1.8–6.7 (m, 10 H). The mother liquors were concentrated and chromatographed on a thin-layer plate (1.5-mm silica gel eluted with 10% ether in benzene). The first band eluted was shown by nmr to be a mixture of 2,5-diphenylpyrazine and 2,5-diphenyl-6-benzylpyrazine. Repeated recrystallization from ethanol produced a very small amount of pure 2,5-diphenyl-6-benzylpyrazine: mp 98–99°; nmr ($CDCl_3$) τ 1.07 (s, 1 H), 1.8–3.3 (m, 10 H), and 5.75 (2 H, s), The second band off the tlc plate proved to be 2,5-diphenyl-3,6-dibenzylpyrazine: mp 145–147°; nmr ($CDCl_3$) τ 2.53 (s, 10 H), 2.83 (s, 10 H), and 5.72 (s, 4 H).

Anal. Calcd for $C_{30}H_{24}N_2$: C, 87.35; H, 5.82; N, 6.79. Found: C, 87.48; N, 5.82; N, 6.78.

1,6-Dibenzyl-3,5-diphenyl-1,6-dihydropyrazine (8).—To 2.0 g of diphenacylbenzylamine hydrobromide was added 1.0 g of benzylamine. The reaction mixture was heated in an oil bath at 120–130° for 40 min. The now red-orange oil was triturated with ether and the benzylamine hydrobromide was filtered. Removal of the ether *in vacuo* gave a red-orange oil which crystallized from ethanol, mp 88–96°. Recrystallization from ethanol gave 0.78 g of yellow crystals: mp 94–98°; nmr ($CDCl_3$) τ 2.00–3.27 (m, 15 H), 3.42 (d, J = 1.0 Hz, 1 H), 5.17, and 5.30 (two doublets, J = 5.0 Hz, further coupled, J = 1.0 Hz, 1 H), 6.10 (q, J = 15.0 Hz, 2 H), and 6.87–7.50 (m, 2 H); ir ($CHCl_3$) 1592, 1493, 1452, 1342, and 692 cm^{-1}.

Anal. Calcd for $C_{30}H_{26}N_2$: C, 86.95; H, 6.28; N, 6.76. Found: C, 86.80; H, 6.41; N, 6.87.

1,6-Dibenzyl-3,5-diphenyl-1,6-dihydropyrazine (8).—To 20.4 g of diphenacylbenzylamine hydrobromide and 13.5 g of benzylamine was added 100 ml of benzene. The reaction was refluxed for 4 hr during which time the water was azeotropically removed with the aid of a Dean-Stark apparatus. The precipitate of benzylamine hydrobromide was removed by filtration and filtrate concentrated *in vacuo* to give an oily residue. This was dissolved in ethanol–ether and on standing over night 10.0 g of yellow crystals precipitated which proved to be **8**.

Pyrolysis of 8.—To a 25.0 × 1.0 cm glass tube was added 600 mg of **8**. The tube was sealed under vacuum (10^{-5} Torr) and heated for 40 min at 300°. The nmr spectrum of the crude product shows the presence of 2,6-diphenylpyrazine, 2,6-diphenyl-3-benzylpyrazine (relative ratio 5:6) and toluene. The products were purified by removal of the toluene *in vacuo* and chromatographing the residue on a thin-layer plate (1.5 mm silica gel eluted with 3:1 benzene ether). The first band eluted was recrystallized from ethanol and gave 2,6-diphenylpyrazine as

(9) Melting points are uncorrected. The microanalyses were performed by Gailbraith Laboratories, Knoxville, Tenn. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord. The nmr spectra were determined with a Varian A-60 spectrophotometer.

(10) Gerald Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).

colorless crystals: mp 80–81° (lit.[4] 88–89); nmr ($CDCl_3$) τ 0.84 (s, 2 H) and 1.8–2.8 (m, 10 H).

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.76; H, 5.17; N, 12.06. Found: C, 82.93; H, 5.31; N, 11.84.

The second band was recrystallized from ethanol and gave 2,6-diphenyl-3-benzylpyrazine as colorless crystals: mp 98–99° (lit.[4] 95°); nmr ($CDCl_3$) τ 1.05 (s, 1 H), 1.8–2.9 (m, 15 H), and 5.75 (s, 2 H).

Registry No.—6, 25827-90-1; 8, 25827-91-2; 2,5-diphenyl-6-benzylpyrazine, 25827-92-3; 2,5-diphenyl-3,6-dibenzylpyrazine, 25827-93-4; 2,6-diphenylpyrazine, 25827-94-5; 2,6-diphenyl-3-benzylpyrazine, 25827-95-6.

Acknowledgment.—This work was supported by the Research Foundation of the State University of New York.

Phytochemical Studies. IX. A New Flavone, Velutin[1]

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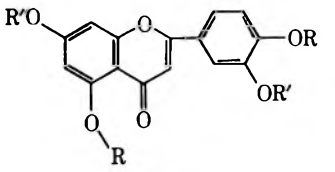
Received April 14, 1970

In connection with a projected phytochemical study of Washington vegetation, *Ceanothus velutinus*, a member of the Rhamnaceae or buckthorn family, was selected for initial examination. This shrub is distributed along the drier, east slopes of the Cascades and can be easily found in cleared timber areas. The leaf oil has been investigated in the past because of a pleasant odor, but only cinnamate esters were reported by earlier workers.[2]

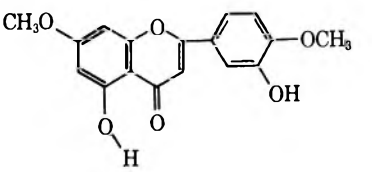
A pentane extract of the leaves deposited a yellow powder, which was purified by crystallization from ethyl acetate. The resulting product or velutin analyzed for $C_{17}H_{14}O_6 \cdot {}^1/_2H_2O$; however, a true molecular weight of 314 was given by mass spectroscopy. A positive ferric chloride test indicated a phenol, and, more specifically, magnesium–hydrochloric acid suggested a flavone. The presence of two hydroxyl groups was shown by the conversion of velutin into a diacetate, $C_{21}H_{18}O_8$.

The infrared spectrum possessed a hydrogen-bonded conjugated carbonyl group and an extended aromatic ring system. In the ultraviolet, the main and secondary absorptions were similar to those reported for tetrasubstituted flavones.[3] Generally, the shape of the bands implied the existence of hydroxyl or methoxyl substituents at the 3′ and 4′ positions in the flavone ring system. The nuclear magnetic resonance spectrum contained two singlet methoxy groups, an upfield pair of doublets with typical meta-coupling constants (centered on their chemical shifts), a singlet due to an olefinic hydrogen, a broad peak of three aromatic hydrogens, and a hydroxyl shifted downfield due to hydrogen bonding. It will be noted that 13 of the 14 protons were definitely identified here; the missing hydroxyl proton probably exchanged with the water of solvation as detected in the microanalysis. These particular assignments were facilitated by use of an extensive compilation of flavone nmr data.[4] A detailed solvent-shift study was not attempted because of the insolubility of velutin.[5,6] The mass spectral fragmentation pattern was rationalized with the aid of known models,[7] especially with flavones containing a 4′-hydroxyl group.[8]

The available chemical and spectral information was sufficient to postulate two alternative structures for the compound: 4′,5-dihydroxy-3′,7-dimethoxyflavone (Ia) or 3′,5-dihydroxy-4′,7-dimethoxyflavone (II). Ve-



Ia, R = H; R′ = CH_3
b, R = Ac; R′ = CH_3
c, R = CH_3; R′ = CH_3
d, R = H; R′ = H



II

lutin on exhaustive methylation formed luteolin tetramethyl ether (Ic), while demethylation produced luteolin (Id).[9] These results verified both the substitution pattern and the ring system existing in the flavone. The crucial placement of the hydroxyl groups in both the A and B rings was made through ultraviolet studies. A shift of 48 mμ with sodium ethoxide in ethanol[3] fixed one hydroxyl at 4′ rather than 3′, while a shift of 35 mμ with aluminum chloride in ethanol[10] confirmed the placement of another hydroxyl group at 5. Compound Ia is known in the form of a dehydrogenation product from a naturally occurring flavanol,[11,12] and the melting points and ultraviolet spectra of both it and the corresponding diacetate are in agreement with the present data.[12] Since comparison samples no longer exist,[13] formula II cannot be completely excluded at this time. However, the weight of the evidence greatly favors Ia; so this structure is now assigned to velutin.

* Author to whom correspondence should be addressed.

(1) For the previous paper in this series, see K.-T. Wang, K. C. Das, Y.-Y. Lin, and B. Weinstein, *Experentia*, **26**, 930 (1970).

(2) L. W. Richards and E. V. Lynn, *Proc. Amer. Pharm. Ass.*, **23**, 332 (1934).

(3) L. Jurd in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 107.

(4) T. J. Batternam and R. J. Highet, *Aust. J. Chem.*, **17**, 428 (1964).

(5) R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, **24**, 1407 (1968).

(6) R. G. Wilson and D. H. Williams, *J. Chem. Soc. C*, 2477 (1968).

(7) A. Pelter, P. Stainton, and M. Barber, *J. Heterocycl. Chem.*, **2**, 1262 (1965).

(8) H. Audier, *Bull. Chem. Soc. Fr.*, 2892 (1966).

(9) We thank Professor T. R. Seshadri, University of Delhi, for a sample of luteolin.

(10) L. Jurd, *Phytochemistry*, **8**, 445 (1969).

(11) S. R. Gupta, N. Narashimhachari, and T. R. Seshadri, *J. Sci. Ind. Res., Sect. B*, **12**, 229 (1953).

(12) T. A. Geissman, *Aust. J. Chem.*, **11**, 376 (1958).

(13) Professor T. A. Geissman, University of California at Los Angeles, personal communication, Feb 25, 1970.

Experimental Section[14]

Velutin (4′,5-Dihydroxy-3′,7-dimethoxyflavone) (Ia).—A collection of *Ceanothus velutinus* was made in late October 1969, about 5 km north along the Lake Kachess Dam Road, near Snoqualmie Pass, Wash. The leaves were air-dried for 1 week, and then ground in a Wiley mill and extracted with hot pentane for 10 days. On standing, the dark solution deposited a yellow powder, which was collected, washed, dried, and crystallized from a large volume of ethyl acetate to yield the analytical sample (0.80 g, from 1.6 kg of leaves): mp 225–227° (lit.[10] 223–224°); R_f 0.66; ν_{max} 3440 (OH), 2950 (CH), 1660 (C=O), 1605 (C=C), and 847 cm^{-1} (1,2,3,5 tetrasubstitution); λ_{max} 238, 250, 268, and 348 mμ (log ε 4.04, 4.05, 4.01, and 4.16); δ 3.85 (OCH_3), 3.92 (OCH_3), 6.35 and 6.75 (6-H and 8-H), 6.90 (3-H), 7.01 (5′-H), 7.5–7.7 (6′,2′-H), and 12.93 (5-OH); mass spectrum 314 (parent), 284 (M − 30), and 137 ($C_7H_5O_3$). The flavone produced a brown color with ferric chloride, and a red-orange with magnesium–hydrochloric acid. The ultraviolet shifts with aluminum chloride (10%) were almost identical with those of 3′,7-di-*O*-methylluteolin.[10]

Anal. Calcd for $C_{17}H_{14}O_6 \cdot {}^1/_2H_2O$ (323.29): C, 63.15; H, 4.61. Found: C, 63.51; H, 4.29.

Treatment with acetic anhydride and a drop of sulfuric acid formed the diacetate (Ib), as colorless needles from benzene, mp 207° (lit.[12] 207°).

Methylation with dimethyl sulfate–potassium carbonate afforded luteolin tetramethyl ether (Ic), purified by sublimation at 175° (0.01 mm): mp 192–194° (lit.[15] 192–193°); mass spectrum 342 (parent), 313 (M − 29), 312 (M − 30), 181 ($C_9H_9O_4$), 180 ($C_9H_8O_4$), 162 ($C_{10}H_{10}O_2$), 152 ($C_8H_8O_3$), 147 ($C_9H_7O_2$), and 137 ($C_7H_5O_3$).

Demethylation with hydrogen iodide (49%) gave luteolin (Id), as yellow crystals from ethanol, mp 328–330° (lit.[15] 330–331°).

Registry No.—Ia, 25739-41-7.

Acknowledgment.—We thank the National Center for Urban and Industrial Health (Public Health Service Grant No. U1 00697) for the support of this work.

(14) Melting points are uncorrected. Microanalyses were provided by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Spectral measurements were made as follows: infrared (potassium bromide), ultraviolet (95% ethanol), and nuclear magnetic resonance (deuteriodimethyl sulfoxide, internal tetramethylsilane, 60 MHz). The mass spectrum was obtained on a double-focusing instrument. Thin layer chromatography employed silica gel G as the support, ethyl acetate as the developer, and iodine for detection.

(15) J. Gripenberg in "The Chemistry of Flavonoid Compounds," T. A. Geissman, Ed., Macmillan, New York, N. Y., 1962, p 406.

Epoxidation of Griseofulvin. A New Reaction of the β-Methoxyenone System

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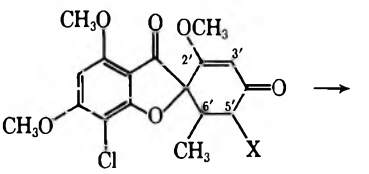
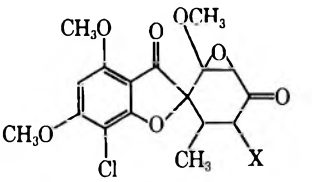
Received May 13, 1970

We would like to report that griseofulvin (**1**) and its 5′-bromo analog (**8**) are converted to their corresponding epoxy derivatives **2** and **9** in good yield by treatment with hydrogen peroxide and base. Epoxidation of **1** and its 5′-methylsulfonyl analog **5** was also achieved with benzoyl peroxide–methoxide in good yield but with poor conversion.

To the best of our knowledge this represents a new reaction of an enol ether of a β-diketone and would be expected to be generally applicable. We were led to this finding in the following manner.



1, X = H
5, X = SO_2CH_3
8, X = Br



2, X = H
5a, X = SO_2CH_3
9, X = Br

When we previously[1] attempted to introduce oxygen at C-5′ in griseofulvin (**1**) by allowing 5′-formylgriseofulvin (**3**)[2] to react as its sodium salt with benzoyl peroxide in methanol, we obtained the overoxidized product, 5′-hydroxydehydrogriseofulvin (**4**), presumably owing to the ready decarbonylation of an initially formed 5′-oxygenated-5′-formyl intermediate. We hoped to circumvent this difficulty by using 5′-methylsulfonylgriseofulvin (**5**) in place of **3**; however, we encountered another unexpected result.

Thus, on treating **5**, readily obtainable from 5′-methylthiogriseofulvin[3] by peracid oxidation, with **1** equiv of sodium methoxide in methanol followed by 1 equiv of benzoyl peroxide, we obtained a product which was indicated by its nmr spectrum to be a 2-component mixture, in approximately a 1:1 ratio, consisting of unreacted **5** and a new substance in which the C-2′–C-3′ double bond appeared to have been transformed. This was suggested by the appearance of a new OCH_3 signal in the spectrum at δ 3.27, 0.39 upfield from the OCH_3 in signal in **5**, and a decrease in intensity (to ~0.5) of the vinyl proton of **5**. Further characterization as detailed in the Experimental Section established its structure as the epoxide **5a**.

Treating griseofulvin (**1**) in a similar manner gave a comparable result. The new product was isolated by thick layer chromatography and was formulated as epoxygriseofulvin (**2**) on the basis of its spectral (ir, nmr, mass spectrum) and analytical data. Its nmr spectrum additionally indicated it be a single isomer.

A significant improvement in the conversion of **1** to **2** was achieved by using hydrogen peroxide–base, the reagent commonly employed for epoxidizing α,β-unsaturated ketones. (The epoxidation with benzoyl peroxide–methoxide is presumed to take place in a manner similar to that postulated for the hydrogen peroxide–base epoxidation,[4] the required benzoyl peroxy anion, $PhCOOO^-$, being generated by methoxide attack on benzoyl peroxide. The poorer conversion obtained with $PhCO–OOCOPh^-$–OCH_3 could be due to the

(1) H. Newman, *J. Heterocycl. Chem.*, **7**, 957 (1970).

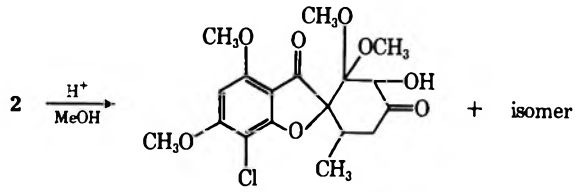
(2) H. Newman and T. L. Fields, *J. Org. Chem.*, **35**, 3156 (1970).

(3) (a) The facile preparation of this compound from **3** and methylthiotosylate[3b] will be published elsewhere shortly. (b) See R. C. Autrey and P. W. Scullard, *J. Amer. Chem. Soc.*, **90**, 4921 (1968).

(4) See the review on epoxy ketones by J. L. Pierre, *Ann. Chim. (Paris)*, 159 (1966).

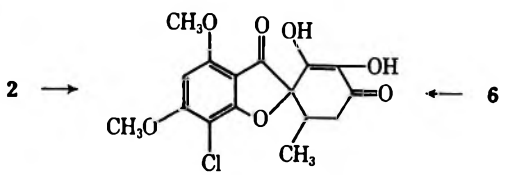
competitive destruction of the oxidizing species by another route.)

Treatment of compound 2 in methanol containing a very small amount of concentrated sulfuric acid at room temperature led to its immediate transformation to the dimethyl ketal 6 and an isomeric product in roughly equal amounts. The structure of 6 follows

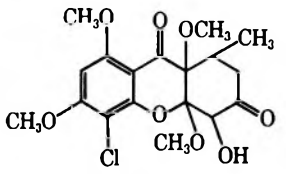


6

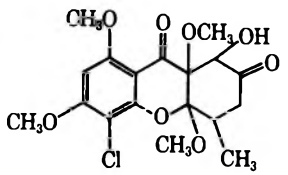
from its spectral (ir, nmr, mass spectrum) and analytical data (See Experimental Section) and its hydrolysis to 3′-hydroxygriseofulvic acid (7).[5] also obtained from the direct aqueous hydrolysis of 2.



The isomeric product, indicated as such by its M^+ at *m/e* 400 in the mass spectrum and its analytical data, exhibits an nmr spectrum (See Experimental Section) which would be consistent with its formulation as the rearrangement product 8 or 8a (no stereochem-

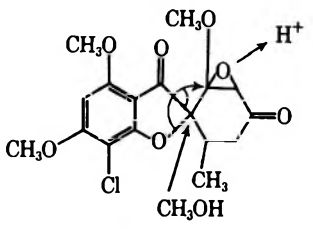


8



8a

istry implied in the structures) and which could arise as indicated by the arrows in A, where epoxide opening is accompanied by migration of either the ring B oxygen or ring B carbonyl followed by methanolysis of the resulting electron deficient center.



A

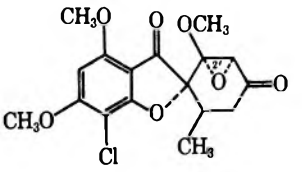
The formation of 8 or 8a is interesting in that it represents a skeletal rearrangement of 2 under mildly acidic conditions. By contrast, the carbon framework of griseofulvin is stable to acid.[6]

The nmr signals of the two ketal OCH_3 groups in 6 were well separated, appearing at δ 3.57 and 3.40. It would appear not unreasonable to assign the higher field signal to the OCH_3 cis to the ring B carbonyl group, it being closer in this configuration to the shielding cone of this group.[7]

With regard to the stereochemistry of the epoxidation, it will become unequivocally known when an X-ray study of 5′-bromoepoxygriseofulvin 9 (by Dr. D. B. Cusulich of our laboratories) currently in progress will be completed. 9 was obtained by epoxidizing 5′-bromogriseofulvin (8) as described above, and was related to 2 by converting it to the common intermediate 6 with triphenylphosphine in methanol. The ketal 6 was isolated directly from the reaction mixture which proved to be acidic, the result of rapid acid-catalyzed opening of the initially formed reduction product 2.

A chemical approach to the solution of the stereochemical problem was attempted, however, predicated on the nmr assignments made above for the two ketal OCH_3's in 6. It was reasoned that acid-catalyzed opening of the epoxide in 2 in CD_3OH should lead, ideally in a completely trans diaxial opening, to the disappearance of one of the OCH_3 signals. The stereochemistry of the epoxide ring would then follow. The acidic conditions of the reaction and the methoxy substituent on the epoxide ring makes a ring opening *via* an SN1-like pathway more likely and the stereospecificity of the opening, therefore, questionable. It would, however, still appear reasonable to expect that, to the extent that one isomer does predominate, it would be that one arising from a trans diaxial opening.

The result of the experiment was that both OCH_3 signals were, in fact, present with the lower field signal predominating in a ratio of ~3:1. If one accepts the foregoing argument, one would conclude that the epoxide ring must have been α oriented (*i.e.*, trans to the ring B carbonyl) as in B resulting in a predominant approach of CD_3OH from the β face or cis to the ring B carbonyl. (In the process the stereochemistry of the OCH_3 at C-2′ is inverted.)



B

We however, emphasize again that the stereochemistry shown in B is at, this point, only tentative, based as it is on intuitively reasonable, but nevertheless unproven assumptions.

Experimental Section[8]

Epoxygriseofulvin (2). A. Hydrogen Peroxide–KOH.—To a cooled (ice water) stirred suspension of 2.8 g (0.008 mol) of griseofulvin (1) in 80 ml of methanol containing 5 ml of 30% H_2O_2 (~0.044 mol) was added ~400 mg of potassium hydroxide (pellets) (~0.007 mol). The reaction mixture was stirred in the cooling bath for 15 min, allowed to come to room temperature (with stirring) during 15 min, and then diluted with ice water,

(5) The tautomeric form shown is done so arbitrarily.

(6) J. F. Grove, J. MacMillan, T. P. C. Muholland, and M. A. T. Rogers, *J. Chem. Soc.*, 3949 (1952).

(7) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 28.

(8) Melting points are uncorrected. Nmr spectra were determined on a Varian A-60A spectrometer using tetramethylsilane as an internal standard and mass spectra on an AEI MS-9 spectrometer. Thin layer chromatograms were run on phosphor-containing silica gel plates (Analtech, Inc., Wilmington, Del.); thick layer chromatograms were run on 2-mm silica gel plates (E. Merck Ag., Darmstadt, Germany; distributed by Brinkmann Instrument Inc., Westbury, N. Y.).

and the colorless solid was collected by filtration, washed well with water, and air-dried, yield 2.8 g. The crude product was heated in boiling ethyl acetate and the mixture filtered to separate an insoluble gummy material. Addition of *n*-hexane to the colorless filtrate caused a colorless crystalline solid to separate, yield 1.75 g. Thin layer chromatography indicated very minor contamination with unreacted griseofulvin, which was removed most efficiently by partition chromatography (on Celite 545 using heptane–$CHCl_3$–methanol–water 50:8:16:1) to yield 1.17 g (41%) of epoxygriseofulvin (**2**), mp 142–160°, which showed a single spot (R_f ~0.6) on tlc (PhH–EtOAc 1:1) and exhibited ir, nmr, and mass spectra identical with those of the analytical sample of **2** prepared as described below.

B. Benzoyl Peroxide–Methoxide.—A stirred suspension of 0.35 g (0.001 mol) of griseofulvin (**1**) and 0.48 g (0.002 mol) of benzoyl peroxide in 10 ml of methanol at room temperature was treated with 2 ml of ~1 *M* NaOMe in methanol (0.002 mol). The mixture was stirred at room temperature for 15 min (after 10 min. the original strongly basic solution was essentially neutral) and filtered to separate 150 mg of insoluble solid corresponding in R_f to griseofulvin. The slightly turbid filtrate was poured into ice water and the solid which formed (during 15 min) was collected and air-dried to yield 130 mg of product which showed two spots on tlc (PhH–EtOAc 1:1), R_f ~0.45 and 0.6, the former corresponding to that of griseofulvin. The products corresponding to the two spots were separated by thick layer chromatography using PhH–EtOAc 1:1 for development and were obtained in A a 1:2 ratio (faster:slower). The colorless faster running product, epoxygriseofulvin (**2**), melted at 149–155° after triturating with methanol: λ_{max}^{KBr} 5.80 and 5.87 μ; $\delta_{TMS}^{CDCl_3}$ 6.16 (aromatic H), 4.05, and 4.00 (aromatic OCH_3's), 3.80 (epoxy H), 3.24 (epoxy OCH_3), 2.65–2.46 (mainly 2.65, C-5′ and C-6′ H's), and 0.83 (doublet J = 6 Hz, C-6′ CH_3). The mass spectrum showed an M^+ at m/e 368 (with the expected 370 peak at *ca.* one-third the intensity owing to Cl isotope 37).

Anal. Calcd for $C_{17}H_{17}O_7Cl$ (368.77): C, 55.50; H, 4.62; Cl, 9.66. Found: C, 55.82; H, 4.82; Cl, 9.72.

5′-Methylsulfonylgriseofulvin (**5**).—A solution of 2 g (0.005 mol) of 5′-methylthiogriseofulvin[3] in 100 ml of methylene chloride was treated with 2 g (0.01 mol) of 85% *m*-chloroperbenzoic acid (K & K Laboratories Inc., Plainview, N. Y.) at room temperature. After 1 hr, the reaction mixture was diluted with methylene chloride and washed with cold aqueous sodium bisulfite, bicarbonate, dried, and evaporated to yield a gummy residue which solidified on heating in methanol: yield 1.4 g (64%) of colorless solid; mp 170–173°; λ_{max}^{KBr} 5.83 (s), 6.02 (m), and 6.17, 6.27 (vs); $\delta_{TMS}^{CDCl_3}$ 6.16 (aromatic H), 5.63 (vinyl H), 4.05 and 3.99 (aromatic OCH_3's), 3.66 (vinyl OCH_3), 3.28 ($-SO_2CH_3$), and 1.25 (doublet, J = 6 Hz, C-6′ CH_3).

Anal. Calcd for $C_{18}H_{19}ClSO_8$ (430.86): C, 50.17; H, 4.44; S, 7.44; Cl, 8.23. Found: C, 49.50; H, 4.46; S, 7.05; Cl, 8.37.

5′-Methylsulfonylepoxygriseofulvin (**5a**).—The addition of 0.52 ml (0.52 mmol) of ~1 *M* NaOMe in methanol to a suspension of 220 mg (0.52 mmol) of **5** in 5 ml of methanol gave a yellow solution to which 126 mg (0.52 mmol) of benzoyl peroxide was added (with stirring) at room temperature. A new solid separated 1–2 min after stirring at room temperature for 15 min, and the solid was collected and washed with methanol to yield 148 mg of product, mp 170–176°, whose nmr spectrum in chloroform showed, in addition to the signals corresponding to the various protons in starting **5**, new signals at δ 3.27 (epoxy OCH_3, *cf.* corresponding chemical shift for these protons in **2** and **9**), 3.09 ($-SO_2CH_3$ in **5**), and 1.11 (doublet, J = 6 Hz, C-6′–CH_3 in **5a**) corresponding to the epoxide **5a**. The chemical shift of the new epoxy H is most probably part of the 3.99 aromatic OCH_3 signal as indicated by the increase in intensity of this signal relative to that of the other aromatic OCH_3 at 4.05. (The two were essentially equal in intensity in starting (**5**). The ratio of the two products, estimated from the relative peak intensities, was 1:1. The two compounds ran very close to each other on tlc (PhH–EtOAc 1:1), the front of the slower running **5** touching the rear of the faster running **5a**.

By recycling the product mixture twice more as described above, virtually all the starting **5** was converted to **5a** as indicated by nmr spectral analysis. The product thus obtained (34 mg) melted at 177–180° (shrinks 174°).

Anal. Calcd for $C_{18}H_{19}ClSO_9$ (446.86): C, 48.38; H, 4.29; Cl, 7.94; S, 7.18. Found: C, 48.54; H, 4.20; Cl, 7.96; S, 6.81.

5′-Bromoepoxygriseofulvin (**9**).—A stirred suspension of 1 g (0.0023 mol) of 5′-bromogriseofulvin (**8**) in 40 ml of methanol containing 2.5 ml (~0.0022 mol) of 30% H_2O_2 was cooled in ice water and treated with 200 mg (0.0035 mol) of potassium hydroxide (pellets). After stirring in the cold for 15 min (the system was homogeneous after ~5 min), the mixture was poured into ice water and extracted first with methylene chloride and then with methylene chloride–ether. The organic extracts were washed with aqueous bisulfite, dried, and evaporated to yield 0.47 g of a pale yellow crystalline solid which showed a single spot on tlc (PhH–EtOAc 1:1), R_f ~0.5, and which melted at 157–160° after recrystallization from ethyl acetate (colorless product): λ_{max}^{KBr} 5.80 and 5.89 μ; $\delta_{TMS}^{CDCl_3}$ 6.16 (aromatic H), 4.35 (doublet, J = 10 Hz, C-5′ H), 4.05 and 4.00 (aromatic OCH_3's), 3.27 (epoxy OCH_3), and 1.00 (doublet, J = 6 Hz, C-6′ CH_3).

Anal. Calcd for $C_{17}H_{16}O_7BrCl$ (447.68): C, 45.61; H, 3.60; Cl, 7.92; Br, 17.85. Found: C, 45.62; H, 3.62; Cl, 7.79; Br, 17.56.

Treatment of Epoxygriseofulvin (2) with Dilute Methanolic Acid. Formation of the Dimethyl Ketal 6 and 5-Chloro-4-hydroxy-1,4,4a,9a-tetrahydro-4a,6,8,9a-tetramethoxy-1-methylxanthene-3(2H),9-dione (**7**).—To 5 ml of commercial grade absolute methanol containing 1 drop (Pasteur pipet) of concentrated sulfuric acid was added 170 mg (0.46 mmol) of epoxygriseofulvin, (**2**) at room temperature. A colorless homogeneous solution formed virtually instantaneously. After 4 min at room temperature, the colorless solution was poured into ice water and the mixture was extracted with methylene chloride. The methylene chloride extract was washed with aqueous bicarbonate, dried, and evaporated to yield ~140 mg of a light yellow gum indicated by tlc (PhH–EtOAc 1:1) to be a two component mixture which was separated by partition chromatography on Celite 545 using heptane–chloroform–methanol–water 50:8:16:1.

Faster Moving Component 6.—A colorless solid, 63 mg, had mp 191–193.5°; λ_{max}^{KBr} 5.81, 5.92 (s), and 6.20, 6.30 μ (vs); $\delta_{TMS}^{CDCl_3}$ 6.17 (aromatic H), 5.27 (doublet, J = 7 Hz which collapses to a singlet on proton exchange, C-3′ H), 4.03 and 4.00 (aromatic OCH_3's), 3.57 (C-2′ OCH_3 trans to ring B carbonyl), 3.40 (C-2′ OCH_3 cis to ring B carbonyl), 0.88 (doublet J = 6 Hz C-6′ CH_3); mass spectrum showed M^+ at m/e 400 (with the expected 402 peak at one-third the intensity); R_f ~0.6 (tlc PhH–EtOAc 1:1).

Anal. Calcd for $C_{18}H_{21}O_8Cl$ (401.82): C, 53.93; H, 5.28; Cl, 8.85. Found: C, 54.22; H, 5.31; Cl, 8.78.

Slower Moving Component 7.—A solid, 52 mg, was rendered colorless by triturating with a small amount of methanol: mp 217–221°; λ_{max}^{KBr} 5.80 (infl) (m), 5.90 (s), and 6.20, 6.30 μ (vs); $\delta_{TMS}^{CDCl_3}$ 6.13 (aromatic H), 4.00 and 3.95 (aromatic OCH_3's), 3.54 and 3.27 (the two junction OCH_3's), 0.93 (doublet, J = Hz, C-6′ CH_3). On proton exchange, a somewhat broadened singlet appeared at δ 4.95 and is assigned to the proton α to the OH group; mass spectrum showed M^+ at m/e 400 [and at 402 (1/3 as intense as that at 400)]; R_f ~0.55 (tlc, PhH–EtOAc 1:1).

Anal. Found: C, 53.46; H, 5.43 (calcd as for **6** above).

Repeating the above reaction in CD_3OD gave **6** in which the C-2′ OCH_3 signals in the nmr spectrum appeared in a ratio of 3:1, lower field (δ 3.57, higher field (δ 3.40). (**6** was separated in this experiment by thick layer chromatography using PhH–EtOAc 1:1 for development.)

Refluxing **2** in neat CD_3OD left it unchanged.

Hydrolysis of Epoxygriseofulvin (**2**). **Formation of 3′-Hydroxygriseofulvic Acid** (**7**).—A suspension of 1.75 g of epoxygriseofulvin (**2**) (slightly contaminated with griseofulvin) in 10 ml of commercial grade spectro quality dioxane and 10 ml of 1 *N* HCl was heated on the steam bath with swirling for 1.5 min. A homogeneous system formed. After allowing the solution to cool for 2 min, it was poured into ice water and the colorless solid collected. The product was dissolved in aqueous bicarbonate, and the solution was washed with methylene chloride–ether (to remove the griseofulvin contaminant; griseofulvin does not hydrolyze under these conditions) and reacidified. The precipitated solid was collected washed well with water and air-dried: yield 0.65 g; mp 155–165° (foaming; sample underwent prior shrinking and wetting); λ_{max}^{KBr} 3.0 (broad, s), 5.91 (s), and 6.20, 6.30 μ (vs); $\delta_{TMS}^{CDCl_3-DMSO-d_6}$ 6.20 (aromatic H), 4.05 and 3.99 (aromatic OCH_3's), 3.5–2.3 (methylene and methine H's), 1.00 (C-6′ CH_3).

Anal. Calcd for $C_{16}H_{15}O_7Cl \cdot 2H_2O$ (390.77): C, 49.17; 4.90; Cl, 9.07; H_2O; 9.2. Found: C, 49.81; H, 3.97; Cl, 9.78; H_2O; 7.6.

3′-Hydroxygriseofulvic Acid 7 from the Hydrolysis of 6.—Half of a solution of 14 mg of **6** in 0.3 ml of commercial grade spectro quality dioxane and 0.5 ml of 1 *N* HCl was heated on the steam bath in an open test tube for 15 min and water was added. The gum which separated, rapidly solidified. The light yellow solid was collected and washed well with water. It was soluble in aqueous bicarbonate and showed an infrared spectrum which was essentially identical with that of 3′-hydroxygriseofulvic acid (**6**) obtained above from the hydrolysis of epoxygriseofulvin (**4**).

(The other half of the solution was kept at room temperature for 16 hr and then poured into water. The solid which separated showed a tlc and infrared spectrum identical with those of starting **6**.)

Formation of 6 by Reductive Hydrolysis of 5′-Bromoepoxygriseofulvin (9).—A suspension of 1.1 g (0.0025 mol) of **9** and 0.65 g (0.0025 mol) of triphenylphosphine in 20 ml of methanol was heated on the steam bath for 1 min during which time the system became homogeneous. After allowing it to cool for 5 min, the reaction mixture was poured into ice water and the organic product extracted with ether–methylene chloride. Drying and evaporating the organic extract left 1.49 g of a light yellow foam which showed one major new spot on tlc (PhH–EtOAc 1:1) corresponding in R_f to that of **6** prepared above. The product corresponding to this spot was separated by thick layer chromatography (of *ca.* a 300-mg sample) using PhH–EtOAc 1:1 for development and was identified as **6** by ir, nmr, and mass spectral comparisons.

Registry No.—**2**, 25966-68-1; **5**, 25966-69-2; **5a**, 25966-70-5; **6**, 26039-32-7; **7**, 25966-71-6; **9**, 25966-72-7.

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Action of *N*-Halosuccinimide on 8-Quinolinol[1]

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A reinvestigation of the action of *N*-halosuccinimide on bis(8-quinolinolato)copper(II) revealed that, on monochlorination, a mixture of 5- and 7-chloro chelates resulted. On monobromination, only the 5-bromo chelate formed, and on monoiodination, the 7-iodo chelate was obtained.[2] This was in disagreement with the results of Prasad, *et al.*,[3] who reported that on monohalogenation of the same chelate with *N*-halosuccinimide, substitution took place exclusively in the 5 position. On the basis of dihalogenation studies of metal chelates with elemental chlorine and bromine and a list of reactivities of free and coordinated ligands found in the literature, Maguire and Jones[4] concluded that, with the exception of tropolone, there are no authenticated instances where coordination changes the reactive position of an aromatic ligand toward electrophilic reagents. Hix and Jones[5] attempted to further strengthen this view by citing 109 reactions tabulated by Blatt[6] and 73 additional reactions listed by Berliner[7] where coordination does not affect orientation. Competitive bromination studies of mixtures of 8-quinolinol and its chelates with iron(III), chromium(III), and cobalt(III) using insufficient bromine indicated that the rate of bromination of the chelates was about 35 times as rapid as that of the free ligands.

The present work was undertaken to further study what appeared to be the anomalous orientation of halogen when bis(8-quinolinolato)copper(II) was treated with *N*-halosuccinimide.[2] It was also of interest to reexamine the concept that chelation does not affect orientation of substituents in electrophilic substitution of aromatic ligands.

To approach the first problem, 8-quinolinol was reacted with *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccinimide (NIS) in chloroform, and the molar ratios of halogenating agent to substrate were 1:1, 2:1, and 3:1. The reaction time was 3 hr and two reaction temperatures were employed, ambient and 40–60°. The rationale for this approach and the identification and quantitation of the products were previously discussed.[2]

Table I contains the results obtained from the halogenation of 8-quinolinol with *N*-halosuccinimide. It

TABLE I

ACTION OF *N*-HALOSUCCINIMIDE ON 8-QUINOLINOL IN CHLOROFORM

Halogenating agent NCS[a]	Molecular ratio of *N*-halosuccinimide to 8-quinolinol	Temp, °C	Products, %			
			Ox[b]	5-ClOx	7-ClOx	5,7-Cl_2Ox
	1	ambient	95	1	4	0
	2	ambient	94	1	5	0
	3	ambient	94	1	5	0
	1	40–60	82	3	15	Tr[c]
	2	40–60	81	4	15	Tr
	3	40–60	77	6	17	Tr
NBS			Ox	5-BrOx	7-BrOx	5,7-Br_2Ox
	1	ambient	16	14	50	20
	2	ambient	0	0	0	100
	3	ambient	0	0	0	100
	1	40–60	14	12	58	16
	2	40–60	0	Tr	Tr	99
	3	40–60	0	0	0	100
NIS			Ox	5-IOx	7-IOx	5,7-I_2Ox
	1	ambient	Tr	94	Tr	5
	2	ambient	Tr	7	Tr	92
	3	ambient	0	Tr	0	99
	1	40–60	12	77	0	11
	2	40–60	Tr	10	0	90
	3	40–60	0	Tr	0	99

[a] NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide. [b] Ox = 8-quinolinol. [c] Tr = trace (<1%).

* To whom correspondence should be addressed.

(1) This work was supported in part by the U. S. Public Health Service Grant No. AI-05808.

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(6) A. H. Blatt, *Org. React.*, **1**, 342 (1942).

(7) E. Berliner, *ibid.*, **5**, 229 (1949).

can be seen that the rate[8] of chlorination with NCS is very slow. The products formed were 5-chloro-, 7-chloro-, and a trace of 5,7-dichloro-8-quinolinol, and the orientation of the chlorine atom favored the 7 position over the 5 position by a ratio of about 4:1. The concentration of halogenating agent did not appear to affect the rate of reaction, but raising the temperature from ambient to 40–60° caused about a threefold increase in rate of chlorination. Bromination with NBS yielded three products in significant quantities, 5-bromo-, 7-bromo-, and 5,7-dibromo-8-quinolinol. The rate of bromination appeared to be rapid, as evidenced by no apparent effect due to temperature change, and on increasing the ratios of halogenating agent to 8-quinolinol, only the dibromo derivative was formed. The formation of 7-bromo-8-quinolinol was about four times that of the 5-bromo analog. The bromination of 8-quinolinol in the 7 position by *N*-bromo compounds has also been observed by Pearson, *et al.*,[9] and reexamined by Gershon, *et al.*[2] Iodination of 8-quinolinol with NIS yielded essentially two iodination products. 5-Iodo-8-quinolinol was the major product and 5,7-diiodo-8-quinolinol was formed in minor quantities. An increase in reaction temperature increased the rate of iodination of 5-iodo-8-quinolinol to yield a greater proportion of the 5,7-diiodo derivative than obtained at ambient temperatures.

A comparison of these results with the data previously reported on the halogenation of bis(8-quinolinolato)copper(II) with *N*-halosuccinimides[2] shows that, on chlorination of 1 equiv of ligand with 1 equiv of NCS, a high per cent of chelate was chlorinated, whereas very little free ligand was chlorinated. These results are in agreement with the conclusion of Hix and Jones,[5] that chelation with metals increases the rate of halogenation of 8-quinolinol. Comparable halogenations with NBS and NIS were not amenable to drawing conclusions as to the effect of chelation on rate of halogenation.

The orientation of the substituents of the monohalogenated products of the free ligand as compared with the chelate was unexpected. The chlorination products of 8-quinolinol consisted of about four times as much 7-chloro-8-quinolinol as 5-chloro isomer, and, on chlorination of the copper(II) chelate of 8-quinolinol, 5- and 7-chloro-8-quinolinols formed in about equal yield. The monobromination products of the free ligand consisted of 7-bromo and 5-bromo-8-quinolinols, also in the ratio of 4:1, but monobromination of the chelate yielded 80% 5-bromo-8-quinolinol and no detectable 7 isomer. The monoiodination products of the free ligand yielded 94% 5-iodo-8-quinolinol, whereas the chelate yielded 90% 7-iodo-8-quinolinol and 10% 5-iodo analog.[10] This is consistent with the hypothesis of Maguire and Jones[4] and Hix and Jones[5] that chelation of a ligand with a metal does not change the reactive positions of an aromatic compound toward electrophilic substitution. However, it is obvious that chelation does affect orientation of substituents in electrophilic substitution with *N*-halosuccinimide.

(8) The term "rate" is used in the sense of percent halogenated 8-quinolinol formed during the 3-hr reaction time.

(9) D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967).

(10) It should be noted that our previous report[2] indicated that 99% 7-iodo-8-quinolinol was formed on iodination of bis(8-quinolinolato)copper(II) with NIS. That assay was obtained by gas chromatography using a 5% QF-1 column. Later work showed that mixtures composed of 10% or less of one of the monoiode-8-quinolinols in the presence of 90% of the other could not be resolved even though mixtures of more nearly equal proportion could be assayed. The ir spectra of mixtures, composed of overwhelming proportions of one isomer, masked the presence of the other. The present work was carried out with a 1% Apiezon L column which can resolve mixtures of 5- and 7-iodo-8-quinolinols in all proportions.

Experimental Section[11]

Halogenation of 8-Quinolinol with *N*-Halosuccinimides.—To a solution of 1 mmol of 8-quinolinol in 10 ml of chloroform was added 1, 2, or 3 mmol of the respective *N*-halosuccinimide. The mixture was stirred on a magnetic stirrer hot plate for 3 hr keeping the volume nearly constant by addition of chloroform, as needed. The hot plate was set to maintain temperatures of 40–60°. At the end of the reaction period, the solution was washed with three 5-ml portions of an aqueous solution containing 5% NaOAc and 5% $NaHSO_3$ in order to destroy unused *N*-halosuccinimide and to remove the succinimide formed. A portion of the chloroform solution was evaporated under a stream of air, and the residue was dissolved in acetonitrile. The quinolinols were converted to the trimethylsilyl derivatives by means of *N*,*O*-bis(trimethylsilyl)acetamide by the method of Klebe, *et al.*,[12] and chromatographed.

Registry No.—8-Quinolinol, 148-24-3; NCS, 128-09-6; NBS, 128-08-5; NIS, 516-12-1.

(11) Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector to which was attached a Varian Aerograph Model 20 recorder. The column and conditions employed for the gas chromatographic separation of the chloro- and bromo-8-quinolinols were previously described.[2] To assay the iodo-8-quinolinols, a stainless steel column, 5 ft × 0.125 in. o.d., was packed with 1% Apiezon L coated on 80–100 mesh acid washed Chromosorb W, previously treated with dimethyldichlorosilane. The instrument was operated at a column starting temperature of 150° which was programmed at 6°/min to 250°. The injector and detector temperatures were maintained at 200 and 250°, respectively, while the flow rate of nitrogen was 22 ml/min. Retention times for 8-quinolinol and the 5-iodo, 7-iodo, and 5,7-diiodo derivatives were 1.7, 5.8, 6.2, and 11.8 min, respectively.

(12) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

The Reaction of Indole with *N*-Chloropyrrolidine and *N*-Chlorodibutylamine[1]

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Evidence is accumulating from recent developments in the chemistry of haloamines[2] which indicates that their reactions with organic substrates involve the intermediacy of electrophilic nitrogen species in either free-radical[3,4] or ionic[5] mechanisms. On this basis we have studied the reaction of indole with *N*-chloropyrrolidine (1) and *N*-chlorodibutylamine (2) with the hope that attack by electrophilic nitrogen intermediates would yield 3-aminoindole derivatives. Our results

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(1) Support from the Department of University Affairs, Province of Ontario, is gratefully acknowledged.

(2) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1965, p 192 ff.

(3) F. Minisci, G. P. Gardini, and F. Bertini, *Can. J. Chem.*, **48**, 544 (1970).

(4) J. Spanswick and K. U. Ingold, *ibid.*, **48**, 546 (1970), and references cited therein; J. Spanswick and K. U. Ingold, *ibid.*, **48**, 554 (1970).

(5) P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970).

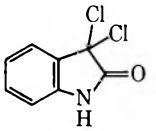
TABLE I
REACTION OF INDOLE WITH CHLORAMINES

Chloramine	Entry	Conditions	Product	% yield[a]
 (1)	A	HOAc, H_2SO_4, 0°, 1 hr, N_2	3	44
	B	HOAc, H_2SO_4, $h\nu$, 35°, 2.5 hr	3	Trace
	C	Ether, $h\nu$, 35°, 17 hr	4	23[b]
	D	CH_3NO_2, H_2SO_4, 0°	3	26
	E	PE[c]–benzene, room temp, dark, 1 day	4	36[b]
	F	CH_3CN, room temp, dark, 2 days	4	50
	G	MeOH, $AgNO_3$, reflux, 4.5 hr	4	22
	H[d]	Toluene, $AgBF_4$, room temp, dark, 1 day	4	10
$(n\text{-}C_4H_9)_2NCl$ (2)	I	PE[c]–benzene, room temp, dark, 3 days	4	51
	J	CH_3CN, room temp, dark, 3 days	4	8

[a] Based on reacted indole. [b] Glc analysis. [c] Petroleum ether. [d] We thank K. S. Bhandari for this experiment.

reported herein show, however, that the chloramines act mainly as electrophilic chlorinating agents[2] in reactions with indole under a variety of conditions. Analogous behavior has been found recently in the reaction of indole with *N,N*-dichlorourethan.[6,7] Nevertheless, our work provides a facile alternate synthesis of 3-chloroindole (**4**).[8]

The results are summarized in Table I. The application of the strongly acidic Hofmann–Loeffler–Freytag conditions[4] to the reaction of indole with **1** gave poor yields of 3,3-dichlorooxindole (**3**) (entries A, B, and D) in agreement with the known ready oxidizability of indole by such reagents.[9] Treatment of indole with **1** in the presence of silver salts under conditions which are known to generate nitrenium ions[5] gave poor yields of **4**, irrespective of the nature of the anion (entries G and H). Finally, when the reaction was carried out in the absence of metal or acidic catalysts in the dark for extended periods of time, fair to good yields of **4** were obtained (entries E and F). The lower yield of **4** obtained in the reaction of indole with *N*-chlorodibutylamine (**2**) in acetonitrile (entry J) is due to the decomposition of **2** to *n*-dibutylamine hydrochloride (30%) in the more polar solvent.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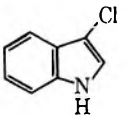
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Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. Ultraviolet spectra were obtained with a Beckman DB-G spectrophotometer. A Jeol C-60 instrument was used for recording nmr spectra. Gas–liquid chromatography (glc) was carried out on an Aerograph Autoprep Model 700 with a 10 ft × 3/8 in. column of 10% SE-30 silicone gum rubber on 60–80 mesh Chromosorb W. The photolyses were performed in a Rayonet Reactor in quartz vessels using 3500 Å lamps. Silica gel (Brinkmann, 0.05–0.20 mm) was used for chromatography. Reagent grade acetonitrile and methanol were used without further purification. Reagent grade benzene and petroleum ether (60–80°) were dried and distilled before use.

Reaction of Indole with *N*-Chloropyrrolidine (1). A. In Sulfuric Acid–Acetic Acid.—A mixture of 4.4 ml of 98% sulfuric acid and 15 ml of glacial acetic acid was stirred under nitrogen in an ice bath for 10 min. An ethereal solution of **1** (9 ml, 9 mmol) was then added and stirring was continued for another 15 min. Indole (1.05 g, 9 mmol) was added in small portions and the resulting green mixture was stirred for 1 hr. It was then poured into 200 ml of ice water and extracted with chloroform. The chloroform extracts were washed with water and dried ($MgSO_4$). Evaporation of solvent gave 3,3-dichlorooxindole (**3**), 0.8 g (44%), which was characterized by identical ir, nmr, melting points, and mixture melting point with an authentic sample.[10]

B. In Acetonitrile.—A mixture of 560 mg (4.8 mmol) of indole in 10 ml of acetonitrile and 8 ml (4.8 mmol) of **1** in ether was stirred at room temperature in the dark for 2 days. The solvent was evaporated and the resulting residue was dissolved in methylene chloride and washed three times with saturated sodium bicarbonate solution. The methylene chloride extract yielded after drying (Na_2SO_4) 990 mg of an oil which was chromatographed. Elution with petroleum ether–benzene (1:1) followed by sublimation gave 386 mg (50%) of **4**.

A blank run showed that **1** was stable under the above conditions for at least 5 days as determined by sodium thiosulfate titration.

Registry No.—**1**, 19733-68-7; **2**, 999-33-7; indole, 120-72-9.

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(10) A. Hantzsch, *Ber.*, **54B**, 1221 (1921).

Synthetic Reactions by Complex Catalysts. XVIII. The Reaction of Azide with Isocyanide by Iron Carbonyl Catalyst. A New Route to Carbodiimide

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This note describes the iron carbonyl catalyzed reaction of an azide with isocyanide, which provides a new method for the preparation of the unsymmetrical carbodiimide (eq 1). In the absence of catalyst, no reac-

$$\underset{\text{I}}{RN_3} + \underset{\text{II}}{R'N{\equiv}C:} \xrightarrow{\text{catalyst}} \underset{\text{III}}{R{-}N{=}C{=}N{-}R'} + N_2 \quad (1)$$

tion occurs; azide and isocyanide were recovered almost quantitatively from the reaction system. In the

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TABLE I
REACTION OF AZIDE WITH ISOCYANIDE[a]

RN_3	Mmol	R'NC	Mmol	Catalyst	Mmol	R—N=C=N—R'	Yield,[b] %
c-$C_6H_{11}N_3$	10	t-C_4H_9NC	36	$Fe(CO)_5$	0.5	c-C_6H_{11}—N=C=N—C_4H_9-t	60
c-$C_6H_{11}N_3$	10	c-$C_6H_{11}NC$	28	$Fe(CO)_5$	0.5	c-C_6H_{11}—N=C=N—C_6H_{11}-c	48
c-$C_6H_{11}N_3$	10	C_6H_5NC	36	$Fe(CO)_5$	0.5	c-C_6H_{11}—N=C=N—C_6H_5	51
c-$C_6H_{11}N_3$	10	c-$C_6H_{11}NC$	37	Cu_2O[c]	1.0	c-C_6H_{11}—N=C=N—C_6H_{11}-c	2
c-$C_6H_{11}N_3$	10	c-$C_6H_{11}NC$	28	None		No reaction	

[a] Reactions were carried out at 90° for 24 hr under nitrogen atmosphere. [b] Product yield is based upon the amount of azide. [c] A considerable amount of tar was produced in this reaction.

presence of iron pentacarbonyl, the reaction proceeds smoothly. Cuprous oxide, which has been employed as an effective catalyst in the reactions of isocyanide[1] and of the azide,[2] exhibits a poor catalytic activity in the present reaction. The results of the azide–isocyanide reaction are shown in Table I. It is important to note that only the carbodiimide of the structure as indicated by III is produced and other carbodiimides having structures of R—N=C=N—R and R'—N=C=N—R' are not formed.

The formation of carbodiimide may be formulated as being the combination of isocyanide and nitrene, which are characterized by lone-pair electrons attached to carbon and nitrogen, respectively. These two species[3,4] are known to form coordination complexes with metal carbonyls. Ligand exchange of iron pentacarbonyl with isocyanide is considered possible in the present reaction conditions.[3a] Therefore, it can be assumed that the isocyanide complex reacts either with azide or nitrene.

Concerning the isocyanide–nitrene reaction, a reaction of cyclohexyl isocyanide with *N*-chloro-*p*-toluenesulfonamide in alkaline methanol has been reported,[5] in which a mechanism of the reaction of isocyanide with an intermediate of *p*-toluenesulfonylnitrene was suggested as one of possible courses.

The reaction found in this study can be compared with the metal carbonyl catalyzed condensation of 2 mol of isocyanate, which also produces carbodiimide (eq 2).[6] The condensation of isocyanate has been

$$2R—N=C=O \longrightarrow R—N=C=N—R + CO_2 \quad (2)$$

explained by the intermediate production of metal isocyanide complex (eq 3) and the subsequent reaction

$$Me(CO) + R—N=C=O \longrightarrow Me(CN—R) + CO_2 \quad (3)$$

of this complex with the second molecule of isocyanate (eq 4). In this connection, the azide–isocyanide

$$Me(CN—R) + R—N=C=O \longrightarrow R—N=C=N—R + Me(CO) \quad (4)$$

reaction by iron carbonyl catalyst in the present study might be regarded as the reaction of isocyanide with isocyanate which is formed intermediately from nitrene and the carbon monoxide ligand. This possibility, however, was not supported by a reference experiment in which an equimolar mixture of cyclohexyl azide and iron pentacarbonyl was heated. The gaseous mixture evolved from the heat treated mixture consisted of nitrogen and carbon monoxide. No carbon dioxide was detected. Furthermore, neither cyclohexyl isocyanate nor dicyclohexylcarbodiimide was detected in the reaction mixture. Consequently, the azide–isocyanide reaction is not depicted by eq 3 and 4. Elucidation of the features of this interesting reaction awaits further study.

Experimental Section

Reaction of Cyclohexyl Azide (I) with *tert*-Butyl Isocyanide (IIa).—To a mixture of IIa (36 mmol) and $Fe(CO)_5$ (0.5 mmol), I (10 mmol) was added dropwise during 15 min at room temperature under nitrogen atmosphere. The reaction mixture was then heated for 24 hr at 90°. From the reaction mixture the insoluble part was removed by filtration, and the filtrate was distilled *in vacuo* to give a distillate (1.1 g) boiling at 63 ~ 65° (2 mm). The distillate was subjected to glpc analysis. The product was shown to be *tert*-butylcyclohexylcarbodiimide (IIIa, 60%). Compound IIIa was identified by ir and nmr spectra and elemental analysis: ir of IIIa (neat) $\nu_{N=C=N}$ 2160 cm^{-1} (vs); nmr ($CDCl_3$) τ 6.50~7.05 (1 H, broad singlet), 7.85~9.0 (10 H, broad multiplet), and 8.70 (9 H, singlet).

Anal. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.55; H, 11.26; N, 15.82.

Reaction of Cyclohexyl Azide (I) with Cyclohexyl Isocyanide (IIb).—The reaction was carried out by a similar procedure. The product was dicyclohexylcarbodiimide (IIIb, 48%). IIIb was identified by comparison of ir and nmr spectra and the glpc retention time with those of the authentic sample.

The reaction of cyclohexyl azide (I) with phenyl isocyanide (IIc) was carried out by a similar procedure. The product, *N*-cyclohexyl-*N*-phenylcarbodiimide (IIIc, 51%), was identified by comparison of ir spectrum and the glpc retention time with those of the authentic sample.

Reaction of Cyclohexyl Azide (I) with Iron Pentacarbonyl (IV).—A mixture of I (10 mmol), IV (10 mmol), and acetonitrile (5 ml) in a 50-ml stainless steel pressure tube was heated at 80° for 15 hr. After the reaction, the gaseous products were trapped and analyzed by glpc with a column of silica gel (column temperature 40° for carbon dioxide, −78° for nitrogen and carbon monoxide). Nitrogen (7.5 mmol, 75%) and carbon monoxide (1.3 mmol) were produced. The nonvolatile part of reaction mixture was analyzed by glpc. Dicyclohexylcarbodiimide (IIIb) and cyclohexylisocyanate could not be detected. The nitrene–iron carbonyl complex[4] may have been produced.

Registry No.—Carbodiimide (R = c-C_6H_{11}; R' = t-C_4H_9), 1202-53-5; carbodiimide (R = R' = c-C_6H_{11}), 538-75-0; carbodiimide (R = c-C_6H_{11}; R' = Ph), 3878-67-9; iron pentacarbonyl, 13463-40-6.

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Stereoselective Total Synthesis of (±)-Fukinone

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The eremophilane-type sesquiterpenoid (+)-fukinone, isolated from *Petasites japonicus* Maxim., has been assigned[2] structure and absolute stereochemistry as depicted in **1**. In view of a recent report[3] regarding the synthesis of (±)-9,10-dehydrofukinone, we describe here a simple, stereoselective total synthesis of (±)-fukinone (**1**) *via* a synthetic sequence which fully corroborates the structural and stereochemical assignments.

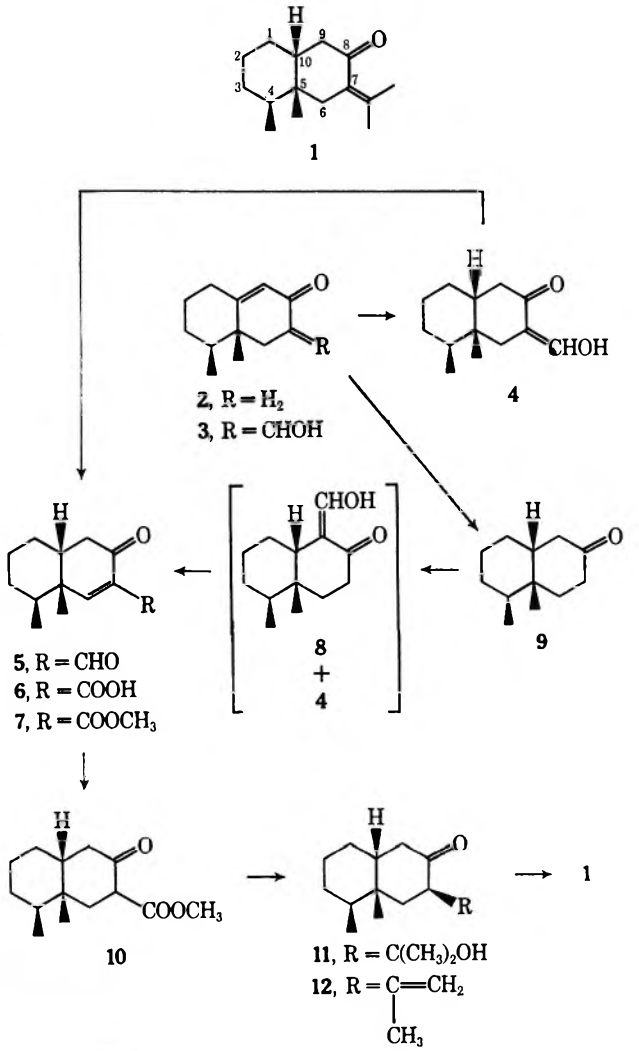
An efficient, stereoselective synthesis of the racemic octalone **2** has already been reported.[4] Conversion of this material into the corresponding hydroxymethylene derivative **3**, followed by catalytic hydrogenation of the latter in ethanolic sodium hydroxide over 10% palladium on charcoal, gave compound **4**, in 84% overall yield. Treatment of **4** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[5] in dioxane for 2 hr afforded, in 60% yield, the crystalline keto aldehyde **5**.

The fact that compounds **4** and **5** possessed the desired stereochemistry was conclusively shown as follows. Hydrogenation of octalone **2** over palladium on charcoal under basic conditions gave, in excellent yield, the cis-fused decalone **9**.[6] This compound was clearly different from the epimeric, trans-fused decalone, obtained from **2** by reduction of the latter with lithium in liquid ammonia.[4] Reaction of **9** with ethyl formate in benzene in the presence of sodium methoxide produced a mixture of hydroxymethylene derivatives **8** and **4** which, as judged by the nmr spectrum, were present in a ratio of approximately 2:3, respectively. Oxidation of this mixture with DDQ[5] in dioxane afforded, albeit in low yield, the unsaturated keto aldehyde **5**. The latter was shown to be identical (ir, nmr, melting point, and mixture melting point) with the keto aldehyde **5** prepared as described previously and thus assured that our synthetic intermediate possessed the desired all-cis stereochemistry.

Oxidation of the keto aldehyde **5** with silver oxide in ethanol–water[7] produced, in 92% yield, the crystalline keto acid **6**. Since treatment of the latter with diazomethane in ether produced a complex mixture of products, esterification was carried out by treatment of **6** with excess methyl iodide in the presence of powdered silver oxide.[8] The resulting keto ester **7**, formed in 92% yield, was subjected to hydrogenation in ethanol over Adams catalyst, affording, in 97% yield, the β-keto ester **10**.

In order to obtain (±)-fukinone (**1**) from the keto ester **10**, it was only necessary to elaborate the carbomethoxy group of the latter into the isopropylidene functionality. Treatment of **10** with one equivalent of sodium hydride in ether, followed by reaction of the resultant enolate with an excess of ethereal methyllithium[9] gave, after suitable work-up, the desired keto alcohol **11** in 80% yield. Attempted dehydration of **11** by treatment with 1% hydrochloric acid in refluxing methanol produced a product which, as shown by gas–liquid chromatographic analysis, consisted mainly of the decalone **9**, undoubtedly formed *via* a retroaldol reaction. However, treatment of **11** with thionyl chloride in pyridine afforded a product which consisted mainly of (±)-isofukinone (**12**), as shown by ir absorptions at 6.10 and 11.27 μ, characteristic of a terminal double bond, and at 5.85 μ, due to the saturated carbonyl group.

When a solution of (±)-isofukinone (**12**) in dry benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 20 hr, there was obtained a product which consisted mainly of (±)-fukinone (**1**). An analytical sample of the latter was obtained by preparative glc. Although we were unable to secure an authentic sample of (+)-fukinone, our synthetic material exhibited spectral data which was in excellent agreement with the spectral data reported[2] for the



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natural product itself, and the structural assignment is, therefore, fully corroborated.

Experimental Section

General.—Melting points and boiling points are uncorrected. Uv spectra were measured in methanol solution on a Unicam Model SP 800 spectrophotometer. Routine ir spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrophotometer, while comparison spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were determined in deuteriochloroform solution and recorded on Varian Associates spectrometers, Model A-60 and/or Model HA-100. Signal positions are given in the Tiers τ scale, with tetramethylsilane as an internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Glc was carried out on an Aerograph Autoprep, Model 700. The following columns (10 ft × 1/4 in., unless otherwise noted) were employed, with the inert, supporting material being 60–80 mesh Chromosorb W in each case: column A, 15% QF-1; column B (10 ft × 3/8 in.), 20% Carbowax 20 M; column C, 3% SE-30; column D (10 ft × 3/8 in.), 30% SE 30. The specific column used, along with column temperature and carrier gas (helium) flow rate (in ml/min), are indicated in parentheses. High-resolution molecular weight determinations were measured on an AEI, type MS-9, mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Preparation of Hydroxymethylene Derivative 3.—To a stirred suspension of sodium methoxide (3.8 g, 70.3 mmol) in 25 ml of dry benzene was added a solution of ethyl formate (5.2 g, 70.3 mmol) in 25 ml of dry benzene. The mixture was cooled to 0° and a solution of octalone **2** (5.0 g, 28.1 mmol) in 25 ml of dry benzene was added. The reaction was stirred, under a nitrogen atmosphere, for 90 min and then allowed to stand at room temperature for an additional 14 hr. To the reaction mixture was added 75 ml of water, the mixture was thoroughly shaken, and the layers were separated. The aqueous solution was washed with ether and then acidified with dilute hydrochloric acid. The resultant mixture was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford a dark oil which, upon distillation under reduced pressure, afforded 2.5 g (89%, based on unrecovered starting material) of compound **3** as pale yellow crystals, bp 110–112° (0.25 mm). An analytical sample was obtained by vacuum sublimation and exhibited mp 68–71°; uv max 248 mμ (ϵ 9280), 311 (3860); uv max (NaOH) 242 mμ (ϵ 13,000), 355 (9620); ir ($CHCl_3$) 6.08, 6.41, 8.42 μ; nmr τ 0.0 (broad m, 1, =CHOH), 2.62 (s, 1, =CHOH), 4.23 (s, 1, vinyl H), 9.06 (s, 3, tertiary CH_3), 9.08 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.99; H, 8.73.

Preparation of Decalone 9.—To a solution of octalone **2** (1.0 g, 5.62 mmol) in 20 ml of 0.3 *N* ethanolic sodium hydroxide was added 100 mg of 10% palladium on charcoal and the resulting mixture was hydrogenated at room temperature and atmospheric pressure for 15 hr. The reaction mixture was filtered, and the filtrate was neutralized with dilute hydrochloric acid and concentrated. The residue was taken up in ether and the ether solution was washed with brine and dried ($MgSO_4$). Removal of the solvent, followed by distillation of the residual material under reduced pressure, produced 920 mg (92%) of a clear, colorless oil, bp 88–90° (0.35 mm) [lit.[6] bp 75° (0.15 mm)]. Glc analysis (column A, 165°, 85) indicated that this material was greater than 95% pure. An analytical sample of decalone **9** was obtained by preparative glc (column B, 240°, 170) and exhibited $n^{20}D$ 1.4953; ir (film) 5.83, 6.91 μ; nmr τ 9.04 (s, 3, tertiary CH_3), 9.13 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.05; H, 11.19.

The 2,4-dinitrophenylhydrazone prepared from decalone **9** exhibited, after recrystallization from ethanol, mp 126–127° (lit.[6] mp 115°).

Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.14; H, 6.94; N, 15.67.

The semicarbazone derivative and the oxime derivative of decalone **9** were also prepared and exhibited, after recrystallization from ethanol, mp 194–195° (lit.[6] mp 190–191°), and mp 148–148.5° (lit.[6] mp 147–148°), respectively.

Conversion of Decalone 9 into Hydroxymethylene Derivatives 8 and 4.—Decalone **9** was converted into a mixture of **8** and **4** *via* a procedure identical with that described above for the preparation of the hydroxymethylene derivative **3**, except that the reaction time in this case was 2 days. From 1.0 g (5.56 mmol) of decalone **9** there was obtained 0.88 g (76%) of a pale yellow oil: bp 105–110° (0.2 mm); uv max 285 mμ (ϵ 6330); uv max (NaOH) 315 mμ (ϵ 17,100); ir (film) 6.07, 6.30, 7.32 μ. As judged by the nmr spectrum, this material consisted of a mixture of the hydroxymethylene derivatives **8** and **4**, in a ratio of approximately 2:3, respectively.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.05; H, 9.73.

Preparation of Keto Aldehyde 5. A. From the Hydroxymethylene Derivative 3.—A solution of the hydroxymethylene derivative **3** (1.5 g, 7.3 mmol) in 75 ml of 0.3 *N* ethanolic sodium hydroxide containing 150 mg of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure until the desired amount of hydrogen had been absorbed. Work-up as described previously for the preparation of compound **9** afforded 1.5 g (95%) of the crude hydroxymethylene decalone **4**: ir (film) 6.07, 6.30, 7.30 μ; nmr showed no vinyl proton. A solution of compound **4** (200 mg, 0.972 mmol) and DDQ (230 mg, 1.13 mmol) in 15 ml of dry dioxane was stirred at room temperature for 2 hr under an atmosphere of nitrogen. The reaction mixture was diluted with 35 ml of methylene chloride and then filtered through a short column of neutral alumina. The alumina column was further eluted with methylene chloride. The combined eluents were concentrated under reduced pressure and the residue was distilled, bp 180–190° (bath temperature) (0.1 mm), affording a yellow oil which crystallized on standing. Recrystallization from hexane yielded 124 mg (62%) of the desired keto aldehyde **5**: mp 81–83°; uv max 283 mμ (ϵ 7740); ir ($CHCl_3$) 5.95, 6.23, 7.44 μ; nmr τ −0.32 (s, 1, CHO), 2.20 (s, 1, vinyl H), 8.74 (s, 3, tertiary CH_3), 9.00 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.92; H, 9.03.

B. From the Mixture of Hydroxymethylene Derivatives 8 and 4.—A solution of the mixture of compounds **8** and **4** (200 mg, 0.972 mmol) and DDQ (225 mg, 1.10 mmol) in 15 ml of dry dioxane was stirred, under an atmosphere of nitrogen, for 2 hr. Upon isolation of the product as described above, there was obtained 30 mg (15%) of the crystalline keto aldehyde **5**. This material was identical (ir, nmr, melting point, mixture melting point) with compound **5** prepared as described above.

Preparation of Keto Acid 6.—To a solution of keto aldehyde **5** (548 mg, 2.66 mmol) and silver nitrate (953 mg, 5.60 mmol) in 7 ml of ethanol and 5 ml of water was added, over a period of 15 min, a solution of sodium hydroxide (436 mg, 10.90 mmol) in 15 ml of water. The reaction mixture was stirred for a total of 2 hr, and then filtered. The filtrate was concentrated under reduced pressure, diluted with water, washed with ether, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated. Recrystallization of the residue from hexane–ether afforded 542 mg (92%) of the desired keto acid **6**: mp 65–67°; uv max 245 mμ (ϵ 6780); ir ($CHCl_3$) 5.75, 6.08, 6.25, 7.00 μ; nmr τ 2.55 (s, 1, vinyl H), 8.77 (s, 3, tertiary CH_3), 9.02 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.31; H, 8.22.

Preparation of Keto Ester 7.—To a stirred solution of keto acid **6** (262 mg, 1.18 mmol) in 10 ml of methyl iodide was added powdered silver oxide (1.10 g, 4.72 mmol). The reaction mixture was stirred at room temperature for 30 min and then filtered. The filtrate was concentrated and the residue was distilled, affording 257 mg (92%) of the desired keto ester **7**: bp 185–190° (bath temperature) (0.1 mm); $n^{20}D$ 1.5208; uv max 236 mμ (ϵ 7740); ir (film) 5.78, 5.96, 6.20, 7.00, 7.86, 9.54, 9.98 μ; nmr τ 2.55 (s, 1, vinyl H), 6.23 (s, 3, $COOCH_3$), 8.82 (s, 3, tertiary CH_3), 9.04 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.42; H, 8.32.

Preparation of Carbomethoxy Decalone 10.—Hydrogenation of the unsaturated keto ester **7** (250 mg, 1.06 mmol) in 10 ml of ethanol at room temperature and atmospheric pressure over Adams catalyst gave, after normal work-up, 242 mg (97%) of the carbomethoxy ketone **10**: $n^{20}D$ 1.5112; uv max 257 mμ (ϵ 7410); uv max (NaOH) 285 mμ (ϵ 13,800); ir (film) 5.78, 5.84,

6.02, 6.17, 6.98, 7.75, 8.14, 8.30 μ; nmr τ −2.11 (s, 1, enol H), 6.28 (s, 3, $COOCH_3$), 9.12 (s, 3, tertiary CH_3), 9.12 (d, 3, J = 6.5 Hz, secondary CH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.84; H, 9.30.

(±)-**Fukinone** (1).—To a stirred solution of the carbomethoxy decalone **10** (200 mg, 0.841 mmol) in 2 ml of dry ether at 0° was added 20 mg (0.841 mmol) of sodium hydride. The reaction mixture was stirred for 10 min and 2.15 ml (5.05 mmol) of 2.35 *M* ethereal methyllithium was added over a period of 5 min. The resulting solution was refluxed for 2 hr, diluted with 15 ml of dry ether and then poured into 35 ml of rapidly stirred water. The ether layer was separated, washed with brine, dried ($MgSO_4$), and concentrated to afford 160 mg (80%) of the keto alcohol **11**, ir (film) 2.90, 5.85 μ. The crude alcohol was dissolved in 10 ml of dry pyridine at 0°, 100 μl of thionyl chloride was added, and the resultant solution was stirred for 15 min. The solvent was removed under reduced pressure at 0° and the residual material was taken up in benzene. The benzene solution was washed with water and brine, dried ($MgSO_4$), and concentrated to afford 134 mg of a pale yellow oil. The latter, as shown by glc analysis (column C, 170°, 90), contained mainly (±)-isofukinone (**12**) and exhibited ir (film) absorptions at 5.85, 6.10, and 11.27 μ. A solution of this dehydration product in 15 ml of dry benzene containing a trace of *p*-toluenesulfonic acid was refluxed for 20 hr. The solution was washed with 10% aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated. Glc analysis (column C, 200°, 85) showed that the residual oil (125 mg) contained approximately 70% (±)-fukinone (**1**), 20% of the decalone **9**, and 10% of an unidentified component. An analytical sample of (±)-fukinone (**1**) was obtained by preparative glc (column D, 230°, 180) and exhibited uv max 251 mμ (ϵ 6640); ir (film) 5.95, 6.17 μ; nmr τ 8.08 (s, 3, vinyl CH_3), 8.24 (s, 3, vinyl CH_3), 9.04 (s, 3, tertiary CH_3), 9.16 (d, 3, J = 6.5 Hz, secondary CH_3). These spectral data are in complete agreement with the spectra data reported[2] for the natural product (+)-fukinone.

Anal. Calcd for $C_{15}H_{24}O$: mol wt, 220.183. Found (high resolution mass spectrometry): mol wt, 220.181.

Registry No.—(±)-**1**, 25828-19-7; (±)-**3**, 25828-20-0; (±)-**4**, 25828-21-1; (±)-**5**, 25828-22-2; (±)-**6**, 25828-23-3; (±)-**7**, 25828-24-4; (±)-**8**, 25828-25-5; (±)-**9**, 25828-26-6; (±)-**10**, 25828-27-7.

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Catalytic Decomposition of α-Haloalkyl Esters

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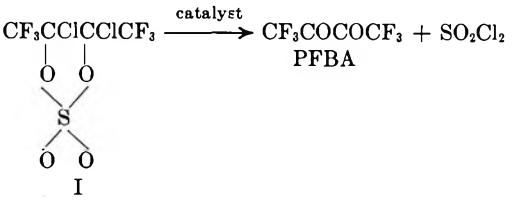
The preparation of perfluorobiacetyl (PFBA) results in the formation of 2,3-dichloro-1,1,1,4,4,4-hexafluorobutane-2,3-diol cyclic sulfate (I) as a coproduct.[1] This material is of little interest of itself; so conversion to PFBA was of interest. This would double the overall yield of PFBA from 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene.

The compound I was not soluble enough in water for hydrolysis to occur at any reasonable rate, but use of a cosolvent, dimethylformamide or dimethyl sulfoxide, resulted in complete hydrolysis. The product was PFBA hydrate. PFBA could then be obtained by dehydration with either fuming sulfuric acid or phosphorous pentoxide. This procedure involves two steps and the best yield obtained was 75%.

It has now been found that I will decompose in the presence of various catalysts to PFBA and sulfuryl



chloride in high yield. Compounds which catalyze this reaction are nitrogen or phosphorous derivatives with an unshared pair of electrons which can complex the sulfate. The results of a series of screening runs are given in Table I. In addition, water, alcohols, ethers, esters, and ketones have been in contact with I with no evidence of catalytic decomposition. Dimethylformamide, DMF, was also shown to be an effective catalyst. The use of more than a catalytic amount of DMF allowed the PFBA formed to distill from the solvent free from chlorine and sulfur dioxide.

All of the effective catalysts have an unshared pair of electrons, being nitrogen or phosphorus derivatives. Related compounds which do not have a pair of electrons available for complexation, ammonium chloride and heptafluorobutyramide, do not act as catalysts, and aromatic amines are poor catalysts.

Compounds with active hydrogens, in particular N–H, undergo side reactions apparently forming amine salts which are inactive. Ammonium hydroxide, *tert*-butylamine, and ethanolamine exemplify this behavior.

A reaction of this type has also been observed in the preparation of perfluoroisopropyl acrylate. The preparation of this acrylate has been reported previously with the comment that dimethylformamide would be

$$(CF_3)_2CFOK + CH_2{:}CHCOCl \longrightarrow CH_2{:}CHCOOCF(CF_3)_2 + KCl$$

the best solvent.[2] This recommendation was based on gas chromatographic analysis of the crude reaction mixture. Attempts at this laboratory to use dimethylformamide as the solvent resulted in poor yields. The difficulty was traced to decomposition during distillation with small amounts of DMF in the still kettle. Acrylyl fluoride and hexafluoroacetone were formed.

This reaction, which may be quite general, provides a means of recovering PFBA from I, but solvents such as DMF and *N*-methylpyrrolidone should be avoided in the preparation and use of α-haloalkyl esters.

Experimental Section

Hydrolysis of I in a Water–Organic Mixture.—To 33 g of I was added 20 g of water and 8 g of dimethyl sulfoxide (DMSO). The mixture was heated at 70° for 1.5 hr until the second phase disappeared. Extraction with ether left, after evaporation of the solvent, 26 g of PFBA hydrate and DMSO. No effort was

(1) L. O. Moore and J. W. Clark, *J. Org. Chem.*, **30**, 2472 (1965).

(2) A. G. Pittman, D. L. Sharp, and R. E. Lundin, *J. Polym. Sci., Part A-1*, **4**, 2637 (1966).

TABLE I
CATALYTIC DECOMPOSITION OF I

No.	Compd	Temperature of initial reaction, °C	Time to completion, hr	Yield of PFBA, %	Comments
1	$(C_6H_5)_3P$	25	1.0	~90	Smooth reaction
2	NH_4OH	25		0	Solids formed
3	$(CH_3)_3CNH_2$	25		0	Solids formed
4	$(C_4H_9)_3N$	40	1.25	~90	Smooth reaction
5	$(CH_2)_4CONCH_3$	40	Not determined	~80	Smooth reaction
6	$(C_6H_5O)_3P$	40	Not determined	~90	Smooth reaction
7	C_5H_5N	42	2.0	~90	Smooth reaction
8	$HOCH_2CH_2NH_2$	50		0	Brown tarry material formed
9	p-$HOC_6H_4NH_2$	150	Slow reaction	~30	Some solids forming
10	$(CH_3)_2SO$	150	No reaction	0	
11	$C_3H_7CONH_2$	150	No reaction	0	
12	NH_4Cl	150	No reaction	0	

made to separate these at this point. The yield of PFBA hydrate was 78% as determined by formation of 2,3-bis(trifluoromethyl)-quinoxaline, mp 118°, from a weighed portion and excess *o*-phenylenediamine.[1]

The reaction was repeated with 8 g of dimethylformamide (DMF) in place of the DMSO and it was noted that some yellow color developed when the DMF came in contact with I even at 25°, but with water present the color disappeared rapidly. The second phase had disappeared in only 0.25 hr and extraction, followed by stripping of the ether, gave 25 g of PFBA hydrate and DMF. The yield of PFBA hydrate was 73%, determined as above.

Dehydration of PFBA Hydrate.—The two portions above were combined and 9 g of the mixture was heated with 40 g of 20% fuming sulfuric acid to 70° for 2.5 hr. Yellow vapors evolved and were trapped in a Dry Ice cooled trap. The melting point, −20°, and boiling point, 20°, indicated that this was nearly pure PFBA. The overall yield was about 75% based on I.

The dehydration was repeated but using 10 g of P_2O_5 in place of the fuming sulfuric acid. Evolution of yellow vapors had stopped after 1.25 hr and the yield was 2 g (39%).

Reaction of I with Excess Dimethylformamide.—A mixture of 43 g of I and 19.7 g of DMF was heated in a 150-cc flask from 30 to 145° over 1.25 hr. There was an immediate reaction and the product, 27 g, which collected in Dry Ice cooled traps, was found to be nearly pure PFBA. The yield was quantitative.

The mixture in the kettle was not identified, but there was no evidence for either SO_2 or Cl_2 evolution. The residue dissolved in water and gave strong sulfate and chloride tests.

Catalytic Preparation of PFBA from I.—DMF (1 g) and 33 g of I were stirred together in a 200-cc flask. Evolution of a yellow vapor was immediately evident and continued as the temperature was raised over 6 hr to 158°. At the end of this time the reaction kettle contained two layers of 1 g each. One was a water soluble material, apparently unreacted DMF, and the other was I.

Distillation of the material collected in a Dry Ice cooled trap gave 5 g of Cl_2, 3 g of SO_2, and 18 g of PFBA. The distillation residue, 4 g, contained 43% of sulfuryl chloride and the remainder was starting material.

Catalyst Screening.—Several compounds were examined as possible catalysts by adding 0.1 g of each to 5 g of I and then heating the mixture to 70° till the reaction was complete. The results are summarized in Table I, no. 1, 4, and 7.

Similarly, several other compounds were evaluated on a smaller scale by mixing 0.01–0.05 g of the test compound with 0.5 g of I and then, when necessary, heating either till a smooth reaction proceeded or to a maximum of 150°. The results of these experiments are summarized in Table I, no. 2, 3, 5, 6, and 8–11. In each case the volatile PFBA was collected in a Dry Ice cooled trap and identified by comparison to known material.[1]

Heptafluoroisopropyl Acrylate. Preparation in Diglyme.—To 300 ml of diethylene glycol dimethyl ether, diglyme, in a 500-cc flask was added 19.2 g of anhydrous KF; the mixture was cooled to −20° with vigorous stirring. Hexafluoroacetone, 54 g, was then added and the suspended salt dissolved. This mixture was allowed to warm to 20–23° and 29 g of acrylyl chloride was added slowly to maintain the temperature. A precipitate formed as the acrylyl chloride was added which was shown to be KCl. The mixture was then stripped to a kettle temperature of 50° (20 mm) to give 56 g of colorless liquid. Distillation separated 40 g of crude product and fractionation gave 25 g (33%) of heptafluoroisopropyl acrylate, bp 85°, $n^{20}D$ 1.3128.[2] In an earlier run, some difficulty had been encountered from polymerization so that the distillation was carried out using a slow purge of air to the kettle and hydroquinone was added to the kettle and the receiver. With these precautions no polymerization was observed.

Heptafluoroisopropyl Acrylate. Preparation in Dimethylformamide.—The above procedure was followed but with the use of DMF in place of the diglyme. The reaction appeared to proceed identically in all respects until the distillation. When the material which had been stripped off was heated to distil the final product, a low boiling material was stripped out which was identified as hexafluoroacetone and then acrylyl fluoride was distilled, bp 32.5°, $n^{20}D$ 1.3465. The acrylyl fluoride structure was confirmed by its mass spectrum and the formation of an anilide derivative, mp 103–104°.[3]

This reaction was repeated using half the quantities used above but a water wash was used to remove DMF from the crude product. Distillation gave 7 g (18%) of heptafluoroisopropyl acrylate.

Registry No.—I, 722-89-4.

(3) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed. Wiley, New York, N. Y., 1948, p 222.

Improved Procedure for Oxidations with the Chromium Trioxide–Pyridine Complex

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In 1948, Sisler, Bush, and Accountius reported the isolation of a brick-red complex, with the empirical composition $CrO_3 \cdot 2C_5H_5N$, from the reaction of anhydrous chromium trioxide with pyridine.[2] Poos,

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(2) H. H. Sisler, J. D. Bush, and O. E. Accountius, *J. Amer. Chem. Soc.*, **70**, 3827 (1948).

Arth, Beyler, and Sarett found that the complex, in pyridine solution, is an effective reagent for the oxidation of primary and secondary alcohols to aldehydes and ketones.[3] The reagent found wide adoption as a method of accomplishing such oxidations under nonacidic conditions. Holum reported a series of oxidations with $CrO_3 \cdot 2C_5H_5N$ dispersed in pyridine or in acetone.[4]

In 1968, Collins, Hess, and Frank found that the anhydrous complex is moderately soluble in polar chlorocarbons.[5] The solvent of choice was found to be methylene chloride, in which the complex is soluble to the extent of 12.5 g/100 ml. By this modification, primary and secondary alcohols were oxidized to aldehydes and ketones in yields of 87–98%. Subsequently, Dauben, Lorber, and Fullerton showed that methylene chloride solutions of the complex are also useful for accomplishing allylic oxidations.[6]

Our own experience with the chromium trioxide–pyridine complex has convinced us that it is the reagent of choice in almost all situations calling for the oxidation of an alcohol. The chief drawbacks are the nuisance involved in preparing the pure complex, its hygroscopic nature, and its great propensity to enflame during preparation.[2,3] We have found that these complications may be avoided by simply preparing methylene chloride solutions of the complex directly (see Experimental Section).

Oxidation of 2-octanol for 15 min with 5% solutions containing 2:1, 3:1, 4:1, and 6:1 mol ratios of complex (prepared *in situ*) to alcohol gave conversions to 2-octanone of 33, 51, 65, and 97%, respectively. When 2-octanol was treated with a 3:1 mol ratio of complex (prepared *in situ*) to alcohol for prolonged periods, conversions to 2-octanone of 54, 73, 89, and 100% were obtained after 1, 26, 50, and 97 hr, respectively. It is clear from the data that 6 mol equiv of oxidant are required for rapid, complete conversion to ketone. With less than the 6:1 mol ratio, a second, extremely slow oxidation step occurs.

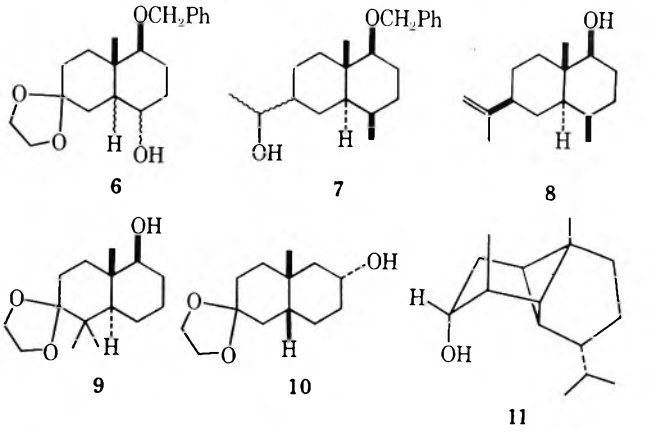
In Table I we list several alcohols which have been oxidized in our laboratories by methylene chloride solutions of the complex, prepared by the *in situ* method. In all cases, the oxidation was done at room temperature for 15 min with a molar ratio of complex to alcohol of 6:1, and the product was the corresponding aldehyde or ketone.

TABLE I

OXIDATION OF ALCOHOLS WITH CHROMIUM TRIOXIDE–PYRIDINE IN METHYLENE CHLORIDE (PREPARED *in situ*)

Alcohol	Mmol alcohol oxidized	% yield of aldehyde or ketone
1 (2-octanol)	5.0	97
2 (1-octanol)	5.0	90
3 (benzyl alcohol)	5.0	89
4 (borneol)	5.0	84
5 (cinnamyl alcohol)	5.0	96
6	137.0	94
7	26.4	99
8	1.4	95
9	42.6	85[a]
10	11.5	90[b]
11	1.3	80[b]

[a] Experiment carried out by Dr. James Macmillan. [b] Experiment carried out by Mr. Bruce Ratcliffe.



In separate experiments, we have tested the stability of the complex by allowing 5% methylene chloride solutions to stand at room temperature, under nitrogen, for periods of 7 and 28 days. In each case, a tarry, black deposit appeared after several days. However, after the specified period, the mixture smoothly oxidized $^1/_6$ mol of 2-octanol in 15 min at room temperature.

Experimental Section

Reagents.—Chromium trioxide (Mallinckrodt analytical reagent) was stored in a vacuum desiccator over phosphorus pentoxide prior to use. Anhydrous pyridine was prepared by distillation of reagent grade material from barium oxide and storing over 4A molecular sieves. Commercial methylene chloride was purified by shaking with concentrated sulfuric acid, washing with water and saturated brine, drying with calcium chloride, distilling, and storing over 4A molecular sieves. Alcohols **1**–**5** were obtained from commercial sources and used without further purification.

General Oxidation Procedure.—Chromium trioxide, 6.00 g (60 mmol), was added to a magnetically stirred[7] solution of 9.49 g (120 mmol) of pyridine in 150 ml of methylene chloride. The flask was stoppered with a drying tube containing drierite, and the deep burgandy solution was stirred for 15 min at room temperature. At the end of this period, a solution of the alcohol (10 mmol) in a small volume of methylene chloride was added in one portion. A tarry, black deposit separated immediately. After stirring an additional 15 min at room temperature, the solution was decanted from the residue, which was washed with 200 ml of ether. The combined organic solutions were washed with three 100-ml portions of 5% aqueous sodium hydroxide solution, 100 ml of 5% aqueous hydrochloric acid, 100 ml of 5% aqueous sodium bicarbonate solution, 100 ml of saturated aqueous sodium chloride solution, and were dried over anhydrous magnesium sulfate. Alternatively, the decanted methylene chloride solution was condensed *in vacuo* and the residue then taken up in ether, filtered to remove insoluble chromium salts, washed with dilute aqueous base and saturated brine, and dried over magnesium sulfate. Evaporation of the solvent at reduced pressure afforded the crude aldehyde or ketone product. The described procedure has been conveniently scaled to the oxidation of various quantities of alcohol ranging from 137 mmol of compound **6** to 1.3 mmol of compound **11**.

Registry No.—**1**, 123-96-6; **2**, 111-87-5; **3**, 100-51-6; **4**, 507-70-0; **5**, 104-54-1; **6**, 25826-83-9; **7**, 25826-84-0;

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

(4) C. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

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

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

(7) For large scale oxidations, ice-bath cooling during the chromium trioxide addition and a mechanical stirrer are recommended.

8, 25826-85-1; **9,** 25826-86-2; **10,** 25826-87-3; **11,** 25877-02-5; chromium trioxide, 1333-82-0; pyridine, 110-86-1.

Acknowledgment.—We thank Professor C. H. Heathcock for suggesting this project and the Public Health Service for support (GM-15302).

Enantiomeric Purity of Phenylethylene Glycol and Reliability of Phenylglyoxylate Asymmetric Reductions in Configurational Assignments[1]

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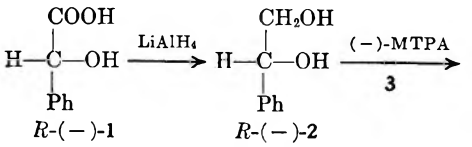
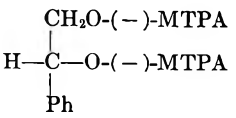
Received May 29, 1970

There exists a conflict in the literature concerning the maximum rotation of phenylethylene glycol.[2-6] Since this poses a crucial problem in the study of the asymmetric reduction of chiral phenylglyoxylic ester,[2] it became necessary to resolve this difficulty before we could undertake related studies.[7]

We have made use of the reagent (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (**3**, MTPA)[8] to determine the enantiomeric purity of phenylethylene glycol, and thereby to establish unequivocally its maximum rotation. The di-MTPA ester prepared



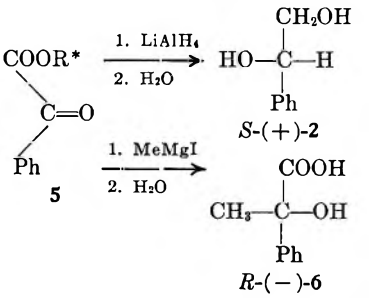
R-(−)-1 *R*-(−)-2



4

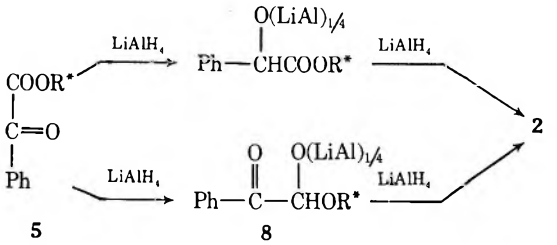
from racemic phenylethylene glycol and enantiomerically pure (*S*)-(−)-MTPA (**3**) exhibited distinct ^{19}F nmr signals for the CF_3 groups of the two diastereomers (**4** and its epimer). The signals from the CF_3 groups, belonging to the MTPA ester of the secondary alcohol function for each of the epimers, were well resolved at δ 5.10 and 4.82 (ppm downfield from the signal for trifluoroacetic acid, TFA, internal, in CCl_4 solvent, 94.1 MHz). Therefore these signals could be used for the quantitative analysis of these diastereomers in a given mixture. A sublimed sample of (*R*)-(−)-phenylethylene glycol (**2**), $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH), $[\alpha]^{25}D$ −63.7° (*c* 5.5, $CDCl_3$), prepared by lithium aluminum hydride reduction of (*R*)-(−)-mandelic acid (**1**), $[\alpha]^{24}D$ −152.3° (c 3.27, H_2O), gave the di-(−)-MPTA derivative **4**, the ^{19}F nmr analysis of which showed that it was 98 ± 2% stereochemically pure. Since the starting mandelic acid was 98 ± 1% enantiomerically pure, we conclude that no appreciable racemization occurs during the $LiAlH_4$ reduction of mandelic acid to phenylethylene glycol, contrary to one report[2] but in accord with previous work.[3,4,6] This finding has been independently confirmed.[9] Therefore the previously determined values for the asymmetric syntheses involving the $LiAlH_4$ reductions of chiral phenylglyoxylate esters[3-5] *need not be corrected* as suggested.[2]

Berson and Greenbaum[2] have found that the stereochemical course of the $LiAlH_4$ reduction of the phenylglyoxylate ester of phenyldihydrothebaine (**5**, R* = phenyldihydrothebainyl) giving (*S*)-(+)-phenylethylene glycol (*S*-**2**) in excess was "opposite" to that encountered for the addition of methylmagnesium iodide to the same ester giving (*R*)-(−)-atrolactic acid (*R*-**6**) in excess. This unexpected finding indicated



5 *R*-(−)-6

the need for further study of asymmetric reductions of chiral phenylglyoxylate esters before these reactions can be used with any confidence for stereochemical correlations. It was theorized[2] that the opposite stereochemical courses of these two reactions were a result of the initial reduction of the ester carbonyl group in **5**, before the keto carbonyl group, to give the keto hemiacetal derivative **8** instead of the expected mandelic ester derivative **7**. The newly created chiral center in **8** would have a different and unpredictable influence on the steric course of the further $LiAlH_4$ reduction to **2**. Thus the assumption that the



5 **8**

* Author to whom correspondence should be addressed.

(1) We gratefully acknowledge support of this research from the National Science Foundation, NSF GP 9432.

(2) J. A. Berson and M. A. Greenbaum, *J. Amer. Chem. Soc.*, **81**, 6456 (1959).

(3) V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954).

(4) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 168 (1961).

(5) I. Tömösközi, *Tetrahedron*, **19**, 1969 (1963).

(6) E. L. Eliel and D. Delmonte, *J. Org. Chem.*, **21**, 596 (1956).

(7) J. A. Dale, Ph.D. Thesis, Stanford University, 1970.

(8) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1970).

(9) (a) J. D. Morrison and J. E. Tomaszewski, private communication. (b) The maximum rotation of phenylethylene glycol is also supported by a series of reactions in which it is related to phenylglycerol: M. H. Denton and G. U. Yuen, *J. Org. Chem.*, **33**, 2473 (1968). (c) This conclusion is consistent with our finding that (−)-menthyl phenylglyoxylate, when treated with excess $LiAlH_4$, gives phenylethylene glycol, $[\alpha]^{19}D$ −6.5 ± 0.1° (*c* 11.2, $CDCl_3$), which calculates to be 10 ± 0.4% enantiomerically pure based upon the maximum rotation of $[\alpha]^{23}D$ −63.8° (c 9.5, $CDCl_3$). Horeau, Kagan, and Vigneron, *Bull. Soc. Chim. Fr.*, 3795 (1968), have reported a 10% asymmetric reduction of (−)-menthyl phenylglyoxylate with 1 equiv of $LiAlH_4$ to give (−)-menthyl mandelate whose maximum rotation is well documented. Thus the extent of asymmetric synthesis as measured by either of these methods is the same, as indeed it should be.

ester group was reduced before the keto group could rationalize the stereochemical findings. The reduction of the same ester with sodium borohydride was also studied.[2] Under several reaction conditions they always obtained (+)-phenylethylene glycol, without detecting the intermediate mandelate ester.[10] These results offered direct evidence that in phenyldihydrothebainyl phenylglyoxylate the ester carbonyl is reduced more rapidly than the keto carbonyl by sodium borohydride and, by implication, by $LiAlH_4$ as well. In support of this they found that the reduction of ethyl phenylglyoxylate with excess sodium borohydride (dioxane solvent, 100°, 15 min) gave a 64% isolated yield of phenylethylene glycol; none of the intermediate ethyl mandelate was observed in the product. Under the same reduction conditions ethyl mandelate was recovered unchanged in 90% yield.[2]

We investigated a number of hydride reductions of phenylglyoxylate esters and found that the ethyl ester with less than 1 equiv of $LiAlH_4$ (ether solvent, 20 min) gave a neutral fraction, the nmr of which indicated a 56:44 ratio of ethyl phenylglyoxylate and ethyl mandelate but *no* phenylethylene glycol. When this substrate was treated with an excess of sodium borohydride (in purified dioxane, 25 min reflux), ethyl phenylglyoxylate and ethyl mandelate were observed in the product by nmr analysis in an 84:16 mol ratio with no observable (less than 3%) phenylethylene glycol. Ethyl mandelate under the same reduction conditions was observed to give an 81:19 ratio of unreacted ethyl mandelate to phenylethylene glycol. Thus both $LiAlH_4$ and sodium borohydride reduce the keto group of ethyl phenylglyoxylate before the ester group, although sodium borohydride does reduce ethyl mandelate to phenylethylene glycol slowly.

We are unable to offer any complete explanation for the differences in our results and those reported previously.[2] We concur with Berson and Greenbaum in the admonition for use of "...extreme caution in the assignment of absolute configurations on the basis of hydride reductions of phenylglyoxylates." However, with due caution and suitable controls, it would appear that the $LiAlH_4$ reduction of chiral phenylglyoxylate esters can be utilized for configurational studies, as Prelog, Wilhelm, and Bright[3] proposed.

Experimental Section

(*R*)-(−)-Phenylethylene Glycol.—An ether solution of (*R*)-(−)-mandelic acid {1.8 g, 1.2 mmol, $[\alpha]^{25}D$ −152.3° (*c* 3.27, H_2O), 98 ± 1% enantiomerically pure[11]} was added to $LiAlH_4$ (2.5 g, 6.6 mmol) in ether. After refluxing 1 hr, the mixture was hydrolyzed with hydrochloric acid and ice. The ether extracts were washed (H_2O, Na_2CO_3, H_2O), dried ($MgSO_4$), and evaporated to give an oil which was filtered through silica gel with benzene (75 ml) and methanol (100 ml). The residue from the eluate was sublimed to give 1.55 g (95% yield): mp 63–65°; $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH); $[\alpha]^{25.5}D$ −63.7° (*c* 5.45, $CDCl_3$). No impurities were detectible by nmr.

Racemic phenylethylene glycol was prepared by reduction of racemic mandelic acid by excess $LiAlH_4$:[13] the nmr spectrum was identical with that of the chiral material described above.

(*RS*)-Phenylethylene Glycol Di-(*S*)-α-methoxy-α-trifluoromethylphenylacetate.—Enantiomerically pure, distilled (−)-α-methoxy-α-trifluoromethylphenylacetyl chloride[8] (0.1644 g, 0.65 mmol) was added to racemic phenylethylene glycol (0.0435 g, 0.31 mmol) in dry pyridine (about 1 ml). After heating the mixture for 1 hr at 45° and allowing it to remain overnight at room temperature, it was treated with water and extracted with ether. The ether extracts were washed (dilute HCl, H_2O, saturated Na_2CO_3), dried ($MgSO_4$), and evaporated to give an oil which was analyzed, without further purification, by nmr: δ 5.10 (q, 3 F), 4.82 (q, 3 F), and 4.68 (overlapping pair of quartets, 6 F) (downfield from internal TFA reference standard in CCl_4 solvent at 94.1 MHz).

(*S*)-Phenylethylene Glycol Di-(*S*)-α-methoxy-α-trifluoromethylphenylacetate.—The above experiment was duplicated except that the (−)-phenylethylene glycol, $[\alpha]^{25}D$ −39.7° (*c* 4.33, 95% EtOH), was employed. Integration of the two downfield ^{19}F signals gave relative areas of 99:1, corresponding to a 98% excess of the (−) enantiomer in the original phenylethylene glycol; the uncertainty is probably about ±1% but cannot be greater than ±2%.

Sodium Borohydride Reduction of Ethyl Phenylglyoxylate.—Following the procedure of Berson and Greenbaum,[2] a mixture of sodium borohydride (1.03 g, 2.72 mmol, Ventron Chem. Co.) in dioxane (80 ml, purified by distillation under vacuum from $LiAlH_4$, pure by nmr analysis) was heated to reflux and ethyl phenylglyoxylate (1.35 g, 0.75 mmol, pure by nmr analysis) in 20 ml of dry dioxane was removed under reduced pressure at room temperature. The residue was hydrolyzed with 4 *N* hydrochloric acid (56 ml) in the presence of ether at 0° or below. The ether extracts were washed (H_2O, saturated Na_2CO_3), dried ($MgSO_4$), and concentrated to give an oil (1.28 g) which analyzed by nmr for 16 mol % ethylmandelate and 84 mol % unreduced ethyl phenylglyoxylate; no phenylethylene glycol (less than 3%) could be detected.

Sodium Borohydride Reduction of Ethyl Mandelate.—When the identical procedure was repeated using ethyl mandelate (1.36 g, 0.75 mmol) as the substrate, the nmr analysis of the resulting oil (1.21 g) showed an 81:19 mol ratio of ethyl mandelate to phenylethylene glycol.

Reduction of Ethyl Phenylglyoxylate with Less Than 1 Equiv of Lithium Aluminum Hydride.—$LiAlH_4$ (0.0566 g, 1.48 mmol) in ether (15 ml) was added to ethyl phenylglyoxylate (1.00 g, 5.64 mmol) dissolved in ether (5 ml). The mixture was stirred for 10 min at room temperature and refluxed for 10 min, and the product was obtained by hydrolysis with hydrochloric acid followed by the usual work-up and filtration through silica gel. The purified reaction product showed by nmr a molar ratio of 44:56 of ethyl mandelate to ethyl phenylglyoxylate. No phenylethylene glycol was detected; control experiment showed that phenylethylene glycol was eluted from the column under the conditions used.

$LiAlH_4$ Reduction of (−)-Menthyl Phenylglyoxylate.—(−)-Menthyl benzoylformate (1.5 g) was treated with excess $LiAlH_4$ (1.0 g in 10 ml of ether). The hydrolyzed reaction mixture was worked up as described under the mandelic acid reduction experiment to give (*R*)-(−)-phenylethylene glycol, $[\alpha]^{19}D$ −6.5 ± 0.1° (*c* 11.22, $CDCl_3$). This corresponds to 10.4% excess of the *R* isomer, based on a maximum rotation of $[\alpha]^{25}D$ 63.7° (*c* 5.45, $CDCl_3$).

Registry No.—*R*-(−)-2, 16355-00-3; ethyl phenylglyoxylate, 7603-79-8; (−)-methyl phenylglyoxylate, 25966-98-7.

(10) Bakshi and Turner[4] however did isolate the intermediate mandelate ester upon $NaBH_4$ reduction of menthyl phenylglyoxylate.

(11) The best literature values are $[\alpha]^{23.6}D$ −154.3 ± 0.6° (*c* 1.64, H_2O);[4] $[\alpha]^{18}D$ +157.5° (*c* 3.5, H_2O);[3] $[\alpha]D$ +156.57° (*c* 2.89, H_2O).[12]

(12) J. Lewkovitch, *Ber.*, **16**, 1573 (1883).

(13) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **69**, 2548 (1947).

Additions and Corrections

Vol. 25, 1960

J. G. Bennett, Jr., and S. C. Bunce: Cyclopropyl Analogs of Hexestrol and Diethylstilbestrol.

Pages 73–79. The reaction of cyclopropylphenylcarbinol with phosphorus tribromide at −15° gives 4-bromo-1-phenyl-1-butene, identified by its nmr spectrum and by its conversion to *trans*-1-phenyl-1,3-butadiene on treatment with sodium amide in liquid ammonia, rather than cyclopropylphenylcarbinyl bromide, in confirmation of the report of A. Maercker and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 1742 (1966).

The product of the bromination of cyclopropylphenylmethane by N-bromosuccinimide, also reported by us as cyclopropylphenylcarbinyl bromide, is 4-bromo-1-phenyl-1-butene.

The crystalline product, mp 70–72°, obtained from reaction of the 4-bromo-1-phenyl-1-butene with ethylmagnesium bromide and cobalt(II) chloride is still assigned the structure of 1,2-dicyclopropyl-1,2-diphenylethane on the basis of nmr data (CCl_4): 0–0.7 (complex multiplet), 1.1 (2 H, complex multiplet), 2.12 (2 H m), and 7.0 (10H).

Vol. 32, 1967

Wendell L. Dilling and Fred Y. Edamura: Carbene and Carbenoid Chemistry. IV. The Effect of Halide Ions on Chloro- and Bromocarbenoid Addition Reactions.

Page 3494. Column 1, lines 17 and 18 of text. "Chloro (**8**)" should read "The chloro compound (**8**)."

N. J. Leonard, D. A. Durand, and F. Uchimaru: Small Charged Rings. X. Expansion of the Aziridinium Ring by Reaction with Nitrones.

Page 3611. Compound **15b** is 5-benzyl-9,9-dimethyl-5-ethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane-3-spiro-1′-cyclohexane perchlorate (not 5-oxa).

Vol. 33, 1968

Nelson J. Leonard and Malcolm Rasmussen: The Synthesis of 3-β-(3′-Deoxy-D-ribofuranosyl)adenine, an Isomer of Cordycepin.

Page 2488 and 2490. The title compound (**5**), Page 2488, should be referred to throughout as 3-(3-deoxy-β-D-ribofuranosyl)adenine. The other corrected names are **3**, 3-(2,5-di-*O*-benzoyl-3-deoxy-β-D-ribofuranosyl)-7-pivaloyloxymethyladenine hydrobromide; **4**, 3-(2,5-di-*O*-benzoyl-3-deoxy-β-D-ribofuranosyl)adenine; compound at bottom of page 2490, column 1, 3-(2,5-di-*O*-benzoyl-3-deoxy-β-D-ribofuranosyl)-N^6-pivaloyladenine. We are grateful to Professor M. L. Wolfrom for calling these necessary corrections to our attention.

A. Hassner: Regiospecificity. A Useful Terminology in Addition and Elimination Reactions.

Page 2684. Column 2. End of paragraph 1 should read "A nearly equimolar isomer distribution is the result of a *nonregioselective* reaction."

W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer: Alkyl-Substitution Effects in the Photochemistry of 2-Cyclohexenones.

Page 4062. Structure **17** should be 3,6,6-trimethylcyclohex-2-enone.

Vol. 34, 1969

P. C. Thomas, I. C. Paul, T. Williams, G. Grethe, and M. Uskoković: The Structures of Two Diastereoisomeric Sulfoxides. 3,5-Dihydro-3-methyl-4,1-benzothiazepin-2(1H)-one 4-Oxides.

Page 365. Table IV. The dihedral angles $C_2C_3S_4O_{12}$, $C_{11}C_3S_4O_{12}$, and $O_{12}S_4C_5C_{5a}$ should be −153.4, 80.9, and 61.6°, respectively, rather than the values presented in the table.

George H. Cleland: The Meerwein Reaction in Amino Acid Synthesis. II. An Investigation of Twenty-one Substituted Anilines.

Page 745. Column 2, third line from bottom of text and ref 4, line 3. "1-oxo-3-chromancarboxylic acid" should read "1-oxo-3-isochromancarboxylic acid."

Page 747. Column 1, twelfth line from bottom. "1-oxo-3-carboxylic acid" should read. "1-oxo-3-isochromancarboxylic acid."

Melvin S. Newman and Abraham O. M. Okorodudu: The Formation of Unsaturated Carbenes by Alkaline Treatment of N-Nitrosooxazolidones.

Page 1220. Column 1, footnote 1 should read as follows.

(1) This research was supported by Research Grant GP-5552X from the National Science Foundation and by Grant DA-ARO-D-31-124-G846 of the Army Research Office, Durham, N. C.

Hamao Watanabe, Frank N. Jones, and Charles R. Hauser: Formation of Cyclopropyl Ring by Action of Sodium Amide on *exo*-Methyleneammonium Ions Obtained from Rearrangement of Certain 2,6-Dimethylbenzyltrimethylammonium Ions.

Page 2395. Column 2, line 52. "3.82" should read "2.15."

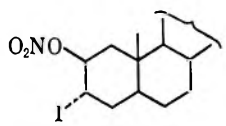
Page 2396. Column 1, line 39. After 44 (2.4), add 43 (2.4).

Page 2397. Column 1, line 20. After 2.4 Hz, add 2.2 H.

Page 2397. Column 2, line 4. "3010" should read "3110."

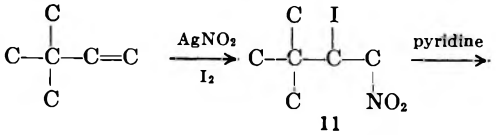
A. Hassner, J. E. Kropp, and G. J. Kent: Addition of Nitryl Iodide to Olefins.

Page 2628. Formula 2 should read

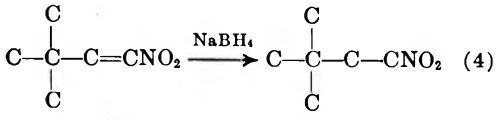


2

Page 2629. Formula 11 and eq 4 should read



11



12 13

Herman E. Zieger and John D. Roberts: Nuclear Magnetic Resonance Spectroscopy. Proton Spectra of Diallylmercury. (*J. Org. Chem.*, **34**, 2826 (1969).

Page 2826. Footnote *e* to Table I actually refers to $J_{14} = J_{15}$ and not to J_{16}, J_{26}, and J_{36}.

N. Indictor, T. Jochsberger, and D. Kurnit: Autoxidation of 1-Octene with *t*-Butyl Hydroperoxide and Chromium(III) Acetylacetonate. I. Kinetics. II. Solvent Effects and Free-Radical Inhibitors.

Page 2855. Column 2, line 8 from bottom. "3-octenal" should read "2-octenal."

Page 2859. Reference 25. "Reference 19" should read "Reference 18."

Page 2863. Column 2, line 11. "exothermic" should read "endothermic."

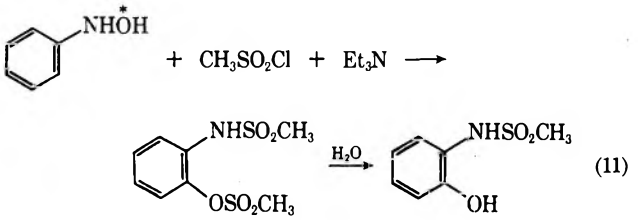
Page 2864. Column 1, line 10. Reference 23 (superscript) should read 2 (superscript).

L. A. Paquette, D. E. Kuhla, J. H. Barrett, and L. M. Leichter: Unsaturated Heterocyclic Systems. LV. Cycloaddition Reactions of Derivatives of 1*H*-Azepine.

Page 2894. The ultraviolet spectra of **42** and **43** should be interchanged. Also, in the nmr characterization of **43**, H_8 appears at δ 5.78 and not 6.78.

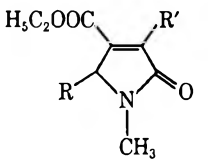
William E. Truce, J. W. Fieldhouse, D. J. Vrencur, J. R. Norell, R. W. Campbell, and D. G. Brady: Reaction of "Sulfenes" with Aryl Nitrones and N-Phenylhydroxylamines to Form Benzoxathiazepines and *o*-Aminophenol Derivatives, respectively.

Page 3101. Formulas in eq 11 should be as follows.



Neal Castagnoli, Jr: The Condensation of Succinic Anhydride with Benzylidinemethylamine.

Page 3187. Column 2. The structure referring to compounds **6**, **7**, and **9** is incorrect and should be as follows.



W. Herz, P. S. Subramaniam, and N. Dennis: Solvent Shift Studies on Pseudoguaianolides of the Helenalin Series.

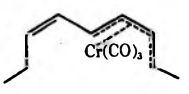
Page 3691. Formulas for compounds 1 and 2 should be corrected as follows: the angeloyloxy group should be at 6-α instead of 5-α and a methyl group should be at 5-β.

E. N. Frankel and R. O. Butterfield: Homogeneous Hydrogenation of Diolefins Catalyzed by Tricarbonyl Chromium Complexes. I. Stereoselective 1,4 Addition of Hydrogen.

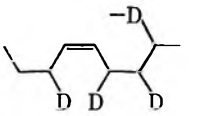
Page 3931. Scheme I. In structure **4**, there should be no bond between D and D.

E. N. Frankel, E. Selke, and C. A. Glass: Homogeneous Hydrogenation of Diolefins Catalyzed by Tricarbonyl Chromium Complexes. II. Deuteration.

Page 3938. Scheme V. Structure **19** should be as shown.

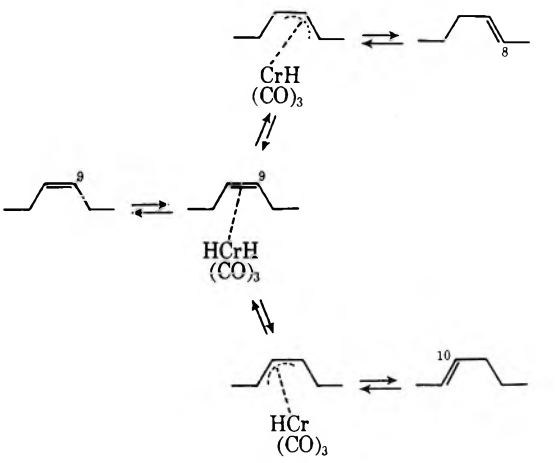


Page 3939. Scheme VI. Equal signs should be horizontal. Structure **22** should be as shown.

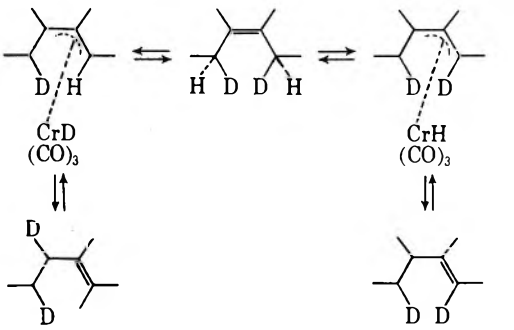


In eq 6, "*d*" should read "d_β."

Page 3940. Column 1. Scheme should be as shown. "HCrH" should read "CrH."



Column 2. Scheme should be as shown. Dashed curved line should be shortened.



Shozo Yanigida, Hiroshi Hayama, and Saburo Komori: The Reaction of Primary Amides with Phosgene in the Presence of Hydrogen Chloride.

Page 4181. Column 1, under Experimental Section, line 3. "boiling" should read "recrystallization." Column 2, Registry No. paragraph. Third compound should be 6-chloro-2-pentyl-5-butyl-4(3H)-pyrimidone.

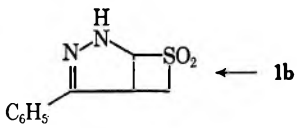
R. Behnke, A. A. Chandross, and F-H. Marquardt: 9-Arylfluorenes. The Energy Barrier for the Inversion of 9-Chloro-9-durylfluorene.

Page 4208. Application of computer-based line shape analysis (with a program which had been supplied by Professor M. Saunders of Yale University) to the collapsing signals of the *o*-methyl groups yielded the values $\Delta H^{\ddagger}$ = 20 kcal/mol and $\Delta S^{\ddagger}$ = 14 eu.

Vol. 35, 1970

Donald C. Dittmer and Robert Glassman: Diazo Alkane Adducts of Thiete Sulfone (Thiacyclobutene 1,1-Dioxide) in Synthesis of Thiabicyclopentane Dioxides, Pyrazoles, and Tetrahydrothiophene Sulfones.

Page 1001. Column 1. The formula following the arrow from **1b** in Scheme II should be



1b

C. G. Overberger and D. A. Labianca: Azo Compounds. Investigation of Optically Active Azonitriles.

Page 1770. In the last experiment, we mention that "A suitable liquid, chosen according to the temperature desired (ethanol at *ca.* 100°), was refluxed in the outer chamber." The parenthetical information should be "ethanol at *ca.* 78°."

K. T. Potts and R. Armbruster: Bridgehead Nitrogen Heterocycles. III. The 3H-[1,2,4]-Thiadiazolo[4,3-*a*]pyridine System.

Pages 1966 and 1967. "π moiety" should read "py moiety."

Harold J. Teague and William P. Tucker: Thiapyrone Chemistry. III. The Reaction of 2,6-Dimethylthio-3,5-diphenylthiapyrone with Hydroxide Ion.

Page 1968. We wish to call attention to the work of Professor Alexander Schönberg and R. von Ardenne [*Chem. Ber.*, **101**, 346 (1968)] on the structure of the alkaline hydrolysis product of 2,6-dimethylthio-3,5-diphenylthiapyrone and of one of its products with diazomethane. We were unaware of this paper at time of submission of our work.

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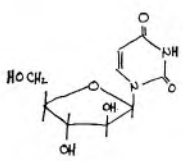
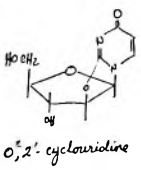
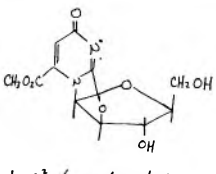
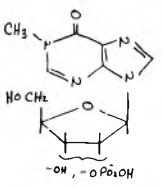
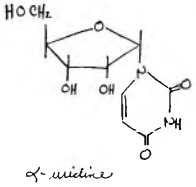
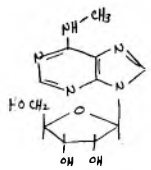

Uracil arabinoside

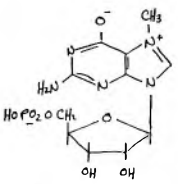

$O^2,2'$-cyclouridine

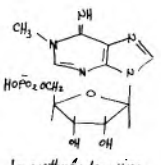

L-$O^2,2'$-cyclocytidine methyl ester

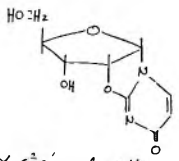

1-methylinosine 2'(3')-monophosphoric acid

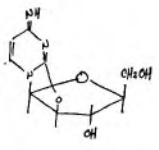

α-uridine


N-6-methyladenosine


7-methylguanosine 5'-phosphoric acid


1-methyladenosine 5'-phosphoric acid


α-$C^2,2'$-cyclouridine


L-$O^2,2'$-cyclocytidine

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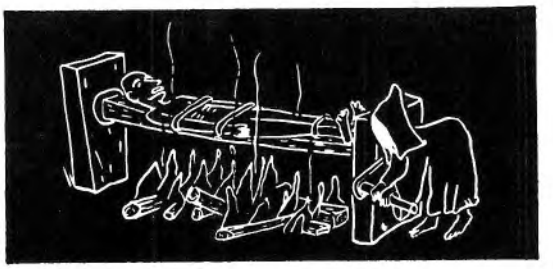

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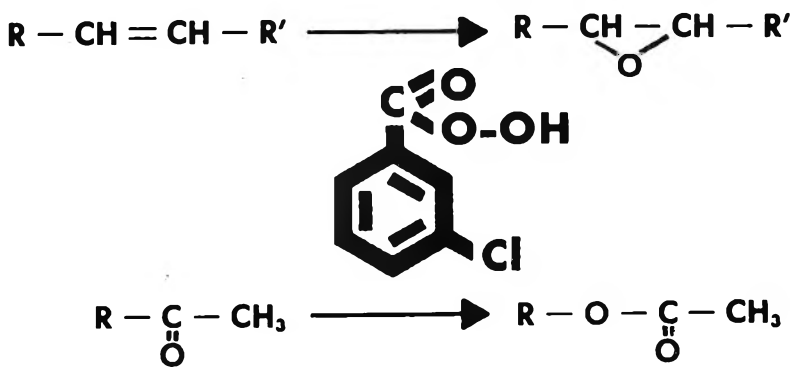

Also of great interest in the preparations of N-oxides[4] and nitrosteroids[5].

(1) L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, p. 135, Wiley, 1967

(2) J. Fried et al., Tetrahedron Letters, 849 (1965)

(3) D. J. Pasto et al., J. Org. Chem., 30, 1271 (1965)

(4) T. J. Delia et al., ibid, 30, 2766 (1965)

(5) C. H. Robinson et al., ibid, 31, 524 (1966)

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