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NEWS FROM "PIERCE PREVIEWS" *

RAPID, DIRECT G.C. METHOD FOR CHROMIUM IN BLOOD OR PLASMA.

In an important and impressive paper, soon to be published,[1] Larry C. Hansen, William G. Scribner, T. William Gilbert and Robert E. Sievers have described a simple, rapid and direct method for the quantitative determination of sub-nanogram amounts of chromium in blood and plasma by electron capture chromatography. This new method utilizes 1,1,1-trifluoro-2,4-pentanedione [H(tfa)] to form a volatile chelate with the chromium. No digestion or ashing of the sample is required in the direct reaction. An earlier method[2] for microgram quantities of chromium in serum also used H(tfa) but required an acid digestion to destroy interfering protein matter.

In developing the new method the authors performed systematic optimization experiments, varying chelating agents, concentration, time and temperature. The results were painstakingly checked by collateral methods of analysis.

The extraordinary sensitivity of fluorinated chelates of chromium (III) to electron capture technique has been shown in earlier studies.[3,4]

The importance of chromium in human nutrition and its role in physiological functions such as glucose metabolism have been somewhat obscured by the arduous methods and length of time required to obtain accurate results. Mertz[5] has extensively reviewed the occurrence and importance of chromium in biological systems. This masterful review points up the need for a simple analytical method in order to really begin research in this important subject and answer vital questions relating to health of the public and the individual.

For several years we have manufactured a number of fluorinated β-diketones as chelating agents for the gas chromatography of metals. It has been our pleasure to work with the authors of the new method in providing chelating agents for this and important earlier efforts. We also supply a number of the chelated metals (as listed in our "Handbook GPA-3"). We have recently added the chromium (III) chelate of H(tfa) for use as a standard. We list it as trifluoroacetylacetonate Cr(III); the H(tfa) as trifluoroacetyl acetone. These materials are available as follows:

118813 **TRIFLUOROACETYLACETONATE, Chromium (III)** $12/1gm

67550 **TRIFLUOROACETYL ACETONE** (1,1,1-Trifluoro2,4-pentanedione) $15/25gm; $45/100gm

References cited:

1. *Rapid Analysis for Sub-Nanogram Amounts of Chromium Using Electron Capture Gas Chromatography*, accepted for publishing in *Analytical Chemistry*. For pre-prints write Dr. W. G. Scribner, Monsanto Research Corporation, Dayton Laboratory, 1515 Nicholas Road, Dayton, Ohio 45407.
2. Savory, J., Mushak, P., Sunderman, F.W., Jr., Estes, R.H. and Roszel, N.O., *Analytical Chemistry*, **42**, 294-296 (1969).
3. Moshier, R.W. and Sievers, R.E., *Gas Chromatography of Metal Chelates*, Pergamom Press. Oxford (1965) and references therein.
4. Ross, W.D. and Sievers, R.E., *Analytical Chemistry*, **47**, 1109-12 (1969).
5. Mertz, W., *Physiological Reviews*, 49, 163-239 (1969).

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FEBRUARY 26, 1971

New Bicyclic Enamines and Iminium Salts. II. Synthesis of 1,4-Dihydro-1,4-ethanoisoquinolinium Salts and 4,5-Dihydro-1*H*-1,4-methano-3-benzazepinium Salts by Reaction of Bridged Lactams with Organometallic Reagents[1]

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Received August 7, 1970

Structures of 1,4-dihydro-1,4-ethanoisoquinolinium salts **6**, earlier synthesized *via* reductive closure of 4-acyl-1-tetralone oximes, were confirmed, and a second, more versatile synthesis of those iminium salts and corresponding enamines **5** was found. Nickel-catalyzed reduction of oximino esters **1d** to amino esters **2**, thermal closure of *cis*-amino esters **2a** to bridged lactams **3**, and reaction of corresponding *N*-alkyl lactams **4** with alkyllithiums yields bridged enamines **5** protonated to give **6**. The synthesis was extended to preparation of 1,4-methanohydrobenzazepinium salts **9** *via* bridged enamines **8** from lactams **7**. Some comparisons of the two types of bridged enamines **5** and **8** are made, and certain alternative routes to lactams **3** and **4** are discussed.

Our first synthesis[2] of benzoisoquinuclideinium salts **6** and corresponding bridged enamines **5** involved palladium-catalyzed reduction of 4-acyl-1-tetralone oximes. That synthesis was limited in scope, owing to difficulties in obtaining required intermediates and the fact that by-products of reductive closure such as *trans*-amino ketones and further-reduced, bridged secondary amines usually accompanied the bridged imines. Bridged iminium salts **6** were at one time of a certain pharmacological interest;[3] hence we wished to enlarge the range of available 1,4-dihydro-1,4-ethanoisoquinolinium and related salts. This paper describes a route serving that purpose, of rather greater versatility than the first, proceeding through lactams, wherein the equivalent of a ketone group is now introduced after, rather than before, conversion of the 1-tetralone to a 1-aminotetralin.

The synthesis of requisite 1-tetralone-4-carboxylic acids **1b** as precursors of oximino esters **1d** is a matter of the very well precedented Michael addition of acrylonitrile or methyl acrylate to various phenylacetic esters and nitriles,[2,4-7] hydrolysis, either directly or *via* glutarimides, to α-arylglutaric acids, acid amides, or acid nitriles, and cyclization to tetralones, as outlined in Scheme I. A direct synthesis of α-phenylglutaric acid and anhydride, beginning with alkoxide-catalyzed monoaddition of methyl acrylate[5] to ethyl phenylacetate, was developed. The same technique worked well with some (R = methyl, aryl, and cyclohexyl) starting phenyl acetonitriles. Other compounds were cyanoethylated initially. Glutarimides, cyano esters, or dinitriles in which R = H or a small alkyl group are not especially difficult to hydrolyze completely to glutaric acids, but, when R = aryl or a hindering cycloalkyl or cycloalkylmethyl group, saponification requires drastic conditions and long periods of time. Cyclization of the glutaric acids or acid amides[7] with concentrated sulfuric acid gave tetralone acids and amides **1b** and **1a**, respectively. Contrary to one report,[8] it was found that at least some of the amides **1a** can be hydrolyzed to acids **1b** under strenuous acid conditions. Thus acids **1b** with a variety of R groups both known and novel were prepared.

Synthesis of **1b** (R = benzyl) was a special problem because all direct PPA or sulfuric acid cyclizations of α-benzyl-α-phenylglutaric acid and its derivatives led to a spiro diketone. A successful approach to the desired tetralonecarboxylic acid was found, consisting of reaction of benzyl homophthalic anhydride with acrylonitrile. In the presence of $KOCMe_3$ in THF, cyanoethylation and Dieckmann closure both occurred, giving a cyano keto acid which on acid hydrolysis af-

(1) Presented in part at the Gordon Research Conference on Heterocyclic Compounds, New Hampton, N. H., July 5, 1966.

(2) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **32**, 2213 (1967), and references therein.

(3) (a) G. N. Walker, U. S. Patents 3,332,953 (1967) and 3,379,731 (1968); *Chem. Abstr.*, **68**, 59449 (1968), **69**, 96497 (1968). (b) G. N. Walker and K. Schenker, U. S. Patent 3,291,806 (1966). (c) G. N. Walker and R. B. Margerison, U. S. Patent 3,324,136 (1967). (d) W. E. Barrett and R. A. Rutledge, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **26**, 356 (1967).

(4) E. D. Bergman, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

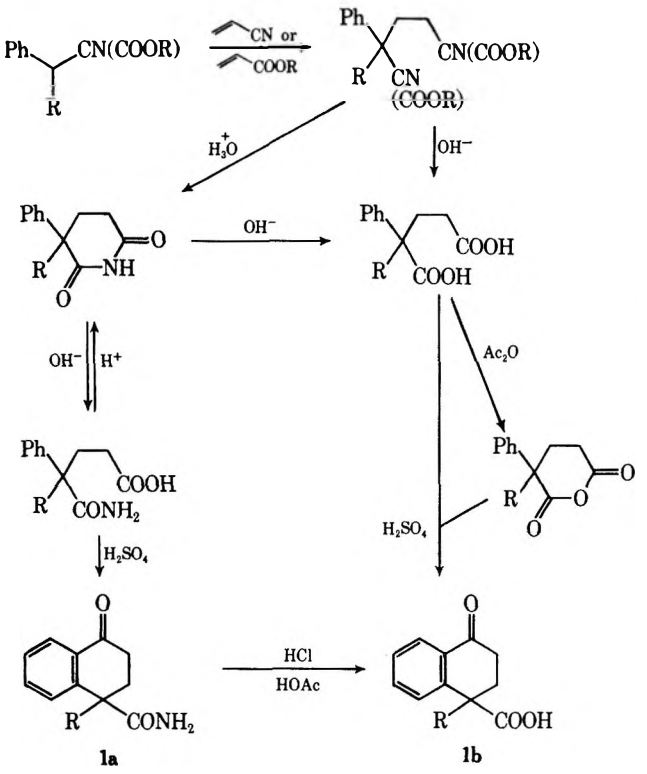
(5) L. A. Walter and R. H. Barry, U. S. Patent 2,524,643 (1950); *Chem. Abstr.*, **45**, 7154 (1951).

(6) C. F. Koelsch, *J. Org. Chem.*, **25**, 164 (1960).

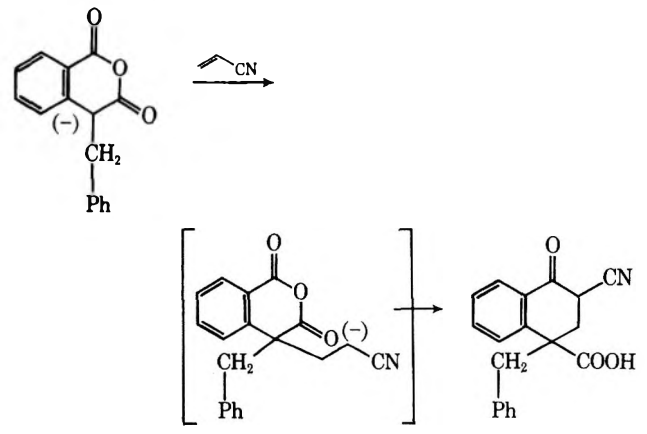
(7) K. Schenker, Belgian Patent 665,189 (1965); Netherlands Application 6,507,339; *Chem. Abstr.*, **65**, 696 (1966).

(8) W. Herz and G. Caple, *J. Org. Chem.*, **29**, 1691 (1964).

SCHEME I



forded **1b** (R = benzyl). This keto acid not only was employed as an additional intermediate in the principal series of 1,4-bridged compounds but also was converted *via* bromination of the corresponding amide[7] to the previously unreported bridged tetralone lactam corresponding to **7** (R = benzyl; R′ = H).



Esterification of the hindered acids **1b** with ethanol in the presence of both concentrated and fuming sulfuric acid conveniently afforded corresponding ethyl esters **1c**. These and certain amides **1a** were converted to corresponding oximes by standard procedures.

Palladium[2] was not suitable for hydrogenation of **1d** (R = Ph), as hydrogenolysis of the resulting amino group occurred. However, Raney nickel catalyzed hydrogenation of **1d** (R = Ph) (Scheme II) gave basic material which proved to be a mixture of both isomers **2a,b** of the amino ester. Each eventually was characterized as the hydrochloride. On standing, the crude **2a,b** (R = Ph) very slowly (weeks) deposited crystals of lactam **3** (R = Ph). This closure was accelerated by warming, and *cis*-**2a** was converted essentially completely to **3** after several days at 100°. Higher temperatures, used as a rule in isoquinuclidone closures not involving benzylamine moieties, seemed inadvisable here, since they promoted undue decomposition. The simple procedure of nickel reduction of oximino esters **1d**, followed by heating of crude amino ester **2** on a steam bath, was adopted for preparation of all the lactams **3** (Table I) from the various carbethoxytetralones. The neutral (and usually crystalline) lactams were in every case separated readily from remaining, oily *trans*-amino esters **2b**.

Another possible route to lactams **3** through hydrogenation of the oxime prepared from ketoamide **1a** (R = Ph) in the presence of nickel, gave an amino amide, but this product consisted almost entirely of the wrong (trans $NH_2/CONH_2$) isomer for lactam closure. The stereochemistry, which in fact may be owing to preferred adsorption of the polar $CONH_2$ group and its face of the molecule on the catalyst, was evident from the fact that hydrolysis of the aminoamide gave quantitatively the same amino acid as that obtained by hydrolysis of noncyclizing amino ester **2b** (R = Ph).

Ketoamide **1a** (R = Ph) and even the corresponding ketonitrile[8] could however be converted directly in one operation to lactam **3** (R = Ph) under the usual, high temperature conditions of the Leuckart reaction.[3c] Another proposed route to the bridged lactams was conversion (HBr) of the carbinol corresponding to **1a** to the bromotetralin carboxamide and internal displacement of bromo atom by amide moiety.[7] However, instead of a lactam, the bromoamide gave by HBr elimination the dihydronaphthalene amide, on treatment with sodium methoxide, sodium amide, or ammonia.

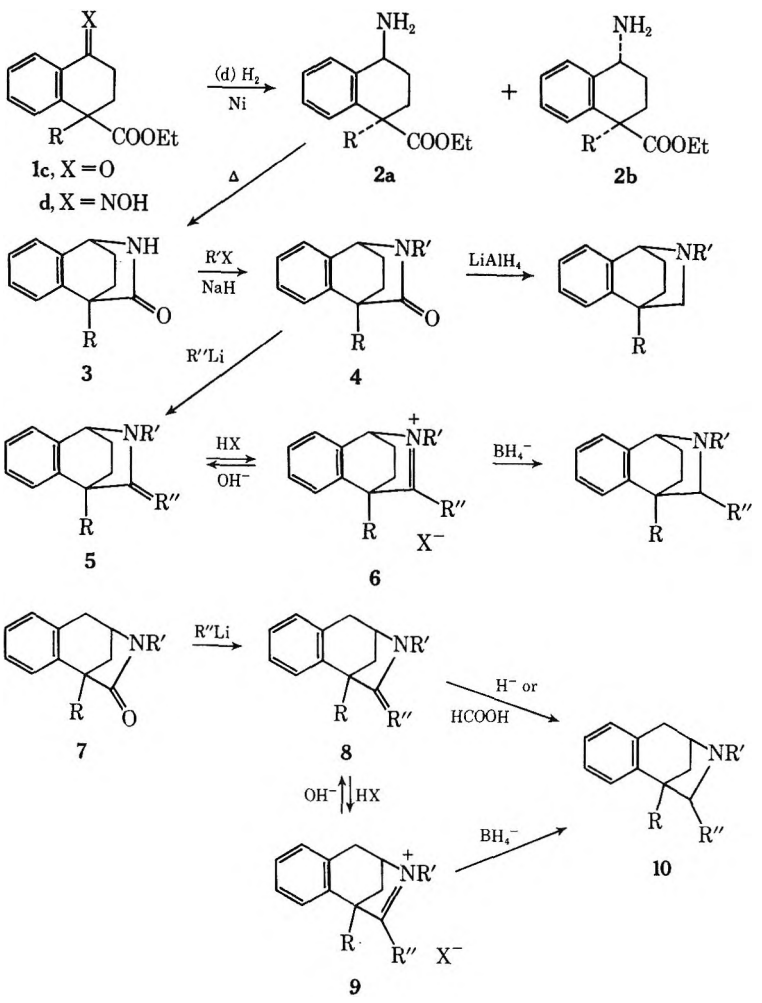
Alkylation of lactams **3** with methyl, benzyl, and other halides in the presence of NaH gave uniformly high yields of *N*-alkyl lactams **4**, also listed in Table I. Compound **4** (R = Ph; R′ = CH_3), key to the most thoroughly investigated members of the series, was identical with that lactam obtained earlier[2] by ozonolysis of enamine **5** (R = Ph; R′ = CH_3; R″ = CH_2), in turn obtained *via* the bridged imine, thus proving unequivocally the structures of the latter compounds.

Reactions of amides (particularly lactams) and nitriles with Grignard reagents[9] have sometimes been employed to synthesize imines or enamines. Except in compounds originating from lactams, there is often the disadvantage that imines, enamines, or iminium systems of common types can react further with the organometallic reagent, giving saturated amines.[10] On the other hand, conversion of phthalimidines to isoindoles, a type of enamine not susceptible to further attack by

(9) (a) R. Lukeš, *Collect. Czech. Chem. Commun.*, **2**, 531 (1930); **8**, 533 (1936); *Chem. Abstr.*, **25**, 102 (1931). (b) M. Mortagne and G. Rousseau, *C. R. Acad. Sci.*, **196**, 1165 (1933). (c) L. C. Craig, *J. Amer. Chem. Soc.*, **55**, 295 (1933). (d) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942). (e) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1278, 1281 (1958). (f) J. Knabe, *Arch. Pharm. (Weinheim)*, **298**, 257 (1965).

(10) M. Sommelet, *C. R. Acad. Sci.*, **183**, 302 (1926); H. Gilman and R. H. Kirby, *J. Amer. Chem. Soc.*, **55**, 1265 (1933), **63**, 2046 (1951); C. R. Hauser, R. M. Manyk, W. R. Brasen, and P. L. Bayless, *J. Org. Chem.*, **20**, 1119 (1955); C. R. Hauser and D. Lednicer, *ibid.*, **24**, 46 (1959); H. Boehme, H. Ellenberg, O. R. Herboth, and W. Lehners, *Ber.*, **92**, 1608 (1959); E. F. Godefroi and L. H. Simanyi, *J. Org. Chem.* **27**, 3882 (1962).

SCHEME II



carbanions, has been accomplished with alkyllithium reagents.[11]

Lactams **4**, especially those wherein R was an aryl or still more hindering group, reacted very sluggishly with excess methylmagnesium iodide; even at 100°, many hours were required to form an appreciable amount of basic product. Reaction with excess methyl-, ethyl-, or butyllithium, on the other hand, was complete in 0.5–1 hr in refluxing benzene when R was aryl or cycloalkyl and in 10–20 min at 30–50° when R was H or a small alkyl group. Moreover, under the appropriate conditions no appreciable tendency of these enamines to react further with even a large excess of the alkyllithium was observed. From **4** (R = Ph; R′ = CH_3) with CH_3MgI (low yield) and with CH_3Li (quantitatively), there was obtained enamine **5** (R = Ph; R′ = CH_3; R″ = CH_2), identical with that compound prepared earlier[2] (by action of bases on the iodomethane-quaternized, corresponding bridged imine), and converted by halogen acids to identical, corresponding iminium salts **6** (R = Ph; R′ = R″ = CH_3). The remaining *N*-alkyl lactams **4** were converted in uniformly high yields (70–90%) to corresponding enamines **5** with excess methyllithium, and thence to the varied, corresponding iminium salts **6**, listed in Table II. Two additional points of identity of products from the present method with those from the earlier route[2] were established, by synthesizing iminium salts **6** in which R = R″ = CH_3 and R′ = methyl and benzyl groups, identical with respective, earlier samples.

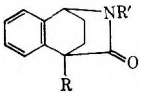
The new route *via* bridged lactams to compounds **6**, in summary, has three distinct advantages over the previous route through diketones,[2] namely (1) greater versatility in synthesis of intermediate tetralones, (2) ease of isolation of bicyclic lactams **3**, and (3) formation of enamines as virtually the only basic products in reaction of lactams **4** with alkyllithiums. Against these advantages one must set the fact that the present synthesis of **6** is longer, about eleven steps overall from available starting phenylacetic ester or nitrile.

Bridged lactams **7** (R = Ph and Et; R′ = CH_3, as well as other relatives), available[7] within our organization, were also found to react with excess methyllithium in benzene, giving bridged enamines **8** (2-methylene-1,4-methano-1,2,3,4-tetrahydro-3-benzazepines), which were converted by mineral acids in the same sense as **5** → **6** to the remaining title compounds, iminium salts **9**.

Enamines **8** appeared to be more readily oxidized by air and reduced by hydrides than were enamines **5**. This premise, founded on qualitative observations, was borne out by the fact that iminium formate **9** (R = Ph; R′ = R″ = CH_3; X = $HCOO^-$) on heating to

(11) G. Wittig and H. Streib, *Justus Liebigs Ann. Chem.*, **584**, 1 (1953); G. Wittig, G. Closs and F. Mindermann, *ibid.*, **594**, 89 (1955); W. Theilacker and H. Kalenda, *ibid.*, **584**, 87 (1953); W. Theilacker and W. Schmidt, *ibid.*, **597**, 95 (1955), and **605**, 43 (1957).

TABLE I
1,4-ETHANO-1,2,3,4-TETRAHYDRO-3-ISOQUINOLONES[a]



R	R'	Registry no.	Ir, C=O, λ_{max} (μ)	Mp, °C
C_6H_5	H	2997-32-2	5.97	268–270
C_6H_5	CH_3	2997-33-3	6.01	198–201
C_6H_5	$(CH_2)_2NMe_2$	27239-94-7	6.02	127–128
H	H	3118-16-9	5.98–6.10	200–201
H	CH_3	3118-05-6	6.00	133–135
CH_3	H	3118-20-5	5.98–6.06	165–166
CH_3	CH_3	2959-77-5	6.03	113–114
CH_3	$-CH_2C_6H_5$	27239-99-2	6.02	Oil
H	$-CH_2C_6H_5$	3036-51-9	6.02	86–87
Et	H	3118-03-4	6.0–6.02	164–165
Et	CH_3	2959-78-6	6.06	82–83
Et	$CH_2C_6H_5$	27240-03-5	6.05	85–88
c-C_5H_9	H	3195-56-0	5.98	157–158
c-C_5H_9	CH_3	2959-80-0	6.03	94–95
c-$C_6H_{11}CH_2$	H	3118-17-0	5.97	186–187
c-$C_6H_{11}CH_2$	CH_3	3118-06-7	5.97	71–73
p-PhF	H	3118-18-1	6.02	291–293
p-PhF	CH_3	3118-07-8	6.03	229–231
p-PhF	$CH_2C_6H_5$	27240-10-4	6.04	191–193
$-CH_2COOEt$	H	27240-11-5	5.98 (5.75)	123–124
$-CH_2COOEt$	CH_3	27240-12-6	5.99 (5.73)	Oil
$-(CH_2)_2COOEt$	H	3118-19-2	5.98 (3.13, 5.75)	123–124
$-(CH_2)_2COOEt$	CH_3	3118-08-9	6.02	Oil
$-CH_2C_6H_5$	H	3118-04-5	5.96	188–190
$CH_2C_6H_5$	CH_3	2959-79-7	6.01	126–128

[a] Satisfactory analyses (±0.4% for C, H, N) were obtained with all compounds listed in tables: Ed.

100° effervesced,[12] and there was isolated amine **10** (R = Ph; R′ = R″ = CH_3), the same as that obtained by $NaBH_4$ reduction of either **8** or **9**. The analogous 1,4-bridged iminium formate **6** (R = Ph; R′ = R″ = CH_3; X = $HCOO^-$) was not reduced under the same conditions, although **5** and **6** are in general reduced by hydrides to corresponding bridged amines.[2,3]

Experimental Section[13]

1-Amino-4-ethoxycarbonyl-4-phenyltetralin (2, R = Phenyl).—Hydrogenation of 24.4 g of 1-oximino-4-ethoxycarbonyl-4-phenyltetralin[2] in 200 ml of ethanol in the presence of 15 g (water and alcohol washed) of commercial Raney nickel, for 4 hr at 60°, resulted in absorption of 2.06 molar equiv of H_2 (13-lb pressure drop). Filtration and evaporation of the solvent gave (100%) a crude, isomeric mixture of amino esters. The material was soluble in dilute HCl.

From the solution of a sample of freshly prepared amine in dry ether with ethanolic HCl, there was precipitated a sample of **2a** (cis NH_2/COOEt) **hydrochloride**. Recrystallization (methanol–ether) gave colorless crystals: mp 187–189°; ir 5.81 μ; uv 265 nm (ϵ 430); soluble in dilute HCl.

Anal. Calcd for $C_{19}H_{21}NO_2 \cdot HCl$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.52; H, 6.65; N, 4.13.

From ether solution of mother liquors left after thermal closure to lactam (see following experiment) and maximal removal of that product, there was similarly obtained **2b** (trans NH_2/COOEt) **hydrochloride**: mp 246–248° (from ether); ir 5.77 μ.

Anal. Calcd for $C_{19}H_{21}NO_2 \cdot HCl$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.48; H, 6.68; N, 4.22.

Closure to Lactam 3 (R = C_6H_5).—Crude amino ester (29 g, mixture of isomers) from the preceding reduction was heated on a steam cone for 5 days; each day the crystalline lactam which had formed was collected and washed with ether, and the filtrate was evaporated and returned to the steam cone, until crystals no longer formed on heating the oil. There was accumulated a total of 10.8 g (44%) of crystals, in four crops: mp 268–270°, not raised on further recrystallization from ether or methanol; ir 3.16 and 5.97 μ; uv 257 nm (ϵ 390); insoluble in dilute acids.

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.0; H, 6.18; N, 5.62.

The lactam was also isolated, in lower yield, from samples of crude amino ester which had been allowed to stand at room temperature several weeks.

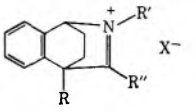
Other **4-substituted 1,2,3,4-tetrahydro-1,4-ethanoisoquinolin-3-ones**, listed in Table I, were prepared from the appropriate 4-carbethoxytetralone oximes by essentially the same two-step (reduction, 100° thermal closure) procedure, in yields of 20–40% and never exceeding 50%, except in the case of the 4-unsubstituted lactam (R = R′ = H) in which adsorption of R = H oximino ester with the carbethoxy group oriented away from surface of catalyst appeared to be particularly favored.

2-Methyl-4-phenyl-1,4-ethano-1,2,3,4-tetrahydro-3-isoquinolone (4, R = C_6H_5; R′ = CH_3).—A suspension of 7.1 g of **3** (R = C_6H_5) and 3.5 g of 56% NaH (oil) in 500 ml of toluene was refluxed and stirred 0.5 hr, cooled, treated with 30 ml of iodomethane, and stirred and refluxed 9 hr longer. The cooled, filtered, ether-diluted, twice water-washed, dried ($MgSO_4$), and evaporated organic solution gave on ether trituration 7.1 g of crystals: mp 198–201°, raised on recrystallization to mp 198.5–201.5°; ir 6.01 μ; uv 246 nm (ϵ 410). The sample was identical (ir, mixture melting point undepressed) with that obtained as described earlier[2] by ozonization of enamine **5** (R = C_6H_5; R′ = CH_3; R″ = H).

(12) Mechanism of the Leuckart reaction: P. L. deBenneville and J. H. MacCartney, *J. Amer. Chem. Soc.*, **72**, 3725 (1950); D. S. Noyce and F. S. Batchelor, *ibid.*, **74**, 4577 (1952); N. J. Leonard and R. R. Sauers, *ibid.*, **79**, 6210 (1957); A. G. Cook, W. C. Meyer, K. E. Ungrodt, and R. H. Mueller, *J. Org. Chem.*, **31**, 14 (1966).

(13) Calibrated melting points were obtained using a Thomas–Hoover silicone oil bath, infrared spectra (Nujol mulls, unless otherwise noted) were recorded with Perkin-Elmer double beam instrument, and ultraviolet spectra (methanol solutions, unless otherwise stated) were measured by Cary recording spectrophotometer. Hydrogenations were performed on the standard Parr shaker apparatus having a 4-l. reserve tank.

TABLE II
1,4-DIHYDRO-1,4-ETHANOISOQUINOLINIUM HALIDES



R	R′	R″	X⁻	Registry no.	Ir, C=O, λ_{max} (μ)	Mp, °C
H	CH_3	CH_3	Cl	2959-86-6	6.01	259–261[a]
H	CH_3	CH_3	I	3956-71-6	6.01	217.5–219.5
H	$CH_2C_6H_5$	CH_3	I	2959-90-2	6.08	169–170
C_6H_5	CH_3	Et	I	2997-37-7[c]	6.05	235–237 dec
			Cl	2997-36-6[d]	6.07	239–241 dec
C_6H_5	CH_3	*n*-Bu	Cl	2997-35-5	6.06	242–244[a]
Et	CH_3	CH_3	I	3063-67-0	6.06	*ca.* 140 dec
Et	$CH_2C_6H_6$	CH_3	I	27240-22-8	6.12	205–207
Cyclopentyl	CH_3	CH_3	I	3123-64-6[c]	6.09	213–216[b]
			Cl	2959-92-4[d]	6.08	243–244[b]
c-$C_6H_{11}CH_2$	CH_3	CH_3	Cl	3036-53-1	6.06	236–238.5
p-FC_6H_5	CH_3	CH_3	I	3022-26-2[e]	6.03	277–278
	$CH_2C_6H_5$	CH_3	I	27298-29-9[f]	6.13	246–247
$-CH_2C(OH)(CH_3)_2$	CH_3	CH_3	I	27240-27-3	6.10 (3.02)	200–201
$-(CH_2)_2C(OH)(CH_3)_2$	CH_3	CH_3	I	2959-87-7	6.10 (3.03)	188.5–190
$CH_2C_6H_5$	CH_3	CH_3	I	2959-91-3	6.09	239–240 dec

[a] Hemihydrate. [b] Monohydrate. [c] The iodide. [d] The chloride. [e] R′ = Me. [f] R′ = $CH_2C_6H_5$

The remaining *N*-alkyl lactams (R′ = methyl, benzyl, and $CH_2CH_2NMe_2$) of Table I were prepared by the same procedure, essentially quantitatively, with appropriate minor modification (extraction with HCl and reprecipitation with NaOH) in work-up procedure for the basic compound and use of ligroin (bp 39–53°) or hexane in recrystallizing the compounds of mp *ca.* 110° or below, and methanol or methanol–ether for others.

2-Methyl-3-methylene-4-phenyl-1,4-dihydro-1,4-ethanoisoquinoline (5, R = Phenyl; R′ = CH_3; R″ = CH_2) and Corresponding Iminium Salts (6, R″ = CH_3).—A solution of 5 g of 4-phenyl-*N*-methyl lactam from the preceding experiment in 750 ml of dry benzene was treated with 120 ml of methyllithium–ether solution (1.92 *M*) and refluxed 1 hr, during which time the solution became yellow and a heavy, white precipitate formed. The cooled mixture was treated with ice and water, and ether was added; the organic layer was washed twice with water and extracted with two portions (50 ml) of ice-cold, 18% hydrochloric acid. Gradual addition of cold 15–20% NaOH to the chilled, acid solution gave the enamine as colorless oil. In this instance, the enamine crystallized, after a short while. The collected, water-washed, air-dried crystals (5 g) had mp 168–172.5°. Recrystallization from ether gave a sample, mp 172–175°; mmp (with the same enamine) 171–175° prepared as described earlier (by action of base on methyliminium iodide from imine with iodomethane)[2] was undepressed, and ir (6.18, shoulder 6.21 μ) and uv (inflection 228 nm, ε 4670) were identical with those of the earlier sample.

The **iminium chloride sesquihydrate**, colorless crystals from ethanol–ether, mp 242–243°, and **iminium iodide monohydrate**, mp 245–247°, were prepared from the enamine using ethereal, ethanolic HCl and aqueous, ethanolic HI, respectively, and the samples of these salts were also respectively identical (mixture melting point, spectra) with those prepared *via* the earlier route[2] through 4-acetyl-4-phenyl-1-tetralone.

Two other enamines (2-methyl-3-alkylidene-4-aryl-1,4-ethano-1,2,3,4-tetrahydroisoquinolines), from reaction of 4-aryl-substituted 2-methyl-bridged lactams **4** with appropriate alkyllithium reagents according to the foregoing procedure, were obtained in crystalline form during the course of this work.

Compound 5 (R = phenyl; R′ = CH_3; R″ = $CHCH_3$) was crystallized from ether, mp 107–109°, ir 6.04 μ.

Anal. Calcd for $C_{20}H_{21}N$: C, 87.22; H, 7.69; N, 5.09. Found: C, 87.47; H, 7.86; N, 5.11.

Compound 5 (R = *p*-fluorophenyl; R′ = CH_3; R″ = CH_2) was crystallized from ether, mp 146–148°, ir 6.15 μ.

Anal. Calcd for $C_{19}H_{18}FN$: C, 81.69; H, 6.49; N, 5.02. Found: C, 81.72; H, 6.48; N, 4.92.

All remaining enamines **5** prepared were colorless or yellowish oils, most of then sensitive to air oxidation or apparent polymerization. The smaller the substituent R at position 4, the less stability they appeared to possess, judging from various qualitative observations made in the course of work-up and isolating individual compounds.

2-Benzyl-3,4-dimethyl-1,4-dihydro-1,4-ethanoisoquinolinium Bromide and Iodide (6, R = R″ = CH_3; R′ = $CH_2C_6H_5$; X = Br and I).—A solution of 1.2 g of crude lactam **4** (R = CH_3; R′ = $CH_2C_6H_5$) in 50 ml of benzene was treated with 15 ml of 1.92 *M* methyllithium–ether solution. After a 10-min reflux, the solution was allowed to stand overnight and then poured into ice and water. The basic fraction was isolated as in the preceding experiment. The crude enamine was a pale yellow, air-sensitive oil, and thus, after its extraction with ether, the ether solution was washed twice with water, dried (K_2CO_3), and concentrated *in vacuo* to a volume of 200 ml, and half of the solution was used to prepare each iminium salt.

A slight excess of saturated, ethanolic HBr solution precipitated the **bromide** initially as an oil, crystallizing after being washed (by decantation) with ether and rubbing with ether–ethanol, as 0.5 g of colorless crystals: mp 233–235° dec; mmp (with the same compound prepared as described earlier[2]) 234–236° dec (undepressed); and ir (6.08 μ) and uv (224–231 nm, ε 3450) identical.

Treatment of the remaining ether solution of enamine with a slight excess of a solution of 1.8 ml of concentrated HI in 5 ml of ethanol gave the iminium **iodide** (0.8 g), crystallizing in ethanol: mp 215–217° dec; ir 6.11 μ; uv 206–208 nm (ε 21,130) with inflection 220 mn (ε 17,290); also identical (mixture melting point, spectra) with an earlier sample.[2]

2,3,4-Trimethyl-1,4-dihydro-1,4-ethanoisoquinolinium Iodide (6, R = R′ = R″ = CH_3; X = I).—Reaction of 0.8 g of **4** (R = R′ = CH_3) in 50 ml of benzene with 15 ml of 1.92 *M* methyllithium–ether solution at 45° for 5 min and at room temperature overnight, followed by work-up as described in the preceding experiment to obtain enamine in a dried (K_2CO_3) ether solution, and treatment with 20% HI aqueous ethanolic solution gave 1 g of solvated crystals, mp *ca.* 179–184°. Recrystallization from acetone–ether and ethanol–ether and drying *in vacuo* gave colorless crystals, mp 213–215° dec; mixture melting point with an earlier sample of the same iodide[2] was undepressed and ir spectra (6.06 μ) of the two samples were identical.

The foregoing experiments suffice to indicate the general method (and its slight modifications) used in preparing the remaining iminium salts **6**, recrystallized as a rule from ethanol or ethanol–ether, listed in Table II, from the appropriate lactams **4**. An excess of the alkyllithium was invariably used, temperature and time of reaction being the critical factors rather than amount of reagent.

Compound 5 (R = Ph; R′ = CH_3; R″ = CH_2) was also prepared by heating a solution of 1.7 g of **4** (R = phenyl; R′ = CH_3) and CH_3MgI (prepared from 1.2 g of Mg) in 220 ml of dry

toluene at 100–110° for 16 hr. The chilled suspension was treated with dilute acid, and the aqueous layer chilled and made basic with K_2CO_3. The crude base, isolated in small amount (0.2 g) by extraction with ether, washing with water, drying (K_2CO_3), and evaporating the ether, was identified as the same enamine obtained by reaction of CH_3Li with the same lactam, by ir and by conversion to the iminium chloride sesquihydrate,[2] mp 239–241° dec, mixture melting point undepressed, and ir spectra identical.

From the neutral fraction of the above reaction, there was recovered 0.7 g of starting *N*-methyl-4-phenyl lactam.

2-Methyl-4-phenyl-1,4-ethano-1,2,3,4-tetrahydroisoquinoline.—Reduction of 3.9 g of lactam **4** (R = Ph; R′ = CH_3) with 12.5 g of lithium aluminum hydride in 1 l. of THF, stirring and refluxing 6 hr, or reduction of 2.1 g of the same lactam with 1.3 g of $LiAlH_2(OEt)_2$ in 250 ml of 1:1 THF–toluene for 3 hr (reflux), and the usual isolation of basic product gave in each case (crude yields 3.7 and 1.7 g, respectively) the same, partly crystalline, amine. Recrystallization of the separated crystals directly, from ether, afforded a sample of the **hemihydrate**, mp 205–215°.

Anal. Calcd for $C_{18}H_{19}N \cdot {}^1/_2H_2O$: C, 83.68; H, 7.80; N, 5.42. Found: C, 83.31; H, 7.62; N, 5.23.

Material which had been dissolved in dilute HCl and recovered by addition of cold NaOH solution was oily initially but crystallized in ether–ligroin giving colorless crystals of the amine, mp *ca.* 88–100°, changed on recrystallization to mp 86–88°.

Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.00; H, 7.99; N, 5.91.

The corresponding **hydrochloride**, from ether–ethanol, had mp 272–275° dec and appeared, even after drying, to be slightly solvated.

Anal. Calcd for $C_{18}H_{19}N \cdot HCl$: C, 75.64; H, 7.05; N, 4.90. Found: C, 75.08; H, 7.15; N, 4.73.

The corresponding **methiodide**, prepared by a 15-min reflux of a sample of the crude base with iodomethane in ethanol and recrystallized from ether–ethanol, had mp 237–239° dec.

Anal. Calcd for $C_{19}H_{22}IN$: C, 58.32; H, 5.67; N, 3.58. Found: C, 58.04; H, 5.68; N, 3.55.

1-Phenyl-1,2,3,4-tetrahydro-4-oximinonaphthalene-1-carboxamide (1a, R = Ph, Oxime).—An ethanol solution of 5 g of ketoamide **1a** (R = Ph) together with hydroxylamine (prepared from 2.5 g of $H_2NOH \cdot HCl$ in 5 ml of water and a slight excess of cold NaOH solution) was refluxed 15 min, treated with a small amount of water, and chilled. The product was collected, washed with water, dried, and recrystallized from methanol: colorless crystals; mp 235–237°; ir 2.91, 3.23 and 5.98 μ.

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.74; N, 9.99. Found: C, 72.76; H, 5.93; N, 9.51.

4-Amino-1-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide.—Hydrogenation of 3.8 g of oximinoamide from the preceding experiment in 150 ml of ethanol with a teaspoon of washed Raney nickel at 60° until H_2 absorption ceased, filtration, evaporation, and ether trituration gave 3.0 g of colorless crystals, mp 169–171°, raised on recrystallization (ethyl acetate) to mp 170–172°. The compound was soluble in aqueous acids.

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.82; H, 6.92; N, 10.58.

The aminoamide showed no sign of change on prolonged heating at 100° and lost NH_3 only when heated to 240–280°; from the glassy residue remaining after the latter treatment, no crystalline compounds could be isolated.

Hydrolysis of a sample of the aminoamide (concentrated HCl, 10-hr reflux) gave, after evaporation of excess reagent and recrystallization from water, the corresponding **amino acid hydrochloride**, as hygroscopic, colorless crystals, mp *ca.* 240° dec. Spectrally (ir 5.89 μ and very strong OH and NH bands) identical material was obtained by similar hydrolysis of crude amino ester **2b**, *i.e.*, the residual amine remaining after closure to lactam **3** (R = Ph).

4-Hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide.—Portionwise, addition of 8 g of $NaBH_4$ to a suspension of 5 g of **1a**, R = Ph, in methanol, and 1 hr heating on a steam cone, followed by addition of water to the concentrated solution, gave crystals which were collected, washed with water, and dried. Recrystallization from ethanol–ethyl acetate gave a sample with mp 198.5–200° and ir 2.86, 2.99–3.10, and 6.02 μ, evidently one of the two possible isomers resulting in this reaction.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.62; H, 6.60; N, 5.27.

1-Phenyl-1,2-dihydronaphthalene-1-carboxamide.—Treatment of a dry benzene solution of crude, dry amide from the preceding experiment with anhydrous HBr, and isolation of 4-bromoamide (by washing with $NaHCO_3$ solution and water, drying over $MgSO_4$ and evaporating) as a colorless, Beilstein-positive solid, mp *ca.* 145–150° dec, was followed by exploratory experiments along familiar lines using various bases. Several of these, notably treatment with $NaNH_2$ in toluene (2 hr at 100°), gave isolable amounts of colorless crystals: mp 172–173° (from ether); ir NH bands and 5.96 μ; uv 206, 261, and 264 nm (ϵ 25,210, 7960, and 7480, respectively).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.92; H, 6.23; N, 5.59.

1-Phenyl-2,3-dimethyl-1,4-methano-4,5-dihydro-1*H*-3-benzazepinium Chloride (9, R = Ph; R′ = R″ = CH_3; X = Cl).—A solution of 2.0 g of lactam **7** (R = Ph; R′ = CH_3)[7] in 100 ml of benzene was treated with 19 ml of 1.92 *M* methyllithium–ether, and the solution was refluxed for 1 hr, then chilled and poured over ice, and the ether-diluted, organic layer was washed twice with water and extracted with three 10-ml portions of 18% HCl. The chilled, aqueous solution was made basic by addition of NaOH solution, and the oily enamine extracted with ether. Evaporation of the water-washed and dried (K_2CO_3) ether solution *in vacuo* to 100 ml, followed by addition of just enough ethanolic HCl to cause complete precipitation of the salt, afforded 2.0 g of dense, pale yellow crystals, mp 148–152° dec, raised on further recrystallization (ethanol–ether) to mp 149.5–152° dec, which, after drying at room temperature, proved to be the **sesquihydrate**: ir 5.99 μ and an OH band indicating water of crystallization; uv 259 nm (ϵ 3960) and inflection 284 (2620).

Anal. Calcd for $C_{19}H_{20}ClN \cdot {}^3/_2H_2O$: C, 70.25; H· 7.14. N, 4.31. Found: C, 70.35; H, 6.98; N, 4.34.

In another experiment, 3 g of lactam and 35 ml of methyllithium (2 *M*) gave enamine which was converted by 10% aqueous, alcoholic HI to 3.8 g of the corresponding iminium **iodide**. Recrystallization from ethanol gave yellowish crystals: mp 265–267° dec; ir 6.02 μ; uv 211 and 258 nm (ϵ 28,700 and 3900, respectively) and inflection 289 (2250).

Anal. Calcd for $C_{19}H_{20}IN$: C, 58.62; H, 5.18; N, 3.60. Found: C, 58.77; H, 5.45; N, 3.61.

Iminium Salt 9 (R = Et; R′ = R″ = CH_3; X = I).—Reaction of 2.4 g of lactam **7** (R = Et; R′ = CH_3)[7] in 100 ml of benzene with 15 ml of 1.92 *M* methyllithium solution was conducted at 45° for 2 min, and the solution was let stand (air absent) overnight. Isolation of basic product as in the preceding experiment gave enamine as a yellow, quite air-sensitive oil. Immediate conversion to the iodide using a slight excess of *ca.* 10% aqueous, alcoholic HI afforded 3.4 g of yellow crystals, mp 249–251° dec. Recrystallization from methanol–ether gave a pure sample as colorless crystals: mp 253–254° dec; ir 6.01 μ; uv 216 and 255 nm (ϵ 19,500 and 2650) with inflection 280 (1800).

Anal. Calcd for $C_{15}H_{20}IN$: C, 52.79; H, 5.91; N, 4.11. Found: C, 52.78; H, 5.99; N, 4.08.

Additional, and more complex, examples of preparation of compounds **9** have been described elsewhere.[3b] However, all attempts to prepare ethylidene amines and salts **9** with R″ = Et, using ethyllithium, were unsuccessful.

Reductions of 9 (R = Ph; R′ = R″ = CH_3) and Corresponding Enamine 8.—A. Sodium borohydride was added in portions to a suspension of the iodide (3.2 g) in methanol (350 ml), and the resulting solution was warmed 1.9 hr on a steam cone, evaporating most of the solvent. The residue, treated with water, gave oily base, ether extract of which after washing (H_2O), drying ($MgSO_4$), and evaporation, gave 1.4 g of amine. Conversion to the corresponding **10** (R = Ph; R′ = R″ = CH_3) **hydrochloride** by addition of ethanolic HCl to an ether solution, and recrystallization from ethanol–ether afforded colorless crystals, mp 294–296° dec. The analytical sample, after drying *in vacuo*, had mp 300–301° dec; ir devoid of C=N band; uv 258 nm (ϵ 380).

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.11; H, 7.40; N, 4.67. Found: C, 76.10; H, 7.59; N, 4.77.

B. Formic acid (2 ml, 98–100%) was added to 1 g of enamine **8** (R = Ph; R′ = CH_3; R″ = CH_2) (prepared directly from 1.1 g of lactam or regenerated from the corresponding iminium salt by treatment with NaOH solution and ether extraction). The iminium formate solution, heated at 100° for 0.5 hr, effervesced slowly. Treatment with water and dilute NaOH and isolation of the base as usual by ether extraction gave crude, yellowish oil. The amine was converted to the hydrochloride and re-

crystallized from ethanol–ether: colorless crystals, mp 295–297° dec; mixture melting point with hydrochloride sample from part A was undepressed; ir and uv spectra were identical; and analytical results on a dried sample were virtually the same as in part A.

Sodium borohydride reductions of other, more complex analogs of 9,[3b] as well as compounds 5 and 6,[2] to corresponding bridged amines, were reported previously.

α-Phenylglutaric Anhydride.—A. Methyl acrylate addition (86 g) during 5 min to a solution of 164 g of ethyl phenylacetate and dry sodium ethoxide (prepared from 4.6 g of sodium) in 1 l. of *tert*-BuOH and 1.5-hr standing, followed by treatment with ice and water and isolation of neutral product, gave 240 g of crude diester. B. Hydrolysis by 9 hr of reflux with 2300 ml of 15% KOH, followed by acidification of ether-washed, basic solution, gave 194 g of crude **α-phenylglutaric acid**. C. Conversion to the **anhydride**, by refluxing 1 hr with 200 ml of acetic anhydride, removal of excess reagent, and distillation *in vacuo* gave 107.6 g (56% overall): bp 170–180° (0.6 mm); mp 95–96°; ir 5.56 and 5.70 μ (lit.[14] mp 95–96°).

α-Methyl-α-phenylglutaric Acid.—A. Alkylation of 115 g of phenylacetonitrile in benzene (800 ml) in the presence of 43 g of $NaNH_2$ was carried out by adding 69 ml of iodomethane during 15 min to the stirred, ice-chilled suspension. After 6-hr stirring, during which time the mixture was allowed to warm gradually to room temperature, the neutral product was isolated as usual, by addition of water and evaporation of the water-washed, dried ($MgSO_4$) organic solution.

B. Methyl acrylate (93 ml) addition to the crude product of A (112 g) in 350 ml of *tert*-BuOH during 5 min, in the presence of 15 ml of 40% benzyltrimethylammonium methoxide solution, 3 hr of standing, addition of water, and isolation of the neutral product gave 148 g of crude cyano ester.

C. Hydrolysis of the crude oil from B by 14 hr of reflux and stirring with 2 l. of 30% KOH solution, until NH_3 was no longer evolved, and acidification of the ether-washed, basic solution, gave 161 g of crude diacid. A sample, recrystallized from ether, had mp 132–134°, ir 5.91 μ.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.61; H, 6.44.

The corresponding **anhydride** was prepared by 1.3-hr reflux of 41 g of diacid with 100 ml of acetic anhydride, followed by removal of excess reagent, distillation *in vacuo*, and recrystallization from ether: 18 g; bp 163–166° (1.45 mm); mp 81–82°; ir 5.55 and 5.68 μ.

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.60; H, 5.78.

α,α-Diphenylglutaric Acid.—This acid was obtained in four ways, as follows. A. Hydrolysis of α,α-diphenylglutaronitrile (98 g, mp 73–74°, prepared by cyanoethylation of diphenylacetonitrile in the presence of Triton B methoxide in tetrahydrofuran) with 545 g of potassium hydroxide in 660 ml of water, refluxing and stirring 4 days, and acidification of the ether-washed solution gave 91.5 g of diacid, mp 180–190°, after washing with water and air drying, suitable for use in cyclizations. A sample, recrystallized from ethyl acetate, had mp 199–200.5° (lit.[15] mp 193–195°), ir 5.80–5.84 μ.

B. Addition of methyl acrylate (72 g) to diphenylacetonitrile (250 g) in 1 l. of tetrahydrofuran in the presence of 40 ml of 40% Triton B methoxide, and hydrolysis of the resulting, crude cyano ester by refluxing 3 days with 3 l. of 30% potassium hydroxide solution, followed by filtration to remove 35 g of neutral material and acidification, gave 127 g of the diacid, mp 190°, suitable for further work.

C. Cyanoethylation of ethyl diphenylacetate (11.6 g) in the presence of dry sodium methoxide (prepared from 0.1 g of sodium) in 100 ml of tetrahydrofuran, using 2.7 g of acrylonitrile and warming at 65° for 1 hr, gave 4 g of crude cyano ester; hydrolysis with 200 ml of 20% potassium hydroxide solution and sufficient ethanol to dissolve the material (4-hr reflux) gave 3.9 g of diacid, mp 195–199°.

D. α,α-**Diphenylglutarimide** was obtained quantitatively by refluxing α,α-diphenylglutaronitrile for 4 hr with equal parts of concentrated hydrochloric and glacial acetic acids [mp 162.5–164° (lit.[15] mp 158–159°); ir 3.15, 3.24, 5.82, and 5.88 μ] and was hydrolyzed by prolonged reflux with 30% potassium hydroxide solution to give the diacid, melting point and spectra the same as in parts A and B.

α-Cyclopentyl-α-phenylglutarimide.—A. Cyanoethylation of 171.5 g of α-cyclopentylphenylacetonitrile[16] in 2 l. of *tert*-butyl alcohol in the presence of dry sodium methoxide (from 5.3 g of sodium) was carried out by adding 67 ml of acrylonitrile and, after the period of spontaneous reaction in which the temperature reached 43°, heating to 70° for 2 hr. The crude dinitrile, isolated as usual, did not crystallize and was used without purification in the next step.

B. Hydrolysis and imide formation were carried out by refluxing the crude product from A in 600 ml each of concentrated hydrochloric and glacial acetic acids for 6.5 hr. Removal of most of the acids *in vacuo*, and treatment of the residue with water gave an oil which was extracted with ether. The ether solution was washed with dilute sodium hydroxide solution and with seven portions of water and dried ($MgSO_4$). Upon evaporation to a smaller volume, the ether solution deposited 175 g of crystals: mp (after recrystallization from ether) 108.5–110°; ir 3.12 and 5.83–5.92 μ.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 75.06; H, 7.50; N, 5.24.

Corresponding Acid Amide.—After heating 175 g of glutarimide from the preceding experiment with 1300 ml of 30% potassium hydroxide solution for a week (90–100°), diluting with water, and acidifying, the crude products were extracted with ether. The water-washed and dried ($MgSO_4$) solution, on evaporation to a smaller volume and addition of a small amount of ethyl acetate, deposited 54.5 g of crystals: mp 157–160°, raised on recrystallization from ethanol–ether to mp 161–162°; ir 2.91, 5.89, and 6.09 μ.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.83; H, 7.85; N, 5.05.

The material remaining in the ether–ethyl acetate solution consisted mainly of the crude, **corresponding diacid** isolated as an oil (135 g) which still contained some of the acid amide. Further hydrolysis of this material with 1 l. of 30% KOH solution at 90–100° for 3 weeks finally removed nitrogen completely and afforded the diacid in suitable condition for further work, as a viscous oil, ir 5.88 μ (broad, unresolved doublet). The **corresponding anhydride**, ir 5.52 and 5.66 μ, was prepared by reaction of the diacid with acetic anhydride, but could not be induced to crystallize.

α-(Cyclohexylmethyl)-α-phenylglutarimide.—A. Alkylation of phenylacetonitrile (117 g) with cyclohexylmethyl bromide (194 g) in the presence of 43 g of sodium amide in 1.2 l. of toluene (refluxed and stirred 3.5 hr) gave 130 g of crude product,[16] an oil which still contained some phenylacetonitrile.

B. Methyl acrylate (60 ml) was added in portions to the crude product from A and 15 ml of 40% Triton B methoxide solution in 350 ml of *tert*-butyl alcohol, and after the exothermic period the solution was refluxed 1 hr. After isolation in the usual way, the crude material was converted without purification to the corresponding glutarimide.

C. Hydrolysis and imide formation. The crude material from part B (190 g), 600 ml of concentrated HCl, and 900 ml of glacial acetic acid were refluxed 3.5 hr. After removal of excess reagents *in vacuo* and treatment with water, the crude, partly crystalline material was collected and triturated with ether. The yield of α-cyclohexylmethyl-α-phenylglutarimide, mp 146–150°, was 48 g. Recrystallization from methanol raised the melting point to 150–151°, ir 3.11 and 5.81–5.89 μ.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 76.46; H, 8.22; N, 4.94.

The **corresponding acid amide** was obtained by 8 hr of reflux of 34.5 g of glutarimide with 600 ml of 30% KOH solution, followed by acidification: yield, 35.5 g of crystals; mp 210–215°, raised on recrystallization (methanol) to 225–226°; ir 2.89, 3.14, 5.88, and 6.10 μ.

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.25; H, 8.21; N, 4.62.

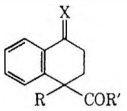
α-Cyclohexyl-α-phenylglutaronitrile.—Acrylonitrile (1.9 g) in tetrahydrofuran (5 ml) was added slowly to a cooled (20–30°) solution of 7.9 g of α-cyclohexylphenylacetonitrile[16] in tetrahydrofuran (25 ml) in the presence of 1.1 ml of 40% Triton B solution. After standing 3 hr, the chilled, evaporated, and acidified solution was treated with water and the product isolated

(14) E. C. Horning and A. Finelli, *J. Amer. Chem. Soc.*, **71**, 3204 (1949); *Org. Syn.*, **30**, 43 (1950).

(15) F. Salmon-Legagneur, *C. R. Acad. Sci.*, **213**, 182 (1941); *Bull. Soc. Chim. Fr.*, 994 (1952).

(16) E. M. Hancock and A. C. Cope, *Org. Syn.*, **25**, 25 (1964); A. C. Cope H. L. Holmes, and H. O. House, *Org. React.*, **9**, 107 (1957).

TABLE III
INTERMEDIATE TETRALONES AND DERIVATIVES[a]



R	R′	X	Registry no.	Mp, °C	Ir (μ) data
H	OEt	NOH	3118-23-8		5.82, 6.15
		=NNHCONH$_2$	3118-22-7	179–180	
CH$_3$	OH	O	3123-55-5	123–124	5.80, 5.87–5.92
C$_2$H$_5$	OEt	=DNP	20016-45-9	181–182	
C$_6$H$_5$	NH$_2$	O	2997-28-6	192–193	
	OEt	O	3389-98-8	89.5–91	
c-C$_5$H$_9$	NH$_2$	O	3123-63-5	110–112	5.95
					6.03
	OH	O	3123-62-4	113–115	5.85, 6.08
	OEt	=DNP	27240-37-5	167–169	
	OEt	NOH	3118-30-7	134–135	5.79
c-C$_6$H$_{11}$CH$_2$	NH$_2$	=DNP	3123-65-7	235–236	
	NH$_2$	NOH	3123-49-7	177–178	
	OH	O	3196-54-1	105–108	
	OEt	NOH	3118-24-9		5.77–5.84, 6.12
p-PhF	OH	O	3345-77-5	158–159	5.79, 6.05
	OEt	O	3118-11-4	112–113	5.80, 5.97
	OEt	NOH	3118-25-0	96–98	5.79
CH$_2$COOH	OH	=DNP	27249-17-8	238–240 dec	
CH$_2$COOEt	OEt	=DNP	27249-18-9	126–128	5.75, 6.13
CH$_2$CH$_2$COOEt	OEt	NOH	3195-61-7		5.76, 6.12
CH$_2$C$_6$H$_5$	OH	=DNP	3123-60-2	273–275 dec	
	OEt	=DNP	3118-29-4	165–167	
	OEt	NOH	3118-28-3	85–87	

[a] =DNP represents 2,4-dinitrophenylhydrazone.

(ether extraction) and triturated with ether to give 2.8 g of crystals: mp 92–96°, raised to 94.5–96° on recrystallization from ether; ir 4.43 μ.

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 81.40; H, 8.04; N, 11.02.

Hydrolysis of this dinitrile (2.6 g) with 30% KOH solution (50 ml) at 100–120° for 15 hr did not lead to an acid amide but gave a corresponding **acid nitrile**, after acidification, isolation of the sodium bicarbonate-soluble fraction (1.7 g), and recrystallization from ethanol: mp 183–186°; ir 5.84 μ, *ca.* 4.4 μ (obscured by carboxyl bands), and no amide peak.

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 74.76; H, 7.80; N, 5.16.

Cyclization of the dinitrile (1.3 g) with concentrated sulfuric acid (25 ml) at 25–30° for 22 hr followed by treatment with ice and isolation of the neutral product (ether extract washed with aqueous base and water) gave **4-cyclohexyl-1-tetralone-4-carboxamide** (0.4 g): recrystallized from ethanol, colorless crystals; mp 197–199°; ir 2.97, 3.18, and 5.99 μ (shoulders); uv 251 and 294 mμ (ε 9740 and 1690, respectively).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.08; H, 7.91; N, 5.28.

This tetralone amide resisted hydrolysis with acids or bases.

α-Phenyl-α-(*p*-fluorophenyl)glutaronitrile, Glutarimide, and Corresponding Glutaric Acid.—A. Phenyl *p*-fluorophenylacetonitrile was prepared following published procedures.[17] Phenylacetonitrile (236 g) was treated with bromine (334 g) at 72–110° over the course of 2 hr, as much HBr as possible being removed *in vacuo* from the crude bromonitrile, which was then condensed with 100 g of fluorobenzene in the presence of 294 g of anhydrous aluminum bromide at 45–50° (3 hr). After ice–HCl hydrolysis and isolation of neutral fraction, the product was distilled *in vacuo*, giving 289 g of oil, bp 148–156° (1.7–2.0 mm) [lit.[17] bp 192° (25 mm)].

B. Cyanoethylation of 289 g of product from part A with 78 g of acrylonitrile in 500 ml of *tert*-butyl alcohol and 41 ml of 40% Triton B methoxide solution during 2 hr with cooling, isolation of neutral product as an ether solution, filtration to remove 10 g of polymeric material, and evaporation gave 300 g of dark red oil which crystallized in the presence of ether–ligroin and afforded 129 g of the **dinitrile**: mp 73–77°, raised to 82–84° on recrystallization from ether (Norit); ir 4.42 μ.

Anal. Calcd for $C_{17}H_{13}FN_2$: C, 77.25; H, 4.96; N, 10.60. Found: C, 77.37; H, 4.91; N, 10.52.

C. Hydrolysis of 129 g of dinitrile with 500 ml of concentrated hydrochloric acid and 700 ml of glacial acetic acid (refluxed 5.5 hr), distillation of excess reagents *in vacuo*, and treatment with water gave 138 g of **glutarimide**, after collecting, washing with water, and air drying: mp 194–196°, raised to mp 197–199° on recrystallization from acetone–methanol; ir 3.14, 3.24, and doublet 5.84–5.91 μ.

Anal. Calcd for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.95. Found: C, 71.92; H, 5.02; N, 4.86.

D. Hydrolysis of 138 g of glutarimide from part C by heating and stirring under reflux with a solution of 540 g of potassium hydroxide in 1 l. of water for 3 days gave after acidification a crude acid which was taken into ether; the ether solution was washed with water, dried ($MgSO_4$), and evaporated, yielding 117 g of **α-phenyl-α-(*p*-fluorophenyl)glutaric acid**, mp 174–178°. Recrystallization from ether gave material, mp 177–178°, ir 5.82–5.90 μ.

Anal. Calcd for $C_{17}H_{15}FO_4$: C, 67.54; H, 5.00. Found: C, 67.61; H, 5.12.

1-Tetralone-4-carboxylic Acids (1b) and -4-carboxamides (1a).—In general, the glutaric acid, anhydride, or acid amide was added, while stirring, to 30–40 parts (by weight) of concentrated H_2SO_4, if necessary cooling by means of a bath to prevent the temperature from rising above 60°. After standing overnight at room temperature, or for several days in the case of acid amides, the sulfuric acid solution was poured over 100 parts (by weight) of ice. The product was isolated by direct filtration if crystalline or extracted with ether, and the ether solution was washed well with water, as well as with dilute sodium carbonate or sodium hydroxide solution if the product were a neutral compound, dried ($MgSO_4$), and evaporated; the tetralones were characterized *per se*, or as suitable derivatives in the case of new compounds, prepared by standard methods and listed in Table III, and by hydrolysis of amides to corresponding acids as described in the following experiment.

Hydrolysis of 1-tetralone-4-carboxamides was carried out, *e.g.*, by refluxing 27 g of 4-cyclohexylmethyl-4-carboxamido-1-tetralone

(17) C. M. Robb and E. M. Schultz, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 347; H. Leditsche, H. Rolly, and H. Schmidt-Ruppin, U. S. Patent 2,843,594 (1958).

with 400 ml of concentrated hydrochloric acid and 200 ml of glacial acetic acid for 7 hr, followed by distillation of excess reagent *in vacuo*, treatment of the residue with water, subsequent filtration or extraction with ether, washing with water, drying ($MgSO_4$), and evaporation to give the crude keto acid which was then purified by recrystallization from ether or ether–ethanol.

Esterification of 1-Tetralone-4-carboxylic Acids.—The keto acid (30 g) was treated with 1 l. of absolute ethanol in which there was dissolved 75 ml of concentrated H_2SO_4 and 10 ml of 30% fuming H_2SO_4, and the solution was refluxed 18 hr. After removing most of the ethanol *in vacuo*, the chilled residue was poured over ice and the neutral product isolated by ether extraction, washing with successive portions of dilute NaOH solution and water, drying ($MgSO_4$), and evaporation. Characteristically the keto esters had ir 5.8 and 5.95 μ bands and uv λ_{max} ~295 mμ. If crystalline, the new compounds are listed in Table III.

Corresponding **oximino esters**, prepared by common procedure,[2,18] were also characterized by typical spectra, and some of them are listed in the table, together with miscellaneous data for various other derivatives of tetralones which were prepared. **Tetralone 1b** (R = CH_2CH_2COOH) was synthesized following Koelsch[6] and was esterified and converted to oxime by the usual procedure. **Tetralone 1c** (R = CH_2COOEt) was prepared starting from ethyl β-cyano-β-phenylpropionate[19] *via* cyanoethylation and hydrolysis by HCl and HOAc, 4-hr reflux, to 2-phenylbutane-1,2,4-tricarboxylic acid, mp 170–172° (from ether–ethyl acetate), ir 5.77–5.88 μ.

1-Cyclopentyl-1-phenyl-2-propanone.—Reaction of 170 g of α-cyclopentyl-α-phenyl acetonitrile[16] with methylmagnesium iodide (from 75 g of Mg) in toluene at 100° overnight, and HCl hydrolysis[20] gave 128 g of ketone, bp 110–127° (2.5 mm), ir 5.87 μ. The **2,4-dinitrophenylhydrazone**, yellow crystals from ethanol, had mp 116–118°.

Anal. Calcd for $C_{20}H_{22}N_4O_4$: C, 62.81; H, 5.80; N, 14.65. Found: C, 62.93; H, 5.84; N, 14.73.

Cyanoethylation of this ketone in THF (Triton B methoxide), tried several times, gave a maximum yield of 1% of **γ-cyclopentyl-γ-phenyl-δ-oxocapronitrile**, crystals from ether, mp 89–90°, ir 4.44 and 5.89 μ.

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.70; H, 8.25; N, 5.72.

α-Benzyl-α-phenylglutaric Acid.—After addition of acrylonitrile or methyl acrylate to α-phenylhydrocinnamonitrile,[16] hydrolysis by prolonged boiling with 20% KOH solution gave the acid, mp 170–172°, ir 5.87 μ.

Anal. Calcd for $C_{18}N_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.32; H, 6.11.

Treatment with acetic anhydride afforded the corresponding **anhydride**: crystals from ether; mp 117–119°; ir 5.56 and 5.71 μ.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.31; H, 5.81.

Cyclization of either of these compounds with PPA (100°, 6 hr), or of the intermediate acid amide with concentrated sulfuric acid, gave the spiro diketone, **spiro[1-indanone-2,1′(4′)-tetralone]**: mp 131–133° from ether; ir 5.88 and 5.97 μ.

Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.41; H, 5.37.

The corresponding **2,4-dinitrophenylhydrazone**, red crystals from ethyl acetate, had mp 270–271°.

Anal. Calcd for $C_{24}H_{18}O_5N_4$: C, 65.15; H, 4.10; N, 12.66. Found: C, 64.55; H, 4.48; N, 12.50.

2-Cyano-4-benzyl-1-tetralone-4-carboxylic Acid.—A stirred solution of 35 g of benzyl homophthalic anhydride[21] (mp 116–118°, prepared from dimethyl homophthalate by $NaOCH_3$ condensation with benzaldehyde, hydrogenation over Pd, NaOH hydrolysis, and treatment with acetic anhydride) in 300 ml of THF was treated with 19 g of $KOCMe_3$ with cooling, then 32 ml of acrylonitrile during 10 min (spontaneous temperature rise from 17–29°), and stirred 1 hr. The initially bright yellow color of the solution faded almost completely. The solution was refluxed gently 0.5 hr; a salt separated. After chilling, treatment with ice and HCl, and addition of water, the oil was extracted with ether. The water-washed and dried ($MgSO_4$) solution on evaporation gave yellow oil, crystallizing partly and giving on trituration with ether 14.5 g of crystals: mp 191–193° from ether; ir 4.44, 5.85, and 5.92 μ; uv 204, 230, and 295 nm (ϵ 26,380, 13,150, 7300); $FeCl_3$ test, weak green; soluble in aqueous NaOH.

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.68; H, 5.02; N, 4.50.

Hydrolysis and decarboxylation of the cyano keto acid (9.9 g) with acetic acid (70 ml) and concentrated HCl (270 ml) and refluxing 4 hr (initial, voluminous precipitate, redissolving on further boiling) gave **4-benzyl-1-tetralone-4-carboxylic acid**, listed, together with its derivatives prepared by usual methods, in Table III.

4-Benzyl-1-tetralone-4-carboxamide.—The acid from preceding hydrolysis (45 g) reacted in mildly exothermic manner with oxalyl chloride (200 ml) in the presence of pyridine (0.5 ml). After warming to 45° for 0.7 hr, removal of excess reagent *in vacuo* gave a residue which was treated with excess concentrated NH_4OH. The ether-extracted, washed, and dried ($MgSO_4$) product crystallized in ether (yield, 20.1 g) and was recrystallized from methanol: mp 159–161°; ir 2.92, 3.15, 6.02, and 6.13–6.26 μ; uv 206, 249, and 293 nm (ϵ 31,000, 9760, 1670).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.60; H, 6.14; N, 4.91.

1-Benzyl-1,4-methano-1,2,4,5-tetrahydro-3*H*-3-benzazepin-2,5-dione.—Bromine (3.6 g), added to a solution of the preceding ketoamide (6 g) in glacial HOAc (60 ml), was absorbed smoothly at 40–50°. After 0.5 hr the crude bromoamide was isolated by removal of the solvent *in vacuo*. A solution of the material in ether was filtered, concentrated, and added to a solution of sodium (1.4 g) in methanol (100 ml), and a slightly exothermic reaction occurred. After standing overnight, the solution was concentrated *in vacuo* and treated with water, and the product was extracted with ethyl acetate. The washed (aqueous $NaHCO_3$, water) and dried ($MgSO_4$) organic layer on evaporation gave red oil, crystallizing slowly and partly in the presence of methanol. Trituration with ethanol and recrystallization from the same solvent gave 0.5 g of colorless crystals: mp 201.5–203°; ir 3.01, 5.85, and 5.98 μ; uv 208, 230, 256, and 294 nm (ϵ 30,030, 9540, 6400, 1980).[7]

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.81; H, 5.61; N, 5.09.

In attempting to characterize the intermediate bromoamide, an ether solution of some of the material was washed with aqueous $NaHCO_3$ and water, dried, and allowed to stand with methanol. There was isolated a sample of what appeared to be **2-methoxy-4-benzyl-1-tetralone-4-carboxamide**: mp 225–226° dec (from methanol); ir 2.90, 2.98, and doublet 5.83–5.93 μ; uv 208, 229, 258–264, and 294 nm (ϵ 33,600, 9560, 7000, 2200).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.72; H, 6.14; N, 4.55.

α-(3,4-Dimethoxyphenyl)-α-phenylacetamide.—Condensation of 117 g of veratrole and 76 g of mandelonitrile with 425 ml of 74% sulfuric acid[22] at 70° for 1 hr, hydrolysis with ice, extraction with ether, and evaporation of washed and dried ether solution gave 36.5 g of crystals: mp 144–147° from ethanol–ether; ir 2.97, 3.15, and 6.07 μ.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.20; H, 6.48; N, 5.10.

The corresponding acid, from HCl–HOAc hydrolysis, had mp 96–98°, ir 5.91 μ.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.38; H, 5.86.

The corresponding **nitrile**, prepared by dehydration of the amide (38 g) with P_2O_5 (165 g) in toluene (2 l., refluxed 3 hr), was an oil, ir 4.44 μ.

α-(3,4-Dimethoxyphenyl)-α-phenylglutaronitrile.—Addition of acrylonitrile (10.3 g) to the foregoing nitrile (33.5 g) in THF (50 ml) in the presence of $NaOCH_3$ (from 0.8 g Na) gave 27.4 g of dinitrile: crystals from ether–methanol; mp 138.5–140°; ir 4.43 μ.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.39; H, 6.05; N, 8.93.

Hydrolysis with 45% KOH solution (20-hr reflux) gave quantitatively the corresponding **diacid**, an oil. Reflux for 1 hr with acetic anhydride converted the acid to the corresponding **anhydride**: crystals from ether–ethyl acetate; mp 123–124°; ir 5.53 and 5.66 μ.

(18) G. N. Walker, D. Alkalay, and R. T. Smith, *J. Org. Chem.*, **30**, 2973 (1965).

(19) C. F. H. Allen and H. B. Johnson, *Org. Syn.*, **30**, 83 (1950).

(20) C. R. Hauser, *et al.*, *J. Org. Chem.*, **15**, 359 (1950); *J. Amer. Chem. Soc.*, **70**, 426 (1948); G. Vasiliu, *et al.*, *Chem. Abstr.*, **34**, 4058 (1940).

(21) W. Dieckmann, *Chem. Ber.*, **47**, 1428 (1914); E. Müller, *Justus Liebigs Ann. Chem.*, **491**, 251 (1931).

(22) A. Müller and M. Vajda, *J. Org. Chem.*, **17**, 800 (1952).

Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.80; H, 5.65.

4-Phenyl-6,7-dimethoxy-1-tetralone-4-carboxylic Acid.—Anhydride from the preceding experiment (13 g) was treated with 130 ml BF_3–HOAc. After standing overnight and hydrolysis with 800 ml of 15% NaOAc solution, acidification with HCl and extraction with ether afforded 13 g of crude keto acid as yellow oil.

The **2,4-dinitrophenylhydrazone** was recrystallized from ethanol–ethyl acetate, red crystals, mp 166–169°.

Two-day reflux of 13.5 g of the keto acid with a solution of 35 ml of concentrated sulfuric acid and 5 ml of oleum in 1 l. of ethanol provided the corresponding **ethyl ester**: crystals (11.1 g) from ethanol; mp 147–149°; ir 5.78 and 5.96 μ; uv 237, 277, and 312 nm (ϵ 23,190, 11,100, 7020).

Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.80; H, 6.30.

The **oxime** was prepared from the ethyl ester as usual: crystals from pentane–ether: mp 148–149°; ir 3.12 and 5.77 μ; uv 212, 269, 303 nm (ϵ 28,760, 15,750, 6270).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.08; H, 6.13; N, 3.84.

1,4-Ethano-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolone.—Hydrogenation (50 psi) of 9.0 g of oximino ester from the preceding experiment in 300 ml of ethanol in the presence of 10 g of Raney nickel for 1.5 hr (4.0-lb pressure drop), filtration, and evaporation gave an oily mixture of amino esters, which was heated (neat) on a steam cone for 2.5 days. On cooling, the material solidified. Trituration with ether gave 1.1 g of the lactam: mp 230–234°, raised on further recrystallization (methanol) to mp 236–237°; ir 3.12 and 5.98 μ; uv 241, 285 nm (ϵ 3980, 3810); insoluble in acids.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.32; H, 6.32; N, 4.62.

Ether solution of the remaining material with pentane gave crystals of **1-amino-4-ethoxycarbonyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene**, evidently the trans-amino ester (1.9 g): acid-soluble; mp 139–141° after recrystallization from methanol–ether; ir 5.78 μ and NH_2 bands. The corresponding **hydrochloride**, recrystallized from ethanol–ether, had mp 244–245°.

Anal. Calcd for $C_{21}H_{26}NO_4Cl$: C, 64.36; H, 6.69; N, 3.57. Found: C, 64.34; H, 6.88; N, 3.69.

The ***N*-methyl lactam**, from NaH–iodomethane alkylation as usual of the lactam, (quantitatively), had mp 200–202° (from methanol–ether), ir 5.99 μ.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.42; H, 6.76; N, 4.42.

1,4-Dihydro-1,4-ethano-2,3-dimethyl-4-phenyl-6,7-dimethoxyisoquinolinium Chloride.—A solution of 0.6 g of *N*-methyl lactam from the preceding experiment in 100 ml of benzene and 25 ml of 1.92 *M* methyllithium–ether was heated under reflux 50 min. After treatment with ice and addition of ether, the basic product was isolated from the water-washed, organic layer by extraction with cold 18% hydrochloric acid, addition of 20% NaOH solution at 0°, and extraction with ether. The water-washed and dried (K_2CO_3) ether solution (100 ml), treated with a slight excess of 5% ethanolic HCl, gave the iminium chloride (0.3 g) as yellow crystals, mp *ca.* 200°. After recrystallization from ethanol–ether and drying *in vacuo*, the salt was obtained in the form of the **monohydrate**: mp 210–213° dec; ir 6.01–6.03 μ and broad OH (H_2O) band; uv 231 and 283 nm (ϵ 7620 and 2830).

Anal. Calcd for $C_{21}H_{24}NO_2Cl \cdot H_2O$: C, 67.10; H, 6.97; N, 3.73. Found: C, 67.32; H, 7.16; N, 3.51.

The salt, like other compounds of Table II, was readily soluble in water. The corresponding base (enamine) discolored and became gradually less ether-soluble on standing exposed to air, and satisfactory spectra could not be obtained.

Registry No.—**1a** (R = Ph) oxime, 27249-23-6; **2a** (R = Ph) HCl, 17772-08-6; **2b** (R = Ph) HCl, 17772-09-7; **5** (R = Ph; R′ = Me; R″ = CH_2), 2997-34-4; **5** (R = Ph; R′ = Me; R″ = $CHCH_3$), 2997-39-9; **5** (R = *p*-fluorophenyl; R′ = Me; R″ = CH_2), 2959-81-1; **6** (R = Ph; R′ = Me = R″) Cl, 3196-50-7; **6** (R = Ph; R′ = Me = R″) I, 2997-13-9; **6** (R = R″ = Me; R′ = CH_2Ph) Br, 2959-89-9; **6** (R = R″ = Me; R′ = CH_2Ph) I, 3123-56-6; **6** (R = R′ = R″ = Me) I, 2959-88-8; **9** (R = Ph; R′ = R″ = Me) Cl, 13695-65-3; **9** (R = Ph; R = R″ = Me) I, 13695-66-4; **9** (R = Et; R′ = R″ = Me) I, 13695-68-6; **10** (R = Ph; R′ = R″ = Me) HCl, 13695-67-5; 2-methyl-4-phenyl-1,4-ethane-1,2,3,4-tetrahydroisoquinoline, 14577-66-3, 14657-45-5 (HCl), 4909-86-8 (methiodide); 4-amino-1-phenyl-1,2,3,4-tetrahydronaphthalene-1-cuboxamide, 27249-39-4, 27249-40-7 (amino acid HCl); 4-hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide, 27249-41-8; 1-phenyl-1,2-dihydronaphthalene-1-carboxamide, 27249-42-9; α-methyl-α-phenylglutaric acid, 3123-54-4; 2897-84-9 (anhydride); α-cyclopentyl-α-phenylglutarimide, 2897-90-7, 3123-61-3 (acid amide); α-(cyclohexylmethyl)-α-phenylglutarimide, 2959-97-9, 3123-48-6 (acid amide); α-cyclohexyl-α-phenylglutaronitrile, 20881-44-1, 27249-49-6 (acid nitrile); 4-cyclohexyl-1-tetralone-4-carboxamide, 27249-50-9; α-phenyl-α-(*p*-fluorophenyl)glutaronitrile, 2897-80-5, 2897-81-6 (glutarimide), 3123-51-1 (glutaric acid); 2-phenylbutane-1,2,4-tricarboxylic acid, 27249-54-3; 1-cyclopentyl-1-phenyl-2-propanone, 27249-55-4, 27249-56-5 (2,4-DNP); γ-cyclopentyl-γ-phenyl-δ-oxocapronitrile, 27249-57-6; α-benzyl-α-phenylglutaric acid, 27272-80-6, 14701-87-2 (anhydride); spiro[1-indanone-2,1′(4′)-tetralone], 27272-82-8, 12505-71-4 (2,4-DNP); 2-cyano-4-benzyl-1-tetralone-4-carboxylic acid, 3123-59-9; 4-benzyl-1-tetralone-4-carboxamide, 27272-84-0; 1-benzyl-1,4-methano-1,2,4,5-tetrahydro-3*H*-3-benzazepin-2,5-dione, 27272-85-1; 2-methoxy-4-benzyl-1-tetratone-4-carboxamide, 27272-86-2; α-(3,4-dimethoxyphenyl)-α-phenylacetamide, 2959-98-0, 17777-02-5 (acid); α-(3,4-dimethoxyphenyl)-α-phenylglutaronitrile, 2960-00-1, 2897-73-6 (anhydride); 4-phenyl-6,7-dimethoxy-1-tetralone-4-carboxylic acid, 2897-72-5 (2,4-DNP), 2897-71-4 (ethyl ester), 2897-74-7 (oxime); 1,4-ethano-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolone, 2897-75-8; 1-amino-4-ethoxycarbonyl-4-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene, 27272-94-2, 27272-95-3 (HCl), 2897-77-0 (*N*-methyl lactam); 1,4-dihydro-1,4-ethano-2,3-dimethyl-4-phenyl-6,7-dimethoxyisoquinolinium chloride, 3123-50-0.

Acknowledgments.—We thank Dr. George de Stevens for his interest and encouragement during the course of this work. We are indebted to Mr. Louis Dorfman, Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Natalie Cahoon, Miss Ruth Behnke, Mrs. Margaret Mulligan, and Mr. Charles Navarro for analytical and spectral data, to Mrs. Angela Aretakis for literature search service, and to Mr. Ronald T. Smith for some technical assistance. The most generous gift of quantities of lactams **7** as well as compound **1c** (R = Et) from Dr. Karl Schenker (CIBA, Basel) is gratefully acknowledged.

A New Bicyclic System. N,N'-Diaryl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octanes

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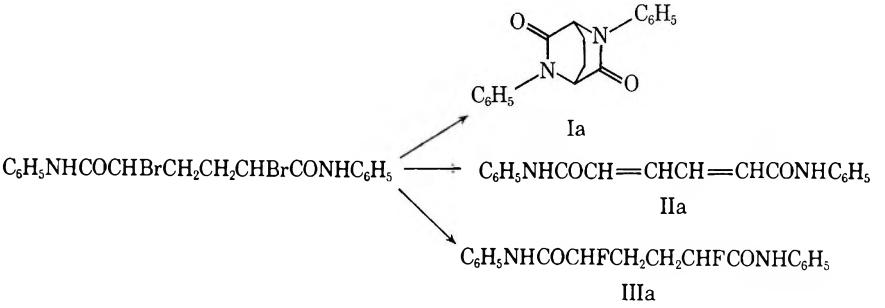
The reaction of α,α'-dibromoadipic acid bisarylamides with anhydrous potassium fluoride gives a new bicyclic system, N,N'-diaryl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octanes, together with the bisarylamides of α,α'-difluoroadipic and muconic acid. The chemical and physical properties of the bicyclic system are reported.

During our investigation of the reaction of amides of α-bromo acids with potassium fluoride,[1] it has been observed that α,α'-dibromoadipic acid dianilide is transformed in this reaction into a mixture of three substances: α,α'-difluoroadipic acid dianilide (IIIa), muconic acid dianilide (IIa), and a third substance which has the structure of N,N'-diphenyl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octane (Ia). This is a general reaction of substituted anilides of α,α'-dibromoadipic acid with potassium fluoride (Table I).



All the substituted muconic acid dianilides (II) are insoluble in methylene chloride and can be easily separated from the reaction mixture; their structure was established by analysis and spectra. It was impossible to hydrolyze them, but their structure was proven by unequivocal syntheses from *trans,trans*-muconic acid.

The mixtures of I and II could be separated by chromatography on alumina. The structure of compound Ia, $C_{18}H_{16}N_2O_2$, was established as follows.

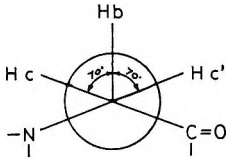
(1) The uv absorption at 238 mμ (ϵ 1.54 $\times$ 10^4) is that of a *saturated* anilide [acetanilide absorbs at λ_{max}^{EtOH} 238 mμ (ϵ 1.05 $\times$ 10^4)[2]].

(2) In the infrared, there is no sign of the NH stretching mode; at 1700 cm^{-1} one finds the carbonyl absorption of a saturated anilide.[3]

(3) The mass spectrum shows the molecular ion *m/e* 292 and the ratio $(M + 1)^+/M^+$ = 18–20% corresponds well with the suggested formula. The main fragments (*m/e* 173, 172, 171, 146, 145, 144, 143, 132, 119) can be explained by Schemes I–III. The peak *m/e* 146 could represent the doubly charged ion M^{2+}; however, this possibility is ruled out by the fact that there is no peak at $(M + 1)^+/2$ = 146.5. See Figure 1.

(4) The Dreiding model of Ia shows that the molecule is symmetrical and rigid. This model is consistent with the nmr spectrum which shows three absorptions: δ (ppm) 7.40 (s, 10 aromatic H), 4.66 (broad line, 2 bridgehead H_b), 2.30 (broad line, 4 methylene H_c). The peak at δ 2.30 ppm is a narrow multiplet as can be seen clearly at a sweep width of 100 cps. Spin decoupling by irradiation at δ 4.66 ppm narrows the width at half-height of the peak at δ 2.30 ppm from 5 to 3 cps. Spin decoupling by irradiation at δ 2.30 ppm narrows the width at half-height of the peak at δ 4.66 ppm from 5 to 1.3 cps.

Newman projection of the Dreiding model of Ia at the bridgehead shows that the dihedral angle between H_b and H_c as well as between H_b and $H_{c'}$ is about 70°. There is a difference, albeit a small one,



between H_c and $H_{c'}$. This is due to the fact that $H_{c'}$ is nearer to the carbonyl group, and H_c to the nitrogen atom. In any event, for such angles, Karplus' equation[4] predicts very small values for $J_{H_bH_c}$ and $J_{H_bH_{c'}}$ (about 0.7 cps), which cannot be determined in our case. It is worthy of note that Fort and Schleyer found in adamantanes (dihedral angle 60°) that J_{vic} = 2.6 $\pm$ 0.2 cps while the Karplus equation gives J_{calcd} = 1.8 cps.[5] The other N,N'-diaryl-2,5-diaza-3,6-dioxobicyclo[2.2.2]octanes have very similar nmr spectra. They are summarized in Table II.

The compounds I are stable when refluxed for 72 hr with a mixture of concentrated hydrochloric and acetic acids or with a 20% solution of sulfuric acid in acetic acid. Ia and Ib can be distilled at about 240–260° (3 mm) without decomposition.

The novel cyclization appears to occur only with potassium fluoride. When potassium carbonate or triethylamine were used under similar conditions, none of the bicyclic compounds has been obtained. One might thus believe that the difluoro dianilide is formed first and assumes a conformation conducive to ring closure. The interaction of the fluorine atoms and the NH groups may play a part in this process.

(1) I. Shahak, S. Rozen, and E. D. Bergmann, *Israel J. Chem.*, in press.
(2) H. E. Ungnade, *J. Amer. Chem. Soc.*, **75**, 432 (1953).
(3) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).
(4) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(5) R. C. Fort and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965); see also K. Tori, Y. Takano, and K. Kitahonoki, *Ber.*, **97**, 2798 (1964).

TABLE I

REACTION OF POTASSIUM FLUORIDE WITH ArNHCOCHBrCH$_2$CH$_2$CHBrCONHAr

Ar	Compound observed	Formula[a]	Yield, %	Mp, °C	Ir, cm^{-1} (in CCl$_4$)	Uv λ_{max}^{EtOH}, mμ	Uv ε × 10^4	R_f[b]
Phenyl	Ia	$C_{18}H_{16}N_2O_2$	36.0	159[c]	1710 (C=O)	238	1.54	0.70
	IIIa	$C_{18}H_{18}F_2N_2O_2$	8.5	207[d]	3330 (NH), 1665 (C=O), 1080 (CF)			
p-Tolyl	Ib	$C_{20}H_{20}N_2O_2$	12.0	166[c]	1705 (C=O)	240	1.88	0.75
	IIb	$C_{20}H_{20}N_2O_2$	11.0	313[d,g]	3280 (NH), 1660 (C=O)	248, 302	29.00, 1.39	
	IIIb	$C_{20}H_{22}F_2N_2O_2$	7.0	210[d]	3330 (NH), 1665 (C=O) 1078 (CF)			
p-Methoxyphenyl	Ic	$C_{20}H_{20}N_2O_4$	16.0	166[c]	1705 (C=O)	243	2.00	0.60
	IIc	$C_{20}H_{20}N_2O_4$	15.0	313[e,h]	3285 (NH), 1650, 1620 (C=O)	264, 343		
	IIIc	$C_{20}H_{22}F_2N_2O_4$	5.0	229[d]	3320 (NH), 1660 (C=O) 1080 (CF)			
p-Nitrophenyl	Id	$C_{18}H_{14}N_4O_6$	18.0	268[f]	1715 (C=O)	220, 310	1.62, 2.10	0.63
p-Chlorophenyl	Ie	$C_{18}H_{14}Cl_2N_2O_2$	46.0	182[c]	1715 (C=O)	245	2.60	0.83
	IIIe	$C_{18}H_{16}Cl_2F_2N_2O_2$	8.0	221[d]	3310 (NH), 1670 (C=O), 1080 (CF)			
m-Chlorophenyl	If	$C_{18}H_{14}Cl_2N_2O_2$	57.0	199[d]	1715 (C=O)	243	2.00	0.86
2-Methyl-4-chlorophenyl	Ig	$C_{20}H_{18}Cl_2N_2O_2$	46.0	195[c]	1710 (C=O)	230	1.74	0.77
	IIg	$C_{20}H_{18}Cl_2N_2O_2$	1.0	325[e,i]	3280 (NH), 1650, 1620 (C=O)	227, 273		

[a] Satisfactory analytical values for C, H, N, and halogen as appropriate (±0.35) were reported for all compounds in the table: Ed. [b] R_f values by tlc, silica gel, 0.25-mm thickness. The developer was 5% methanol in benzene. The presence of compounds of type I was easily demonstrated by tlc since their R_f's are much larger than those of all other products present. [c] Recrystallized from benzene. [d] Recrystallized from methanol–THF. [e] Recrystallized from DMF. [f] Recrystallized from DMSO. [g] This compound is different from the independently synthesized *trans,trans*-muconic acid di-*p*-toluidide, mp 327°, from DMF. We assume cis–trans configuration: ν_{max}^{Nujol} 3290, 1640, 1600 cm^{-1}; λ_{max}^{EtOH} 233, 273, 330 mμ. [h] *trans,trans*-Muconic acid dianisidide. Comparison (mixture melting point and ir) with an authentic sample, synthesized from *trans,trans*-muconyl chloride: P. S. Bailey and J. H. Ross, *J. Amer. Chem. Soc.*, **71**, 2370 (1949). This compound is accompanied by another, more soluble isomer [mp 312° (from DMF); ν_{max}^{Nujol} 3265, 1660, 1650 cm^{-1}; λ_{max}^{EtOH} 252, 315 mμ], which is probably the cis–trans isomer. [i] The configuration has not been determined.

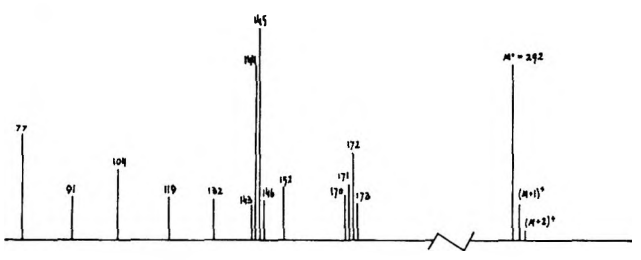


Figure 1.—The main peaks of the mass spectrum.

In the parallel reaction of potassium fluoride with α,α′-dibromoadipic acid bis-*N*-methylanilide (IV) in which an analogous cyclization is impossible, only *trans,trans*-muconic acid bis-*N*-methylanilide (V) was obtained in 45% yield. This confirms earlier results with α,α′-dibromoadipic acid bis-*N*,*N*-diethylamide.[1]

$$\underset{\text{IV}}{C_6H_5N(CH_3)COCHBrCH_2CH_2CHBrCO(CH_3)NC_6H_5} \xrightarrow{KF} \underset{\text{V}}{C_6H_5N(CH_3)COCH{=}CHCH{=}CHCON(CH_3)C_6H_5}$$

V could be hydrolyzed to *trans,trans*-muconic acid by 70% sulfuric acid and was synthesized from *trans,trans*-muconyl chloride[6] and *N*-methylaniline.

(6) P. S. Bailey and J. H. Ross, *J. Amer. Chem. Soc.*, **71**, 2370 (1949).

Experimental Section

The melting points have been determined with a Thomas–Hoover capillary melting point apparatus. The nmr spectra were measured with a Varian T-60 instrument; the samples were dissolved in $CDCl_3$ except when otherwise indicated.

Preparation of α,α′-Dibromoadipic Acid Bisarylamides (Table III).—A mixture of 14.6 g of adipic acid (0.1 mol) and 50 g of thionyl chloride was refluxed until the acid had completely dissolved. After a further hour, 35 g of bromine (0.22 mol) was added during 2–3 hr to the boiling solution, and the heating was continued for an additional 4 hr. The excess of bromine and thionyl chloride was distilled off under reduced pressure (below 100°), and two portions (250 ml each) of toluene were added and evaporated again under reduced pressure. The crude α,α′-dibromoadipoyl chloride was diluted with 150 ml of dry benzene and used in this form.

The freshly distilled arylamine, dissolved in dry benzene (0.22 mol in 70 ml), was then added to the solution with stirring and cooling. After 1 hr at room temperature, 100 ml of cold 10% hydrochloric acid was added and the mixture was stirred for 1 hr and filtered. Thus the arylamides, which are only very sparingly soluble, were obtained in practically quantitative yields. As it is difficult to recrystallize them, they were purified by refluxing with 2% HCl for 1 hr, filtering, and drying at 100° under reduced pressure. The analytical samples were further purified by refluxing them for 30 min in THF–methanol (1:1) in which the compounds are insoluble.

The preparation of α,α′-dibromoadipic acid bis-*N*-methylanilide is slower, and the mixture of *N*-methylaniline and α,α′-dibromoadipoyl chloride had to be left at room temperature for 24 hr, yield 75%, recrystallized from methanol.

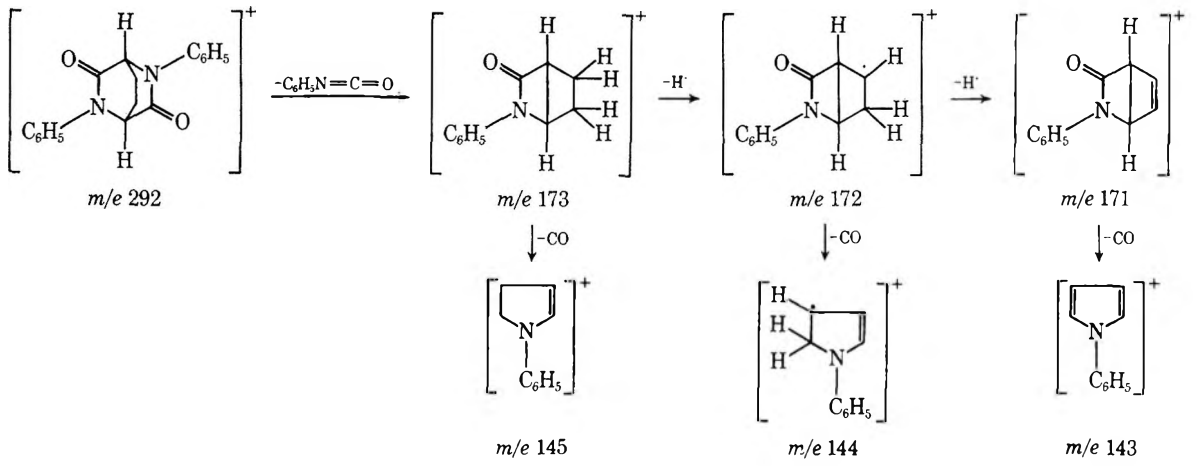
TABLE II

NMR SPECTRA OF *N,N*-DIARYL-2,5-DIAZA-3,6-DIOXOBICYCLO[2.2.2]OCTANES (I)

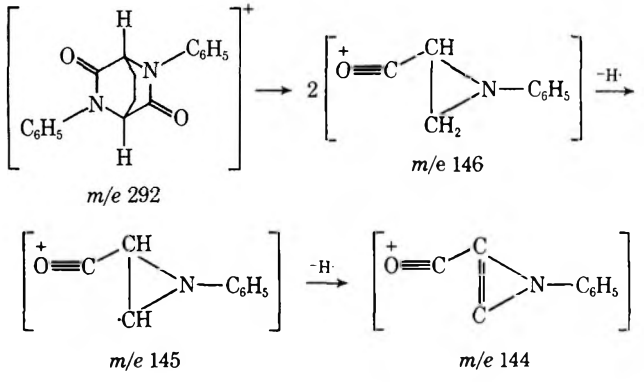
		Bridgehead hydrogen atom (H_b)			Methylene hydrogen atoms (H_c, H_c')		
			Width at half-height (cps)			Width at half-height (cps)	
Compd	Ar[a]	Signal position (ppm)	Before irradn at H_c, H_c'	After irradn at H_c, H_c'	Signal position (ppm)	Before irradn at H_b	After irradn at H_b
Ib	*p*-Tolyl	4.62 (2 H)	3.5	1.7	2.31 (4H)	*b*	
Ic[c]	*p*-Methoxyphenyl	4.55 (2 H)	3.5	1.5	2.29 (4 H)	5.0	3.0
Id[d]	*p*-Nitrophenyl	5.12 (2 H)	4.0		2.58 (4 H)	6.0	
Ie	*p*-Chlorophenyl	4.63 (2 H)	5.0	2.0	2.30 (4 H)	6.0	4.0
If[e]	*m*-Chlorophenyl	4.70 (2 H)	5.0	2.1	2.39 (4 H)	4.5	3.0
Ig[f]	2-Methyl-4-chlorophenyl	4.34 (2 H)	6.0	2.5	2.33 (4 H)	3.5	2.0

[a] The signals for the aromatic protons were observed in the range of 7.05–7.49 ppm. In one case (I, Ar = *p*-nitrophenyl) an AB spectrum has been observed as follows: A = 8.33 (d, 4 H, J = 9 cps); B = 7.88 (d, 4 H, J = 9 cps). [b] The two methyl groups resonate at 2.37 ppm (s, 6 H). [c] The six methoxy protons appear as a singlet at 3.81 ppm. [d] Because of the slight solubility in $CDCl_3$, the spectrum was measured in $(CD_3)_2SO$. [e] This spectrum was determined in $CDCl_3$ and in $(CD_3)_2SO$. The chemical shifts and the widths at half-height, before and after irradiation, in the two solvents are identical. [f] The six methyl protons appear as a singlet at 2.38 ppm.

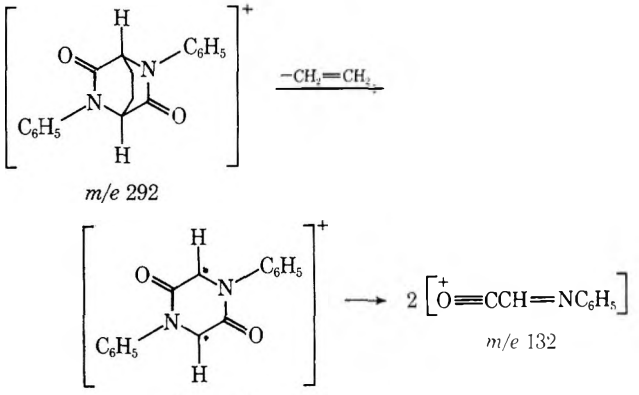
SCHEME I



SCHEME II



SCHEME III



Reaction of α,α'-Dibromoadipic Acid Bisarylamides with Potassium Fluoride.—The bisarylamide (0.15 mol) was added to a solution of 52 g (0.9 mol) of dry potassium fluoride (dried at 180° for 10 hr) in 300 ml of diethylene glycol. The mixture was heated, with stirring, at 125–130° for 2.5 hr, cooled, and poured into 3 l. of ice water. The precipitate was filtered off, washed with water, and added to 2 l. of methylene chloride. The organic phase, in which sometimes a solid was suspended, was washed three times with 200 ml of water and filtered. The insoluble phase proved always to be the substituted muconic acid bisarylamide. The filtrate was dried over anhydrous potassium carbonate and evaporated. The residue was refluxed for 30 min with 500 ml of benzene and filtered. Filtration of the mixture, while still hot, left the benzene-insoluble α,α'-difluoroadipic acid bisarylamide. The benzene filtrate was cooled, whereupon a portion of the bicyclic compound I precipitated. Concentration of the mother liquid and chromatography on alumina (Merck, neutral activity I), 2% acetone in benzene serving as eluent, gave the balance of compound I. Subsequent elution with 3% methanol in benzene gave some additional α,α'-difluoroadipic acid bisarylamide.

The reaction mixture obtained from α,α'-dibromoadipic acid *p*-nitroanilide behaved somewhat differently. The residue, after evaporation of the methylene chloride, was the bicyclic compound Id. It was purified by refluxing the compound with 200 ml of chloroform and filtration of the hot solution from the solid Id. No defined substance could be isolated by chromatography of the filtrate. The ir, uv, and R_f data of the compounds of type I, II, and III are included in Table I.

TABLE III

RR'NCOCHBrCH$_2$CH$_2$CHBrCONRR'

Compd	R	R'	Mp,[a] °C	Empirical formula[b]	Ir (cm^{-1})[c] NH	Ir (cm^{-1})[c] C=O
a	Phenyl	H	243	$C_{18}H_{18}Br_2N_2O_2$	3300	1660
b	*p*-Tolyl	H	236	$C_{20}H_{22}Br_2N_2O_2$	3260, 3300	1660, 1700
c	*p*-Anisyl	H	238	$C_{20}H_{22}Br_2N_2O_4$	3280, 3300	1660, 1690
d	*p*-Nitrophenyl	H	239	$C_{18}H_{16}Br_2N_4O_6$	3290, 3320	1680, 1700
e	*p*-Chlorophenyl	H	246	$C_{18}H_{16}Br_2Cl_2N_2O_2$	3270, 3300	1660, 1700
f	*m*-Chlorophenyl	H	220	$C_{18}H_{16}Br_2Cl_2N_2O_2$	3280, 3310	1660, 1700
g	2-Methyl-4-chlorophenyl	H	244	$C_{20}H_{20}Br_2Cl_2N_2O_2$	3270	1660
h	Phenyl	CH_3	161	$C_{20}H_{22}Br_2N_2O_2$		1670

[a] All compounds, except Ih, decompose at the melting point. [b] Satisfactory analytical values for C, H, N, and halogen as appropriate (±0.35) were reported for all compounds in the table: Ed. [c] Ir spectra in Nujol mulls.

Registry No.—Ia, 27062-59-5; Ib, 27062-60-8; Ic, 27062-61-9; Id, 27062-62-0; Ie, 27062-63-1; If, 27062-64-2; Ig, 27062-65-3; IIb, 27062-66-4; *trans,trans*-IIc, 27062-67-5; *cis,trans*-IIc, 27062-68-6; IIg, 27062-69-7; IIIa, 27062-70-0; IIIb, 27062-71-1; IIIc, 27062-72-2; IIIe, 27062-73-3. Table III—a, 27062-74-4; b, 27062-75-5; c, 27062-76-6; d, 27062-77-7; e, 27062-78-8; f, 27062-79-9; g, 27062-80-2; h, 27062-81-3.

The Synthesis and Acetolysis of 6-Oxabicyclo[3.2.1]octane-1-methyl *p*-Bromobenzenesulfonate[1]

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The intramolecular oxymercuration of 4,4-bis(hydroxymethyl)-1-cyclohexene (2) followed by sodium borohydride reduction of the chloromereurial gave 1-hydroxymethyl-6-oxabicyclo[3.2.1]octane (4a). The brosylate 5a derived from this alcohol was solvolyzed in acetic acid. The products included the unrearranged acetate 6, 4,4-bis(acetoxymethyl)-1-cyclohexene (7a), and the two ring-expanded bridgehead acetates 8 and 9. Sodium borodeuteride reduction of the oxabicyclic chloromercurial gave 1-hydroxymethyl-6-oxabicyclo[3.2.1]octane-4-*d* (4b). The brosylate 5b of this alcohol was also solvolyzed in acetic acid. The 4,4-bis(acetoxymethyl)-1-cyclohexene isolated from this acetolysis had lost approximately 50% of the deuterium originally located in the brosylate. The nature of the solvolytic rearrangements and the significance of the results of the deuterium experiments are discussed.

Numerous investigations of the solvolyses of bicyclic bridgehead methanol derivatives have been reported.[3-10] These studies have enhanced our understanding of bond-angle deformation and polar effects on reactivity in constrained neopentyl-type systems, particularly as regards the influence of these effects on 1,2- and 1,3-cationic rearrangements and fragmentations. The study of norbornenyl-1-carbinyl derivatives by Wilt and coworkers[8] has served to define the geometrical requirements for homoallylic delocalization. Their work in this system has provided a measure of the inductive (or field) effect of a vinyl group β to the solvolyzing center uncomplicated by homoallylic delocalization. Similar considerations led us to the investigation of the title bicyclic system in order to determine the effects of carbon–oxygen dipoles on solvolyses at the 1-carbinyl position.

In the solvolyses of compounds containing an alkoxyl group as a substituent elsewhere in the molecule, it is often difficult to assess the inductive (or field) effect of a C–O dipole on the cationic reaction center since appropriately located alkoxyl groups can facilitate solvolysis by intramolecular attack to form cyclic oxonium ions.[11-13] This competing process is eliminated in solvolyses of compounds such as **5a**. Furthermore, the precise orientation of the O–C bonds is held relatively fixed with respect to the reaction center and can be estimated with a high degree of certainty. It was also of interest to learn whether a 1,3-hydride shift from C-7 to the solvolyzing center would be observable in view of the potential cation-stabilizing effect of the ether oxygen.

Results

Syntheses.—The title brosylate **5a** and its deuterated analog **5b** were prepared using a four-step sequence

(1) Abstracted in part from the thesis of R. A. Froehlich, submitted to San Diego State College in partial fulfillment of the requirements for M.S. Degree, Sept 1969.

(2) National Science Foundation High School Teacher Research Participant, 1967.

(3) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).

(4) K. B. Wiberg and B. R. Lowry, *J. Amer. Chem. Soc.*, **85**, 3188 (1963).

(5) R. S. Bly and Q. E. Cooke, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, Abstract 80-S; R. S. Bly and E. K. Quinn, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstract 91-O.

(6) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connar, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965).

(7) W. D. Closson and G. T. Kwiatowski, *ibid.*, **21**, 2779 (1965).

(8) J. W. Wilt, C. T. Parsons, C. A. Schneider, D. G. Schultenover, and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968).

(9) W. G. Dauben, J. L. Chitwood, and K. V. Scherer, Jr., *J. Amer. Chem. Soc.*, **90**, 1014 (1968).

(10) S. H. Graham and D. A. Jonas, *J. Chem. Soc. C*, 188 (1969).

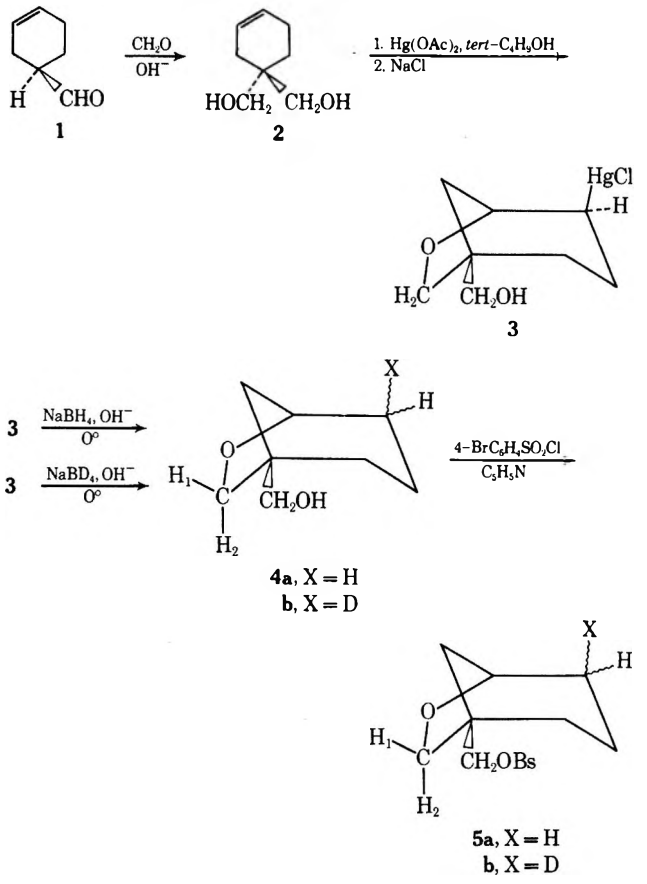
(11) E. L. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 3991, 3998, 4008, 4012 (1967).

(12) P. W. Austin, J. G. Buchanan, and D. G. Large, *Chem. Commun.*, 418 (1967).

(13) D. S. Noyce, B. R. Thomas, and B. N. Bastian, *J. Amer. Chem. Soc.*, **82**, 885 (1960); D. S. Noyce and B. N. Bastian, *ibid.*, **82**, 1246 (1960).

starting from the commercially available 3-cyclohexene-1-carboxaldehyde (**1**) as shown in Scheme I.

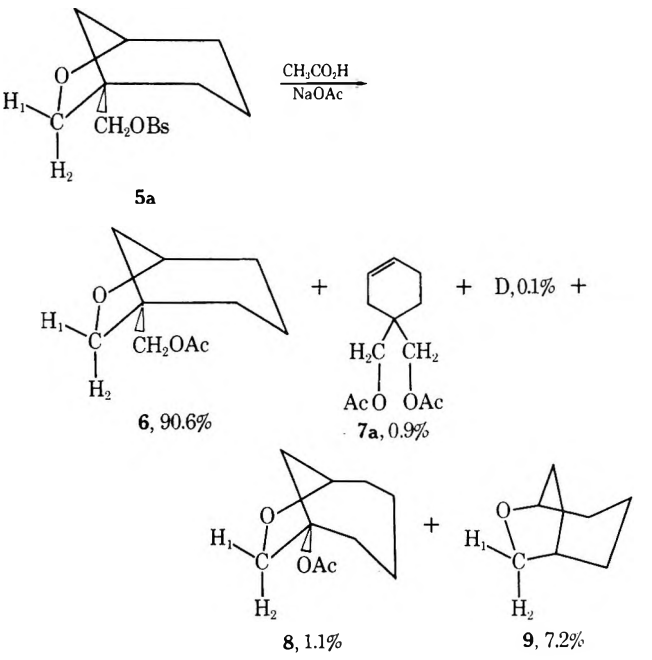
SCHEME I



The intramolecular oxymercuration of **2** was suggested by the related ring closure of 4-methylenecyclohexanemethanol to chloromercurimethylnorcineole reported by Weinberg and Wright.[14] In principle, the cyclization of **2** can lead to two isomers possessing respectively the [2.2.2] and the [3.2.1] bicyclic skeleton. In the present study only one product could be isolated and no evidence for the presence of a second isomer was obtained. That the ring-closed oxabicyclic product isolated possessed the [3.2.1] ring system was clearly demonstrated by the nmr spectrum of **4a**. The protons at the 7 position appear as an AB doublet of doublets with calculated chemical shifts of 3.67 and 3.82 ppm. It is clear that the methylene protons α to the ether oxygen would be magnetically equivalent in the [2.2.2] isomer.[15] The C–Hg bond of the chloromercurial **3** would be expected to be axially oriented since oxymercurations of cyclohexene are known to proceed stereospecifically trans.[21–23] The borohydride reduction of **3** under basic conditions gave **4a** in reasonably good yield. However, the desired product was accompanied by approximately 20% of **2**, the deoxymercuration product. Bordwell and Douglass[24] carried out sodium borohydride reduction demercurations on a wide variety of β-oxy mercurials. Under basic conditions these reductions were reportedly free of deoxymercuration. For example, *trans*-2-methoxy-1-chloromercuricyclohexane was reduced to cyclohexyl methyl ether in 86% yield with no evidence for the presence of cyclohexene. The modest amount of strain in **3** may contribute to the ease of this ring-opening demercuration; however, the postulated mechanism[24] for previous reductive deoxymercurations normally observed at pH 7 or below (and requiring protonation of the β oxygen) would appear to require modification in this case. The brosylate **5a** was prepared by the usual method. The monodeuterated analogs **4b** and **5b** were prepared for purposes discussed below.

Acetolyses.—The brosylate **5a** was solvolyzed in boiling acetic acid containing a 20% molar excess of anhydrous sodium acetate to give a 91% yield of products. The glpc analysis showed the presence of five products which were isolated by preparative glpc. Four of the compounds were in sufficient quantity to be identified (see Scheme II). Compounds **6** (the main product) and **7** were identified by comparison with authentic samples. Compounds **8** and **9** were identified by elemental, glpc, infrared, nmr, and mass spectral analyses. In the nmr spectra, the increase in the integrated areas upfield from about 2.0 ppm (as compared with **5a** or **6**) coupled with the disappearance of the methylene singlet

SCHEME II



(14) N. L. Weinberg and G. F. Wright, *Can. J. Chem.*, **43**, 24 (1965).

(15) The [3.2.1] bicyclic hydrocarbon system (as well as the oxabicyclic analog) appears to be thermodynamically more stable than the [2.2.2] system.[16–19] However, it is interesting to note that a carbonyl group in these oxabicyclic ring systems may change the thermodynamic preference. Noyce, Weingarten, and Dolby[20] observed that the lactone of *cis*-3-hydroxycyclohexanecarboxylic acid rearranges to the lactone of *cis*-4-hydroxycyclohexanecarboxylic acid. However, the latter isomer was isolated in relatively low yield and no other product in the reaction mixture was characterized.

(16) W. von E. Doering and M. Farber, *J. Amer. Chem. Soc.*, **71**, 1514 (1949).

(17) M. S. Newman and Y. T. Yu, *ibid.*, **74**, 507 (1952).

(18) N. Wendler, D. Taub, and C. H. Kuo, *J. Org. Chem.*, **34**, 1510 (1969).

(19) A. Isard and F. Weiss (to Ugine Kuhlmann), French Patent 1,514,315 (1968); *Chem. Abstr.*, **70**, 87552y (1969).

(20) D. S. Noyce, H. I. Weingarten, and L. J. Dolby, *J. Org. Chem.*, **26**, 2101 (1961).

(21) M. M. Kreevoy and F. R. Kowitt, *J. Amer. Chem. Soc.*, **82**, 739 (1960).

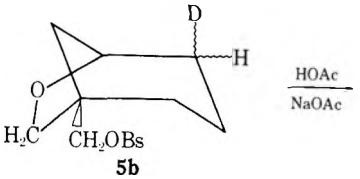
(22) T. G. Traylor and A. W. Baker, *ibid.*, **85**, 2746 (1963).

(23) Surprisingly, the *A* value of the bromomercuri group is zero within experimental error (±5%) with a probable small preference for the axial orientation [F. R. Jensen and L. H. Gale, *ibid.*, **81**, 6337 (1959)].

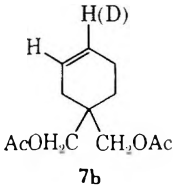
(24) F. G. Bordwell and M. L. Douglass, *ibid.*, **88**, 993 (1966).

($-CH_2O-$ at C-1) indicates ring expansion in the rearranged acetates. Furthermore, the persistence of the AB doublet of doublets (see Experimental Section) in **8** and **9** shows that ring expansion did not involve the methylenoxy bridge. In agreement with structures **8** and **9**, the chemical shifts for the protons H_1 and H_2 (Scheme II) are shifted downfield (compared with H_1 and H_2 in **6**) by magnitudes ranging from 0.14 to 0.34 ppm. These protons are now bound to carbons with oxygen functions at both the α and β positions. The magnetic environments of the bridgehead protons (C-6 H in **8** and C-5 H in **9**) are nearly identical with chemical shifts at 4.48 and 4.47 ppm, respectively. This represents a very small downfield shift of approximately 0.04 ppm compared with **6**. Although 1,3-hydride shifts in a related system have been reported,[10] structures for **8** and **9** resulting from similar 1,3-hydride shifts from C-2, C-7, or C-8 to the primary carbon bearing the departing brosylate group or from ring expansion followed by a 1,2-hydride shift can be excluded. The former case would require a *C*-methyl singlet near 1 ppm which is not observed. The latter possibility can be ruled out by the observation that no new absorption below 2.5 ppm is found in the nmr spectrum of either **8** or **9**. The structures for **8** and **9** have been tentatively made as indicated on the following basis. A multiplet (roughly appearing as a broadened, unsymmetrical doublet) is found well separated and downfield from the remaining methylene protons at approximately 2.35 ppm in **8**. The integral of this absorption corresponds to two protons. This is probably due to the two protons on the single methylene bridge. It will be noted that this C-9 position is now β to two oxygen functions, although conformational changes in the orientation of the acetate carbonyl (and its spacial relationship to the methylene bridge protons) may be causing this difference in chemical shift of **8** compared to **9**. A second notable difference between the nmr spectra of **8** and **9** is seen in the doublet of doublets attributable to the protons labeled H_1 and H_2 in either **8** or **9**. The difference in chemical shift ($\Delta\delta$) between the two doublets in **8** is 0.38 ppm while the same difference in **9** is only 0.16 ppm. From gross structural considerations it would appear likely that the protons H_1 and H_2 in **8** would experience greater differences in magnetic environment than would H_1 and H_2 in **9**. Again, the conformational preference of the acetoxy carbonyl group in these two compounds may be important.

The acetolysis of **5b** was conducted under conditions identical with those used for **5a**. The 4,4-bis(acetoxymethyl)-1-cyclohexene (**7b**) was isolated by preparative glpc and analyzed for deuterium content using both nmr and mass spectrometric methods. The starting brosylate **5b** was monodeuterated to the extent of 90.6%. The olefinic diacetate **7b** isolated was 47 ± 3% monodeuterated.



5b

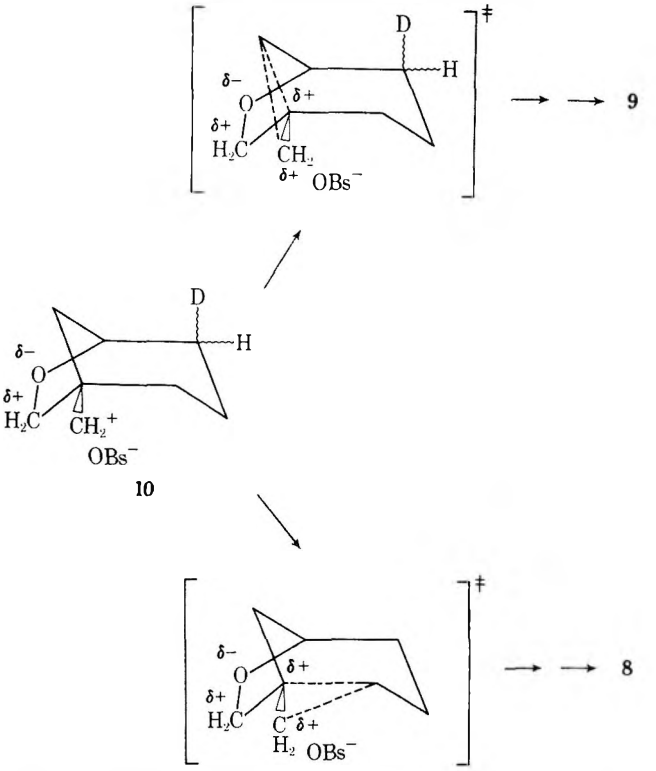


+ other products

7b

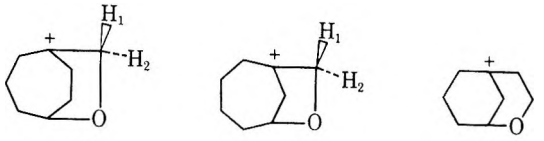
Discussion

One of the most striking observations made in this solvolytic study is the remarkably small amount of rearrangement which occurs. Although the bicyclo[3.2.1]octane-1-methyl brosylate itself has not yet been prepared for parallel studies, it is interesting to compare the present results with those reported by Graham and Jonas.[10] Under conditions similar to those employed here, bicyclo[3.3.1]nonane-1-methyl brosylate solvolyzes with 36% of the product rearranged through ring expansion. Presumably the rearrangement products **8** and **9** found in the acetolysis of **5a** are generated by a 1,2 migration of an initially formed ion pair **10** (although concerted migration and loss of OBs^- cannot be ruled out). If one considers the partial positive charge (result of C–O dipole) residing on the carbon (C-7 of the brosylate) adjacent to the new center of developing charge (C-1), it is not surprising that these paths are relatively energetically unfavorable. It is also noteworthy that the methylenoxy bridge is not involved at all in a ring-expanding rearrangement (or, if it is, it cannot account for more than 0.1% of the acetolysis product). This is reminiscent of the absence of vinyl migration in the hydrolysis of norbornenyl-1-carbinyl tosylate.[8] The lack of proclivity toward rearrangement of these two "groups" may be related. It is generally accepted that in 1,2-cationic rearrangements a migrating carbon bears a portion of the total positive charge. The cationic character of the migrating group is probably fairly substantial in Baeyer–Villiger rearrangements,[25] but in carbon to carbon rearrangements



(25) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Amer. Chem. Soc.*, **80**, 6393 (1958); J. A. Berson and S. Suzuki, *ibid.*, **81**, 4088 (1959).

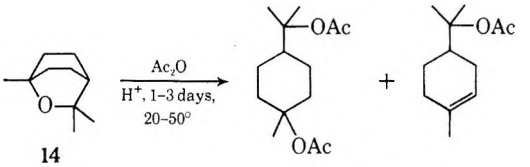
the charge on the migrating carbon may be considerably less.[26] Nonetheless, an attractive explanation for the absence of alkoxymethylene migration in the acetolysis of **5a** may derive from the fact that for migration to occur some charge delocalization onto the migrating carbon is important. Since the methylenoxy carbon already bears substantial charge in **10**, it would be energetically unfavorable for it to accept additional charge. And π-electron delocalization of charge by oxygen would appear to be unavailable on geometrical grounds.[27] To the extent that the three cations **11**, **12**, and **13** can serve as models for the transition



11 **12** **13**

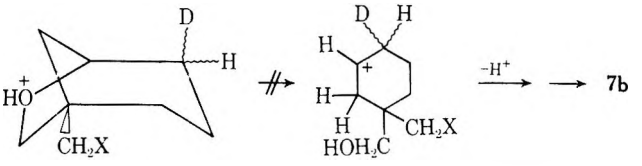
states for the three possible migrations of carbon, an examination of their relative strain may be instructive. A consideration of the framework molecular models of **11**, **12**, and **13** (with sp^2 hybridization at the positively charged bridgehead carbons and sp^3 hybridization elsewhere) suggests that **12** would possess the greatest amount of angle strain and destabilization from nonbonded interactions. The ions **11** and **13** would clearly be more stable on both counts, although a choice between **11** and **13** as the least stable ion cannot be made with certainty. Thus the assignment of structures for compounds **8** and **9** (considering their relative yields) is in accord with predictions based upon comparisons of ions **11** and **12**. The retardation of migration of the oxymethylene bridge in **5a** is probably less a result of ring strain in the transition state leading to **13** than of the type of charge interactions suggested above. This is in agreement with the results of a recent study of the buffered acetolysis of bicyclo[3.2.1]octane-1-methyl *p*-toluenesulfonate.[28] The acetolysis leads to the formation of two products: 1-acetoxybicyclo[3.2.2]nonane and 1-acetoxybicyclo[3.3.1]nonane in a ratio of about 2:1. Clearly, ring expansion of the two-carbon bridge in this "hydrocarbon" analog of the oxabicyclic system is competitive with ring expansion of the one-carbon bridge. If ions such as **11** and **12** (or corresponding ion pairs) are intermediates in the acetolysis of **5a**, they might be expected to undergo rapid 1,2-hydride shifts of H_1 or H_2. Such a shift would lead to an ion stabilized by the adjacent oxygen. Considering the stabilities of the corresponding hydrocarbon bicyclic bridgehead olefins[29] such a rearrangement would be more likely for **12** than for **11**. Future solvolyses under conditions expected to give larger amounts of rearrangement may yet reveal this type of shift.

An unexpected acetolysis product from **5a** was 4,4-bis(acetoxymethyl)-1-cyclohexene (**7a**). This diacetate presumably is formed *via* acid-catalyzed, ring-opening elimination and esterification. A few elimination reactions which involve loss of R–OH from an ether have been observed. They usually require strong acids and/or elevated temperatures.[30] An interesting example which bears a resemblance to the formation of **7a** is the ring opening of cineole (**14**) in acetic anhydride containing small amounts of sulfuric acid or ferric chloride.[31] In the hopes of learning more about the



14 50:50 mixture

elimination reaction forming **7a** and determining the stereochemistry of the borohydride reduction of **3**, the deuterated brosylate **5b** was subjected to acetolysis as before. As indicated above, the olefinic diacetate **7b** isolated had lost approximately 50% of the deuterium contained in the starting material. Regardless of the equatorial–axial distribution of deuterium in **5b**, this result removes from serious consideration one mechanistic possibility, namely ring opening to form a "free"



carbonium ion followed by proton loss. Were this the case, the deuterium content of **7b** would have been expected to be considerably higher. Furthermore, such a mechanism would lead to two isomeric olefinic diacetates. No evidence for the presence of a second diacetate was found, and the diacetate isolated from the solvolysis of **5a** was identical in all respects with that of an authentic sample of 4,4-bis(acetoxymethyl)-1-cyclohexene.

The mechanism and stereochemistry of borodeuteride reductions of organomercurials has been the subject of several investigations. Retention of configuration in the borodeuteride reduction of *exo-cis*-2-hydroxy-3-chloromercurinorbornane[24] and *trans*-2-hydroxycyclopentylmercuric acetate[32] has been observed. However, the earlier four-centered mechanism based upon the assumption that retention was general is not in agreement with recent observations of loss of stereochemistry[31] and the occurrence of radical-type rearrangements[32,33] during numerous other reductions of organomercurials. The synthetic sequence in Scheme I combined with the acetolysis of **5b** to form **7b** appeared to offer the possibility of determining the stereochemistry of the borohydride reduction of a chloromercurial group in a cyclohexyl system. If the reduction of **3** were stereospecific leading to deuterium in the axial position and the ring opening involves concerted attack by a base (such as

(26) See J. A. Berson, D. Wege, G. M. Clarke, and R. G. Bergman, *J. Amer. Chem. Soc.*, **90**, 3240 (1968); J. R. Owen and W. H. Saunders, Jr., *ibid.*, **88**, 5809 (1966).

(27) An ether oxygen can usually stabilize a cation forming on an adjacent carbon through π delocalization of an electron pair (note, for example, accelerated rates of solvolyses of α-halo ethers). However, the oribital on C-7 (involved in C-7, C-1 bond) which could conceivably develop 2p character is nearly orthogonal to the orbital(s) of the unshared electrons on oxygen.

(28) Private communication. We thank Professor J. R. Wiseman for communicating these results to us.

(29) J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, **92**, 957 (1970), and references therein; see also J. A. Marshall and H. Faubl, *ibid.*, **89**, 5965 (1967).

(30) R. Burwell, Jr., *Chem. Rev.*, **54**, 615 (1954).

(31) E. Knoevenagel, *Justus Liebigs Ann. Chem.*, **402**, 133 (1914).

(32) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **91**, 719 (1969).

(33) G. A. Gray and W. R. Jackson, *ibid.*, **91**, 6205 (1969).

acetate ion), carbon–carbon double bond formation, and cleavage of the carbon–oxygen bond,[34] the deuterium analysis of the product would require that the attack by base be equally probable on an exo (axial) or endo (equatorial) hydrogen. However, most evidence in the literature indicates that β eliminations in cyclohexane derivatives are highly stereoelectronically controlled[35] with trans (antiperiplanar) eliminations predominating.[36] Consequently, this can be taken as evidence that the borodeuteride reduction of **3** is not stereospecific. This is in agreement with a previous observation of the absence of stereospecificity in the borodeuteride reductions of 4-methylcyclohexylmercuric halides.[37]

The extent to which the ring-opening elimination proceed from the brosylate **5** and the acetate **6** is unknown. However, it is interesting to note that, in the course of preparing **6** from the corresponding alcohol **4a** and acetic anhydride containing anhydrous sodium acetate, 17% of the ring-opened diacetate **7a** was formed.

Rate and product study comparisons of the title brosylate and tosylate with the parent bicyclo[3.2.1]-1-carbinyl derivatives and related studies in smaller bicyclic systems are planned or in progress.

Experimental Section[38]

4,4-Bis(hydroxymethyl)-1-cyclohexene (**2**) was prepared from 3-cyclohexene-1-carboxaldehyde employing the crossed Cannizzaro reaction, mp 90–91° (lit.[39] mp 92.0°).

1-Hydroxymethyl-4-chloromercuri-6-oxabicyclo[3.2.1]octane (**3**).—To a mixture of 45.3 g (0.142 mol) of mercuric acetate and 920 ml of dry *tert*-butyl alcohol (stirred for 10 min) was added in one portion 20.0 g (0.141 mol) of 4,4-bis(hydroxymethyl)-1-cyclohexene. The resulting mixture was stirred at room temperature for 49 hr. It was then clarified by filtration. To the clear filtrate was added 14.0 g (0.240 mol) of sodium chloride. The white precipitate which formed was collected on a funnel and washed with several 5-ml portions of water affording 39.1 g of **3**, mp 179–182°. A second crop (4.8 g) was obtained by concentrating the filtrate. The combined product was recrystallized from 95% aqueous ethanol affording 39.0 g (73%) of fine white crystals, mp 177–178°.

Anal. Calcd for $C_8H_{13}ClHgO_2$: C, 25.47; H, 3.47; Cl, 9.39. Found: C, 25.71; H, 3.80; Cl, 9.22.

1-Hydroxymethyl-6-oxabicyclo[3.2.1]octane (**4a**).—A mixture of 43.4 g (0.115 mol) of 1-hydroxymethyl-4-chloromercuri-6-oxabicyclo[3.2.1]octane and 80 ml of 5% aqueous sodium hydroxide was stirred for several minutes at 0°. A solution of 1.18 g (0.0312 mol) of sodium borohydride in 180 ml of cold, 10% aqueous sodium hydroxide was then added dropwise over a 20-min period. The resulting mixture was stirred at 0° for 1 hr and then subjected to continuous ether extraction. The ether extract was washed successively with 0.12 *N* hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water. The extract was dried and concentrated to 15.9 g of a yellow oil. The desired bicyclic product **4a** was contaminated with approximately 20% **2**. A sample of the oil (13.1 g) was chromatographed on a support mixture obtained by adding 30.2 g of silver nitrate dissolved in 100 ml of water to a mixture of 68.0 g of Celite and 412 g of 100 mesh silicic acid. The column was prepared from the thoroughly mixed support material in an ether–petroleum ether slurry. The desired product **4a** was eluted with ether as a colorless oil: 9.49 g (58% corrected for sample size used in separation); nmr ($CDCl_3$) 1.20–2.10 (m, 8 ring methylene protons), 2.93 (s, 1, –OH), 3.54 (s, 2, $-CH_2OH$), 3.67 and 3.82 (AB d of d,[40,41] 2, J_{AB} = 7.5 Hz, $-OCH_2C<$), 4.40 (broadened t, 1, C-5 H).

The 3,5-dinitrobenzoate of **4a** was prepared and melted at 104–105° (cor) (lit.[19] mp 100–101°). The nmr spectrum of the dinitrobenzoate ($DCCl_3$) revealed the following absorptions: 1.44–2.3 (m, 8, ring methylene protons), 3.74 and 3.96 (AB d of d,[40] 2, J_{AB} = 8 Hz, $-OCH_2C<$), 4.43 (s,[42] 2, $-CH_2O_2CAr$), 9.05–10.3 (m, 3, aromatic protons).

1-Hydroxymethyl-6-oxabicyclo[3.2.1]octane-4-*d* (**4b**).—The deuterated analog of **4a** was prepared by reducing 8.00 g (0.0212 mol) of the chloromercuri derivative **3** with 0.220 g (0.00526 mol) of sodium borodeuteride using the conditions previously described. The crude product was chromatographed using the silicic acid–Celite–silver nitrate column previously described and eluting with 20% by volume petroleum ether (bp 30–60°) in diethyl ether. The separation afforded 0.458 g of **2** and 1.613 g (54%) of **4b** (obtained as a colorless oil). The nmr spectrum of **4b** ($CDCl_3$) revealed the following features: 1.25–2.10 (m, 7 ring methylene protons), 2.98 (s, 1, –OH); 3.51 (s, 2, $-CH_2OH$), 3.64 and 3.80 (AB d of d,[40,43] 2, J_{AB} = 7.5 Hz, $-OCH_2C<$), 4.38 (broadened t, 1, C-5 H). The infrared spectrum ($CDCl_3$) of **4b** was very similar to that of the undeuterated analog **4a**. The major exception was a band at 2160 cm^{-1} (CD stretch) in **4b**. The mass spectrum (15 eV) of **4b** showed the weak parent ion at *m/e* 143 (5.5) and major peaks at 112 (100), 95 (8.8), and 82 (3.4). Using the intensities of the ions at *m/e* 112 (P + 1) and 111 (P), the % deuteration was calculated to be 91%. The intense peak at *m/e* 112 corresponds to loss of $\cdot CH_2OH$ from the molecular ion.

6-Oxabicyclo[3.2.1]octane-1-methyl *p*-Bromobenzenesulfonate (**5a**).—The bicyclic alcohol **4a** (9.49 g, 0.0668 mol) was dissolved in 70 ml of cold (0°), freshly distilled pyridine. To the solution was added 23.0 g (0.0901 mol) of *p*-bromobenzenesulfonyl chloride. The resulting mixture was swirled to effect solution and was then allowed to stand for 15 hr at −3°. The solution was warmed to room temperature for 45 min, cooled again to 0°, treated with cold 6 *N* hydrochloric acid to neutralize, and extracted with chloroform. The extract was washed successively with water, 10% aqueous sodium carbonate, and finally water. It was dried and concentrated leaving 28.1 g of the crude brosylate **5a**. The crude brosylate was recrystallized from ether affording three crops of colorless crystals: first crop, 10.5 g, mp 95–96.5°; second crop, 4.81 g, mp 94.5–95.0°; third crop 1.93 g, mp 94–96° (total yield 72%). A sample recrystallized from ether for elemental analysis melted at 97.0–97.8°.

Anal. Calcd for $C_{14}H_{17}O_4BrS$: C, 46.56; H, 4.71; Br, 22.13. Found: C, 46.35; H, 4.61; Br, 22.38.

The nmr spectrum ($CDCl_3$) of the brosylate revealed the following absorptions: 1.10–2.0 (m, 8 methylene ring protons), 3.56 and 3.81 (AB d of d,[44] 2, J_{AB} = 7.5 Hz, $-OCH_2C<$), 3.98 (s, 2, $-CH_2OBs$), 4.40 (broadened t, C-5 H), 7.76 (s, 4, aromatic protons).

(34) The argument would also be true if ionization of the carbon–oxygen bond to form a vibrationally excited cation preceded loss of the proton (or deuteron at C-4).

(35) S. J. Cristol, *J. Amer. Chem. Soc.*, **69**, 338 (1947); S. J. Cristol, N. L. Hause, and J. S. Meek, *ibid.*, **73**, 674 (1951); E. D. Hughes, C. K. Ingold, and J. B. Rose, *J. Chem. Soc.*, 3839 (1953); S. J. Cristol and F. R. Stermitz, *J. Amer. Chem. Soc.*, **82**, 4962 (1960); C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *ibid.*, **87**, 2421 (1965).

(36) A recent exception to this rule was recently reported by T. Cohen and A. R. Daniewski, *ibid.*, **91**, 533 (1969).

(37) Private communication. Unpublished results of Professor T. G. Traylor.

(38) All melting points and boiling points are uncorrected unless otherwise specified. The infrared spectra were determined on a Perkin-Elmer Model 621 grating spectrophotometer. Proton magnetic resonance spectra were determined on a Varian Model A-60 spectrometer. The chemical shifts are relative to tetramethylsilane used as an internal reference in the solvents cited. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Vapor phase chromatographic separations and analyses were effected using a Varian Aerograph Model 90-P gas chromatograph. Elemental analyses were performed by MHW Laboratories (Garden City, Mich.) or by Mr. C. F. Geiger (Ontario, Calif.). Deuterium analyses were performed by Josef Nemeth (University of Illinois) or mass spectrometrically by Mr. R. Steed (San Diego State College).

(39) R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **70**, 946 (1948).

(40) Calculated chemical shifts: see L. M. Jackman and S. Sternhell, *Int. Ser. Monogr. Org. Chem.*, **5**, 129 (1969).

(41) The highest field component of the "quartet" is partially obscured by the singlet at 3.54.

(42) The C-5 H proton (presumably a broadened triplet) appears as broadening in the base of this singlet.

(43) The highest field component of the "quartet" is partially obscured by the singlet at 3.51.

(44) The two peaks constituting the higher field doublet are slightly broadened by secondary coupling of undetermined origin. The chemical shifts are calculated.[40]

6-Oxabicyclo[3.2.1]octane-4-*d*-1-methyl *p*-Bromobenzenesulfonate (5b).—The deuterated brosylate **5b** was prepared from 1.61 g (0.0113 mol) of the deuterated oxabicyclic alcohol (**4b**) and 4.09 g (0.0160 mol) of *p*-bromobenzenesulfonyl chloride using the conditions previously described. The crude product (3.08 g) was light yellow in color, mp 85–89°. The pure brosylate was obtained after two recrystallizations from ether as 2.46 g (60%) of colorless needles, mp 96–98°. The nmr spectrum ($CDCl_3$) of **5b** showed the following absorptions: 1.24–2.15 (m, 7, methylene ring protons), 3.52 and 3.80 (AB d of d,[44] 2, J_{AB} = 7.5 Hz, $-OCH_2C<$), 3.97 (s, 2, $-OCH_2OBs$), 4.37 (broadened t, C-5 H), 7.71 (s, 4, aromatic protons). The mass spectrum (80 eV) showed the very weak but characteristic molecular ions as a two-peak isotopic "cluster" at *m/e* 363 and 361 (0.8). The complex fragmentation ions included major peaks at *m/e* 157 and 155 (11) 125 (68), and 112 (100). Using the intensities of the ions at *m/e* 125 (P + 1) and 124 (P), the per cent deuteration was calculated to be 94%. A similar estimate using intensities of the *m/e* 112 (P + 1) and 111 (P) ions led to a value of 92%. The result of combustion analysis of the deuterated brosylate **5b** (by Mr. Josef Nemeth) was 5.33 atom % excess which corresponds to 90.6% monodeuteration.

1-Acetoxymethyl-6-oxabicyclo[3.2.1]octane (6).—A mixture of 0.220 g (0.00155 mol) of 1-hydroxymethyl-6-oxabicyclo[3.2.1]-octane, 0.174 g (0.00214 mol) of anhydrous sodium acetate, and 2 ml of acetic anhydride was allowed to stand overnight at room temperature and then boiled under reflux for 2.5 hr. The mixture was diluted with 20 ml of water, allowed to stand for 2 days, and then extracted with ether. The extract was washed successively with water, 10% aqueous sodium carbonate, and water. It was dried and concentrated to 0.181 g of a yellow oil consisting of approximately 83% **6** and 17% of a side product later shown to be the diacetate **7a**. A pure sample of **6** was collected by preparative glc (5 ft × 0.25 in., 20% silicon oil on Chromosorb W column).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.78; H, 8.74.

The nmr spectrum of **6** ($CDCl_3$) revealed the following features: 1.20–2.00 (m, 8 methylene ring protons), 2.08 (s, 3, CH_3CO_2-), 3.68 and 3.88 (AB d of d,[40] 2, J_{AB} = 7.5 Hz, $-OCH_2C<$), 4.05 (s, 2, $-CH_2OAc$), 4.44 (broadened t, 1, C-5 H). The infrared spectrum of **6** ($CDCl_3$) showed a strong band at 1730 cm^{-1} (ester C=O).

4,4-Bis(acetoxymethyl)-1-cyclohexene (7a).—A mixture of 0.500 g (0.00352 mol) of 4,4-bis(hydroxymethyl)-1-cyclohexene, 0.785 g (0.00957 mol) of anhydrous sodium acetate, and 9 ml of acetic anhydride was heated at 110° for 4 hr. It was then diluted with 30 ml of water, stirred for 1.5 hr at room temperature, and extracted with ether. The ether extract was washed successively with water, 10% aqueous sodium carbonate, and water. It was dried and concentrated affording 0.689 g of a yellow oil. A 0.393-g sample of the crude product was distilled under vacuum through a short-path micro still (0.35 mm, pot temperature 50°). The first fraction was obtained as a colorless oil, 0.283 g, $n^{25}D$ 1.4646. A second fraction weighed 0.056 g (combined yield corrected for sample size distilled, 75%). An analytical sample was obtained by preparative glpc (5 ft × 0.25 in., 10% FFAP[45] on Chromosorb W).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.52; H, 8.02.

The nmr spectrum ($CDCl_3$) of **7a** showed the following absorptions: 1.40 to approximately 2.05 (m, 6 ring methylene protons), 2.05 (s, 6, $-O_2CCH_3$), 3.98 (s, 4, $-CH_2OAc$), 5.63 (broad s, 2, vinyl CH). The infrared spectrum ($CDCl_3$) of **7a** showed a strong band at 1730 cm^{-1} (ester C=O).

Acetolysis of 6-Oxabicyclo[3.2.1]octane-1-methyl *p*-Bromobenzenesulfonate.—The brosylate (17.5 g, 0.0485 mol), anhydrous sodium acetate (4.80 g, 0.0585 mol), and 455 ml of glacial acetic acid[46] were mixed in a round-bottom flask equipped with a condenser surmounted by a drying tube. The mixture was boiled under reflux for 369 hr. The mixture was cooled and the solution decanted from the precipitated sodium brosylate. To the solution were added, slowly, 238 g of sodium carbonate and 250 ml of water. This solution was subjected to manual and continuous ether extraction, affording 9.56 g of a yellow oil. This product mixture was redissolved in ether and washed with 10% aqueous sodium bicarbonate and water. It was dried and concentrated. Analysis of the reaction mixture by glpc using a 10% DEGS (diethylene glycol succinate) on Chromosorb W column (7 ft × 0.25 in.) with a column temperature of 158° and a flow rate of 46 cc/min revealed the presence of five compounds. The retention times in minutes measured from the air injection peak and percentages determined from ratios of integrated areas (shown in parentheses) are as follows: A, 11 (1.1); B, 13 (7.2); C, 17 (90.6); D, 34 (0.1); and E, 39 (0.9).

Glpc Collection of Acetolysis Products and Structural Characterizations.—The acetolysis products were collected using one or a combination of the following columns: 10% DEGS on Chromosorb W (7 ft × 0.25 in.), 20% DEGS on Chromosorb W (5 ft × 0.25 in.,), and 10% FFAP[44] (5 ft × 0.25 in.).

The nmr spectrum ($CDCl_3$) of compound A showed the following absorptions: 1.2–2.0 (broadened s, 8 ring methylene protons, 2.07 (s, 3, CH_3CC_2-), 2.33 and 2.41 (unsymmetrical[47] d, 2 ring methylene protons), 3.82 and 4.20 (AB d of d,[44] 2, J_{AB} = 8.5 Hz, $-OCH_2C<OAc$), 4.48 (broadened t, 1, C-5 H). The infrared spectrum of compound A ($CDCl_3$) showed strong bands at 1730 (ester C=O) and 1367 cm^{-1} (shoulder at 1377 cm^{-1}) (acetate CH_3). The mass spectrum (15 eV) of A shows a very weak molecular ion at *m/e* 184 and among the complex fragmentation ions an intense peak at *m/e* 124.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.08; H, 8.76. The structure assigned to A was **8** (see discussion under section titled Acetolyses).

The nmr spectrum of compound B showed the following absorptions: 1.15–2.00 (m, 10 ring methylene protons), 2.10 (s, 3, CH_3CO_2-), 4.02 and 4.18 (AB d of d,[40] 2, J_{AB} = 12 Hz, $-OCH_2C<OAc$), 4.47 (m, 1, C-5 H). The infrared spectrum of compound B ($CDCl_3$) showed a strong band at 1730 cm^{-1} (ester C=O) and a doublet at 1367 and 1387 cm^{-1} (acetate CH_3). The mass spectrum (15 eV) of B shows a molecular ion at *m/e* 184 and among the complex fragmentation ions an intense peak at *m/e* 124. The fragmentation patterns of A and B were quite similar.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.11; H, 8.71. The structure assigned to B was **9** (see discussion under section titled Acetolyses).

Compound C was identified as 1-acetoxymethyl-6-oxabicyclo-[3.2.1]octane (**6**) by comparison of its glpc retention time, nmr spectrum, and irspectrum with those of an authentic sample.

Compound E was identified as 4,4-bis(acetoxymethyl)-1-cyclohexene (**7a**) by comparison of its glpc retention time, nmr spectrum, and ir spectrum with those of an authentic sample.

Compound D could not be characterized because of insufficient sample size.

Acetolysis of 6-Oxabicyclo[3.2.1]octane-4-*d*-1-methyl *p*-Bromobenzenesulfonate.—The acetolysis was conducted as described for the acetolysis of the undeuterated brosylate starting with 2.46 g (0.00678 mol) of the deuterated analog **5b**. Using the same work-up procedure as previously described, 1.27 g of the solvolysis products were obtained as a yellow oil. Analysis of the reaction mixture by glpc using a 20% DEGS on Chromosorb W column (5 ft × 0.25 in.) with a column temperature of 162° and a flow rate of 46 cc/min revealed the presence of the five expected products. The retention times and relative percentages were as follows: A′, 13 (1.1); B′, 17 (6.7); C′, 20 (90.5); D′, 41 (0.2); and E′, 47 (1.4). The nmr spectrum ($CDCl_3$) of E′ (prime denotes deuterated analog) showed the following absorptions: 1.40 to approximately 2.05 (m, 6 ring methylene protons), 2.06 (s, 6, $-O_2CCH_3$), 3.99 (s, 4, $-CH_2OAc$), 5.63 (broadened s, approximately 1, vinyl CH). Careful comparisons of the integrated areas of this vinyl peak and the adjacent singlet at 3.99 indicated that E′ was approximately 45% monodeuterated. The intensities of the characteristic peaks in the mass spectrum (80 eV) at *m/e* 167 and 166 ($M^+ - CH_3CO_2H$) led to a value of 47% monodeuteration. The mass spectral analysis is probably accurate to within ±3%. The extent of deuteration determined above by nmr area integral comparisons is no better than ±5%.

Registry No.—**3**, 27025-13-4; **4a**, 21619-54-5; **4b**, 27025-15-6; **5a**, 27025-16-7; **5b**, 27025-17-8; **6**, 27025-18-9; **7a**, 27025-19-0; **8**, 27025-20-3; **9**, 27025-21-4.

(45) The abbreviation FFAP refers to "free fatty acid phase." It is a special reaction product from Carbowax 20M and 2-nitroterephthalic acid (see K. P. Dimrick, "G. C. Preparative Separations," Varian Aerograph, Palo Alto, Calif., 1966).

(46) Purified by treating with 1% by volume acetic anhydride and fractionally distilling.

(47) The higher field component of the "apparent doublet" is broadened through coupling of undetermined origin.

Base-Promoted Reactions of Epoxides. VI. Bicyclo[2.2.1]heptene and Bicyclo[2.2.2]octene Oxides[1,2a]

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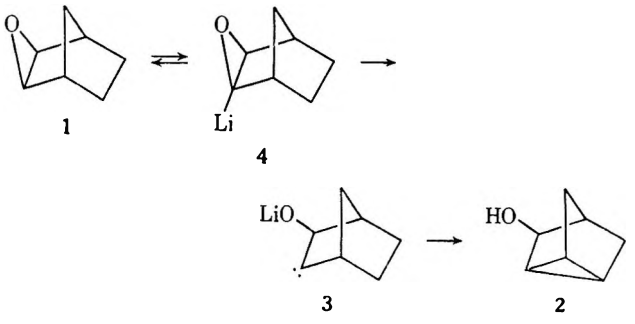
The details of the previously observed lithium diethylamide isomerization of 2,3-epoxybicyclo[2.2.1]heptane to nortricyclanol have been examined. By deuterium labeling methods, it has been shown that reversible metalation occurs at the epoxide ring and that base attack does not remove the exo hydrogens of the transannular bridge. These observations support a carbenoid mechanism for the rearrangement. The *endo*-5-methyl derivative **5** is transformed into the analogous tricyclic alcohol **7**, whereas epoxide **6**, with both transannular endo positions blocked with methyl groups, isomerizes to bicyclic ketone **9**. Bornylene oxide gives camphor, epicamphor, and tricyclic alcohols **13** and **14**. 2,3-Epoxybicyclo[2.2.2]octane gives ketone **19** along with minor amounts of tricyclic alcohol **20**. 2,3-Epoxybicyclo[3.3.0]octane yields allylic alcohol **25** as well as lesser amounts of ketones **23** and **24**. These results are used to outline the scope of the base-promoted isomerization of epoxides as a source of products derived from carbenoid insertion into transannular C–H bonds.

In connection with our interest in carbenoid reactions of epoxides,[3] we have reported on the base isomerization of *exo*-2,3-epoxybicyclo[2.2.1]heptane (**1**), which was found to rearrange smoothly to nortricyclanol (**2**).[4] The suggested mechanistic pathway for this transformation invoked carbene **3** or its carbenoid[5] equivalent as a key intermediate.[6] In the present work further aspects of the strong-base isomerization of 2,3-epoxybicyclo[2.2.1]heptanes and related epoxides have been examined.



1 4 3 2

Support for the proposed α-elimination–insertion reaction over a γ-elimination route was obtained by deuterium labeling techniques. Epoxide **1** specifically labeled with deuterium at the exo 5,6 positions was prepared from the corresponding olefin.[7] Isomerization of this material with lithium diethylamide yielded tricyclic alcohol **2** which retained all of the deuterium label as evidenced by nmr and mass spectral analysis. This result clearly demonstrates that γ elimination involving the more accessible exo hydrogens of the transannular carbons does not take place.

Direct evidence for metalation at the epoxide ring was secured by performing the isomerization in the presence of an excess of *N*,*N*-dideuteriocyclohexylamine. The reaction was halted prior to completion, and both the starting material and the product were examined for deuterium incorporation by nmr. In this fashion it was ascertained that recovered **1** had exchanged 83% of its epoxy protons while 69% deuterium was present at the carbinol position of alcohol **2**. This experiment shows unequivocally that the organolithium species **4** is generated reversibly during the course of the rearrangement, and it is most reasonable to assume that **4** is an intermediate on the mechanistic pathway to tricyclic alcohol **2**.[8] Taken together then, these experiments provide strong support for the carbenoid mechanism described above.

In order to determine if insertion could occur into a C–H bond more remote from the reactive center or possibly into a C–C bond,[9] methyl-substituted epoxides **5** and **6** were prepared and subjected to base treatment. The epoxides were synthesized by peracid oxidation of the corresponding bicyclo[2.2.1]heptenes of established stereochemistry and can be assigned the exo stereochemistry at the epoxy ring with confidence.[10] The monomethyl derivative **5** was isomerized to tricyclic alcohol **7** and two unidentified minor products. The structure of **7** follows from its spectroscopic properties and conversion to tricyclanone **8** by chromic acid oxidation.[11] Thus, the major reaction for **5** is analogous to that of **1**. Selective reaction at one of the epoxide carbons is in agreement with reversible metalation and selective insertion into the single C–H bond in the requisite position for reaction. This particular possibility is, of course, not available to the dimethyl derivative **6** in which both transannular endo hydrogens have been replaced by methyl groups. In this instance an entirely different type of transformation led to bicyclic

(1) Part V: J. K. Crandall and L. C. Lin, *J. Org. Chem.*, **33**, 2375 (1968).

(2) (a) Supported by a research grant from the National Science Foundation; (b) Alfred P. Sloan Research Fellow, 1968–1970; (c) National Science Foundation Undergraduate Research Participant.

(3) (a) J. K. Crandall and L. H. Chang, *J. Org. Chem.*, **32**, 435 (1967); (b) *ibid.*, **32**, 532 (1967); (c) J. K. Crandall and L. H. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526, 4527 (1967).

(4) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

(5) G. Köbrieh, *Angew. Chem., Int. Ed. Engl.*, **6**, 41 (1967).

(6) Independent examination of the simple carbene of this system has shown just this behavior: J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Amer. Chem. Soc.*, **89**, 1442 (1967); W. Reusch, M. W. DiCarlo, and L. Traynor, *J. Org. Chem.*, **26**, 1711 (1961).

(7) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Amer. Chem. Soc.*, **87**, 2596 (1965).

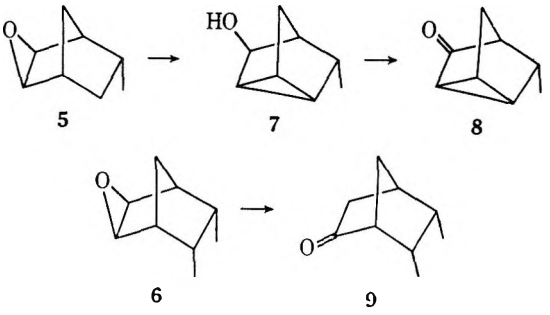
(8) The possibility that a reactive species may be formed but not lie along the reaction pathway has been emphasized: R. Breslow, *Tetrahedron Lett.*, 399 (1964). Irrelevant exchange of the epoxide hydrogens would allow for γ elimination with specific removal of an endo transannular proton by the base as a possible mechanism. See A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3915 (1967).

(9) Such a rearrangement has been reported for the copper-catalyzed decomposition of a diazo ketone of this ring system: P. Yates and S. Danishefsky, *ibid.*, **84**, 879 (1962).

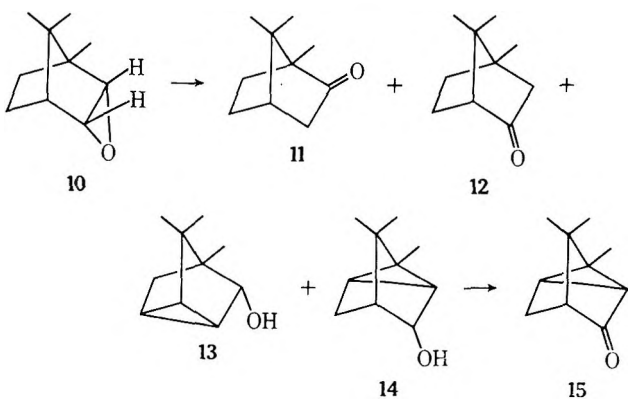
(10) The endo methyl substituents should increase the preference for exo epoxidation: H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).

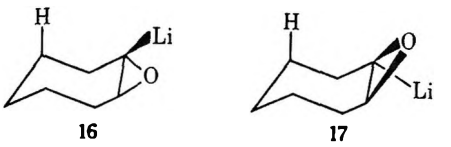
(11) B. C. Henshaw, D. W. Rome, and B. L. Johnson, *Tetrahedron Lett.*, 6049 (1968).

ketone **9** as the sole product. Similar base isomerizations of epoxides to ketones have been observed previously.[3] No evidence was obtained for products resulting from transannular insertion into the methyl C–H bonds or into the C–CH_3 bond. Failure to observe such products suggests that there may be severe restrictions on the insertion reaction.[12]



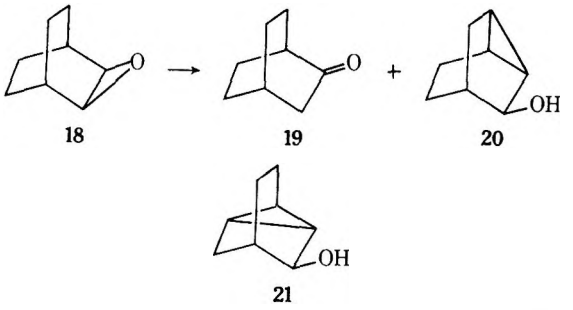
Attention was next focused on the influence of the epoxide stereochemistry by examining the reaction of bornylene oxide (**10**), a compound known to possess an endo epoxy group.[13] Four products were formed in the ratio of 41:33:12:16 under the usual reaction conditions. The first three of these materials were identified as camphor (**11**), epicamphor (**12**), and tricyclanol **13** by comparison with authentic samples. The remaining compound was assigned structure **14** on the basis of its spectroscopic properties and those of the corresponding ketone **15** which was obtained by chromic acid oxidation. Thus, transannular insertion can also ensue from base isomerization of an endo epoxide, although the major rearrangement pathway results in conversion of the epoxy function into a carbonyl group. Consequently, it is concluded that, although the exo configuration of the epoxide facilitates transannular reaction relative to ketone formation, it is not an absolute requirement in order for this transformation to proceed. This result has some bearing on earlier work[3a,14] with flexible systems, for example, cycloheptene oxide. It was suggested[3a] that the *observed specificity* for reaction through a transition state array as indicated in **16** (backside attack) over that of **17** (frontside attack) could have arisen owing to a stereoelectronic requirement for the former.[15] The present results appear to rule out such an argument, since **10** can only give tricyclic alcohols by way of a geometry analogous to **17**.





Thus, it seems that an alternate explanation[3a] based on conformational interactions in the respective transition states best accounts for the preference for **16** in flexible systems.

Reaction of 2,3-epoxybicyclo[2.2.2]octane[16] (**18**) also gave mainly the corresponding ketone **19**.[17] However, about 5% of *endo*-tricyclo[2.2.2.$0^{2,6}$]octan-3-ol[18] (**20**) was also isolated from the reaction mixture. None of the epimeric exo alcohol[18] (**21**) was found, although as little as 0.5% would have been detected. Interestingly, the less-strained bicyclic skeleton of **18** leads to less transannular reaction than its lower homolog **1**. A similar but less dramatic difference in reaction propensities is observed for the simple carbenes of these systems.[6,19] This effect is almost certainly a result of the greater distance between the reactive center and the transannular C–H bond.[20] A second point of concern is the preference for the production of alcohol **20** over **21**. In the more symmetrical bicyclo[2.2.2]octane system where both modes of transannular insertion can occur without substantial bias (the oxygen stereochemistry is the only important difference), the favored process is that corresponding to **17**, the unfavorable one for cycloheptene oxide. This observation confirms the conclusions drawn above and, in fact, points toward a preference for the "frontside" process when other things are equal.



Finally, the isomerization of *exo*-2,3-epoxybicyclo[3.3.0]octane[21] (**22**) yielded ketones **23** and **24** in addition to allylic alcohol **25** (14:10:76 ratio). The ketones were identical with authentic samples;[22] **25** was converted to the known saturated alcohol[23] for comparison. Noteworthy here is the absence of carbenoid

(12) A recent report notes a substantial predominance for reaction with a methine position (exo substituent) over a methylene group: E. J. Corey and R. S. Glass, *J. Amer. Chem. Soc.*, **89**, 2600 (1967).

(13) A. Suzuki, M. Miki, and M. Itoh, *Tetrahedron*, **23**, 3621 (1967).

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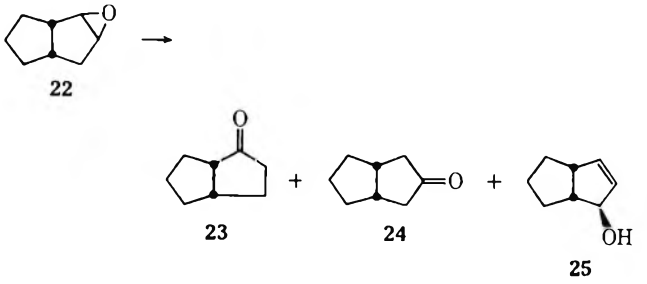
insertion products paralleling the reaction of the unadorned carbene.[24] The major product is derived from β elimination, normally an important pathway where not precluded by structural features.[3,25]



In summary, while the C–H insertion reaction proceeds cleanly in favorable cases, it appears to be restricted in scope to molecules with special geometric features. A guide for predicting where this reaction mode will obtain is the behavior of the corresponding carbene generated by conventional means. In instances where transannular reactions are not effective and β elimination is impossible, base rearrangement of epoxides produces isomeric ketones. This transformation has been discussed previously,[3] but experimental evidence bearing on the mechanism of this interesting rearrangement is unavailable as yet.

Experimental Section

General.—Nuclear magnetic resonance (nmr) spectra were taken in carbon tetrachloride solution with tetramethylsilane as internal standard with Varian A-60 or HA-100 spectrometers. Infrared spectra (ir) were obtained with Perkin–Elmer Model 137 and 137G Infracord spectrophotometers on neat samples, unless otherwise noted. Gas chromatography (glpc) was performed on Aerograph A600, A1200 (analytical, hydrogen flame detector), and A700 (preparative) instruments. Analytical columns were 10 ft × $^3/_8$ in. 15% Carbowax 20M on 60–80 Chromosorb W; preparative columns were 20 ft × $^3/_8$ in. 15% SE-30 or 20 ft × $^3/_8$ in. 15% Carbowax on 60–80 Chromosorb W. Percentage composition data were estimated by peak areas and are uncorrected. Anhydrous magnesium sulfate was used for all drying operations. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind., and Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Preparation of Epoxides.—Epoxides were prepared by the buffered peracetic acid method.[3] The following epoxides were prepared by this method.

2,3-Epoxy-*cis*-bicyclo[3.3.0]octane (90% yield) was shown by glpc to contain 13% of the endo and 87% of the exo epoxide.[21] Separation by preparative glpc gave the pure endo isomer [ir 9.6, 9.8, 10.9, and 11.8 μ; 100-MHz nmr δ 1.1–2.2 (m, 8), 2.41 (m, 2, bridgehead CH), 3.22 (broad s, 1, epoxide CH), and 3.31 (broad s, 1, epoxide CH)] and the pure exo isomer (**22**) [ir 9.8, 9.9, 10.8, and 11.9 μ; 100-MHz nmr δ 1.1–1.9 (m, 7), 2.0–2.7 (m, 3), 3.12 (d, 1, J = 2 Hz, epoxide CH), and 3.28 (t, 1, J = 2 Hz, epoxide CH)].

2,3-Epoxybicyclo[2.2.2]octane (**18**) was prepared in 82% yield: ir (CCl_4) 8.1, 10.5, 11.6, and 11.8 μ; nmr δ 1.4–1.8 (m, 8), 2.04 (m, 2, bridgehead CH), and 3.05 (broad s, 2, epoxide CH).[16]

exo-2,3-Epoxy-*endo*-*cis*-5,6-dimethylbicyclo[2.2.1]heptane (**6**) was prepared from the corresponding olefin[26] (71% yield): bp 107–112° (20 mm); mp 75–77°; ir (CCl_4) 3.27, 9.9, and 11.7 μ; nmr δ 0.90 (d, 6, CH_3), 0.97 (broadened AB quartet, 2, $\Delta\nu$ = 37 Hz, J = 9 Hz, CH_2), 2.2 (m, 2), 2.25 (m, 2), and 3.04 (s, 2, epoxide CH).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.5; H, 10.2.

exo-2,3-Epoxy-*endo*-5-methylbicyclo[2.2.1]heptane (**5**) was prepared from *endo*-5-methylbicyclo[2.2.1]hept-2-ene in 87% yield: bp 88–90° (100 mm); mp 50.5–52°; ir 3.27, 9.9, and 11.7 μ; nmr δ 0.5–2.0 (m, 5), 1.02 (d, 3, J = 7 Hz, CH_3), 2.21, 2.35 (broad s, 2, bridgehead protons), and 3.02 (m, epoxide CH).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.1; H, 9.6.

***endo*-5-Methylbicyclo[2.2.1]hept-2-ene.**—A modification of the literature procedure was utilized.[27] Ethyl bicyclo[2.2.1]hept-2-ene-*endo*-5-carboxylate was obtained from the highly stereoselective aluminum chloride catalyzed Diels–Alder reaction of ethyl acrylate and cyclopentadiene.[28] This was reduced with lithium aluminum hydride to the alcohol, converted to the crystalline *p*-toluenesulfonate (mp 42–44°), and reduced again with lithium aluminum hydride to give the desired olefin.[27]

Bicyclo[2.2.2]oct-2-ene.—The decarboxylation procedure of Cimarusti and Wolinsky[29] was used. After oxygen was bubbled through 20 ml of pyridine (distilled from BaO) for 20 min, 2.00 g of dried bicyclo[2.2.2]octane-2,3-dicarboxylic acid[17] and 15.0 g of lead tetraacetate (dried over KOH *in vacuo*) were added, and the flask was immersed in an oil bath maintained at 65°. The mechanical stirrer was started and after 2 min a vigorous evolution of carbon dioxide was observed. The mixture was heated for 5 min after all evidence of gas evolution had ceased, then removed from the bath, and cooled to room temperature. The mixture was poured into excess dilute nitric acid and extracted with ether. The ether was washed with saturated sodium bicarbonate solution, saturated salt solution, and dried. Removal of the solvent gave a light yellow oil which was placed on 30 g of Merck neutral alumina and eluted with pentane to yield 0.66 g (60%) of bicyclo[2.2.2]octene as a volatile white solid, mp 109–111° (lit.[30] 111–112°).

Bornylene Oxide (**10**).—The epoxide was prepared from α-pinene following the literature procedure, mp 169–171° (lit.[31] 170–171°).

***exo*-2,3-Epoxybicyclo[2.2.1]heptane-*exo*-5,5-d_2.**—The catalytic reduction of 46 g of norbornadiene with deuterium gas was performed according to the procedure of Arnold.[7] The crude product was fractionated on a spinning-band column to give a 9.5-g fraction boiling at 95–101°. Eight grams of this material was epoxidized by the standard procedure, the solvent was removed by distillation through a Vigreux column, and the residue was sublimed to give 2.1 g of volatile epoxide. A pure sample was obtained by preparative glpc. The nmr spectrum integrated for two less protons in the δ 1.0–1.6 ppm region when compared with the spectrum of undeuterated material but was otherwise identical. Analysis by mass spectrometry indicated the following distribution of deuterated species: 4.0% d_1, 94.6% d_2, and 1.4% d_3.[32]

Rearrangement of *exo*-2,3-Epoxybicyclo[2.2.1]heptane-*exo*-5,6-d_2.—The crude product from the previous experiment (1.5 g) was treated with lithium diethylamide according to the usual procedure to yield 0.85 g of a white solid which was purified by preparative glpc to give nortricyclanol (**2**), mp 109–110°. The nmr spectrum was identical with that of an authentic sample except for changes in the δ 1.0–1.5 ppm region which integrated for four protons rather than six. Mass spectral examination of this material showed the following distribution of deuterated species: 4% d_1, 95% d_2, and 1% d_3.[32]

Dideuteriocyclohexylamine.—Cyclohexylamine (270 ml) and deuterium oxide (108 ml) were stirred under a nitrogen atmosphere for 3 hr, 200 ml of benzene was added, and the benzene–water azeotrope was removed by distillation. This procedure was repeated twice more. The remaining benzene was removed and the product purified by distillation through a spinning-band column to yield 250 ml (92%) of a colorless liquid, bp 132–133°.

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(32) We thank Drs. P. J. Kropp and J. H. Collins of Procter and Gamble for this measurement.

Nmr integration indicated 93% replacement of the amino hydrogens.

Rearrangement of Norbornene Oxide.—To a predried flask cooled to 0° under a nitrogen atmosphere was added 9.2 g of dideuteriocyclohexylamine in 50 ml of benzene and 3.75 ml of 1.6 *M* *n*-butyllithium solution in hexane. After stirring for 30 min, the ice bath was removed, a solution of 1.0 g of norbornene oxide in 10 ml of benzene was added, and the reaction mixture was heated to reflux for 12 hr. The mixture was cooled and poured into water, the layers were separated, and the aqueous layer was extracted with ether. The organic portions were washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, water, and dried. Glpc analysis showed that 60% rearrangement to nortricyclanol had occurred. The remaining starting material and rearranged product were collected by glpc. The deuterium content of recovered norbornene oxide was determined by nmr which showed a slightly simplified spectrum and integrated for 17% hydrogen in the epoxide ring. The rearranged product, nortricyclanol, was similarly shown to contain 31% hydrogen at the carbinol position.

A model experiment with dideuterioamine alone showed that no hydrogens were exchanged on norbornene oxide. Similarly, lithium deuteriocyclohexylamide did not exchange either the carbinol or cyclopropyl hydrogens of nortricyclanol.

General Procedure for Rearrangement of Epoxides by Lithium Diethylamide.—To a predried flask cooled to 0° under a nitrogen atmosphere was added 2.5 equiv of diethylamine in anhydrous ether and 2.5 equiv of 1.6 *N* *n*-butyllithium in hexane solution. After stirring for 15 min, a solution of 1 equiv of the appropriate epoxide in anhydrous ether was added, the ice-bath was removed, and the solution was heated to reflux for the specified time or until the starting material was consumed. The reaction mixture was cooled and quenched carefully with water, and the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with 1 *N* hydrochloric acid, saturated sodium bicarbonate solution, water, and dried. The solvent was removed by distillation and the residue purified by distillation. If the product was a mixture, further purification was performed by preparative glpc.

Rearrangement of 5.—The rearrangement was carried out on 1.0 g of **5** in benzene. Glpc examination of the crude product showed one major product accounting for 95% of the volatile material. Two minor peaks constituted the remainder but were not separated or identified other than noting absorption for OH and C=O (5.73 μ, probably bicyclo[2.2.1]heptanone)[33] in the ir. The major product was collected by preparative glpc and assigned as *syn*-5-methyltricyclo[2.2.1.$0^{2,6}$]heptan-*anti*-3-ol (**7**):[11] ir 3.0, 3.3, 9.2, 9.3, 9.6, 9.7, 12.3, and 12.4 μ; nmr δ 0.92 (d, 3, CH_3), 1.0–2.0 (m, 7), 4.10 (broad s, 1, CHOH), and 4.39 (s, 1, OH).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.1; H, 10.0.

Oxidation with chromic acid in acetone gave *syn*-5-methyltricyclo[2.2.1.$0^{2,6}$]heptan-3-one:[11] ir 5.68, 8.7, 8.9, 11.6, and 11.9 μ; 2,4-DNP, mp 190.5–191° (lit.[11] mp 192–194°).

Rearrangement of 6.—**6** (1 g) was treated in the usual fashion in 50 ml of ether. The crude product (0.91 g) was shown to be greater than 95% one product by glpc. Sublimation gave a pure sample assigned as *endo-cis*-5,6-dimethylbicyclo[2.2.1]heptan-2-one (**9**): mp 65–65.5°; ir (CCl_4) 5.73 μ;[33] nmr δ 0.78 (d, 3), 0.89 (d, 3), 1.66 (s, 2), 1.86 (m, 2), and 2.30 (m, 4).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.3; H, 10.1.

Rearrangement of 10.—Refluxing 1.33 g of **10** in 40 ml of benzene for 12 hr according to the normal procedure gave 1.05 g (79%) of a yellow oil. Glpc analysis indicated the presence of four components which were isolated by preparative glpc in a ratio of 41:33:12:14. The two major components were identified as camphor (**11**) and epicamphor (**12**), respectively, by comparison with authentic samples.

The third product (12%) was identified as *endo*-isocyclanol (**13**) by comparison with an authentic sample:[34] 100-MHz nmr δ 0.79 (s, 3), 0.81 (s, 6), 1.10 (m, 3), 1.47 (AB quartet, 2, $\Delta\nu$ = 30 Hz, J = 11 Hz), 3.06 (s, 1, OH), and 3.70 (s, 1, CHOH).

The fourth product (14%) was assigned as *endo*-1,7,7-trimethyltricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (**14**): mp 56–58°; ir (CCl_4) 2.76, 3.00, 3.28 (cyclopropyl CH),[35] and 9.6 μ (broad); 100-MHz nmr δ 0.84 (s, 3), 0.90 (s, 3), 1.00 (s, 3), 1.30 (m, 3), 1.68 (broad s, 2), 2.07 (s, 1, OH), and 4.12 (t, 1, J = 2 Hz, CHOH).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.2; H, 10.9.

When the same reaction was conducted at room temperature for 12 hr, glpc analysis indicated the same four products were formed in a ratio of 35:26:24:15.

Oxidation of 14.—To an ice-cold solution of 70 mg of glpc purified **14** in 10 ml of acetone was added dropwise with stirring 1.6 ml of 0.67 *N* chromic solution. The reaction mixture was stirred until the acetone layer became clear, poured into water, and extracted with ether. The combined extracts were washed with water, saturated sodium bicarbonate solution, water, and dried. Distillation of the solvent gave 55 mg of crude solid. Isolation by preparative glpc gave 1,7,7-trimethyltricyclo-[2.2.1.$0^{2,6}$]heptan-3-one (**15**) as a white solid: mp 97.5–100°; ir (CCl_4) 5.68 μ;[33] 100-MHz nmr δ 0.97 (s, 6), 1.00 (s, 1), 1.12 (s, 3), 1.31 (s, 1), and 1.5–2.0 (m, 3).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.8; H, 9.2.

Rearrangement of 18.—Isomerization of 1.00 g of **18** in refluxing ether for 20 hr gave 0.95 g (95%) of a yellow solid. Analysis by glpc indicated two products in a ratio of 95:5. Column chromatography using 50 g of Merck neutral alumina (activity I) and pentane–ether as eluent separated the two components easily. The major product was identified as bicyclo[2.2.2]-octan-2-one (**19**): mp 177–178° (lit. 178–179°); ir compares with the published spectra;[17] nmr δ 1.6–1.9 (m, 7) and 2.0–2.3 (m, 5).

The minor product was identified as *endo*-tricyclo[2.2.2.$0^{2,6}$]-octan-3-ol (**20**) by comparison with an authentic sample. None of the epimeric alcohol **21** was detectable in the crude reaction mixture by nmr; less than 0.5% was present by glpc.

Tricyclo[2.2.2.$0^{2,6}$]octan-3-ol.—A mixture of 0.842 g of tricyclo-[2.2.2.$0^{2,6}$]octan-3-one[36] and 4.0 g of sodium metal in 35 ml of absolute ethanol was refluxed for 19 hr. The mixture was diluted with 30 ml of 95% ethanol, poured into 200 ml of water, and extracted with ether. The ether layer was dried and concentrated to give 1.5 g of crude yellow liquid of which 1.0 g was placed on 80 g of Merck neutral alumina. Elution with increasing amounts of ether in pentane afforded 70 mg of unreacted ketone, 100 mg of pure *exo*-tricyclo[2.2.2.$0^{2,6}$]octan-3-ol[18] (**21**) [mp 154–156° (lit. 156.5–158.2°); ir identical with the published spectra; nmr δ 0.7–2.1 (m, 10), 3.02 (s, 1, OH), and 4.30 (broad m, 1, CHOH)], 290 mg of a mixture of alcohols, and 50 mg of pure *endo*-tricyclo-[2.2.2.$0^{2,6}$]octan-3-ol[18] (**20**) [mp 124–126° (lit.125–127.1°); ir identical with that reported; 100-MHz nmr δ 0.7–2.1 (m, 11) and 3.83 (s, 1, CHOH)].

Rearrangement of 22.—Refluxing 0.5 g of **22** in an ethereal solution of lithium diethylamide for 48 hr gave a 72% yield of a colorless liquid. Analysis by glpc indicated the presence of three products in a ratio of 14:10:76. The minor products were identified as *cis*-bicyclo[3.3.0]octan-2-one (**23**) and *cis*-bicyclo[3.3.0]-octan-3-one (**24**) by comparison of glpc retention times and ir data with those of authentic samples.[22] The major product was identified as *exo-cis*-bicyclo[3.3.0]octen-2-ol (**25**): ir 3.05, 3.31, and 6.15 μ; nmr δ 1.2–1.7 (m, 6), 2.38 (m, 1, bridgehead CH), 3.23 (m, 1, allylic bridgehead CH), 4.30 (m, 1, CHOH), 4.57 (broad s, 1, OH), and 5.62 (broad s, 2, olefinic CH).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.3; H, 9.6.

Hydrogenation of 120 mg of **25** in methanol using Adams catalyst gave *exo*-bicyclo[3.3.0]octan-2-ol identical with an authentic sample.[23]

Registry No.—**1**, 3146-39-2; **5**, 27141-82-8; **6**, 27141-83-9; **7**, 27141-84-0; **9**, 27141-85-1; **14**, 27141-86-2; **15**, 27150-45-4; *exo*-**22**, 24454-42-0; *endo*-**22**, 24454-41-9; **25**, 27141-89-5.

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Synthesis and Photolysis of Some Substituted Quinoxaline Di-*N*-oxides[1]

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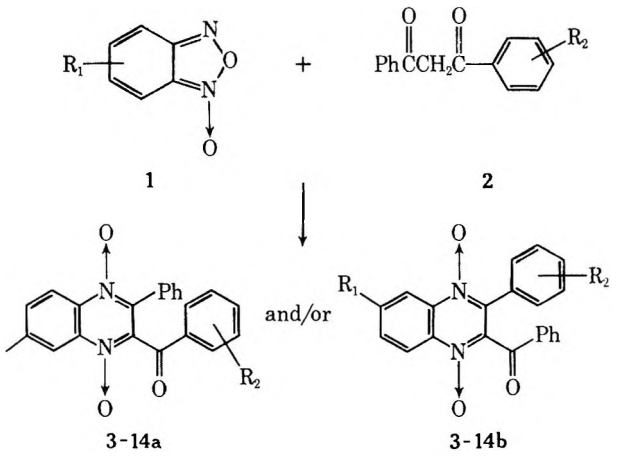
This paper reports qualitative studies of substituent effects on the scope of the reaction of benzofurazan oxide with aroylacetophenones to form quinoxaline di-*N*-oxides, as well as the photochemical rearrangements of the latter compounds to 1,3-diaroylbenzimidazolones. Mechanistic possibilities for these two transformations are discussed.

In a previous report[2] we have shown that benzofurazan oxide (**1**) reacted with enolate anions to give quinoxaline di-*N*-oxides. For example, benzofurazan oxide (**1**, R_1 = H) reacted with diaroylmethanes (**2**, R_2 = H) in the presence of amines to give 2-phenyl-3-benzoylquinoxaline di-*N*-oxide (**3a,b**, $R_1 = R_2$ = H). With unsymmetrical 1,3 diketones, this reaction could conceivably yield one or two isomeric quinoxaline di-*N*-oxides.

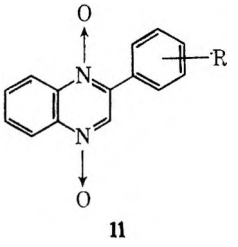


The purpose of this work was twofold: first, to investigate whether ortho or para substituents in 1,3-diaroylmethanes, and/or whether substituents in benzofurazan oxide, would have a directive, effect in controlling the nature of the product(s) of this reaction; second, to study the generality of the photolytic rearrangement of the products of the reaction, namely, 2-aryl-3-aroylquinoxaline di-*N*-oxides, to 1,3-dibenzoylbenzimidazolones.

Synthesis.—The specific substituted aroylacetophenone and benzofurazan oxide were dissolved in warm diethylamine, the solution was allowed to stand at room temperature, and the precipitated product was collected (Table I).

It was found that two isomeric quinoxaline di-*N*-oxides **a** and **b** (**4a,b**; **5a,b**; **6a,b**; **7a,b**) were obtained from *para*-substituted aroylacetophenone **2** (R_2 = *p*-Br, *p*-OCH_3, *p*-CH_3, *p*-NO_2) and benzofurazan oxide, respectively. ortho-Substituted aroylacetophenone **2** (R_2 = *o*-CH_3, *o*-OCH_3) each gave a single product, namely, 2-phenyl-3-(*o*-methylbenzoyl)quinoxaline di-*N*-oxide (**8a**) and 2-phenyl-3-(*o*-methoxybenzoyl)quinoxaline di-*N*-oxide (**9a**), respectively. *o*-Nitrobenzoylacetophenone (**2**, R_2 = *o*-NO_2) yielded (2-*o*-nitrophenyl)-3-benzoylquinoxaline di-*N*-oxide (**10b**) and 2-phenyl-3-(*o*-nitrobenzoyl)quinoxaline di-*N*-oxide (**10a**). Attempts to separate these isomeric mixtures by column chromatography were unsuccessful; integration of the nmr signals of the methyl groups in **5a,b** and of the methoxy groups in **6a,b** indicated that isomers **a** and **b** were formed in about the same amount.

The following experiments support the structural assignments of the above di-*N*-oxides. Cleavage of quinoxaline di-*N*-oxides **8a** and **9a** with methanolic potassium hydroxide yielded 2-phenylquinoxaline di-*N*-oxide (**11**, R = H) as the sole product, the identity of which was established by comparison with an authentic sample.[1] On the other hand, cleavage of the isomeric mixtures of quinoxaline di-*N*-oxides **4a,b**, **5a,b**, **6a,b**, **7a,b**, and **10a,b** with methanolic potassium hydroxide yielded a mixture of **11** (R = H) and 2-phenyl-substituted quinoxaline di-*N*-oxides (**11**, R = *p*-Br, *p*-CH_3, *p*-OCH_3, *p*-NO_2, and *o*-NO_2). These mixtures, after recrystallization, showed a wide range in melting points, and their infrared spectra displayed bands at 800–825 (para-substituted phenyl), and at 760–780 cm^{-1} (ortho-substituted phenyl). The formation of quinoxaline di-*N*-oxides **5a,b** and **6a,b** was confirmed by their nmr spectra. Products **5a,b** showed two peaks at τ 6.26 and 6.34 as expected for two different methoxy groups. Similarly, quinoxaline di-*N*-oxides **6a,b** displayed two peaks for two methyl groups at τ 7.62 and 7.70. The nmr spectra of **8a** and **9b** each exhibited a single band at τ 7.6 and 6.4, respectively.



Additional structural information came from infrared spectra which showed a characteristic band of aromatic *N*-oxides at 1320–1330 cm^{-1}, and nmr spectra which displayed two multiplets centered at τ 1.3 and 2.4, where the τ 1.3 multiplet is consistent with the expected considerable deshielding of the aromatic protons at positions 5 and 8.

From the above findings, it appears that, whereas para substituents in aroylacetophenones have no directive effect that would control the nature of the product, ortho substituents seem to favor the formation of a single product. The selectivity of the latter can be explained by postulating species **15** as an intermediate

(1) Abstracted in part from the M.S. Thesis of Mr. G. Agopian, American University of Beirut, June 1968.

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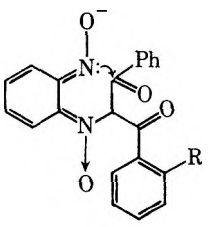
TABLE I[a]

Quinoxaline di-*N*-oxide	R_1	R_2	Mp, °C	% yield	Infrared, cm^{-1}	Nmr, τ (multiplicity)
4a,b	H	*p*-Br	222–224 dec	60	1675, 1585, 1340, 1250, 1090, 900, 875, 805, 765, 680	1.3 (m) 2.36 (m)
5a,b	H	*p*-OCH_3	197–198 dec	47	1670, 1600, 1340, 1250, 1170, 1090, 1025, 900, 875, 760, 680	1.24 (m) 2.64 (m) 6.26 (s) 6.34 (s)
6a,b	H	*p*-CH_3	217–218 dec	54	1670, 1600, 1335, 1240, 1090, 900, 870, 800, 760, 690	1.36 (m) 2.36 (m) 7.62 (s) 7.70 (s)
7a,b	H	*p*-NO_2	204–205 dec	62	1680, 1600, 1580, 1520, 1345, 1280, 1235, 1090, 1000, 905, 870, 770, 725, 690	1.32 (m) 2.20 (m)
8a	H	*o*-CH_3	223–225 dec	52	1670, 1600, 1510, 1345, 1220, 1090, 1000, 890, 877, 780, 750, 700, 670	1.32 (m) 2.60 (m) 7.60 (s)
9a	H	*o*-OCH_3	217–218 dec	40	1650, 1600, 1518, 1345, 1250, 1160, 1010, 900, 875, 760, 710, 665	1.32 (m) 2.60 (m) 6.40 (s)
10a,b	H	*o*-NO_2	127–129 dec	57	1675, 1600, 1525, 1340, 1170, 1075, 880, 850, 790, 705, 690	1.32 (m) 2.32 (m)
11a,b	CH_3	H	220–228	34	1675, 1335, 1100, 888, 845, 820, 775, 740, 700	1.6 (m) 2.2 (m) 2.6 (m) 7.4 (s)
12a,b	OCH_3	H	221–224	36	1670, 1610, 1595, 1330, 1245, 900, 885, 770, 710, 700, 655	1.4 (d) 2.2 (m) 2.8 (s) 6.0 (s)
13a,b	Cl	H	211–216	31	1680, 1590, 1580, 1400, 1335, 1310, 1230, 1100, 890, 840, 760, 700, 670	1.4 (m) 2.8 (m) 2.6 (m)
14	6,7-Dimethyl	H	240–242	46	1675, 1335, 1180, 1160, 893, 830, 740, 690	1.56 (s) 1.64 (s) 2.6 (m) 7.5 (s)

[a] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds, and mixtures of isomers, in the table except for the mixture of **7a,b** (Calcd: C, 65.11. Found: C, 63.10.).

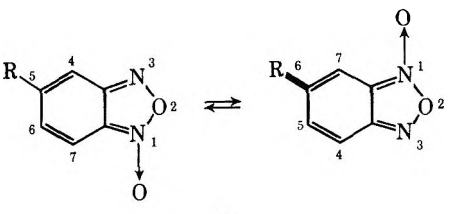
in the reaction. Ring closure in this intermediate is more feasible *via* an attack on the carbonyl group at-



15

tached to the phenyl group that carries no ortho substituent, a process that entails minimum steric hindrance. Such interaction is absent in the case of para-substituted aroylacetophenones; therefore, no selectivity was observed. The formation of a mixture of **10a** and **10b** from **2** (R_2 = *o*-NO_2) is not easy to explain; yet it is plausible that the inductive effect of the *o*-nitro group activates the neighboring carbonyl group to an extent that this effect counterbalances the steric effect.

The reaction of substituted benzofurazan oxide with 1,3-dibenzoylmethane could give rise to one or two quinoxaline di-*N*-oxides. Two obvious factors might contribute to the determination of the nature of the product(s). First, the structure of the substituted benzofurazan oxide. It has been shown by Katritzky,[3] *et al.*, that tautomerism in substituted benzofurazan oxides is rather facile. Nmr evidence indicated that electron-acceptor groups favored the 6 position, and electron-donor groups the 5 position (**16**). It is clear



16

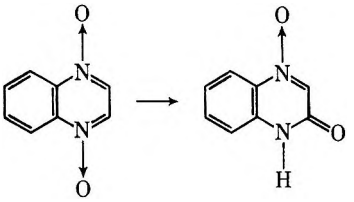
(3) A. R. Katritzky, S. Øksne, and R. K. Harris, *Chem. Ind. (London)*, 990 (1961); A. J. Boulton, A. R. Katritzky, M. J. Sewell, and B. Wallis, *J. Chem. Soc. B*, 914 (1967).

that a reaction of substituted benzofurazan oxide could involve either or both tautomers. Assuming that a substituted benzofurazan oxide reacted with 1,3-dibenzoylmethane by a single mode of reaction (see below), two quinoxaline di-*N*-oxides would result if both tautomers took part in the reaction and one product would be obtained if only one tautomer reacted.

The second factor involves the mode by which the enolate anion attacks the substituted benzofurazan oxide. Essentially, the question is whether the enolate anion attacks nitrogen 1 or/and nitrogen 3 (the latter mode of attack is analogous to a 1,4-addition reaction). Although a specific attack on nitrogen 1 with a synchronous cleavage of the N_1–O_2 bond would result in a relief of strain in the five-membered ring, the mechanism of this reaction is not discernible at this point. The ease of cleavage of the N_1–O_2 bond is apparent from the facile tautomerism of benzofurazan oxides.

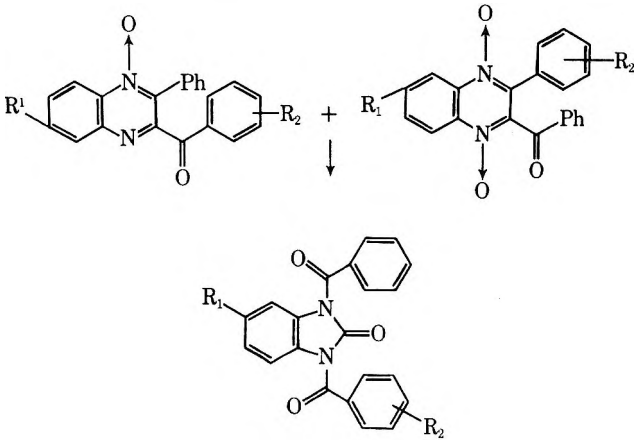
The reaction of 5(6)-substituted benzofurazan oxide (**1**, R_1 = CH_3, OCH_3, Cl) with 1,3-dibenzoylmethane resulted in the formation of quinoxaline di-*N*-oxides **11a,b**, **12a,b**, and **13a,b** which, after recrystallization, melted over a range of temperature and therefore indicated the formation of a mixture of the possible isomers **a** and **b**. 5,6-Dimethylbenzofurazan oxide gave 2-phenyl-3-benzoyl-6,7-dimethylquinoxaline di-*N*-oxide (**14**). The structures of the above products were established by elemental analysis and spectroscopic data (see Table I).

Photolysis.—The photochemical reactions of aromatic amine oxides have recently been the subject of intensive investigations.[4a] Little is known about the photochemical reactions of quinoxaline di-*N*-oxides. Landquist[4b] briefly reported the photolysis of quinoxaline di-*N*-oxide (**27**) to yield 2-quinoxalone 4-*N*-oxide (**28**).



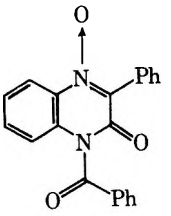
27 **28**

We have shown that 2-phenyl-3-benzoylquinoxaline di-*N*-oxide, when irradiated in methanol, rearranged into 1,3-dibenzoylbenzimidazolone in good yield.[5] In this study, the generality of this novel rearrangement was examined. The irradiation of 2-aryl-3-aroylquinoxaline di-*N*-oxides **4a,b**, **5a,b**, **6a,b**, **7a,b**, **8a,b**, **9a**, **11a,b**, **12a,b**, **13a,b**, and **14** in methanol yielded the corresponding 1,3-diaroylbenzimidazolones listed in Table II (**17**–**26**).



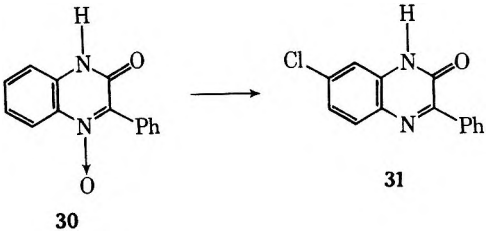
The progress of the reaction was monitored by thin layer chromatography. The yields were fair to good. Quinoxaline di-*N*-oxides **10a** and **10b** did not give the corresponding benzimidazolone and, instead, decomposed into an intractable tarry material. The decomposition of these reactants could probably be due to the intramolecular interaction of ortho nitrochromophore with the carbonyl group.[6]

The mechanism proposed for the above rearrangement[5] involved **29** as an intermediate.



29

In one unsuccessful attempt to prepare **29**, 3-phenyl-2(1*H*)-quinoxalone 4-oxide[7] (**30**) was treated with benzoyl chloride in pyridine. This reaction did not yield **29** but gave 3-phenyl-7-chloro-2(1*H*)-quinoxalonone (**31**) in high yield. This transformation is analogous to that reported by Ahmad, *et al.*[8] Other approaches to the synthesis of **29** are in progress. The elusiveness of **29** to synthesis is not surprising in the light of the recent findings of Curtin and Englemann who have shown that the O- or N-benzoylation of 5(6*H*)-phenanthrolinone are effected under strict conditions.[9]



30 **31**

In conclusion, it was shown that para substituents in aroylacetophenones and monosubstituents in benzofurazan oxides have no directive effect on the resulting quinoxaline di-*N*-oxides, while ortho substituents in aroylacetophenones do have such an effect. The photolysis of a number of 2-aryl-3-aroylquinoxaline di-*N*-oxides to yield unsymmetrical 1,3-diaroylbenzimidazolones was shown to be a general reaction and a simple method for the preparation of 1,3-benzimidazolone derivatives.

(4) (a) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970); (b) J. K. Landquist, *J. Chem. Soc.*, 2830 (1953).

(5) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 753 (1967).

(6) G. M. J. Schmidt in "Reactivity of Photoexcited Organic Molecule," Interscience, London, 1967, pp 227–284.

(7) G. Tennant, *J. Chem. Soc.*, 2666 (1964).

(8) Y. Ahmad, M. S. Habib, Ziauddin, and N. Bashir, *Bull. Chem. Soc. Jap.*, **38**, 1654 (1965).

(9) D. Y. Curtin and J. H. Engelmann, *Tetrahedron Lett.*, 3911 (1968).

TABLE II[a]

Quinoxaline di-*N*-oxide	Photolysis time	Diaroylbenzimidazolone	R_1	R_2	Mp, °C	% yield	Infrared, cm^{-1}
4a,b	45 min	**17**	H	*p*-Br	225	50	1743, 1700, 1335, 1160, 1050, 845, 753, 720, 700
5a,b	1 hr	18	H	*p*-CH_3	214	55	1740, 1693, 1600, 1330, 1300, 1255, 1160, 1050, 1030, 910, 850, 760, 720, 675
6a,b	45 min	**19**	H	*p*-OCH_3	226	40	1750, 1700, 1600, 1520, 1335, 1160, 1050, 865, 830, 775, 700, 667
7a,b	45 min	**20**	H	*p*-NO_2	208	20	1750, 1700, 1600, 1520, 1335, 1160, 1050, 865, 830, 775, 700, 667
8a	2 hr	**21**	H	*o*-CH_3	154	40	1745, 1700, 1330, 1160, 1040, 900, 835, 793, 760, 700, 670
9a	1 hr	**22**	H	*o*-OCH_3	211	45	1765, 1680, 1600, 1340, 1250, 1160, 1025, 750, 700, 670
11a,b	2 hr	**23**	CH_3	H	224–225	33	1750, 1700, 1600, 1500, 1320, 1190, 1150, 1050, 1020, 930, 820, 750, 720, 710, 695, 680
12a,b	2 hr	**24**	OCH_3	H	209–211	18	1780, 1690, 1600, 1490, 1320, 1170, 1050, 1020, 860, 840, 800, 750, 720, 700, 670
13a,b	1 hr	**25**	Cl	H	194–196	33	1750, 1700, 1600, 1485, 1320, 1160, 1050, 1020, 910, 820, 790, 750, 700, 615, 610
14	2 hr	**26**	5,6-Dimethyl	H	221–223	25	1755, 1690, 1490, 1320, 1175, 1155, 745, 705, 615

[a] Satisfactory analytical values (±0.25% for C, H, and N) were reported for compounds **17**–**26** inclusive: Ed.

Experimental Section[10]

All of the 1,3 diketones used in this study were prepared according to reported methods.[11,12]

General Procedure for the Preparation of Quinoxaline Di-*N*-oxides.—A warm solution of benzofurazan oxide and the specific 1,3 diketone in diethylamine was left to stand at room temperature for a time that varied between 2 and 3 days. The precipitated products were collected, washed with ethanol, and dried. Recrystallization from ethanol yielded yellow crystalline quinoxaline di-*N*-oxides. It should be pointed out that the melting points of quinoxaline di-*N*-oxides depend on the rate of heating, and hence are not good criteria for purity.

General Procedure for the Photolysis of Quinoxaline Di-*N*-oxides.—A solution of the specific quinoxaline di-*N*-oxide (0.5–1.0 g) in either methanol or ethanol was irradiated by a Hanovia 450-W ultraviolet lamp. On concentration of the solution (25–50 ml), the precipitated product was collected and recrystallized from ethanol. Physical and spectroscopic properties of the quinoxaline di-*N*-oxides and their photolysis products are listed in Tables I and II.

Conversion of 3-Phenyl-2(1*H*)-quinoxalone 4-Oxide (30) into 3-Phenyl-7-chloro-2(1*H*)-quinoxalone (31).—A solution of 3-phenyl-2(1*H*)-quinoxalone 4-oxide[7] (2.4 g) in pyridine (100 ml) and benzoyl chloride (1.5 g) was refluxed for 30 min. The cold solution was diluted with water and the resulting solid was collected, washed with water–ethanol, and dried. Recrystallization from ethanol gave 2.1 g of 3-phenyl-7-chloro-2(1*H*)quinoxalone (**31**) as pale yellow needles, mp 277–278° (lit.[8] mp 274–275°).

Cleavage of Quinoxaline Di-*N*-oxides with Base.—A suspension of the specific quinoxaline di-*N*-oxide (0.1–0.2 g) in 5% methanolic potassium hydroxide (20 ml) was heated until the solid dissolved. The yellow precipitate (0.07–0.15 g), obtained on cooling, was collected and recrystallized from ethanol. See Table III.

TABLE III

Quinoxaline di-*N*-oxide	Cleavage product(s)
4a,b	2-Phenylquinoxaline di-*N*-oxide and 2-(*p*-bromophenyl)quinoxaline di-*N*-oxide
5a,b	2-Phenylquinoxaline di-*N*-oxide and 2-(*p*-methoxyphenyl)quinoxaline di-*N*-oxide
6a,b	2-Phenylquinoxaline di-*N*-oxide and 2-(*p*-methylphenyl)quinoxaline di-*N*-oxide
7a,b	2-Phenylquinoxaline di-*N*-oxide and 2-(*p*-nitrophenyl)quinoxaline di-*N*-oxide
8a	2-Phenylquinoxaline di-*N*-oxide
9a	2-Phenylquinoxaline di-*N*-oxide
10a,b	2-Phenylquinoxaline di-*N*-oxide and 2-(*o*-nitrophenyl)quinoxaline di-*N*-oxide

(10) Melting points are uncorrected. Infrared spectra were taken in Nujol using a Perkin-Elmer grating infrared spectrophotometer Model 257. Nmr spectra were run in deuterated chloroform on a Varian A-60D spectrometer. Elemental analyses were performed by F. Pascher, Bonn, Germany.

(11) F. J. Pond, O. P. Maxwell, and G. M. Norman, *J. Amer. Chem. Soc.*, **21**, 955 (1899).

(12) W. Bradley and R. Robinson, *J. Chem. Soc.*, 2356 (1926).

Registry No.—**4a**, 27017-72-7; **4b**, 27017-73-8; **5a**, 27017-74-9; **5b**, 27017-75-0; **6a**, 27017-76-1; **6b**, 27017-77-2; **7a**, 27017-78-3; **7b**, 27017-79-4; **8a**, 27017-80-7; **9a**, 27017-81-8; **10a**, 27017-82-9; **10b**, 27017-83-0; **11a**, 27017-84-1; **11b**, 27017-85-2; **12a**, 27017-86-3; **12b**, 27062-07-3; **13a**, 27062-08-4; **13b**, 27017-87-4; **14**, 27017-88-5; **17**, 27017-89-6; **18**, 27017-90-9; **19**, 27017-91-0; **20**, 27017-92-1; **21**, 27017-93-2; **22**, 27017-94-3; **23**, 27017-95-4; **24**, 27017-96-5; **25**, 27017-97-6; **26**, 27017-98-7.

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The *s*-Triazolone Ring System as a New *cis*-Azo Dienophile

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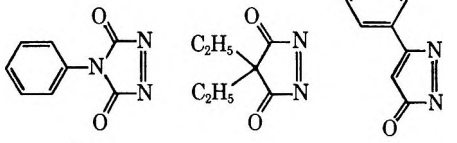
The oxidation of 5-substituted *s*-triazolin-3-ones (**1a–e**) with lead tetraacetate (LTA) led to the formation of the intermediate *s*-triazolone ring system (**2a–e**) which in the absence of 1,3-dienes decomposed to nitriles plus carbon monoxide and nitrogen. In the presence of 1,3-dienes, 5-aryl-*s*-triazolones (**2a–c**) formed Diels–Alder adducts, the 5,8-dihydro-3-aryl-*s*-triazolo[1,2-*a*]pyridazin-1-one ring system (**3–10**). The oxidation of 5-benzyl- and 5-methyl-*s*-triazolin-3-ones by LTA in the presence of 1,3-dienes did not yield Diels–Alder adducts, and only nitriles and α-phenyldiacetamide and diacetamide, respectively, were isolated.

The reaction of electron-deficient azo compounds with 1,3-dienes has recently been receiving wider attention.[1] Previous workers have investigated the oxidation of five-membered heterocycles *N*-phenylurazole[2,3] (**12**), 4,4-diethylpyrazolidine-3,5-dione[4–6] (**13**), and 3-phenyl-2-pyrazolin-5-one[7] (**14**) with lead tetraacetate (LTA) to give 4-phenyl-1,2,4-triazoline-3,5-dione (**12a**), 4,4-diethylpyrazoline-3,5-dione (**13a**), and 3-phenylpyrazol-5-one (**14a**) which afford Diels–Alder adducts in the presence of 1,3-dienes. The reactivity of **12a** > **13a** > **14a** has been established based on

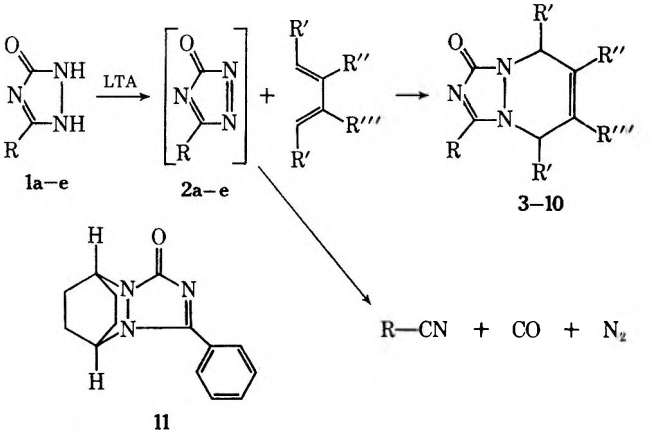


12a **13a** **14a**

the comparison of the number and types of dienes with which adduct formation occurs. These *cis*-azo dienophiles are more reactive than ethyl azodicarboxylate, a *trans*-azo dienophile.[8]

In continuing these investigations, 5-substituted *s*-triazolin-3-ones **1a–e** were oxidized with LTA to give the 5-substituted *s*-triazolones **2a–e**, a new series of *cis*-azo dienophiles as intermediates. Compound **2a** is a 4-aza analog of **14a**. Unlike the oxidations of **12**, **13**, and **14** with LTA, no transient visible color was observed when **1a–e** were treated with LTA. The oxidation products **2a–e** decomposed to nitriles.

The major product of the oxidation of **1a** and **1b** are benzonitrile and *p*-methoxybenzonitrile in 95–99% yield. The oxidation of **1c** with LTA is extremely sluggish. After 1 week of stirring at room temperature only a small quantity of *p*-nitrobenzonitrile was isolated. Isolation of the insoluble materials obtained upon filtration of the reaction mixture afforded unreacted 5-(*p*-nitrophenyl)-*s*-triazolin-3-one (**1c**). This result is consistent with the reduced electron density on the heteroatoms due to the electron-withdrawing *p*-nitro group, thus decreasing the ability of the heterocycle to coordinate with LTA. When **1d** and LTA were allowed to react, phenylacetonitrile was isolated in 75% yield, along with α-phenyldiacetamide which was identified by chemical analysis and infrared and nmr spectroscopy. Saponification of the amide afforded phenylacetic acid. Formation of the amide may be rationalized by either the formation of an azoacetate (A) which may then decompose to B followed by decomposition to the nitrile. Azoacetate A may

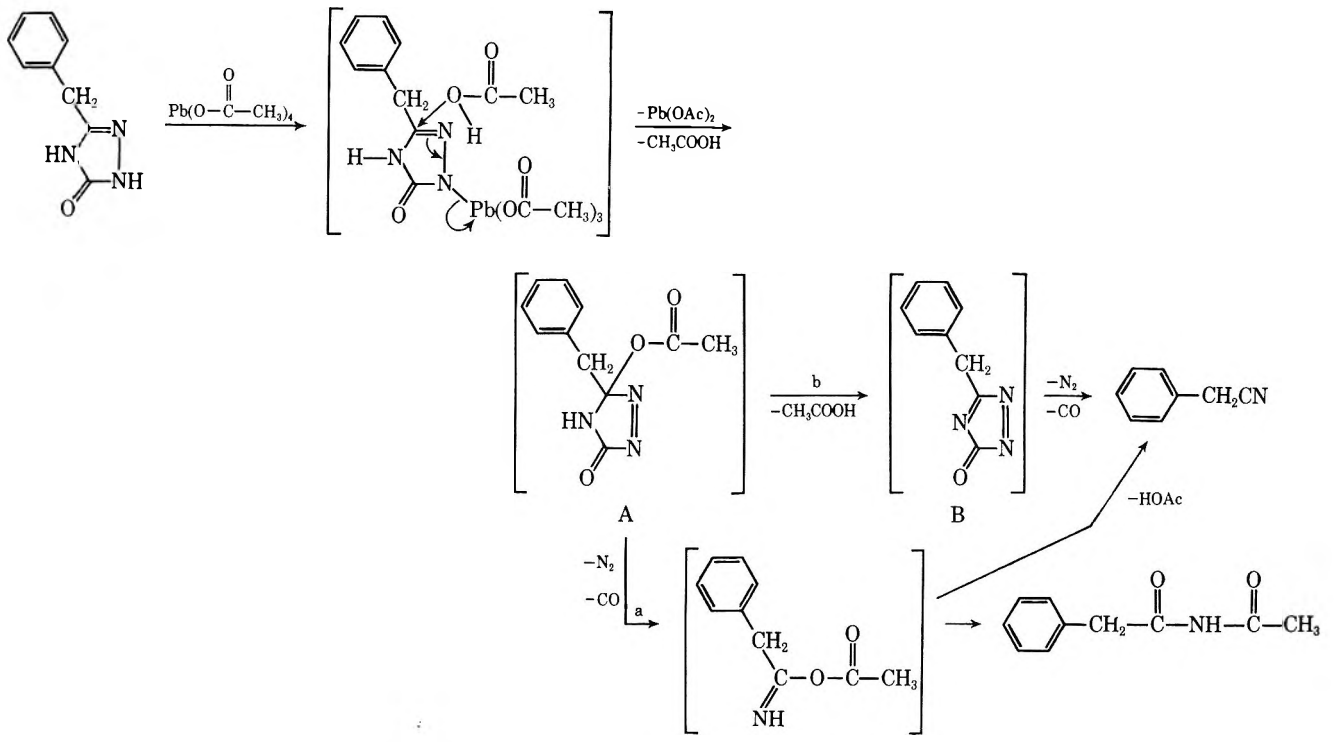


Compounds	R	R′	R″	R‴
1a, 2a, 3	Phenyl	H	H	CH_3
1a, 2a, 4	Phenyl	H	CH_3	CH_3
1a, 2a, 5	Phenyl	Phenyl	H	H
1a, 2a, 6	Phenyl	CH_2	H	H
1b, 2b, 7	*p*-Methoxyphenyl	H	CH_3	CH_3
1b, 2b, 8	*p*-Methoxyphenyl	Phenyl	H	H
1b, 2b, 9	*p*-Methoxyphenyl	CH_2	H	H
1c, 2c, 10	*p*-Nitrophenyl	H	CH_3	CH_3
1d, 2d,	Benzyl			
1e, 2e,	Methyl			

* To whom correspondence should be addressed: Indiana University of Pennsylvania, Indiana, Pa.

(1) B. T. Gillis, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, Chapter 6.
(2) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C*, 1905 (1967).
(3) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).
(4) B. T. Gillis and R. A. Izydore, *ibid.*, **34**, 3181 (1969).
(5) H. Stetter and P. Woernle, *Justus Liebigs Ann. Chem.*, **724**, 150 (1969).
(6) A. B. Evnin, A. Y. Lam, J. J. Maher, and J. J. Blyskal, *Tetrahedron Lett.*, 4497 (1969).
(7) B. T. Gillis and R. Weinkam, *J. Org. Chem.*, **32**, 3321 (1967).
(8) B. T. Gillis and P. E. Beck, *ibid.*, **27**, 1947 (1962).

Scheme I



also decompose *via* pathway a which may lead to α-phenyldiacetamide. When **1e** and LTA were allowed to react, acetonitrile and diacetamide were obtained. Their formation may be rationalized by the proposed pathway shown in Scheme I. In the presence of 1,3-dienes, intermediates **2a**, **2b**, and **2c** were trapped before complete decomposition to yield new Diels–Alder adducts, the 5,8-dihydro-3-aryl-*s*-triazolo[1,2-*a*]pyridazin-1-one ring system (**3**–**10**).

Thus, when **1a** was oxidized with LTA in the presence of 2-methyl-1,3-butadiene, 2,3-dimethyl-1,3-butadiene, 1,4-diphenyl-1,3-butadiene, and 1,3-cyclohexadiene, Diels–Alder adducts **3**, **4**, **5**, and **6** were obtained, respectively. Diels–Alder adducts **7**, **8**, and **9** were obtained when **1b** was oxidized by LTA in the presence of 2,3-dimethyl-1,3-butadiene, 1,4-diphenyl-1,3-butadiene, and 1,3-cyclohexadiene. The oxidation of **1c** by LTA in the presence of 2,3-dimethyl-1,3-butadiene afforded **10** in low yield owing to the decreased reactivity of the heterocycle toward oxidation, and most of the LTA was utilized in the oxidation of the diene. Higher yields of adducts **3**–**10** were obtained when the reaction was carried out at ambient temperatures rather than at 0–5°. At 0–5° the reaction required 24 hr for completion, while at −40 or −70° the reaction required longer than 72 hr. No adduct was obtained from **1a** and 1,3-cyclopentadiene; this is not surprising in view of the low reactivity of the 5-aryl-*s*-triazolin-3-one ring system toward LTA and the high reactivity of 1,3-cyclopentadiene. Even at −10° or below oxidation of the diene was rapid.[12] When **1d** or **1e** was oxidized by LTA in the presence of 1,3-dienes, no Diels–Alder adducts were obtained and only decomposition products were isolated. This may be due to the formation of the azoacetate A which is not a reactive dienophile. Decomposition *via* pathway a affords an imino ester which may also decompose to give the nitrile and the amide.

The infrared spectra of the 5-aryl-*s*-triazolin-3-ones **1a**, **1b**, and **1c** exhibited a C=O stretch at 1754, 1724, and 1680 cm^{-1}, respectively. These values are in agreement with the structures indicated by **1a**–**c**.[9] A band of medium intensity was exhibited by **1a**, **1b**, and **1c** at 971 cm^{-1} (N—N stretch)[10] which was absent in the adducts **3**–**9**. The C=O stretch in the adducts **3**–**6**, **7**–**8**, and **9** appeared at 1681, 1667, and 1651 cm^{-1}, respectively.

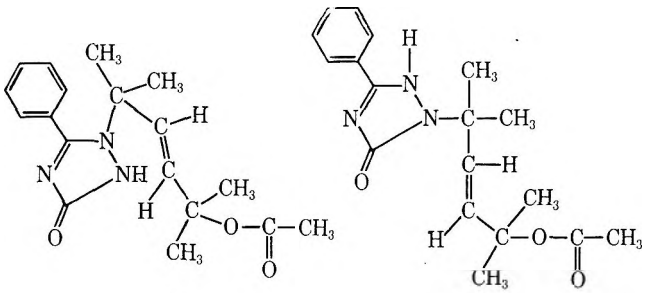
The nmr spectra of the adducts **4** and **8** exhibited nonequivalence of the methylene protons due to the different adjacent environments of each of the two nitrogen atoms. In adducts **6** and **9** nonequivalent methine protons were also observed. An A_2B_2 splitting pattern to adducts **6** and **9** was observed due to the different magnetic environments of the hydrogens of the 5,8-ethano group. Upon hydrogenation of **6** to **11**, the A_2B_2 pattern coalesced to one peak while the methine protons underwent a large shift in position. The shift of the λ_{max} in the ultraviolet spectrum of **6** to shorter wavelength in **11** is indicative of a transannular interaction similar to that reported by Weinkam.[7] The assignment of **3** from isoprene and **2a** is arbitrary since no conclusive evidence has been found to indicate a preferred structure.

The reaction of **1a**, LTA, and 2,5-dimethyl-2,4-hexadiene afforded a new compound, **15a**, which was found to be similar to **16** isolated by Hagarty[3] and is not related to **17** isolated by Weinkam.[7] That the structure is **15a** and not **15b** is based on the observation that the anions of the *s*-triazolin-3-ones absorb at longer wavelengths in the ultraviolet spectrum than the neutral substances, except in the case of a 2-sub-

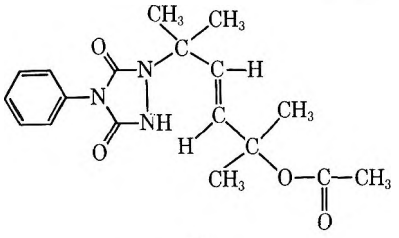
(9) Yu. N. Sheinker, I. Ya. Postovskii, and N. M. Voronina, *Zh. Fiz. Khim.*, **33**, 302 (1959); *Chem. Abstr.*, **54**, 4147*b* (1960).

(10) A. Braibanti, F. Dallavalle, M. Pellinghelli, and E. Leporati, *Inorg. Chem.*, **7**, 1430 (1968).

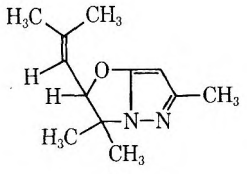
stituted s-triazolin-3-one which undergoes a shift to shorter wavelength.[11]



15a 15b



16



17

The difference in reactivity of 5-phenyl-s-triazolin-3-one (**1a**) and that of 3-phenyl-2-pyrazoline-5-one (**14**)[7] toward LTA is to be noted. In spite of the name given for **14** the infrared spectrum reveals a strong hydrogen bonding absorption between 3300 and 2000 cm^{-1} and absence of C=O absorption, and the compound exists as the hydroxy tautomer.[12] The infrared spectrum of **1a** reveals a C=O stretch typical of a carbonyl system in the five-membered ring. There is little evidence to indicate the presence of a hydroxy tautomer in the solid state. Polya[11] found that 1-phenyl-s-triazolin-3-one has a similar λ_{max} in the ultraviolet spectrum as does 1-phenyl-2-methyl-s-triazolin-3-one and concluded that the lactam formed in the monosubstituted s-triazolin-3-ones is more important. The infrared spectra of 4,4-diethyl-pyrazolidine-3,5-dione,[13] maleic hydrazide,[14] and phthalazinedione[15] reveal a C=O stretch typical for their ring size, but there is also a considerable amount of hydrogen bonding exhibited, indicating the presence of the hydroxy tautomer. These cyclic hydrazides are readily oxidized by LTA and the oxidation products are potent *cis*-azo dienophiles. Based on this evidence it appears that the presence of the hydroxy tautomer is important for the rapid oxidation of a cyclic hydrazide.

Thus the oxidation by LTA of the readily available 5-aryl-s-triazolin-3-ones affords a facile route to the previously unreported 5,8-dihydro-3-aryl-s-triazolo[1,2-*a*]pyridazin-1-one ring system.

(11) M. R. Atkinson, E. A. Parkes, and J. B. Polya, *J. Chem. Soc.*, 4256 (1954).

(12) P. E. Gagnon, J. L. Boivin, and R. J. Raquin, *Can. J. Chem.*, **31**, 1025 (1953).

(13) P. E. Gagnon, J. L. Boivin, R. MacDonald, and L. Yaffe, *ibid.*, **32**, 823 (1954).

(14) H. Feuer and H. Rubinstein, *J. Amer. Chem. Soc.*, **80**, 5873 (1958).

(15) Y. Kanda and M. Mashima, *Mem. Fac. Sci., Kyushu. Univ., Ser. C*, **1**, 183 (1950); *Chem. Abstr.*, **46**, 9989*b* (1952).

Experimental Section[16]

The 5-substituted s-triazolin-3-ones **1a,b,d,e** were prepared by the cyclization of acylsemicarbazides[17] and **1c** was prepared by the reaction of *p*-nitrobenzonitrile with semicarbazide.[18] Acylsemicarbazides are readily available from the reaction of acylhydrazides and potassium cyanate in dilute hydrochloric acid or dilute acetic acid.[17]

Oxidation of 5-Substituted s-Triazolin-3-ones with LTA. General Procedure.—To a stirred slurry of 8 g (0.05 mol) of 5-phenyl-s-triazolin-3-one (**1a**) or 4.8 g (0.025 mol) of 5-(*p*-methoxyphenyl)-s-triazolin-3-one (**1b**) or 5.2 g (0.025 mol) of 5-(*p*-nitrophenyl)-s-triazolin-3-one (**1c**) or 8.8 g (0.05 mol) of 5-benzyl-s-triazolin-3-one (**1d**) was added an equivalent mole quantity of LTA dissolved in 150 ml of dry methylene chloride over a period of 0.5 hr at room temperature. An equivalent mole quantity of solid LTA was added to a slurry of 5-methyl s-triazolin-3-one (**1e**) in 75 ml of dry chlorobenzene. Stirring was continued in all cases until 1 drop of the reaction mixture when added to 5 drops of water no longer gave a precipitate of lead oxide. The reaction mixture of **1a**, **1b**, **1c**, or **1d** was filtered and the organic phase was washed with 100 ml of water, separated, and then washed with 100 ml of 10% potassium carbonate solution. The organic phase was then collected and dried over anhydrous magnesium sulfate and evaporated to yield the products indicated below. The reaction mixture of **1e** was distilled at atmosphere pressure. Collection of the distillate was terminated when the flask temperature reached 100°.

From **1a** was obtained 4.4 ml (94% yield) of crude benzonitrile. The crude product was dissolved in 100 ml of petroleum ether (low boiling), adsorbents were added, and the solution was filtered. The clear filtrate was evaporated to give benzonitrile, $n^{25}D$ 1.5230 (lit.[19] $n^{25}D$ 1.5298).

From **1b** was obtained 3.2 g (97% yield) of *p*-methoxybenzonitrile: mp 55–60° (lit.[20] mp 60–61°); ir (Nujol) 2200 (CN), 1250 cm^{-1} (C-O-C).

The reaction mixture from **1c** was stirred for 1 week at room temperature after which time the reaction was still incomplete as evidenced by the appearance of lead oxide when 1 drop of the reaction mixture was added to 5 drops of water. Filtration of the solid afforded a mixture of starting material and lead salts. The solid was extracted with 2 l. of concentrated ammonia–water. Heating of the ammonia–water extracts to remove the ammonia afforded 4 g of starting material **1c**. The filtrate of methylene chloride was treated as previously described which gave a copious precipitate of lead oxide which was removed by filtration. The methylene chloride solution was evaporated to yield 0.2 g of *p*-nitrobenzonitrile: mp 147–149° (recrystallized from acetic acid–water) (lit.[20] mp 148–149°); ir (Nujol) 2220 cm^{-1} (CN).

From **1d** 4.9 g of a liquid was isolated which, upon standing at room temperature for 24 hr, afforded a precipitate. The precipitate was collected and washed with cold diethyl ether. The filtrate and all the ether washings were combined and evaporated to give 2.4 ml of a liquid which was demonstrated to be phenylacetonitrile by comparison of its infrared spectrum with that of authentic phenylacetonitrile, $n^{20}D$ 1.5120 (lit.[21] $n^{20}D$ 1.5240).

The solid material was determined to be α-phenyldiacetamide: mp 127–130° (lit.[22] 129–130°); ir (Nujol) 3260, 3165 (NH), 1720 cm^{-1} (C=O); nmr δ 9.5 (s, 1, NH), 7.3 (s, 5, Ar H), 3.8 (s, 2, CH_2), and 2.3 (s, 3, CH_3).

(16) Melting points are corrected. Microanalyses were performed by Dr. Alfred Bernhardt, Mülheim, Germany. Infrared spectra were taken with a Perkin-Elmer Model 137 double-beam spectrophotometer. The nmr spectra were taken with a Varian Model A-60 using deuteriochloroform as a solvent and tetramethylsilane as an internal reference standard. The ultraviolet spectra were taken with a Cary Model 14 spectrophotometer.

(17) H. Gehlen, *Justus Liebigs Ann. Chem.*, **563**, 185 (1949).

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(21) N. A. Lange, Ed., "Handbook of Chemistry," 10th ed, McGraw-Hill, New York, N. Y., 1961, p 1283.

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Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.21; N, 7.91. Found: C, 67.68; H, 6.08; N, 8.07.

Saponification of the product afforded phenylacetic acid, mp 77° (lit.[23] mp 76°).

The infrared spectrum and qualitative tests of the distillate from **1e** revealed the presence of a nitrile, halogenated aromatic hydrocarbon, and acetic acid. The infrared spectrum of the distillate was identical with the infrared spectrum of a sample of the distillate to which authentic acetonitrile was added. Enhancement of the nitrile band was observed and no new bands in the infrared spectrum were observed. Filtration of the solids in the reaction vessel followed by evaporation afforded an oil from which diacetamide slowly crystallized: ir (Nujol) 3448, 3226 (NH), 1754–1667 cm^{-1} (C=O); mp 72–75° (lit.[24] mp 76°).

Reaction of 5-Substituted *s*-Triazolin-3-ones with LTA in the Presence of 1,3-Dienes. General Procedure.—To a stirred slurry of 0.025 mol of 5-substituted s-triazolin-3-one and 0.025 mol of 1,3-diene in 100 ml of dry methylene chloride was added 11 g (0.023 mol) of LTA (94% purity) or other molar ratio as indicated, over a period of 30 min at room temperature. The reaction mixture was treated as previously described when 1 drop of the reaction mixture no longer gave a precipitate of lead oxide when added to 5 drops of water. Upon evaporation of the solvent, the solid adducts were obtained. The crude product was washed with 20 ml of diethyl ether to remove unreacted 1,3-diene, nitrile, and acetoxylated materials and the product was then collected on the Büchner funnel and air-dried. The product (1 g) was recrystallized from benzene or methanol to a constant melting point.

5,8-Dihydro-3-phenyl-6-methyl-*s*-triazolo[1,2-*a*]pyridazin-1-one (3).—From a mixture of 8 g (0.05 mol) of **1a** and 5 ml (0.05 mol) of isoprene and 23.5 g (0.027 mol) of LTA was obtained 2.6 g (25%) of **3**: mp 203–205° (benzene); uv λ_{max} (95% ethanol) sh 276 mμ (ε 5470) and 237 (12,650); nmr ($DCCl_3$) δ 7.5 (m, 5, Ar H), 5.75 (s, 1, vinyl H), 3.3 (s, 4, $NCH_2C=$), and 1.8 (s, 3, $CH_3C=$).

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.49. Found: C, 68.60; H, 5.93; N, 18.62.

5,8-Dihydro-3-phenyl-6,7-dimethyl-*s*-triazolo[1,2-*a*]pyridazin-1-one (4).—From a mixture of 4 g of **1a** and 3.1 ml of 2,3-dimethyl-1,3-butadiene and LTA was obtained 3 g (50%) of **4**: mp 198–200° (benzene); uv λ_{max} (95% ethanol) sh 276 mμ (ε 5390) and 237 (12,400); nmr ($DCCl_3$) δ 7.5 (m, 5, Ar H), 4.4 (bs, 2, $NCH_2C=$), 4.2 (bs, 2, $NCH_2C=$), and 1.9 (s, 6, $CH_3C=CCH_3$).

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.28; N, 17.42. Found: C, 69.56; H, 6.12; N, 17.22.

5,8-Dihydro-3,5,8-triphenyl-*s*-triazolo[1,2-*a*]pyridazin-1-one (5).—From a mixture of 4 g of **1a** and 5.2 g of 1,4-diphenyl-1,3-butadiene and LTA was obtained 3.9 g (38%) of **5**: mp 248–250° (methanol); uv λ_{max} (95% ethanol) 285 mμ (ε 4670) and 245 (11,700).

Anal. Calcd for $C_{24}H_{19}N_3O$: C, 78.78; H, 5.25; N, 11.50. Found: C, 78.66; H, 5.27; N, 11.57.

5,8-Dihydro-3-phenyl-5,8-ethano-*s*-triazolo[1,2-*a*]pyridazin-1-one (6).—From a mixture of 4 g of **1a** and 2.5 ml of 1,3-cyclohexadiene and LTA was obtained 4 g (66%) of **6**: mp 201–203° (benzene); uv λ_{max} (95% ethanol) 280 mμ (ε 5924) and 235 (12,950); nmr ($DCCl_3$) δ 7.85–7.32 (m, 5, Ar H), 6.6–6.19 (m, 2, vinyl H), 5.16 (s, 1, methine CH), 5.10 (s, 1, methine CH), and 2.39–1.62 (AB quartet with δ_A 2.3, δ_B 1.6, J_{AB} = 10 Hz, 4, CH_2CH_2).

Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.39; H, 5.34; N, 17.70.

5,8-Dihydro-3-(*p*-methoxyphenyl)-6,7-dimethyl-*s*-triazolo[1,2-*a*]pyridazin-1-one (7).—From a mixture of 4.8 g of **1b** and 3.1 ml of 2,3-dimethyl-1,3-butadiene and LTA was obtained 2.8 g (38%) of **7**: mp 227–230° (benzene); uv λ_{max} (95% ethanol) 263 mμ (ε 16,200); nmr ($DCCl_3$) δ 7.75–6.86 (AB quartet with δ_A 7.7, δ_B 7.0, J_{AB} = 9 Hz, 4, Ar H), 4.26 (bs, 2, NCH_2=C=), 4.15 (bs, 2, $NCH_2C=$), 3.8 (s, 3, CH_3O), and 1.75 (s, 6, $CH_3C=CCH_3$).

Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.25; H, 6.46; N, 15.45.

5,8-Dihydro-3-(*p*-methoxyphenyl)-5,8-diphenyl-*s*-triazolo[1,2-*a*]pyridazin-1-one (8).—From a mixture of 4.8 g of **1b** and 5.2 g of 1,4-diphenyl-1,3-butadiene and LTA was obtained 3 g (30%) of **8**: mp 253–255° (methanol); uv λ_{max} (95% ethanol) 265 mμ (ε 16,750); nmr ($DCCl_3$) δ 7.55–6.8 (m, 14, Ar H), 6.16 (d, 2, benzylic CH), 5.8 (m, 2, vinyl H), and 3.8 (s, 3, CH_3O).

Anal. Calcd for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63. Found: C, 75.73; H, 5.32; N, 10.81.

5,8-Dihydro-3-(*p*-methoxyphenyl)-5,8-ethano-*s*-triazolo[1,2-*a*]pyridazin-1-one (9).—From a mixture of 4.8 g of **1b** and 2.5 ml of 1,3-cyclohexadiene and LTA was obtained 4.5 g (67%) of **9**: mp 185–187° (benzene); uv λ_{max} (95% ethanol) 265 mμ (ε 15,100); nmr ($DCCl_3$) δ 7.8–6.9 (AB quartet with δ_A 7.7, δ_B 7.0, J_{AB} = 9 Hz, 4, Ar H), 5.1 (s, 1, methine CH), 5.05 (s, 1, methine CH), 6.5–6.1 (m, 2, vinyl H), 3.85 (s, 3, CH_3O), and 2.36–1.6 (AB quartet with δ_A 2.35, δ_B 1.64, J_{AB} = 10 Hz, 4, CH_2CH_2).

Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 67.06; H, 5.78; N, 15.41.

5,8-Dihydro-3-(*p*-nitrophenyl)-6,7-dimethyl-*s*-triazolo[1,2-*a*]pyridazin-1-one (10).—From a mixture of 5.2 g of **1c** and 3.1 ml of 2,3-dimethyl-1,3-butadiene and LTA was obtained 0.2 g (3%) of **10**: mp 269° dec (methanol); uv λ_{max} (95% ethanol) 260 mμ (ε 14,100).

Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.56; H, 4.98; N, 19.40.

5,6,7,8-Tetrahydro-3-phenyl-5,8-ethano-*s*-triazolo[1,2-*a*]pyridazin-1-one (11).—To a slurry of 0.1 g of 5% palladium-on-carbon catalyst in 25 ml of 95% ethanol was added a solution of 2 g (0.0084 mol) of **6** in 60 ml of 95% ethanol. The slurry was stirred under hydrogen at 1 atm a 25° until the theoretical amount of hydrogen had been absorbed (1 hr). The catalyst was removed by filtration and the solvent was removed under reduced pressure to give 1.9 g (90%) of **11**. Recrystallization gave pure **11**: mp 247–248° (benzene); uv λ_{max} (95% ethanol) 277 mμ (ε 5890) 235 (12,500); nmr ($DCCl_3$) δ 8–7.3 (m, 5, Ar H), 5.8 (s, 1, methine CH), 4.7 (s, 1, methine CH), and 1.98 (s, 8, CH_2CH_2).

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.28; N, 17.42. Found: C, 69.53; H, 6.38; N, 17.22.

Reactions of 5-Phenyl-*s*-triazolin-3-one (1a) with Other 1,3-Dienes.—From a mixture of 8 g (0.05 mol) of **1a** and 7.9 ml of 2,5-dimethyl-2,4-hexadiene and 23.5 g of LTA was obtained 8 g (55%) of **15a**: mp 101–103° (50% methanol–water); uv λ_{max} (95% ethanol) 272 mμ (ε 14,900); uv λ_{max} (0.1 *N* NaOH in 95% ethanol) 282 mμ (ε 8470); nmr ($DCCl_3$) δ 13.5 (s, 1, NH), 8–7.4 (m, 5, Ar H), 6.25 (s, 1, vinyl H), 6.12 (s, 1, vinyl H), 2.08 (s, 3, CH_3), 1.88 (s, 6, CH_3), and 1.75 (s, 6, CH_3).

Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.65; H, 7.35; N, 12.93.

From a mixture of **1a** and 1,3-cyclopentadiene at 0–5, −40, and −70°, only **1a** and acetoxylated materials were recovered. No benzonitrile was observed in the infrared spectrum of the materials isolated. With **1a** and 1,3-cyclooctadiene or anthracene, only benzonitrile, oxidized diene, or anthracene were recovered.

Reactions of 5-Benzyl-*s*-triazolin-3-one and 5-Methyl-*s*-triazolin-3-one with 1,3-Dienes.—When 8.8 g (0.05 mol) of **1d**, 6.2 ml of 2,3-dimethyl-1,3-butadiene, and 23 g of LTA were allowed to react, only phenylacetonitrile and α-phenyldiacetamide were isolated. Similar results were obtained with equimolar quantities of **1d**, 1,3-cyclohexadiene, and LTA. With **1e** and 2,3-dimethyl-1,3-butadiene or 1,3-cyclohexadiene, no adducts were obtained from either the organic phase or from the aqueous washings.

Registry No.—**3**, 27192-78-5; **4**, 27192-79-6; **5**, 27192-80-9; **6**, 27192-81-0; **7**, 27248-71-1; **8**, 27192-82-1; **9**, 27192-83-2; **10**, 27192-84-3; **11**, 27192-85-4; **15a**, 27248-72-2.

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Syntheses from 4-Chlorotetrahydropyran

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The utilization of 4-chlorotetrahydropyran (1), which has recently become readily available, as a starting material in organic synthesis was investigated. Nucleophilic displacement of the chlorine atom is difficult, but moderate yields of 4-aminotetrahydropyran (4), 4-piperidinotetrahydropyran (6), and 4-morpholinotetrahydropyran (7) were obtained by treatment with the appropriate amine at 200°. Sodium sulfide gave a low yield of 4-tetrahydropyranyl sulfide (8). A Grignard reagent prepared from 1 in tetrahydrofuran reacted normally with cyclohexanone, and Friedel–Crafts alkylation of benzene or toluene with 1 gave 4-phenyltetrahydropyran (13a) and 4-tolyltetrahydropyran (13b) (as a mixture of isomers) in good yields. Ring cleavage with hydrobromic acid provided 1,5-dibromo-3-chloropentane (14) and treatment with acid chlorides gave esters of 3,5-dichloro-1-pentanol (15). Synthesis of 3-chloroglutaric acid (17) by nitric acid oxidation of 1 was found to be feasible in high yield at low temperature.

The condensation of 1-olefins, paraformaldehyde, and hydrogen halides has provided a convenient one-step synthesis of 3-alkyl-4-halotetrahydropyrans in good yields from readily available starting materials.[1] In view of the ease of preparation of the 4-chloro compounds, the synthetic utility of those compounds was studied with particular emphasis on syntheses based on the parent 4-chlorotetrahydropyran (1).

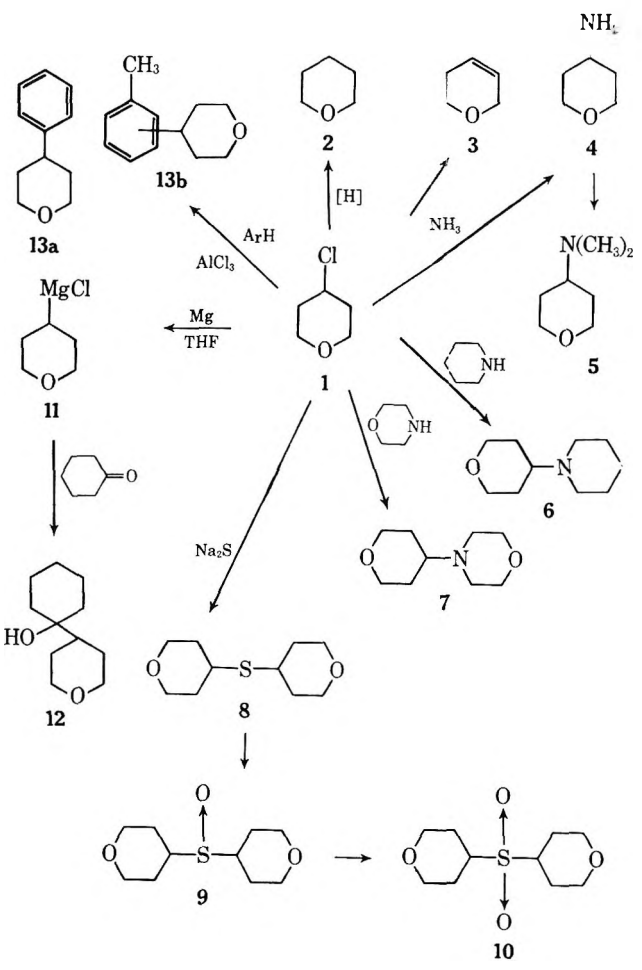
4-Chlorotetrahydropyran is only slightly soluble in water but miscible in all proportions with ether, aliphatic hydrocarbons, aromatic hydrocarbons, and chlorinated solvents. Also soluble in concentrated hydrochloric acid and concentrated sulfuric acid, it can be recovered unchanged upon dilution. Lewis acids such as aluminum chloride, zinc chloride, phosphorus pentachloride, boron fluoride, and stannic chloride dissolve readily in 1 to give deeply colored solutions from which 1 can be recovered on treatment with water. Sulfur trioxide forms stable complexes with both 1 and the 3-alkyl-4-chlorotetrahydropyrans; these may be of particular utility as sulfonating agents since, unlike the sulfur trioxide complexes with dimethylformamide and dioxane, the complexing agent can be readily recovered from aqueous solutions.

In a study of compounds available from 1, two types of reactions were available, *i.e.*, syntheses based on replacement of the chlorine atom, and sequences based on the cleavage of the tetrahydropyran ring. Outlined in Scheme I are a number of compounds prepared which retained the tetrahydropyran ring.

Sodium and methanol reduction of the halotetrahydropyrans to the tetrahydropyran was described previously.[1] In addition, catalytic hydrogenation over palladium on carbon at 1000 psig and 175° provided good yields of tetrahydropyran (2) from 1 and 3-methyltetrahydropyran from 4-chloro-3-methyltetrahydropyran. Dehydrochlorination of 1 to 3,6-dihydro-2*H*-pyran (3) in nearly quantitative yields was readily effected with alcoholic potassium hydroxide, by distillation from potassium fluoride in ethylene glycol, or catalytically over sodium borate on Celite[2] at 430°. Pyrolysis of 1 in a quartz reactor in a flow system at 500° also provided good yields of 3 at *ca.* 20% conversion levels. At 400° 1 was thermally stable; under identical conditions cyclohexyl chloride was nearly completely dehydrochlorinated.

Nucleophilic displacement reactions of 1 were also studied, and, as expected, rather stringent conditions were required and considerable dehydrochlorination occurred as a side reaction. 4-Aminotetrahydropyran (4) was formed in 33% yield by treatment with a large excess of ammonia in 85% aqueous isopropyl alcohol at 200° in an autoclave. The use of pure isopropyl alcohol gave a low conversion and reaction in ether solution in the presence of potassium hydroxide gave almost exclusively dihydropyran (3). Methylation of 4 using the Eschweiler–Clarke procedure[3] provided 4-dimethylaminotetrahydropyran (5). Displacement of the chlorine in 1 was also effected by treatment with piperidine or morpholine at 200° in ethanol solution in an autoclave to provide 4-piperidino-

SCHEME I



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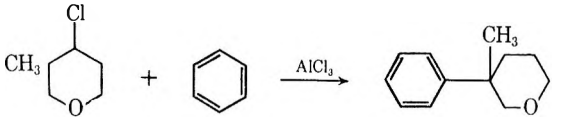
(2) We wish to thank Mr. V. C. Vives for carrying out this experiment.

(3) M. L. Moore, *Org. React.*, **5**, 301 (1949).

tetrahydropyran (6) and 4-morpholinotetrahydropyran (7), respectively, in moderate yields. Reaction of 1 with sodium sulfide in boiling ethanol was slow; in the higher boiling methoxyethanol, however, a low yield of 4-tetrahydropyranyl sulfide (8) was obtained. No improvement in yield was noted when *N*-methylpyrrolidone was used as solvent. The sulfide was oxidized to the sulfoxide (9) and the sulfone (10) in high yield with hydrogen peroxide in acetic acid.[4]

Formation of Grignard reagents from 1 is useful in the introduction of the 4-tetrahydropyranyl moiety into various substrates. The use of 1 and magnesium in tetrahydrofuran led to the formation of 4-tetrahydropyranylmagnesium chloride (11), which, after reaction with cyclohexanone and hydrolysis, led to the crystalline product 12. While formation of Grignard reagents from 3-alkyl-4-chlorotetrahydropyrans was not investigated, it is assumed that suitable conditions would lead to analogous reagents.

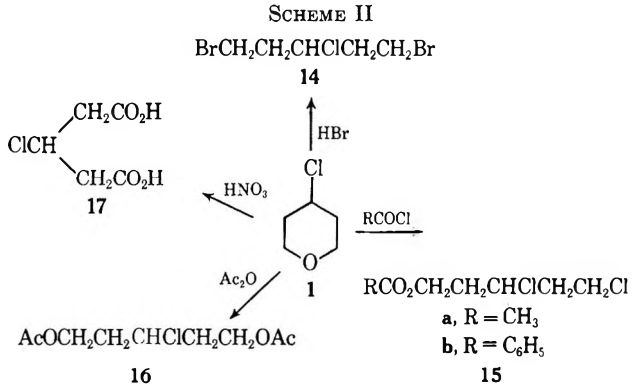
The behavior of 1 in Friedel–Crafts reactions was also examined. With aluminum chloride as the catalyst, benzene and toluene were smoothly alkylated to give 91 and 76% yields of 4-phenyltetrahydropyran (13a) and 4-tolyltetrahydropyran (13b) as a mixture of ortho, meta, and para isomers. A similar alkylation of benzene with *cis,trans*-4-chloro-3-methyltetrahydropyran, under conditions chosen to give about a 50% conversion, gave the rearranged product, 3-methyl-3-phenyltetrahydropyran. The recovered 4-chloro-3-



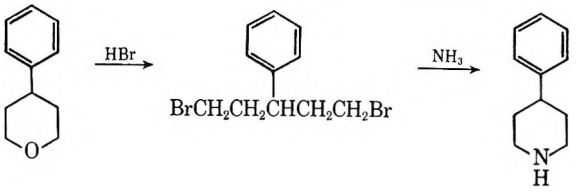
methyltetrahydropyran had the same cis/trans ratio as the starting material.

Investigation of ring opening with chemical reagents to provide polyfunctional intermediates also appeared to present possibilities for the utilization of 1 in synthesis. Scheme II illustrates a number of reactions of this type.

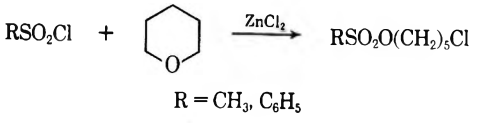
SCHEME II



Reaction of 1 with a 48% hydrobromic acid–concentrated sulfuric acid mixture[5] at reflux for 2.5 hr gave a 72% yield of 1,5-dibromo-3-chloropentane (14). The use of constant-boiling hydrobromic acid alone gave low conversions under the same conditions. The analogous cleavage with hydrochloric acid or zinc chloride–hydrochloric acid gave only very small amounts of 1,3,5-trichloropentane even after extended reaction times. Similar cleavage of 4-phenyltetrahydropyran (13a) with 48% hydrobromic acid gave 64% of 1,5-dibromo-3-phenylpentane which, upon treatment with a 100 mol excess of ammonia, gave the expected 4-phenylpiperidine. The conversion of tetrahydropyran



to 5-chloropentyl esters by reaction with acid chlorides in the presence of zinc chloride has been previously reported.[6] This reaction was extended to include the preparation of 3,5-dichloro-1-pentyl acetate (15a) and 3,5-dichloro-1-pentyl benzoate (15b) from 1 and acetyl chloride or benzoyl chloride in good yields. A related reaction, which has apparently not been previously described, is the conversion of tetrahydropyran to the corresponding 5-chloropentyl sulfonates upon treatment with either methanesulfonyl chloride or benzenesulfonyl chloride and zinc chloride. 5-Chloropentyl methanesulfonate was obtained as a rather unstable yellow oil and characterized by its nmr spectrum but decomposition of the benzenesulfonate occurred on attempted distillation. Although this procedure was



not applied to 1, there seems little doubt that the corresponding 3,5-dichloropentyl sulfonates could be prepared in a similar fashion.

Acetic anhydride reacted with 1 in the presence of zinc chloride at elevated temperature with either an excess of anhydride or 1 as solvent, to give 20 to 40% yields of 1,5-diacetoxy-3-chloropentane (16). The diacetate (16) was always contaminated with 15a (by glpc).

Nitric acid oxidation of 1 according to a procedure for the oxidation of tetrahydropyran to glutaric acid gave only 30% of the known 3-chloroglutaric acid (17). A more detailed study developed conditions (extended reaction time, low temperature) which raised the yield to 95%.

In summary, synthetic procedures were developed to convert 4-chlorotetrahydropyran to a variety of previously rather inaccessible compounds. In most cases, more detailed study of the individual synthesis to optimize conditions, should also result in increased yields. Although most of these experiments were conducted using only 1 as the starting material, these synthetic procedures should be equally adaptable to the entire family of 3-alkyl-4-halotetrahydropyrans.

Experimental Section

4-Aminotetrahydropyan (4).—A mixture of 150 g (1.25 mol) of 1, 45 ml of water, 255 ml of isopropyl alcohol, and 178.1 g (10.5 mol) of ammonia was heated 5 hr at 200° in a stirred, stainless

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(5) D. W. Andrus, "Organic Syntheses," Collect Vol. III, Wiley, New York, N. Y., 1955, p 692.

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steel autoclave. The autoclave was vented and the reaction mixture was treated with 75 g of solid sodium hydroxide, stirred for 1 hr, filtered, and fractionated. There was obtained 41.1 g (33%) of **4**, bp 148–151° [lit.[7] bp 52–53° (13 mm)].

4-Dimethylaminotetrahydropyran (5).—A mixture of 10.1 g (0.1 mol) of **4**, 23 g of 97% formic acid, and 18 g of 36.6% formalin was refluxed for 12 hr, cooled, treated with 10 ml of concentrated hydrochloric acid, and evaporated to dryness. The residue was dissolved in water, made strongly alkaline with 50% potassium hydroxide solution, and saturated with potassium carbonate. The product was extracted into ether and dried over KOH pellets, the ether was removed, and the product was distilled to give 11.4 g (89%) of colorless oil, bp 71–72° (26 mm) [lit.[8] bp 58–59° (12 mm)].

4-Piperidinotetrahydropyran (6).—A mixture of 115 g (0.95 mol) of **1**, 300 ml of 95% ethanol, 128 g (1.5 mol) of piperidine, and 83.8 g (0.6 mol) of anhydrous potassium carbonate was heated at 200° for 24 hr in the autoclave. The reaction mixture was filtered and distilled to a head temperature of 110° to remove solvent and excess piperidine. The residue was taken up in ether and filtered again, the ether was removed, and the residue was distilled under reduced pressure. There was obtained 43.2 g (27%) of colorless liquid, bp 111–115° (12 mm), $n^{20}D$ 1.4864.

Anal. Calcd for $C_{10}H_{19}NO$: C, 71.0; H, 11.2; N, 8.3. Found: C, 70.9; H, 11.5; N, 8.5.

4-Morpholinotetrahydropyran (7).—The reaction was carried out as for the piperidino compound using 130 g (1.5 mol) of morpholine in lieu of the piperidine. After work-up and removal of solvent and excess morpholine, the residue crystallized. Recrystallization from ether–pentane gave 46.2 g (27%) of colorless, dense needles, mp 62–64°.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.2; H, 10.0; N, 8.2. Found: C, 62.9; H, 9.9; N, 7.9.

4-Tetrahydropyranyl Sulfide (8).—A mixture of 60 g (0.5 mol) of **1**, 60 g (0.25 mol) of sodium sulfide nonahydrate, and 300 ml of methoxyethanol was refluxed with stirring for 24 hr. The reaction mixture was filtered and the inorganic salts were washed thoroughly with dry ether. Removal of the solvents gave 13.3 g of oil which was distilled, bp 99–101° (0.5 mm), and 10.8 g was recovered.

Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.4; H, 8.9; S, 15.8. Found: C, 59.4; H, 9.1; S, 15.5.

4-Tetrahydropyranyl Sulfoxide (9).—To a warm solution of 10 g (0.05 mol) of **8** in 100 ml of glacial acetic acid was added 6.6 ml of 30% hydrogen peroxide over 30 min. The acetic acid was removed on a rotary evaporator and the residue was recrystallized from methanol to give 8.7 g (80%) of **10**, as colorless platelets, mp 140–142°.

Anal. Calcd for $C_{10}H_{18}O_3S$: C, 55.0; H, 8.3; S, 14.7. Found: C, 54.8; H, 8.0; S, 14.6.

4-Tetrahydropyranyl sulfone (10) was prepared similarly using 13 ml of 30% hydrogen peroxide. The product was recrystallized from 95% ethanol to give 11.1 g of colorless crystals, mp 156–157°.

Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.2; H, 7.7; S, 13.7. Found: C, 50.9; H, 7.8; S, 14.0.

1-(4-Tetrahydropyranyl)cyclohexanol (12).—A Grignard reagent was prepared in the usual manner from 36 g (0.3 mol) of **1** and 7.3 g (0.3 g-atom) of magnesium turnings in 150 ml of dry tetrahydrofuran. Most of the magnesium was consumed. A solution of 29.4 g (0.3 mol) of cyclohexanone in 50 ml of dry tetrahydrofuran was added dropwise over 30 min, refluxed for 30 min, cooled, and hydrolyzed with saturated ammonium chloride. After extraction into ether and drying, the product was fractionated to give 24.1 g (42%) of material, bp 95–125° (0.2 mm), which crystallized. Recrystallization of an 11-g portion from heptane gave 7.0 g of colorless crystals, mp 68–69°.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.8; H, 10.9. Found: C, 71.7; H, 10.9.

Preparation of 4-Phenyltetrahydropyran (13a).—To 53.4 g (0.4 mol) of anhydrous aluminum chloride and 200 ml of dry benzene was added 42.2 g (0.35 mol) of **1** in 50 ml of dry benzene over a 20-min period. The reaction was moderated from time to time when HCl evolution was too rapid by cooling in an ice bath. After the exothermic reaction had subsided, the reaction was stirred for 1 hr at room temperature and poured over 600 g of crushed ice. The product was extracted into ether and dried, and the ether was removed to leave a crystalline solid which was recrystallized from aqueous ethanol to give 38.5 g of colorless platelets, mp 48–49° (lit.[9] mp 46–47°), and a second crop of 13 g of slightly yellow material, mp 42–46°, or a total yield of 51.5 g (91%).

4-Tolyltetrahydropyran (13b).—Treatment of a toluene suspension of aluminum chloride with **1** using identical conditions and quantities gave, after work-up and distillation, 46.9 g (76.4%) of colorless oil, bp 88–90° (0.6 mm), $n^{20}D$ 1.5295.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.8; H, 9.1. Found: C, 81.8; H, 9.1.

The nmr spectrum of **13b** had methyl resonances at −131 and −133 Hz (relative to TMS) in a ratio of 37:63 ascribed to the para isomer and a mixture of ortho and meta, respectively. The infrared spectrum also was indicative of a mixture with strong adsorption at 695, 720, 749, 781, and 812 cm^{-1}. A similar reaction at 5–10° gave incomplete reaction with recovery of 70% of unreacted **1** after 2 hr. The nmr spectrum indicated the product to contain 44% para and 56% ortho and meta.

3-Methyl-3-phenyltetrahydropyran was prepared by reaction of 67.3 g (0.5 mol) of *cis,trans*-4-chloro-3-methyltetrahydropyran, 300 ml of benzene, and 70 g (0.52 mol) of aluminum chloride at 50–60° for 30 min. Distillation of the products after work-up gave 43.0 g of unreacted *cis,trans*-4-chloro-3-methyltetrahydropyran (*ca.* 55% trans by glpc on a 10 ft × 0.25 in. UCON-LB-550-X on Chromosorb P column), bp 48–51° (10 mm), and 22.4 g (77% based on reacted chloride) of 3-methyl-3-phenyltetrahydropyran: bp 80–81° (0.5 mm); $n^{20}D$ 1.5293; nmr ($CDCl_3$) δ 6.95–7.5 (m, 5, Ar H), 3.25–4.0 (m, 4, CH_2O), 1.2–2.2 (m, 4, CH_2), and 1.1 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.8; H, 9.1. Found: C, 81.7; H, 9.0.

1,5-Dibromo-3-chloropentane (14).—To a warm (40°) solution, prepared by addition of 120 ml of concentrated sulfuric acid to 510 ml of 48% hydrobromic acid was added 120.5 g (1.0 mol) of **1**. The mixture became warmer (60°) and was mixed by swirling and refluxed for 2.5 hr. The dark reaction mixture was cooled, poured over 1 kg of crushed ice, and extracted into methylene chloride. After drying and removal of solvent, the product was distilled through a short column and 167.4 g (72%) of crude product, bp 120–151° (30 mm), was obtained. This was refractionated and a center cut, bp 108–110° (5 mm), $n^{20}D$ 1.5363, was analyzed.

Anal. Calcd for $C_5H_9Br_2Cl$: C, 22.7; H, 3.4; Br, 60.5; Cl, 13.4. Found: C, 22.4; H, 3.5; Br, 60.9; Cl, 13.2.

1,5-Dibromo-3-phenylpentane.—A mixture of 500 ml of 48% hydrobromic acid and 90 g (0.55 mol) of **13a** was refluxed with stirring for 17 hr. After work-up and distillation there was obtained 110.1 g (64%) of slightly yellow oil, bp 117–119° (0.5 mm).

Anal. Calcd for $C_{11}H_{14}Br_2$: C, 43.1; H, 4.6; Br, 52.3. Found: C, 43.41; H, 4.6; Br, 51.9.

4-Phenylpiperidine.[10]—A mixture of 10 g (0.033 mol) of 1,5-dibromo-3-phenylpentane, 30 ml of isopropyl alcohol, and 112 g (6.6 mol) of ammonia was heated 5 hr at 110° in a rocking autoclave. The reaction mixture was treated with 100 ml of 5% sodium hydroxide solution and extracted with chloroform. After drying the solvent was removed to leave 4.6 g (87%) of crystalline solid which was recrystallized from pentane to give pale yellow crystals, mp 60–62° (lit.[11] 57–60°).

Anal. Calcd for $C_{11}H_{15}N$: C, 81.9; H, 9.4; N, 8.7; neut equiv, 161. Found: C, 82.0; H, 9.8; N, 8.8; neut equiv, 165.

3,5-Dichloro-1-pentyl Acetate (15a).—A mixture of 60.3 g (0.5 mol) of **1**, 5 g of anhydrous zinc chloride, 100 ml of carbon tetrachloride, and 39.8 g (0.5 mol) of acetyl chloride was refluxed with stirring for 3 hr and allowed to stand overnight. Unreacted acetyl chloride was hydrolyzed with 50 ml of water, the layers were separated, and the organic material was washed with water, sodium bicarbonate solution, and dried. After removal of solvent, the residue was fractionated to give 36.1 g of unreacted **1**, bp 64–66° (38 mm), 3.2 g of an intermediate fraction, bp 56–121° (13 mm), and 27.8 g (78%) of product, bp 122–125° (13 mm): $n^{20}D$ 1.4596; nmr ($CDCl_3$) δ 4.0–4.45 (m, 3, CHCl and CH_2Cl),

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(8) E. Cerkovnikov and V. Prelog, *Chem. Ber.*, **74B**, 1648 (1941).

(9) M. G. J. Beets and H. van Essen, *Recl. Trav. Chim. Pays-Bas*, **76**, 1009 (1957).

(10) We wish to thank Mr. R. P. Williams for carrying out this experiment.

(11) C. F. Koelsch, *J. Amer. Chem. Soc.*, **65**, 2459 (1943).

3.6–3.85 (t, 2, OCH_2), and 1.85–2.20 (m, 7, CH_2CH_2 overlapping a singlet at 2.05, CH_3).

Anal. Calcd for $C_7H_{12}Cl_2O_2$: C, 42.3; H, 6.0. Found: C, 42.5; H, 6.2.

3,5-Dichloro-1-pentyl benzoate (15b) was prepared similarly in 74% yield, bp 131–135° (0.2 mm), $n^{20}D$ 1.5288.

Anal. Calcd for $C_{12}H_{14}Cl_2O_2$: C, 55.4; H, 5.4; Cl, 26.9. Found: C, 55.2; H, 5.4; Cl, 26.8.

5-Chloropentyl Methanesulfonate.—A mixture of 128 g (1.49 mol) of tetrahydropyran, 114.5 g (1.0 mol) of methanesulfonyl chloride, and 10 g of anhydrous zinc chloride was refluxed under nitrogen for 3 hr. The reaction mixture was taken up in ether, washed with water, and dried, and the ether was removed. The residue was distilled to give 101.4 g (51%) of bright yellow oil, bp 121–124° (0.5 mm), which darkened rapidly: nmr ($CDCl_3$) δ 4.2 (t, 2, $SO_2OCH_2CH_2$), 3.6 (t, 2, $-CH_2Cl$), 3.0 (s, 3, CH_3SO_2O), and 1.3–2.15 (m, 6, $-CH_2CH_2CH_2-$).

3-Chloroglutaric Acid (17).—To 200 ml of concentrated nitric acid at 80° was added a few drops of 1. After the reaction had initiated, the oxidation solution was cooled and 40 g (0.33 mol) of 1 was added dropwise at 30–40° over a 3-hr period. The reaction mixture was stirred an additional 18 hr at 20°, and the excess nitric acid was removed on a rotary evaporator at 20°. The resulting solid was dried over phosphorus pentoxide in a vacuum desiccator to give 52 g (95%) of colorless 3-chloroglutaric acid, mp 125–126° (lit.[12] mp 125–126°).

Anal. Calcd for $C_5H_7ClO_4$: C, 36.1; H, 4.2; Cl, 21.3; neut equiv, 83.3. Found: C, 36.2; H, 4.4; Cl, 21.5; neut equiv, 83.4.

Registry No.—**1**, 1768-64-5; **6**, 27070-15-1; **7**, 27070-16-2; **8**, 27070-17-3; **9**, 27070-18-4; **10**, 27070-19-5; **12**, 27070-20-8; **13b**, 27054-52-0; **14**, 27111-66-6; **15a**, 27070-21-9; **15b**, 27070-22-0; 3-methyl-3-phenyltetrahydropyran, 27070-23-1; 1,5-dibromo-3-phenylpentane, 27070-24-2; 5-chloropentyl methanesulfonate, 4337-21-7.

Acknowledgment.—We wish to thank Dr. J. C. Randall and Mrs. Joy Buell for recording the nmr spectra and Messrs. G. R. Herrington and W. F. Bowen for their technical assistance.

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The Redox Cleavage of the Sulfur–Sulfur Bond and Carbon–Sulfur Bond in Tetramethylthiuram Disulfide by *N*-Benzyl-1,4-dihydronicotinamide

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The interaction between *N*-benzyl-1,4-dihydronicotinamide and *N,N,N',N'*-tetramethylthiuram disulfide in ethanol at room temperature in the dark has led to the formation of *N*-benzyl-3-carbamylpyridinium *N,N*-dimethyldithiocarbamate, carbon disulfide, and possibly *N,N*-dimethylperthiocarbamate. The mode of formation and the nature of these salts are discussed.

In an earlier study we have proposed[2] that the cleavage of the sulfur–sulfur bond in diphenyl disulfide by *N,N*-dimethylaniline and by ethanolamine may proceed by a one-electron transfer mechanism, analogous to the redox reaction between hydrogen peroxide and ferrous ion.[3] The corresponding thiyl radical, mercaptide ion, and amine cation radical are formed.[2]

$$ArS—SAr + R_3N: \rightleftharpoons R_3N\cdot^+ \cdots ArS^- + ArS\cdot$$

In the extension of this study, we have examined the reactions between *N*-benzyl-1,4-dihydronicotinamide with *N,N,N',N'*-tetramethylthiuram disulfide and monosulfide and wish to report these findings.

The reports by Westheimer and others on the oxidation of 1,4-dihydropyridines by certain carbonyl compounds[4,5] and by olefinic double bonds[6] and further on the oxidation of 1-alkyl-1,4-dihydronicotinamide by malachite green[7] and thiobenzophenone[8] have led to information relevant to the biological oxidation–reduction involving the coenzyme, nicotinamide–adenine nucleotide (NAD) and its reduced form (NADH).

These reactions appear to proceed by an ionic hydride transfer mechanism. However, free-radical mechanisms were not ruled out since *N*-alkyl-1,4-dihydronicotinamide reduces α,α-diphenyl-β-picrylhydrazyl[8] and quinone[9] which are indeed free-radical reactions. The free-radical mechanism has been further enhanced by other findings of Westheimer and coworkers on the photochemical reduction of bromotrichloromethane by derivatives of 1,4-dihydropyridine[10] and the isolation of stable pyridinyl free radicals by Kosower.[11] Another report on the oxidation of 3,5-dimethyl-2,4-dicarbethoxy-1,4-dihydropyridine by 2-mercaptobenzophenone suggests that a thiyl radical intermediate is involved in this transformation.[12]

Results and Discussion

Reduction of Tetramethylthiuram Disulfide (TMTD) with *N*-Benzyl-1,4-dihydronicotinamide.—*N*-Benzyl-1,4-dihydronicotinamide reacts with an equimolar quantity of TMTD in absolute ethanol at room temperature in the dark to afford two products with ultraviolet absorption maxima at 410 and 435 mμ, respectively. A trace amount of carbon disulfide was also

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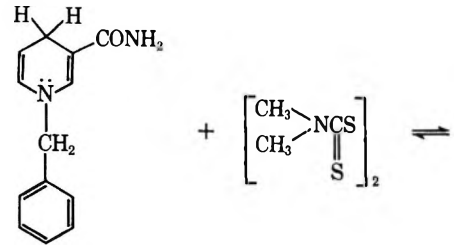
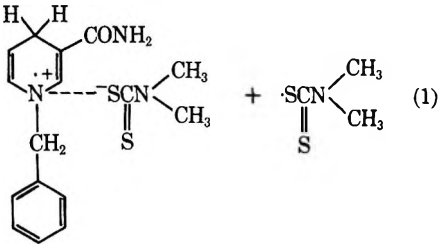
obtained. The compound with absorption maximum at 410 mμ was identified as *N*-benzyl-3-carbamylpyridinium *N*,*N*-dimethyldithiocarbamate. One can suggest a plausible mechanism for this reaction parallel to the one proposed for diphenyl disulfide and *N*,*N*-dimethylaniline.[2] Since this reaction can proceed at 25° in total darkness, one can assume that no prior homolytic dissociation of the sulfur–sulfur bond occurred.





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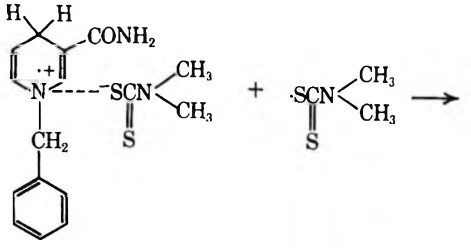

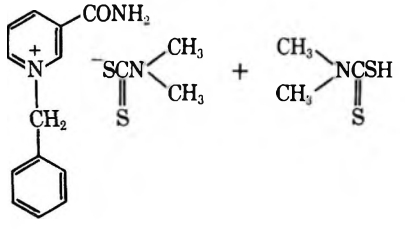

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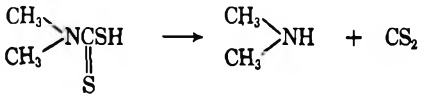

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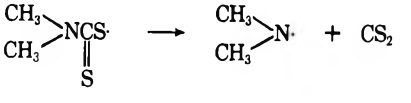
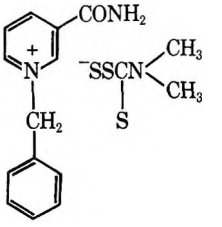


(4)

It is not clear whether the carbon disulfide is formed from the hypothetical dithiocarbamic acid as reported previously[13] or from the thiyl radical. The low yield of carbon disulfide and our failure to detect dimethylamine are consistent with reports that TMTD undergoes rather complicated decompositions leading to numerous minor products.[14] We have perhaps detected only a few of the major products of this reaction. The fact that this pyridinium salt absorbs at much longer wavelengths, 410 mμ, compared with the expected λ_{max} at 265 mμ for other pyridinium ion salts suggests that this pyridinium salt is not a typical one but resembles *N*-methylpyridinium iodide, a known charge-transfer complex species[15] which possesses an ultraviolet absorption maximum at much longer wavelength than 265 mμ. We were unable to isolate and identify the compound with absorption maximum at 435 mμ because it decomposes on exposure to air. We tentatively suggest that the product with absorption maximum at 435 mμ is *N*-benzyl-3-carbamylpyridinium dimethylperthiocarbamate, arising from cleavage of the carbon–sulfur bond



in TMTD. It has been reported that TMTD undergoes homolytic cleavage of the sulfur–sulfur bond thermally or photochemically to form thiyl radicals[16] and also the cleavage of the carbon–sulfur bond to give a carbon radical and a thiyl radical.[17]

A comparison of bond dissociation energies between carbon–sulfur and sulfur–sulfur bonds offers a partial explanation for this reaction. In organic peroxides, the oxygen–oxygen bond is considerably weaker than the carbon–oxygen bond, and, in their decomposition, oxygen–oxygen bond rupture becomes the sole primary reaction. In organic disulfides, the carbon–sulfur bond and sulfur–sulfur bonds are cited to be nearly equal in strength.[18]

It is not surprising that decomposition of disulfides follows a more complex route than that of peroxide, and it is not unreasonable to suggest that the cleavage of the sulfur–sulfur bond and carbon–sulfur bond in TMTD under the attack of *N*-benzyl-1,4-dihydronicotinamide happens concurrently, leading to both *N*-benzyl-3-carbamylpyridinium dimethyldithiocarbamate and dimethylperthiocarbamate.

More pertinent information is obtained by treating *N*-benzyl-1,4-dihydronicotinamide with *N*,*N*,*N*′,*N*′-tetramethylthiuram monosulfide (TMTM). In this reaction, only *N*-benzyl-3-carbamylpyridinium *N*,*N*-dimethyldithiocarbamate, with λ_{max} at 410 mμ, was obtained. The other compound absorbing at 435 mμ is completely missing. It is known that TMTM initiates free-radical polymerization of methyl methacrylate under heat or photolysis by homolytic cleavage of the carbon–sulfur bond.[16] It appears reasonable that the reduction of TMTM by *N*-benzyl-1,4-dihydronicotinamide should occur at the same site. The longer absorption maximum for the perthiocarbamate salt than that of the dithiocarbamate may result because the dithiocarbamate ion is more stabilized by resonance and

(13) C. W. Bedford and H. Gray, *Ind. Eng. Chem.*, **15**, 720 (1923).

(14) D. Craig, W. L. Davidson, and A. E. Juve, *J. Polym. Sci.*, **6**, 177 (1951).

(15) E. M. Kosower and P. E. Klinedust, Jr., *J. Amer. Chem. Soc.*, **78**, 3493 (1956).

(16) T. E. Ferrington and A. V. Tobolsky, *ibid.*, **77**, 4570 (1955).

(17) T. E. Ferrington and A. V. Tobolsky, *ibid.*, **80**, 3215 (1958).

(18) J. L. Franklin and H. E. Lumpkin, *ibid.*, **74**, 1023 (1952).

may have a higher ionization potential,[19] and more energy should be required to remove the electron from one of the sulfur atoms to the pyridine ring than in the case of perthiocarbamate. It seems unlikely that either the dithiocarbamate or perthiocarbamate ion add to the pyridinium ring to produce the dihydropyridinine analog, in a reaction analogous to the attack by other nucleophiles.[20] All such addition products have absorption maxima in the 340–360-mμ region in their ultraviolet absorption spectra, similar to the dihydropyridine compound. The products from reactions of TMTD and TMTM with *N*-benzyl-1,4-dihydronicotinamide do not absorb in this region.

Attempts to use TMTD and TMTM with *N*-benzyl-1,4-dihydronicotinamide as a redox couple to initiate free-radical polymerization of ethyl acrylate or acrylonitrile were unsuccessful. A possible explanation for this result is that both 1,4-dihydropyridine and the cation radical are effective hydrogen donors and therefore scavenge the growing polymer chain.

The reactions which were carried out in acetone as solvent did not produce 2-propanol or pinacol. The thiyl radical produced by the redox cleavage of the disulfide bond is apparently a better acceptor of hydrogen atom from the 1,4-dihydropyridine than the carbonyl group in acetone.

Experimental Section[21]

Reagents.—***N*-Benzyl-1,4-dihydronicotinamide** was prepared according to the method of Karrer and Stare.[22] Nicotinamide (Eastman, mp 129–130°, 10 g, 0.08 mol) was refluxed with 100 ml (0.87 mol) of benzyl chloride (Eastman, bp 179°) for 2 hr. The mixture was filtered hot and the solid was washed three times with 15 ml of ether. The yield of the crude *N*-benzyl-3-carbamylpyridinium chloride was 15 g, mp 234°. The reduction of this salt to *N*-benzyl-1,4-dihydronicotinamide was carried out following the procedure of Westheimer[7] and coworkers. Ten grams of the salt was shaken with 13.8 g of sodium carbonate and 25 g of sodium dithionite (Merck) in 150 ml of water for 10 min. The yellow crystals were filtered and recrystallized from the ethanol–water mixture: 4 g; mp 115–119° (lit.[22] 115–123°); λ_{max} 350 mμ (ε 7220).

***N*,*N*,*N*′,*N*′-Tetramethylthiuram monosulfide**, TMTM (Eastman), was recrystallized from ethanol, mp 106–108° (lit.[23] 108–110°).

***N*,*N*,*N*′,*N*′-Tetramethylthiuram disulfide**, TMTD (Eastman), was recrystallized from ethanol, mp 153–154° (lit.[24] 145–146°).

***N*-Benzyl-3-carbamylpyridinium *N*,*N*-dimethyldithiocarbamate** was prepared by reacting 1.4 g (1×10^{-2} mol) of sodium *N*,*N*-dimethyldithiocarbamate (Eastman) and 1.9 g (1×10^{-2} mol) of *N*-benzyl-3-carbamylpyridinium chloride in 50 ml of acetone. A yellow-colored solution and a precipitate were produced instantly when the two reagents were mixed in acetone. The solid was separated and extracted three times with 50-ml portions of acetone. The acetone solution upon concentration under reduced pressure afforded 1.51 g (~55%) of a yellow solid: mp 245–250° dec; λ_{max} 410 mμ (ε 1700) in ethanol. The analytical sample was recrystallized from ethanol, mp 248–250° dec.

Anal. Calcd for $C_{16}H_9N_3OS_2$: C, 57.6; H, 5.8; N, 12.6. Found: C, 57.7; H, 5.82; N, 12.63.

Reactions. TMTD and *N*-Benzyl-1,4-dihydronicotinamide.—Equal moles (5×10^{-3} mol) of each reactant were dissolved in 100 ml of absolute ethanol, and the solution was allowed to stand in the dark at 25° under nitrogen atmosphere. The reactions were carried out in duplicate, and each experiment was accompanied by a blank run where only the *N*-benzyl-1,4-dihydronicotinamide or TMTD was present under identical experimental conditions. The progress of the reactions and of the blank was followed by withdrawing an aliquot with a syringe at regular time intervals and noting the gradual decrease in absorbance of dihydropyridine at 350 mμ on a Beckman Model D.B. spectrophotometer. No attempt was made to follow the kinetics, but the half-life of the reaction was estimated to be ~6 days. The yield of the product with absorption maximum at 410 mμ (ε 1700) was estimated to be 67% from absorbance measurement. The yield of carbon disulfide, ~1%, was obtained by gas chromatographic analysis (Wilkens Aerograph, Model A-90-P, helium as carrier gas, 35 psi, flow rate 60 ml/min; column 20% Carbowax 20M on Chromosorb W 60–80; column temperature, 73°; injector, 148°; and detector, 282°). Effort directed to detect dimethylamine was not fruitful in any of the experiments. In the control runs, gas chromatography was sensitive enough to detect a minimum concentration of 1×10^{-5} mol of dimethylamine which corresponds to 0.1% yield.

In the blank runs, TMTD alone in ethanol was stable over a period of 5 weeks and *N*-benzyl-1,4-dihydronicotinamide showed no significant change in absorbance after 4 weeks.

***N*-Benzyl-3-carbamylpyridinium Dimethylthiocarbamate.**—In another run, a mixture of 1.2 g (5×10^{-3} mol) of TMTD and 1.07 g (5×10^{-3} mol) of *N*-benzyl-1,4-dihydronicotinamide in 100 ml of ethanol was allowed to stand for a period of 6 weeks under nitrogen at 25° in the dark. The mixture upon concentration by evaporation under reduced pressure furnished a yellow solid in 43% yield (0.72 g). Analytical sample after recrystallization from ethanol melted with decomposition at 249–250° with gas evolution and its ultraviolet absorption maximum in ethanol was 410 mμ (ε 1700).

Anal. Calcd for $C_{16}H_9N_3OS_2$: C, 57.7; H, 5.8; N, 12.6. Found: C, 57.4; H, 5.89; N, 12.64.

A mixture melting point with an authentic sample of *N*-benzyl-3-carbamylpyridinium *N*,*N*-dimethyldithiocarbamate prepared from sodium *N*,*N*-dimethyldithiocarbamate and *N*-benzyl-3-carbamylpyridinium chloride showed no depression.

Concentration of the mother liquor afforded a low-melting, viscous material but it deteriorated upon exposure to air. Effort directed to solidify this oily substance was not successful.

TMTM and *N*-Benzyl-1,4-dihydronicotinamide.—When a mixture of 1.02 g (5×10^{-3} mol) of TMTM and 1.07 g (5×10^{-3} mol) of *N*-benzyl-1,4-dihydronicotinamide in 100 ml of ethanol was allowed to stand in the dark under nitrogen atmosphere at 25° for 6 weeks, it gave a 65% yield of *N*-benzyl-3-carbamylpyridinium dimethyldithiocarbamate from absorbance measurement at 410 mμ. No band absorbing at 435 mμ was detected. In the blank run, TMTM was stable under identical conditions for a period of 2 months. In this and subsequent repeated runs under identical or different conditions, the yield of carbon disulfide was always nil.

Attempted Polymerization of Vinyl Monomers by TMTD and *N*-Benzyl-1,4-dihydronicotinamide.—Attempts were made to induce polymerization of acrylonitrile and ethyl acrylate with TMTD and *N*-benzyl-1,4-dihydronicotinamide. In a typical run, a solution of equal moles (5×10^{-5} mol) of TMTD and *N*-benzyl-1,4-dihydronicotinamide in 10 ml of ethyl acrylate was allowed to stand under nitrogen at 37° for 3 weeks. By that time, the 350-mμ absorbance peak due to the dihydronicotinamide had vanished. However, when the reaction mixture was diluted with excess methanol, no polymeric substance was obtained.

Attempted Reduction of Acetone to Isopropyl Alcohol by *N*-Benzyl-1,4-dihydronicotinamide and TMTD.—A series of reactions between TMTD and *N*-benzyl-1,4-dihydronicotinamide were run in reagent grade acetone in the dark and room light. Gas-phase chromatographic analysis was unable to detect any isopropyl alcohol in any of the experiments.

Registry No.—*N*-Benzyl-1,4-dihydronicotinamide, 952-92-1; *N*,*N*,*N*′,*N*′-tetramethylthiuram disulfide, 137-26-8; *N*-benzyl-3-carbamylpyridinium *N*,*N*-dimethyldithiocarbamate, 27192-77-4.

(19) R. S. Mulliken, *J. Amer. Chem. Soc.*, **74**, 811 (1952).
(20) J. Van Eys and N. O. Kaplan, *J. Biol. Chem.*, **228**, 305 (1957).
(21) Melting points are uncorrected. Elementary analyses are by M. S. Nagy of the Massachusetts Institute of Technology.
(22) P. Karrer and F. Stare, *Helv. Chim. Acta*, **20**, 418 (1937).
(23) M. Zbirovsky and V. Ettel, *Chem. Listy*, **51**, 2094 (1957).
(24) S. Akerstrom, *Ark. Kemi*, **14**, 387 (1959).

Mixed Sulfonic–Carboxylic Anhydrides. I. Synthesis and Thermal Stability. New Syntheses of Sulfonic Anhydrides

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Two new high-yield syntheses of mixed sulfonic–carboxylic anhydrides are described. Two modes of thermal decomposition of the products, disproportionation to simple anhydrides, and ketene extrusion take place, relative rates being dependent upon the temperature of reaction. The disproportionation reaction is used to effect a general synthesis of sulfonic anhydrides, whose behavior toward heat is also studied.

Mixed sulfonic–carboxylic anhydrides, formally derived by elimination of one molecule of water from a carboxylic and a sulfonic acid, have in the past received very little attention, although known for over 35 years. While *o*-sulfobenzoic anhydride, readily prepared from the acid, has been known since 1889,[2] the more active aliphatic sulfonic–carboxylic anhydrides were first mentioned in 1933 when Baroni[3] allegedly prepared a series of such compounds by treating silver or sodium carboxylate salts with aromatic or aliphatic sulfonyl chlorides at temperatures of between 120 and 200° for up to 10 hr, the products being collected by distillation (20 mm). Since, however, the products themselves, as will be demonstrated, are unstable at such temperatures and pressures, the validity of this work must remain open to question. A more efficient and unambiguous synthesis was pioneered by Overberger and Sarlo,[4] who treated acetonitrile solutions of silver sulfonates with acyl halides obtaining the mixed anhydride in moderate yield. Other syntheses of mixed anhydrides involved the reactions of sulfonic acids with ketene[5] and of sulfonyl chlorides with aromatic carboxylic acids in pyridine.[6] However, the yields in the former case were no greater than 10%, while the latter appeared to be restricted to aryl acyl chlorides.

We have developed two simple alternative modes of synthesis of mixed sulfonic–carboxylic anhydrides utilizing sulfonic acid and either acyl chloride or anhydride. Concurrently we have utilized this new method to effect two new high-yield syntheses of sulfonic anhydrides which possess advantages of yield, simplicity of operation, and cost over the available syntheses.[7] It is with these syntheses and some aspects of the thermal behavior of the mixed anhydrides that the present paper is concerned. The chemistry of mixed sulfonic–carboxylic anhydrides has been alluded to briefly[8] and will be more extensively considered in further publications in this series.[9]

Synthesis *via* Acid Chloride.—The synthetic method of choice consists in reacting an excess of carboxylic acid chloride with a sulfonic acid (eq 1). The method appears quite general, the ease of reaction decreasing

$$RCOCl + R'SO_3H \longrightarrow RCOOSO_2R' + HCl \quad (1)$$

$$R = CH_3 = C_2H_5 = C_6H_5CH_2 = (CH_3)_2CH = C_6H_5$$
$$R' = CH_3 = CH_3C_6H_4$$

markedly with the increase in electronegativity of the group attached to the carbonyl group of the acid chloride. The reaction course is readily charted by observation of the HCl gas, evolved as the only other primary product. In general, aliphatic acid chlorides present no difficulty, reaction being conducted either in the acid chloride itself as solvent, or in benzene (whose reflux temperature of 80° proves convenient). Thus with acetyl chloride, evolution of HCl ceases after 3–5 hr. When reaction is complete the solvent, if any, and excess acid chloride are removed at reduced temperature and pressure. The residue contains the mixed anhydride. Table I lists the anhydrides prepared by this method. All these products were characterized by a strong single carbonyl stretching frequency between 1780 and 1820 cm^{-1} and by their nmr spectra, details of which are given (Table I).

As prepared in this manner the products are contaminated by traces of free acid and by sulfonic anhydrides, the proportions of which were simply estimated from the nmr spectra. The presence of acid is due either to incomplete reaction, to thermal decomposition (*vide infra*), or to adventitious hydrolysis, to which the mixed anhydrides are exceedingly susceptible. The presence of sulfonic anhydride is the result of thermal disproportionation (*vide infra*). Purification by distillation is applicable only to the simplest member of the series, acetyl methanesulfonate, whose distillation temperature at 10^{-2} mm is sufficiently removed from the decomposition temperature as to enable almost quantitative recovery in analytically pure condition. All other mixed anhydrides suffered extensive decomposition upon attempted distillation. The products from aryl sulfonic acids are generally low-melting crystalline solids. Although purification by crystallization from hexane,[4,10] benzene, acetic anhydride,[11] or methylene chloride[6] have been reported for some of these compounds, we have found recrystallization to be unreliable as a means of purification, effecting partial hydrolysis. In general, mixed anhydrides could be used without further purification for most purposes.

When the acyl group is substituted by more electronegative groups, the reaction rate is correspondingly

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(1) Weizmann Fellow, 1967–1969.

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(9) M. H. Karger and Y. Mazur, *ibid.*, **91**, 5663 (1969).

(10) We found mixed anhydrides to be almost insoluble in hydrocarbon solvents. The best solvent for recrystallization is acetic anhydride. *Cf.* W. Flavell and N. C. Ross, *J. Chem. Soc.*, 5474 (1964).

(11) See ref 10: Flavell and Ross found that mesitylene disulfonyl chloride and silver acetate in acetic anhydride at 80° for 18 hr gave 27% mixed anhydride but after 16 hr in acetonitrile gave only a 50% yield of the anhydride.

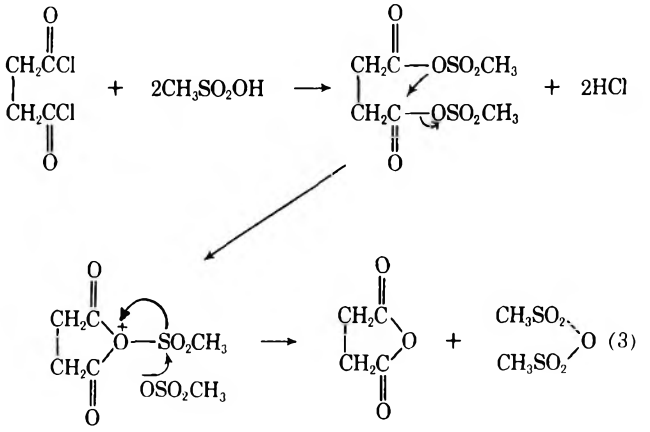
reduced, and higher temperature and more prolonged reaction times become necessary. Thus chloroacetyl chloride and methanesulfonic acid did not react completely until heated for 4 hr at 110° when almost all starting material was consumed. The reaction mixture was, however, a complex mixture of decomposition products together with less than 20% of the desired product (Table I).

Synthesis *via* Acid Anhydride.—An alternative synthetic procedure to that outlined above consists of heating an excess of carboxylic anhydride with the sulfonic acid for 20–30 min at 120° followed by removal under high vacuum of the excess anhydride together with the free acid formed in the reaction (eq 2).

$$(CH_3CO)_2O + CH_3C_6H_4SO_2OH \longrightarrow CH_3COOSO_2C_6H_4CH_3 + CH_3COOH \quad (2)$$

Acetyl *p*-toluenesulfonate and trichloroacetyl *p*-toluenesulfonate were prepared in this fashion. With higher molecular weight anhydrides, reaction in this manner is complicated by the involatility of both anhydride and acid, necessitating higher temperatures for their removal which cause decomposition of product. In general, the acid chloride method is much to be preferred from such practical considerations.

Reaction of Diacyl Chloride and Sulfonic Acids. Synthesis of Sulfonic Anhydrides.—When succinoyl chloride was reacted with sulfonic acids the expected di-mixed anhydrides were not isolated, but presumably decomposed under the reaction conditions (60°, 2 hr) to give a mixture of sulfonic anhydride and succinic anhydride. Trituration of the reaction mixture with ether effected complete separation, succinic anhydride being almost insoluble (eq 3). This reaction provided



(3)

a good synthesis of sulfonic anhydrides in a clean reaction of great simplicity. Yield averaged 80%. With oxalyl chloride the sulfonic anhydride was also obtained but in low yield (Table II).

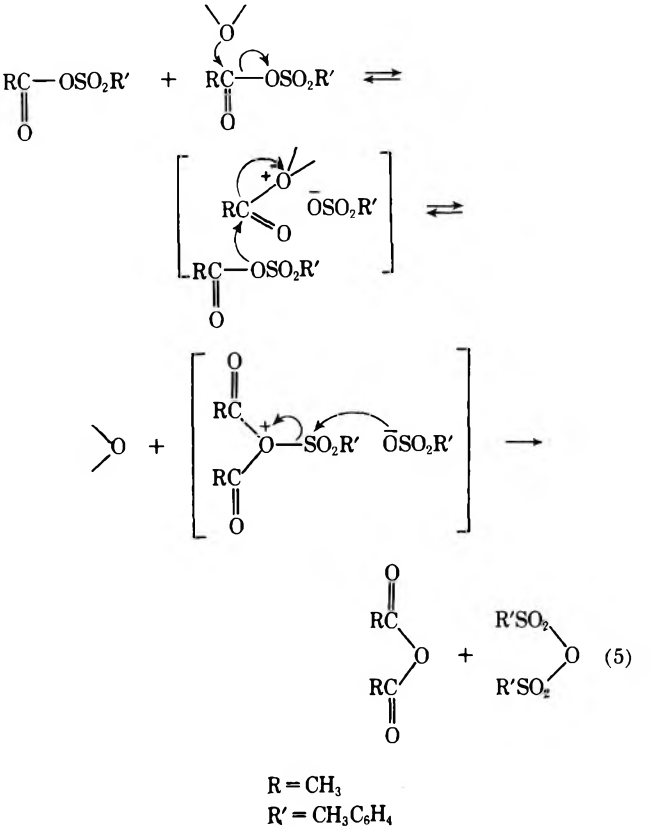
Thermal Decomposition of Mixed Sulfonic–Carboxylic Anhydrides. Below 130°.—The disproportionation of acyl sulfonates has been reported by Flavell and Ross[10] who stated that, as a preparative method for sulfonic anhydrides, thermal disproportionation was unsatisfactory due to decomposition of the sulfonic anhydrides at the temperature required for disproportionation. We have studied the thermal behavior of both mixed sulfonic–carboxylic and simple sulfonic anhydrides and wish to report that careful heating of the former provides an eminently satisfactory synthetic method by which large amounts of the latter can be prepared in excellent yield and very simple fashion.

We have found that not one but two thermal decomposition reactions are simultaneously underway when mixed sulfonic–carboxylic anhydrides (with one or more hydrogens β to the carbonyl) are heated. Below a fairly specific temperature of 130° only a simple disproportionation reaction leading to a mixture of carboxylic and sulfonic anhydrides is observed (eq 4). This reaction is

$$2CH_3COOSO_2CH_3 \longrightarrow (CH_3CO)_2O + (CH_3SO_2)_2O \quad (4)$$

a general one. The disproportionation reaction appears to be acid catalyzed. Thus, when acetyl methanesulfonate in which the acid content had been reduced to less than 0.5% by prolonged reflux in acetyl chloride was distilled at 120° (10^{-3} mm), 85% of the mixed anhydride was recovered. When, however, the acid content was increased to 5%, distillation under identical conditions gave only 10% of mixed anhydride, disproportionation having been promoted to the extent that over 50% yield of recrystallized methanesulfonic anhydride was obtained from the residue.

In solution the disproportionation was facilitated by polar solvents as has been observed previously.[10] Thus in acetonitrile we observed 25% disproportionation of acetyl methanesulfonate after 16-hr reflux, the remaining 75% being unchanged.[11] A more rapid catalytic effect is observed in oxygenated solvents; acetyl *p*-toluenesulfonic anhydride dissolved in ether does not recrystallize and the nmr spectrum of the evaporated solution shows obstinate retention of ether even after 2 hr at 10^{-3} mm. The residual oil on heating at 30° for 12 hr undergoes almost complete disproportionation. The extent of this catalysis is a consequence of coor-



(5)

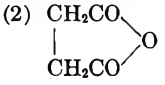
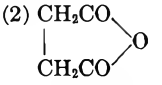
R = CH_3
R′ = $CH_3C_6H_4$

TABLE I
PREPARATION OF MIXED SULFONIC–CARBOXYLIC ANHYDRIDES

Acid chloride[a]	Acid	Product	Registry no.	Reaction conditions (hr, °C, solvent)	Yield,[b] %	Nmr, δ (ppm)[c]
CH_3COCl (2.5)	CH_3SO_3H	$CH_3COOSO_2CH_3$	5539-53-7	16, 55	85[d]	2.28 s, 3.33 s
CH_3COCl	$C_7H_7SO_3H$	$CH_3COOSO_2C_7H_7$[e]	26908-82-7	5, 55	97 (90, 4)	2.13 s, 2.44 s, 7.64 q
C_2H_5COCl (3.0)	$C_7H_7SO_3H$	$C_2H_5COOSO_2C_7H_7$	26926-29-4	2, 70	100 (75, 2)	1.08 t, 2.45 q, 2.47 s, 7.6 m
C_2H_5COCl	CH_3SO_3H	$C_2H_5COOSO_2CH_3$	26926-30-7	4, 80	98 (80, 15)	1.20 t, 2.58 q, 3.26 s
$C_6H_5CH_2COCl$	CH_3SO_3H	$C_6H_5CH_2COOSO_2CH_3$	26926-31-8	16, 80, C_6H_6	100 (70, 5)	3.20 s, 3.73 s, 7.32 s
$C_6H_5CH_2COCl$	$C_7H_7SO_3H$	$C_6H_5CH_2COOSO_2C_7H_7$	26926-32-9	5, 80, C_6H_6	100 (65, 10)	2.42 s, 3.68 s, 7.27 s, 7.6 m
$CH_3CH_2CH_2COCl$	CH_3SO_3H	$CH_3CH_2CH_2COOSO_2CH_3$	26926-33-0	5, 80, C_6H_6	93 (70, 15)	1.00 t, 1.71$_6$, 2.52 t, 3.3 s
$(CH_3)_2CHCOCl$	CH_3SO_3H	$(CH_3)_2CHCOOSO_2CH_3$	26926-34-1	5, 80, C_6H_6	94 (70, 20)	1.26 d, 2.70$_6$, 3.32 s
C_6H_5COCl (1.0)	CH_3SO_3H	$C_6H_5COOSO_2CH_3$	26926-35-2	5, 80, C_6H_6	90 (50, 25)	3.48 s, 7.80 m
C_6H_5COCl (1.0)	$C_7H_7SO_3H$	$C_6H_5COOSO_2C_7H_7$[f]	13079-28-2	5, 80, C_6H_6	88 (60, 25)	2.42 s, 7.7 m
$ClCH_2COCl$ (1.0)	CH_3SO_3H	*g*		4, 110		8 singlets[g]

[a] Twofold molar excess used except where noted in parentheses. [b] First figure gives crude yield, second gives percentage product in crude material as estimated from the nmr spectrum, and the final figure gives the *molar* percentage of free acid estimated from the intensity of the acid proton in the nmr. [c] s = singlet, etc.; number subscript = multiplicity. [d] Distilled analytically pure, bp 70–72° (10^{-3} mm); lit. (ref 6) 56° (10^{-2} mm). [e] Mp 54–56°. [f] Mp 55–58°, ref 4. [g] The product was a mixture of six compounds: (1) CH_3SO_3H, (2) $(CH_3SO_2)_2O$, (3) $(ClCH_2CO)_2O$, (4) $ClCH_2COCl$, (5) $ClCH_2CO_2H$, (6) $ClCH_2COOSO_2CH_3$.

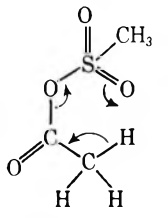
TABLE II
SYNTHESIS OF SULFONIC ANHYDRIDES FROM DIACYL CHLORIDES

Acid chloride	Acid	Product	Reaction conditions (hr, °C, solvent)	Yield, %	Nmr, δ (ppm)
$(CH_2COCl)_2$ (0.5)	CH_3SO_3H	(1) $(CH_3SO_2)_2O$	2, 60	90	3.43 s
		(2) 		73	3.00 s
$(CH_2COCl)_2$ (0.5)	$C_7H_7SO_3H$	(1) $(C_7H_7SO_2)_2O$	2, 80, C_6H_6	73	2.45 s 7.56 q
		(2) 		100	3.00 s
$(COCl)_2$ (0.5)	CH_3SO_3H	$(CH_3SO_2)_2O$	6, 63	30	3.43 s

dination with oxygen depicted in eq 5 and observed in the facile cleavage of ethers by acyl sulfonates.[8,9]

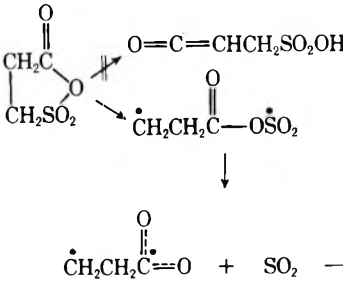
Synthesis of Sulfonic Anhydrides by Pyrolysis of Mixed Anhydrides.—From the above observations it is clear that as long as the temperature remains below 130°, pyrolysis of mixed sulfonic–carboxylic anhydrides can provide a facile synthesis of sulfonic anhydrides. Simple heating of freshly prepared mixed anhydride on a water bath for sufficient time to ensure complete disproportionation gives almost complete conversion. The product can be recovered either by distillation or by extraction of the residue with ether, which deposits the pure anhydride on cooling, leaving any sulfonic acid formed *via* the alternative pathway (*vide infra*) in the residue. Yields are good, up to 80% on unrecovered sulfonic acid.

Thermal Decomposition of Mixed Sulfonic–Carboxylic Anhydrides. B. Above 130°.—At about 130° a second reaction predominates (for those anhydrides with transferable hydrogen β to the carbonyl group), in which the sulfonic acid is regenerated with simultaneous evolution of ketene.[12] This latter was trapped in cooled hexane and characterized by its ir frequency (2310 cm^{-1} [13]) and by its conversion on addition of ethanol to ethyl acetate (eq 6). The thermal decomposition of the cyclic anhydride of β-sulfopropionic



$$\xrightarrow{130^\circ} H_2C{=}C{=}O + CH_3SO_3H \quad (6)$$

acid[14] does not follow this course to yield the expected ring-opened sulfonic acid–ketene or a derivative. Under conditions in which acetyl sulfonates speedily decompose quantitatively to the respective sulfonic acid (2 min at 130°), β-sulfopropionic anhydride remains unchanged even after 2 hr at 130°. More vigorous heating to 180° has been observed to induce a slow decomposition to yield, ultimately, acrylic acid after extrusion of SO_2[15] (eq 7). This result would argue in favor of



$$CH_2CH_2C{=}O + SO_2 \longrightarrow (CH_2{=}CHCOOH) \quad (7)$$

(12) The ease of ketene formation (130°) is in contrast with the temperature (500°) required for its generation from acetic anhydride. See, for example, G. J. Fisher, A. F. Mclean, and A. W. Schnizer, *J. Org. Chem.*, **18**, 1055 (1953).

(13) For which in the vapor state a strong band at 2150 cm^{-1} is observed: L. Grimke Drayton and H. W. Thompson, *J. Chem. Soc.*, 1416 (1948).

(14) M. S. Kharasch, T. H. Chao, and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 2393 (1940).

(15) T. Nagai, K. Nishitomi, and N. Togura, *Tetrahedron Lett.*, 2419 (1966).

intramolecular reaction for high-temperature thermal decomposition of mixed anhydrides since, in such a case, β-sulfopropionic anhydride would remain inert or follow an alternative reaction path as indeed is observed. On the other hand an intermolecular mechanism would favor an analogous reaction for the cyclic mixed anhydride as for the general acyclic case.

Thus reaction 6 is more likely to be intramolecular in contradistinction to reaction 4 which is most easily visualized as intermolecular.

Thermal Decomposition of Sulfonic Anhydrides.—That the above reaction of mixed anhydrides to give sulfonic acid and ketene is not merely a consequence of prior disproportionation followed by decomposition of the sulfonic anhydride to sulfonic acid was established by examining the thermal behavior of sulfonic anhydrides. Thus, methanesulfonic anhydrides decomposed only above 250° to give methanesulfonic acid (70%), residual intractable polymer (15%), and sulfene which presumably did not survive its conditions of generation (eq 8). The reaction is analogous to mixed anhydride

$$CH_3SO_2OSO_2CH_3 \xrightarrow{250^\circ} CH_3SO_3H + (CH_2{=}SO_2) \qquad (8)$$

intramolecular decomposition (eq 6). Under the terms of this reaction *p*-toluenesulfonic anhydride should not decompose in the same manner. When this anhydride was heated in a sealed evacuated tube to 230°, a black intractable polymeric solid, which gave no acid reaction on boiling with water, was the only nonvolatile product. Liquid SO_2 and toluene were collected at the mouth of the tube.

Experimental Section[16]

Mixed Sulfonic-Carboxylic Anhydrides.[17] A. From Acid Chloride-Acetyl Methanesulfonate.—A mixture of 96.1 g of methanesulfonic acid (1.0 mol) and 200 g of acetyl chloride (2.5 mol) was gently heated under reflux for 16 hr, moisture being carefully excluded. No further evolution of HCl gas being observed, the excess acetyl chloride was removed under vacuum at room temperature from the deep red reaction mixture. Careful distillation ($<10^{-2}$ mm, oil bath temperature below 120°) gave 117.2 g (85%) of acetyl methanesulfonate, a pale yellow oil solidifying below 0°: ir (smear) 1810 cm^{-1} (C=O); nmr δ 2.28 (s, 3, $COCH_3$) and 3.33 (s, 3, SO_2CH_3).

Anal. Calcd for $C_3H_6O_4S$: C, 26.08; H, 4.38; S, 23.21. Found: C, 26.11; H, 4.46; S, 23.18.

Acetyl *p*-Toluenesulfonate.—Anhydrous *p*-toluenesulfonic acid (92.5 g, 0.54 mol) was gently heated under reflux in 150 g of acetyl chloride (1.9 mol) until evolution of HCl had ceased (3–5 hr). The excess acetyl chloride was removed at room temperature under vacuum, leaving 112.5 g (97.5%) of crude acetyl *p*-toluenesulfonate as an off-white crystalline mass: mp 54–56°; ir ($CHCl_3$) 1820 (C=O) and 1600 cm^{-1} (aromatic C=C); nmr δ 2.13 (s, 3, $COCH_3$), 2.44 (s, 3, $C_6H_4CH_3$), and 7.64 (AB system J_{AB} = 8 Hz, Δ_{AB} = 35 Hz, 4, *p*-C_6H_4). *p*-Toluenesulfonic anhydride, present as an impurity (*ca.* 10%), was removed by cooling an ether solution of the crude product when the *p*-toluenesulfonic anhydride present was deposited from solution.

B. From Acid Anhydride-Acetyl *p*-Toluenesulfonate.—Anhydrous *p*-toluenesulfonic acid (264 g, 1.5 mol) was dissolved in an excess of 375 g of acetic anhydride (2.7 mol) and the mixture heated in an oil bath at 130° for 30 min. Excess acetic anhydride together with acetic acid formed in the reaction were removed by distillation under high vacuum at a temperature <70°. The residual oil, on cooling, solidified to 315 g (96%) of a red crystalline mass. The nmr spectrum of the product was identical with that of the sample prepared above, the proportion of free acid being about 10%, as estimated from the relative intensity of the free acid proton in the nmr.

Sulfonic Anhydrides.[18] Methanesulfonic Anhydride. Method 1.—A mixture of 200 g of acetyl chloride (2.5 mol) and 96.1 g of methanesulfonic acid (1.0 mol) was refluxed for 5 hr, when the proportion of free acid estimated from the nmr was 5%. The mixture was slowly distilled at a bath temperature of 120° (0.1 mm) until no more acetyl methanesulfonate came over (5–15%). The almost black pot residue was repeatedly extracted with ether; the extracts were dried, decolorized, concentrated, and cooled, depositing 45 g (52%) of methanesulfonic anhydride, mp 68°, mmp 70° (lit.[19] 69.5–70.5°), nmr δ 3.45 (s, 3, CH_3SO_2). Methanesulfonic acid (32 g, 33%) was recovered by distillation from the ether-insoluble residue, bp 140–142 (0.1 mm).

Method 2 (Table II).—A mixture of 34.4 g of succinoyl chloride (0.22 mol) and 42.3 g of methanesulfonic acid (0.44 mol) was heated at 60° for 2 hr, after which the mixture was placed under high vacuum at room temperature.[20] The residual solid was triturated with dry ether leaving 16.5 g (73%) of succinic anhydride, mp 119°, mmp 120°. The ether solution was concentrated and cooled to 0° collecting 24.3 g of methanesulfonic anhydride, mp 56–60°. Repeated concentration and cooling yielded two further crops (8.0 g, mp 62–64°; and 2.7 g, mp 66–68°). Total yield was 35.0 g (90%).

Thermal Decomposition of Acetyl Methanesulfonate. A.—A stream of dry nitrogen was passed through 6.65 g of acetyl methanesulfonate (20.7 mmol) into dry hexane cooled below −30°. The sulfonate was then heated at 130° for 15 min. The nmr spectrum of the residue showed the total absence of starting material or of material other than methanesulfonic acid. The residue (6.2 g) was dissolved in water. Extraction with ether yielded 80 mg (1.3%) of nonacidic material. The solution ir spectra of the hexane before and after heating were compared. They were not identical, an intense band at 2310 cm^{-1} being present in the latter. This band disappeared on warming the solution to room temperature and was converted, on addition of ethanol, to a band at 1720 cm^{-1}. When the experiment was repeated, passing the effluent gas into a solution of diisopropylamine in ether, evaporation of this solution to dryness left an oil, whose nmr spectrum possessed a sharp singlet at δ 2.0. When the experiment was repeated in a sealed system and heating commenced at 70°, the sulfonate remained unchanged until 128°, when it rapidly darkened and decomposed, with evolution of gas, which was complete in 2 min.

B.—A solution of acetyl methanesulfonate (10 ml) in dry acetonitrile (25 ml) was refluxed for 16 hr. The acetonitrile was removed *in vacuo*. The nmr spectrum of the residue showed it to consist of starting material (75%) and an equimolar mixture acetic and methanesulfonic anhydrides (25%). No methanesulfonic acid was detected.

C.—When acetyl *p*-toluenesulfonate was heated to 130° in a manner identical with that of the methanesulfonate (A above), the dark residue consisted solely of *p*-toluenesulfonic acid (97%).

Thermal Decomposition of Methanesulfonic Anhydride.—Methanesulfonic anhydride (4.0 g) was heated at progressively higher temperatures from 25 to 300° under a stream of nitrogen. Decomposition commenced at 250° as evidenced by evolution of gas and darkening of the hitherto clear liquid and was complete after 15 min. The black residue contained mostly methanesulfonic acid, recovered by high vacuum distillation (1.6 g, 71%). The residue, an insoluble black solid, was completely intractable (600 mg).

Thermal Decomposition of *p*-Toluenesulfonic Anhydride.—*p*-Toluenesulfonic anhydride (600 mg) was heated in a sealed, evacuated tube to 230°, when a colorless liquid distilled and collected at the mouth of the tube. After heating for a further 15 min, the tube was cooled and opened. The liquid at the mouth consisted of toluene and SO_2. The residue at the foot of the tube, a black intractable solid, gave no reaction to litmus after being boiled with water.

(16) Melting points are uncorrected. Infrared spectra were determined with Perkin-Elmer Infracord recording spectrophotometer. The nmr spectra were determined on a Varian A-60A spectrophotometer in $CDCl_3$; peak positions are indicated in ppm downfield from TMS serving as internal reference. Mass spectra were measured with an Atlas CH-4 instrument.

(17) The preparative procedures for all mixed anhydrides described in Table I closely followed these described below. Exact conditions, where these vary, are given in Table I.

(18) The two procedures illustrated below for methanesulfonic anhydride are equally applicable to other sulfonic anhydrides, the reaction conditions and work-up procedure being identical.

(19) L. Field and P. H. Settlage, *J. Amer. Chem. Soc.*, **76**, 1222 (1954).

(20) The observed loss of weight was 16.0 g. That required for evolution of 2 mol of HCl is 15.06 g.

Mixed Sulfonic–Carboxylic Anhydrides. II.[1] Reactions with Aliphatic Ethers and Amines

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The powerful acylating ability of mixed sulfonic–carboxylic anhydrides is demonstrated by their facile cleavage of ethers. The nature of this cleavage process is discussed and its distinction and advantages over acyl halide cleavage indicated. Potential synthetic uses of this reaction are pointed out and a brief summary of the results with amines is included.

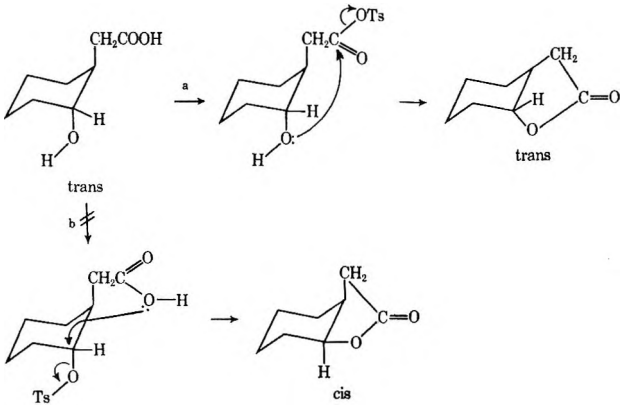
The chemistry of mixed sulfonic–carboxylic anhydrides has been but sporadically and sparsely investigated,[1–12] although it had already been pointed out in 1955 that mixed anhydrides should be "highly reactive acylating agents."[3] Following their general synthesis,[1,4–6] this surmise was confirmed, and the reagents were indeed observed to function as powerful acylating agents. Thus anilines, primary alcohols, and phenols were speedily acylated in good yield, and the reactivity of mixed anhydrides compared favorably with that of benzoyl chloride;[4] hydrogen fluoride reacted to give the relatively inaccessible acetyl fluoride. Acylation reactions on O and N with subsequent cleavage were observed with species which were readily cleavable with mild acid. Thus, such reactions were observed to proceed upon the epoxide ring[4] and with both 1,1-diamines and dialkylamino ethers, these latter both yielding immonium sulfonate salts.[6]

* To whom correspondence should be addressed.

(1) Part I: M. H. Karger and Y. Mazur, *J. Org. Chem.* **36**, 528 (1971).

(2) A preliminary account of some of the work described in this paper has previously appeared: M. H. Karger and Y. Mazur, *J. Amer. Chem. Soc.*, **90**, 3878 (1968).

(3) J. H. Brewster and C. J. Ciotti, Jr., *ibid.*, **77**, 6214 (1955). In order to account for the observation that *trans*-2-hydroxycyclohexaneacetic acid is lactonized with *retention* of configuration on treatment with sulfonyl chlorides in pyridine, it was suggested that the reaction proceeded *via* a mixed anhydride intermediate (path a) rather than the expected sulfonate (path b); see J. B. Brewster and C. H. Kucera, *ibid.*, **77**, 4564 (1955).



(4) C. G. Overberger and E. Sarlo, *ibid.*, **85**, 2446 (1963).

(5) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **27**, 2667 (1962).

(6) H. Boehme and K.-H. Meyer-Dulheuer, *Justus Liebigs Ann. Chem.* **688**, 78 (1965).

(7) M. S. Kharasch, T. H. Chao, and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 2393 (1940).

(8) T. Nagai, K. Nishitomi, and N. Tokura, *Tetrahedron Lett.*, 2419 (1966).

(9) W. Flavell and N. C. Ross, *J. Chem. Soc.*, 5474 (1964).

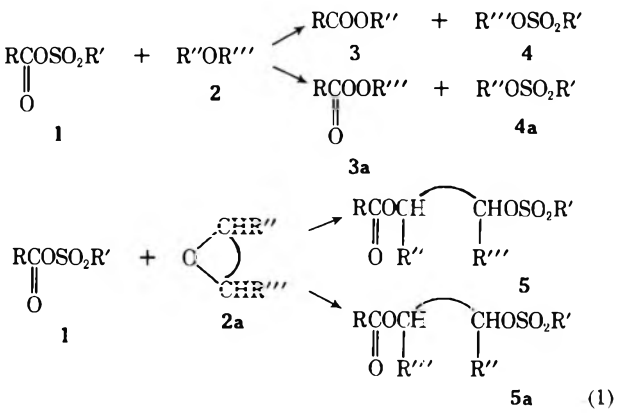
(10) A. Baroni, *Atti Accad. Naz. Lincei, Mem., Cl. Sci. Fis. Mat. Natur.*, **17**, 1081 (1933).

(11) M. H. Karger and Y. Mazur, *Isreal J. Chem.*, **6**, 3 (1968).

(12) W. J. Knoth, *J. Amer. Chem. Soc.*, **86**, 3973 (1964).

We wished to demonstrate the considerable acylating ability of mixed anhydrides and, to this end, have examined their reactions with aliphatic ethers, ordinarily inert to all but the most powerful electrophiles. Our results have shown the acylating ability of the system to be extremely high and we have developed from these experiments a general method for the cleavage of aliphatic ethers.

I. Reactions of Mixed Sulfonic–Carboxylic Anhydrides with Ethers.—Treatment of a wide variety of aliphatic ethers (simple or mixed, cyclic or acyclic) with mixed anhydrides effected cleavage represented in the general case by eq 1. An ether, R″OR‴, **2**,



(1)

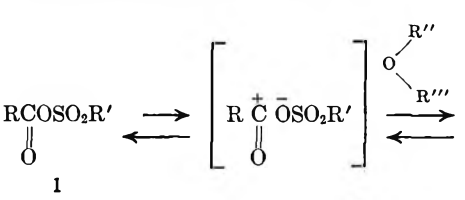
should suffer cleavage by an acyl sulfonate, $RCOOSO_2R'$, **1**, being converted in the process to a mixture of carboxylate **3** and **3a** and sulfonate ester **4** and **4a** or, if the initial ether were cyclic, to a cyclic diester or, in unsymmetrical cyclic ethers, **2a**, to a potential mixture of two cyclic diesters **5** and **5a**. Table I lists the ethers cleaved in this manner. The yields obtained are high, reaction occurring under mild conditions without the necessity for added Lewis acid catalyst. Thus the most unreactive ethers, the diprimary acyclic cases, are cleaved in 1 hr or so at 130°, or in several hours under reflux in acetonitrile. All other ethers require less drastic conditions. Cleavage of asymmetric ethers occurs with a higher specificity than observed with other reagents, and the products are clean and free of secondary products. We believe the reaction to proceed *via* initial acylation of the ether oxygen atom followed by cleavage of one of the two adjoining carbon–oxygen bonds.

The first step can be visualized in either of two ways. The acylation could take place *via* the highly reactive acylium ion, present in small concentrations and gener-

TABLE I
CLEAVAGE OF ALIPHATIC ETHERS WITH MIXED SULFONIC–CARBOXYLIC ANHYDRIDES

Ether	Mixed anhydride	Reaction conditions (°C, hr, solvent)	Product	Yield, %
$(n\text{-}C_3H_7)_2O$	$CH_3COOSO_2C_7H_7$	91, 15	$CH_3COOC_3H_7$	...[a]
			$C_3H_7OSO_2C_7H_7$	30
$(n\text{-}C_4H_9)_2O$	$CH_3COOSO_2C_7H_7$	80, 15, CH_3CN	$CH_3COOC_4H_9$	...[a]
			$C_4H_9OSO_2C_7H_7$	50
$C_2H_5O\text{-}n\text{-}C_4H_9$	$CH_3COOSO_2CH_3$	130, 2	$CH_3COOC_2H_5$	47 } 66 total
			$CH_3COOC_4H_9$	19 }
			$C_2H_5OSO_2CH_3$	...[a]
			$C_4H_9OSO_2CH_3$	...[a]
$(C_6H_5CH_2)_2O$	$CH_3COOSO_2C_7H_7$	25, 48, CH_3CN	$CH_3COOCH_2C_6H_5$	50
			$C_6H_5CH_2OSO_2C_7H_7$	76[b]
	$CH_3COOSO_2C_7H_7$	25, 2,[d] CH_3CN	$CH_3COOCH_2CH_2OSO_2C_7H_7$	80
	$CH_3COOSO_2CH_3$	25, 2,[d] CH_3CN	$CH_3COOCH_2CH_2OSO_2CH_3$	63
	$CH_3COOSO_2C_7H_7$	25, 12[c]	$CH_3COO(CH_2)_4OSO_2C_7H_7$	82
	$C_2H_5COOSO_2C_7H_7$	25, 48[d]	$C_2H_5COO(CH_2)_4OSO_2C_7H_7$	95
	$CH_3COOSO_2CH_3$	25, 12[d]	$CH_3COO(CH_2)_4OSO_2CH_3$	95
	$CH_3COOSO_2CH_3$	82, 48	$CH_3COO(CH_2)_6OSO_2CH_3$	80[e]
	$CH_3COOSO_2C_7H_7$	82, 48	$CH_3COO(CH_2)_6OSO_2C_7H_7$	95[e]
	$CH_3COOSO_2C_7H_7$	80, 24	$CH_3COOCH_2CH_2OCH_2CH_2OSO_2C_7H_7$	87
	$C_2H_5COOSO_2C_7H_7$	80, 48	$C_2H_5COOCH_2CH_2OCH_2CH_2OSO_2C_7H_7$	67
	$CH_3COOSO_2C_7H_7$	80, 16, CH_3CN	$CH_3COOCH_2CH{=}CHCH_2OSO_2C_7H_7$	82
	$CH_3COOSO_2C_7H_3$	80, 16, CH_3CN	$CH_3COOCH_2CH{=}CHCH_2OSO_2CH_3$	54
$i\text{-}(C_3H_7)_2O$	$CH_3COOSO_2C_7H_7$	80, 18, CH_3CN	$i\text{-}C_3H_7OCOCH_3$	...[a]
			$i\text{-}C_3H_7OSO_2C_7H_7$	80
$i\text{-}(C_3H_7)_2O$		80, 24	$i\text{-}C_3H_7OCOCH_2CH_2SO_2OiC_3H_7$	42
	$CH_3COOSO_2C_6H_4CH_3$	25, 12	$CH_3CO(CH_2)_3CH(CH_3)OSO_2C_7H_7$[f]	95
	$CH_3COOSO_2C_7H_7$	25, 2	$CH_3COOCH_2CH(CH_3)OSO_2C_7H_7$	88
			$CH_3COOCH(CH_3)CH_2OSO_2C_7H_7$	
	$CH_3COOSO_2CH_3$	25, 2	$CH_3COOCH_2CH(CH_3)OSO_2CH_3$	40
			$CH_3COOCH(CH_3)CH_2OSO_2CH_3$	
$(tert\text{-}C_4H_9)OC_2H_5$	$CH_3COOSO_2CH_3$	25, 0.5, CH_3CN	$CH_3COOC_2H_5$[f]	
			$(CH_3)_2C{=}CH_2$	
$CH_3COOCH_2CH_2O$				
	$CH_3COOSO_2C_7H_7$	130, 2	$CH_3COOCH_2CH_2OSO_2C_7H_7$[f]	45
$C_7H_7SO_2OCH_2CH_2$				

[a] The ester was not separated from the excess of ether used. [b] Yield based on yield of polybenzyl after distillation of benzyl acetate. [c] Following the reaction course by nmr spectroscopy showed reaction to be complete after 3 hr. [d] Reaction immediate and exothermic. [e] Yield after 4 hr, reflux 35°. [f] No trace of alternative products were observed showing cleavage to be specifically unidirectional.



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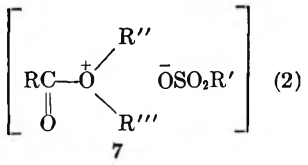

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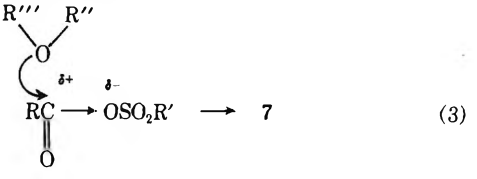
(2)

ated by the equilibrium outlined in eq 2.[13] Alternatively acylation could take place by attack of the ether on an un-ionized molecule of mixed anhydride (eq 3).



6

(3)

In either case, the reason for the high reactivity of mixed anhydrides is the powerful electron-withdrawing nature of the sulfonate group.

We could find no direct evidence for the presence of the complex **7**.[14] Thus careful and continuous examination of mixtures of various concentrations of mixed anhydride in both easily cleaved (tetrahydrofuran), and less easily cleaved (*n*-butyl ether, 1,4-dioxane) ethers at ambient temperatures revealed neither a shift in the nmr frequencies of the $-CH_2O-$ group, nor any new peak (minimum shift observable 0.5 cps). This is in direct contrast to the equilibrium between ethyl ethers and boron halides where the nmr frequencies of the CH_2O group hydrogens shift downfield, the magnitude of the shift increasing with the molar ratio of boron trihalide.[15] The results indicate that in an ether–mixed anhydride solution the concentration of complex

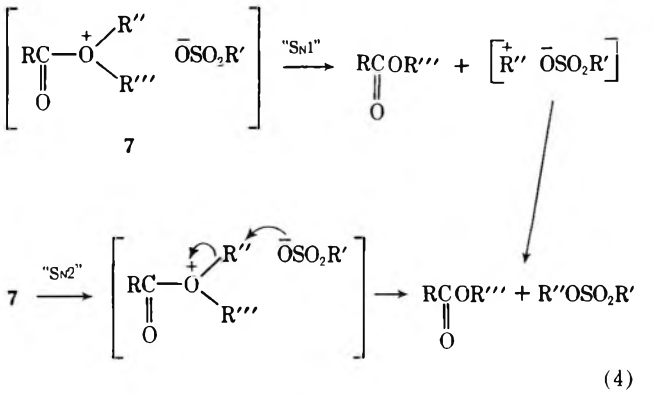
(13) Similar equilibria have been put forward to explain the mode of acylation of trifluoroacetic anhydride in carboxylic acids [E. J. Bourne, M. J. Stacey, J. C. Tatlow, and J. Randles, *J. Amer. Chem. Soc.*, **76**, 3206 (1954)], and of acyl halides in acetic anhydride [G. Jander, E. Rusberg, and H. Schmidt, *Z. Anorg. Chem.*, **255**, 238 (1948)].

(14) The compound $(CH_3CO^+)SbCl_6^-$ is thought, from conductivity measurements, to be present in mixtures of antimony pentachloride–acetyl chloride [F. Seel and H. Bauer, *Z. Naturforsch. B*, **2**, 397 (1947)], while the formation of a complex salt of structure $(CH_3COOEt_2^+)BF_4^-$ from acetyl fluoride and the ethyl ether complex of BF_3 has been reported at low temperatures [F. Seel *Z. Anorg. Chem.*, **250**, 331 (1943)].

(15) E. Gore and S. S. Danyluk, *J. Phys. Chem.*, **69**, 89 (1965); R. A. Craig and R. E. Richards, *Trans. Faraday Soc.*, **59**, 1962 (1963). The downfield shift at a 1:1 ratio of diethyl ether–boron trifluoride is *ca.* 25 Hz. Only one signal is observed in these mixtures indicating a rapid exchange of boron halide between ether molecules at room temperature.

7, in relation to unchanged ether, was too small to be observed by nmr (<2%).

The mechanism of cleavage of the complex 7 closely parallels that observed for the Lewis acid catalyzed cleavage of ethers by acyl halides, which have been extensively covered in two reviews.[16,17] For these reactions SN1 mechanism is the rule for all but primary ethers which appear to undergo cleavage by an SN2 mechanism (eq 4). Our cleavage reactions appear to follow a similar course. Thus we have observed the reactivity toward mixed anhydrides to be in the order tertiary ethers ≫ secondary ether > primary ethers, with benzylic ethers showing the expected enhanced

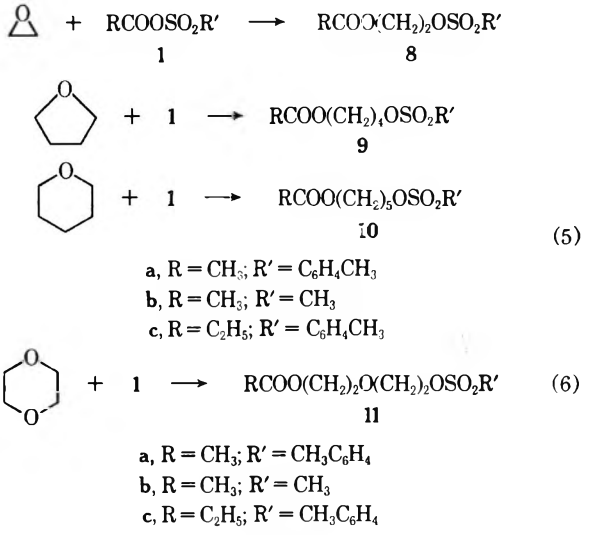


(4)

reactivity (Table I). Mixed anhydrides do, however, exhibit one important mechanistic difference stemming from the fact that sulfonate ion is an exceptionally weak nucleophile.[18] Thus the tendency for reaction to follow the SN2 path is less pronounced in any given case than for the corresponding acyl halide and, in cases where SN1 cleavage is the rule, the lifetime of the generated carbonium ion will be greater than for acyl halide cleavage. Using the recent suggestion of Sneen and Larson,[19] we can say that mixed anhydride–ether cleavage will be displaced toward the SN1 end of the mechanistic spectrum compared with acyl halide–ether cleavage. This has two important consequencies. Cleavage of mixed ethers will favor cleavage of the bond to the more substituted radical to a greater extent. In addition, the longer lifetime of a carbonium ion generated by mixed anhydride cleavage allows alternative pathways to that of immediate ion pair collapse which is suffered following cleavage by acyl halide. Reaction conditions, products, and yields are listed in Table I.

A. Primary Acyclic.—These were the most unreactive of the ethers examined. Overnight reflux of higher boiling diprimary ethers in acetonitrile, generally found to be the most effective solvent for mixed anhydride reactions, led to yields of 30–60% of the alkyl sulfonate based on the weight of mixed anhydride used. This yield is lowered somewhat from the maximum attainable since overnight reflux of mixed anhydride in acetonitrile has been found to effect up to 25% disproportionation.[1] With diprimary asymmetric ethers, cleavage was in both directions, giving all four possible products. Thus the cleavage of ethyl *n*-butyl ether with acetyl methanesulfonate at 130° led to 47% ethyl acetate and 19% butyl acetate.[20] With dibenzyl ether reaction proceeded rapidly, being complete within 48 hr at room temperature. Benzyl acetate was isolated by distillation in 50% yield but the benzyl sulfonate could not be isolated because it decomposed upon mild heating to a mixture of sulfonic acid and polybenzyl. This accords with the known tendency of benzyl sulfonates to polymerize on standing.[21]

B. Primary Cyclic.—With unstrained ring systems reaction proceeded at about the same rate as with the acyclic primary analogs. Thus tetrahydropyran (eq 5) gave the ring-opened diester **10** in 30% yield after 4-hr reflux, and in 80% yield after 48 hr reflux. Similarly, 1,4-dioxane gave an 87% yield of the diester **11** (eq 6) after 24-hr reflux without solvent.[22] In this

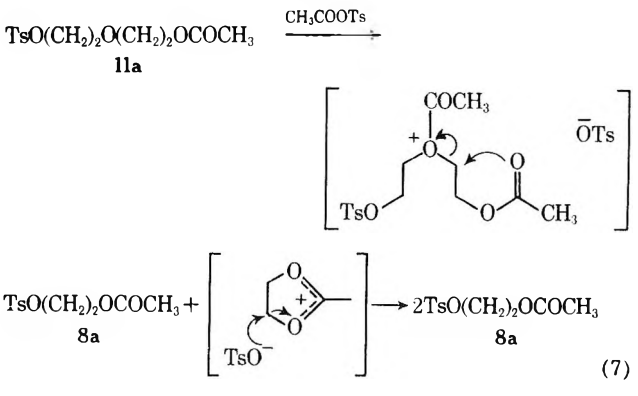


(5)

a, R = CH_3; R′ = $C_6H_4CH_3$
b, R = CH_3; R′ = CH_3
c, R = C_2H_5; R′ = $C_6H_4CH_3$

(6)

a, R = CH_3; R′ = $CH_3C_6H_4$
b, R = CH_3; R′ = CH_3
c, R = C_2H_5; R′ = $CH_3C_6H_4$



(7)

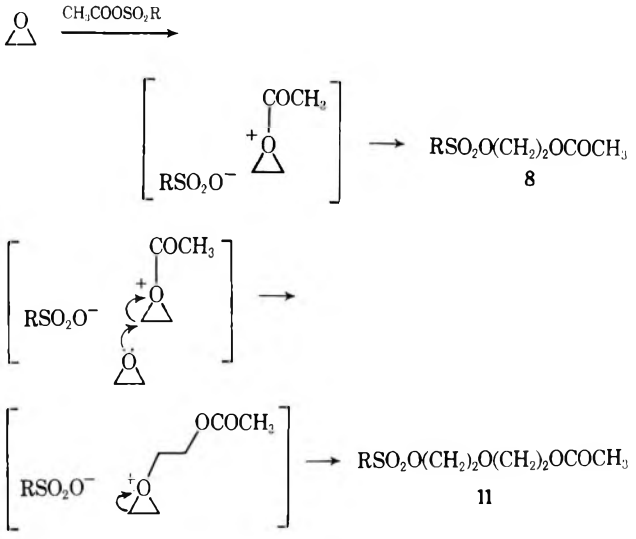
case the product, a diprimary ether, was less reactive than the starting material and did not suffer cleavage as long as the dioxane remained in excess. When the isolated diester **11** was treated at 130° with a second

(16) R. L. Burwell, Jr., *Chem. Rev.*, **54**, 615 (1954).
(17) Francis Johnson in "Friedel–Craft's and Related Reactions," Vol. IV, G. Olah, Ed., Interscience, New York, N. Y., 1965, p 1.
(18) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 261.
(19) R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 362 (1969).

(20) Cleavage of the same ether with acetyl chloride gave 34% ethyl acetate and 58% *n*-butyl acetate at room temperature, and 23% ethyl acetate and 76% *n*-butyl acetate at 60° [J. F. Norris and G. W. Rigby, *ibid.*, **54**, 2088 (1932)]. At higher temperature in the reaction with acetyl chloride, cleavage of the bond to the ethyl group, favored by SN2 cleavage, increasingly predominates at higher temperatures. With acetyl sulfonates this is less true and even at 80° ethyl acetate formation predominates by over 2:1, a consequence of the weakness of sulfonate nucleophile SN2 cleavage.
(21) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3443 (1953).
(22) The cleavage of 1,4-dioxane illustrates the advantages of the present method of ether cleavage over more conventional acylating systems. Thus with acetyl chloride and Lewis acid, 1,4-dioxane gives the 2-chloroethyl acetate in 16% yield after 30 hr at 200° [Ya. L. Gol'dfard and L. M. Smorgonskii, *J. Gen. Chem. USSR*, **8**, 1516 (1938)]; prolonged heating with acetic anhydride and ferric chloride gives an even smaller yield of a mixture of di(2-acetoxyethyl) ether and glycol diacetate [M. Macleod, *J. Chem. Soc.*, 3092 (1928)].

mole of mixed anhydride, it was speedily cleaved. Interestingly, only a single product, ethylene glycol acetate tosylate,[8a] was obtained, no trace of the alternative cleavage products being noted when the reaction was monitored by nmr. That only unidirectional cleavage, in fact, occurs may be explained by the nature of the two functional groups, the acetate group being capable of assisting cleavage in the direction indicated in eq 7 by participating in the formation of the stabilized intermediate 2-methyl-1,3-dioxolenium ion. Such AcO-5 neighboring-group participation, involving formation of this stabilized ion, is well known.[22]

With strained ring systems reaction was considerably faster. Ethylene oxide (eq 5) opened on contact at room temperature, the reaction, even in a solvent, being considerably exothermic. Yields were again around 80%. In addition, diesters of the same structural type as **11** were formed in small yield when excess ethylene oxide was taken, a consequence of an attack of a second molecule of ethylene oxide on the acylated intermediate, rather than simple ion-pair collapse (eq 8). Tetra-

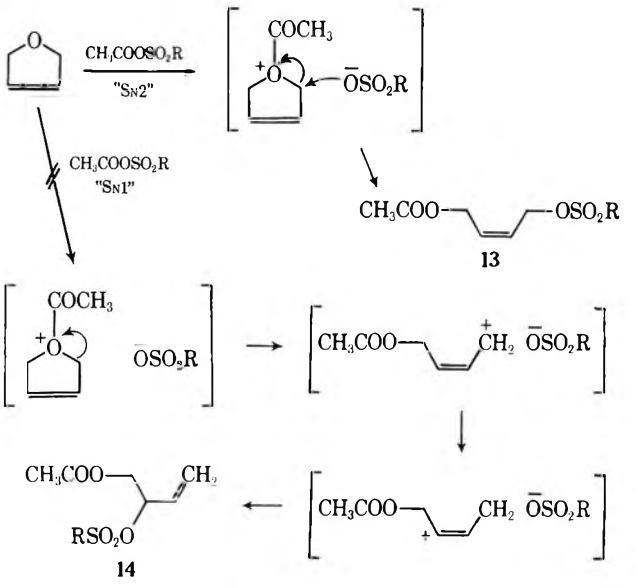


a, R = $C_6H_4CH_3$
b, R = CH (8)

hydrofuran was opened with exceptional ease, the diester **9** being isolated in 80–95% yield, upon treatment with mixed anhydride at room temperature for a few hours (eq 5).[23] 2,5-Dihydrofuran (**12**) requires several hours reflux to effect complete reaction, but the product is exclusively the terminal diester **13** with no trace of the product formed by allylic rearrangement, **14**, which might be anticipated from an SN1 cleavage process (eq 9).

The degree of acid catalysis in these mixed anhydride reactions was ambiguous due to the variable quantities of sulfonic acid initially present as impurity in most of the reactions conducted. When tetrahydrofuran was treated with acetyl methanesulfonate freshly prepared and containing a maximum of 0.5% free acid (as estimated from the low-field signal in the nmr) for 16 hr at room temperature, the yield of diester was 47.5%. Repetition of the reaction under identical conditions but with the prior addition of 5% methanesulfonic acid

(23) This reaction is in marked contrast with the cleavage by acetic anhydride which requires both the presence of zinc chloride as catalyst and heating for 8 hr at 230° to give the diacetate in 66% yield [R. Paul, *Bull. Soc. Chim. Fr.*, **6**, 1162 (1939)].



a, R = $CH_3C_6H_4$
b, R = CH_3 (9)

led to an increase in yield to 81%. This result leads one to suspect that reaction in the complete absence of acid, a condition experimentally difficult to attain, would considerably lower the rate of reaction. The presence of free acid probably serves to catalyze the reaction *via* carbonyl group protonation.[24]

Tetrahydrofuran could also be cleaved to the bissulfonate by reaction with sulfonic anhydride. The reaction was considerably slower than that of the mixed anhydride and the yield somewhat lower (30%).

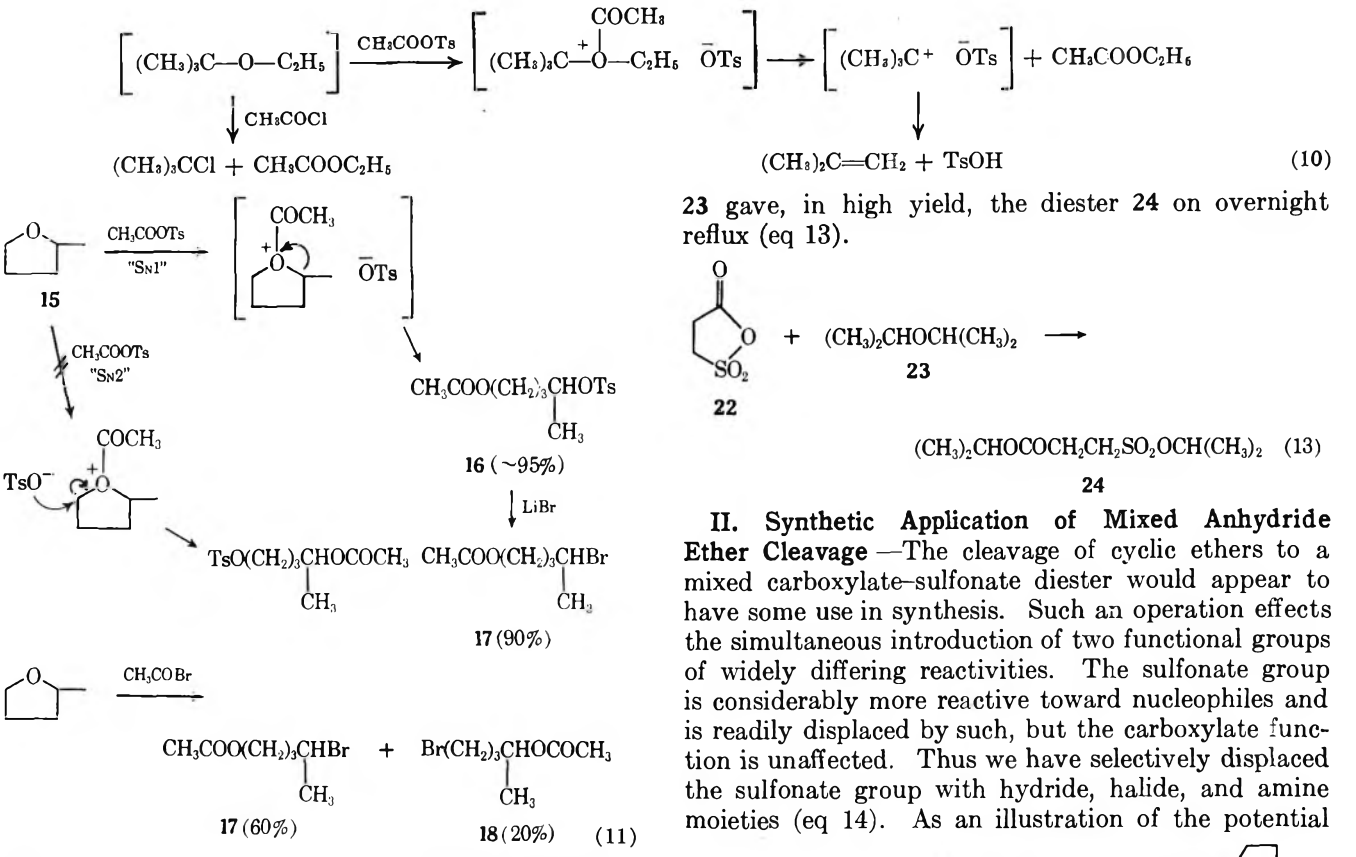
C. Secondary and Tertiary Acyclic.—Although secondary ethers cleaved only slightly faster than primary ethers, tertiary ethers cleaved almost instantaneously at room temperature. Thus diisopropyl ether gave 80% of the two isopropyl esters after overnight reflux. Ethyl *tert*-butyl ether cleaved specifically in one direction giving, ethyl acetate, isobutylene (detected by its appearance in the nmr), and *p*-toluenesulfonic acid. *tert*-Butyl *p*-toluenesulfonate was a minor product[25] (eq 10).

D. Mixed Ethers.—The cleavage of unsymmetrical ethers was investigated in order to ascertain the specificity of mixed anhydride cleavage. 2-Methyltetrahydrofuran was most closely examined, since abundant documentation as to the specificity of cleavage with acyl halide existed.[26] Treatment of 2-methyltetrahydrofuran **15** with acetyl *p*-toluenesulfonate led, in 95% yield, to a single product, the diester **16** (eq 11). The structure was verified by conversion to the bromoacetate **17** with lithium bromide in near-quantitative yield. By comparison, 2-methyltetrahydrofuran was converted to a mixture of two isomeric bromoacetates, **17** and **18**, in a ratio of 3:1 in 80% yield when treated with acetyl bromide. Comparison by glc of the product

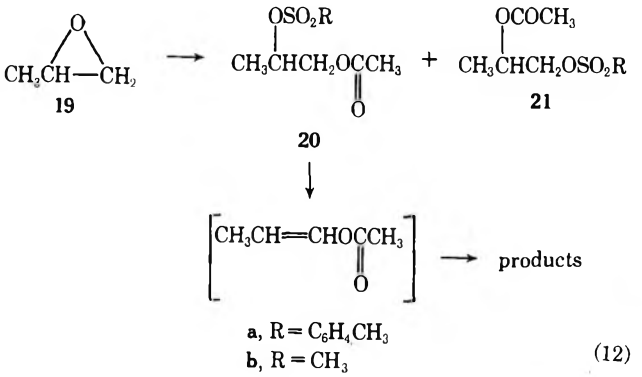
(24) S. C. Datta, J. N. E. Day, and C. K. Ingold, *J. Chem. Soc.*, 838 (1939).

(25) This result is in marked contrast with the cleavage of this ether with acetyl chloride–zinc chloride which is reported (ref 20) to give a quantitative yield of *tert*-butyl chloride. This different result is a consequence of the more powerfully nucleophilic chloride ion attacking the *tert*-butyl carbonium ion as soon as its charge begins to develop. The weakly nucleophilic sulfonate ion on the other hand by allowing the carbonium ion a longer lifetime permits it to react by an alternative pathway losing a proton to give the olefin (eq 10).

(26) D. Ganaire and A. Butt, *Bull. Soc. Chim. Fr.*, 309 (1960).

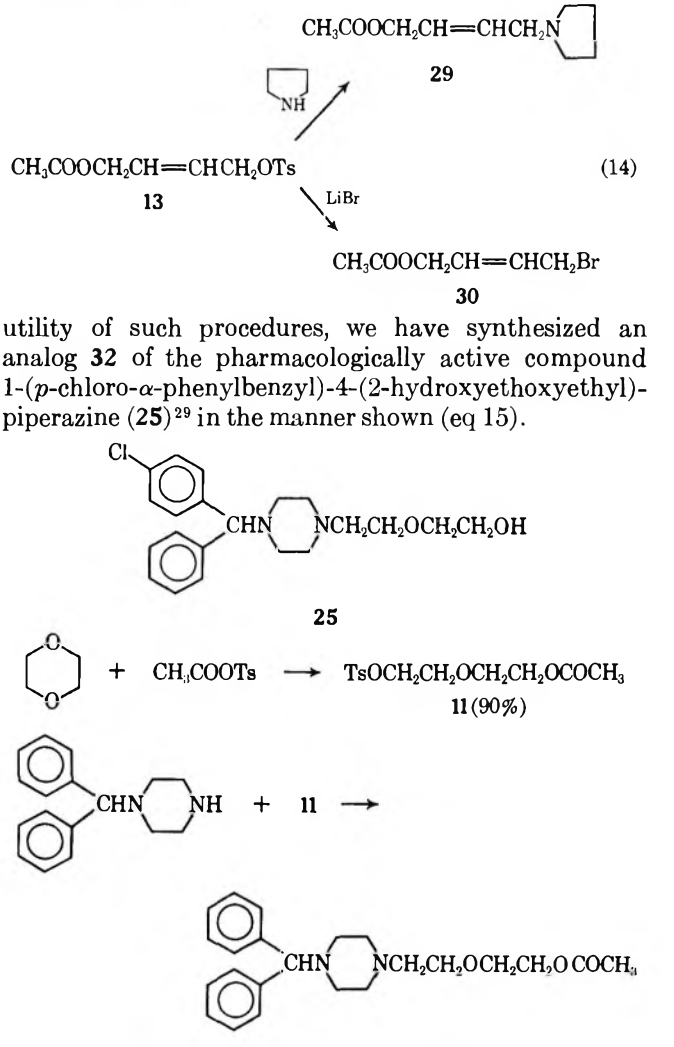


from the mixed anhydride cleavage with that from the acetyl bromide cleavage showed the former to contain none of the second isomer present in the latter. Thus in the former case, cleavage is exclusively from the most substituted carbon while in the latter 25% of cleavage is from the least substituted carbon.[27] Interestingly, the cleavage of propylene oxide (**19**) led to an almost equal proportion of the two isomers, **20** and **21**, in around 40% yield. In this cleavage of a highly strained ring, the ring opening could be so rapid as to admit to a measure of kinetic control as a factor determining the product distribution. Furthermore, the isomer **20** which would be expected to predominate is capable of a facile acid-catalyzed elimination to a vinyl ether which would not survive the work-up conditions (eq 12).



E. Ether Cleavage with Sulfopropionic Anhydride.—This cyclic mixed anhydride[28] **22** reacted with ethers in the anticipated fashion. Thus diisopropyl ether **23** gave, in high yield, the diester **24** on overnight reflux (eq 13).

II. Synthetic Application of Mixed Anhydride Ether Cleavage—The cleavage of cyclic ethers to a mixed carboxylate–sulfonate diester would appear to have some use in synthesis. Such an operation effects the simultaneous introduction of two functional groups of widely differing reactivities. The sulfonate group is considerably more reactive toward nucleophiles and is readily displaced by such, but the carboxylate function is unaffected. Thus we have selectively displaced the sulfonate group with hydride, halide, and amine moieties (eq 14). As an illustration of the potential utility of such procedures, we have synthesized an analog **32** of the pharmacologically active compound 1-(*p*-chloro-α-phenylbenzyl)-4-(2-hydroxyethoxyethyl)-piperazine (**25**)[29] in the manner shown (eq 15).



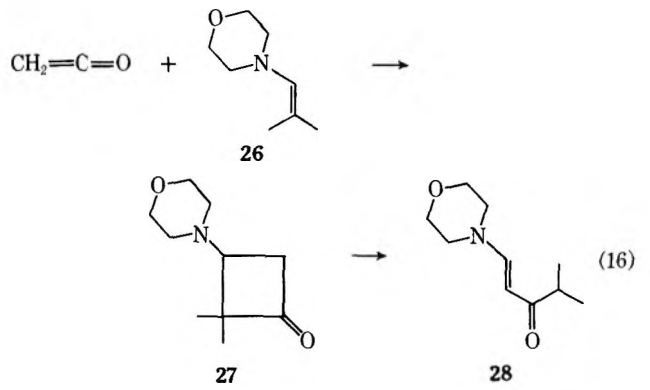
(27) This result confirms the greater tendency for mixed anhydride cleavage to proceed *via* SNI mechanism and points to the possible advantages of mixed anhydride cleavage of unsymmetrical ethers in eliminating the presence of contaminating isomers (eq 11).

(28) M. S. Kharasch, T. H. Chao, and H. C. Brown, *J. Amer. Chem. Soc.*, **62**, 2393 (1940).

(29) U. S. Patent 2,899,436 (1959).

III. The Reaction of Mixed Anhydrides with Amines. A. Tertiary Amines.—Acetyl sulfonates, when treated with tertiary amines, yielded ketene and the amine sulfonate salt. This reaction was undergone by all those mixed anhydrides the acyl portion of which possessed a β hydrogen atom. The reaction *proceeded at low temperature, below 0°, compared with* the temperature of 130° required to generate ketene thermally from mixed anhydride.[1] The ketene was trapped by using it *in situ* to form a cycloadduct with an enamine.[30] Thus acetyl methanesulfonate treated with triethylamine in the presence of 1-(*N*-morpholino)-isobut-1-ene (**26**) gave a mixture of the cyclobutanone adduct **27** and its ring-opened degradation product **28** in 62% yield (eq 16).

$$CH_3COOSO_2CH_3 + (C_2H_5)_3N \longrightarrow [(C_2H_5)_3{}^+NH\ {}^-OSO_2CH_3] + CH_2{=}C{=}O$$



(16)

26 **27** **28**

B. Primary and Secondary Amines—Amines containing labile hydrogen gave moderate yields (20–40%) of the *N*-acyl salt. The yield of amine sulfonate salt was far higher (80–95%), testifying to the simultaneous base-induced formation of ketene observed to proceed with tertiary amines.

Experimental Section[31]

***n*-Butyl Ether and Acetyl *p*-Toluenesulfonate.**—Acetyl *p*-toluenesulfonate (6.0 g, 75% pure, 21 mmol) in acetonitrile (15 ml) was refluxed with a large excess of *n*-butyl ether (12.5 ml) for 15 hr. The reaction mixture was worked up in the usual manner and the crude product distilled at atmospheric pressure. The distillate, a mixture of excess ether and *n*-butyl acetate, was collected in three fractions, bp 120–126°, 126–135°, and 135–141°. Each fraction had ν_{max} 1750 cm^{-1} ($OCOCH_3$). The nonvolatile residue was distilled under reduced pressure, to afford *n*-butyl tosylate: bp 110° (10^{-2} mm); yield 2.6 g (50%); ν_{max} 1600 (ArC=C), 1380 cm^{-1} (OSO_2); nmr δ 0.85 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.5 (m, 4 H, $CH_3CH_2CH_2CH_2O$), 2.43 (s, 3 H, $ArCH_3$), 4.04 (t, J = 7 Hz, 2 H, OCH_2), and 7.57 (AB quartet, Δ_{AB} = 28 Hz, J_{AB} = 8 Hz, 4 H, *p*-C_6H_4).

Anal. Calcd for $C_{11}H_{16}SO_3$: C, 57.87; H, 7.06; S, 14.04. Found: C, 57.95; H, 6.93; S, 14.15.

***n*-Propyl Ether and Acetyl *p*-Toluenesulfonate.**—Acetyl *p*-toluenesulfonate (6.0 g, 75% pure, 21 mmol) was refluxed in an excess of *n*-propyl ether (12.5 ml) for 15 hr. The reaction mixture was worked up in the usual way and the crude product distilled at atmospheric pressure. The distillate was a mixture of *n*-propyl ether and *n*-propyl acetate, bp 90–94°, ν_{max} 1750 cm^{-1}. The residue was distilled collecting *n*-propyl tosylate: bp 100° (0.01 mm); yield 1.4 g (30%); ν_{max} 1600 and 1360 cm^{-1}; nmr δ 0.86 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.65 (s, J = 7 Hz, 2 H, $CH_2CH_2CH_2$), 2.42 (s, 3 H, $ArCH_3$), 4.0 (t, J = 7 Hz, 2 H, OCH_2CH_2), and 7.60 (AB quartet Δ_{AB} = 27 Hz, J_{AB} = 8 Hz, 4 H, *p*-C_6H_4).

Anal. Calcd for $C_{10}H_{14}SO_3$: C, 56.05; H, 6.59; S, 14.96. Found: C, 55.97; H, 6.53; S, 14.91.

Ethyl *n*-Butyl Ether and Acetyl Methanesulfonate.—Ethyl *n*-butyl ether (10.2 g, 0.1 mol) and acetyl methanesulfonate (13.8 g, 0.1 mol) were heated at 130° for 24 hr in a sealed evacuated tube. The dark liquid was distilled under atmospheric pressure collecting two fractions, bp 76–90 and bp 90–100°. Vpc (5% Carbowax, 160°) showed each fraction to consist of a mixture, in different proportions, of ethyl acetate, *n*-butyl ethyl ether, and *n*-butyl acetate. The total weights of product calculated from the vpc traces follow: ethyl acetate, 4.15 g (47%); *n*-butyl acetate, 2.21 g (19%); total yield, 66%. The distillate residue, a mixture of the two respective methanesulfonates was distilled under reduced pressure but speedily decomposed, the only product isolated in the distillate being methanesulfonic acid.

Benzyl Ether and Acetyl *p*-Toluenesulfonate.—To a solution of acetyl *p*-toluenesulfonate (11.0 g, 51.3 mmol) in acetonitrile (50 ml) was added dibenzyl ether (9.0 g, 45 mmol). The reaction mixture was kept at room temperature for 48 hr and then worked up in the usual manner to yield a pale yellow oil (14.0 g, 76%) which was distilled under reduced pressure collecting benzyl acetate: bp 53–56° (0.005 mm); yield 3.4 g (50%); ν_{max} 1740 cm^{-1} ($OCOCH_3$); nmr δ 2.0 (s, 3 H, $COCH_3$), 5.05 (s, 2 H, $ArCH_2O$), and 7.30 (s, 5 H, C_6H_5).

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.79; H, 6.67.

The distillate residue was extracted with methanol and the methanol evaporated under reduced pressure to yield an oil containing mostly *p*-toluenesulfonic acid, contaminated with traces of polybenzyl (4.0 g, 52%); nmr was superimposable upon that of authentic *p*-toluenesulfonic acid. The methanol-insoluble residue consisted of polybenzyl: yield 3.1 g (76%); nmr[32] δ 3.8 (m, 2 H, $ArCH_2$), 7.1 (m, 5 H, C_6H_4).

Ethylene Oxide and Acetyl *p*-Toluenesulfonate.—Ethylene oxide (2.1 g, 47.7 mmol) was added to a solution of acetyl *p*-toluenesulfonate (12.0 g, 75% pure, 47.2 mmol) in acetonitrile (50 ml). A rapid exothermic reaction ensued, the temperature reaching 75°. After cooling to room temperature and keeping for 24 hr, the reaction mixture was worked up in the usual manner to give the pure ethylene glycol acetate tosylate (**8a**): yield 8.2 g (80%); ν_{max} 1760 ($OCOCH_3$), 1600 (ArC=C), and 1360 cm^{-1} (OSO_2); nmr δ 1.96 (s, 3 H, $OCOCH_3$), 2.42 (s, 3 H, $ArCH_3$), 4.21 (s, 4 H, OCH_2), and 7.56 (AB quartet, Δ_{AB} = 27 Hz, J_{AB} = 8 Hz, 4 H, *p*-C_6H_4). Attempted distillation of the oil at reduced pressure (10^{-3} mm) led to decomposition.

Repetition of the reaction using a threefold excess of ethylene oxide gave a crude product containing, in addition to an estimated 66% of the expected diester, 33% of 2-acetoxyethyl-2′-tosyloxyethyl ether (**11a**), the nmr of which could be superimposed over that of an authentic sample (*vide infra*) and the proportion of which was readily estimated by comparison of the nmr integrated intensities.

(30) G. Optiz and M. Kleeman, *Justus Liebigs Ann. Chem.*, **665**, 114 (1963).

(31) Melting points are uncorrected. All ir spectra were carried out on a Perkin-Elmer Infracord double beam spectrophotometer, all nmr spectra on a Varian A-60A instrument. Vpc analyses were done on an Aerograph A-90P. All spectra unless otherwise stated were done on liquid films (ir) or in $CDCl_3$ solution (nmr). In cases where the compounds were unstable and the analytical data were unobtainable, their characterizations were based mainly on the nmr data. All abbreviations used were standard except q^4 = quartet, q^5 = quintet, and s^7 = septet. All solvents as well as the ethers used were obtained commercially and were scrupulously dried and distilled prior to use. The mixed anhydrides were prepared as described previously.[1] Reactions were carried out under anhydrous conditions prior to aqueous work-up. To save unnecessary repetition the phrase, "the reaction mixture was worked up in the usual manner" denotes the following procedure. The reaction mixture was cooled to room temperature and poured into water. A double volume of ether was added, the mixture thoroughly shaken and allowed to settle, and the lower aqueous layer withdrawn. The remaining ether solution was thrice successively extracted with half volumes of a 5% solution of sodium bicarbonate and finally extracted with an equal volume of water. The ether solution was dried by standing over anhydrous magnesium sulfate for at least 1 hr, filtered, and, if colored, decolorized by standing over active charcoal for 1 hr. After filtration, the ether solution was cooled to 0°, any crystals of sulfonic anhydride crystallizing at this stage being filtered off. The ether solution was evaporated under reduced pressure at room temperature and the residual oil was submitted to high vacuum for 1 hr leaving the crude product. The yields, where based on the weight of mixed anhydride taken, make allowance for the purity of the mixed anhydride when stated but are based on the weight taken when this latter is not stated.

(32) J. P. Kennedy and R. B. Isaacson, *J. Macromol. Chem.*, **1**, 541 (1966).

Ethylene Oxide and Acetyl Methanesulfonate.—Ethylene oxide (2.1 g, 47.2 mmol) in acetonitrile (25 ml) was added to acetyl methanesulfonate (3.4 g, 25 mmol) in acetonitrile (25 ml) at room temperature. Work-up in the usual manner left an oil, essentially pure ethylene glycol acetate methanesulfonate (**8b**); yield, 2.8 g (63%); bp 125° (0.01 mm); ν_{max} 1760 and 1360 cm^{-1}; nmr δ 2.10 (s, 3 H, CH_3CO), 3.10 (s, 3 H, CH_3SO_2), 4.40 (s, 4 H, OCH_2).

Anal. Calcd for $C_6H_{10}O_5S$: C, 32.96; H, 5.53; S, 17.60. Found: C, 32.50; H, 5.53; S, 17.28.

Propylene Oxide and Acetyl *p*-Toluenesulfonate.—To a solution of acetyl *p*-toluenesulfonate (6.0 g, 75% pure, 21 mmol) in acetonitrile (25 ml) was added at room temperature propylene oxide (2.75 g, 47.2 mmol). An exothermic reaction ensued and was allowed to proceed, the reaction mixture being kept for a further 2 hr at room temperature. Work-up in the usual manner gave, as a colorless oil, an almost 1:1 mixture of propane-1,2-diol acetate tosylate (**20a**), and propane-1,1-diol tosylate acetate (**21a**) which was not separated: yield, 5.0 g (88%); ir ν_{max} 1760, 1600, and 1360 cm^{-1}; nmr δ 1.20, 1.29 (two overlapping doublets, J = 7 Hz, $CHCH_3$), 1.83, 1.90 (two singlets, ratio *ca.* 5:4, $OCOCH_3$), 2.45 (s, $ArCH_3$), 4.05, 4.07 (two overlapping doublets, J = 7 Hz, OCH_2CH), 4.90 (m = two overlapping sextets, J = 7 Hz, CH_3CHCH_2), and 7.73 (A_2B_2 system, Δ_{AB} = 27 Hz, J_{AB} = 8 Hz, p-C_6H_4). Attempted distillation led to decomposition; thus no analytical samples could be prepared.

Propylene Oxide and Acetyl Methanesulfonate.—Acetyl methanesulfonate (6.5 g, 47.2 mmol) was dissolved in acetonitrile (25 ml) and propylene oxide (2.75 g, 47.2 mmol) in acetonitrile (25 ml) added at room temperature. An exothermic reaction ensued and after keeping the reaction mixture at room temperature for 24 hr it was worked up in the usual way to yield an oil, **20b** and **21b**: yield, 3.7 g (40%); ir ν_{max} 1760, 1360 cm^{-1}; nmr δ 1.33, 1.45 (two overlapping doublets, J = 8 Hz, $CHCH_3$), 2.07, 2.10 (two singlets, ratio 1:1, $OCOCH_3$), 3.08 (s, OSO_2CH_3), 4.18, 4.25 (two overlapping doublets, J = 8 Hz, CCH_2CH), 5.05 (m, two overlapping sextets, J = 8 Hz, CH_3CHCH_2).

Anal. Calcd for $C_6H_{12}O_5S$: C, 36.72; H, 6.16; S, 16.34. Found: C, 37.01; H, 6.16; S, 16.86.

Tetrahydrofuran and Acetyl *p*-Toluenesulfonate.—Acetyl *p*-toluenesulfonate (11.0 g, 51.4 mmol) was dissolved in a large excess of tetrahydrofuran (25 ml) and the mixture kept at room temperature for 12 hr. The reaction mixture was worked up in the usual manner yielding an essentially pure yellow oil, yield 12.0 g (82%). The oil was distilled under reduced pressure to afford a single component, butane-1,4-diol acetate tosylate (**9a**): yield, 73%; bp 164–172° (0.005 mm); ν_{max} 1740 ($OCOCH_3$), 1600 (Ar C=C), and 1360 cm^{-1} (OSO_2); nmr δ 1.70 (q, 4 H, $CH_2CH_2CH_2CH_2$), 2.02 (s, 3 H, $OCOCH_3$), 2.44 (s, 3 H, $ArCH_3$), 4.05 (m, 4 H, $CH_2CH_2CH_2CH_2$), and 7.59 (AB quartet Δ_{AB} = 28 Hz, J_{AB} = 8 Hz, 4 H, p-C_6H_4).

Anal. Calcd for $C_{13}H_{18}SO_6$: C, 54.53; H, 6.34; S, 11.20. Found: C, 54.59; H, 6.28; S, 10.97.

In a separate small scale reaction, periodically monitored by nmr, the reaction was found to be complete after 3 hr at room temperature.

Tetrahydrofuran and Propionyl *p*-Toluenesulfonate.—Propionyl *p*-toluenesulfonate (18 g, 60% pure, 4.75 mmol) was dissolved in an excess of tetrahydrofuran (15 ml). An immediate exothermic reaction ensued which was complete within minutes. The reaction mixture was kept at room temperature for a further 48 hr and worked up in the usual manner to give an oil which was distilled at reduced pressure to afford a single component, butane-1,4-diol propionate tosylate (**9c**): bp 185–187° (0.001 mm); yield 13.5 g (95%); ν_{max} 1750, 1600, and 1360 cm^{-1}; nmr δ 1.09 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.70 (q^5, J = 3 Hz, 4 H, CH_2-$CH_2CH_2CH_2$), 2.27 (q^4, J = 7.5 Hz, 2 H, CH_2CH_3), 4.04, (t, J = 7 Hz, 2 H, OCH_2), 4.07 (t, J = 7 Hz, 2 H, OCH_2), and 7.60 (AB quartet, Δ_{AB} = 28 Hz, J_{AB} = 8 Hz, 4 H, p-C_6H_4).

Anal. Calcd for $C_{14}H_{20}SO_6$: C, 55.98; H, 6.71; S, 10.67. Found: C, 55.43; H, 6.36; S, 10.87.

Tetrahydrofuran and Acetyl Methanesulfonate.—Acetyl methanesulfonate (6.7 g, 48.6 mmol) was dissolved in an excess of tetrahydrofuran (12 ml). An immediate exothermic reaction ensued. The reaction mixture was kept overnight at room temperature and worked up in the usual manner to give an oil, essentially pure butane-1,4-diol acetate methanesulfonate (**9b**), yield 9.7 g (95%). On attempted distillation under reduced pressure at 130° the distillate was found to contain tetrahydrofuran, formed by thermal cyclization of the diester. An analytical sample could not, thus, be obtained: ν_{max} 1750 and 1360 cm^{-1}; nmr δ 1.7 (m, 4 H, $CH_2CH_2CH_2CH_2$), 2.03 (s, 3 H, $OCOCH_3$), 3.04 (s, 3 H, CH_3SO_2O), 3.45 (m, 2 H, OCH_2) and 4.15 (s, 2 H, OCH_2).

Catalytic Effect of Acid.—The above reaction was repeated using twice distilled acetyl methanesulfonate (>99.5%). After 16 hr at room temperature careful work-up yielded 47.5% of the pure diester. It was noted that no warming was observed when the two reagents were mixed. When the same sample of acetyl methanesulfonate to which 5% of methanesulfonic acid had been added was treated with tetrahydrofuran under identical conditions 81% of the pure diester was isolated. It was noted that the reagents became warm on mixing.

Tetrahydropyran and Acetyl *p*-Toluenesulfonate.—Acetyl *p*-toluenesulfonate (5.0 g, 90% pure, 21 mmol) was refluxed for 48 hr in tetrahydropyran (25 ml). Work-up in the usual manner gave as an oil, pentane-1,5-diol acetate tosylate (**10a**), yield 6.0 g (95%). Attempted distillation at reduced pressure led to decomposition: ν_{max} 1740, 1600, and 1360 cm^{-1}; nmr δ 1.5 [m, 6 H, $CH_2(CH_2)_3CH_3$], 2.03 (s, 3 H, $OCOCH_3$), 2.43 (s, 3 H, $ArCH_3$), 4.1 (m, 4 H, OCH_2), and 7.64 (AB quartet, Δ_{AB} = 27 Hz, J_{AB} = 8 Hz, 4 H, p-C_6H_4).

Anal. Calcd for $C_{14}H_{20}O_5S$ (unpurified material): C, 55.99; H, 6.71; S, 10.65. Found: C, 55.77; H, 6.85; S, 11.05.

Tetrahydropyran and Acetyl Methanesulfonate.—Acetyl methanesulfonate (2.6 g, 18.8 mmol) was refluxed in an excess of tetrahydropyran (25 ml) for 48 hr. Work-up in the usual manner gave, as an oil, pentane-1,5-diol acetate methanesulfonate (**10b**), yield 3.4 g (80%). The product distilled under reduced pressure without decomposition: bp 138–139° (0.005 mm); ν_{max} 1740, 1360 cm^{-1}; nmr δ 1.6 [m, 6 H, $CH_2(CH_2)_3CH_2$], 2.04 (s, 3 H, CH_3CO_2), 3.02 (s, 3 H, CH_3SO_2O), and 4.15 (m, 4 H, OCH_2).

Anal. Calcd for $C_8H_{16}O_5S$: C, 42.85; H, 7.19; S, 14.27. Found: C, 42.80; H, 7.31; S, 14.54.

1,4-Dioxane and Acetyl *p*-Toluenesulfonate.—Acetyl *p*-toluenesulfonate (12.0 g, 5.6 mmol) was refluxed in an excess of dioxane (25 ml) for 24 hr and worked up in the usual manner to yield 2-acetoxyethyl 2′-tosyloxyethyl ether (**11a**), yield 14.8 g (87%). The oil was distilled under reduced pressure to afford the pure diester with near-quantitative recovery: bp 175–180° (0.002 mm); ν_{max} 1750, 1600, and 1360 cm^{-1}; nmr δ 2.05 (s, 3 H, CH_3CO), 2.45 (s, 3 H, $ArCH_3$), 3.65 (m, 4 H, CH_2OCH_2), 4.16 (m, 4 H, CH_2OCO, CH_2OSO_2), and 7.6 (AB quartet, Δ_{AB} = 28 Hz, J_{AB} = 8 Hz, 4 H, p-C_6H_4).

Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.65; H, 6.00; S, 10.59. Found: C, 51.73; H, 5.96; S, 10.81.

1,4-Dioxane and Propionyl *p*-Toluenesulfonate.—Propionyl *p*-toluenesulfonate (18 g, 60% pure, 4.75 mmol) was refluxed in an excess of dioxane (25 ml) for 48 hr. The reaction mixture was worked up in the usual manner to yield an oil which was distilled collecting 2-propionoxyethyl 2′-tosyloxyethyl ether (**11c**): bp 190–200° (0.001 mm); yield 10.0 g (67%); ν_{max} 1755, 1600, and 1360 cm^{-1}; nmr δ 1.08 (t, J = 8 Hz, 3 H, CH_2CH_3), 2.34 (q^4, J = 8 Hz, 2 H, CH_2CH_3), 2.44 (s, 3 H, $ArCH_3$), 3.70 (m, 4 H, CH_2OCH_2), 4.15 (m, 4 H, CH_2OCO, CH_2OSO_2), and 7.60 (AB quartet, Δ_{AB} = 27 Hz, J_{AB} = 8 Hz, 4 H, p-C_6H_4).

Anal. Calcd for $C_{14}H_{20}O_6S$: C, 53.16; H, 6.37; S, 10.13. Found: C, 53.24; H, 6.22; S, 10.29.

2-Acetoxyethyl 2′-Tosyloxyethyl Ether (11) and Acetyl *p*-Toluenesulfonate.—The diester **11a** (2.0 g, 6.6 mmol) was heated with an excess of acetyl *p*-toluenesulfonate (6.0 g, 75% pure, 21 mmol) at 130° for 2 hr. The nmr of the crude reaction mixture showed total disappearance of starting ether. The only peak in the region δ 3.0–6.0 was a sharp singlet at 4.21 ppm. Work-up in the usual manner gave pure ethylene glycol acetate tosylate **8a** identified as such by the identity of its ir and nmr spectra with an authentic sample prepared from ethylene oxide and acetyl *p*-toluenesulfonate, yield 1.5 g (45%).

Repetition of the reaction in acetonitrile after 48-hr reflux gave only complete recovery of starting material.

2,5-Dihydrofuran and Acetyl *p*-Toluenesulfonate.—Acetyl *p*-toluenesulfonate (13.0 g, 60 mmol) and an excess of 2,5-dihydrofuran (10 ml) was refluxed in acetonitrile (15 ml) for 16 hr. The reaction mixture was worked up in the usual manner to yield as an oil, but-2-ene-1,4-diol acetate tosylate (**13a**): yield, 13.3 g (81%); ν_{max} 1750, 1600, and 1360 cm^{-1}; nmr δ 2.02 (s, broad 3 H, CH_3CO), 2.42 (s, 3 H, $ArCH_3$), 4.60 (m, 4 H, CH_2), 5.73 (m, 2 H, CH=CH), and at 7.60 (AB quartet, Δ_{AB} = 26 Hz, J_{AB} = 8 Hz, 4 H, p-C_6H_4).

On standing for 4 days at room temperature, the oil turned black and deposited a crystalline material identified as *p*-toluenesulfonic acid. The rest of the material had undergone extensive decomposition as revealed by a second examination of the nmr spectrum. Preparation of an analytical sample by distillation under reduced pressure failed due to extensive decomposition.

2,5-Dihydrofuran and Acetyl Methanesulfonate.—Acetyl methanesulfonate (6.5 g, 47 mmol) and an excess of 2,5-dihydrofuran (10 ml) in acetonitrile (15 ml) were refluxed for 16 hr. The reaction mixture was worked up in the usual manner to yield, as an oil, but-2-ene-1,4-diol acetate methanesulfonate (**13b**): yield, 5.3 g (54%); ν_{max} 1730 and 1360 cm^{-1}; nmr δ 2.05 (s, 3 H, CH_3CO), 3.05 (s, 3 H, CH_3SO_2), 4.70 (d, J = 5 Hz, 2 H, CH_2CH), 4.88 (d, J = 5 Hz, 2 H, CH_2CH), and 5.88 (m, 2 H, CH=CH). No analytical sample could be obtained; the compound decomposed on attempted distillation.

Isopropyl Ether and Acetyl *p*-Toluenesulfonate.—Acetyl *p*-toluenesulfonate (13.0 g, 75% pure, 61 mmol) in acetonitrile (25 ml) was refluxed for 18 hr with isopropyl ether (15 ml) in excess. After working up in the usual manner the excess ether and isopropyl acetate formed in the reaction were evaporated under reduced pressure to leave an oil which was distilled collecting isopropyl tosylate: bp 110° (0.01 mm); yield, 8.0 g (80%); ν_{max} 1600 and 1360 cm^{-1}; nmr δ 1.30 [d, J = 7 Hz, 6 H, $CH(CH_3)_2$], 2.46 (s, 3 H, $ArCH_3$) 4.77 [s[7], J = 7 Hz, 1 H, $CH(CH_3)_2$], and 7.61 (AB quartet, Δ_{AB} = 28 Hz, J_{AB} = 8 Hz, 4 H, *p*-C_6H_4).

Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.59. Found: C, 56.26; H, 6.39.

Isopropyl Ether and β-Sulfopropionic Anhydride[28] (22).—β-Sulfopropionic anhydride (1.5 g, 9.1 mmol) was refluxed in an excess of isopropyl ether (10 ml) for 24 hr. The excess ether was evaporated to yield a colorless oil (2.36 g) which was worked up in the usual manner and distilled collecting diisopropyl β-sulfopropionate (**24**, colorless liquid): bp 120° (0.05 mm); ν_{max} 1740 and 1360 cm^{-1}; nmr δ 1.27 [d, J = 7 Hz, 6 H, $CH(CH_3)_2$], 1.43 [d, J = 7 Hz, 6 H, $CH(CH_3)_2$], 3.12 (A_2B_2 symmetrical 16-line system, 4 H, $SO_2CH_2CH_2CO$), 5.00 [s[7], J = 7 Hz, 1 H, $CH(CH_3)_2$], and 5.09 [s[7], J = 7 Hz, 1 H, $CH(CH_3)_2$].

Anal. Calcd for $C_8H_{16}O_5S$: C, 45.37; H, 7.62; S, 13.43. Found: C, 45.60; H, 7.48; S, 13.65.

2-Methyltetrahydrofuran (15) and Acetyl *p*-Toluenesulfonate.—Acetyl *p*-toluenesulfonate (6.0 g, 75% pure, 21 mmol) was dissolved in an excess of 2-methyl tetrahydrofuran (10 ml) and the mixture kept at room temperature for 12 hr. The reaction mixture was worked up in the usual manner to give an oil whose nmr spectrum showed as essentially pure pentane-1,4-diol 1-acetate tosylate (**16**). On standing the diester gradually reverted to 2-methyl tetrahydrofuran. Attempted distillation of **16** under reduced pressure gave no distillate, and thus no analytical sample could be prepared, the residue being identified as pure *p*-toluenesulfonic acid formed from the intramolecular cyclization reaction: yield (**16**), 6.0 g (95%); ν_{max} 1750, 1600, and 1360 cm^{-1}; nmr δ 1.25 [d, J = 7 Hz, 3 H, $CH(CH_3)$], 1.60 (m, 4 H, CH_2CH_2), 2.02 (s, 3 H, CH_3CO), 2.43 (s, 3 H, $ArCH_3$), 3.99 (t, J = 7 Hz, 2 H, OCH_2) 4.7 [m, 1 H, $CH_2CH(CH_3)$] and 7.63 (AB quartet, Δ_{AB} = 28 Hz, J_{AB} = 8 Hz, 4 H, *p*-C_6H_4).

Reaction of Pentane-1,4-diol 1-Acetate 4-Tosylate (16) with Lithium Bromide.—The diester (**16**) prepared as above (6.0 g, 20 mmol) in acetone (50 ml) was treated with lithium bromide (2.5 g, 29 mmol) and the solution maintained at room temperature for 24 hr. The mixture was cooled to 0°, the lithium tosylate and excess lithium bromide were filtered off, and the residual solution was evaporated to dryness under reduced pressure. Extraction of this residue with cold ether followed by removal of the ether under reduced pressure gave 1-acetoxy-4-bromopentane (**17**) as an oil, yield 3.8 g (90%). A sample was distilled, bp 60° (0.01 mm). The crude oil as isolated above contained only one spot on tlc (silica gel) and a single peak on vpc (5% Carbowax) with no trace of the isomer (see below): ν_{max} 1760 cm^{-1}; nmr 1.75 (d, J = 7 Hz, 3 H, $CHBrCH_3$), 1.83 (m, 4 H, CH_2CH_2), 2.06 (s, 3 H, CH_3CO), and 4.13 m, 3 H, CHBr, CH_2OCOCH_3).

Anal. Calcd for $C_7H_{13}O_2Br$: C, 40.21; H, 6.27; Br, 38.22. Found: C, 39.95; H, 6.26; Br, 37.28.

Reaction of 2-Methyltetrahydrofuran with Acetyl Bromide.—To a sample of 2-methyltetrahydrofuran (15.6 g, 0.18 mmol), maintained at reflux and containing a few milligrams of zinc chloride, was added dropwise acetyl bromide (25 g, 0.2 mol). The reaction mixture was heated under reflux for 1 hr. This was then worked up in the usual manner to yield the product, an oil, yield 30 g (80%). The crude oil thus isolated was observed to comprise two components, one minor; the major component has the same retention time as 1-acetoxy-4-bromopentane. Vpc analysis revealed this latter to comprise some 70–80% of the material. The two components could not be separated by distillation and only the major component was isolated and identified by comparison with an authentic sample.[26] The minor component was readily identified, and its proportion precisely defined, from the nmr spectrum which, in addition to the peaks assigned to 1-acetoxy-4-bromopentane (**17**), showed the second component to be 4-acetoxy-1-bromopentane (**18**) present in a ratio of 1:3: nmr (minor component) δ 1.25 (d, J = 7 Hz, 3 H, $CHOAcCH_3$), 1.85 (m, 4 H, CH_2CH_2), 3.48 (t, J = 7 Hz, 2 H, CH_2Br), and 4.95 (s[6], J = 7 Hz, 1H, $CH_2CHOAcCH_3$).

Reaction of But-2-ene-1,4-diol Acetate Tosylate (13) with Lithium Bromide.—The diester (5.68 g, 20 mmol) and lithium dibromide (3.5 g, 40 mmol) in acetone (50 ml) were maintained at room temperature for 24 hr. The reaction mixture was then cooled to 0°, the lithium tosylate and excess lithium bromide were filtered off, and the residue was evaporated to dryness at reduced pressure. This residue was extracted with cold ether and the ether removed under vacuum leaving the pure bromoacetate (**30**): yield, 3.8 g (98%); ν_{max} 1740 cm^{-1}; nmr δ 2.11 (s, 3 H, CH_3CO), 4.08 (d, J = 8 Hz, 2 H, $=CHCH_2Br$), 4.75 (d, J = 8 Hz, 2 H, $CHCH_2OCOCH_3$), and 5.88 (m, 2 H, –CH=CH–).

Anal. Calcd for $C_6H_9O_2Br$: C, 37.33; H, 4.70; Br, 41.40. Found: C, 37.01; H, 4.50; Br, 40.30.

Reaction of But-2-ene-1,4-diol Acetate Tosylate (13) with Pyrrolidine.—The diester (2.0 g, 7.3 mmol) was dissolved in ether and a large excess of pyrrolidine (2 ml) was added at room temperature. An immediate precipitate of amine sulfonate salt was observed. The ether was decanted and worked up in the usual way to give a yellow oil, 1-acetoxy-4-*N*-pyrrolidinebut-2-ene (**29**): yield, 550 mg (41%); ν_{max} 1740 cm^{-1}; nmr δ 1.75 (m, 4 H, CH_2CH_2) 2.03 (s, 3 H, CH_3CO), 2.50 (m, 4 H, NCH_3), 3.18 (d, J = 7 Hz, $=CCH_2N$), 4.68 (d, J = 7 Hz, $=CHCH_2OCOCH_3$), and 5.72 (m, 2 H, –CHCH–).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 56.90; H, 10.00; N, 6.74.

***tert*-Butyl Ethyl Ether and Acetyl Methanesulfonate.**—To a solution of acetyl methanesulfonate (0.94 g, 6.75 mmol) in acetonitrile (2 ml) was added, at room temperature, *tert*-butyl ethyl ether (750 mg, 7.5 mmol) and the reaction was periodically monitored by nmr. After 30 min no trace of the starting ether was observed to be present as shown by the complete disappearance of the CH_2 quartet at δ 3.40. Quantitative formation of ethyl acetate was observed, evidenced by the appearance of a new CH_2 quartet at δ 4.15. In addition the presence of methanesulfonic acid was confirmed by the peaks at δ 3.00 (SO_2CH_3) and at δ 12.7 (SO_3H), to an extent no less than 75%, as estimated from intergration measurements. The presence of isobutene was inferred from the terminal olefinic proton multiplet (J = 1.5 Hz) at 4.70 and the corresponding finely split singlet (J = 1.5 Hz) at 1.7 [$C=C(CH_3)_2$]. Both these latter signals progressively diminished in intensity on standing at room temperature, having disappeared after 22 hr. The simultaneous growth of a singlet at δ 1.22 appeared to indicate the probable fate of the olefin as acid-catalyzed polymerization.

Synthesis of 1-(α,α′-Diphenylmethyl)-4-(2′-acetoxyethoxyethyl)piperazine (32).—A solution of 1-(α,α′-diphenylmethyl)-piperazine (**31**) (1.26 g, 5 mmol) and 2-acetoxyethyl-2′-tosyloxyethyl ether (**11**) (850 mg, 2.8 mmol) in tetrahydrofuran (20 ml) was refluxed for 18 hr. The solution was evaporated to dryness under reduced pressure, ether was added, and the precipitated salt was collected, dried, and weighed, yield 1.05 g (100%). The filtrate was extracted with 2 *N* HCl which extract was made alkaline with NaOH and reextracted with ether to yield, after drying and evaporation to dryness under reduced pressure, the required amino acetate (**32**), a colorless oil, which gave only a single spot on silica gel tlc: yield, 650 mg (63%); ν_{max} 1760 ($COCH_3$), 1600, 705, 745, and 755 cm^{-1} (Ar 5 H); nmr δ 1.95 (s, 3 H, $COCH_3$), 2.5 (m, 10 H, NCH_2), 3.6 (m, 4 H, OCH_2), 4.25 [s, 1 H, $(Ar)_2CH$], 4.2 (t, J = 6 Hz, 2 H, OCH_2), and 7.2 (m, 10 H, C_6H_5).

Tetrahydrofuran and *p*-Toluenesulfonic Anhydride.—*p*-Toluenesulfonic anhydride was refluxed for 18 hr in an excess of tetrahydrofuran (25 ml). The solution was evaporated to dryness and worked up in the usual manner to yield, as a pure oil, butane-1,4-diol bistosylate: ν_{max} 1600 and 1360 cm^{-1}; nmr

(identical with an authentic specimen[33]) δ 1.7 (m, 4 H, CH_2CH_2), 2.45 (s, 6 H, $ArCH_3$), 4.0 (m, 4 H, OCH_2), and 7.60 (AB quartet, Δ_{AB} = 29 Hz, J_{AB} = 8 Hz, 8 H, p-C_6H_4).

Tribenzylamine and Acetyl p-Toluenesulfonate.—Solutions of acetyl p-toluenesulfonate (8.7 g, 75% pure, 30 mmol) in ether (100 ml) and tribenzylamine (11.7 g, 40 mmol) in ether were mixed at room temperature. An immediate white precipitate was deposited and the reaction mixture left at room temperature for 24 hr. The crystalline material was filtered and dried, mp 202–203°. It was identified as the tosylate salt of tribenzylamine: yield, 13.2 g (96%); ν_{max} 1600, 750, 700, and 690 cm^{-1}; nmr δ 2.40 (s, 3 H $ArCH_3$), 4.31 (d, J = 5 Hz, 6 H, $ArCH_2N$), 7.3 (m, 15 H, Ar), and 7.70 (AB quartet J_{AB} = 8 Hz, 4 H, p-C_6H_4).

Anal. Calcd for $C_{28}H_{29}NO_3S$: C, 73.5; H, 5.95; N, 3.06; S, 6.99. Found: C, 73.41; H, 6.20; N, 2.78; S, 6.72.

The identity was confirmed by synthesis of the salt from p-toluenesulfonic acid and tribenzylamine, mp 204–205°, mmp (with product) 202–203°.

Trimethylamine and Acetyl Methanesulfonate.—To a solution of acetyl methanesulfonate (3.32 g, 24 mmol) in ether (100 ml) was added at room temperature an excess of trimethylamine (5 ml). After standing for some minutes the resulting white precipitate was filtered off and recrystallized from acetonitrile, mp 204–205°. It was identified as the methanesulfonate salt of trimethylamine by comparison with an authentic sample prepare from methanesulfonic acid, mp 204–206°, mmp 204°, yield 3.8 g (97%).

The residual ether solution was now evaporated to dryness under high vacuum. The resulting oil appeared to be polymerized ketene: yield, 800 mg (79%); ν_{max} 1790, and 1830 cm^{-1} [(C=O (saturated), C=O (anhydride)]; nmr δ 2.25 (s, CH_2).

Triethylamine and Acetyl Methanesulfonate in the Presence of 1-(*N*-Morpholino)isobut-1-ene (26).—A solution of acetyl methanesulfonate (4.14 g, 30 mmol) in ether (25 ml) was added dropwise at room temperature to a solution of triethylamine (3.0 g, 30 mmol) and 1-(*N*-morpholino)isobut-1-ene (**26**) (4.2 g, 30 mmol) in 50 ml of ether. The reaction mixture was kept at room temperature for 2 hr and the precipitated sulfonate salt of triethylamine was filtered off. The solution was evaporated to dryness under reduced pressure leaving a colorless oil, yield 3.43 g (62%). The oil was distilled under reduced pressure collecting two compounds: 3-morpholino-2,2-dimethylcyclobutanone[30] (**27**) [bp 64° (0.1 mm); ν_{max} 1780 cm^{-1} (cyclobutane C=O); nmr δ 1.17, 1.21, (s, 6 H, CH_3), 2.12 (s, 2 H, $COCH_2$), 2.45 (m, 4 H, NCH_2), 2.92 (s, 1 H, NCH), and 3.70 (m, 4 H, OCH_2)] and 1-morpholino-4-methylpent-1-ene-3-one[30] (**28**) {bp 110–112° (0.1 mm); ν_{max} 1640 cm^{-1} (N-C=C); nmr δ 1.08 [d, J = 7 Hz, 6 H, $CH(CH_3)_2$], 2.5 (s,[7] J = 7 Hz, 1 H, $CH(CH_3)_2$], 3.32 (m, 4 H, NCH_2), 3.70 (m, 4 H, OCH_2), and 6.38 (AB quartet, Δ_{AB} = 136.5 Hz, J_{AB} = 13 Hz, 2 H, NCH=CH)}.

Registry No.—**8a**, 19859-09-7; **8b**, 26923-81-9; **9a**, 19859-06-4; **9b**, 19859-00-8; **9c**, 19859-11-1; **10a**, 26923-85-3; **10b**, 26923-86-4; **11a**, 26923-87-5; **11c**, 26923-88-6; **13a**, 19859-10-0; **13b**, 26923-90-0; **16**, 19859-07-5; **17**, 26923-92-2; **18**, 26923-93-3; **20a**, 26923-94-4; **20b**, 26923-95-5; **21a**, 26923-96-6; **21b**, 26923-97-7; **24**, 26923-98-9; **27**, 2618-48-6; **28**, 2618-47-5; **29**, 26924-01-6; **30**, 26924-02-7; **32**, 26924-03-8; *n*-butyl tosylate, 778-28-9; *n*-propyl tosylate, 599-91-7; benzyl acetate, 140-11-4; isopropyl tosylate, 2307-69-9; butane-1,4-diol bistosylate, 4724-56-5; tribenzylamine (tosylate salt), 26924-09-4.

(33) N. Frydmann and Y. Mazur, unpublished results.

Mixed Sulfonic–Carboxylic Anhydrides. III.[1] Reactions with Aromatic Ethers and Aromatic Hydrocarbons

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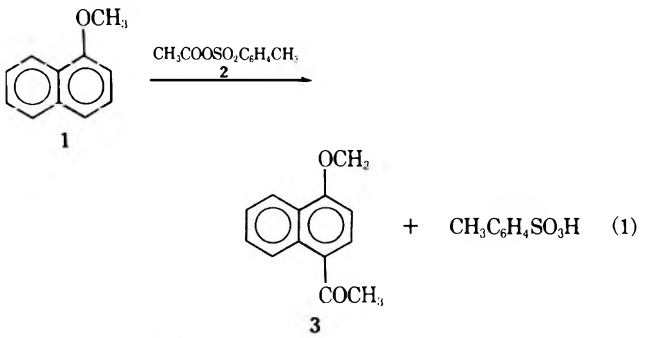
Mixed sulfonic–carboxylic anhydrides are shown to react with aromatic ethers. The products isolated depend upon the reaction conditions. When these are mild, the monoacylated aromatic ethers are formed but under more vigorous conditions these latter undergo self-condensation to the respective dypnones or triphenylbenzenes. Reaction with aromatic hydrocarbons is slow but the reaction with 9,10-dihydroanthracene effects aromatization in good yield, a reaction shown not to be of the ionic type of mechanisms usually associated with mixed anhydride reactions.

Previous publications in this series have demonstrated the reactive nature of mixed sulfonic–carboxylic anhydrides[1,2] as acylating agents. Aliphatic ethers were shown to undergo facile cleavage following initial acylation of the ether oxygen atom,[1] and thus it was of interest to examine the behavior of these reagents toward aromatic ethers.

With aromatic ethers the reaction was swift and comparatively clean. Thus reaction at room temperature of 1-methoxynaphthalene (**1**) with acetyl p-toluenesulfonate (**2**) in acetonitrile gave exclusively the 4-acetyl isomer **3** in 82% yield (eq 1), while under similar conditions 2-methoxynaphthalene (**4**) gave a 65% yield of the 1-acetyl isomer **5** (eq 2).



With the smaller, less hindered molecules, anisole and phenetole, reaction could be made to proceed further. Thus anisole **6** refluxed in acetonitrile with acetyl p-toluenesulfonate (**2**) gave, in addition to the expected p-methoxyacetophenone (**7**), a yellow crystalline material

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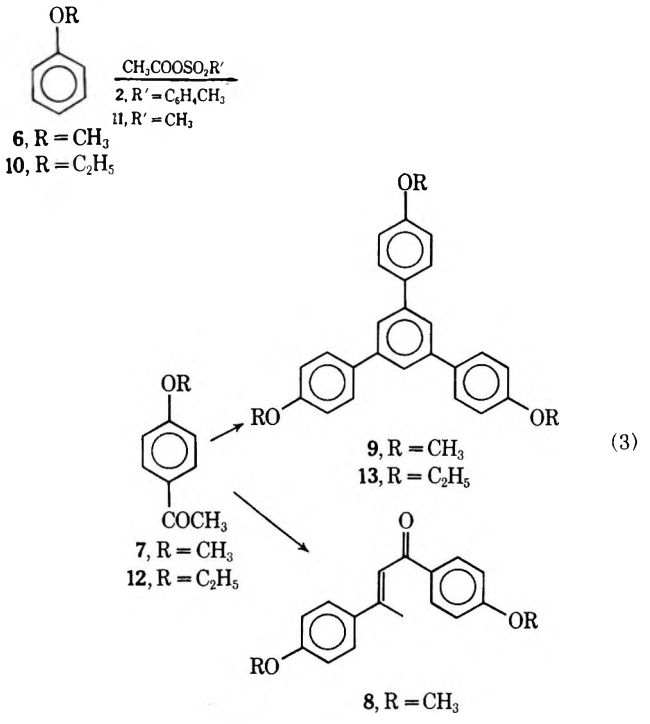
(1) Paper II in this series: M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 532 (1971).

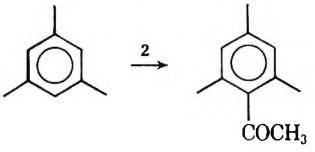
(2) M. H. Karger and Y. Mazur, *J. Amer. Chem. Soc.*, **90**, 3878 (1968); *cf.* C. G. Overberger and E. Sarlo, *ibid.*, **85**, 2446 (1963).

identified as the dypnone (**8**). More concentrated solutions of the two reagents gave, however, the triphenylbenzene, **9**, with none of the dypnone being isolated. A precisely similar result was observed with phenetole (**10**) and acetyl methanesulfonate (**11**) which gave the expected 4-acetylphenetole (**12**) as the major product under all conditions, but only the triphenylbenzene, **13**, in the absence of solvent. Thus, in dilute solution we witness a condensation of two molecules, but in concentrated solution three molecules condense with cyclization to the aromatic derivative. Such condensations are readily rationalized since initial acylation by mixed anhydride results in the release of 1 mol of sulfonic acid. The use of sulfonic acid ion-exchange resin to effect self-condensation of acetophenones is well known[3] as is the mineral acid catalyzed condensation of acetophenones to their respective 1,3,5-triarylbenzenes.[4] The formation of the two condensation products appears far more rapid and effective with mixed anhydride than by either of these two methods.[5]



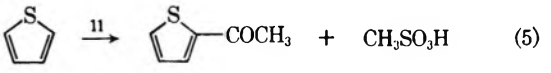
(3)

The reaction of acyl halides with aromatic hydrocarbons is well known and extensively documented.[6] This reaction is, however, invariably performed in the presence of Lewis acid, a procedure which may have inherent disadvantages, particularly of inter- or intramolecular alkyl group migration. While milder catalysts such as mineral acids or polyphosphoric acid have in some cases been used effectively, weaker acids such as the alkanesulfonic acids have been less successful. Acylations with carboxylic acids in the presence of trifluoroacetic anhydride have been successfully employed under mild conditions.[7] The high reactivity of mixed sulfonic–carboxylic anhydrides led us to investigate their reactions with aromatic hydrocarbons in the hope that acylation could be effected under mild conditions without the need of added catalyst. Reaction with aromatic hydrocarbons proved less straightforward and much slower than with aromatic ethers. Only polymethylbenzenes, while requiring forcing conditions, tended to react to give the nuclear acylated product alone. Thus mesitylene gave the monoacetyl product in 64% yield after treatment with mixed anhydride at 100° for 24 hr (eq 4). Xylenes, toluene, and naphthalene gave, under similar conditions, mostly unchanged starting material. What reaction there was resulted in complex mixtures of acetylated products which were not separated. Benzene itself under maximally vigorous conditions failed to react at all. Thus nuclear acylation on a benzene nucleus by mixed anhydride requires considerable activation by attached alkyl group.[7a]



(4)

Thiophene was readily acylated in 69% yield, the reaction proceeding exothermically at room temperature (eq 5). Reaction with furan was uncontrollable giving polymeric material, a consequence of the acid sensitivity of furan derivatives.[7b] Diphenyl ether gave no



(5)

(3) N. B. Lorrete, *J. Org. Chem.*, **22**, 347 (1967), who found that acetophenone, for example, when maintained at 70–75° for 246 hr over Dowex 50 sulfonic acid ion-exchange resin gave 24% dypnone and 10% 1,3,5-triphenylbenzene.

(4) R. E. Lyle, E. J. Dewitt, N. M. Nichols, and W. Cleland, *J. Amer. Chem. Soc.*, **75**, 5959 (1953), and references cited therein. *p*-Methoxyacetophenone in a solution of hydrogen chloride in ethanol maintained at room temperature for 4 months gave a 54% yield of the triphenylbenzene. The yield at the end of 34 days was 2%.

(5) A likely reason for this appears to us the possibility that initial reaction to give the acetophenone is followed by attack by unreacted mixed anhydride to give the enol acetate, which rapidly reacts with unreacted acetophenone to give the dypnone. This latter by reaction with a second mole of enol acetate gives ultimately the triphenylbenzene. This explains the usually observed yield of acetylated aromatic ether as being no greater than 50%. That methanesulfonic acid is the sole agent of the condensations is unlikely. When we took an equimolar mixture of acetophenone and methanesulfonic acid and maintained the mixture overnight at room temperature, the acetophenone was recovered unchanged to the extent of 90%. Only traces of other material were observed to be present.

(6) P. Gore, "Friedel–Crafts and Related Reactions," G. Olah, Ed., Interscience, New York, N. Y., 1964, p 1, and references therein.

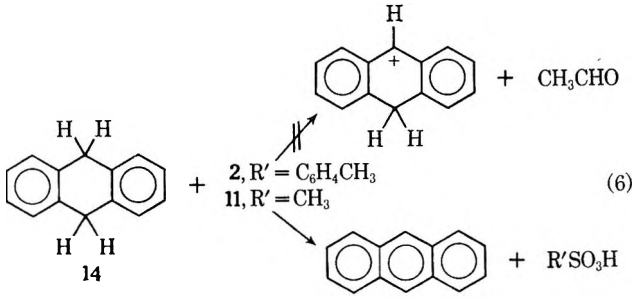
(7) (a) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 718 (1951). This reaction is thought to proceed *via* an initial equilibration between the carboxylic acid and trifluoroacetic anhydride. The resulting mixed anhydride can itself then dissociate to the trifluoroacetate ion and the acyl cation, which species acts as the effective acylating agent. Since mixed sulfonic–carboxylic anhydrides can participate in analogous equilibria (see ref 2) they should undergo similar reactions to those observed toward aromatic nuclei by carboxylic acid–trifluoroacetic anhydride mixtures.

$$(CF_3CO)_2O + RCO_2H \longrightarrow CF_3CO_2H + CF_3COOCOR$$
$$CF_3COOCOR \longrightarrow [CF_3COO^- + RCO^+]$$
$$R'SO_2OCOR \longrightarrow [R'SO_2O^- + RCO^+]$$

(b) By comparison, acylation of thiophene with trifluoroacetic anhydride and acetic acid required 1 hr at 40–50° to yield 2-acetylthiophene in 50% yield.[7] Furan was acylated at room temperature in 43% yield. From this comparison and that of the acylation of hydrocarbons, the mixed anhydride method of acylation would appear to be more effective than that described by Bourne, *et al.* Interestingly, these workers found that acylations with *p*-toluenesulfonic acid and trifluoroacetic anhydride gave only the sulfone (in 64% yield). In other words equilibrium a predominates over b below.

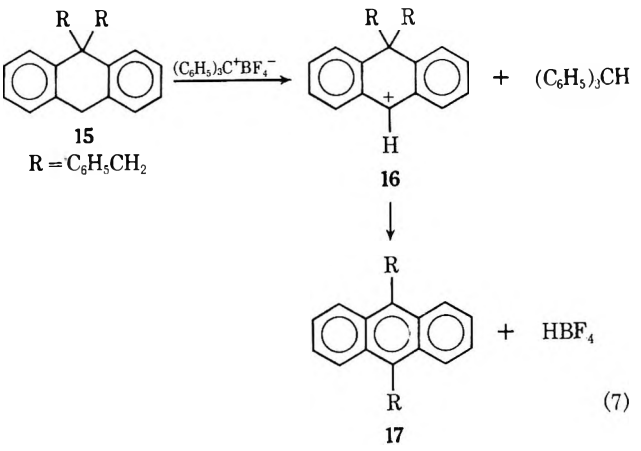
$$(CF_3CO)_2O + CH_3C_6H_4SO_3H \longrightarrow CF_3COOSO_2C_6H_4CH_3 + CF_3CO_2H$$
$$CF_3COOSO_2C_6H_4CH_3 \underset{b}{\overset{a}{\rightleftharpoons}} [CF_3COO^- + CH_3C_6H_4SO_2^+] \quad [CF_3CO^+ + CH_3C_6H_4SO_2^-]$$

detectable reaction. Finally, we have briefly examined the reactions of mixed anhydrides with dihydroaromatic compounds exemplified by 9,10-dihydroanthracene. Since mixed anhydrides can conceivably act as good sources of acylium cations which in turn are capable of hydride ion abstraction,[8] we anticipated that 9,10-dihydroanthracene (**14**) and similar compounds might undergo facile dehydrogenation when heated with mixed sulfonic–carboxylic anhydrides in the manner depicted in eq 6.



(6)

When acetyl *p*-toluenesulfonate (**2**) and the dihydroanthracene (**14**) were heated in a flask open to the air but protected from moisture, for 2 hr at 130°, and 83% yield of anthracene was indeed obtained. Nmr monitoring of the reaction showed its half-life at 130° to be between 4 and 6 min. The reaction temperature was critical. Thus reaction at 100° for 2 hr or prolonged reflux in acetonitrile gave no trace of aromatized product or of anything other than unchanged starting material. The reaction was, in addition, moderately affected by the presence of air, the yield in the absence of air being little more than one half of that observed in its presence. Finally, in a blank experiment to determine the effect, if any, of the presence of sulfonic acid, the dihydroanthracene (**14**) was heated for 2 hr at 150° in the presence of this acid. Only a trace amount of anthracene was formed. The observation that the reaction began only at the precise temperature for which mixed sulfonic–carboxylic anhydrides have been observed to undergo intramolecular decomposition (probably *via* a free-radical mechanism[9]) cast doubt on the assumed ionic hydride abstraction nature of the reaction. Recent observation has shown that carbonium ions of general type **16** containing substituents R capable of facile migration, undergo aromatization by transannular migration of one of the R[10] groups. When 9,9-dibenzyl-9,10-dihydroanthracene[10] (**15**) was refluxed in acetic acid with triphenylmethyl fluoroborate, a reagent of known hydride abstracting ability,[11] the aromatization was observed to proceed smoothly and the dibenzylanthracene (**17**) was observed among the products, being identified by its uv spectrum which was characteristic of anthracene derivatives (eq 7). When the dihydroanthracene **15** was heated with mixed anhydride under a variety of conditions, however, no trace of anthracene was observed, the only product being recovered starting material (eq 7). This was to us strong



(7)

evidence against an ionic mechanism in the dihydroanthracene dehydrogenation. Were such a mechanism to hold sway we should have observed the same rearranged product **17** when **15** was heated with mixed anhydride as when it was heated with triphenylmethyl fluoroborate. Thus initiation of the dehydrogenation by hydride abstraction by acylium cation is ruled out. Further evidence against this mechanism was obtained by the observation that diphenylmethane was recovered almost in total after heating at 130° with mixed anhydride, the remainder of the material consisting of nuclear acetylated derivatives. With diphenylmethane, the criteria involved in carbonium ion formation *via* a hydride abstractive process are identical with those of 9,10-dihydroanthracene (**14**) and, while aromatization is a pathway no longer open, we might anticipate the isolation of diphenylmethanol derivatives if indeed hydride abstraction did take place. That such derivatives were not isolated is a further indication that the dehydrogenation reaction under discussion does not involve hydride ion abstraction as its first step. It would therefore appear that the dehydrogenation reaction does not proceed by an ionic mechanism. The nonreaction of tetrahydronaphthalene toward mixed anhydride indicates that the dehydrogenation may be confined to dihydroaromatic systems.

Experimental Section

General experimental details, followed in this paper, have been given in part II of this series.[1]

1-Methoxynaphthalene (1) and Acetyl *p*-Toluenesulfonate (2).—A mixture of 1-methoxynaphthalene (**1**) (6.0 g, 37.8 mmol) and acetyl *p*-toluenesulfonate (**2**) (12 g, 75% pure, 42 mmol) in acetonitrile was kept at room temperature for 24 hr. Work-up in the usual manner gave a dark oil with a single major component on tlc (25% ether–hexane on silica), yield 6.2 g, 82%. This component was readily purified by column chromatography (Woelm alumina, activity grade I) and identified as 4-acetyl-1-methoxynaphthalene (**3**): mp 68–70° (lit.[12a] 70–71°); ir (Nujol mull) ν_{max} 1670, 1580, 840, 825, and 765 cm^{-1}; nmr δ 2.55 (s, 3 H, $ArCOCH_3$), 3.80 (s, 3 H, CH_3), 7.0 (AB quartet, Δ_{AB} = 75 Hz, J_{AB} = 8 Hz, 2 H, 1,2,3,4-substituted OC_6H_2), and 7.34–8.7 (16-line multiplet, 4 H, OC_6H_4). Comparison of the nmr spectra of the pure compound and of the crude oil showed the latter to contain not less than 90% of the former.

2-Methoxynaphthalene (4) and Acetyl *p*-Toluenesulfonate (2).

(8) I. Tabushi, K. Fujita, and R. Oda, *Tetrahedron Lett.*, 4247, 5455 (1968).

(9) M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971).

(10) A. L. J. Beckwith, W. B. Renfrow, A. Renfrow, and J. K. Teubner, *Tetrahedron Lett.*, 3463 (1968). Thus 9,9-dibenzyl-9,10-dihydro-10-hydroxyanthracene (**14**) (R = $CH_2C_6H_5$) when refluxed in acetic acid for 12 hr afforded 9,10-dibenzylanthracene (**16**) (R = $CH_2C_6H_5$) in 60% yield (eq 6).

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

(12) (a) C. R. Noller and R. Adams, *J. Amer. Chem. Soc.*, **46**, 1893 (1924); (b) E. C. Dodds, R. L. Huang, W. Lawson, and R. Robinson, *Proc. Roy. Soc., Ser. B*, **140**, 470 (1953); (c) W. Schneider and F. Seabach, *Chem. Ber.*, **54B**, 2298 (1921); (d) K. Fries, *ibid.*, **54**, 712 (1921); (e) W. Schneider and F. Kunau, *ibid.*, **54B**, 2304 (1921); (f) J. R. Johnson and G. E. May, *Org. Syn.*, **18**, 1 (1938); (g) A. L. J. Beckwith and W. A. Waters, *J. Chem. Soc.*, 1001 (1957).

—A mixture of 2-methoxynaphthalene (4) (2.0 g, 12.6 mmol) and excess acetyl *p*-toluenesulfonate (2) (10 g, 47 mmol) in acetonitrile was kept for 24 hr at room temperature. Work-up in the usual manner gave a pale yellow oil. To an ether solution of this oil was added pentane until the point of crystallization was reached, when the solution was cooled, depositing colorless needles of 1-acetyl-2-methoxynaphthalene (5), mp 50–54°. Recrystallization from ether–pentane gave pure material: mp 59–60° (lit.[12d] 59–60°); yield, 1.6 g (65%). The mother liquor (0.36 g) contained mostly 1-acetyl-2-methoxynaphthalene (5) as shown on tlc (5% ether–pentane on silica): ir (Nujol mull) ν_{max} 1690, 1620, 1600, 840, 820, and 740 cm^{-1}; nmr δ 2.60 (s, 3 H, ArCOCH$_3$), 3.85 (s, 3 H, OCH$_3$), and 7.45 (m, 5 H, Ar).

Anisole (6) and Acetyl Sulfonates 2. A.—A mixture of anisole (6) (4.7 g, 47.2 mmol) and acetyl *p*-toluenesulfonate (2) (13.0 g, 75% pure, 47.2 mmol) was refluxed for 48 hr in acetonitrile (25 ml). The reaction mixture was worked up in the usual manner leaving a pale yellow oil, yield 5.3 g (77%). A sample of the product (4.0 g) was distilled under reduced pressure collecting two fractions: *p*-methoxyacetophenone (7) [bp 105° (1 mm) [lit.[12a] 139° (15 mm)]; yield 1.15 g; ir ν_{max} 1660 (ArCO), 1600 (ArC=C), and 840 cm^{-1} (2 adjacent free H); nmr δ 2.51 (s, 3 H, ArCOCH$_3$), 3.83 (s, 3 H, OCH$_3$), and 7.40 (AB quartet, Δ_{AB} = 60 Hz, J_{AB} = 8.5 Hz, 4 H, *p*-C$_6$H$_4$)] and a yellow solid [bp 210–220° (1 mm); yield 2.4 g]. The yellow solid was dissolved in ether and cooled, collecting pale yellow crystals of 1,3-bis-*p*-methoxybut-3-ene-1-one (8): mp 93–94° (lit.[12b] 96°); uv λ_{max} 325 mμ (ϵ 23,700); ir (Nujol mull) ν_{max} 1650 (C=C-C=O), 1600 (Ar C=C), 810 and 830 cm^{-1} (2 adjacent free H); nmr δ 2.55 (d, J = 1.5 Hz, 3 H, C=CCH$_3$), 3.85 (s, 3 H, OCH$_3$), 3.87 (s, 3 H, OCH$_3$), and 6.8–8.1 [m, 9 H, *p*-C$_6$H$_4$ (2), C=CH-C=O)]. The mother liquor (*ca.* 1.7 g) was complex, tlc (20% ether–pentane on silica) showing eight spots.

B.—A mixture of anisole (6) (11.0 g, 90 mmol) and acetyl methanesulfonate (11) (15 g, 90 mmol) were kept at room temperature for 16 hr. After an initial induction time of 2 or 3 min, the temperature of the reaction mixture rose considerably, indicating an exothermic reaction. The deep yellow reaction mixture was poured into chloroform–bicarbonate solution and worked up in the usual manner to yield a deep red oil (14.0 g). The oil was then distilled under reduced pressure collecting *p*-methoxyacetophenone (7), yield 7.0 g (46%), bp 86° (0.3 mm), identified by comparison of its ir and nmr spectra with the sample previously obtained. The residual dark oil (7.0 g) was placed on a Kieselgel column and eluted with 25% ether–hexane to afford, as the only product, a pale yellow crystalline material, recrystallized from ether, mp 140–142°. It was identified as 1,3,5-tri(*p*-methoxyphenyl)benzene (9) (lit.[12c] mp 142°), yield 5.4 g (77% column recovery, 41% overall yield).

Acetyl Methanesulfonate (2) and Phenetole (10). A.—A mixture of phenetole (10) (10.0 g, 82 mmol) and acetyl methanesulfonate (11) (11.3 g, 82 mmol) were kept at room temperature for 16 hr. The dark brown reaction mixture was then poured into chloroform–bicarbonate solution and worked up in the usual manner. The resultant deep red oil (12 g) was distilled under reduced pressure to afford 4-acetylphenetole (12), bp 97° (1 mm), which solidified on standing and was recrystallized from ether as pale yellow prisms: mp 34–36° (lit.[1] mp 36–37°); yield 6.7 g (49%); ir ν_{max} 1680, 1600, 1580, 1270, and 850 cm^{-1}; nmr δ 1.40 (t, J = 7.5 Hz, 3 H, CH$_2$CH$_3$), 2.50 (s, 3 H, ArCOCH$_3$), 4.07 (q, J = 7.5 Hz, 2 H, CH$_2$CH$_3$), and 7.32 (AB quartet, Δ_{AB} = 62 Hz, J_{AB} = 8 Hz, 4 H, *p*-C$_6$H$_4$).

The nonvolatile residue from the distillation (4.8 g) was shown on tlc (20% ether–hexane on silica) to contain, as a major component, a uv active compound running as a single spot. Accordingly, this residue, a black viscous oil, was placed on a Kieselgel column and eluted with 20% ether–hexane. A single component was collected, running as a single spot on tlc, identical with the uv active material initially observed. It was purified by recrystallization from hexane to give colorless needles, mp 60–61°, yield 3.4 g (71% column recovery, 24% overall yield). It was identified as 1,3,5-tri(*p*-ethoxyphenyl)benzene (13): ir ν_{max} 1610, 1250, 840, 830, and 705 cm^{-1}; uv (in ether) λ_{max} 267 nm (ϵ 77,300); nmr δ 1.40 (t, J = 8 Hz, OCH$_2$CH$_3$), 4.04 (t, J = 8 Hz, 6 H, OCH$_2$CH$_3$), 7.30 (AB quartet, Δ_{AB} = 38 Hz, J_{AB} = 8 Hz, 12 H, *p*-C$_6$H$_4$), and 7.63 (s, 3 H, all *m*-C$_6$H$_3$); mass spectrum *m/e* 438 (M$^+$), 410 (M$^+$ − 28), 382 (M$^+$ − 56), and 354 (M$^+$ − 84).

Anal. Calcd for C$_{30}$H$_{30}$O$_3$: C, 82.16; H, 6.90. Found. C, 82.07; H, 7.07.

B.—Phenetole (10) (10.0 g, 82 mmol) in acetonitrile (25 ml) was mixed with acetyl methanesulfonate (11) (11.3 g, 82 mmol). After 4 hr at room temperature no reaction was detectable, the ir of the mixture being unchanged. The mixture was refluxed for 90 min when it had turned a deep red. The infrared spectrum of the crude solution showed no mixed anhydride remaining. It was poured into chloroform–bicarbonate and worked up in the usual manner to yield a red-brown oil (11.7 g). Distillation under reduced pressure gave 4-acetylphenetole (12), bp 83° (0.04 mm), yield 5.2 g (52%).

Benzene and Acetyl *p*-Toluenesulfonate (2). A.—Acetyl *p*-toluenesulfonate (13.0 g) was refluxed in benzene (50 ml) for 18 hr. Work-up in the usual manner gave only *p*-toluenesulfonic anhydride.

B.—Acetyl *p*-toluenesulfonate in an excess of benzene was heated in a sealed tube at 130° for 2 hr. Work-up in the usual manner gave only *p*-toluenesulfonic anhydride.

Mesitylene and Acetyl *p*-Toluenesulfonate (2).—Mesitylene (1.20 g, 10 mmol) was heated with acetyl *p*-toluenesulfonate (2.4 g, 11.2 mmol) at 100° for 4 hr, when reaction was judged from the absence of starting material in the nmr to be complete. Work-up in the usual manner gave a brownish oil which was distilled under reduced pressure, collecting acetomesitylene: bp 80° (2.0 mm) [lit. 90° (3 mm)]; yield, 1.1 g (64%); ir ν_{max} 1690 (ArC=O), 1600 (ArC=C), and 855 cm^{-1} (one free hydrogen atom); nmr δ 2.20 (s, 6 H, OCH$_3$), 2.26 (s, 3 H, *p*-CH$_3$), 2.46 (s, 3 H, ArCOCH$_3$), and 6.85 (s, 2 H, ArH).

Acetyl Methanesulfonate (11) and Thiophene.—Acetyl methanesulfonate (11) (13.0 g, 94 mmol) was slowly added to thiophene (15.9 g, 190 mmol). An exothermic reaction ensued, and the reaction mixture was kept at room temperature for 2 hr before being worked up in the usual manner to yield a reddish oil (12.3 g). This oil was distilled under reduced pressure collecting colorless 2-acetylthiophene: bp 60–62° (0.1 mm) [lit.[12f] 89–91 (3 mm)]; yield, 8.1 g (69%); ir ν_{max} 1670 cm^{-1}; nmr δ 2.51 (s, 3 H, ArCOCH$_3$), 7.10 (m, 1 H, SCHCH–), and 7.62 (m, 2 H, SCHCHCH=).

9,10-Dihydroanthracene (14) and Acetyl *p*-Toluenesulfonate (2). A.—9,10-Dihydroanthracene (14) (2.5 g, 14 mmol) was heated with a large excess of acetyl *p*-toluenesulfonate (2) (9.8 g, 45 mmol) in an open flask protected from moisture at 130° for 2 hr. Work-up in the usual manner gave a solid residue (2.05 g, 83%). Recrystallization from ether gave yellow-green crystals, mp 202–205°, mmp (with anthracene) 204°. The crude material was shown on tlc to run as a single spot with identical R_f value as anthracene. The nmr spectrum contained only a characteristic ten-line multiplet between δ 7.2 and 8.5 with no trace of the two singlets at δ 3.90 and 7.20 associated with 9,10-dihydroanthracene (14).

B.—The reaction A above was repeated in an nmr tube on a small scale, the tube being maintained at 130° and the singlet at δ 3.90 (aliphatic CH$_2$) from the starting material being rescanned and integrated at 2-min intervals. The intensity of this line was observed to decrease rapidly, the estimated half-life of the reaction being 4–6 min. After 45 min the line remained only as a weak shoulder and the full spectrum of the reaction product was identical with that of anthracene.

C.—The reaction A repeated at 100° for 2 hr gave only recovered starting material. Similarly when repeated under reflux in acetonitrile (25 ml) for 12 hr only recovered starting material in 83% yield was obtained.

D.—Identical reactions were carried out by heating two samples of 2.5 g of dihydroanthracene (14) with 3.3 g of mixed anhydride 2 at 130° for 2 hr, (a) under nitrogen, and (b) under dry air. Identical work-up procedures gave, in the latter case, a 52% yield and, in the former case, a 30% yield of recovered solid. The two products contained exactly the same proportion of anthracene (16) (57%) and 9,10-dihydroanthracene (14) (43%) as estimated by nmr integration measurements.

E.—In a blank experiment 9,10-dihydroanthracene (14) (4.0 g, 22.4 mmol) and *p*-toluenesulfonic acid (2) (1.0 g, 5.8 mmol) were heated at 150° for 2 hr. Work-up in the usual manner gave a solid product (2.3 g, 58%) whose composition, as estimated from the nmr spectrum, was, 9,10-dihydroanthracene (14) (94%) and anthracene (6%).

Acetyl Methanesulfonate (11) and 9,10-Dihydroanthracene (14).—Acetyl methanesulfonate (11) (2.8 g, 20 mmol) and 9,10-dihydroanthracene (14) (1.76 g, 9.8 mmol) were heated in a sealed tube at 130° for 2 hr. Work-up in the usual manner gave

a solid (1.2 g, 69%) containing equal proportions of starting material and anthracene as estimated from nmr and tlc.

Acetyl Methanesulfonate (11) and 9,9-Dibenzyl-9,10-dihydroanthracene (15). A.—Acetyl methanesulfonate (11) (1.3 g. 9.4 mmol) was heated with the dibenzyldihydroanthracene (15) (500 mg, 1.4 mmol) at 130° for 2 hr. Work-up in the usual manner (but with chloroform as solvent) gave a dark solid whose nmr showed the presence of only starting material.

B.—Repeat of reaction A (2.6 g of mixed anhydride + 360 mg of reagent) in refluxing acetic acid (10 ml) for 30 min gave again only recovered starting material (280 mg).

Triphenylmethyl Fluoroborate and 9,9-Dibenzyl-9,10-dihydroanthracene (15).—The dihydroanthracene (15) (358 mg, 1.0 mmol) and triphenylmethyl fluoroborate (1.5 g, 3.8 mmol) were refluxed in acetic acid (10 ml) for 30 min when the color of the reaction mixture was observed to change to a deep red from the original yellow. Work-up in the usual manner gave an oil (1.65 g) whose nmr spectrum and tlc showed the absence of starting material and the probable presence of triphenylmethane and triphenylmethanol. The crude oil was placed on a silica column which was then eluted with pentane followed by 5% ether. The first fraction contained triphenylmethane which was recrystallized from hexane to give pure material, mp 92°, mmp 92°, yield 300 mg. Elution with 5% ether gave a glass which could not be crystallized but which was shown to contain 9,10-dibenzylanthracene (17). The glass was purified by precipitation from ether with pentane and sublimation at 300° under reduced pressure (0.01 mm). The resulting glass registered as a single spot on tlc (20% ether–pentane on silica): uv λ_{max} 270 mμ (ε 58,000) [lit.[12g] λ_{max} 266 mμ, (ε 84,000)]: nmr δ 4.70, 5.0 (m, CH_2Ar), and 7.2 (m, ArH); yield 242 mg (67%).

Diphenylmethane and Acetyl *p*-Toluenesulfonate (2).—Diphenylmethane (2.5 g, 15 mmol) was heated with acetyl *p*-toluenesulfonate (2) (10 g, 47 mmol) at 130° for 2 hr. Work-up in the usual manner gave an oil (2.2 g) whose composition, as judged from the nmr and tlc, was 90% diphenylmethane. The remaining 10% (seven distinct spots on tlc) appeared from the nmr (singlets at δ 2.0, 2.15) to contain some acetylated material.

Registry No.—**1**, 2216-69-5; **2**, 26908-82-7; **4**, 93-04-9; **6**, 100-66-3; **10**, 103-73-1; **11**, 100-06-1; **13**, 7509-23-1; mesitylene, 108-67-8; thiophene, 110-02-1; **14**, 613-31-0; **15**, 26908-83-8; triphenylmethyl fluoroborate, 341-02-6.

Boron Photochemistry. VI. The Possible Role of Bridged Intermediates in the Photolysis of Borate Complexes

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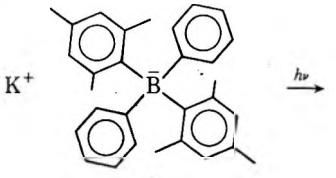
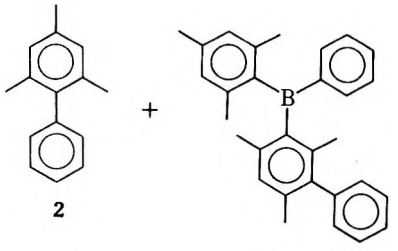
Received July 1, 1970

Several hindered tetraarylborate salts have been synthesized and photolyzed. The unexpected nature of some of the photolysis products has led us to reexamine the photolysis of potassium dimesityldiphenylborate labeled with a deuterium atom in each of the 4-position methyl groups. An examination of the products from the photolysis of this compound has demonstrated that an unusual and unanticipated rearrangement involving a 1,3 shift of a diarylbora group has taken place. A possible mechanism involving bridged intermediates has been proposed to account for this rearrangement.

In a previous publication[1] we discussed the photochemistry of the highly hindered potassium dimesityldiphenylborate (1) in the presence of oxygen to yield 2,4,6-trimethylbiphenyl (2) and (2,4,6-trimethyl-3-biphenylyl)mesitylphenylborane (3).



1



2 3

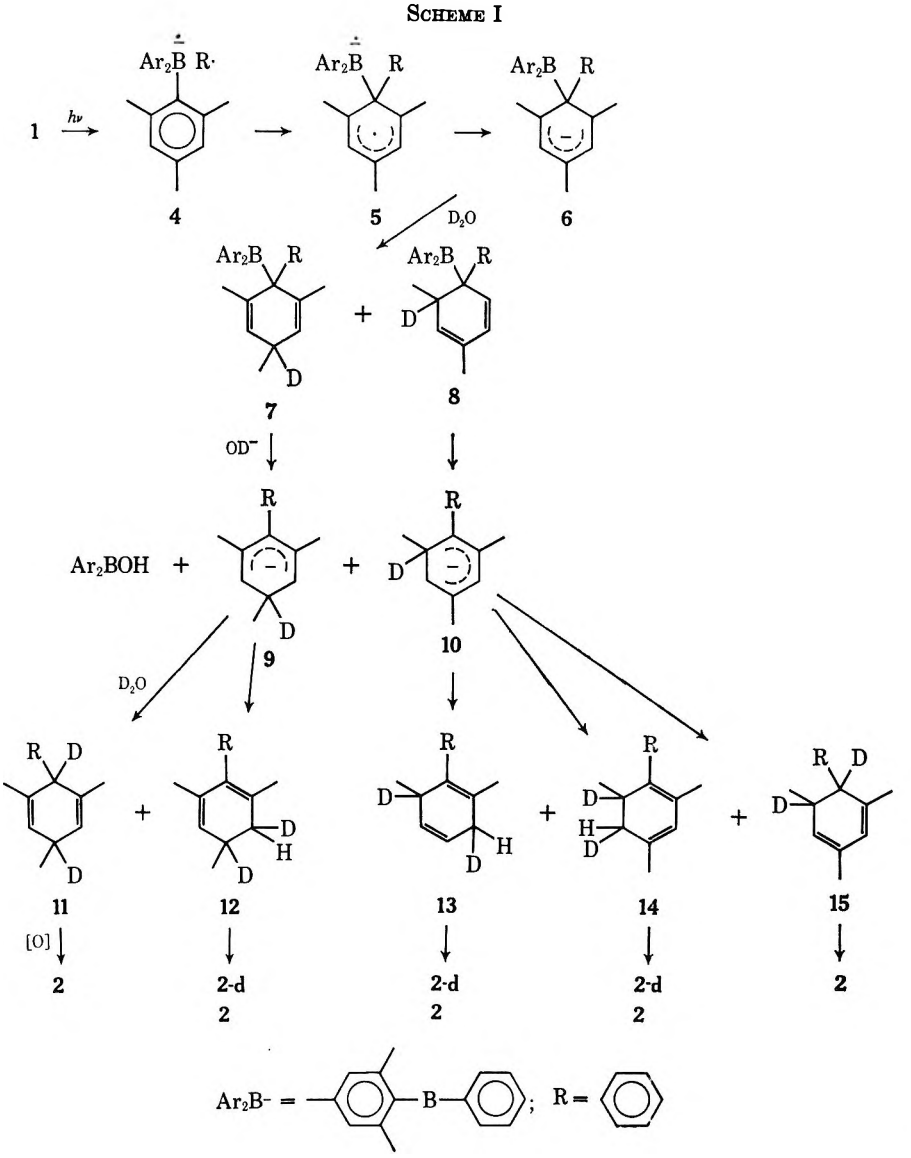
Three possible routes to 2 were discussed but at that time no attempt was made to distinguish between them. We have now conducted the photolysis of 1 in D_2O–1,2-dimethoxyethane in place of the H_2O–dimethoxyethane used earlier. Previously we considered two primary photochemical processes: (1) the generation of a phenyl radical (R·) by homolytic fission of a phenyl boron bond in the "ate" complex 1; (2) the generation of a mesityl radical by an analogous process. Path a based on process 1 is shown in Scheme I[2] and reveals that in D_2O the 2,4,6-trimethylbiphenyl (2) should contain zero or one D atom/molecule. The deuterium would be located in the mesityl ring since a phenyl radical has attacked the mesityl ring. A similar route, b (not shown), based on process 2, would predict 2,4,6-trimethylbiphenyl (2), which would have a maximum of two D atoms/molecule incorporated into the phenyl ring. A third route, c, which involves the radical pair, 4, of route a is shown in Scheme II. Route c leads to 2,4,6-trimethylbiphenyl (2) containing one deuterium atom per molecule, located on the mesityl ring. Therefore, by examining the position and content of deuterium in the isolated 2, we hoped to be able to determine the route followed by the rearrangement.

2,4,6-Trimethylbiphenyl (2) containing approximately 10% monodeuterated material was obtained experimentally. We were unable to determine the exact ring location of the deuterium label. However, the small extent of incorporation of deuterium is consistent when route a is considered as the major route to 2. Further examination of the proposed routes to 2 reveals a second distinction. Paths a and b yield 2,4,6-tri-

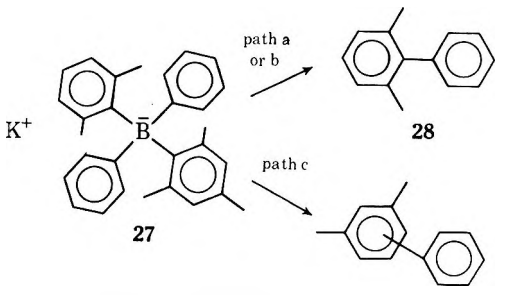
(1) P. J. Grisdale, B. E. Babb, J. C. Doty, T. H. Regan, D. P. Maier, and J. L. R. Williams, *J. Organometal. Chem.*, **14**, 63 (1968).

(2) The spin state of the biradical 5 is unknown. As a singlet 5 and 6 become canonical structures.

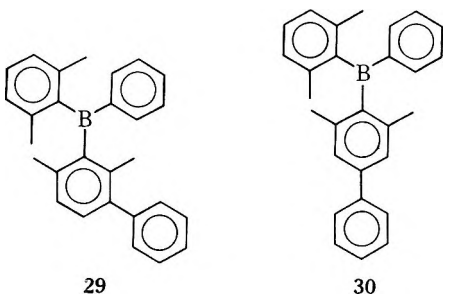
SCHEME I



methylbiphenyl (**2**) with the phenyl attached to the mesityl residue at the position originally bonded to boron, whereas path c leads to compound **2** with the phenyl group attached to a position on the mesityl ring, which was *not* originally bonded to boron. We have, therefore, synthesized and studied the photolysis of potassium 2,6-dixylyldiphenylborate (**27**) and examined the hydrocarbon products. The biphenyl fraction consisted solely of the 2,6-dimethyl isomer **28**, which was isolated by preparative glc and identified by its spectral properties. This result is consistent with paths a or b. In addition to the biphenyl fraction, we had anticipated two isomeric triarylboranes, **29** and **30**, which would be formed from **27** *via* the intermediate produced by attack of a phenyl radical on a xylyl group. This rearrangement would be analogous to that shown in Scheme II for the production of **3** from **1** *via* **16** and **17**.



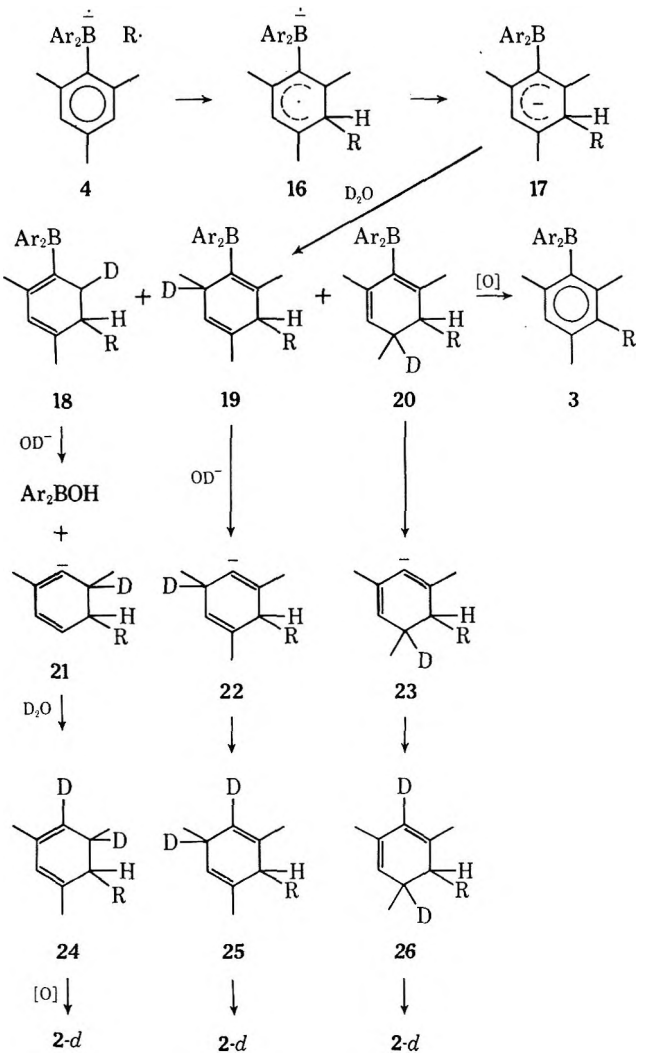
However, we were unable to detect any products in the photolysis mixture whose *m/e* values in the mass spectrum corresponded to those expected for **29** or **30**.



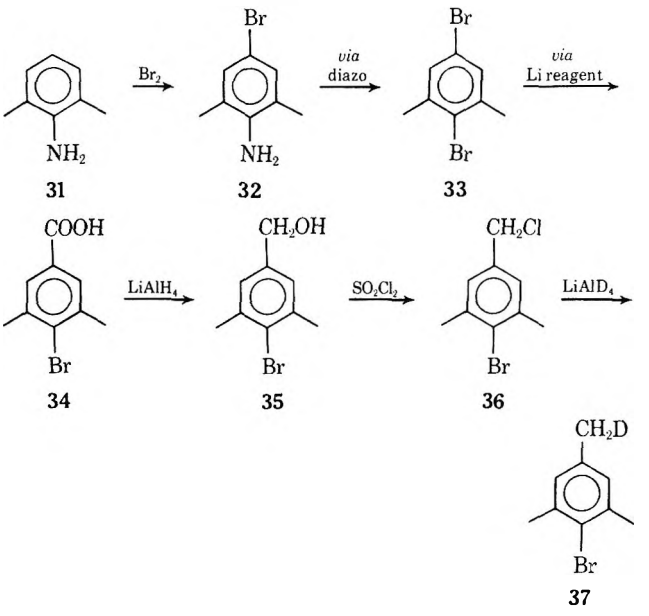
In the case of the photolysis of compound **1**, the triarylborane (**3**) is isolated as a stable product. The stability is due to the shielding of the B atom by the four *o*-methyl groups, which prevent the oxidative decomposition. Such an explanation has been proposed to account for the stability of trimesitylborane toward oxidation.[3]

(3) H. C. Brown and V. H. Dodson, *J. Amer. Chem. Soc.*, **79**, 2302 (1957).

SCHEME II



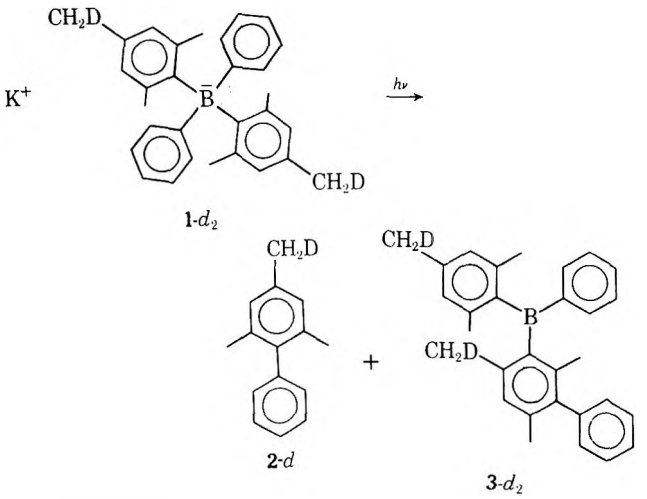
SCHEME III



Compounds **29** and **30** have steric crowding similar to **3** and consequently, if they were formed, one would expect them to be isolable. We suspected that these products were not formed because an unexpected rearrangement had taken place during the photolysis, which in the case of **27** had produced neither **29** nor **30**, but isomeric triarylboranes in which four methyl groups were no longer ortho to the boron atom. Such compounds would be easily oxidized. The unexpected rearrangement would go unobserved during the photolysis of **1** owing to the symmetry of the mesityl groups. We have, therefore, labeled each of the 4-position methyl groups of **1** with a single deuterium atom to enable us to determine if any rearrangement of the diarylboron group occurs during the photolysis. The route to the required intermediate, monodeuterated bromomesitylene (**37**), is shown in Scheme III.

The monodeuterated bromomesitylene (**37**) was converted to dimesitylfluoroborane-d_2 and potassium dimesityldiphenylborate-d_2 (**1**-d_2) by the methods mentioned previously.[1] We have studied the photolysis of this compound as described previously[1] and examined the products, 2,4,6-trimethylbiphenyl-*d* (**2**-*d*) and the (2,4,6-trimethyl-3-biphenylyl)mesitylphenylborane-d_2 (**3**-d_2), by nmr spectroscopy. We have already published the nmr data for the undeuterated compounds.[1] These data and those for the deuterated compounds are compared in Table I. The resonances corresponding to the CH_2D– groups appeared as 1:1:1 triplets in **2**-*d* and **38**-*d*. The triplet signal for the CH_2D– in **3**-d_2 was less clearly defined than those for this group in **2**-*d* and **38**-*d*, but integrated as a two-proton resonance. An inspection of the data for the isolated **2**-*d* clearly establishes the structure as 4-deuteriomethyl-2,6-dimethylbiphenyl. This is in agreement with our previous observations that the biaryl fractions are formed by coupling of the aryl groups at positions originally linked to boron.[4]

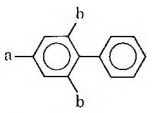
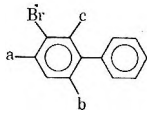
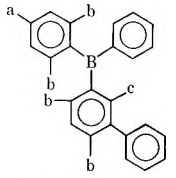
The nmr data for **3**-d_2 are inconclusive. One CH_2D– residue is, of course, on the mesityl group linked to boron, while the second could occupy either of positions "b" of the trimethylbiphenylyl group. Compound **3**-d_2 was degraded with mercuric acetate and bromine[1] to yield the 3-bromo-2,4,6-trimethylbiphenyl derivative (**38**-*d*). This procedure introduces a bromine atom in the position originally bonded to boron. A comparison of the nmr data for **38**-*d* and **38** clearly fixes the position of the CH_2D– group in position 4 relative to the phenyl group. As a further check on the correctness of our assignments for the spectrum of **38**, we have debrominated **38**-*d via* its lithium derivative to yield **2**-*d*, identical with



(4) J. L. R. Williams, J. C. Doty, P. J. Grisdale, R. Searle, T. H. Regan, G. P. Happ, and D. P. Maier, *J. Amer. Chem. Soc.*, **89**, 5153 (1967).

TABLE I

SHIFTS FOR THE METHYL PROTON RESONANCES OF THE DEUTERATED AND UNDEUTERATED COMPOUNDS[a]

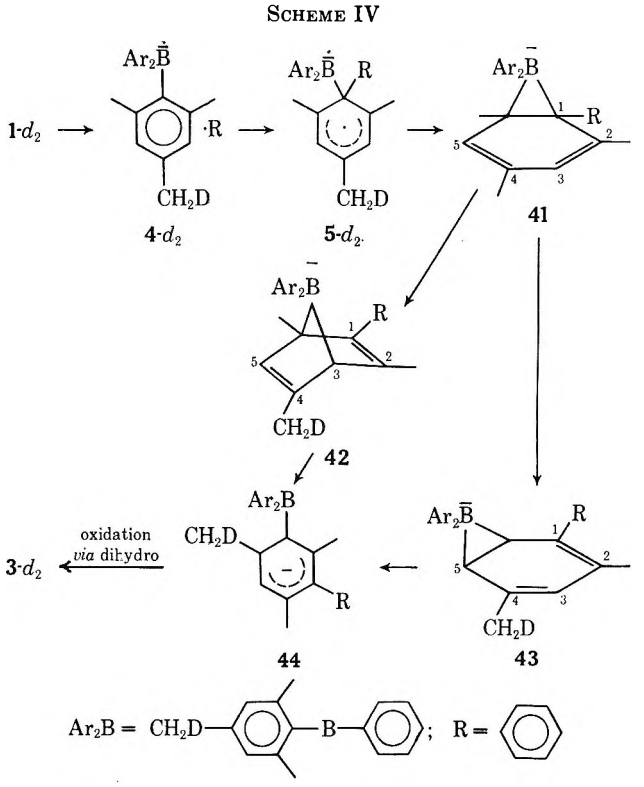
Compd	No.	CH_3[a]	CH_3[b]	CH_3[c]
	**2**	137 (3 H)	119 (6 H)	
	2-*d*	138 (2 H)	120 (6 H)	
	**38**	146 (3 H)	116 (3 H)	128 (3 H)
	38-*d*	146 (2 H)	116 (3 H)	128 (3 H)
	**3**	138 (3 H)	123 (12 H)	103 (3 H)
	3-d_2	136 (2 H)	124 (11 H)	106 (3 H)

[a] In hertz downfield from TMS in $CDCl_3$.

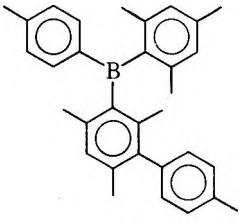
the 4-deuteriomethyl-2,6-dimethylbiphenyl (**2-*d***), which we obtained as a direct photolysis product. The overall reaction is, therefore, that given above.

The phenyl group in **3-d_2** occupies the position originally occupied by the diarylboron group which has undergone a 1,3 shift. A possible reaction mechanism to account for these facts is shown in Scheme IV. Such

SCHEME IV



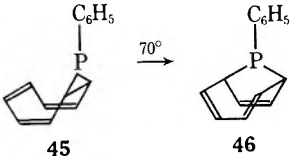
a scheme requires that (a) the reaction be intramolecular, and (b) the phenyl ring be bonded to the mesityl ring at the C atom originally bonded to boron. Both requirements are met. We have photolyzed a mixture of potassium dimesityldiphenylborate (**1**) and potassium dimesityldiperdeuteriophenylborate (**1-d_{10}**) and examined the triarylborane fraction **3**. It consisted of **3** (*m/e* 402), **3-d_{10}** (*m/e* 412), but no **3-d_5** (*m/e* 407). We have also photolyzed potassium dimesityldi-*p*-tolylborate (**39**). The structure of the triarylborane **40** derived from this photolysis was determined by comparison with an authentic sample. This finding established the position of the bonding in the tolyl group. Our reasons for favoring the original gen-



40

eration of a radical species have already been presented.[1] The intramolecularity of the reaction necessitates the caged radical pair **4-d_2**.

The intermediate **41** is the analog of one proposed recently by us to account for the production of 1,1- and 1,6-diphenylhexadiene from the photolysis of sodium tetraphenylborate.[5] The proposed concerted rearrangements **41** → **42** and **41** → **43** are of interest. If one considers the symmetry of the orbitals involved in the phenylpentadienyl system ($R-C_1C_2C_3C_4C_5$),[6] then the C_1-C_3 bond migration to yield **42** is photochemically allowed but thermally forbidden, while the C_1-C_5 bond migration to yield **43** is photochemically forbidden and thermally allowed. Since both proposed intermediates lead to the same product, either thermal or photochemical processes could be involved. There is a very close analogy here to the rearrangement of the cyclic phosphorus compound **45** reported recently by Katz.[7] An



45 **46**

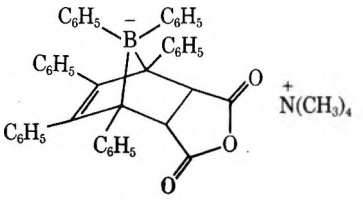
(5) J. L. R. Williams, P. J. Grisdale, and J. C. Doty, presented at the Fourth International Conference on Organometallic Chemistry, Bristol, England, 1969.

(6) A. Streitweiser and J. Brauman, "Supplemental Tables of Molecular Orbital Calculations," Vol. 1, Pergamon Press, New York, N.Y., 1965, p 90.

(7) T. J. Katz, C. R. Nicholson, and C. A. Reilly, *J. Amer. Chem. Soc.*, **88**, 3832 (1966).

alternative description would involve π-allyl complex intermediates with delocalization of the π electrons on just three carbon atoms of the mesityl ring.[8] Such bonding is well known for transition metal–allyl interactions, but the stability of such complexes is due partly to interaction of the d orbitals of the metal with the antibonding π orbitals of the allyl system.[9]

So far, attempts to obtain direct evidence of bridged or cyclic intermediates have failed. Bridged aluminates analogous to our intermediate **42** have recently been synthesized and do open readily with water to yield trisubstituted aluminum derivatives.[10] We have recently reported on the first boron-containing analog **47**



47

of the norbornene system, which is a stable crystalline material.[11] However, we have been unsuccessful in preparing the corresponding norbornadiene analog.

Experimental Section

All melting points are corrected. Various spectra were determined on Cary Model 15 (uv), Perkin-Elmer Infracord (ir), and Varian A-60 (nmr) instruments. Mass spectra were determined with a CEC 21-110B instrument equipped with a heated inlet system.[12] All the deuterated products described below were more than 95% enriched unless otherwise stated (mass spectral analyses). Glc analyses were run on a Model 5750 F & M gas chromatograph equipped with a 0.25-in. stainless steel column 10 ft long, packed with 5% SE-30 on Chromosorb G, acid washed, DMCS treated. The column temperature was usually programmed from 150 to 300° at 10°/min. Preparative glc separations were performed under similar conditions on an F & M Model 776 instrument equipped with a $^3/_8$-in. stainless-steel column 7 ft long.

Photolyses.—Solutions of the potassium tetraarylborates, 1.0 g, 0.23 mmol, were photolyzed with a mixture of dimethoxyethane (DME) and water (or deuterium oxide) as described previously.[1] The neutral products were isolated and the following results obtained. Potassium dimesityldiphenylborate (**1**) in DME–D_2O yielded 2,4,6-trimethylbiphenyl (**2**) (10% monodeuterated by mass spectral analysis, 0.1 g) and (2,4,6-trimethyl-3-biphenylyl)mesitylphenylborane (**3**, 0.28 g). A mixture of potassium dimesityldiphenylborate (**1**) and potassium dimesityldiperdeuteriophenylborate (**1**-d_{10}) yielded a mixture of 2,4,6-trimethylbiphenyls (**2** and **2**-d_5) (0.11 g), and a mixture of the boranes **3** and **3**-d_{10} (0.29 g), but *no* **3**-d_5. Potassium dideuteriomesityldiphenylborate (**1**-d_2) yielded 4-deuteriomethyl-2,6-dimethylbiphenyl (**2**-d, 0.12 g) and (4-deuteriomethyl-2,6-dimethyl-3-biphenylyl)(4-deuteriomethyl-2,6-dimethylphenyl)phenylborane (**3**-d_2, 0.25 g). Potassium diphenyldi-2,6-xylylborate (**27**) yielded only 2,6-dimethylbiphenyl (**28**, 0.1 g). The nmr ($CDCl_3$) spectrum showed that the methyl groups were equivalent and a six-proton absorption band occurred at δ 2.0. The uv spectrum was identical with published data,[13] and the mass spectrum indicated a parent ion at m/e 182. Potassium dimesityldi-4-tolylborate (**39**) gave a tetramethylbiphenyl (mass spectrum m/e 210) with a characterless uv spectrum typical of a hindered biphenyl. In addition, (2,4,4′,6-tetramethyl-3-biphenylyl)mesityl-4-tolylborane (**40**), 0.32 g, mp 186–187°, was produced. It was identical in every respect with an authentic sample (see below).

Degradation Experiments.—The degradation of the (4-deuteriomethyl-2,6-dimethyl-3-biphenylyl)(4-deuteriomethyl-2,6-dimethylphenyl)phenylborane (**3**-d_2) was carried out as described previously using bromine.[1] The crude bromo compounds (0.2 g) after separation by glc yielded 3-bromo-4-deuteriomethyl-2,6-dimethylbiphenyl (**38**-d, 0.075 g), identical in retention time with the undeuterated analog.[1] (For nmr data see Table I.) This bromo compound (0.075 g) in 20 ml of dry ether was treated with 2 *M* butyllithium solution (0.2 ml). After 15 min, water was added and the ether layer was washed, dried, and evaporated. The residue was chromatographed to yield unchanged starting material and 4-deuteriomethyl-2,6-dimethylbiphenyl (**2**-d, 0.017 g), identical in retention time with the undeuterated analog.[1] (For nmr data see Table I.)

Materials.—All operations involving lithium and Grignard reagents were conducted under a nitrogen atmosphere. Fluorodimesitylborane was prepared by the method of Brown and Dodson.[3] The potassium tetraarylborates were prepared *via* their lithium salts by the general method described by Wittig and Herwig[14] from 2 mol of aryllithium and 1 mol of fluorodimesitylborane. The following example is typical but utilizes the fluorodi-2,6-xylylborane.

Potassium Di-2,6-xylyldiphenylborate (**27**).—A solution of 2,6-dimethylbromobenzene (148 g, 0.8 mol) in dry ether (200 ml) was added slowly with stirring and heating to magnesium turnings (20 g) and dry ether (100 ml). When the magnesium had dissolved, the Grignard reagent was treated with boron trifluoride ethyl etherate (55 g, 0.39 mol) in ether (100 ml) and the resulting solution heated under reflux for 1 hr. Dry hexane (500 ml) was then added and the supernatant liquid decanted from the residue. The liquid was evaporated to yield the crude fluoroborane. It was distilled at 153–155° (6 mm) giving 50 g, 54%, of pure product, which was converted to the tetraarylborate as follows. A solution of phenyllithium prepared from bromobenzene (32 g, 0.2 mol) and *n*-butyllithium (95 ml, 2 *M* solution) in dry ether (300 ml) was added to a stirred solution of fluorodi-2,6-xylylborane (21 g, 0.09 mol). The resulting mixture was heated under reflux for 2 hr and then poured into water (1000 ml). The ether layer was dried and evaporated yielding the crude lithium tetraarylborate. This was dissolved in water and the aqueous solution washed with hexane and then treated with a solution of potassium chloride. The white potassium salt was filtered off, washed with water, and dried under vacuum, yield 14 g, 38%.

Anal. Calcd for $C_{28}H_{28}BK$: C, 81.1; H, 6.8; B, 2.6; K, 9.4. Found: C, 80.7; H, 7.0; B, 2.6; K, 9.1.

4-Bromo-3,5-dimethylbenzoic Acid (**34**).—1,4-Dibromo-3,5-dimethylbenzene (26 g, 0.1 mol), prepared from 2,6-dimethylaniline by bromaintion[15] and a Sandmeyer reaction,[16] was dissolved in ether (300 ml). The resulting solution was chilled in an acetone–Dry Ice bath and treated with *n*-butyllithium solution (50 ml, 2 *M* solution). This solution was allowed to warm slowly to room temperature and then poured onto crushed Dry Ice. When the mixture had warmed up, the solid was filtered off and dissolved in water and the aqueous solution was treated with concentrated hydrochloric acid. The white solid was collected and recrystallized from acetonitrile to give the desired 4-bromo-3,5-dimethylbenzene acid as white needles, 10.0 g, 48%, mp 217–219° (lit.[17] 214–215°).

4-Hydroxymethyl-2,6-dimethylbromobenzene (**35**).—Lithium aluminum hydride (0.95 g, 0.025 mol) in dry ether (60 ml) was added slowly to a solution of 4-bromo-3,5-dimethylbenzoic acid (5.0 g, 0.02 mol) in dry ether (60 ml). After 15 min the solution was treated with water and dilute hydrochloric acid. The ether layer was washed with dilute hydrochloric acid, dried, and evaporated to yield the crude product, mp 50–53°. It was

(8) We are grateful to Dr. P. Heimbach (Mülheim-Ruhr) for helpful discussion on this point.

(9) A reviewer has pointed out that a π-allyl bond requires that the boron atom adopts an sp^2 hybridization since the + + + symmetry of the allyl group must be matched by a + orbital on the boron, and the higher energy + 0 − symmetry on the allyl must be matched by a + − symmetry orbital on the boron. Hybrid sp^3 orbitals on boron would not fulfill these conditions.

(10) H. Lehmkuhl, *Justus Liebigs Ann. Chem.*, **719**, 20 (1968).

(11) P. J. Grisdale and J. L. R. Williams, *J. Organometal. Chem.*, **22**, C19 (1970).

(12) The system is described by V. J. Caldecourt, *Anal. Chem.*, **27**, 1670 (1955), but was constructed of glass instead of metal.

(13) G. H. Beaven and E. A. Johnson, *Spectrochim. Acta*, **14**, 67 (1959).

(14) G. Wittig and W. Herwig, *Chem. Ber.*, **88**, 962 (1955).

(15) E. Noelting, A. Braun, and G. Thesmar, *ibid.*, **34**, 2242 (1901).

(16) J. J. Blanksma, *Recl. Trav. Chim. Pays-Bas*, **25**, 171 (1906).

(17) H. J. Schmitz, *Justus Liebigs Ann. Chem.*, **192**, 174 (1878).

crystallized from ligroin (bp 60–65°) giving the pure product, 3.5 g, 85%, mp 53–54°.

Anal. Calcd for $C_9H_{11}BrO$: C, 50.2; H, 5.1; Br, 37.2. Found: C, 50.6; H, 5.4; Br, 37.6.

4-Chloromethyl-2,6-dimethylbromobenzene (36).—The 4-hydroxymethyl derivative (26 g, 0.12 mol) in dry benzene (100 ml) was treated with thionyl chloride (25 g). After 30 min the benzene was evaporated and the residue recrystallized from ligroin (bp 35–40°) at low temperature to yield the pure product, 20 g, 75%, mp 43–44°.

Anal. Calcd for $C_9H_{10}BrCl$: C, 46.2; H, 4.3; Br, 34.2. Found: C, 46.5; H, 4.5; Br, 33.8.

4-Deuteriomethyl-2,6-dimethylbromobenzene (37).—The chloromethyl derivative (19 g, 0.08 mol) in dry ether (200 ml) was treated with lithium aluminum deuteride (5 g, 0.12 mol). The mixture was heated under reflux for 6 hr and then treated with water and dilute hydrochloric acid. The ether layer was separated, dried, and evaporated to yield the crude deuterated product. It distilled at 225–227° (lit.[18] 225°, undeuterated), 13 g, 81%. The nmr ($CDCl_3$) spectrum showed absorption bands at δ 6.85 (s, 2 H), 2.37 (s, 3 H), and 2.2 (1:1:1 t, 2 H).

3-Bromo-2,4,6,4′-tetramethylbiphenyl.—A solution of *p*-toluidine (53 g, 0.5 mol) in water (100 ml) and concentrated hydrochloric acid (100 ml) was diazotized at 0–5°. The resulting solution was added to 2-bromomesitylene (250 ml). To this mixture was added, with vigorous stirring, ice-cold 50% sodium hydroxide solution until the mixture was basic. The organic layer was separated, washed with water, dried, and evaporated to yield a colored residue. This residue was treated with ligroin (1000 ml, bp 60–65°) and the solution poured through a 3 × 3 in. column of alumina (Woelm neutral activity grade I). Evaporation of the eluent afforded a pale yellow oil (10 g) which was distilled under vacuum to give a fraction, bp 114–118° (0.3 mm), 8.0 g, 6%.

(18) P. S. Varma and T. S. Subrahmanian, *J. Indian Chem. Soc.*, **13**, 192 (1936).

Anal. Calcd for $C_{16}H_{17}Br$: C, 66.4; H, 5.9; Br, 27.7. Found: C, 66.8; H, 6.3; Br, 27.7.

***n*-Butoxymesityl-4-tolylborane.**—4-Tolylboronic acid was heated with *n*-butyl alcohol providing the di-*n*-butoxy-4-tolylborane. This diester (124 g, 0.5 mol) in dry ether was vigorously stirred and treated at −70° with the Grignard reagent prepared from 2-bromomesitylene (100 g, 0.5 mol) in dry ether. The resulting suspension was allowed to warm to room temperature overnight and then washed with 10% aqueous hydrochloric acid. The ether layer was separated, washed with water, dried, and evaporated to yield a colorless residue. It was treated with *n*-butyl alcohol (30 ml) and then fractionated to give the desired compound, 66 g, 45%, bp 182–185° (1.4 mm).

Anal. Calcd for $C_{20}H_{27}BO$: C, 81.6; H, 9.2; B, 3.7. Found: C, 81.3; H, 9.6; B, 3.6.

(2,4,4′,6-Tetramethyl-3-biphenylyl)mesityl-4-tolylborane (40).—The mesityltolyl ester (2.9 g, 0.01 mol) in dry ether (30 ml) was treated with a solution of the lithium reagent prepared from the 3-bromo-2,4,4′,6-tetramethylbiphenyl (2.9 g, 0.01 mol) and *n*-butyllithium (5 ml, 2 *M* solution) in dry ether (20 ml). The solution was then heated under reflux for 1 hr and poured into dilute hydrochloric acid. The ether layer was washed with water, dried, and evaporated to give a pale yellow oil. This oil was triturated with methanol (two 5-ml portions) and the methanol discarded. The oil was scratched under ether (5 ml) to yield a crystalline residue, mp 178–182°. This residue was washed with warm ether to yield the pure borane, 1.1 g, 26%, mp 185–186°.

Anal. Calcd for $C_{32}H_{35}B$: C, 89.3; H, 8.2; B, 2.5. Found: C, 89.1; H, 8.4; B, 2.8.

Registry No.—**1**, 20623-88-5; **1**-d_2, 26985-33-1; **2**-*d*, 26965-68-4; **3**-d_2, 26965-69-5; **27**, 26985-34-2; **35**, 27006-02-6; **36**, 26965-70-8; **38**-*d*, 26965-71-9; **40**, 26992-54-1; 3-bromo-2,4,4′,6-tetramethylbiphenyl, 26941-22-0; *n*-butoxymesityl-4-tolylborane, 26941-23-1.

Displacement of Tertiary Phosphines from Methylolphosphonium Salts by Tributylphosphine

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Tributylphosphine displaces tris(hydroxymethyl)phosphine (II), triphenylphosphine, and, to a limited extent, butylbis(hydroxymethyl)phosphine (Vb) from the corresponding methylolphosphonium salts. No formaldehyde is liberated. Tetrakis(hydroxymethyl)phosphonium chloride (I) reacts with mercuric chloride in ethanol giving the mercuric chloride adduct of II, $(HOCH_2)_3P \cdot HgCl_2$, in 88% yield.

In connection with some other work in these laboratories on the flameproofing of cotton, we had a need for a method of preparing formaldehyde-free methylolphosphines and, in particular, tris(hydroxymethyl)phosphine (II). Methylolphosphines such as Va or Vb [$RP(CH_2OH)_2$, R = Me or Bu] can be rendered formaldehyde-free by repeated distillation, but II decomposes when distilled under vacuum.[2]

Methylolphosphines are usually prepared from the corresponding methylolphosphonium salts by treatment with a base (B) such as sodium hydroxide[3] or triethylamine.[4] Formaldehyde (1 equiv) is liberated in the process by either reagent.

$$\underset{\text{I}}{(HOCH_2)_4PCl} + B \longrightarrow \underset{\text{II}}{(HOCH_2)_3P} + CH_2O + B \cdot HCl$$

Gordon's method,[5] in which the base was sodium sulfite, was an effort to overcome this problem by tying up the formaldehyde as the bisulfite addition compound. This procedure, however, requires a careful attention to pH, as the sodium hydroxide liberated in the formation of the bisulfite addition compound is capable of destroying the product.[6a]

In this paper, we report our investigation of the use of a tertiary phosphine as the base, on the premise that tertiary phosphines, unlike tertiary amines,[7] are

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) K. A. Petrov and V. A. Parshina, *Usp. Khim.*, **37**, 1218 (1968); *Russ. Chem. Rev.*, **37**, 532 (1968).

(3) M. Grayson, *J. Amer. Chem. Soc.*, **85**, 79 (1963); U. S. Patent 3,243,450 to American Cyanamid Co. (March 29, 1966).

(4) K. A. Petrov, V. A. Parshina, and M. B. Luzanova, *Zh. Obshch. Khim.*, **32**, 553 (1962).

(5) I. Gordon and G. M. Wagner, U. S. Patent 3,257,460 to Hooker Chemical Corp. (June 21, 1966).

(6) J. F. Walker, "Formaldehyde," 3rd ed, Reinhold, New York, N. Y., 1964: (a) p 486; (b) p 494; (c) p 493; (d) p 507.

(7) Crystalline *N*-methylol compounds having the composition $R_3NCH_2OH^+Cl^-$ can be prepared from tertiary amines, but decompose in water; see T. D. Stewart and H. P. Kung, *J. Amer. Chem. Soc.*, **55**, 4813 (1933).

capable of reacting with formaldehyde in the presence of acid forming stable *P*-methylol phosphonium salts.[8,9]

Results and Discussion

Tributylphosphine reacted with tetrakis(hydroxymethyl)phosphonium chloride (I) in ethanol within 30 min at reflux, giving tris(hydroxymethyl)phosphine (II) and tributylhydroxymethylphosphonium chloride (IIIa). The product, a colorless oil, was soluble in

$$\underset{\text{I}}{(HOCH_2)_4PCl} + Bu_3P \longrightarrow \underset{\text{II}}{(HOCH_2)_3P} + \underset{\text{IIIa}}{[Bu_3PCH_2OH]Cl}$$

ether (I is not) and gave only a faint test with carbon disulfide,[10] showing that the displacement was substantially complete, but unfortunately the solubility characteristics of II and IIIa were so similar that we were unable to separate them by partition between solvents, either by extraction or by chromatography on a cellulose powder column.

The presence of II in the oil was established by nmr which clearly showed the II methylene doublet at δ 4.28 (J = 7.5 Hz) superimposed on the spectrum of IIIa (minus the OH peak, owing to exchange with II), and by precipitation of the mercuric chloride adduct,[5,11] mp 133–134° dec, in 58% yield when the oil was treated with mercuric chloride in ethanol. The phosphonium salt (IIIa), which has not been described previously, was precipitated in 90% yield as the tetraphenylboron derivative (IIId), mp 135–136°, when the oil was treated with $NaBPh_4$ in water. IIIa does not react with mercuric chloride in ethanol, nor II with $NaBPh_4$ in water, Analysis of the oil for free formaldehyde by the dimedone method[6b] showed that only 0.03% was present.

No reaction was observed when I was treated under the same conditions with triphenylphosphine, a much weaker base.

The reaction of tributylphosphine with butyltris(hydroxymethyl)phosphonium bromide (IV) gave a mixture of butylbis(hydroxymethyl)phosphine (Vb) and unreacted tributylphosphine.

$$\underset{\text{IV}}{BuP(CH_2OH)_3Br} + Bu_3P \longrightarrow \underset{\text{Vb}}{BuP(CH_2OH)_2} + \underset{\text{IIIb}}{Bu_3P(CH_2OH)Br}$$

The composition of the mixture was estimated from its refractive index and nmr spectrum to be 1.2:1, on a molar basis. The mixture also contained some free formaldehyde (1.46%), but this was traced to the starting material (IV).

The reaction of tributylphosphine with triphenylhydroxymethylphosphonium chloride (VI) gave, under the same conditions, a 95% yield of triphenylphosphine, mp 79–80°.

$$\underset{\text{VI}}{Ph_3P(CH_2OH)Cl} + Bu_3P \longrightarrow Ph_3P + \underset{\text{IIIa}}{Bu_3P(CH_2OH)Cl}$$

It appears, therefore, that methylolphosphines such as II and Vb are *capable of being displaced from the corresponding methylolphosphonium salts by strongly basic tertiary phosphines*, such as tributylphosphine (pK_a = 8.43),[12] *but not by weakly basic tertiary phosphines*, such as triphenylphosphine (pK_a = 2.30,[13] 2.73[12]).

The base strength of II, based on titration data with I, has been calculated to be 5.5 pK_a units.[3,14] Use of the σ^* value[15] of +0.555 for the methylol group in the Henderson–Streuli equation[16] gives a theoretical pK_a of 3.40. Fodor[17] argues that the titration data should include a term for formaldehyde release, and estimates the basicity of II itself to be very much lower ($pK_a < 3$) than the basicity of its formaldehyde adduct $(HOCH_2)_3P^+CH_2O^-$ (pK_a = 7.06). The present work places II in the range between 2.30 and 8.43.[18,19]

The base strength of Vb is not known, but by analogy with methylbis(hydroxymethyl)phosphine (Va), which has a pK_a of 7.18,[11b] it must be much closer to tributylphosphine than to II. The relative order of basicity is, then, $Ph_3P < II < Va,b < Bu_3P$.

In other experiments incidental to this work it was discovered that the methylolphosphonium salts could be purified by steam distillation, to remove the excess formaldehyde, and that I reacts with mercuric chloride, even at room temperature, giving the mercuric chloride adduct of II, mp 133–134° dec.

Experimental Section[20]

Starting Materials.—Tributylphosphine (FMC Corp.)[21] and triphenylphosphine (Eastman Kodak Co.) were used as obtained. Tetrakis(hydroxymethyl)phosphonium chloride (I) (Hooker Chemical Corp.) was recrystallized, mp 149–149.5° (*i*-PrOH). Butyltris(hydroxymethyl)phosphonium bromide (IV), $n^{20}D$ 1.5403, and triphenylhydroxymethylphosphonium chloride (VI), mp 190–192° (*i*-PrOH), were prepared by known methods.[3,9] Butyl = *n*-butyl throughout this paper.

All operations with tertiary phosphines were carried out under nitrogen.

Reactions of Tributylphosphine. A. With Tetrakis(hydroxymethyl)phosphonium Chloride (I).—Tributylphosphine (4.0 g, 0.02 mol) was added rapidly from a gas-tight syringe to a solution of 3.8 g (0.02 mol) of I in 25 ml of anhydrous ethanol and heated to reflux for 30 min. No solids separated on cooling, nor when ether was added (I is insoluble in ether). The solvents were distilled off, and the residual oil was taken up in 25 ml of water, transferred to a separatory funnel (under nitrogen), and extracted twice with ether. The extract gave only a faint red color with carbon disulfide.[10] The aqueous layer was concentrated under reduced pressure, distilled with benzene to remove the last of the water as the azeotrope,[22] and stripped again under reduced pres-

(8) H. Hoffmann, L. Horner, and G. Hassel, *Chem. Ber.*, **91**, 58 (1958).

(9) H. Hellmann, J. Bader, H. Birkner, and O. Schumacher, *Justus Liebigs Ann. Chem.*, **659**, 49 (1962).

(10) Tributylphosphine and Va both give strongly positive tests (red color) with carbon disulfide; II does not. This test is characteristic of tertiary phosphines; see G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, pp 25–26.

(11) (a) M. Reuter and L. Orthner, German Patent 1,035,135 to Farbwerke Hoechst A.-G. (July 31, 1958); (b) E. I. Grinshtein, A. B. Bruker, and L. Z. Soborovskii, *Zh. Obshch. Khim.*, **30**, 302 (1966).

(12) C. A. Streuli, *Anal. Chem.*, **32**, 985 (1960).

(13) H. Goetz and A. Sidhu, *Justus Liebigs Ann. Chem.*, **682**, 71 (1965).

(14) P. A. Chopard, unpublished work, cited by E. A. C. Lucken, *J. Chem. Soc. A*, 1357 (1966).

(15) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 619.

(16) W. A. Henderson, Jr., and C. A. Streuli, *J. Amer. Chem. Soc.*, **82**, 5791 (1960).

(17) L. M. Fodor, Ph.D. Dissertation, Cornell University, 1963, p 14.

(18) Since there is no gain or loss of formaldehyde in the exchange, it should not matter whether one compares the base strengths of II and tributylphosphine or of the corresponding phosphonium hydroxides.

(19) An example of the displacement of an even weaker base from a phosphonium salt by II was given by E. S. Kozlov, A. I. Sedlov, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **38**, 1881 (1968).

(20) All melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were run on a Perkin-Elmer Model 137B spectrophotometer with NaCl optics. Nmr spectra were taken on a Varian A-60 spectrometer using TMS as internal standard.

(21) Naming of firms or their products in this paper does not imply their endorsement by the Department of Agriculture.

(22) R. K. Valetdinov, E. V. Kuznetsov, R. R. Belova, R. K. Mukhaeva, T. I. Malikina, and M. Kh. Khasanov, *Zh. Obshch. Khim.*, **37**, 2269 (1967.

sure, giving 7.8 g (100%) of colorless oil, $n^{20}D$ 1.5165. The oil was soluble in water, ethanol, and acetone, partially soluble in methylene chloride, and insoluble in other organic solvents.

A portion of the oil (0.660 g, 1.68 mmol) was taken up in 3 ml of anhydrous ethanol and treated with a solution of 1.0 g of mercuric chloride in 10 ml of ethanol. The white, crystalline solid which separated was collected next day on a filter, washed with ethanol, and dried, giving 0.381 g (58%) of $(HOCH_2)_3P \cdot HgCl_2$, mp 133–134° dec (lit.[5,11] mp 135°), ir and melting point identical with those of the complex prepared from II.

Another portion of the oil (0.743 g, 1.89 mmol) was taken up in 5 ml of water and treated with s solution of 0.75 g of sodium tetraphenylboron in 10 ml of water. The tetraphenylboron derivative (IIId) separated within minutes as a mass of fine needles, 0.932 g (90%), mp 135–136°.

Anal. Calcd for $C_{37}H_{50}BOP$: C, 80.42; H, 9.10; P, 5.61. Found: C, 80.06; H, 9.15; P, 4.90.

In separate experiments, it was established that II does not react with sodium tetraphenylboron, nor IIIa with mercuric chloride.

The original experiment was then repeated in order to ascertain the composition of the reaction mixture by nmr. After 30 min reflux, the solvent was stripped carefully under vacuum, leaving 8.1 g of a colorless oil containing only 0.03% CH_2O by dimedone analysis. Its nmr spectrum showed the II methylene doublet at δ 4.28 ppm (J = 7.5 Hz) superimposed on the usual IIIa spectrum, minus its OH peak (see below), together with a little solvent ethanol. The CH_2 (II):Bu (IIIa) ratio was 4.5:27 (theoretical 4.0:27).

B. With Butyltris(hydroxymethyl)phosphonium Bromide (IV).—A similar reaction between tributylphosphine (4.0 g, 0.02 mol) and IV (5.2 g, 0.02 mol) in 25 ml of anhydrous ethanol gave, on work-up, an ether-soluble fraction, 2.8 g, $n^{20}D$ 1.4808, and an ether-insoluble fraction, 6.4 g, $n^{20}D$ 1.5198. The ether extract, which gave a strong red color with CS_2,[10] contained bands in the ir spectrum (neat) at 3330 s (OH) and 1020 vs (C–O) cm^{-1} which were not present in the tributylphosphine, but its refractive index was much too low for Vb (lit.[22] $n^{20}D$ 1.5010), suggesting that the product might contain some unreacted tributylphosphine.[23] The nmr spectrum ($CDCl_3$) confirmed this [δ 4.38 (s, 2 H, CH_2OH, vanishes when D_2O is added), 4.03–4.33 (m, 4 H, CH_2OH) and the 2:4:3 butyl peaks at 1.61, 1.39, and 0.97 ppm (m, 31.4 H, C_4H_9; IIc has only 9 H)]. From the $HOCH_2$:Bu ratio it was calculated that the ether extract contained 47.2% Vb and 52.8% tributylphosphine. The composition calculated from the refractive index data[23] was almost identical.

Distillation of the extract gave a fraction, bp 91–92° (5.0 mm), $n^{20}D$ 1.4735, enriched in tributylphosphine, but still containing some Vb (ir, nmr).

Analysis of the ether extract for free formaldehyde by the dimedone method showed that it contained 1.46% CH_2O. This was traced to the IV from which it was prepared (CH_2O, 1.40%).

C. With Triphenylhydroxymethylphosphonium Chloride (VI).—A mixture of tributylphosphine (4.0 g, 0.02 mol) and VI (6.6 g 0.02 mol) in 25 ml of anhydrous ethanol gave a negative CS_2 test[10] after 30-min reflux. Triphenylphosphine (2.6 g, mp 79–80°) crystallized on cooling; another 2.35 g, mp 79–80° (95% total), separated upon dilution with water. Extraction of the aqueous solution with ether gave 0.25 g of low-melting solid which yielded 0.05 g (0.9%) of triphenylphosphine oxide, mp 152–154° (correct ir), upon precipitation from benzene with low-boiling petroleum ether. The aqueous solution, stripped to dryness on a rotary evaporator, left 5.2 g (98%) of a colorless oil, $n^{20}D$ 1.5075, which crystallized after drying in a drying pistol at 80° (1 mm): mp 47–49°; ir (CH_2Cl_2) almost identical with that of pure IIIa.

Formaldehyde Analysis.—Since the objective of this work was to prepare formaldehyde-free phosphorus compounds, a reliable method of analyzing for small quantities of formaldehyde was needed. Tests showed that the methylolphosphines (II, Va, and Vb) interfered with both the sulfite method[6a] and the hydroxylamine method.[6c,25]

A small sample of Va (112.0 mg) was covered with 25 ml of saturated aqueous dimedone reagent[6b] and stirred on a mechanical stirrer for 20 hr, in a stoppered flask under nitrogen, and then filtered; the crystalline methylene bismethone was washed with water and air-dried, yielding 14.0 mg (1.3%), mp 188–188.5° (lit.[6b] mp 189°), correct ir. Further stirring of the undiluted filtrate produced only a trace of solid.

This method was applied to several other tertiary phosphines and phosphonium salts with encouraging results (Table I).

TABLE I

EFFECT OF STEAM DISTILLATION ON FREE FORMALDEHYDE CONTENT OF METHYLOLPHOSPHINES AND -PHOSPHONIUM SALTS

Compd	Per cent CH_2O Before	After
I	0.60[a]	0.26[a]
II[b]		0.02
IIIa	0.78	0.06
IIIb[c]	0.58	0.42
IV	1.40	1.68
Va	0.19	1.45
Vb[d]	1.46	
VI		1.18[e]

[a] Methylene bismethone, mp 187.5–188.5° (lit.[6b] mp 189°). [b] Freshly prepared from I by treatment with 1 N NaOH to pH 7.40, and kept under nitrogen until used. [c] Mixture with IV. [d] Mixture with tributylphosphine. [e] Together with 13.0% triphenylphosphine.

The sample size was such that not more than 10 mg of formaldehyde (equivalent to 100 mg of the methylene bismethone) was present, owing to the limited solubility of the reagent in water.[6b]

Compound VI gave erroneous results, owing to a tendency to precipitate triphenylphosphine. This could be corrected by dissolving the methylene bismethone in 1 N NaOH, filtering, and reprecipitating the methylene bismethone with dilute HCl; concentrated HCl dissolves both substances.

Steam Distillation.—The phosphonium salt IV used in the preparation of Vb was found to contain 1.40% free formaldehyde, which subsequently contaminated the products (see above). Table I summarizes the results of efforts to purify IV and other phosphonium salts, and also some tertiary phosphines, by steam distillation. A simple assembly was used in which the evolved formaldehyde was trapped under water and subsequently was analyzed by the dimedone method. The time was 1 hr in every case.

The phosphonium salts IIIa, IIIb, IV, and even, surprisingly, VI, appeared to be unaffected by this treatment, although some triphenylphosphine was precipitated from VI during the subsequent dimedone analysis. I, which is reported to be stable to boiling water,[26] was recovered virtually unchanged. The melting point was low (140–142°) and the product had an offensive, phosphine-like odor, but the ir and nmr were correct and the recovery was quantitative (99.7%).

The two tertiary phosphines subjected to steam distillation, II and Va, were both partially converted to the phosphine oxides, despite the care taken to avoid oxidation during the steam distillation or after.

An inspection of the data in Table I revealed that formaldehyde could be removed from some compounds by this method, while others showed little or no improvement.

Tributylhydroxymethylphosphonium Chloride (IIIa).—Hellmann's method[9] gave a product which was high in carbon and chlorine. The following is an adaptation of Vullo's method.[27]

Tributylphosphine (4.0 g, 0.02 mol) was added in one portion to a solution of 37% formalin (2.0 g, 0.025 mol), 10 ml of ethanol, and 10 ml of water containing 3 drops of phenolphthalein indicator. The solution turned pink immediately.[27] An attempt to titrate the solution under nitrogen with 1 N HCl was unsuccessful as the reaction was slow, even when heated to 50° and treated with another 2.0 g of formalin. The remainder of the HCl (total 20.0 ml, 0.02 mol) was then run in, and the solution,

(23) The best literature data, based on MR_D fits, are, for Vb,[22] bp 120–122° (5 mm), $n^{20}D$ 1.5010, d^{20}_4 1.0252 (MR_D, calcd 43.16; found 43.15), and, for tributylphosphine,[24] bp 83–84° (1 mm), $n^{20}D$ 1.4630, d^{20}_4 0.8201 (MR_D, calcd 67.99; found 67.95). Based on these values a mixture having $n^{20}D$ 1.4808 contains 46.8% Vb and 53.2% tributylphosphine.

(24) Z. N. Mironova, E. N. Tsvetkov, A. V. Nikolaev, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **37**, 2747 (1967).

(25) W. M. D. Bryant and D. M. Smith, *J. Amer. Chem. Soc.*, **57**, 57 (1935).

(26) A. Hoffman, *ibid.*, **43**, 1684 (1921).

(27) W. J. Vullo, *J. Org. Chem.*, **33**, 3665 (1968).

now colorless, was heated to reflux for 15 min, allowed to cool (I_2 test negative), and extracted with benzene to remove any organic impurities. The aqueous layer, stripped of solvent under reduced pressure, left a colorless oil, 5.1 g, $n^{20}D$ 1.5040, with a faint formaldehyde odor (CH_2O, 0.78%).

The product was taken up in 25 ml of water, steam distilled for 1 hr, and again stripped under vacuum to constant weight at 60–70°: 5.1 g of colorless oil, $n^{20}D$ 1.5032, neutral to pH paper and odorless (CH_2O, 0.06%). It crystallized in the freezer, mp 40–47°.

Anal. Calcd for $C_{13}H_{32}ClO_2P$ (hydrate): C, 54.43; H, 11.25; Cl, 12.36; P, 10.80. Found: C, 54.86; H, 11.18; Cl, 13.27; P, 10.93.

The analyses showed the substance to be a hydrate which was then heated for several hours in a drying pistol at 80° (0.8 mm). On cooling, it solidified to a hard mass of crystals: mp 49–50°; ir (CH_2Cl_2) 3300 m, sh, 3100 vs (OH), 1370 m, 1090 s, 1055 vs (C–O), 1000 m, 965 m, 910 cm^{-1} s; nmr ($CDCl_3$ δ 6.35 (s, 1.3 H, CH_2OH, vanishes when D_2O added), 4.62 (s, 2 H, CH_2OH; like compound IV,[28] not split in $CDCl_3$), and the 2:4:3 butyl triad[29] at 2.38, 1.56, and 0.99 ppm (m, 27 H, C_4H_9).

Reaction of IIIa with sodium iodide in acetone gave the iodide (IIIc), $n^{20}D$ 1.5386, mp 14–17° (lit.[22] yellowish oil), ir almost identical with that of IIIa. With sodium tetraphenylboron in water, IIIa gave the tetraphenylboron derivative (IIId): mp 134.5–135° after recrystallization from either isopropyl alcohol or benzene; soluble in ethanol, acetone, and chloroform and insoluble in water; ir (Nujol) 3500 m (OH, not H-bonded), 1590 w (arom), 1185 w, 1145 w, 1050 w, 1035 w (C–O), 848 w, 743 vs, 735 s, 709 cm^{-1} vs (arom); nmr ($CDCl_3$) δ 7.03–7.53 (m, 20 H, C_6H_5), 2.74 (q, 3 H, CH_2OH), 0.89, 1.13 ppm (m, 27 H, C_4H_9). Addition of D_2O changes the quartet at 2.74 to a sharp doublet, δ 2.80 ppm (d, 2 H, CH_2OH, J = 2.0 Hz).

Reaction of Tetrakis(hydroxymethyl)phosphonium Chloride (I) with Mercuric Chloride.—In experiments carried out in connection with the identification of the products of the reaction of I with tributylphosphine, it was established that mercuric chloride did not react with paraformaldehyde, tris(hydroxymethyl)-phosphine oxide, or IIIa, but a slow reaction did take place with I, giving 15% of the II adduct, $(HOCH_2)_3P \cdot HgCl_2$, mp 133–134° dec, after 3 days at room temperature, and another 42% after 17 days. The same reaction took place in 30 min at 78°, as follows.

A solution of 0.579 g (2.13 mmol) of mercuric chloride in 10 ml of anhydrous ethanol was added all at once to a warm solution of 0.258 g (1.36 mmol) of I in 20 ml of ethanol and heated to reflux in an assembly protected from moisture but not from air. Solids started to separate in less than 1 min. The mixture was heated at reflux for 30 min, allowed to cool with constant stirring, and filtered. The product, a white, crystalline solid, was washed thoroughly with ethanol and dried, giving 0.472 g (88%) of $(HOCH_2)_3P \cdot HgCl_2$, mp 133–134° dec, identical with the product prepared from pure II: ir (Nujol) 3350 s (OH), 1410 w, 1265 w, 1170 w, 1035 s (C–O), 909 w, 885 w, 808 w, 749 cm^{-1} w.

Portions of the filtrate were analyzed for free formaldehyde by the sulfite method[6a] (after carefully neutralizing with NaOH) and by the dimedone method;[6b] both were negative. A phloroglucinol test for combined formaldehyde in formals,[6d] however, was positive. The amount of resin obtained corresponded to 67.5 mg of CH_2O (theoretical 40.8 mg, 1.36 mmol).

Attempts to further characterize the $II \cdot HgCl_2$ adduct were not successful. The adduct was insoluble in all the common organic solvents and gave an immediate black precipitate with ammonia, pyridine, or dimethyl sulfoxide. It hydrolyzes in water, forming a gray, opalescent solution which is strongly acidic. When heated to boiling, a flocculent yellow precipitate forms and then redissolves, depositing mercury.

The mercuric bromide adduct, $(HOCH_2)_3P \cdot HgBr_2$, was prepared by refluxing 0.360 g (1.0 mmol) of mercuric bromide with 0.194 g (1.0 mmol) of I in 30 ml of anhydrous ethanol for 6 hr, yielding a pale yellow, crystalline solid, 0.177 g (37%): mp 121–122° dec; ir (Nujol) 3330 s (OH), 1270–1280 w, 1150–1170 w, and 1025 cm^{-1} s (C–O). Similarly, with red mercuric iodide, I gave the bright yellow $(HOCH_2)_3P \cdot HgI_2$ complex (9%): decomposes >160°; ir (Nujol) 3340 s (OH), 1270–1300 w, 1160 w, 1030 s (C–O), 890 cm^{-1} w.

Registry No.—Tributylphosphine, 998-40-3; I, 2245-60-5; II–mercuric bromide adduct, 27150-36-5; II–mercuric iodide adduct, 27150-41-0; IIIa, 20507-22-6; IIId, 27178-07-0; IV, 4762-82-7; VI, 5293-83-4.

Acknowledgment.—We are indebted to G. J. Boudreaux for the nmr spectra.

(28) D. W. Allen, I. T. Millar, and J. C. Tebby, *Tetrahedron Lett.*, 745 (1968).

(29) Butyl proton resonances in $[Bu_3PR]^+X^-$ appear at δ 2.42–2.53 (2 H, PCH_2), 1.45–1.60 (4 H, CH_2CH_2), and 0.90–0.98 (3 H, CH_3) ppm: C. E. Griffin and M. Gordon, *J. Organometal. Chem.*, **3**, 414 (1965).

Reactions of Fluorenones and Tetraphenylcyclopentadienones with Tricovalent Phosphines and Phosphites[1]

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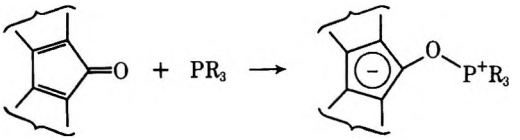
Fluorenone (**3**) or 2,7-dibromofluorenone (**4**) react with triethyl phosphite (TEP) to give carbanion oxyphosphonium dipoles which react with a second mole of ketone to give 2:1 adducts of pentaoxyphosphoranes. Reaction of **3** or **4** with tributylphosphine (TBP, neat) gives the corresponding bifluorenylidine, while reaction in solvents which contain abstractable hydrogen gives the corresponding fluorene, bifluorenyl, and tribiphenyleneпropane. These reactions are rationalized as proceeding through carbene or carbenoid species. The phosphoranes are thermally rearranged to biphenylenephenanthrones and are converted to oxazolines upon reaction with acetonitrile. Initial reaction of **3** or **4** with TEP at higher temperatures gives the phenanthrones directly. Tetraphenylcyclopentadienone (**1**) reacts with TBP to give dihydrooctaphenylfulvalene and a $C_{58}H_{40}$ hydrocarbon which is also obtained from **1** upon reaction with triphenylphosphine. Other ketones, which cannot form stabilized carbanion adducts, do not react with TEP or TBP under similar or more strenuous conditions.

Ketones such as tetraphenylcyclopentadienone (**1**), 2,3-diphenylindenone (**2**), or fluorenone (**3**) should have enhanced reactivity toward P(III) reagents, when compared with simple ketones which are mainly unreactive.[3] The reactivity is expected to be due to the formation of 1,3-carbanion oxyphosphonium dipoles such as i wherein the negative charge is delocalized in a cyclic-6-π-electron system.



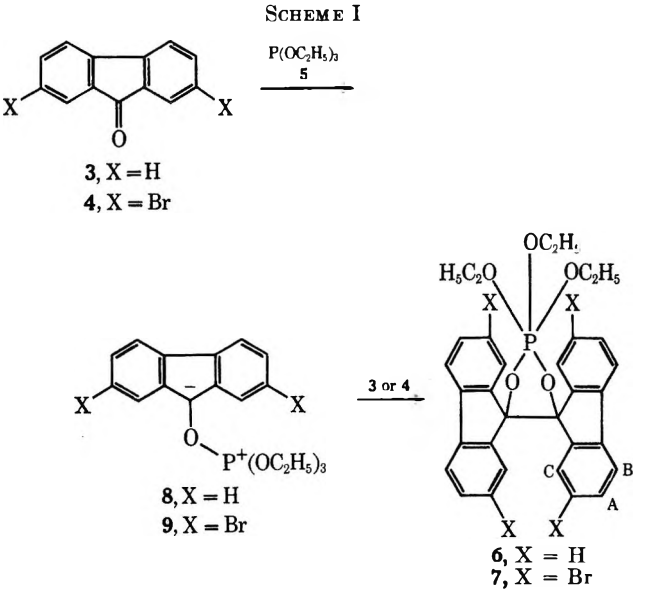
i

Fluorenone (**3**) or 2,7-dibromofluorenone (**4**) reacts with triethyl phosphite (**5**, TEP) at room temperature to give 2,2,2-triethoxy-4,5-bisbiphenylene-1,3,2-dioxaphospholane (**6**), or the corresponding tetrabromo derivative **7**.[3-5] These reactions are interpreted as occurring *via* the further reaction of the 1,3 dipoles **8** and **9** with a second mole of ketone (Scheme I).

Attempts to trap the postulated species **8** with acenaphthalene or benzaldehyde failed in that only the usual product **6** was obtained. A competition of **3** and **4** for **5** gave only **7** (71%).

The phosphoranes are fairly stable solids characterized by their ^1H and ^{31}P nmr spectra. Thus **6** has ^{31}P nmr absorption at +48 ppm ($CDCl_3$, *vs.* 85% H_3PO_4)[6] which is related to similar values for other pentaoxyphosphoranes.[4,7]

SCHEME I



The key intermediates in these reactions are the postulated dipolar species **7** and **8**. The isolation of such a species, from the reaction of **1** with tris(dimethylamino)phosphine,[8] and the reactions of **3**, hexafluoroacetone, and trifluoroacetophenone with tris(dimethylamino)phosphine[4b] lend support to our arguments on the intermediacy of these species. The initial site of attack in the formation of **6** or **7**, and the related phosphoranes isolated by Ramirez[4] remains a problem.

It may be best to defer the question of the detailed mechanistic pathways involved and to concentrate on the factors which stabilize one or another of the forms of the 1:1 adducts. In the present work it is clear that stabilized carbanions allow further reaction of P–O–C forms.[9]

Reactions of the Phosphoranes.—When **6** or **7** is heated under a variety of conditions, two reactions occur: (a) reversion to the fluorenone, and (b) rearrangement to the 9-biphenylenephenanthrones **10** and **11**. The relative extent of the two reaction path-

(1) This investigation was supported by National Science Foundation Grant GP-1354 and Grant 2563-A1 from the Petroleum Research Fund of the American Chemical Society. This is part XII of the series "Organophosphorus Chemistry."

(2) To whom correspondence should be addressed at the Belfer Graduate School of Science, Yeshiva University, New York, N. Y. 10033.

(3) (a) I. J. Borowitz and M. Anschel, *Tetrahedron Lett.*, 1517 (1967); (b) See correction, *ibid.*, 5032 (1967).

(4) (a) The formation of **6** and related phosphoranes from other trialkyl phosphites has also been noted by F. Ramirez and C. P. Smith, *Chem. Commun.*, 662 (1967); (b) for related reaction of fluorenones, hexafluoroacetone, and trifluoroacetophenone, see F. Ramirez, A. S. Gulati, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 6283 (1967).

(5) For a review of oxyphosphoranes see F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

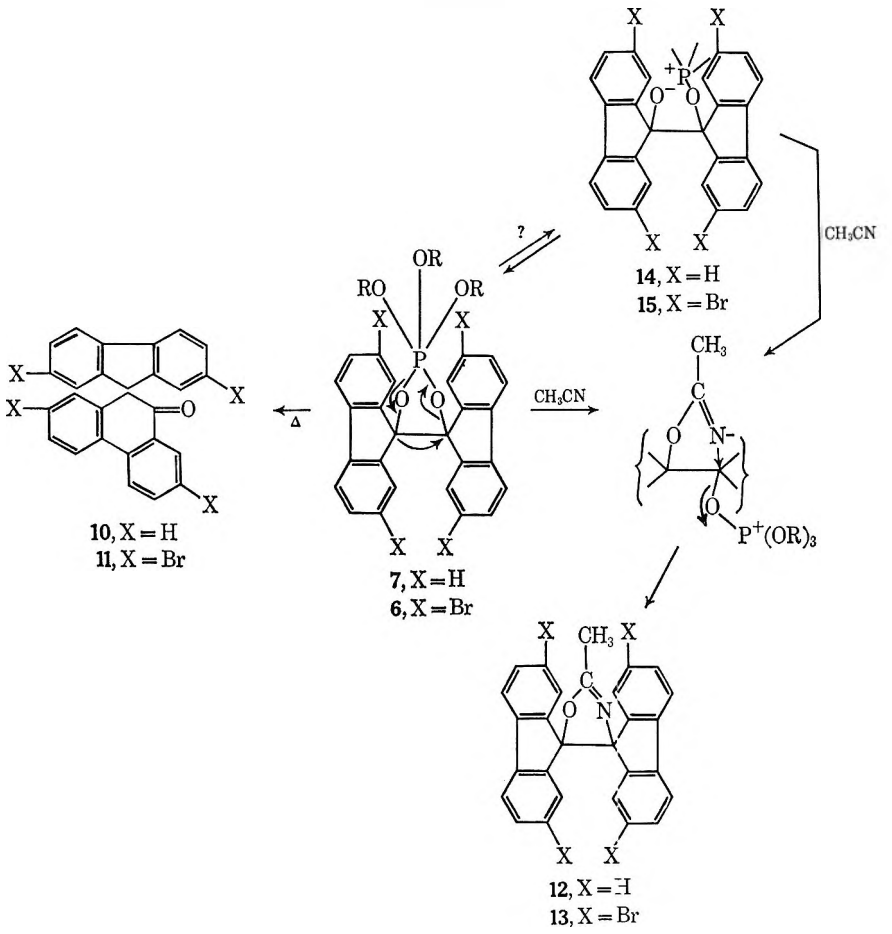
(6) ^{31}P nmr spectrum done by Dr. J. Lancaster, American Cyanamid.

(7) (a) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (b) *Bull. Soc. Chim. Fr.*, 2443 (1966); (c) for X-ray evidence confirming P(V) structures, see W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *J. Amer. Chem. Soc.*, **87**, 127 (1965).

(8) (a) M. J. Gallagher and I. D. Jenkins, *J. Chem. Soc. C*, 2605 (1969). (b) We disagree with these authors' designation of a minor role to the stabilization of the carbanion end of the 1,3 dipoles. As our evidence indicates, such stabilization is necessary for the reactions of many carbonyl compounds with P(III) species.

(9) For a related discussion see F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 6276 (1967).

SCHEME II



ways depends upon the solvent. Thus **7** rearranges to **11** more in nitromethane than in the less polar methylene chloride, and it mainly reverts to **4** in benzene. The rearrangement of **6** to **10** occurs more readily, even in benzene–hexane upon heating.

In control experiments, **11** was found to be stable to TEP or tributylphosphine (TBP).

Reaction of **6** or **7** with acetonitrile gives the oxazoline **12** (18%) or **13** (54%) as well as the phenanthrones **10** (71%) or **11** (31%) (Scheme II).[10] The oxazoline may form *via* **6** or **7**, or the tetracovalent dipolar form **14**, **15**.[11] This novel formation of a heterocyclic system indicates a synthetic use of pentaoxyphosphoranes which we will investigate further.

Confirmation of the oxazoline structure of **12** was obtained from its mass spectral fragmentation pattern at 75 eV which exhibits major peaks at 385 ($M\cdot^+$), 342 ($M^+ - CH_3CO$), 205 (b), 180 (a), 164 (c), and 152 (d) (Scheme III). Metastable peaks are observed at 304 (calcd for $385^+ \rightarrow 342^+ + CH_3CO$), 131 (calcd for $205^+ \rightarrow 164^+$), 128 (calcd for $180^+ \rightarrow 152^+ + CO$), and 109 (calcd for $385^+ \rightarrow 205^+$). A similar fragmentation pattern is observed for **13** with metastable peaks observed for the processes 2 and 3 (see Experimental Section).

The observed fragmentation of processes 1 and 2 are not compatible with the isomeric isoxazoline [–ON=C(CH_3)–] structure. The loss of CH_3CO from the molecular ions may actually be occurring from the acetylaziridines **16** and **17** which may form from **12** and **13** upon electron impact. Thermal rearrangement of oxazolines to *N*-acylaziridines have been postulated.[12]

Treatment of **7** with TEP or TBP gives tetrabromobifluorenylidine (**19**, 14,44%) as well as the fluorenone **4** and the phenanthrone **11** (20, 1%). The formation of **19** probably occurs directly from the reaction of **7** with P(III). It may also occur *via* the reversion of **7** to **4** which then reacts with P(III). Evidence against the latter pathway is found in the observation that the reactions of TEP with **3** or **4** give little **18** or **19** (see below).

Other Reactions of Fluorenones with P(III).—The reaction of **3** or **4** with TEP at 150–180 or 100°, respectively, gives the phenanthrone **10** (74%) or **11** (58%), most likely *via* the phosphoranes **6** and **7**. The bifluorenylidines are formed in small yield: **18** (2–3%), **19** (2%). The conversion of **3** to **10** with triisopropyl phosphite has been noted by Poshkus and Herweh.[13] Triphenylphosphine (TPP) gives no reaction with **3** or even with 2,7-dinitrofluorenone (**20**). TBP reacts with **3** or **4** to give **18** or **19**. The highest yields are obtained in neat reaction (44% of **19**) or in benzene (54% of **19**). Treatment of **4** with TBP in toluene or benzene–cyclohexene gives neither **19** nor **11**. The products in these reactions, as exemplified by the benzene–cyclohexene run, are 2,7-dibromofluo-

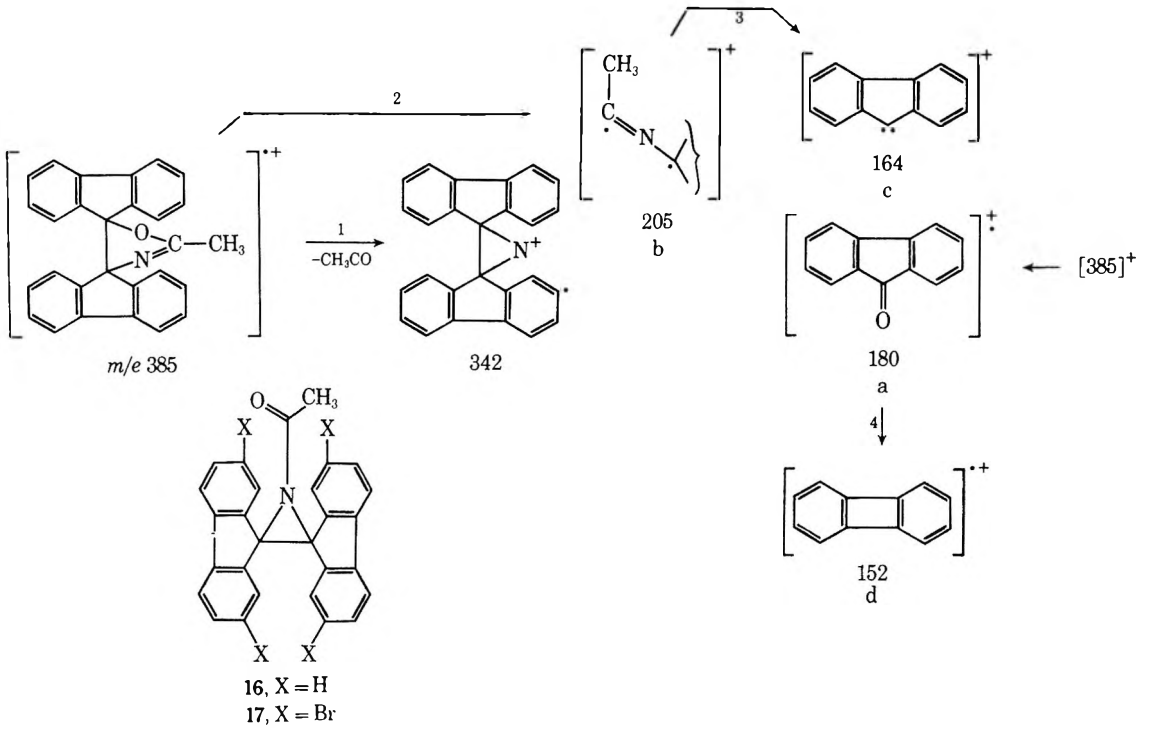
(10) (a) I. J. Borowitz, P. D. Readio, and P. E. Rusek, *Chem. Commun.*, 240 (1968). (b) This work corrects the error in ref 3a.

(11) Alternatively, **6** and **7** may revert to **8** and **9** which react with acetonitrile and then with **3** and **4** as suggested by a referee.

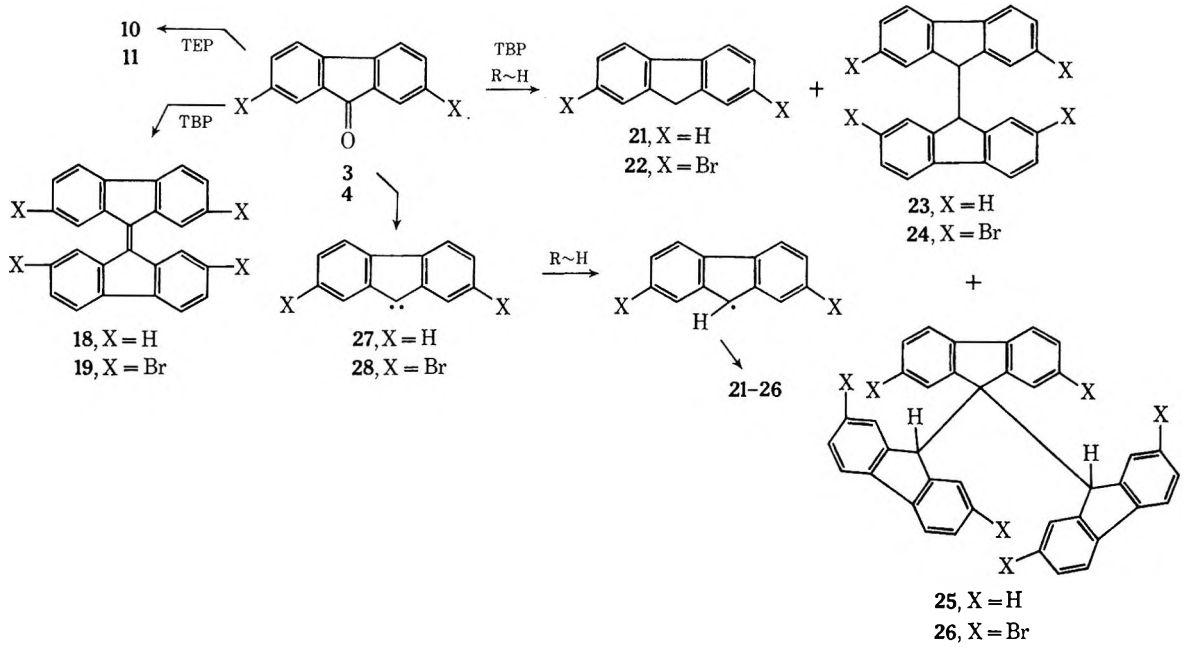
(12) H. L. Wehrmeister, *J. Org. Chem.*, **30**, 664 (1965).

(13) A. C. Poshkus and J. E. Herweh, *ibid.*, **29**, 2567 (1964).

SCHEME III



SCHEME IV



rene (**22**, 4%), 2,7,2′,7′-tetrabromobifluorenyl (**24**, 0.9%), and 2,7,2′,7′,2″,7″-hexabromotribiphenylenepropane (**26**, 13%) (Scheme IV). The yields are minimal due to isolation and purification difficulties.

Compounds **22** and **24** were identical with genuine samples. The trimer **26** was identical with a genuine sample (melting point, ir and nmr spectrum) kindly supplied by Professor Suzuki.[14] Its mass spectrum was consistent with the assigned structure.[15] Thus the presence of solvents with abstractable hydrogen (the toluene methyl group or cyclohexene) diverts the conversion of **4** from **19** to **22**, **24**, and **26**. These results can be rationalized by the intermediacy of the 2,7-dibromofluorenylcarbene (**28**), which abstracts hydrogen and reacts further. Support for this pathway is found in (a) the photochemical decomposition of 9-diazofluorene (**29**) in the presence of norbornadiene to give the dimer **23** and the trimer **25**[16] and (b) the photochemical conversion of **29** to **23** in the presence of cyclohexane as a hydrogen donor.[17] Our attempts to trap the postulated carbene **28** by cyclopropane formation with acenaphthalene or cyclohexene were

(14) K. Suzuki, M. Minabe, M. Fujimoto, and N. Nobara, *Bull. Chem. Soc. Jap.*, **42**, 1609 (1969). Genuine **26** was kindly supplied by Professor Suzuki.

(15) High resolution mass spectra of **24** and **26** were done by JEOLCO and by Varian Associates (the latter on an Atlas CH-5 mass spectrometer).

(16) N. Filipescu and J. R. DeMember, *Tetrahedron*, **24**, 5181 (1968).

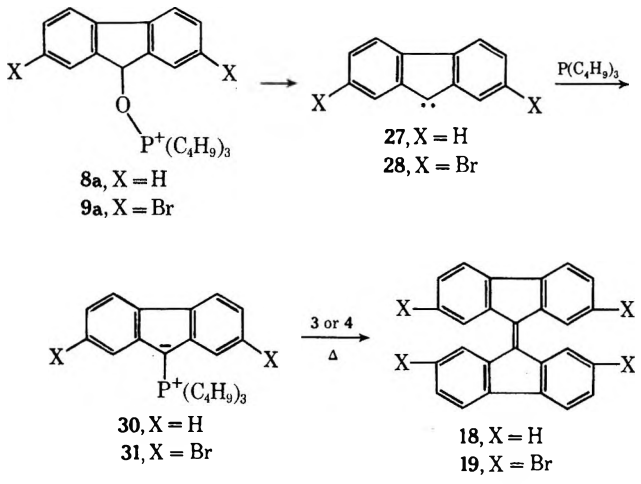
(17) W. Kirmse, L. Horner, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **614**, 19 (1958).

unsuccessful presumably because the observed products (**19** or **22**, **24**, **26**) were formed more readily.

It is unlikely that **4** is converted to **19** *via* dimerization of the carbene **28** even if it is present. Such dimerizations are rare. Thus while **29** is converted mainly to **18** photochemically,[18] even such reactions may proceed by reaction of diazo compound with carbene.[19]

A reasonable pathway for the formation of **18** or **19** could involve conversion of the 1,3 dipole **8a**, or **9a**, to the carbene **27** or **28** which reacts with TBP to give the ylides **30** or **31**. A Wittig reaction of the ylides **30** or **31** with the fluorenone **3** or **4** would then give **18** or **19**. While the reaction of **30** and **3** does not proceed at low or moderate temperatures,[20] we found that reaction does occur to give **18** (75%) at 145–160°, the approximate temperature range used in our conversion of **3** to **18** with TBP. Thus **18** and **19** may be forming from **3** and **4** by this pathway[21] (Scheme V).

SCHEME V



The Reactions of Tetraphenylcyclopentadienone (1) with P(III) Species.—Our results on the reactions of **1** with P(III) species agree with the pathways postulated for the fluorenone reactions. We had, in the initial phase of our research,[22] found that TPP reacts with **1** at 220–240° to give a $C_{58}H_{40}$ hydrocarbon **32** (54%) which had one allylic hydrogen [nmr ($CDCl_3$) τ 4.79]. The hydrocarbon could not therefore be the initially anticipated octaphenylfulvalene (**33**). Our chemical evidence for the structure of **32** was inconclusive,[22] and we had hoped that an X-ray analysis would solve the problem.[23]

Gallagher and Jenkins have recently found that tris(dimethylamino)phosphine reacts with **1** to give the dipole **34** which when pyrolyzed gives a hydrocarbon which is probably the same as our **32**.[24] They have reasonably postulated the structure to be a benz[*e*]-*as*-indacene (**32**) on the basis of more extensive data then was available to us (Scheme VI). Structure **32** is in full agreement with our spectral and limited degradation data (see Experimental Section). It can be reasonably derived from dipoles such as **34** upon further reaction with the carbene **37**,[8a] or possibly *via* the isomerization of initially formed **33**.[8a,25]

We have found that TBP reacts with **1** at 100–105° to give **32** (10%) and dihydrooctaphenylfulvalene (**36**, 28%). The latter compound, identical with a genuine sample synthesized from the reaction of 5-bromotetraphenylcyclopentadiene (**39**) with zinc,[26] may arise *via* the intermediacy of the carbene **37** and tetraphenylcyclopentadienyl radical **38** which then dimerizes. Formation of the tetraphenylcyclopentadienyl 5-tributylphosphonium ylide **40** by the pathway possible for the fluorenones is presumably hindered in this case relative to hydrogen abstraction and carbene–dipole reactions, which give **36** and **32**, respectively.[27]

The steric hindrance inherent in the tetraphenylcyclopentadienone system is also reflected in the reported reactions of **1** with trimethyl phosphite[8a] when compared to the fluorenone results. Products arising from internal reactions of the postulated 1:1 dipole were obtained but no 2:1 adduct or its derived products.

As we have already discussed,[3] one of the factors which may influence the formation of bifluorenylidenes and related products from fluorenones by TBP, as opposed to the formation of phosphoranes by TEP, may be the decreased stability of phosphoranes which incorporate a tributylphosphine moiety. Instead the 2:1 adducts may remain in tetracovalent phosphorus "open" forms (related to **14** or **15**) which are in equilibrium with the 1:1 dipole. The 1:1 dipolar adducts can be converted to **18** and **19** as already discussed. The tendency for phosphorus pentacovalency to be favored by electronegative alkoxy groups as found in phosphites has been recently stressed.[9]

Attempted Reaction of Other Ketones with P(III) Species.—In contrast to the substituted cyclopentadienone systems **1**–**4**,[28a] hexafluoroacetone, and trifluoroacetophenone,[4b] other ketones, which cannot form stabilized carbanion oxyphosphonium dipoles, give no reaction with P(III) reagents. The following ketones gave no reaction with TPP, TBP, or TEP under conditions related to those used for **1**, **3**, and **4**: benzophenone,[28b] dibenzo[2,3:6,7]cycloheptanone, xanthone, and benzanthrone (7*H*-benz[*de*]anthracen-7-one).

Mass Spectra of Dihydrofulvalenes.—Tetrabromodifluorenyl (**24**) gave a mass spectral fragmentation pattern shown in Scheme VII.[29]

Metastable peaks were found at 497 (calcd for 646 → 567), 183.5 (calcd for 323 → 244), 161.5 (calcd for 646 → 323), and 109.5 (242 → 163 and 244 → 163), in support of the suggested pathway.

(18) (a) H. Staudinger and O. Kupfer, *Chem. Ber.*, **44**, 2197 (1911); (b) H. Staudinger and J. Goldstein, *ibid.*, **49**, 1923 (1916).

(19) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 83.

(20) A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960), report that **30** does not react with ketones. Their systems involved reaction temperatures lower than ours, however.

(21) Other pathways are also possible.

(22) M. A. Anschel, Ph.D. Thesis, Lehigh University, 1967.

(23) The hydrocarbon has been submitted for an X-ray analysis to Professor J. White, Fordham University.

(24) Based on similar nmr and uv spectra, melting point data, and chemical behavior.

(25) I. J. Borowitz and P. D. Readio, unpublished observations.

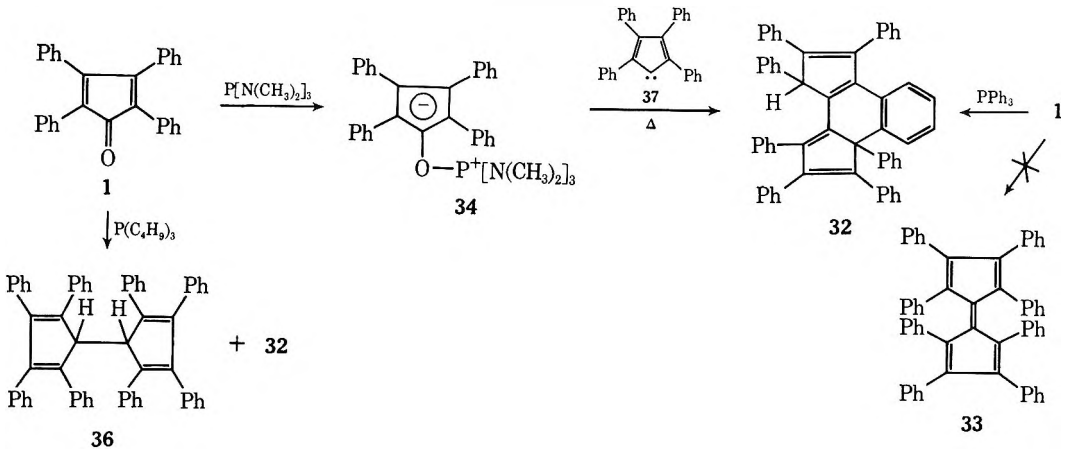
(26) P. L. Pauson and B. J. Williams, *J. Chem. Soc.*, 4158 (1961).

(27) Previous attempts to prepare octaphenylfulvalene have failed.[26]

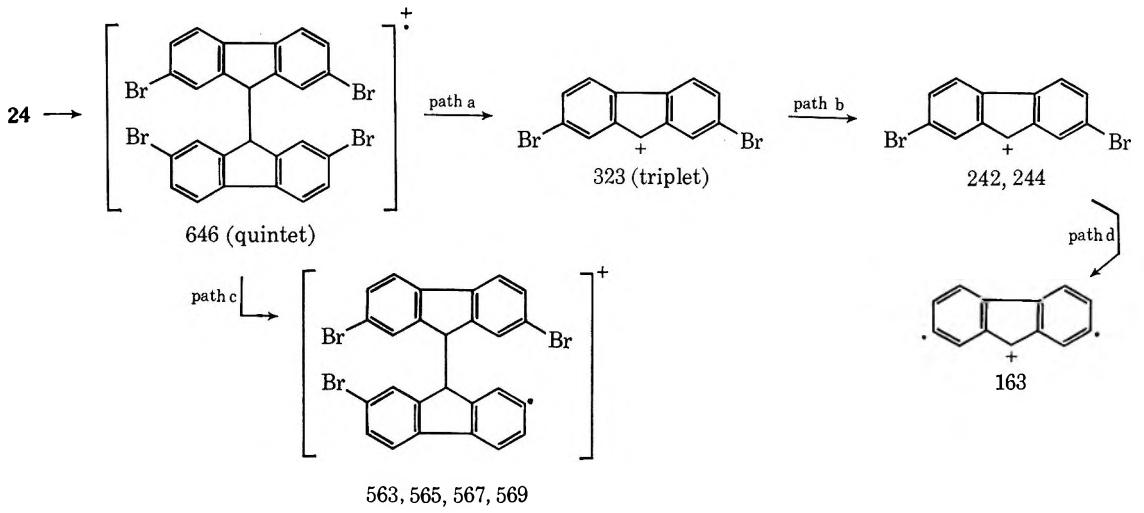
(28) (a) A study of the reactions of 2,3-diphenylindenone with P(III) species will be reported at a later date. (b) Benzophenone reacts with triisopropyl phosphite.[13]

(29) Performed by Mr. David Baugher (Sun Oil), Dr. Jonathan Kurland (Harvard), Dr. Karl Untch (Mellon Institute), and Miss V. Parmakovitch (Columbia) on CEC-103C, MS-9, and Hitachi RMU-6E mass spectrometers.

SCHEME VI



SCHEME VII



Bifluorenyl (**23**) and dihydrooctaphenylfulvalene (**36**) similarly gave abundant M/2 cleavage. In contrast, **32** and the fulvalenes **18** and **19** gave fragmentations with notable absence of M/2 cleavage and the presence of doubly charged ions characteristic of aromatic ring systems.[30]

Experimental Section[31]

All of the solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions were usually conducted under an atmosphere of dry nitrogen. Organic solutions were dried over magnesium sulfate.

2,7-Dibromofluorenone (4). A. By Bromination of Fluorenone.—A mixture of fluorenone [30.0 g, 0.166 mol; uv max (95% C_2H_5OH) 248, 256.5 nm], bromine (67 g, 0.42 mol), and water (250 ml) was heated at reflux for 24 hr to give an insoluble solid which was washed with aqueous $NaHSO_3$ and dissolved in methylene chloride (*ca.* 1 l.). The resultant solution was dried and cooled to give **4** in several crops (27.8 g, 0.082 mol, 50%): mp 201–202°, lit.[32] mp 202°; tlc (5% EtOAc–C_6H_6) one spot with larger R_f than that of fluorenone; uv max (95% C_2H_5OH) 415 nm; ir (KBr) 5.90 μ.

B. By Oxidation of 2,7-Dibromofluorene.—The bromination of fluorene[33] gave 2,7-dibromofluorene (87%): mp 164°; nmr ($CDCl_3$) τ 2.4, 2.5 (m, 6, aryl H), 6.24 (s, 2, CH_2). Chromic acid oxidation of 2,7-dibromofluorene gave **4** (59%, overall yield 51%), mp 202–203.5°.

2,2,2-Triethoxy-4,5-bisbiphenylene-1,3,2-dioxaphospholane (6).—A mixture of fluorenone (9.8 g, 0.054 mol) and triethyl phosphite (18.6 g, 0.11 mol) was stirred at 25° for 24 hr under nitrogen. Solution of the fluorenone slowly occurred followed by precipitation of **6** which was filtered with suction, washed several times with cold hexane, and dried *in vacuo* to give **6** (8.0–8.65 g, 0.015–0.016 mol, 56–62%): mp 131–135° (sealed tube); ir (KBr) 6.9, 8.3, 8.6, 9.03, 9.6, 10.7 μ; nmr ($CDCl_3$) τ 2.45, 2.97 (m, 16, aryl H), 5.83 (quintet, 6, CH_2, $J_{HH} = J_{PH} = 7$ Hz) and 8.68 (d of t, 9, CH_3, $J_{HH} = 7$ Hz, $J_{PH} = 1.5$ Hz).

Anal. Calcd for $C_{32}H_{31}O_5P$: C, 72.99; H, 5.93; P, 5.88. Found: C, 72.77; H, 5.82; P, 5.64.

The melting behavior of **6** was erratic in that large melting ranges were sometimes observed. This is probably due to the tendency of **6** to rearrange to **10** and triethyl phosphate (see below).

Tetrabromo-2,2,2-triethoxy-4,5-bisbiphenylene-1,3,2-dioxaphospholane (7).—2,7-Dibromofluorenone (**4**, 6.4 g 0.019 mol) was added to triethyl phosphite (9.6 g, 0.058 mol) in methylene chloride (40 ml) with stirring under nitrogen. After 20 min **4** had completely dissolved. After another 20 min acetonitrile (120 ml) was added to give a precipitate which was washed with acetonitrile and dried to give **7** (6.7 g, 0.008 mol, 84%): mp 155–165° (sintering), 197–198°; ir (KBr) 6.90, 7.09, 8.60, 9.64, 10.55, 11.39, 12.34, 12.86, and 13.03 μ; ^1H nmr ($CDCl_3$, see Scheme I for proton designations) τ 2.44 (d, 4, H_C, $J_{PH} = 1.5$ Hz), 2.68, 2.81 (d, 4, H_A, $J_{PH} = 1.8$ Hz), 2.94, 3.08 (s, 4, H_B), 5.84 (quintet, $J_{PH} = J_{HH} = 7$ Hz), and 8.62 (d of t, $J_{HH} = 7$ Hz, $J_{PH} = 2$ Hz); ^{31}P nmr ($CDCl_3$) +48 ± 2 ppm (relative to 85% H_3PO_4).[5]

Anal. Calcd for $C_{32}H_{27}O_5Br_4P$: C, 45.64; H, 3.23; Br, 37.96; P, 3.68; mol wt, 842. Found: C, 45.45; H, 3.27; Br, 37.86; P, 3.53; mol wt (osmometric), 836.

Reaction of **4** with TEP in the presence of benzaldehyde or acenaphthalene gave **7** (*ca.* 80%): melting point and nmr spec-

(30) K. Biemann, "Mass Spectrometry. Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, p 157; see also ref 36, p 49.

(31) The instrumental and other techniques used have been recorded in I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(32) J. Schmidt and K. Bauer, *Chem. Ber.*, **38**, 3767 (1905). In the original procedure, recrystallization was done from HOAc.

(33) E. Bergmann and J. Hervey, *Chem. Ber.*, **62**, 909 (1929).

trum identical with genuine **7**. Other products were not isolated. Reaction of **4** with TEP in the presence of acetonitrile for 2 hr also gave **7** (92%); nmr identical with genuine **7**.

Competition of 3 and 4 for TEP.—A mixture of **3** (1.00 g, 0.0056 mol) and **4** (1.90 g, 0.0056 mol) was added to TEP (2.40 g, 0.0144 mol) in methylene chloride (10 ml). The resultant mixture was stirred at 25° for 40 min, and acetonitrile (30 ml) was added to give **7** (1.68 g, 0.0020 mol, 71%). Nmr ($CDCl_3$) was identical with that of genuine **7**. No evidence of other phosphoranes was found.

Reactions of Phosphorane 6. A. Thermal.—Warming **6** in benzene–hexane gave 9-diphenylenephenanthrone (**10**): mp 262–263°, mmp 262–263° with genuine sample[34] of mp 262–264°; ir (KBr) 5.95, 6.24 μ.

Anal. Calcd for $C_{26}H_{16}O$: C, 90.67; mol wt, 344. Found: C, 90.56; H, 4.79; mol wt (osmometric), 337.

B. Reaction with Acetonitrile to Form Dispiro[fluorene-9,4′-Δ^2-2′-methyloxazoline-5′,9″-fluorene] (12).—Phosphorane **6** (5.0 g, 0.0095 mol) in dry acetonitrile (125 ml) was stirred at 43–46° for 20 hr and cooled to give **10** (1.70 g, 0.0050 mol) and a filtrate which was evaporated *in vacuo* to give a liquid fraction and a solid fraction which was washed with hexane. The liquid fraction and hexane washings were combined to give crude triethyl phosphate (1.54 g; ir, nmr identical with those of a genuine sample). The solid fraction (1.24 g) consisted of **10** (0.61 g, 0.0017 mol) and the oxazoline **12** (0.63 g, 0.0017 mol) as determined by nmr analysis. Total yields follow: **10** (0.0067 mol, 71%) and **12** (18%). A mixture of **10** and **12** was separated by thick layer chromatography (on Brinkman silica gel $PF_{254+366}$ plates) using 5% EtOAc–C_6H_6 to give **10** (R_f 0.53) and **12** [R_f 0.17; mp 249–249.5° (recrystallized from EtOH); ir (KBr) 6.05 μ; nmr ($CDCl_3$) τ 7.45 (s, 3, CH_3) and 2.40 (m, 16, aryl H); mass spectrum (70 eV) *m/e* (rel intensity) 385 ($M\cdot^+$ 1.5), 342 (1.9), 205 (100), 180 (5.6), 164 (58), 163 (19), and 152 (4.3)].

Anal. Calcd for $C_{28}H_{19}NO$: C, 87.23; H, 4.97; N, 3.64. Found: C, 87.48; H, 5.00; N, 3.73.

Reactions of Phosphorane 7. A. Thermal.—Phosphorane **7** (1.82 g, 0.0022 mol) in benzene (20 ml) at reflux for 3.5 hr gave **4** (100%) and triethyl phosphite (tlc).[35] No phenanthrone **11** was formed since it was shown that a maximum of 0.021 g of **11** is soluble in 20 ml of benzene at reflux.

Treatment of **7** with nitromethane at 45–50° for 12 hr or 25° for 20 hr gave phenanthrone **11** (50, 38%), ir identical with that of genuine **11** (see below), and **4** (43, —%). Treatment of **7** with methylene chloride at 25° for 9 days gave **11** (19%).

B. Reaction with Acetonitrile to Form the Tetrabromooxazoline 13.—A suspension of **7** (6.7 g, 0.0080 mol) in dry acetonitrile (140 ml) was stirred at 42–48° for 21 hr to give a light orange colored solid (4.7 g) which contained phenanthrone **11** [1.65 g, 0.0025 mol, 31%; tlc (as above) R_f 0.73] and oxazoline **13** (3.05 g, 0.0044 mol, 54%, R_f 0.50. Yields are based on nmr analysis of the mixture using CH_2Cl_2 as an internal standard. Oxazoline **13**, separated by thick layer chromatography as above, had mp 273–274.5° (recrystallized from C_6H_6); ir (KBr) 6.05, 6.91, 7.08, 7.98, 8.43, 8.54, 9.40, 9.98, 12.40, and 14.82 μ; nmr ($CDCl_3$) τ 2.50–3.02 (m, 12, aryl H) and 7.44 (s, 3, CH_3); mass spectrum[29] (70 eV) *m/e* (rel intensity) 701 center of quintet ($M\cdot^+$, 0.6), 658 center of quintet ($M - CH_3CO$, 0.97), 363 center of triplet ($C_{15}H_9Br_2N$, 100), 338 center of triplet ($C_{13}H_6OBr_2$, 5.5), and 322 center of triplet ($C_{13}H_6Br_2$, 28.7). Metastable peaks were observed at 283, 285.5, and 287.5 (calcd 284, 285.6, and 287.6 for 361, 363, and 365 → 320, 322, and 324), and 180, 182, and 184 (calcd 187 for 701 → 363). The triplets ($n - 2$, n, $n + 2$) and quintets ($n - 4$, $n - 2$, . . . , $n + 4$) are due to the presence of ^{79}Br and ^{81}Br isotopes.[36]

C. Reaction with Tributylphosphine.—Reaction of **7** (1.42 g, 0.00169 mol) and TBP (0.72 g, 0.0036 mol) without solvent at a bath temperature of 102° with stirring for 1 hr gave, after addition of acetone for fluidity, (a) a red solid which consisted of **7** (0.40 g, 0.00048 mol, 28% recovered, $CHCl_3$ soluble) and 2,7,-2′,7′-tetrabromobifluorenylidene (**19**, 0.16 g, 0.00025 mol, 15%), mp 452–453°, red solid (see below); and (b) a green filtrate which contained **4** (melting point, tlc) among other products. A similar reaction with TBP in greater excess (6.8 equiv) gave **19** (44%) and a small amount of phenanthrone **11** (*ca.* 1%). Reaction of **7** with TBP (6.0 equiv) in benzene at reflux for 49 hr gave **19** (11%) and 2,7-dibromofluorene (**22**, 8%): mp 165–167°, mmp 163.5–165° with genuine **22** of mp 163.5–165.5°.

D. Reaction with Triethyl Phosphite.—Reaction of **7** (1.56 g, 0.00186 mol) with TEP (2.33 g, 0.014 mol) at 100° (bath temperature) for 6 hr gave **19** (0.116 g, 0.00026 mol, 14%), **4** (0.75 g, 0.00022 mol, 3%), and **11** (0.24 g, 0.0036 mol, 20%): melting point, tlc, and ir spectrum identical with those of a genuine sample.

E. Reaction with Triphenylphosphine.—Phosphorane **7** (0.842 g, 0.001 mol) and TPP (1.05 g, 0.004 mol) in toluene (14 ml) were heated at reflux for 24 hr. The resultant mixture contained 2,7-dibromofluorenone (uv) and no **19** (uv).

Reaction of Fluorenone with Triethyl Phosphite.—A mixture of fluorenone (**3**, 2.46 g, 0.0136 mol) and TEP (4.65 g, 0.028 mol) was heated at 150–180° (bath temperature) for 38 hr (**3** left) and another 27 hr to give **10** (1.74 g, 0.0051 mol, 74%): mp 262–263°, mmp 262–263° with genuine sample (see above).

Anal. Calcd for $C_{26}H_{16}O$: C, 90.67; H, 4.69. Found: C, 90.79; H, 4.64.

Phenanthrone **10** was mainly obtained as a C_6H_6-insoluble fraction. The filtrate was chromatographed on silicic acid (45 g, 390 × 20 mm column) to give **18** (0.14 g, 0.00043 mol, 6%): red solid; tlc (5% EtOAc–C_6H_6) R_f 0.86 as for genuine **18** and an impurity of R_f 0.68. The melting points of **18** thus obtained and of **18** prepared from the reaction of 9-bromofluorene with potassium *tert*-butoxide[37] were low (165–179°) when compared with lit.[37] mp 187–189°. Tlc and uv spectral data of our **18** were identical with those of genuine samples.[37,38]

Mass Spectra of Bifluorenylidene (18) and Bifluorenyl (23).—The mass spectrum of **18** (70 eV) had *m/e* (rel intensity) 328 ($M\cdot^+$, 100), 181 (41.5), 164 (11), 77 (18), and 76 (16), while that of **23** had 330 ($M\cdot^+$, 9), 165 (M/2, 100), 163 (4), 139 (2), 115 (1), 77 (0.3), and 76 (0.3).[29]

Reaction of 2,7-Dibromofluorenone with TEP.—A mixture of **4** (3.24 g, 0.0096 mol) and TEP (4.65 g, 0.028 mol) was heated at 100° (bath temperature) for 6 hr with stirring to give an orange solid which was filtered and washed with hot benzene, cold CH_3CN, and cold EtOAc to give the phenanthrone **11** (1.84 g, 0.0028 mol, 58%): mp 391–392° dec; ir (KBr) 5.95 μ; mass spectrum (70 eV) *m/e* (rel intensity, center of multiplets) 660 (M^+, 42), 632 ($M - CO$, 0.4), 579, 581 ($M - Br$, 7), 550 ($M - 2\,Br$, 0.2), 471 ($M - 2Br - CO$, 0.4), 419, 421 ($M - 3Br$, 3.5), 338 ($M - 4Br$, $M - C_{13}H_6Br_2$, 100), 310 (338 − CO, 13).[39]

Anal. Calcd for $C_{26}H_{12}OBr_4$: C, 47.34; H, 1.83; Br, 48.46. Found: C, 47.17; H, 2.05; Br, 48.55.

Control Experiments with Phenanthrone 11.—Attempted reaction of **11** with TEP for 24 hr at 100°, or with TBP for 6 hr at 105–110°, gave only recovered **11** and no trace of **19** or other products (tlc).

Attempted Reactions of Triphenylphosphine with Fluorenones.—Treatment of fluorenone (**3**) with TPP in xylene at reflux for 38 hr gave the starting compounds in 98 and 97% yields, respectively, and minor amounts of triphenylphosphine oxide and three unidentified compounds (tlc). Neat reaction of **3** with TPP at 150–160° (bath temperature) for 38 hr similarly gave starting compounds and a trace of **18**. Similar treatment of 2,7-dinitrofluorenone with TPP at 85° for 1.3 hr gave only starting compounds.

Reaction of Fluorenone with Tributylphosphine.—A mixture of **3** (2.46 g, 0.0136 mol) and TBP (5.67 g, 0.028 mol) was heated (bath temperature of 155–165°) for 76 hr with stirring to give a dark red solution which was chromatographed on acid-washed alumina (205 g) to give bifluorenylidene (**18**, 0.383 g, 0.0027 mol, 40%) upon benzene elution. No **10** was obtained.

Reactions of 2,7-Dibromofluorenone with Tributylphosphine. A. Neat.—A mixture of **4** (3.24 g, 0.0096 mol) and TBP (5.67 g, 0.028 mol) was heated at 100° (bath temperature) for 4 hr with stirring to give a dark red solid which was washed with benzene and ethanol to give 2,7,2′,7′-tetrabromobifluorenylidene (**19**, 1.36 g, 0.0021 mol, 44%): mp 454–455° (red needles from bromobenzene) (lit.[40] mp >370°); ir (KBr) 6.9, 7.15, 8.55, 9.15, 9.9, 11.2, 11.5, and 12.4 μ.

(34) A genuine sample of **10** was kindly provided by Dr. A. Poshkus.[13]

(35) The originally claimed rearrangement of **7** to **11** *under these conditions*[33a,22] was not repeatable.

(36) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1966, p 20.

(37) P. M. G. Bavin, *Can. J. Chem.*, **38**, 882 (1960).

(38) Genuine **18** was kindly provided by Professor E. Bergmann (Jerusalem).

(39) Performed by J. Landis on an Atlas CH-5.

(40) L. A. Pinck and G. E. Hilbert, *J. Amer. Chem. Soc.*, **68**, 2014 (1946).

Anal. Calcd for $C_{26}H_{12}Br_4$: C, 48.46; H, 1.86; Br, 49.68. Found: C, 48.23; H, 1.75; Br, 49.45.

The combined filtrate and washings contained at least seven compounds (tlc).

B. In Benzene.—Reaction of **4** (2.00 g, 0.0059 mol) and TBP (6 ml, 4.86 g, 0.024 mol) in benzene (10 ml) at reflux for 69 hr gave crude **19** (1.08 g, *ca.* 54%): mp 450–451° (from bromobenzene); ir as for genuine **19** (see above) but with impurities. The filtrate contained **26** (by ir, see below) and other compounds.

C. In Acetonitrile.—Reaction of **4** (1.62 g, 0.0048 mol) and TBP (2.88 g, 0.014 mol) in dry acetonitrile (distilled from CaH_2 and P_2O_5) at reflux for 2 hr gave **19** (0.371 g, 0.00058 mol, 24%) and **2,7-dibromofluorene** (**22**, 0.667 g, 0.0021 mol, 43%): mp 165.5–166.5° (from C_6H_6), no depression in mixture melting point with genuine sample (see above); ir identical with genuine ir spectrum, Sadtler I.R. Tables, Spectrum No. 25066.

Anal. Calcd for $C_{13}H_8Br_2$: C, 48.19; H, 2.49; Br, 49.32. Found: C, 48.12; H, 2.47; Br, 49.13.

Similar reaction of **4** and TBP in acetonitrile–water (15:1 ml) gave **22** (20%) and **24** (5%) but no **19**. Tetrabromobifluorenyl (**24**), mp 333–337°, had an ir spectrum identical with that of a genuine sample (see below).

D. In Benzene–Cyclohexene.—A mixture of **4** (2.00 g, 0.00592 mol) and TBP (6.0 ml, 4.86 g, 0.0239 mol) in benzene (10 ml)–cyclohexene (10 ml) was heated at reflux for 51 hr to give a solid fraction and a green filtrate. The filtrate was distilled to give benzene and cyclohexene as the only low-boiling components, tributylphosphine, bp 54–59° (0.05 mm), and a residue which gave further solid identical with the above solid fraction. This solid was identified as **2,7,2′,7′,2″,7″-hexabromotribiphenylenepropane** (**26**), 0.239 g, 0.000247 mol, 13%: mp 338° dec; nmr (CS_2, 49 accumulations on a Varian C-1024 "CAT") τ 1.29 (s, 2), 2.00 (m, 4), 2.50 (m, 8), 3.46 (s, 2), 4.34 (s, 2), and 4.68 (s, 2); ir (KBr) 6.30, 6.40, 6.95, 7.95, 8.65, 9.4, 12.4, and 12.7 μ; mass spectrum (70 eV) *m/e* (rel intensity, center of multiplets) 962, 964, 966, 968, 970, 972, 974 ($M\cdot^+$, $C_{39}H_{20}Br_6$, 7.8), 887 ($C_{39}H_{20}Br_5$, 0.7), 808 ($C_{39}H_{20}Br_4$, 1.4), 725, 727, 729, 731 ($C_{39}H_{20}Br_3$, 2.6), 641, 643, 645, 647, 649 ($C_{26}H_{13}Br_4$, 70), 562, 564, 566, 568 ($C_{26}H_{13}Br_3$, 100), 483, 485, 487 ($C_{26}H_{13}Br_2$, 23), 404, 406 ($C_{26}H_{13}Br$, 78), 321, 323, 325 ($C_{13}H_7Br_2$, 41), 242, 244 ($C_{13}H_7Br$, 15), 162 ($C_{13}H_6$, 13), and 161 ($C_{13}H_5$, 15).[15]

A genuine sample of **26**[14] gave identical nmr and ir (KBr) spectra with the above sample: mp 333° dec, mmp 335° dec.

Anal. Calcd for $C_{39}H_{20}Br_6$: C, 48.39; H, 2.08; Br, 49.53. Found C, 48.23; H, 2.28.

The residue from the green filtrate also gave **22** (0.075 g, 0.000232 mol, 4%) and **24** (0.017 g, 0.000026 mol, 0.9%): mp 315–328° upon crystallization from C_2H_5OH and $CHCl_3$; ir (KBr) identical with genuine **24** ir. No evidence for species such as bicyclohexenyl or other cyclohexene derived compounds was obtained.

Synthesis of 2,7,2′,7′-Tetrabromobifluorenyl (24). A. 2,7,9-Tribromofluorene (41).—A mixture of 2,7-dibromofluorene (**22**, 3.24 g, 0.0100 mol) and *N*-bromosuccinimide (1.78 g, 0.0100 mol) in CCl_4 (50 ml) was stirred and irradiated with a 100-W clear incandescent light bulb for 18.5 hr to give **41** (1.78 g, 0.0044 mol, 44%): mp 196–198° (from glyme); nmr ($CDCl_3$) τ 2.2–2.7 (m, 6, aryl H) and 4.07 (s, 1, methine H).

B. Reaction of 41 with Zinc.—A mixture of **41** (1.21 g, 0.00300 mol) and zinc powder (4.50 g, 0.0690 g-atom) in benzene (70 ml) was stirred and heated at reflux for 48 hr to give a mixture which was filtered to give a filtrate from which was obtained **24** (0.45 g, 0.00070 mol, 46%): mp 331–335°; ir (KBr) 6.22, 6.33, 6.9, 7.05 7.15, 8.62, 9.92, 14.2, 15.1 μ; nmr (CS_2, 81 accumulations on CAT) τ 2.55, 2.8 (m, 12, aryl H) and 5.22 (s, 2); mass spectrum[25] (75 eV) *m/e* (rel intensity) 650 (2.4), 648 (8.7), 646 (13.5), 644 (9.7), 642 (2.8), 569 (0.5), 567 (1.3), 565 (1.4), 563 (0.5) 488 (0.5), 486 (1.2), 484 (0.8), 325 (51.6), 323 (100), 321 (52.8), 244 (15.2), 242 (14.9), 163 (62.7), and 150 (4.4). Calcd for $C_{25}H_{14}{}^{81}Br_3{}^{79}Br$: 647.7769. Found: 647.7763.[41]

Anal. Calcd for $C_{26}H_{14}Br_4$: C, 48.34; H, 2.18; Br, 49.48. Found: C, 48.44; H, 2.20.

Reaction of Ylide 30 with Fluorenone.—9-Fluorenyl tributylphosphonium bromide (75% from 9-bromofluorene and TBP[20]), mp 196–198°, lit.[20] mp 194–195°), was converted with aqueous NaOH to ylide **30** (72%, yellow solid), mp 121–122° (lit.[20] mp 123–124°). Reaction of **30** (0.890 g, 0.00230 mol) and **3** (0.414 g, 0.00230 mol) at 145–160° for 24 hr gave a dark red oil which contained tributylphosphine oxide, **3**, and **18** by tlc. Chromatography of the oil on neutral alumina (200 g) gave, upon benzene elution, **18** (0.564 g, 0.00172 mol, 75%) uv spectrum and tlc R_f identical with genuine sample.

Attempted reaction of **30** with **3** in dry benzene at reflux for 19 hr gave a three-component mixture (by tlc) which contained no **18**.

Reaction of Tetraphenylcyclopentadienone (1) with Triphenylphosphine.—A mixture of **1** (2.0 g, 0.0052 mol) and TPP (3.2 g, 0.012 mol) was kept at 220–240° for 98 hr, dissolved in benzene (10 ml), and then chromatographed on acid washed alumina (566 g). Elution with benzene gave, in the initial fractions, gray-white solid $C_{58}H_{40}$ hydrocarbon (probably **32**,[8a] 1.03 g, 0.0014 mol, 54%), mp 325–326.5° (from acetonitrile). Other runs gave this hydrocarbon, triphenylphosphine oxide, and unreacted starting compounds as the only compounds present by tlc analysis. Longer reaction time and a greater excess of TPP did not improve the yield of **32**: ir (KBr) 3.4, 6.24, 6.9, 7.25, 9.3, 9.7, 13.15, and 14.30 (monosubstituted benzene ring[42]), and 13.30 μ (1,2-disubstituted benzene ring[42]); nmr[43] ($CDCl_3$) τ 2.3–2.8 (m, 10), 2.8–2.9 (m, 5), 2.9–3.05 (m, 5), 3.05–3.2 (m, 10), 3.2–3.5 (m, 4), 3.5–3.7 (d of d, 2), 3.7–3.95 (t of d, 3) and 4.79 (s, 1, benzylic H); uv max (CH_3CN) 235 nm (log ϵ 4.65), 255 (4.59) and 363.5 (4.16); mass spectrum[44] (70 eV) *m/e* (assignment) 736 ($M\cdot^+$), 737 (M + 1, 64% of M, calcd 63%), 659 (M − C_6H_5), 582 (M − $2C_6H_5$), 567, 505 (M − $3C_6H_5$), 504, 491, 428 (M − $4C_6H_5$), 413, 368 (M^{2+}), 351 (M − $5C_6H_5$), 274 (M − $6C_6H_5$), 251, 178 ("$C_6H_5C{\equiv}CC_6H_5$"), 165 (e), 152 (f),

165 e 152 f

91, and 77.

Anal. Calcd for $C_{58}H_{40}$: C, 94.53; H, 5.47. Found: C, 94.59; H, 5.28.

Reactions of the $C_{58}H_{40}$ Hydrocarbon.—The hydrocarbon in solution ($CHCl_3$) was sensitive to oxygen; the ir spectrum changed with time to slowly give C=O peaks at 5.75 and 5.95 μ. Reaction of the hydrocarbon with *N*-bromosuccinimide (3.6 equiv) in CCl_4 under reflux for 95 hr gave a **monobromo derivative** (**42**), mp 185–187°.

Anal. Calcd for $C_{58}H_{39}Br$: C, 85.39; H, 4.82; Br, 9.79. Found: C, 85.44; H, 4.94; Br, 9.66.

Oxidation of a suspension of the $C_{58}H_{40}$ hydrocarbon with 50% aqueous HNO_3 at reflux for 3.5 days gave a clear yellow solution from which was isolated *p*-nitrobenzoic acid (1.8 equiv based on structure **32** which has seven phenyl groups): mp 237–238°; mixture melting point, tlc, and ir spectrum in agreement with genuine sample. Similar oxidation of tetraphenylcyclopentadiene gave 3.1 equiv of *p*-nitrobenzoic acid. Other oxidations (ozone, $KMnO_4$, and O_2) of **32** gave complex mixtures.

Reaction of Tetraphenylcyclopentadienone with TBP.—A slurry of **1** (5.3 g, 0.014 mol) and TBP (5.66 g, 0.0278 mol) was stirred at 100–105° for 24 hr to leave a black solid which was triturated with hot acetonitrile to give the $C_{58}H_{40}$ hydrocarbon (0.526 g, 0.00072 mol, 10%): mp 325–327° (from $CHCl_3$–hexane), mmp 323–326.5° with genuine hydrocarbon (see above) of mp 323–327°. The filtrate of the original trituration gave **dihydrooctaphenylfulvalene** (**36**, 1.43 g, 0.0019 mol, 28% crude): mp 197–200° (from C_2H_5OH), mmp 196–200° with genuine sample (see below) of mp 196–200°; nmr ($CDCl_3$) τ 2.45–3.30 (m, 40, phenyl H) and 4.98 (s, 2 benzylic H); mass spectrum[29,41] (70 eV) *m/e* (rel intensity) 739 (64), 738 ($M^+\cdot$, 100), 369 (M/2, 64), 292 (M/2 − Ph), 291 (67), 267 (Ph_3C_3, 8), 191 (Ph_2C_3H, 29), 178 ("PhC≡CPh," 6), 91 (29), 77 (4). Metastable peaks were observed at 230 (calcd for 369 → 292), 185 (calcd for 738 → 369), and 99 (calcd for 369 → 191).

Anal. Calcd for $C_{58}H_{42}$: C, 94.28; H, 5.72. Found: C, 94.55; H, 5.63.

Dihydrooctaphenylfulvalene (**36**).—Reaction of 5-bromo-1,2,3,4-cyclopentadiene (33% from the reaction of *N*-bromosuc-

(41) Performed by F. Abramson on a CEC 21-492.

(42) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 107.

(43) Performed by E. A. Pier of Varian Associates on an HA-100 nmr spectrometer.

(44) Performed by Professor Klaus Biemann (M.I.T.) and Professor Carl Djerassi (Stanford).

cinimide with tetraphenylcyclopentadiene)[26] with zinc (20 equiv) in benzene at reflux for 24 hr gave **36** (21–34%):[26] mp 197–199°; spectral and melting point data agreed with the data presented for **36** obtained from **1** (see above).

Registry No.—**6**, 14935-22-9; **7**, 15071-25-7; **10**, 1749-36-6; **11**, 27192-88-7; **12**, 19968-81-1; **13**, 19968-82-2; **18**, 746-47-4; **19**, 27192-91-2; **22**, 16433-88-8; **23**, 1530-12-7; **24**, 27192-94-5; **26**, 27192-95-6; **32**, 26307-13-1; **36**, 26307-16-4; **46**, 27250-99-3.

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Electron Spin Resonance Studies of Substituent Effects. IV.[1] Nitroxide Radicals from Bis(*N*-arylnaphthylamines)

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Oxidation of bis(*N*-arylnaphthylamines) produces stable nitroxide radicals if the reactive naphthalene positions are blocked. Hyperfine splitting constants and substituent effects are reported and compared with analogous systems. The nitrogen hyperfine splitting in the β derivative is larger than that found in the α derivative. McLachlan molecular orbital calculations are carried out on *N*-phenyl-1-naphthyl nitroxide, *N*-phenyl-2-naphthyl nitroxide, and di-2-naphthyl nitroxide. The nitroxide radicals from these oxidative dimers may be responsible in part for electron spin resonance signals obtained during oxidation of aromatic amines such as *N*-phenyl-1- and *N*-phenyl-2-naphthylamine.

While various derivatives of phenyl nitroxides and diphenyl nitroxides have been studied in detail by electron spin resonance (esr),[3-6] no convincing spectra of *N*-arylnaphthyl nitroxides have appeared in the literature. Hoskins[7] reported spectra generated from aromatic amines added to base-catalyzed autoxidations of toluene–alcohol mixtures. Although the spectrum of diphenyl nitroxide was generated from diphenylamine, the spectrum produced from *N*-phenyl-2-naphthylamine did not exhibit the expected nitrogen hyperfine splitting constant (hfsc) and was quite narrow, suggesting a possible semiquinone radical arising from the oxidation products of *N*-phenyl-2-naphthylamine.[8]

Buchachenko[9] has reported spectra assigned to *N*-phenyl-1- and *N*-phenyl-2-naphthyl nitroxides. The 1-naphthyl derivative exhibited, in addition to a 10.8-G nitrogen hfs, a 2.4-G hfs characteristic of the ortho and para protons of the phenyl group, but no mention is made of the relatively large hfs expected of the 2- and 4-naphthyl protons. The 2-naphthyl derivative gave a gross triplet of 9.5 G with fine lines discernible on the main pattern. In their excellent review,[4] Forrester, Hay, and Thomson briefly refer to unpublished work on *tert*-butyl-1- and *tert*-butyl-2-naphthyl nitroxides, but no spectra are given. They note A^N's for these nitroxides are 13.5 and 11.75 G, respectively, for the α- and β-naphthyl derivatives.

Several recent studies[8,10] of the *N*-phenyl-2-naphthylamino radical reveal that its chemistry is dominated by the high reactivity at the 1 carbon, resulting in coupling products when generated by oxidation of the amine or thermolysis of the tetrazene,[10] and mixtures of quinoid products when generated by reaction of the amine with peroxy radicals in the presence of hydroperoxide.[8,11] These results suggest that many routes to *N*-arylnaphthyl nitroxides will be diverted to other products. Since the oxidative dimers may be responsible in part for esr signals observed on oxidation of *N*-arylnaphthylamines, an investigation of the nitroxide radicals of these dimers should be instructive. The present paper deals with nitroxides derived from oxidation products of *N*-phenyl-1- and *N*-phenyl-2-naphthylamine.

(1) (a) Part III: E. T. Strom and J. R. Norton, *J. Amer. Chem. Soc.*, **92**, 2327 (1970); (b) presented in part at the Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970.

(2) (a) Author to whom inquiries should be addressed at the Central Research Laboratory; (b) Field Research Laboratory.

(3) E. T. Strom, A. L. Bluhm, and J. Weinstein, *J. Org. Chem.*, **32**, 3853 (1967).

(4) A. R. Forrester, J. M. Hay, and R. H. Thomson, "Organic Chemistry of Stable Free Radicals," Academic Press, New York, N. Y., 1968, Chapter 5.

(5) (a) A. Calder and A. R. Forrester, *J. Chem. Soc. C*, 1459 (1969); (b) *Chem. Commun.*, 682 (1967).

(6) (a) H. Lemaire, Y. Marechal, R. Ramasseul, and A. Rassat, *Bull. Soc. Chim. Fr.*, 372 (1965); (b) G. Barbarella and A. Rassat, *ibid.*, 2378 (1969); (c) A. J. W. Wajer, A. Mackor, and Th. J. deBoer, *Tetrahedron Lett.*, 1941 (1967); (d) A. B. Sullivan, *J. Org. Chem.*, **31**, 2811 (1966); (e) O. Kikuchi and K. Someno, *Bull. Chem. Soc. Jap.*, **40**, 2549 (1967); (f) J. Yamauchi, H. Nishiguchi, K. Mukai, Y. Deguchi, and H. Takaki, *ibid.*, **40**, 2512 (1967); (g) P. H. H. Fischer and F. A. Neugebauer, *Z. Naturforsch. A*, **19**, 1514 (1964); (h) F. A. Neugebauer and P. H. H. Fischer, *ibid. B*, **21**, 1036 (1966); (i) J. C. Baird and J. R. Thomas, *J. Chem. Phys.*, **35**, 1507 (1961).

(7) R. Hoskins, *ibid.*, **25**, 788 (1956).

(8) D. F. Bowman, B. S. Middleton, and K. U. Ingold, *J. Org. Chem.*, **34**, 3456 (1969).

(9) (a) A. L. Buchachenko, "Stable Radicals," Consultants Bureau, New York, N. Y., 1965, p 119; (b) A. L. Buchachenko, *Opt. Spectrosk.*, **18**, 795 (1962).

(10) (a) R. F. Bridger, D. A. Law, D. F. Bowman, B. S. Middleton, and K. U. Ingold, *J. Org. Chem.*, **33**, 4329 (1968); (b) R. F. Bridger, *ibid.*, **35**, 1746 (1970).

(11) K. Adamic and K. U. Ingold, *Can. J. Chem.*, **47**, 295 (1969).

TABLE I

NITROXIDE RADICALS FROM BIS(*N*-ARYLNAPHTHYLAMINES)

Radical	Amine	A^N	A^H[a] Ortho	Meta	Para	Naphthyl
1b	1,1′-Bis(*N*-phenyl-2-naphthylamine)[b]	10.26 ± 0.08	2.52	0.82	2.52	0.82 (2 protons)
3b	4,4′-Bis(*N*-phenyl-1-naphthylamine)[c]	9.93 ± 0.07	2.48	0.83	2.48	0.83 (2 protons)
2b	1,1′-Bis(di-2-naphthylamine)[d]	10.3 ± 0.2				4.2 ± 0.2 (α-naphthyl)

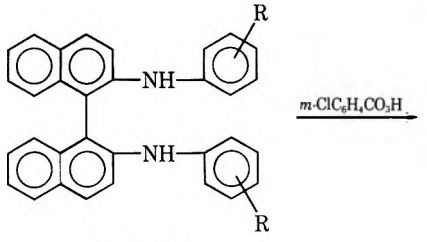
[a] ±0.05 G. [b] Line width, 0.6 G. [c] Line width, 0.4 G. [d] Line width, 3.3 G.

Experimental Section

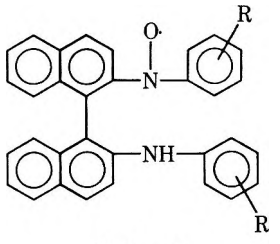
Radicals were generated by mixing a 20-fold excess of amine (1.25×10^{-2} *M*) with *m*-chloroperbenzoic acid (6.25×10^{-4} *M*) at room temperature in benzene. Solutions were outgassed by two freeze–thaw cycles, and sample tubes were sealed. Within 30 min after mixing, esr signals were well developed. All nitroxide radicals were stable at room temperature. The spectrum of **1b** was slightly diminished after standing 48 hr at room temperature. Spectra were measured with a Varian V-4500-10 esr spectrometer equipped with a 12-in. magnet and 100-kc/sec field modulation. Simulated spectra were computed using the program of Snowden and Strom.[12] The preparation of the amines has been described.[10] The reactions of *m*-chloroperbenzoic acid with *N*-phenyl-1-naphthylamine, *N*-phenyl-2-naphthylamine, and *N*-(2-naphthyl)-*N*,*N*′-diphenyl-1,2-naphthylenediamine[10] produced only very weak esr signals which were ill-defined and which exhibited no hydrogen hyperfine splitting.

Results

The reaction of 1,1′-bis(*N*-phenyl-2-naphthylamine) (**1a**) with *m*-chloroperbenzoic acid at room temperature produced a stable nitroxide radical, resulting in the esr spectrum shown in Figure 1. Because of the ex-



1a, R = H



1b, R = H

treme steric requirements of **1b**, the contribution of the first, as well as the second, naphthyl group to the hyperfine splitting was expected to be negligible. Inspection of the spectrum of **1b** suggested hfsc of A^N (1 N) = 10.26, $A^H_{o,p}$ (3 H) = 2.52, and A^H_m (2 H) = 0.82 G. This predicts a spectrum of 36 lines. The observed spectrum consists of 38 distinct lines, however, and the observed intensities do not agree with those predicted using only the phenyl hydrogen hfsc. It was necessary to include two small naphthyl hfs of A^H = 0.82 G. The computed spectrum using these hfsc with the experimental line width of 0.6 G is shown in Figure 1 and agrees well with the experimental spectrum.

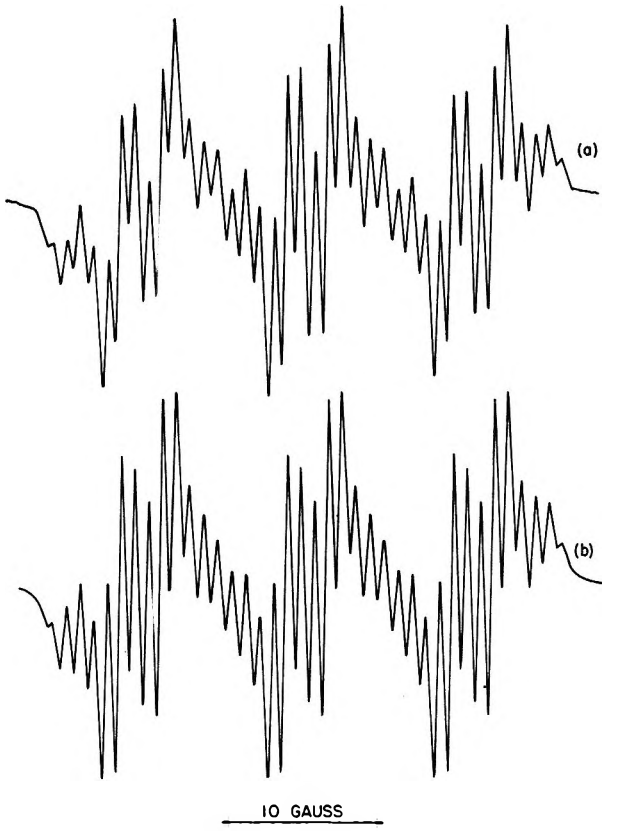
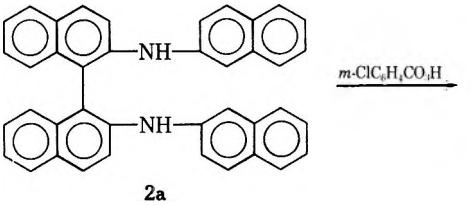
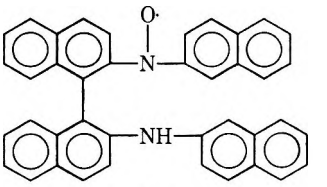


Figure 1.—Nitroxide radical from 1,1′-bis(*N*-phenyl-2-naphthylamine): (a) experimental, (b) simulated.

Oxidation of 1,1′-bis(di-2-naphthylamine) (**2a**) produced nitroxide radical **2b**. The radical concentration



2a



2b

was quite low, possibly because of extensive disproportionation[5,13] *via* the reactive α-naphthyl carbon. Because of the high gain and modulation amplitude required for detection, the line width was quite broad (3.3 G) and much of the hyperfine splitting was lost. It was possible, however, to resolve A^N (1 N) of 10.3

(12) B. S. Snowden, Jr., and E. T. Strom, QCPE Program No. 160.

(13) A. R. Forrester and R. H. Thomson, *Nature*, **203**, 74 (1964).

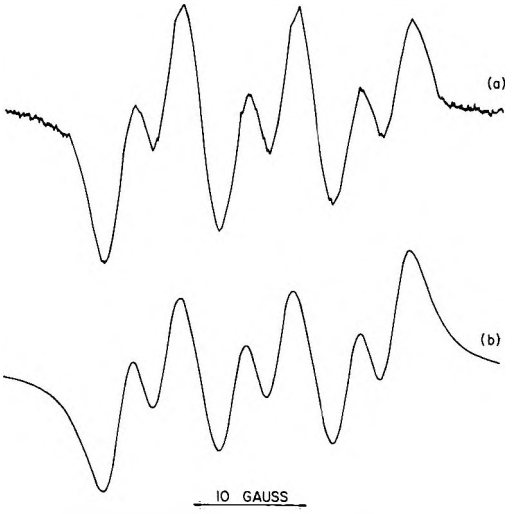
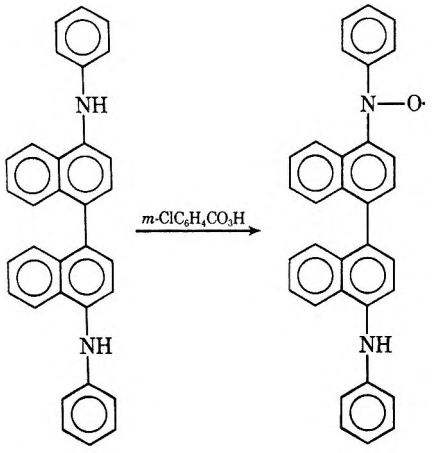


Figure 2.—Nitroxide radical from 1,1′-bis(di-2-naphthylamine): (a) experimental, (b) simulated.

and A^H (1 H) of 4.2 G. The hydrogen hfsc is of the magnitude expected for the α-naphthyl proton (*vide infra*). The experimental and simulated spectra are shown in Figure 2.

4,4′-Bis(*N*-phenyl-1-naphthylamine) (**3a**) produced upon oxidation with *m*-chloroperbenzoic acid radical



3a **3b**

3b. Analysis produced the computed spectrum which is compared with the experimental spectrum in Figure 3. The splittings used were A^N (1 N) = 9.93, $A^H_{o,p}$ (3 H) = 2.48, and $A^H_{m,naph}$ (4 H) = 0.83 G. These values are very similar to those found for **1b**. Results for **1b**, **2b**, and **3b** are summarized in Table I.

Finally, the effect of substituents in the benzene ring of **1b** on the nitrogen hfs was measured by oxidizing a series of substituted 1,1′-bis(*N*-aryl-2-naphthylamines). The nitrogen hfsc are shown in Table II. A plot of $A^H_{subst}/A^H_{p\text{-}H}$ *vs.* σ yielded a slope of -0.100 (Figure 4).

Discussion

The experimental results for **1b** and **3b** indicate little delocalization of the spin into the naphthyl group. This is expected for **1b** because of the severe steric requirements of the 1,1′-binaphthyl system. Forrester, *et al.*,[4] reason from their and Buchachenko's[9] data that nitroxides substituted at the α position of naphthalene

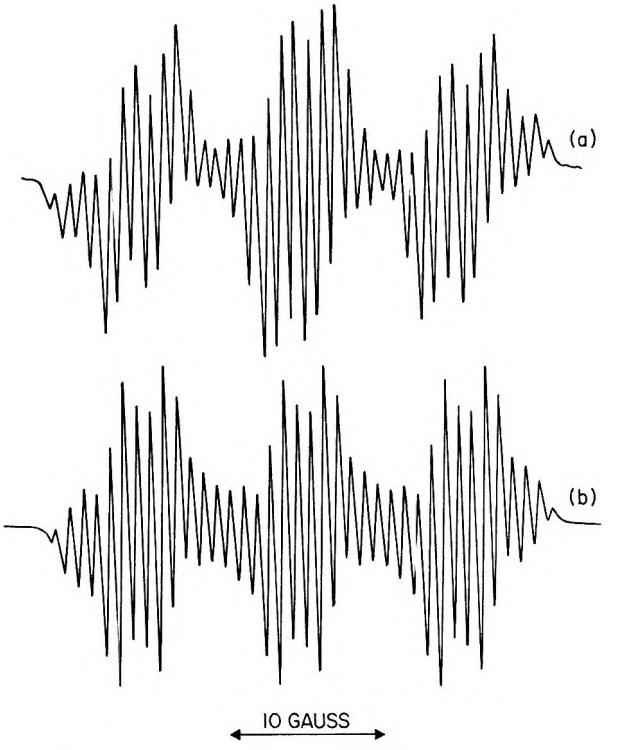


Figure 3.—Nitroxide radical from 4,4′-bis(*N*-phenyl-1-naphthylamine): (a) experimental, (b) simulated.

TABLE II

NITROXIDE RADICALS FROM PHENYL-SUBSTITUTED 1,1′-BIS(*N*-ARYL-2-NAPHTHYLAMINES)

Substituent on 1b	A^N
p-OCH_3[a]	10.59 ± 0.09
p-CH_3	10.45 ± 0.05
m-CH_3	10.33 ± 0.05
H	10.26 ± 0.08
m-OCH_3	10.24 ± 0.05
m-Cl[b]	9.89 ± 0.08

[a] Also resolved was A^H_o of 2.69 G. [b] $A^H_{o,p}$ 2.55 and A^H_m 0.73 G were observed.

will have larger nitrogen hfs than the corresponding β derivatives because of steric interaction between the nitroxide oxygen and the peri hydrogen. In **3b** this factor could reduce delocalization into the naphthyl group. The net result is that radicals **1b** and **3b** have larger values of A^N and A^H_{phenyl} than diphenyl nitroxide, in which the unpaired electron can be delocalized over two rings. The splittings for diphenyl nitroxide in xylene are A^N = 9.66, $A^H_{o,p}$ = 1.83, and A^H_m = 0.79 G.[6h] The observed hfsc of the ortho and para hydrogens of **1b** and **3b** are intermediate in value between those of phenyl nitroxide (A^H_o = 2.74, 3.07, A^H_p = 3.07 G[6c]) and phenyl-*tert*-butyl nitroxide ($A^H_{o,p}$ = 2.05 G[5]).

Recently, extensive data have become available concerning substituent effects on hfsc in free radicals,[1a,3,6b,14] and a review on the subject has appeared.[15] The nitroxide function, with its high spin density, was found by Strom, *et al.*,[3] to be less sensitive to substituents than certain anion radical functions. The slope of -0.100 found for **1b** derivatives is very close to the slopes found for phenyl nitroxides and phenyl-*tert*-

(14) E. T. Strom, *J. Amer. Chem. Soc.*, **88**, 2065 (1966).
(15) E. G. Janzen, *Accounts Chem. Res.*, **2**, 279 (1969).

butyl nitroxides. (The data for the latter series are for a protonic solvent with a concomitant reduction in slope.) Data taken from the compilation in ref 3 are shown in Table III. The magnitude of the slope for

TABLE III
SUBSTITUENT EFFECTS OF NITROXIDE RADICALS

Radical	Solvent	Ref	ρ^a
$ArN^{+}(O^{-})H$	$PhCH_3$	6c	−0.0930
$ArN^{+}(O^{-})C(CH_3)_3$	$(CH_2OH)_2$	6a	−0.0659
$ArN^{+}(O^{-})Ar$	PhH and xylene	3, 6h	−0.1160
1b	PhH	This work	−0.100

[a] Slope of A^{N}_{subst}/A^{N} *vs.* σ.

radicals of structure **1b** and monophenyl nitroxides appears to be less than that found in symmetrically disubstituted diphenyl nitroxides. Although the difference is small, it appears to be real and probably reflects the presence of the second substituent. In all systems of Table III, the correlations reflect (in valence bond language) the stabilization of resonance structure II by electron-donating substituents.[15]

$$>\ddot{N}-\dot{O} \qquad >\overset{+}{N}-O^{-}$$
I II

In order to gain some insight into the possible sites producing the naphthyl splittings in **1b** and **3b** and to better assess the literature data for *N*-phenylnaphthyl nitroxides, we undertook theoretical calculations on *N*-phenyl-1-naphthyl nitroxide (III), *N*-phenyl-2-naphthyl nitroxide (IV), and di-2-naphthyl nitroxide (V). The method chosen was McLachlan's modification of simple Hückel molecular orbital theory.[16] In applying an approximate method to complex systems like these, one should look only for broad trends rather than quantitative correspondence of theoretical spin densities with experimental values. For calculations on the model nitroxides to have any pertinence to radicals **1b**–**3b**, the extra attached naphthyl group must be regarded as an inert substituent. We submit that this is a basically correct assumption, as models of the radicals show that the naphthyl groups must be approximately perpendicular. A possible complication would be increasing σ character of the molecular orbital containing the unpaired electron due to steric perturbations. This has been found to occur in ortho-substituted phenyl-*tert*-butyl nitroxides.[17] In such cases, however, the ratio of ortho,para to meta splitting is abnormal. The normal phenyl proton splittings found in **1b** and **3b** indicate that the unpaired electron is in a π molecular orbital.

Heteroatom parameters suitable for use with the nitroxide function have been developed by Ayscough and Sargent,[18] who studied solvent effects on the esr spectra of mono- and diphenyl nitroxide. Their parameters were $h_N = 1.5$, $k_{NO} = 1.6$, $k_{CN} = 1.05$[19] with h_O allowed to vary with solvent. From their table it appeared that $h_O = 1.2$ was suitable for use with a benzene solvent. It also seemed likely that, in radicals **1b**–**3b**, the aromatic moieties would be more twisted than in the model radicals. Accordingly, calculations were also carried out in which the parameter k_{CN} for the nitrogen–naphthyl carbon bond was decreased. Ayscough and Sargent evaluated spin densities using the McConnell[20] equation and a Q^{H}_{CH} of 23.7 G. McLachlan[16] found a Q^{H}_{CH} of 24.2 G to be suitable for condensed aromatic systems. We calculated theoretical proton hfsc's using $Q^{H}_{CH} = 24.0$ G. Semiempirical parameters have been developed to calculate nitrogen hfsc in systems in which the nitrogen is attached to an oxygen and two carbons,[18,21,22] but in view of the unavoidable arbitrariness of such parameters[23] we prefer to tabulate only the nitrogen spin densities. The numbering system is shown in Chart I, and the results of the calculations are given in Tables IV–VI.

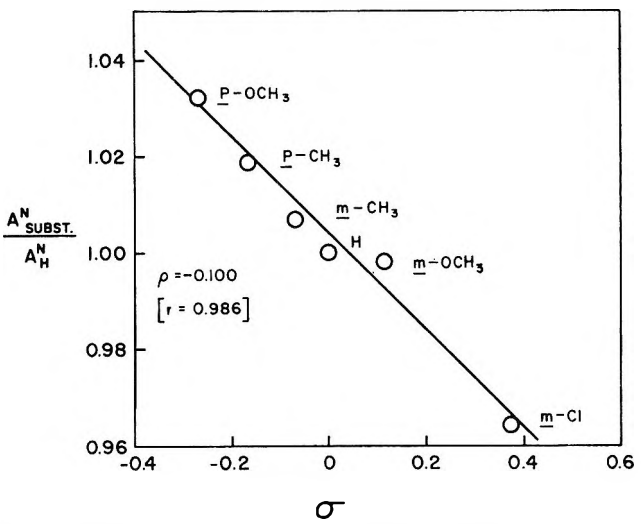
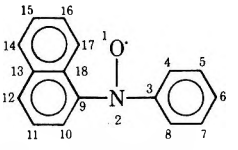
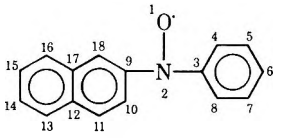


Figure 4.—Substituent effects on A^{N} of nitroxide radicals from 1,1′-bis(*N*-aryl-2-naphthylamines).

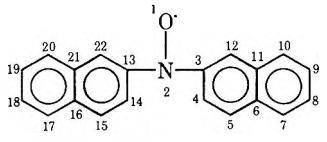
CHART I
NUMBERING OF MODEL NITROXIDES



N-phenyl-1-naphthyl nitroxide (III)



N-phenyl-2-naphthyl nitroxide (IV)



di-2-naphthyl nitroxide (V)

(16) A. D. McLachlan, *Mol. Phys.*, **3**, 233 (1960).
(17) A. Calder, A. R. Forrester, J. W. Emsley, G. R. Luckhurst, and R. A. Storey, *ibid.*, **18**, 481 (1970).
(18) P. B. Ayscough and F. B. Sargent, *J. Chem. Soc. B*, 907 (1966).
(19) Defined in the usual manner: $\alpha_X = \alpha_C + h_X\beta_{CC}$, $\beta_{XY} = k_{XY}\beta_{CC}$.
(20) H. M. McConnell, *J. Chem. Phys.*, **24**, 632 (1956).
(21) T. Kubota, K. Nishikida, H. Miyazaki, K. Iwatani, and Y. Oishi, *J. Amer. Chem. Soc.*, **90**, 5080 (1968).
(22) E. G. Janzen and J. W. Happ, *J. Phys. Chem.*, **73**, 2335 (1969).
(23) J. Q. Adams, S. W. Nicksic, and J. R. Thomas, *J. Chem. Phys.*, **45**, 654 (1966).

TABLE IV

CALCULATED SPIN DENSITIES AND HYPERFINE SPLITTINGS IN *N*-PHENYL-1-NAPHTHYL NITROXIDE[a]

	$k_{2,9}$ = 1.05		$k_{2,9}$ = 0.9		$k_{2,9}$ = 0.7		$k_{2,9}$ = 0.5	
Position	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|
O	0.428		0.466		0.514		0.553	
N	0.244		0.270		0.307		0.337	
4	0.075	1.80	0.082	1.97	0.090	2.16	0.098	2.35
5	−0.030	0.72	−0.033	0.79	−0.036	0.86	−0.041	0.98
6	0.069	1.66	0.076	1.82	0.083	1.99	0.088	2.11
10	0.137	3.29	0.103	2.47	0.060	1.44	0.025	0.60
11	−0.046	1.10	−0.039	0.94	−0.029	0.70	−0.019	0.46
12	0.133	3.19	0.098	2.35	0.051	1.22	0.017	0.41
14	0.033	0.79	0.023	0.55	0.009	0.22	−0.003	0.07
15	−0.019	0.46	−0.016	0.38	−0.012	0.29	−0.009	0.22
16	0.028	0.67	0.020	0.48	0.010	0.24	0.002	0.05
17	−0.020	0.48	−0.019	0.46	−0.018	0.43	−0.017	0.41

[a] λ = 1.2.

TABLE V

CALCULATED SPIN DENSITIES AND HYPERFINE SPLITTINGS IN *N*-PHENYL-2-NAPHTHYL NITROXIDE[a]

	$k_{2,9}$ = 1.05		$k_{2,9}$ = 0.9		$k_{2,9}$ = 0.7		$k_{2,9}$ = 0.5	
Position	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|
O	0.457		0.488		0.523		0.556	
N	0.258		0.282		0.312		0.338	
4	0.080	1.92	0.085	2.04	0.091	2.18	0.095	2.28
5	−0.033	0.79	−0.035	0.84	−0.039	0.94	−0.042	1.01
6	0.074	1.78	0.079	1.90	0.083	1.99	0.084	2.02
10	0.047	1.13	0.038	0.91	0.026	0.62	0.013	0.31
11	−0.026	0.62	−0.023	0.55	−0.020	0.48	−0.016	0.38
13	−0.020	0.48	−0.017	0.41	−0.014	0.34	−0.011	0.26
14	0.030	0.72	0.020	0.48	0.009	0.22	0.000	0.00
15	−0.019	0.46	−0.015	0.36	−0.010	0.24	0.006	0.14
16	0.037	0.89	0.025	0.60	0.010	0.24	−0.001	0.02
18	0.144	3.46	0.104	2.50	0.056	1.34	0.019	0.46

[a] λ = 1.2.

TABLE VI

CALCULATED SPIN DENSITIES AND HYPERFINE SPLITTINGS IN DI-2-NAPHTHYL NITROXIDE[a]

	$k_{2,13}$ = 1.05		$k_{2,13}$ = 0.9		$k_{2,13}$ = 0.7		$k_{2,13}$ = 0.5	
Position	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|	Calcd ρ	Calcd |hfs|
O	0.449		0.476		0.510		0.536	
N	0.257		0.277		0.303		0.324	
4	0.036	0.86	0.039	0.94	0.042	1.01	0.046	1.10
5	−0.028	0.67	−0.028	0.67	−0.031	0.74	−0.032	0.77
7	−0.019	0.46	−0.020	0.48	−0.022	0.53	−0.024	0.58
8	0.030	0.72	0.031	0.74	0.032	0.77	0.030	0.72
9	−0.018	0.43	−0.020	0.48	−0.021	0.50	−0.023	0.55
10	0.036	0.86	0.038	0.91	0.039	0.94	0.039	0.94
12	0.145	3.48	0.152	3.65	0.164	3.94	0.168	4.03
14	Identical		0.030	0.72	0.021	0.50	0.013	0.31
15	for		−0.024	0.58	−0.018	0.43	−0.012	0.29
17	symmetrical		−0.016	0.38	−0.012	0.29	−0.008	0.19
18	positions		0.020	0.48	0.010	0.24	0.002	0.05
19			−0.014	0.34	−0.010	0.24	−0.006	0.14
20			0.025	0.60	0.011	0.26	0.000	0.00
22			0.104	2.52	0.057	1.37	0.019	0.46

[a] λ = 1.2.

The similarity of the phenyl splittings in **1b** and **3b** is mirrored in the calculations. The differences in calculated values of A^{H}_{phenyl} in III and IV for identical values of $k_{2,9}$ are indeed small. The calculations also predict that, for identical values of $k_{2,9}$, ρ_N (and presumably A^N) is larger in the β-naphthyl derivative than in the α-naphthyl derivative. We find experimentally that **1b** does have a larger value of A^N than **3b**. It appears that the twist angles relating the naphthyl moiety with the phenyl nitroxide function are similar in **1b** and **3b**. The absolute magnitude of the calculated phenyl splitting is low when compared to the experimental value, which indicates that the parameters of Ayscough and Sargent are not completely suitable for the phenylnaphthyl nitroxide system. Assigning the ~0.8-G splitting to given naphthyl positions is risky, but the trends with decreasing $k_{2,9}$ would suggest that in both **1b** and **3b** the ~0.8-G naph-

thyl splittings arise from the 10 and 11 positions, as numbered in Chart I.

The calculations on V demonstrate quite clearly that the 4.2-G splitting in **2b** comes from the α-naphthyl proton (position 12 in Chart I). The calculations also predict that ρ_N in V is extremely close to ρ_N in IV, for identical values of k_{CN}. The A^N values for **1b** and **2b** are very close.

In view of our experimental results and the calculations shown above, Buchachenko's results for *N*-phenyl-2-naphthyl nitroxide are surprising. The nitroxide was made by heating H_2O_2 and the amine together with a trace of cobalt salt to 50–80° in an unspecified hydrocarbon solvent and then cooling the solution and recording the spectrum.[9b] Our results would indicate that a doublet splitting of ~4.0 G from the α-naphthyl proton ought to be readily resolvable. Thus, the possibility that Buchachenko's spectra partly involve radicals from these oxidative dimers must be considered. A complete answer to this question will have to entail unambiguous syntheses of *N*-phenyl-1- and *N*-phenyl-2-naphthyl nitroxides in larger amounts than heretofore possible.

Registry No.—**1b** (R = *p*-OCH_3), 27067-21-6; **1b** (R = *p*-CH_3), 27067-22-7; **1b** (R = *m*-CH_3), 27067-23-8; **1b** (R = H), 27067-24-9; **1b** (R = *m*-OCH_3), 27067-25-0; **1b** (R = *m*-Cl), 27067-26-1; **2b**, 27067-27-2; **3b**, 27067-28-3; **4b**, 27067-24-9; III, 27067-30-7; IV, 27067-31-8; V, 27067-32-9.

Acknowledgment.—The authors are grateful to O. M. Epifanio for technical assistance in measuring the spectra.

Restricted Rotation of Aryl Rings in *cis*-1,2-Diarylcyclopentanes and Diarylmethylcyclobutanes[1,2]

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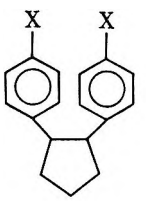
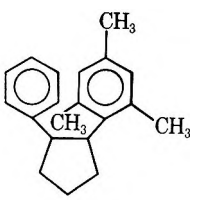
cis-1-Mesityl-2-phenylcyclopentane (*cis*-I) has been found to undergo rotation of the mesityl ring slowly enough to permit detection by a change in nmr line shape at low temperatures. At the coalescence temperature (−44°), the rate of rotation is approximately 160 sec^{-1}. Cyclobutylmesitylphenylmethane (IX), 3-bromomesitylcyclobutylphenylmethane (X), isopropylmesitylphenylmethane (XI), and β,β'-dimesityladipic acid (XIII) and its ester XII show restriction of rotation of the mesityl rings at room temperature or below; results of the studies of these compounds are compared with related examples which have been described previously. In the course of the synthetic work it has been found that, although cyclobutyldiphenylcarbinol and cyclobutyl(2,4-dimethylphenyl)phenylcarbinol (V) undergo dehydration with ring expansion on treatment with hot formic acid, cyclobutylmesitylphenylcarbinol (II), 9-anthrylcyclobutylphenylcarbinol (XIV), and cyclobutyl(2,3-dimethyl-9-anthryl)phenylcarbinol undergo dehydration under the same conditions without skeletal rearrangement. All of these dehydrations occur without skeletal rearrangement when the reaction is catalyzed by iodine. Mesitylphenylmethylenecyclobutane (IV) can be converted to 1-mesityl-2-phenylcyclopentene by treatment with hot trifluoroacetic acid.

In a search for isomerism due to restriction of rotation of adjacent aromatic rings, several *cis*-1,2-di(*p*-substituted phenyl)cyclopentanes (A) were previously investigated.[4] Nmr studies showed that the phenyl rings in such compounds rotate rapidly on the nmr



A



cis-I

time scale at room temperature around the single bonds joining them to the cyclopentane ring. The objective of the present work was to decrease the rate of rotation by placing substituents on the phenyl rings in such a way as to increase the energy barrier to rotation.

The preparation of *cis*-1-mesityl-2-phenylcyclopentane was undertaken as a point of departure. A possible synthetic route seemed to be through cyclobutylmesitylphenylcarbinol (II). It was anticipated that conversion of carbinol II to olefin III would occur with the desired carbon skeletal rearrangement, since the analogous cyclobutyldiphenylcarbinol had been reported[5] to undergo such a Wagner–Meerwein rearrangement when treated with hot formic acid. Instead, the reaction of carbinol II with formic acid under the conditions reported previously for the diphenylcarbinol gave only the unrearranged methylenecyclobutane IV. The structure of IV was established by a comparison of its nmr, uv, and ir spectra with those of related compounds and by oxidation to mesityl phenyl ketone. This difference in behavior led to a reinvestigation of the dehydration reactions of the parent cyclobutyldiphenylcarbinol to be described later in this paper.

The conversion of the methylenecyclobutane IV to the desired cyclopentene III was accomplished by treatment with trifluoracetic acid. Catalytic hydrogenation of III gave the desired *cis*-cyclopentane *cis*-I. A similar series of reactions was employed to prepare the related 2,4-dimethylphenylcyclopentane *cis*-VII.

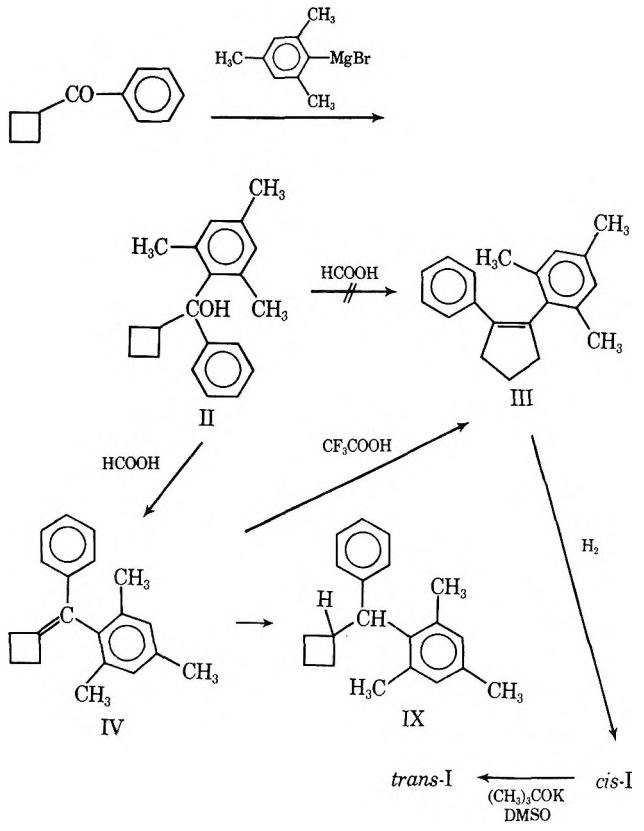
(1) Taken from the Ph.D. Theses, University of Illinois, of D. S. H. (1968) and P. E. B. (1969).

(2) We are indebted to the Army Research Office, Durham, and to the National Science Foundation for grants supporting this work.

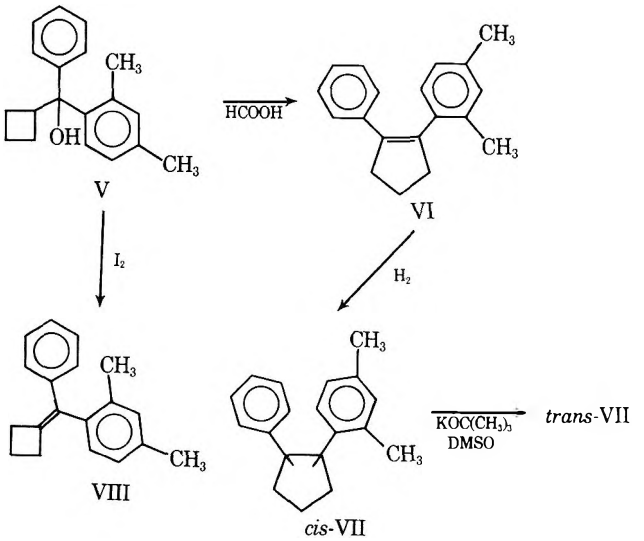
(3) U. S. Public Health Service Trainee, 1966–1969.

(4) D. Y. Curtin and S. Dayagi, *Can. J. Chem.*, **42**, 867 (1964).

(5) R. Criegee, A. Kerckow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).



In this case the carbinol was converted directly by treatment with formic acid to the desired cyclopentene VI which was hydrogenated to the *cis*-cyclopentane *cis*-VII. Dehydration of the carbinol with iodine in benzene solution gave the corresponding methylene cyclobutane VIII. *cis*-Cyclopentanes I and VII could

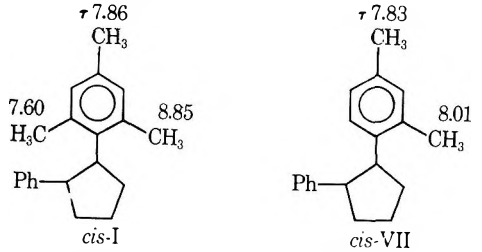


each be converted to its isomeric trans compound by treatment with potassium *tert*-butoxide in dimethyl sulfoxide.[6]

At room temperature the *cis*-mesitylphenylcyclopentane I showed an nmr spectrum indicative of rapid rotation of the mesityl group around the single bond to the cyclopentane ring. Thus, the absorption in carbon tetrachloride solution of the two *o*-methyl group protons occurred as a sharp singlet at τ 8.08 (with the para at τ 7.86). The broad benzylic proton absorption at τ 6.48 in *cis*-I was 0.1 ppm to lower field than the corresponding absorption of *trans*-I, a difference qualitatively similar to that between *cis*- and *trans*-1,2-diphenylcyclopentane and thus confirming the assigned configurations.[7] A similar difference was observed between *cis*- and *trans*-VII.

When the temperature of a solution of *cis*-I in carbon disulfide was lowered, the spectrum showed a broadening of the *o*-methyl absorption, and when $-56°$ had been reached, the original peak had disappeared and two new peaks had become visible. At $-81°$ fully developed sharp singlets of nearly equal intensity were seen at τ 7.6 and 8.9. (In carbon disulfide at room temperature the absorption resulting from coalescence is at τ 8.2, approximately equidistant from these two peaks.) The absorption of the *p*-methyl group was unchanged when the temperature was lowered. It seems clear that the nonequivalence of the *o*-methyl protons is due to the restriction of rotation of the mesityl ring so that at low temperatures the "inside" methyl group (more nearly over the cyclopentane ring) has a different chemical shift from the "outside" methyl group (away from the cyclopentane ring). This explanation is supported by the change in the mesityl ring proton spectrum at low temperatures. At room temperature *cis*-I showed a broad absorption due to the protons on the unsubstituted phenyl ring as was observed[7b] with *cis*-diphenylcyclopentane and, in addition, a sharp singlet at very slightly higher field (τ 3.49) due to the two meta ring protons of the mesityl group. At lower temperatures the mesityl ring proton absorption broadened, then disappeared, and at $-62°$ a new doublet appeared, one arm of which, however, overlapped with the phenyl proton spectrum. The complexity of the spectra precludes an accurate calculation of the isomerization rate or even the coalescence temperature, but it seems clear that coalescence occurred near $-44°$; the method of Gutowsky and Holm[8] gives an estimated rate at that temperature of about 160 sec^{-1}. The assignment of this change in the nmr spectrum to restriction of the rotation of the mesityl ring was supported by the fact that no such change in the spectrum of the *cis*-VII was observed when it was cooled to $-60°$. The absence of even one of the *o*-methyl groups as in *cis*-VII would, of course, be expected to permit rotation of the dimethyl ring at a rate similar to that of the unmethylated compound *cis*-diphenylcyclopentane and its para-substituted derivatives previously studied.

The positions of the methyl group chemical shifts are summarized below, next to the formulas of *cis*-I and *cis*-VII. That in VII the *o*-methyl group's ab-



(6) See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1963, p 32 ff.

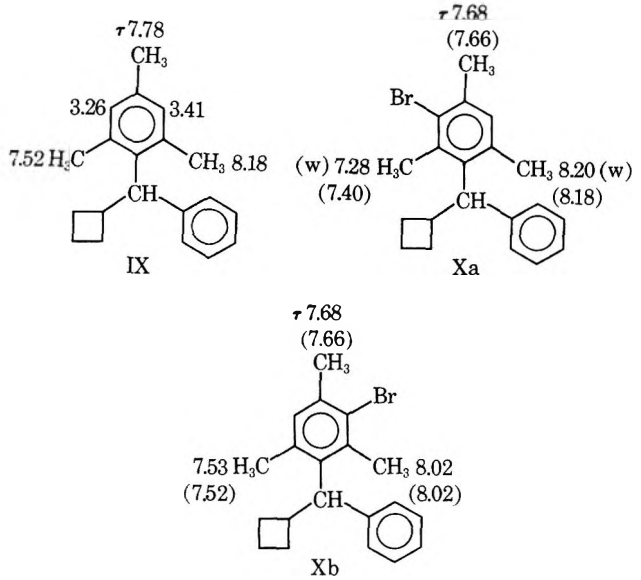
(7) (a) D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind. (London)*, 1205 (1958); (b) D. Y. Curtin, H. Gruen, Y. G. Hendrickson and H. E. Knipmeyer, *J. Amer. Chem. Soc.*, **84**, 863 (1962).

(8) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1962)

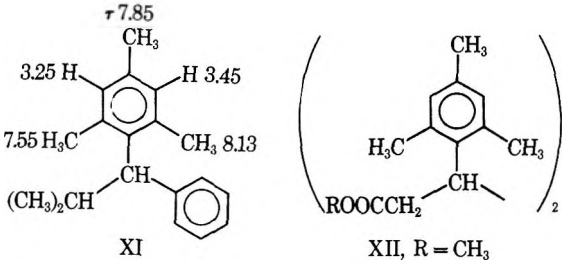
sorption position lies between the positions of the two *o*-methyl groups of *cis*-I is in agreement with the postulation that VII exists as a mixture of rapidly equilibrating conformers, one with the methyl group in the "inside" position and one "outside."

The temperature dependence of the nmr spectrum of cyclobutylmesitylphenylmethane (IX) prepared by hydrogenation of the methylenecyclobutane IV was also examined. At ambient temperature (38°) the mesityl ring proton absorption occurred as a singlet at τ 3.3, well separated from the phenyl proton singlet at τ 2.92. The *p*-methyl group on the mesityl ring appeared as a sharp singlet at τ 7.75; the *o*-methyl protons, however, gave rise to very broad absorption at the base of the *p*-methyl singlet and overlapping with the cyclobutane ring methylene proton absorption. At 0° the mesitylene ring protons had separated to a doublet at τ 3.26 and 3.41, and the *o*-methyl protons' absorption also had separated and sharpened so that the three methyl groups now appeared as singlets at τ 7.52, 7.78, and 8.18. In the case of this compound, as with *cis*-I, rotation of the mesityl group around its single bond is slow on the nmr time scale at low temperatures; the mesityl ring exists in a conformation such that its two sides have nonequivalent environments. The rate of rotation was estimated to be of the order of 100 sec^{-1} at the coalescence temperature of 38°. At 30°, the coalescence temperature of the mesityl ring proton absorption, the rate was calculated to be 20 sec^{-1} in reasonable agreement with the results from the *o*-methyl absorptions.

Bromination of the mesityl phenyl compound IX in acetic acid gave a monobromo compound shown by the nmr spectrum to have a single mesityl ring proton and therefore assigned the structure X. At ambient temperature the nmr spectrum resembled that of the unbrominated compound IX with a relatively sharp ring proton absorption but with broad *o*-methyl absorption. At 90° the *o*-methyl proton signals had sharpened so that there had appeared the three methyl absorptions expected if the mesityl ring is rotating rapidly. At −10° the spectrum of X was that to be expected from a mixture of two isomers in unequal amounts shown schematically and designated Xa and Xb without any attempt to describe their precise geometry. If the effect of a bromine atom on an *o*-methyl group is assumed to lower the absorption position 0.12 ppm,[9] and if the effect on a *p*-methyl absorption is assumed to be negligible, the positions of the methyl absorptions of Xa and Xb can be deduced from the methyl positions of the unbrominated compound IX with the further assumption that the bromine atom does not effect the position of the rotational equilibrium. The values so calculated are shown in parentheses beside the formulas together with the values observed in the spectrum of X. The absorptions at τ 7.28 and 8.20 were less intense than those at τ 7.53 and 8.02; an estimate of the relative intensities of the τ 7.28 and 7.53 absorptions led to an estimate of the ratio Xa/Xb as 1:2. The internal consistency of the chemical shift values provides support for the interpretation presented here.



To determine the extent to which the barrier to rotation of the mesityl ring of *cis*-VII was a result of the presence of the cyclobutane ring, the related compound, isopropylmesitylphenylmethane (XI), with an isopropyl substituted for the cyclobutyl group, was prepared and the nmr spectrum determined. At ambient temperature the mesityl methyl proton absorption was a sharp singlet, as was the mesityl ring proton absorption. At lower temperatures (carbon disulfide solvent) the *o*-methyl proton absorption broadened, as did the absorption due to the mesityl ring protons, and at −52° the mesityl methyl group absorption appeared as three sharp well-separated peaks and the mesityl ring proton absorption appeared as a pair of sharp peaks. Chemical shift positions are shown on the accompanying formula. Using the method of Gutowsky and Holm,[8] the rate constant for rotation of the mesityl ring was estimated to be 78 sec^{-1} at the coalescence temperature of −4° for the methyl proton absorption and 28 sec^{-1} at the coalescence temperature of 16° for the mesityl ring proton absorption.



XI

XII, R = CH_3
XIII, R = H

A further example of nonequivalence of *o*-methyl groups on a mesityl ring was provided by examination of the nmr spectrum of dimethyl *meso*-β,β'-dimesityladipate (XII), which was prepared by electrolytic reduction[10] of 2,4,6-trimethylcinnamic acid followed by esterification with methanol and hydrochloric acid. Although the nmr spectrum of the ester XII showed the mesityl ring protons as a singlet at τ 3.16, the methyl groups of the mesityl ring were clearly separated from each other, the *p*-methyl group absorption appearing at τ 7.70 and the *o*-methyl group absorption at τ 7.32 and 7.40 (relative areas indicated that the latter two peaks which were not completely resolved from each

(9) R. R. Fraser, *Can. J. Chem.*, **38**, 2226 (1960).

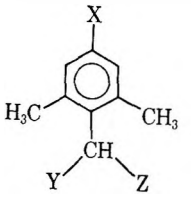
(10) We are very much indebted to Professor Sherlock Swann for helpful advice concerning this part of the work.

other, obscured the four methylene carbon protons). The corresponding carboxylic acid, β,β′-dimesityladipic acid (XIII), showed a mesityl ring spectrum like that of the ester.

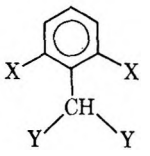
Compounds IX–XIII have in common restriction of rotation of a 2,6-dimethylphenyl ring around a single bond joining it to a tetrahedral carbon atom having two additional substituents. Related examples of such restriction of rotation have been reported recently[11-14] and are presented in Table I together with a summary of our results.

TABLE I

COALESCENCE TEMPERATURE (T_c) AND FREE ENERGIES OF ACTIVATION FOR 2,6-DISUBSTITUTED ARYL RINGS



B



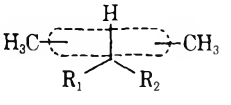
C

Structure	T_c, °C	$\Delta G^{\ddagger}$ at T_c (kcal/mol)	$\Delta\nu$, $ArCH_3$, ppm
Mesityldiphenylmethane[a,b] (B1, X = CH_3; Y = Z = C_6H_5)	−90[c]	8.8	
Mesitylisopropylphenylmethane[b,d] (XI) (B2, X = CH_3; Y = $(CH_3)_2CH$; Z = C_6H_5)	−4[c] (−16)[e]	13	0.58
Mesitylcyclobutylphenylmethane (IX)[b,d] (B3, X = CH_3; Y = C_4H_7; Z = C_6H_5)	38[c] (30)[e]	16	0.66
Dimethyl *meso*-β,β′-dimesityladipate (XII)[d,f] (B4, X = CH_3; Y = $CH(CH_2COOCH_3)C_6H_2(CH_3)_3$-2,4,6; Z = CH_2COOCH_3)	>30[c]		0.08
β,β′-Dimesityladipic acid (XIII)[d,g] (B5, X = CH_3; Y = $CH(CH_2COOH)C_6H_2(CH_3)_3$-2,4,6; Z = CH_2COOH)	>30		0.06
1,2-Dimethyl-1,2-bis(2,6-dimethylphenyl)ethanes[h,i] (B6, X = H; Y = CH_3; Z = $CH(CH_3)C_6H_3(CH_3)_2$-2,6)			
meso	104[c]	24	0.14
dl	171[c]	19	0.80
9-Mesitylfluorene[j] (B7, X = CH_3; Y, Z = $-C_6H_4C_6H_4-$)	>200[f]	≥26	1.54
Tri(2,6-dimethoxyphenyl)methane[a] (C1, X = CH_3O; Y = Z = $C_6H_2(OCH_3)_2$-2,6)	−57[b]	11	
2,6-Dichlorobenzal chloride[k] (C2, X = Y = Cl)	25[e]	15	

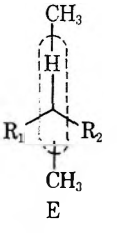
[a] Reference 11. [b] Solvent CS_2. [c] Coalescence of the methyl proton spectrum. [d] Present results. [e] Coalescence of the ring spectrum protons. [f] Solvent $CDCl_3$. [g] Solvent dimethyl sulfoxide. [h] Reference 12. [i] Solvent C_6H_5Cl. [j] Reference 14. [k] Reference 13.

The compound in Table I with structure B which has the lowest coalescence temperature and barrier to rotation is mesityldiphenylmethane, in which groups X and Y are phenyl rings. Replacement of one phenyl ring with an isopropyl group (structure XI) increases the interference to rotation of the mesityl ring, and replacement with a cyclobutyl group as in IX increases the interference even more. Substitution of much bulkier groups, as is found in the compounds further along in Table I, leads to increasing barriers to rotation. It is particularly striking that the compound B7, with the largest barrier to rotation of the mesityl ring (9-mesitylfluorene), differs from the compound B1 with the smallest barrier (mesityldiphenylmethane) only by virtue of having the two phenyl rings joined together by an extra bond. A difference of this kind was qualitatively anticipated by Adams and Campbell[15] and by Siddal and Stewart[14] on the basis that synchronous rotation possible in the diphenyl compound is prevented by the joining of the rings in the fluorenyl molecule. Such a "cogwheel effect" has been invoked in other systems by Kwart and Alekman[16] and may be partially responsible for the difference between the rate of rotation of the mesityl ring in the isopropyl compound XI as compared with the cyclobutyl compound IX in the present work.

In previous considerations[11,12,14] of the conformations of minimum energy associated with rotation of the mesityl group of molecules of type B (Table I), two states have been given particular attention. In one (D), viewed along the bond joining the tetrahedral carbon atom to the mesityl ring, the mesityl methyl groups lie between R_1 or R_2 and the hydrogen atom. In the other (E), one methyl lies between R_1 and R_2, with the other in a position more or less opposed to the hydrogen atom. In each case (B1, B6, and B7 of Table I) the conformation E has been chosen[11,12,14] as the one of minimum energy, and it seems likely that the same considerations apply to the compounds examined in the present work (B2, B3, B4, and B5 of Table I). The difference in magnetic environment of



D



E

the two methyl groups of the mesityl ring under condition in which rotation is slow on the nmr time scale is given by the chemical shift difference in Table I. Evidence that the dimesityl adipate XII has the meso configuration is provided by the similarity of the $\Delta\nu$ (0.08 ppm) to that of the *meso*- but not the *dl*-dimesityldimethylethane B5 (Table I). The reason for the difference between *meso*- and *dl*-B6 has been discussed.[12]

Dehydration of Diarylcyclobutylcarbinols.—Our observation that formic acid dehydration of cyclobutylmesitylphenylcarbinol II produced dehydration without carbon skeleton rearrangement, in contrast to the reported[5] behavior of the related compound, cyclobutyldiphenylcarbinol, led to a reinvestigation of the latter reaction. The literature was somewhat con-

(11) H. Kessler, A. Moosmayer, and A. Rieker, *Tetrahedron*, **25**, 287 (1969).

(12) A. J. M. Reubers, A. Sinnema, F. van Rantwijk, J. D. Remijnse, and H. van Bekkum, *ibid.*, **25**, 4455 (1969).

(13) T. Schaefer, R. Schwenk, C. J. McDonald, and W. F. Reynolds, *Can. J. Chem.*, **46**, 2187 (1968).

(14) T. H. Siddall, III, and W. E. Stewart, *J. Org. Chem.*, **34**, 233 (1969).

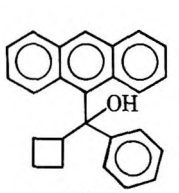
(15) R. Adams and J. Campbell, *J. Amer. Chem. Soc.*, **72**, 153 (1950).

(16) H. Kwart and S. Alekman, *ibid.*, **90**, 4482 (1968).

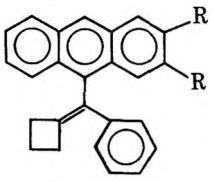
fusing with regard to this dehydration. Kishner[17] first reported that the dehydration of cyclobutyldiphenylcarbinol with oxalic acid dihydrate gave diphenylmethylenecyclobutane without carbon skeleton rearrangement. This work was not mentioned in the report of the dehydration with carbon skeleton rearrangement by formic acid by Criegee, Kerckow, and Zinke,[5] which in turn was not referred to in a later report by Graham and Williams[18] that either iodine in benzene or oxalic acid dihydrate gave only unrearranged diphenylmethylenecyclobutane. Because of the coincidental agreement of many of the properties of diphenylmethylenecyclobutane with those of 1,2-diphenylcyclopentene (see the Experimental Section), these dehydrations were reinvestigated. The report of Graham and Williams[18] that dehydration of the diphenylcarbinol with iodine proceeded without rearrangement and that of Criegee that reaction with formic acid gave only rearranged product were both confirmed. However, oxalic acid dihydrate was found to give a nearly equimolar mixture of rearranged and unrearranged olefin, in contrast to the report of Graham and Williams.[18]

It deserves mention that infrared and ultraviolet spectroscopy, unlike the nmr and mass spectra, provided easy differentiation between the diarylmethylene cyclobutanes and the 1,2-diarylcyclopentenes. Diphenylmethylenecyclobutane and its methyl derivatives IV and VIII showed absorption at 2983 ± 3, 2918 ± 3, 2824 ± 4, and 1414 ± 1 cm^{-1}. The diarlycyclopentenes (1,2-diphenylcyclopentene, III, and VI) showed none of these absorptions and instead had characteristic absorptions at 2891 ± 1, 2868 ± 3, and 2843 ± 3 cm^{-1}. The diarylmethylenecyclobutanes showed their longer wavelength absorption maxima in the ultraviolet spectrum at 260 cm^{-1} or less, whereas the corresponding absorption in the diarylcyclopentenes was at a longer wavelength than 260 nm; with a particular pair of aryl groups the absorption of the diarylcyclopentene was 16–20 nm higher in wavelength than that of the corresponding diarylmethylenecyclobutane.

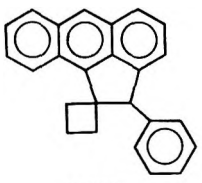
In an effort to increase dramatically the steric interference to rotation in this *cis*-1,2-diarylcyclopentane systems, cyclobutyl(9-anthryl)phenylcarbinol (XIV) was prepared from 9-anthryllithium and phenylcyclobutyl ketone. The structure was confirmed by the infrared spectrum which showed the absorptions characteristic of the methylene cyclobutane system. Dehydration with either iodine–benzene or with formic acid gave only the methylenecyclobutane (XV). The related olefin XVI was prepared from 2,3-dimethyl-9-anthryllithium in a similar manner. An attempt to cause rearrangement of the methylenecyclobutane XV to the corresponding anthrylphenylcyclopentene failed, and instead there was obtained a product believed to have resulted from a Friedel–Crafts ring closure and to be XVIIa or XVIIb.



XIV



XV, R = H
XVI, R = CH_3



XVIIa

XVIIb

It follows that dehydration of cyclobutyldiarylcarbinols when carried out with hot formic acid leads to rearrangement to the diarylcyclopentene when both aryl groups are relatively unhindered as with cyclobutyldiphenylcarbinol or with the 2,4-dimethylphenyl compound V. The demonstration that the compounds II and XIV were dehydrated with no observable rearrangement suggests that steric factors are responsible for the difference in behavior.

Experimental Section[19]

Cyclobutylmesitylphenylcarbinol (II).—To a solution of mesitylmagnesium bromide prepared from 52 g (0.25 mol) of bromomesitylene[20] and 7 g (0.29 g-atom) of magnesium turnings in 250 ml of tetrahydrofuran (THF) freshly distilled from $LiAlH_4$ was added 40 g (0.25 mol) of cyclobutylphenyl ketone in 100 ml of dry THF over a 10-min period. After the mixture was stirred for 4.5 hr, decomposition by pouring into 1 l. of cold saturated NH_4Cl solution and extraction with ether gave on distillation a fraction with bp 110–175° (0.5 mm). Redistillation gave a viscous yellow oil which crystallized on standing. Recrystallization from pentane yielded 14.7 g (21%) of carbinol II, mp 89–91°. Recrystallization gave product, mp 91–92°. The infrared spectrum showed absorption at 3605 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}O$: C, 85.7; H, 8.6. Found: C, 85.4; H, 8.6.

Mesitylphenylmethylenecyclobutane (IV). A. Dehydration with Formic Acid.—The carbinol II (10 g, 3.6 mmol) in 400 ml of 98% formic acid was heated for 10 hr with stirring under reflux. After dilution with water, extraction with chloroform, washing with aqueous $NaHCO_3$, drying of the chloroform solution, and distillation, there was obtained 8.15 g (90% yield) of a clear oil, bp 138–145° (0.4 mm), which crystallized on standing. Recrystallization from ethanol gave the methylenecyclobutane IV: mp 47–48°; uv max 255 nm (ε 17,350, sh), 262 (18,100), 272 (12,300, sh); ir 2980, 2910, 2820 (w), 1650 (w), 1412 cm^{-1}; nmr τ 2.96 (s, 5), 3.26 (s, 2), 6.87 (t, 2), 7.60 (m, 2), 7.76 (s, 4), 7.96 (s, 7).

(17) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **42**, 1288 (1910).

(18) S. H. Graham and A. J. S. Williams, *J. Chem. Soc.*, 4066 (1959); *ibid.*, *C*, 655 (1966); 390 (1969).

(19) The more important spectra are reproduced in the two dissertations available from University Microfilms, Ann Arbor, Mich. Mesitylphenylmethylenecyclobutane (IV), its reduction product (IX), and the bromo derivative (X) of IX, first described in the thesis[1] of D. S. H., are there incorrectly referred to as the cyclopentene III, the cyclopentane *cis*-I, and the bromo derivative of *cis*-I, respectively. Similarly, the anthrylphenylmethylenecyclobutanes XV and XVI are there incorrectly identified as 1-anthryl-2-phenylcyclopentenes.

Melting points were determined on a Kofler hot stage or a Thomas–Hoover apparatus and are corrected. Ultraviolet spectra were obtained with a Spectronic 505 or a Cary Model 14 spectrophotometer; hexane solutions were used unless otherwise indicated. Infrared spectra (10–20% solutions in carbon tetrachloride unless otherwise indicated) were measured in part by Mr. D. Johnson and his associates and were obtained with a Perkin-Elmer Model 21 or 521 spectrophotometer. Nmr spectra were determined in part by Mr. R. Thrift, Mr. O. Norton, and Mr. D. Johnson and their associates with Varian Model A-60, A-60A, 56-60A, or HA-100 instruments (CCl_4 unless otherwise specified), with tetramethylsilane as in internal standard. Solutions (5–30%) employed in the temperature dependence studies were degassed. Mass spectra (70 eV) were obtained with an Atlas CH-4 spectrometer by Mr. J. Wrona. Microanalyses were determined by Mr. J. Nemeth and his associates.

(20) L. I. Smith, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 45.

Anal. Calcd for $C_{20}H_{22}$: C, 91.6; H, 8.5. Found: C, 91.3; H, 8.4.

B. Dehydration with Iodine.—When the carbinol II (2.5 g, 8.9 mmol) in 60 ml in benzene with 0.1 g of iodine was heated under reflux for 16 hr and the solution washed with aqueous sodium thiosulfate and then water, dried, heated with Darco, filtered through a Celite pad, and distilled, there was obtained 1.85 g (80% yield) of the methylenecyclobutane IV as an oil which crystallized on standing, mp 46.2–47.8°. A mixture with the product obtained by the dehydration with formic acid showed no melting point depression.

Oxidation of Mesitylphenylmethylenecyclobutane (IV).—Treatment of 400 mg (1.53 mmol) of olefin IV in 120 ml of *tert*-butyl alcohol with 1.68 g (7.85 mol) of sodium periodate, 0.31 g (1.96 mmol) of potassium permanganate, 0.28 g (2.03 mmol) of potassium carbonate, and 250 ml of water for 64 hr[21] gave, after dilution with water, extraction with ether, drying of the ether solution, and removal of the ether on a rotary evaporator, 191 mg of an oil whose behavior on thin layer chromatography (benzene, silica gel G) showed a major component with a R_f like that of mesitophenone. Column chromatography on alumina (ligroin:benzene, 1:1, as eluent) of the original reaction product gave a fraction with the nmr spectrum characteristic of mesitophenone: τ 2.26 (m, 2), 2.66 (m, 3), 3.20 (s, 2), 7.26 (m, 1), 7.70 (s, 3), 7.96 (s, 6). The ir spectrum contained every band present in the spectrum of authentic mesitophenone.

1-Mesityl-2-phenylcyclopentene (III). Isomerization of IV with Trifluoroacetic Acid.—A solution of 3.0 g (11.4 mmol) of the methylenecyclobutane IV in the minimum amount of carbon tetrachloride was heated under reflux for 12 hr with 50 ml of trifluoroacetic acid. After it was poured into ice water, the product was isolated by extraction with chloroform, washing with cold, saturated sodium carbonate solution, drying, removal of the solvent with a rotary evaporator, and chromatography on silica gel (petroleum ether eluent). There was obtained 28 g (93%) of III as a colorless oil. Tlc on silica gel G (petroleum ether) showed evidence of only one component as did glc (15% FFAP on Chromosorb G, 180°). Collection of this material gave an analytical sample: ir absorption at 3090, 3060, 3030, 2945, 2920, 2890 sh, 2865, 2840, 2725, 1610, 1595, 1495, 1442, 1375, 1030, 845, 690 cm^{-1}; nmr τ 3.00 (s, 5), 3.25 (s, 2), 6.8–7.6 (m, 4), 7.74 (s, 3, *p*-CH_3), 7.93 (s superimposed on a multiplet with total area 8); uv max 263 nm (ϵ 16,300).

Anal. Calcd for $C_{20}H_{22}$: C, 91.6; H, 8.5. Found: C, 91.8; H, 8.6.

***cis*-1-Mesityl-2-phenylcyclopentane (*cis*-I).**—Reduction of the olefin III (2.8 g, 10.7 mmol) in 50 ml of absolute ethanol was carried out with hydrogen at 800 psi for 96 hr with 1.0 g of Pd on carbon as catalyst. After filtration through a Celite pad, removal of the solvent with a rotary evaporator, and recrystallization from absolute ethanol, there was obtained 1.9 g (67%) of *cis*-I as colorless prisms: mp 57.5–58.6°; further recrystallization gave mp 58.3–58.9.°; uv max 268 nm (ϵ 355), 262 (379); ir 3085, 2950, 1600 cm^{-1}; nmr (CCl_4) τ 3.05 (m, 3), 3.30 (s, 2), 3.49 (s, 2), 6.48 (m, 2), 7.86 (s), 8.08 (s) (the last two superimposed upon a multiplet, total area 15); mass spectrum (rel intensity) *m/e* 264 (81), 173 (18), 159 (51), 147 (27), 145 (45), 144 (75), 133 (100), 129 (37), 91 (24).

Anal. Calcd for $C_{20}H_{24}$: C, 90.9; H, 9.2. Found: C, 90.9; H, 9.3.

***trans*-1-Mesityl-2-phenylcyclopentane (*trans*-I).**—The isomerization of *cis*-I (1.5 g, 5.67 mmol) was carried out by heating it for 12 hr at 100° under nitrogen with 3.0 g (26.7 mmol) of potassium *tert*-butoxide in 150 ml of dry dimethyl sulfoxide. The reaction mixture was then poured into 600 ml of ice water and extracted with petroleum ether, and the solvent evaporated. The brown oil so obtained (1.06 g, 63% yield estimated from the nmr spectrum) was distilled and submitted to glc. Collection of the major component (Apiezon L on Chromosorb W) gave *trans*-I: uv max 271 (ϵ 493), 267 (464), 264 (499), 262 (491); ir 3080, 2955, 1600, 1450 cm^{-1}; nmr τ 2.99 (s, 5), 3.38 (s, 2), 6.58 (m, 2), 7.85 (s), 7.88 (s) (the last two singlets superimposed on a multiplet, the total areas being 15).

Anal. Calc for $C_{20}H_{24}$: C, 90.9; H, 9.2. Found: C, 90.6; H, 9.1.

Cyclobutyl(2,4-dimethylphenyl)phenylcarbinol (V) was prepared by the addition of 20.3 g (0.127 mol) of cyclobutyl phenyl ketone to the Grignard reagent from 23.5 g (0.127 mol) of 2,4-dimethylbromobenzene and 3.2 g (0.132 g-atom) of Mg turnings in 200 ml of dry THF. After 10 hr under reflux, the reaction mixture was treated with cold saturated NH_4Cl solution, and the product isolated by extraction with ether and distillation to give 20 g (58%) of V as a clear oil, bp 145–146° (0.16 mm), which crystallized on standing. Recrystallization from pentane gave carbinol V: mp 66.0–66.5°; ir 3605 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.4; H, 8.3.

1-(2,4-Dimethylphenyl)-2-phenylcyclopentene (VI) was formed when 20 g (0.075 mol) of carbinol V was heated under reflux in 500 ml of 98% formic acid for 11 hr. After dilution with water, extraction with chloroform, washing with saturated $NaHCO_3$ solution, and drying, distillation under vacuum gave 17 g (91%) of VI as a clear, viscous liquid: bp 130° (0.25 mm); $n^{28}D$ 1.5980; uv max 265 nm (ϵ 15,750); ir 1445, 700 cm^{-1}; nmr τ 3.0 (s, 5), 3.10 (s, 3), 7.25 (m, 4), 7.76 (s, 3), 8.03 (s, superimposed on multiplet, total area 5).

Anal. Calcd for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 91.8; H, 8.1.

Oxidation of 1-(2,4-Dimethylphenyl)-2-phenylcyclopentene (VI). 1-(2,4-Dimethylphenyl)-5-phenylpentane-1,5-dione.—Potassium permanganate (28 ml of 0.4% aqueous solution) was added dropwise over 40 hr to 0.5 g of cyclopentene VI, 2.89 g of sodium metaperiodate, 0.48 g of potassium carbonate, and 5 ml of water in 60 ml of *tert*-butyl alcohol. Dilution with water, extraction with ether, and removal of the ether left an oil which was subjected to vpc (5-ft column, 265°). In addition to 34% of recovered starting material and 25% of an unidentified fraction, there was obtained 41% of the dione (as a third fraction), a yellow oil which crystallized from ethanol. The dione had mp 72–73°; ir 1680, 1480, 1240, 885, 685 cm^{-1}; nmr τ 2.1 (m, 2), 2.6 (m, 3), 3.1 (m, 2), 7.1 (m, 4), 7.7–8.2 (multiplet punctuated by two sharp peaks, 8).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.1; H, 7.4.

***cis*-1-(2,4-Dimethylphenyl)-2-phenylcyclopentane (*cis*-VII).**—Hydrogenation of the olefin (8.0 g, 0.032 mol) in 250 ml of ethanol was carried out for 6 hr at room temperature in the presence of 1.0 g of 5% Pd on carbon with a H_2 pressure of 300 psi. After filtration through a Celite pad and removal of the solvent under vacuum, distillation gave 6 g (74%) of clear oil, bp 154–157° (1.3 mm), which crystallized on cooling. Recrystallization from ethanol gave *cis*-VII (40% yield) as white needles: mp 63–63.5°; uv max 279 nm (ϵ 418), 270 (528), 262 (469); ir 3080, 1600, 1452 cm^{-1}; nmr τ 3.08 (m, 3), 3.37 (m, 5), 6.57 (m, 2), 7.83 (s), 8.01 (s), the last two peaks superimposed on a multiplet (total area 12); mass spectrum (rel intensity) *m/e* 250 (100), 159 (92), 146 (23), 145 (66), 144 (28), 133 (28), 132 (51), 131 (64), 129 (31), 120 (23), 119 (75), 117 (49), 115 (35), 106 (34), 105 (23), 91 (54).

Anal. Calcd for $C_{19}H_{22}$: C, 91.1; H, 8.9. Found: C, 90.9; H, 8.8.

(2,4-Dimethylphenyl)phenylmethylenecyclobutane (VIII).—Dehydration of 8.0 g (0.03 mol) of carbinol V with 0.2 g (0.8 mmol) of iodine in 300 ml of benzene was accomplished by heating under reflux (argon atmosphere) for 7 hr in apparatus equipped with a Dean–Stark water separator. After removal of the iodine by extraction with aqueous sodium thiosulfate, washing with water, drying, and removal of the solvent under vacuum, there resulted an orange oil which after two crystallizations from ethanol gave 6.1 g (82%) of the cyclobutane VIII: mp 39.2–40.0°; ir 3084, 3058, 3020, 2980, 2952, 2920, 2864, 2820, 1655 (w), 1415 cm^{-1}; uv max 272 nm (ϵ 12,400, sh), 261 (18,600), 257 (18,400), 247 (15,500), sh).

Anal. Calcd for $C_{19}H_{20}$: C, 91.9; H, 8.1. Found: C, 92.0; H, 8.2.

***trans*-1-(2,4-Dimethylphenyl)-2-phenylcyclopentane (*trans*-VII).**—Isomerization of *cis*-VII (0.51 g, 2.04 mol) was carried out by heating it for 12 hr at 95–100° under argon with a solution of 1.05 g (9.38 mmol) of potassium *tert*-butoxide in 35 ml of dry dimethyl sulfoxide. The solution was poured into water and extracted with benzene, and *trans*-VII was separated by chromatography on silica gel (ligroin eluent) of the oil remaining after distillation of the benzene. Analysis by glc (Chromosorb W–Apiezon L, 252°) showed only two peaks corresponding to the starting material and a single product. Distillation at 0.1 mm gave *trans*-VII as a colorless oil: uv max 279 nm (ϵ 528), 271 (681), 264 (573); ir 3080, 2950, 1600, 1450 cm^{-1}; nmr τ 2.82–3.29 (m, 8), 6.86 (m, 2), 7.80 (s), 8.08 (s), the last two sin-

(21) E. von Rudloff, *Can. J. Chem.*, **34**, 1413 (1956).

glets superimposed on broad absorption, the total area being 12.

Anal. Calcd for $C_{19}H_{22}$: C, 91.1; H, 8.9. Found: C, 90.7; H, 8.8.

Cyclobutylmesitylphenylmethane (IX) was prepared by hydrogenation of 11.5 g (4.4 mmol) of the methylenecyclobutene IV in 250 ml of absolute ethanol over 1 g of 5% Pd on carbon for 24 hr at 300 psi. After filtration through a Celite pad and removal of the solvent, there was formed a clear oil which slowly crystallized. Recrystallization from ethanol gave 9.8 g (83%) of IX as white needles: mp 57.5–58°; uv max 245 (ϵ 370), 253 (490), 264 (581), 271 (535), 276 (280), 280 (185); ir 1445, 850, 710, 690 cm^{-1}; nmr 2.92 (s, 5), 3.30 (s, 2), 5.45 (d, 1, J = 9.9 Hz), 6.16 (m, 1), 7.25-8.6 (broadened multiplet with a sharp singlet at τ 7.7, total area 15); mass spectrum (rel intensity) m/e 264 (31), 209 (100), 165.5 (ms).

Anal. Calcd for $C_{20}H_{24}$: C, 90.9; H, 9.2. Found: C, 90.7; H, 9.4.

Bromomesitylcyclobutylphenylmethane (X) was prepared by treatment of 2.0 g (7.6 mmol) of hydrocarbon IX with 0.5 ml (9 mmol) of bromine in 75 ml of glacial acetic acid for 6 hr in the dark at ambient temperature. Addition of water, extraction with ether, washing with saturated Na_2CO_3 solution, drying over $MgSO_4$, and distillation of the ether left a clear oil which crystallized from ethanol to give 2.4 g (89%) of X as fine white needles: mp 73°; nmr 2.95 (d, 5), 3.16 (s, 1), 5.42 (d, 1), 6.75 (m, 1), 7.1–8.6 (broad multiplet punctuated by a sharp singlet at 7.68, total area 15); mass spectrum (rel intensity) m/e 344 (32), 342 (32), 289 (100), 287 (100), 243 (ms), 241 (ms).

Anal. Calcd for $C_{20}H_{23}Br$: C, 70.0; H, 6.8; Br, 23.3. Found: C, 69.8; H, 6.6; Br, 23.3.

1-Mesityl-1-phenyl-2,2-dimethylethylene.—To mesitylmagnesium bromide prepared from 30.0 g (0.15 mol) of mesityl bromide and 4.1 g (0.17 g-atom) of magnesium turnings in 350 ml of dry tetrahydrofuran was added 18.2 g (0.12 mol) of isobutyrophenone. After 15 hr under reflux, the solution was acidified with cold saturated aqueous ammonium chloride and extracted with ether, the ether solution separated and dried, the ether removed on a rotary evaporator, and the residue distilled to give a yellow oil, bp 131.5–154° (0.12 mm). Chromatography on silica gel (elution with benzene–petroleum ether) followed by recrystallization from absolute ethanol gave 2.2 g (7.1%) of the desired diarylethylene as colorless prisms: mp 61–62°; uv max 242.5 (ϵ 13,500); ir 1610 cm^{-1} (C=C); nmr τ 2.94 (s, 5), 3.26 (s, 2), 7.79 (s, 3), 7.91 (s, 6), 8.04 (s, 3), 8.47 (s, 3).

Anal. Calcd for $C_{19}H_{22}$: C, 91.1; H, 8.9. Found: C, 91.3; H, 9.0.

Isopropylmesitylphenylmethane (XI).—Hydrogenation of 1-mesityl-1-phenyl-2,2-dimethylethylene (2.07 g, 8.7 mmol) in 80 ml of absolute ethanol was carried out for 160 hr at 600 psi over 1.0 g of 5% Pd on carbon at ambient temperature. After filtration through a Celite pad, removal of the solvent, and distillation, there was obtained 1.3 g (64%) of colorless oil, bp 98.5–100.5°. Preparative glc through a column packed with 20% Apiezon L on Chromosorb W (230°) removed two minor components and gave XI as the major fraction: ir no absorption at 1610 cm^{-1}; nmr τ 2.87 (s, 5), 3.35 (s, 2), 5.90 (d, 1, J = 10.5 Hz), 7.26 (m, 1), 7.81 (s, 9), 8.80 (d, 3, J = 6.5 Hz), 9.26 (d, 3, J = 6.5 Hz).

Anal. Calcd for $C_{19}H_{24}$: C, 90.4; H, 9.6. Found: C, 90.1, 89.9; H, 9.5, 9.5.

Dimethyl β,β'-Dimesityladipate (XII).—β,β'-Dimesityladipic acid[22] (25 g, 0.21 mol) was reduced in 300 ml of dimethylformamide containing 65 ml of 28% aqueous sulfuric acid at 20° at a mercury electrode with a current density of 0.03 A/cm^2 for 1.25 hr following a procedure analogous to that previously described[23] for the reduction of cinnamic acid.

The yellow catholyte, after decantation from the mercury, was poured into 1.5 l. of cold water, and the flocculent precipitate was filtered and washed with benzene and ether to leave a pasty white solid. Recrystallization from isopropyl alcohol gave 3.36 g (13.5%) of white crystals of acid (XIII): mp 297–299°; ir (KBr disk) 1710, 852 cm^{-1}; nmr (DMSO-d_6) τ 3.18 (s, 4), 5.76 (m, 2), 7.5 (d, broadened, 14), 7.83 (s, 5); nmr (pyridine) τ 5.20 (m, 2), 6.5–7.1 (m, 2), 7.21 (d, 15), 7.89 (s, 6); mass spectrum m/e 382.

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.4; H, 7.9. Found: C, 74.5; H, 8.0.

(22) N. Thomas and R. C. Fuson, *J. Org. Chem.*, **18**, 1762 (1953).

(23) C. L. Wilson and K. B. Wilson, *Trans. Electrochem. Soc.*, **84**, 153 (1943).

The acid XIII (0.295 g, 0.785 mmol) was heated under reflux for 12 hr with 35 ml of anhydrous methanol saturated with HCl. Removal of the solvent under vacuum gave 0.205 (65%) of white needles, which after recrystallization from methanol gave XII: mp 140–141°; ir ($CHCl_3$) 1725, 1165, 855 cm^{-1}; nmr ($CDCl_3$) τ 3.16 (s, 4), 5.60 (m, 2), 6.70 (s, 6), 7.15 (m, 1), 7.45 (d, 15), 7.79 (s, 6).

Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.1; H, 8.4. Found: C, 75.7; H, 8.5.

Dehydration of Cyclobutyldiphenylcarbinol. A. With Iodine.—The reaction carried out according to the directions of Graham and Williams[18] gave a 76% yield of diphenylmethylenecyclobutane in agreement with their work. The physical properties of the product are reported in Table II to permit ready comparison with those of the isomeric substance 1,2-diphenylcyclopentene.

TABLE II

COMPARISON OF THE PHYSICAL AND SPECTRAL PROPERTIES OF DIPHENYLMETHYLENECYCLOBUTANE AND 1,2-DIPHENYLCYCLOPENTENE AND THEIR DERIVATIVES

Property obsd	Diphenylmethylene-cyclobutane	1,2-Diphenylcyclo-pentane
Mp,[a] °C	57.0–57.5 (lit.[b] 57–58)	59.5–60.5 (lit.[b,c] 59, 62.5–63)
Uv, nm (ϵ)	max 257 (15,600) [lit.[d] max 257 (17,000)]	max 274 (11,300)
Ir	3085, 3060, 3028, 2985 2955, 2915, 2828 (w), 1650 (w), 1598, 1415 cm^{-1}	3085, 3060, 3028 (d), 2955, 2892 (sh), 2870, 2845, 1600 cm^{-1}
Nmr, τ	2.88 (s, 10), 7.10 (t, 4.0, J = 7.8 Hz), 8.01 (q, 2.0, J = 7.8 Hz)	2.93 (s, 10.3), 7.12 (t, 4.0, J = 7.3 Hz), 8.01 (q, 2.0, J = 7.3 Hz)
Mass spectrum (rel intensity), m/e	220 (100), 219 (20.2), 205, 53.9), 192 (46.6), 191 (56), 165 (20.2), 129 (32.6), 91 (20.7)	220 (100), 219 (24.8), 205 (14), 192 (6.2), 191 (8.8), 165 (4.6), 129 (16.8), 91 (16.4)
Mp of oxidation products, °C	48,[e] 87.5–89.5[f]	65–66[g]

[a] A 50:50 mixture of diphenylmethylenecyclobutane and 1,2-diphenylcyclopentene showed a 12° depression. [b] Reference 18. [c] Reference 5. [d] K. V. Scherer, Jr., and R. S. Lunt III, *J. Org. Chem.*, **26**, 5183 (1961). [e] Benzophenone, ref 7. [f] 2,2-Diphenylcyclopentanone: N. R. Easton and S. J. Nelson, *J. Amer. Chem. Soc.*, **75**, 640 (1953). [g] 1,5-Diphenylpentane-1,5-dione, ref 2, 3.

B. With Formic Acid.—Formic acid dehydration carried out following the directions of Criegee, Kerckow, and Zinke[6] gave 1,2-diphenylcyclopentene as reported by them. The physical and spectral properties are reported in Table II.

C. With Oxalic Acid.—Cyclobutyldiphenylcarbinol (4.0 g, 0.017 mol) which had been ground with 16 g (0.178 mol) of oxalic acid dihydrate was heated for 4 hr at 160° under argon in equipment which permitted distillation of volatile products. Addition of ether and extraction with dilute aqueous sodium hydroxide solution gave after evaporation of the ether an oil which solidified on standing. Since the component olefins were shown not to be readily separated by glc under the conditions attempted, the mixture was oxidized by the prodedure of von Rudloff;[24] 300 mg (1.4 mmol) of the olefin mixture was treated with 1.2 g (5.9 mmol) of sodium periodate, 0.23 g (1.4 mmol) of potassium permanganate, and 0.21 g (1.5 mmol) of potassium carbonate in 300 ml of 31% aqueous *tert*-butyl alcohol for 50 hr. After dilution with water, extraction with ether, and drying and evaporation of the ether, the mixture of oxidation products was analyzed with glc on a column of 10% SF-96 on Chromosorb W (268°). There was found to be 53% 1,5-diphenylpropane-1,3-dione and 47% benzophenone. When the same procedure was applied to a mixture of diphenylmethylenecyclobutane and 1,2-diphenylcyclopentene (1:1), the analysis gave 52% pentanedione and

(24) E. von Rudloff, *Can. J. Chem.*, **34**, 1413 (1956).

48% benzophenone. Oxidation of authentic diphenylmethylenecyclobutane and glc analysis by this procedure gave peaks with the retention time of benzophenone (2.97 min) and 1,5-diphenylpentane-1,5-dione (27 min) with areas which when standardized with known mixtures of the ketones showed the presence of 99.3% benzophenone and 0.7% diphenylpentanedione (seeding with benzophenone induced cyrstallization of the oily product) with a yield of 78%. A similar procedure applied to 1,2-diphenylcyclopentene gave a 48% yield of crystalline 1,5-diphenylpentane-1,5-dione, mp 65.2–66° (compare Table II), shown by glc to be free from benzophenone.

Preparation and Dehydration of Cyclobutyl(9-anthryl)phenyl carbinol (XIV). (9-Anthryl)phenylmethylenecyclobutane (XV).—To a 9-anthryllithium solution prepared from 5.14 g (0.02 mol) of 9-bromoanthracene and 14 ml of 1.6 *M* *n*-butyllithium (hexane) in 350 ml of diethyl ether freshly distilled from $LiAlH_4$ was added 3.2 g (0.02 mol) of cyclobutyl phenyl ketone. After 1 hr the solution was poured into cold water and extracted with ether, the ether layer was separated and dried and the ether evaporated, and the resulting brown semisolid chromatographed on neutral alumina (1:1 benzene–hexane eluent). The third fraction was carbinol XIV obtained as a yellow oil which crystallized from 1:4 benzene–hexane to give 3 g (45%) of cream-colored crystals: mp 172–173°; ir 3590, 1438, 878, 689 cm^{-1}.

Treatment of the carbinol XIV (2.0 g, 5.9 mol) with 0.1 g (0.39 mmol) of I_2 in 50 ml of benzene under reflux for 16 hr gave, after washing the solution with sodium thiosulfate solution, washing, drying, treatment with decolorizing charcoal, removal of the solvent, and three recrystallizations from 2-propanol–benzene, 1.6 g (85%) of pale yellow needles of the methylenecyclobutane XV: mp 171.5–172.5°; ir 3080, 3055, 3030, 2980, 2955, 2910, 2820, 1650 (w), 1594, 1412 cm^{-1}. The same product was obtained in 71% yield by heating the carbinol XIV for 16 hr in 250 ml of 98% formic acid under reflux. Recrystallization from ethanol gave XV: mp 174–175°; uv max 258 nm (ϵ 220,000), 349 (5350), 367 (10,700); nmr τ 1.75 (s, 0.8), 2.1 (m, 3.9), 2.75 (m, 3.9), 2.91 (s, 5.2), 6.65 (t, 1.9), and 7.82 (m, 4.2).

Anal. Calcd for $C_{25}H_{20}$: C, 93.7; H, 6.3. Found: C, 93.7; H, 6.3.

Treatment of 2.6 g (7.68 mmol) of carbinol XIV with 25 ml of an ice-cold mixture of sulfuric and trifluoroacetic acids (1:1) for 20 min followed by pouring into ice water, extraction with chloroform, drying of the chloroform solution, removal of the solvent, and recrystallization (five times) from absolute ethanol–benzene gave 145 mg (5.9% yield) of hydrocarbon, probably XVII: mp 149–150°; uv (ethanol) max 396 nm (ϵ 8830), 375 (10,200), 356 (6700), 340 (3220), 325 (1430); nmr τ 1.85 (s, 1), 2.00–3.23 (m, 12), 5.01 (s, 1), 7.30–8.33 (m, 6); mass spectrum (rel intensity) *m/e* 320 (56), 292 (100), 291 (50), 215 (73), 28 (>250).

Anal. Calcd for $C_{25}H_{20}$: C, 93.7; H, 6.3. Found: C, 93.6; H, 6.2.

Reduction of the methylenecyclobutane XV (0.16 g, 0.5 mmol) in 80 ml of 1:1 ethanol–ethyl acetate over 0.135 g of 83% PtO_2 with H_2 at 1 atm for 1.5 hr (at which time uptake of H_2 ceased) gave after recrystallization from ethanol 0.11 g (68%) of the reduction product, probably (9,10-dihydro-9-anthryl)phenylmethylcyclobutane, as white crystals: mp 131–132°; uv max 235 nm (ϵ 60,800), 256 (14,700), 293 (6550), 305.

Anal. Calcd for $C_{25}H_{24}$: C, 92.5; H, 7.6. Found: C, 92.7; H, 7.6.

9-Bromo-2,3-dimethylanthracene.—To 6.0 g (0.029 mol) of 2,3-dimethylanthracene[25] in 400 ml of CS_2 cooled in an ice bath was added 3.0 g (0.019 mol) of bromine in 50 ml of CS_2 over a 2.5-hr period. After 1 hr under reflux the solvent was removed to give 7.7 g (93%) of bright yellow crystals of the 9-bromoanthracene: mp 117–118°; nmr τ 1.65 (d, 1), 2.10 (m, 2), 2.35 (m, 1), 2.70 (m, 3), 7.76 (d, 6).

Anal. Calcd for $C_{16}H_{13}Br$: C, 67.4; H, 4.6. Found: C, 67.4; H, 4.6.

(2,3-Dimethyl-9-anthryl)phenylmethylenecyclobutane (XVI).—9-Bromo-2,3-dimethylanthracene (2.73 g, 9.5 mmol) was converted to the carbinol by the same procedure described above for the preparation of the carbinol XIV. The dimethylanthrylcarbinol was not characterized but was heated with 250 ml of 98% formic acid under reflux for 12 hr. Chromatography of the product over neutral alumina (hexane eluent) gave a small amount of dimethylanthracene as the first fraction followed by 1.83 g (55%) of hydrocarbon XVI. Recrystallization from benzene–hexane (1:1) gave XVI as white crystals: mp 214–215°; uv max 253 nm (ϵ 8800), 261 (168,000), 342 (3480), 370 (6960); nmr ($CDCl_3$) τ 1.70 (s, 1), 2.23 (s, 2), 2.65 (m, 3), 2.85 (s, 5), 6.61 (t, 2), 7.58 (d, 6), 7.81 (m, 3).

Anal. Calcd for $C_{27}H_{24}$: C, 93.1; H, 6.9. Found: C, 93.3; H, 7.0.

Registry No.—*cis*-I, 27069-94-9; *trans*-I, 27069-95-0; II, 27067-12-5; III, 27111-60-0; IV, 27067-13-6; V, 27067-14-7; VI, 27067-15-8; *cis*-VII, 27069-96-1; *trans*-VII, 27069-97-2; VIII, 27067-16-9; IX, 27067-17-0; X, 27067-18-1; XI, 27067-19-2; XII, 27067-20-5; XIII, 27111-61-1; XIV, 27069-98-3; XV, 27069-99-4; XVI, 27070-004; XVIIa, 27070-01-5; XVIIb, 27070-12-8; 1-mesityl-1-phenyl-2,2-dimethylethylene, 27070-02-6; (9,10-dihydro-9-anthryl)phenylmethylcyclobutane, 27070-03-7; 9-bromo-2,3-dimethylanthracene, 27111-62-2; mesityldiphenylmethane, 7505-15-9; *meso*-1,2-dimethyl-1,2-bis(2,6-dimethylphenyl)ethane, 25140-35-6; (±)-1,2-dimethyl-1,2-bis(2,6-dimethylphenyl)-ethane, 25248-75-3; 9-mesitylfluorene, 18153-40-7; tri(2,6-dimethoxyphenyl)methane, 20460-09-7; 2,6-dichlorobenzal chloride, 81-19-6; 1-(2,4-dimethylphenyl)-5-phenylpentane-1,5-dione, 27070-11-7.

(25) E. de B. Barnett and F. C. Marrison, *Ber.*, **64**, 535 (1931).

Isotopic Evidence for an Aryl-Group Migration during Chromic Acid Oxidation of 1,1-Di(*p*-iodophenyl)ethane

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The use of 1,1-di(*p*-iodophenyl)ethane-*2*-^{14}C allows the unequivocal assignment of the source of *p*-iodobenzoic acid obtained in the course of oxidation by means of chromic acid. At room temperature, and in acetic acid, a 11.2 molar excess of chromic acid produces 25% of oxidation with a 1,2 migration of the *p*-iodophenyl group, while the oxidative rearrangement is decreased to 17% at reflux temperatures.

In 1956 Szmant and Yoncoskie[4] reported the formation of an unexpected product, *p*-iodobenzoic acid, in addition to the expected benzophenone, during the oxidation of 1,1-di(*p*-iodophenyl)ethane and 1-*p*-iodophenyl-1-phenylethane with chromic acid. This result, plus the fact that the *p*-nitro- and *p*-cyano-substituted 1,1-diarylethanes behaved similarly while the *p*-methoxy derivative and the parent hydrocarbon did not, led to the suggestion[5] of a homolytic reaction mechanism.

Since unsubstituted benzophenone is slowly oxidized by chromic acid to benzoic acid,[6] the action of chromic acid at high concentration on *p,p'*-diiodobenzophenone was examined, and it was found that this compound is indeed degraded to *p*-iodobenzoic acid. Thus, it became highly desirable to determine unequivocally the contributions of both processes, rearrangement and oxidative degradation, to the yield of the benzoic acid in the oxidation of 1,1-di(*p*-iodophenyl)ethane. The reaction is complicated by the fact that the solvent, glacial acetic acid, is oxidized by chromic acid even in the cold. Since variable amounts of carbon dioxide are generated in this way, the stoichiometric approach is inconvenient and, therefore, ^{14}C labeling becomes the most practical way of establishing the extent of rearrangement.

The labeled reactant was synthesized by means of the Wittig reaction, followed by photochemical reduction of the 1,1-diphenylethylene, and iodination of the diphenylethane, according to Scheme I.

SCHEME I

$$(C_6H_5)_3P + {}^*CH_3I \longrightarrow (C_6H_5)_3\overset{+}{P}\overset{*}{C}H_3\bar{I} \xrightarrow{BuLi} (C_6H_5)_3P{=}{}^*CH_2$$

$$(C_6H_5)_2CO + (C_6H_5)_3P{=}{}^*CH_2 \longrightarrow (C_6H_5)_2C{=}{}^*CH_2 \xrightarrow{\bigcirc,\ I,\ h\nu}$$

$$(C_6H_5)_2CH{}^*CH_3 \xrightarrow[H_2SO_4]{Ag_2SO_4,I_2} (p\text{-}IC_6H_4)_2CH{}^*CH_3$$

The iodination was performed at the end rather than at the beginning of the synthesis due to the difficulty in preserving the iodine substituents during the reduction of the diphenylethylene. The position of the label was confirmed by degradation with potassium permanganate.

The oxidation of 1,1-di(*p*-iodophenyl)ethane-*2*-^{14}C allows one to distinguish neatly the different mechanistic possibilities. (a) Degradative oxidation of the initial oxidation product involves the destruction of one aryl group and leads to the formation of inactive benzoic acid.

$$(p\text{-}IC_6H_4)_2CH{}^*CH_3 \longrightarrow (p\text{-}IC_6H_4)_2CO \longrightarrow IC_6H_4COOH$$

(b) Oxidation with migration of an aryl group is expected to give a molar activity of the benzoic acid that is half of that of the starting material.

$$(p\text{-}IC_6H_4)_2CH{}^*CH_3 \longrightarrow IC_6H_4{}^*COOH + IC_6H_4CO_2H$$

If both processes a and b are operative, as turns out to be the case, the respective contributions of processes a and b can be easily ascertained from the molar activities of the diarylethane (m) and benzoic acid (n) according to the expression

$$\%\ \text{acid from rearrangement} = \frac{2 \times n \times 100}{m} \qquad (1)$$

In either case the benzophenone should be inactive unless there is an unlikely scrambling of the aryl groups, and, indeed, in all experiments the activity of purified benzophenone was undistinguishable from background radioactivity.

The activity of the liberated carbon dioxide was also determined and a good activity balance was established. This indicates that material losses should be attributed only to those of the benzophenone. This seems reasonable since the benzophenone yield is given after purification by recrystallization, while the isolation of *p*-iodobenzoic acid is practically quantitative because of its low solubility in water. Table I shows the results of the oxidation with a chromic acid–diarylethane molar ratio of 11.2 at both room and reflux temperatures. The stoichiometric amount of chromic acid required for either process is 3.33 mol to 1 mol of the diarylethane.

Table II reports the contributions of processes a and b to the observed yield of the iodobenzoic acid. The origin of the acid is calculated on the basis of the molar activities according to the previously given expression, and from these values, and assuming a quantitative recovery of the acid, the percentages of "normal" oxidation and that involving a migration of the aryl group rearrangement are derived. "Normal" oxidation represents oxidation according to pro-

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(4) H. H. Szmant and R. Yoncoskie, *J. Org. Chem.*, **21**, 78 (1956).

(5) H. H. Szmant and J. F. Deffner, *J. Amer. Chem. Soc.*, **81**, 958 (1959).

(6) R. Slack and W. A. Waters, *J. Chem. Soc.*, 1666 (1948).

TABLE I

OXIDATION OF 2.32 MMOL OF DI(*p*-IODOPHENYL)ETHANE OF MOLAR SPECIFIC ACTIVITY 0.1955 μCi WITH 26.0 MMOL OF CrO_3[a]

	Reflux temperature			Room temperature		
Products	Yield, mmol	Yield, %	Molar sp act., μCi/mmol	Yield, mmol	Yield, %	Molar sp act., μCi/mmol
Diiodobenzophenone	0.50	21.6	0.0000	0.80	34.5	0.000
Iodobenzoic acid	1.21	26.1[b]	0.0613	1.45	31.2[b]	0.0793

[a] Each value is an average of two determinations. [b] % yield of iodobenzoic acid based on eq 1.

TABLE II

"NORMAL" OXIDATION *vs.* OXIDATIVE REARRANGEMENT OF 1,1-DI(*p*-IODOPHENYL)ETHANE WITH CHROMIC ACID

	Acid origin, %		"Normal" oxidation, %	Oxidation with rearrangement, %
	Rearrangement	Degradation		
Reflux	63	37	83	17[a]
Room temp	81	19	75	25

[a] Example of the calculation: 0.63 (fraction of benzoic acid originating from rearrangement) × 26.1 (% yield of benzoic acid; see Table I) = 17 (% oxidation with rearrangement at reflux temperature).

cess a regardless of whether the diaryl ketone survives or is further oxidized to the benzoic acid.

As expected, the percentage of acid derived from degradation of the benzophenone is larger at the higher temperature, and it is clear that rearrangement is favored at the lower temperature.

In the "normal" oxidation process, the activity at C-2 is retained in the liberated carbon dioxide, and a further check of the contributions of the two oxidation paths can be obtained by examining the total activity of carbon dioxide collected in the form of barium carbonate. These results are shown in Table III.

TABLE III

% "NORMAL" OXIDATION BASED ON THE TOTAL ACTIVITY OF CARBON DIOXIDE

	$BaCO_3$ yield, mmol	Molar sp act., μCi/mmol	Total activity recovered as $BaCO_3$ μCi	"Normal" oxidation, %
Reflux	17.52	0.0218	0.382	84
Room temp	10.83	0.0316	0.342	75

It can be seen that the yield of carbon dioxide is much higher at the reflux temperature as a consequence of increased normal oxidation and degradation. The measure of the total activity provides values for the relative contribution of "normal" oxidation that agree well with those given in Table II that are derived from the yield of *p*-iodobenzoic acid and its specific activity.

Experimental Section

Radioactivity Determinations.—A Beckman liquid scintillation spectrometer, Model LS-II, without refrigeration, was used for counting by means of the ^{14}C plug-in module. With two exceptions, all the samples (about 10 mg) were prepared and counted under air in toluene solution containing 0.5% PPO. Efficiencies were determined by the external standard, double channel method. Methyltriphenylphosphonium iodide is insoluble in toluene and, although it can be incorporated into a dioxane-based scintillator by dissolving it first in a very small volume of methanol and then adding the scintillating solution, the samples turn intensely yellow. It was finally successfully counted in solution by using the new scintillation solvent, benzonitrile.[7] Barium carbonate was finely ground in an agate mortar and counted in 100-mg portions as a suspension in the scintillation solution already mentioned containing also 4.0% of the thixotropic agent Cab-O-Sil. The efficiency was determined by the internal standard method.

Preparation of Methyltriphenylphosphonium Iodide-^{14}C.—Triphenylphosphine, 45 g (0.172 mol), was dissolved in 250 ml of anhydrous ether in a three-necked, round-bottomed flask provided with a magnetic stirrer, a condenser, and an addition funnel. Methyl iodide, 24.4 g (0.172 mol, 0.37 mCi), was added slowly. The reaction was allowed to proceed for 96 hr. The resulting solid was filtered and recrystallized from isopropyl alcohol to give 59.3 g of the product melting at 179–181°.[8] The chemical and radiochemical yield was based on methyl iodide, 94%.

Preparation of 1,1-Diphenylethylene-2-^{14}C.—Methyltriphenylphosphonium iodide, 44.8 g (0.111 mol), plus 10.1 g (0.025 mol) of the previously labeled iodide and 500 ml of anhydrous ether were placed in a three-necked, round-bottomed flask fitter with a condenser, stirrer, nitrogen inlet, and septum cap. Butyllithium, 8.71 g (0.136 mol), as a 20% heptane solution was injected and the mixture stirred for 1 hr. Benzophenone, 24.8 g (0.136 mmol), was rapidly added under increased flow of nitrogen and the reaction continued for 24 hr. The resulting suspension was filtered and the solid washed with ether. The ether solution and washings were evaporated in a rotary evaporator; the resulting oil was distilled under reduced pressure [123–128° (3.9 mm)] to yield the 1,1-diphenylethylene-2-^{14}C. The product was redistilled [90.5° (1.0 mm)] to give 19.0 g (78%).

Preparation of 1,1-Diphenylethane-2-^{14}C.—The ethylene was reduced to the ethane photochemically.[9]

1,1-Diphenylethylene-2-^{14}C, 18.0 g (0.100 mol), 45.8 g (0.572 mol) of 1,4-cyclohexadiene, and 6.0 g (0.024 mol) of iodine were mixed and exposed to sunlight for 24 hr. Analysis of the reaction products by gas chromatography on a silicone column showed the presence of 1,4-cyclohexadiene, iodocyclohexane, 4-iodocyclohexene, 1,1-diphenylethane, and a trace of 1,1-diphenylethylene. The first three products were removed by distillation at atmospheric pressure. The 1,1-diphenylethane was distilled under reduced pressure [91–95° (0.5 mm)], yield 16.1 g (88%).

Preparation of 1,1-Di(*p*-iodophenyl)ethane-2-^{14}C.—The technique of Szmant and Yoncoskie[4] was followed with a slight modification in order to improve the yield of the diiodo derivative. A mixture of 50 ml of water, 75 ml of concentrated sulfuric acid, 23.4 g (0.075 mol) of silver sulfate, 7.1 g (0.050 mol) of anhydrous sodium sulfate, and 38.4 g (0.151 mol) of iodine was cooled with mechanical stirring to −5°. 1,1-Diphenylethane-2-^{14}C, 11.4 g (0.063 mol), was added over the period of 1 hr. The mixture was stirred for an additional 48 hr and poured over crushed ice, and, finally, filtered. Both the solution and the solid were extracted repeatedly with ether. The combined ethereal extracts were washed with 5% sodium hydroxide to eliminate the excess iodine, then with water, and dried over anhydrous calcium chloride. The clear yellowish solutions were taken to dryness and the resulting oil was kept in a desiccator for several days in order to crystallize the diiodo compound. Seeding accelerates this process. The oil was separated by decantation and the crystals were dissolved in hot heptane, treated with activated charcoal, filtered, and allowed to crystallize to give 8.5 g (31%) of colorless crystals melting at 85–86° (lit.[5] mp 87–87.5°). The overall yield based on methyl iodide was 20%. The yield can be improved considerably if the separated oil (essentially the monoiodo compound plus a trace of the diiodo compound as well as some starting material) is recycled. The product's activity was 0.365 μCi/mmol, and, since this was ample for the tracer experiments, it was diluted with 7.40 g of inactive diiodophenylethane in order to obtain an activity of 1000 dpm/mg.

(7) E. Gómez, J. Freer, and J. Castrillón, *Int. J. Appl. Radiat. Isotopes*, to be published.

(8) All melting points are uncorrected.

(9) M. K. Eberhardt, *Tetrahedron*, **23**, 3029 (1967).

Oxidation of 1,1-Di(*p*-iodophenyl)ethane-*2*-^{14}C with Potassium Permanganate.—1,1-Di(*p*-iodophenyl)ethane-*2*-^{14}C, 1.06 g (2.44 mmol), and 1.45 g (9.18 mmol) of potassium permanganate were refluxed in 50 ml of glacial acetic acid for 4 hr. Water was added to the reaction mixture and the solution was filtered. The solid was extracted with 10 ml of a 10% solution of sodium hydroxide. The extract was acidified with concentrated hydrochloric acid, but no precipitate was formed. Since *p*-iodobenzoic acid is very insoluble in water, it can be concluded that no rearrangement can be detected on oxidation of the diarylethane with potassium permanganate. The remaining solid was repeatedly washed with water, dried, and recrystallized from toluene to yield 0.927 g (87%) of *p,p'*-diiodobenzophenone, mp 229–230°. Three more recrystallizations from toluene yielded a product melting at 240–241° whose activity was undistinguishable from background showing that the label was indeed at C-2.

Oxidation of *p,p'*-Diiodobenzophenone with Chromic Acid.—*p,p'*-Diiodobenzophenone, 1.01 g (2.33 mmol), and 2.61 g (26.1 mmol) of chromic acid were refluxed for 4 hr in 25 ml of acetic acid. The products were isolated according to the procedure described in the next paragraph. *p*-Iodobenzoic acid, 0.11 g, mp 268–268, was obtained in a 19% yield (0.112 g).

General Procedure for the Oxidation of 1,1-Di(*p*-iodophenyl)ethane with Chromic Acid.—1,1-Di(*p*-iodophenyl)ethane, 1.00 g (2.30 mmol), 2.60 g (26.0 mmol) of chromic acid, and 25 ml of glacial acetic acid were placed in a three-necked, round-bottomed flask fitted with a nitrogen inlet, a condenser, and either a magnetic stirrer for reactions at room temperature or boiling stones for reactions at reflux temperature. The condenser was connected to three traps containing 50 ml of 5% sodium hydroxide in each. Pure, dry nitrogen was bubbled through the system in order to sweep the carbon dioxide into the traps. Reflux time was 4 hr, while the reactions at room temperature were allowed to run for 24 hr. After the reaction time was completed, water was added to the mixture and it was filtered. The solid was extracted three times with 10% sodium hydroxide and the mother liquor was extracted with benzene. The benzene solution was also extracted with 10% sodium hydroxide. The combined sodium hydroxide extracts were acidified to precipitate the *p*-iodobenzoic acid. The benzene solution was washed with water, dried over calcium chloride, and taken to dryness. This residue was combined with the previously mentioned solid fraction and recrystallized from toluene to yield *p,p'*-diiodobenzophenone. The yields reported are for the crude precipitated acid and for the recrystallized benzophenone. For counting, the products were recrystallized until constant activity (zero, in the case of the ketone) and melting point [240–241° for the ketone, and 268–269° for the acid (lit.[5] mp 237–238° and 268–270°, respectively)] were attained. The contents of the traps were combined, 15 g of NH_4Cl was added, and then 90 ml of a 10% solution of $BaCl_2$. The carbonate was filtered on a tared, sintered glass funnel, dried in the oven at 100°, and kept in a desiccator.

Registry No.—Chromic acid, 7738-94-5; 1,1-di(*p*-iodophenyl)ethane, 5216-55-7; 1,1-di(*p*-iodophenyl)-ethane-*2*-^{14}C, 27067-11-4.

Synthesis of 6,6-Difluoronorethindrone[1]

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Two syntheses of 6,6-difluoronorethindrone (**13**) are described, utilizing the reactions of NOF and SF_4 with steroids. The more direct approach from norethindrone (**20**) was less satisfactory than the longer route from 19-nortestosterone (**1**). Some of the chemistry of 6,6-difluoro-4-estrene-3,17-dione (**7**), a useful intermediate, is also discussed.

The enhancement of endocrine activity of steroids by fluorine substitution has been studied extensively.[2] We have recently described[3] the application of nitrosyl fluoride as a useful fluorinating agent for steroids, and, together with sulfur tetrafluoride,[3-5] it may be used in the key stages of a multistep steroid synthesis. In the present work, two synthesis of 6,6-difluoronorethindrone (**13**) are described, suitable starting materials being 19-nortestosterone (**1**) and norethindrone (**20**). The more direct route from norethindrone (Scheme III) was less satisfactory than the longer route from 19-nortestosterone (Scheme I) because the 17α-ethynyl group of **20** is sensitive both to NOF and to acidic oxidizing conditions.

The preferred synthesis (Scheme I) starts with the conversion of 19-nortestosterone to 3β,17β-dihydroxy-5-estrene-3,17-diacetate (**2**) by the procedure of Villotti, Djerassi, and Ringold.[6] This step protects the 3 and 17 positions and shifts the double bond from the 4 to the 5 position, for the introduction of 5 and 6 substituents by means of NOF and SF_4. Treatment of the Δ^5-diacetate **2** with NOF in dichloromethane[3] gave two major products in addition to unreacted starting material (Scheme II). When excess NOF was used, the major product was the 5α-fluoro-6-nitrimino steroid **17**, which was hydrolyzed to 3β,17β-dihydroxy-5α-fluoro-estran-6-one-3,17-diacetate (**3**) on hydrated alumina chromatography.[3] The second product, which is more abundant when insufficient NOF is used, is 3β,17β-dihydroxy-5α-fluoro-6-nitrosoestrane-3,17-diacetate dimer[7] (**18**). **18** was also converted to ketone **3** in 70% overall yield by allowing it to tautomerize in methanol solution to 3β,17β-dihydroxy-5α-fluoro-6-oximinoestrane-3,17-diacetate[3f] (**19**), which was then deaminated to **3** with nitrous acid. The conversion of **2** to **3**, by combining the two procedures, was 40%.

(1) Presented in part at the Fifth Middle Atlantic Regional Meeting of the American Chemical Society, Newark, Del., April 2, 1970.

(2) (a) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **76**, 1455 (1954); (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y. 1959, pp 593, 682–686; (c) C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, pp 155–177; (d) A. A. Akhrem, I. G. Reshetova, and Yu. A. Titov, *Russ. Chem. Rev.*, **34**, 926 (1965); (e) V. M. Khutoretskii, L. V. Okhlobystina, and A. A. Fainzilberg, *ibid.*, **36**, 145 (1967); (f) G. Schiemann and B. Cornils, "Chemie und Technologie Cyclischer Fluorverbindungen," Ferdinand Enke Verlag, Stuttgart, 1969, pp 114–127.

(3) (a) G. A. Boswell, Jr., *Chem. Ind. (London)*, 1929 (1965); (b) U. S. Patent 3,219,673 (1965); (c) *J. Org. Chem.*, **31**, 991 (1966); (d) U. S. Patent 3,235,571 (1967); (e) S. Andreades and G. A. Boswell, Jr., U. S. Patent 3,320,291 (1967); (f) G. A. Boswell, Jr., *J. Org. Chem.*, **33**, 3699 (1968).

(4) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960).

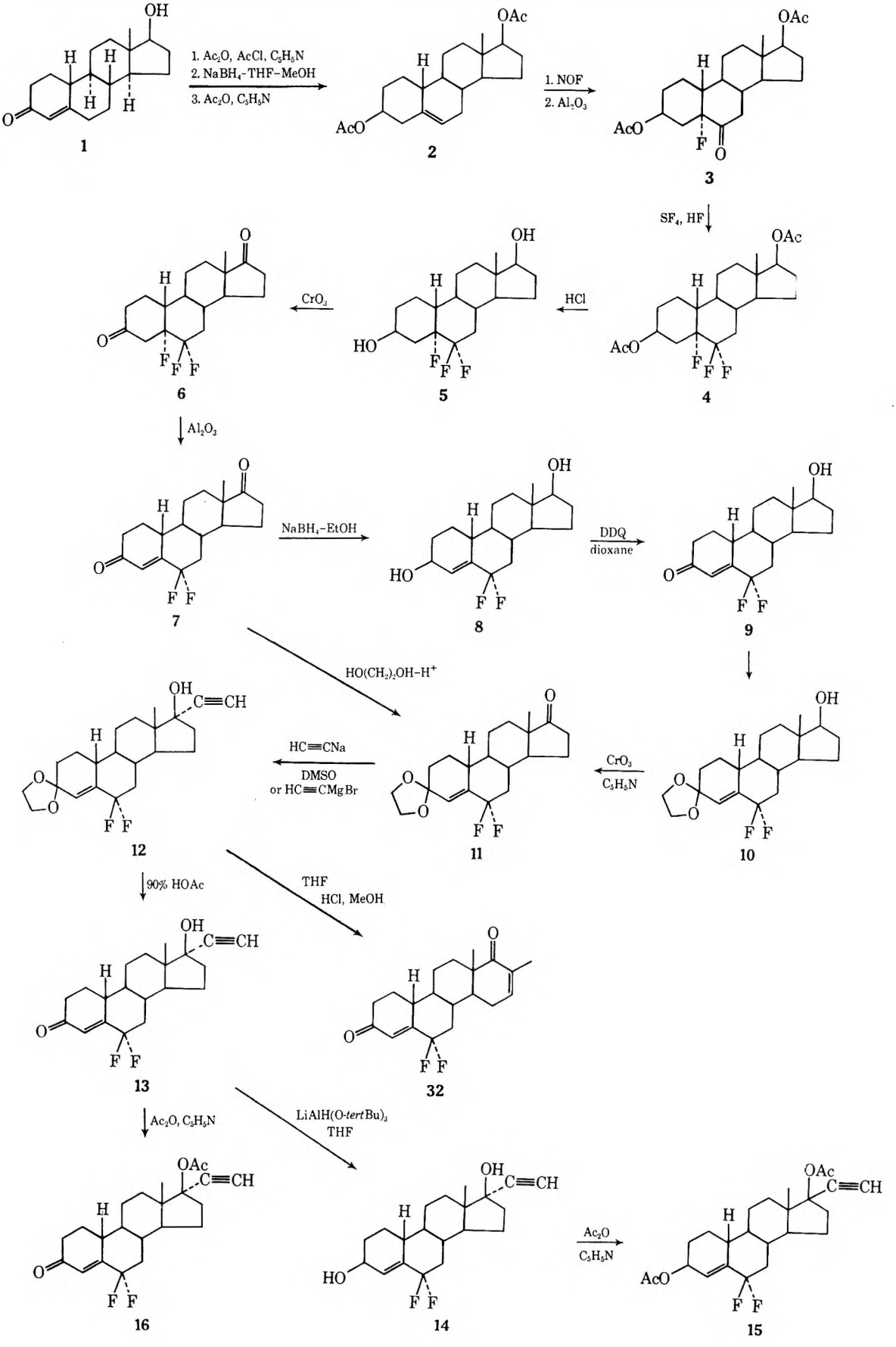
(5) (a) J. S. Tadanier and J. W. Cole, German Patent 1,183,077 (1961); (b) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962); (c) D. G. Martin and J. E. Pike, *ibid.*, **27**, 4086 (1962).

(6) R. Villotti, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 4566 (1959).

(7) In ref 3f, Table II, footnote 1, we stated that this product arose from excess NOF, but the reverse situation now appears to be true.

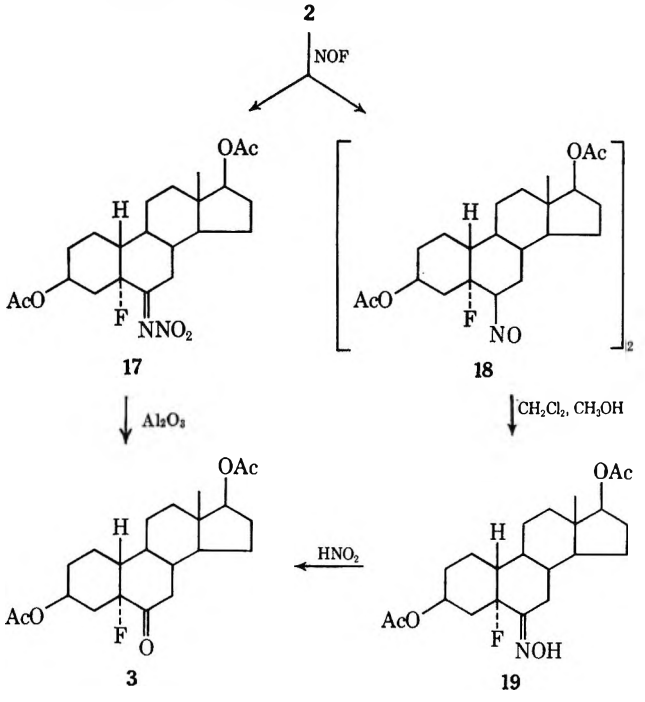
SCHEME I

SYNTHESIS OF 6,6-DIFLUORO-17α-ETHYNYL-19-NORTESTOSTERONE AND DERIVATIVES FROM 19-NORTESTOSTERONE



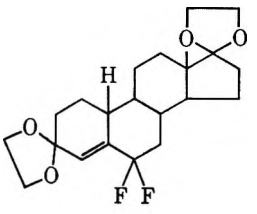
Treatment of the 5α-fluoro 6-ketone **3** with SF_4 under mild conditions[4,5] gave an 85% yield of 3β,17β-dihydroxy-5α,6,6-trifluoroestrane-3,17-diacetate (**4**). Inspection of Scheme I shows that all the necessary fluorine has been introduced into the steroid at an early stage; there are two reasons for this. These are (a)

SCHEME II
DETAILS OF THE REACTION OF NOF WITH 2



the *gem*-difluoro group in the 6 position is very stable toward hydrolysis and reduction under a variety of acidic and basic conditions, provided that there is no $\Delta^{5(10)}$ double bond; (b) because in compound **6** the 5α-fluorine substituent will be β to a carbonyl at position 3, the hydrogen atoms at position 4 are more acidic than the 10β-hydrogen atom, and the double bond produced by elimination of HF from **6** is found exclusively in the 4 position. Furthermore, the 5α-fluorine in **4** and **5** is stable to acidic conditions, so the hydrolysis of the acetate functions in **4** with methanolic HCl and the Jones oxidation[8] of the resulting diol (**5**) to the trifluorodione (**6**) can be readily carried out. The trifluorodione **6**, because of the activated methylene group with its acidic hydrogen atoms at position 4, readily underwent elimination on hydrated alumina to form the conjugated 6,6-difluoro-4-estrene-3,17-dione (**7**), an important intermediate in this synthesis. The alternative mode of elimination to form the unconjugated $\Delta^{5(10)}$ isomer (**26**) was not observed under these conditions, even though the 10β-hydrogen is in a trans-diaxial relationship to the 5α-fluorine. Treatment of the conjugated ketone **7** with a strong base such as sodium acetylide in DMSO caused isomerization to the unconjugated isomer **26**, presumably through protonation of the 3,5(10)-dienolate anion at position 4 during isolation. The stability of the geminal difluoro grouping during this isomerization is noteworthy.

The synthesis was completed by the preferential ethynylation of the 17-carbonyl group of **7**. The conjugated 3-carbonyl group was blocked as the ethylene ketal derivative. Originally, it was believed necessary to use the four-step sequence **7** → **8** → **9** → **10** → **11**, but it was subsequently shown that ketalization occurred more readily at position 3 than at position 17, with only minor amounts of the 3,17-bisketal (**25**)



25

being produced. Since the 3,17-bisketal was unaffected by the ethynylation step, was reconverted to dione **7** on acid hydrolysis, and could be separated chromatographically from the final product **13**, its presence was not a real disadvantage. Sodium borohydride reduction of dione **7** to the corresponding diol (**8**) was followed by preferential DDQ oxidation of the allylic hydroxyl in the 3 position to regenerate the Δ^4-3-ketone. 17β-Hydroxy-6,6-difluoro-4-estren-3-one (**9**) was converted to the ketal (**10**) using oxalic acid as the ketalization catalyst. The use of *p*-toluenesulfonic acid as a ketalization catalyst in this reaction causes extensive degradation of **9**. Furthermore, the normal course of *p*-toluenesulfonic acid catalyzed ketalization of a Δ^4-3-keto steroid is the formation of a Δ^5-3-ketal,[9] but the presence of the geminal difluoro group at position 6 prevents this isomerization from occurring. The formation of a steroid Δ^4-3-ketal is usually observed only with oxalic or adipic acid catalyzed ketalization.[10] A similar observation is also true for the direct conversion of **7** to **11**, oxalic acid again being the preferred catalyst. Sarett oxidation[11] of the 3-ketal 17-alcohol **10** produced 6,6-difluoro-4-estrene-3,17-dione 3-ethylene ketal (**11**).

The most satisfactory ethynylating agent was sodium acetylide in DMSO,[12] which reacted completely within 30 min. The crude ethynylated ketal (**12**) was usually hydrolyzed directly to the final product, 6,6-difluoronorethindrone (**13**), with 90% acetic acid. A pure sample of ketal **12** was prepared from **13** using the oxalic acid method. The reduction of **13** with lithium aluminum tri-*iert*-butoxy hydride gave the 3β,17β-diol (**14**), which was readily acetylated to 6,6-difluoroethynodiol diacetate (**15**). Direct acetylation of **13** gave 6,6-difluoronorethindrone acetate (**16**). Direct ethynylation of dione **7** with sodium acetylide in DMSO (Scheme IV), in addition to causing the isomerization to the unconjugated isomer **26**, described above, gave some of the 17α-ethynyl derivative, 6,6-difluoronorethynodrel (**27**). The treatment of **27** with dilute methanolic HCl caused hydrolysis of the allylic fluoride[13] to 17β-hydroxy-17α-ethynyl-5(10)-estrene-3,6-dione (**28**). Attempts to isomerize the $\Delta^{5(10)}$ isomer

(8) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951); (c) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2555 (1953); (d) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(9) (a) E. J. Salmi, *Ber.*, **71**, 1803 (1938); (b) J. W. Dean and R. G. Christiansen, *J. Org. Chem.*, **28**, 2110 (1963).

(10) J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 309 (1962).

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

(12) C. H. Robinson, N. F. Bruce, and E. P. Oliveto, *J. Org. Chem.*, **28**, 975 (1963).

(13) For a discussion of difluoromethylene groups see the following sources: (a) M. Hudlický, "Chemistry of Organic Fluorine Compounds," MacMillan, New York, N. Y., 1962 pp 203–205; (b) ref 2f, pp 184–231; (c) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 411–415.

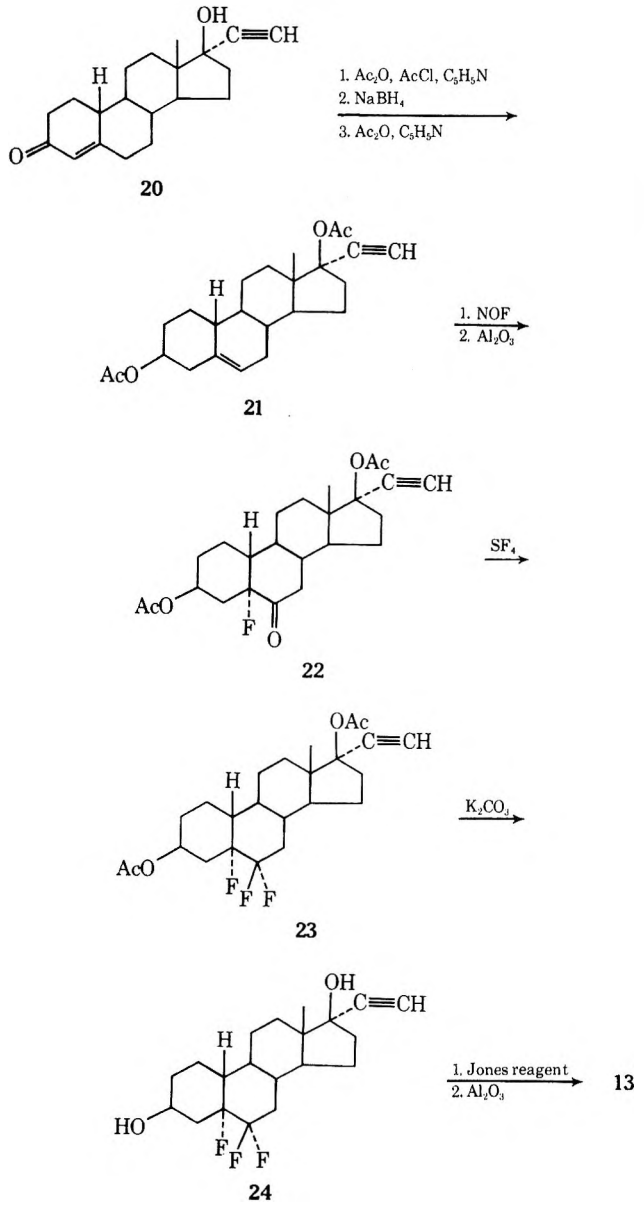
to the Δ^4 isomer fail in acidic media because of the hydrolysis of **27** to **28**, and in basic media no change is observed because the $\Delta^{5(10)}$ isomer is more stable to base than the Δ^4 isomer. A series of simple reactions can be used to convert dione **7** into some interesting 19-nor steroid derivatives, the remarkable feature of which is the stability of the Δ^4-6,6-*gem*-difluoro group to a variety of conditions, permitting a considerable amount of molecular modification once the fluorine atoms have been introduced.

An example of D homoannulation was observed during the isolation procedure in one synthesis of **13**. After ketal **11** had been treated with ethynylmagnesium bromide, hydrolysis of the Grignard complex with 5% methanolic HCl produced some 6,6-difluoronorethindrone, but the major product was 6,6-difluoro-17-methyl-4,16-*D*-homoestradiene-3,17a-dione (**32**) (Scheme I).

The second synthesis of 6,6-difluoronorethindrone (Scheme III) was more direct but less satisfactory.

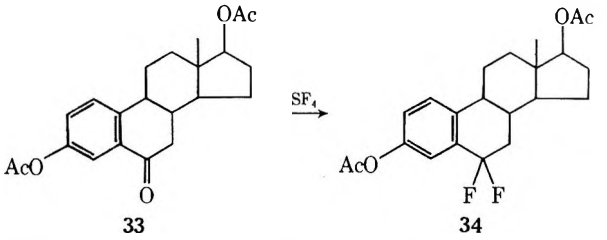
SCHEME III

SYNTHESIS OF 6,6-DIFLUORO-17α-ETHYNYL-19-NORTESTOSTERONE FROM 17α-ETHYNYL-19-NORTESTOSTERONE



Norethindrone (**20**) was converted to 3β,17β-dihydroxy-17α-ethynyl-5-estrene-3,17-diacetate (**21**) by the literature procedure,[6,14] for reasons already discussed above. The treatment of **21** with NOF is complicated not only by dimerization of the 5α-fluoro-6-nitroso steroid, but by overreaction in which the ethynyl group reacts with NOF.[3f,15] It is essential to use only slight excess of NOF if a reasonable yield of 3β,17β-dihydroxy-5α-fluoro-17α-ethynylestran-6-one-3,17-diacetate (**22**) is to be obtained by hydrated alumina chromatography of the intermediate nitrimine. Treatment of this 5α-fluoro-6-ketone **22** with SF_4 gave the trifluorodiacetate (**23**), albeit in poorer yield than in the conversion of **3** to **4**. The sequence of hydrolysis of the acetate functions to diol **24**, Jones oxidation to the corresponding ketone, and dehydrofluorination of the latter on hydrated alumina to 6,6-difluoronorethindrone (**13**), identical with that obtained by the first synthesis, is similar to that described above for Scheme I. A considerable amount of degradation occurs in the Jones oxidation of **24**, so that, while fewer steps are involved in the second synthesis, yields in at least three of the steps are poorer, and the first synthesis is the preferred one.

Finally, dehydrogenation and dehydrofluorination both occurred when dione **7** was heated to 180° in the presence of 10% palladium on carbon (Scheme IV). The major product of this reaction is 6-fluoroequilenin (**29**), accompanied by lesser amounts of the completely dehydrofluorinated products equilenin (**30**) and 3ξ-hydroxy-5,7,9,(10)-estratrien-17-one (**31**). A-Ring aromatization is thus accompanied by spontaneous dehydrofluorination in the B ring. The initially formed benzylic fluoride would be expected to be unstable under these conditions.[3,16] An attempt to prepare a steroidal benzylic fluoride was unsuccessful. Treatment of 3,17β-estradiol-6-one-3,17-diacetate[17] (**33**) with SF_4 gave a dark residue from which no identifiable



product, such as 6,6-difluoro-3,17β-estradiol-3,17-diacetate (**34**), could be isolated.

The ^{19}F nmr spectra of various 5α,6,6-trifluoro and 6,6-difluoro steroids can be fairly readily interpreted. In compounds **3**, **4**, and **5** the 5α-fluorine appears as a triplet (J = 35 Hz) near +10,000 Hz the coupling being due to the neighboring axial protons at positions 4 and 10. In compounds **7**, **8**, **13**, **14**, **24**, and **32**, the geminal difluoride substituent at position 6 appears near +6000 Hz as a pair of doublets (J = 230–250 Hz) representing the axial and equatorial fluorine atoms. In compounds **7**, **8**, and **32**, the axial fluorine can be distinguished by the further splitting. (J = 30 Hz)

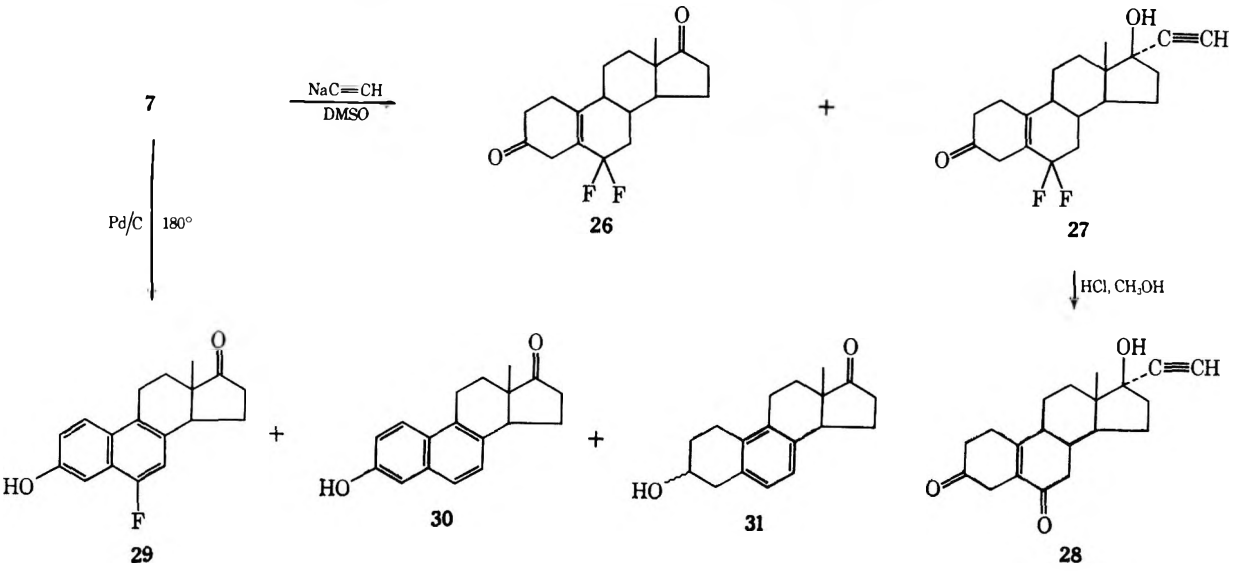
(14) (a) J. Iriarte, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 436 (1959); (b) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, and H. J. Ringold, *ibid.*, **82**, 1230 (1960).

(15) This reaction is under study and will be reported in the near future.

(16) (a) Reference 13a pp 263–277; (b) ref 13c, p 349.

(17) B. Longwell and O. Wintersteiner, *J. Biol. Chem.*, **133**, 219 (1940).

SCHEME IV
REACTIONS OF 6,6-DIFLUORO-4-ESTRENE-3,17-DIONE (7)



of its member signals by the neighboring axial proton in the 7 position.

Experimental Section[18]

3β,17β-Dihydroxy-5-estrene-3,17-diacetate (**2**) was prepared from 19-nortestosterone (**1**) (1852 g) in 44% overall yield by the procedure of Villotti, Djerassi, and Ringold.[6]

3β,17β-Dihydroxy-5α-fluoroestran-6-one-3,17-diacetate (**3**) was prepared by Boswell's procedure[3] using 60-g batches of **2** and 20 g of nitrosyl fluoride in dichloromethane solution. A total of 470 g (33%) of the fluoro ketone **3** was obtained by chromatography of the intermediate nitrimine **17**, and a further 90 g of **3** was obtained from the 5α-fluoro-6-nitroso dimer[3,19] (**18**), which accompanies the nitrimine **17**, by the following procedure.

The crude dimer **18** (50.5 g) was dissolved in CH_2Cl_2 (350 ml) and filtered. The filtrate was diluted with MeOH (150 ml) and left for 3 days at 25°. The crude fluoro oxime (**19**), obtained by evaporating the solution, was redissolved in CH_2Cl_2 (250 ml) and treated at 25° with water (200 ml), glacial HOAc (25 ml), and a solution of sodium nitrite (33.0 g) in water (100 ml). The mixture was stirred for 2.5 hr, the layers were separated, and the aqueous layer was extracted with two 100-ml portions of CH_2Cl_2. The foamy residue of crude fluoro ketone **3**, isolated by evaporation of the dried extracts, was chromatographed on Woelm neutral activity III alumina (1000 g). Successive elution with hexane, hexane–benzene (3:1), and benzene, returned fluoro ketone **3**, which was recrystallized from a mixture of acetone (65 ml) and hexane (340 ml), recovery 33.7 g (70%), identified by comparison of melting point and infrared, ultraviolet, and nmr spectra with those of fluoro ketone obtained by chromatography of the nitrimine.

3β,17β-Dihydroxy-5α,6,6-trifluoroestrane-3,17-diacetate (**4**).—A mixture of 3β,17β-dihydroxy-5α-fluoroestran-6-one-3,17-diacetate (**3**) (7.0 g), CH_2Cl_2 (75 ml), water (1.0 ml), and sulfur tetrafluoride (160 g) was shaken at 20° for 10 hr in an autoclave.[4,5] The mixture was shaken successively with water, 5% $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$ and evaporated to leave a tan solid which was recrystallized from CH_2Cl_2–hexane to give pure 3β,17β-dihydroxy-5α,6,6-trifluoroestrane-3,17-diacetate (6.15 g, 83%): mp 188–190° $[\alpha]^{23}D$ ±0° (c 1.73, $CHCl_3$); ν_{max}^{Nujol} 1730 (OAc) and 1170 cm⁻ (C–F); ^{19}F nmr δ +6330 (m) (6-F) and +10,017 Hz (t, J = 32) (5α-F); ^1H nmr δ 121 (s) (OAc) and 49 Hz (s) (18-H).

Anal. Calcd for $C_{22}H_{31}F_3O_4$: C, 63.44; H, 7.50; F, 13.69. Found: C, 63.40; H, 7.30; F, 13.28.

In larger scale runs, the crude trifluorodiacetate **4** was chromatographed on Florisil before recrystallization. The product **4** was eluted with 5–10% acetone in hexane, whereas unreacted **3** required 10–20% acetone in hexane. A total amount of 705.7 g of **3** was processed in batches to give 558.3 g (85%) of **4**.

3β,17β-Dihydroxy-5α,6,6-trifluoroestrane (**5**).—A solution of the trifluorodiacetate **4** (5.35 g) in MeOH (50 ml) and concentrated HCl (6 ml) was heated under reflux for 1 hr. The hot solution was carefully diluted with hot water and allowed to cool slowly to 25°, when long colorless needles of diol **5** appeared (4.28 g). Pure 3β,17β-dihydroxy-5α,6,6-trifluoroestrane (4.13 g, 97%) was obtained by recrystallization from acetone–hexane mixture. It had mp 170–171°; $[\alpha]^{23}D$ ±0° (c 1.04, $CHCl_3$); ν_{max}^{Nujol} 3590 cm⁻¹ (OH); ^{19}F nmr δ +6297 (m) (6-F) and +1948 Hz (t, J = 38) (5α-F); ^1H nmr ($CDCl_3$, TMS) δ 45 Hz (s) (18-H).

Anal. Calcd for $C_{18}H_{27}F_3O_2$: C, 65.20; H, 8.18; F, 17.10. Found: C, 65.06; H, 8.07; F, 16.87.

5α,6,6-Trifluoroestrane-3,17-dione (**6**).—A mixture of the trifluorodiol **5** (3.5 g) and acetone was cooled to 15° and treated with Jones reagent[8d] (3.0 ml). The excess oxidizing agent was reduced with methanol, and the product was precipitated by the addition of water. The crude product was filtered, washed with water, air-dried, and recrystallized from acetone. Pure 5α,6,6-trifluoroestrane-3,17-dione (2.35 g, 65%), large colorless cubes, had mp 178–207° dec; $[\alpha]^{24}D$ +84° (c 1.30, $CHCl_3$); ν_{max}^{Nujol} 1720 (OAc) and 1140 cm⁻¹ (C-F); ^1H nmr δ 56 Hz (s) (18-H).

Anal. Calcd for $C_{18}H_{23}F_3O_2$: C, 65.90; H, 7.06; F, 17.33. Found: C, 65.93; H, 7.08; F, 17.11.

6,6-Difluoro-4-estrene-3,17-dione (**7**).—A solution of 5α,6,6-trifluorodione **6** (2.35 g) in benzene (25 ml) was adsorbed onto Woelm neutral activity III alumina (80 g). After standing on the column for 30 min the product was eluted with benzene and recrystallized from a mixture of acetone and hexane. Pure 6,6-difluoro-4-estrene-3,17-dione formed colorless needles: mp 153.5–155.5°; $[\alpha]^{24}D$ +7° (c 1.38, $CHCl_3$); λ_{max}^{EtOH} 225 nm (ε 13,300), 298 (55), and 330 (40); ν_{max}^{Nujol} 1735 (17-CO), 1685 (3-CO) and 1170 cm⁻¹ (C-F); ^{19}F nmr δ +5146 (d, J = 251, each member split J = 30), and +6020 Hz (d, J = 251); ^1H nmr δ 379 (m) (4-H), and 57 Hz (s) (18-H).

Anal. Calcd $C_{18}H_{22}F_2O_2$: C, 70.12; H, 7.19; F, 12.32. Found: C, 69.98, 70.00; H, 7.15, 7.22; F, 12.24, 12.34.

In larger batches, a total of 705.7 g of trifluorodiacetate **4** was processed without purification of intermediates **5** and **6**, to 342 g (61%) of pure **7**.

3β,17β-Dihydroxy-6,6-difluoro-4-estrene (**8**).—A mixture of 6,6-difluoro-4-estrene-3,17-dione (1.85 g), absolute ethanol (75

(18) Melting points (uncorrected) were determined in capillary tubes in a Mel-Temp apparatus or on a Kofler block. Infrared spectra were determined on Perkin-Elmer 21 or 221 instruments, ultraviolet spectra in 1-cm solution cells on a Cary Model 14 spectrophotometer, proton nmr spectra in $CDCl_3$ *vs.* TMS on a Varian Associates A-60 instrument, and fluorine nmr spectra in $CDCl_3$ *vs.* F11 on a modified Varian Associates HR-60 instrument. Mass spectra were determined by direct injection into Consolidated CEC-103 (low-resolution) or CEC-110B (high resolution) instruments, and optical rotations were determined in 1-dm tubes on a Zeiss instrument.

(19) The molecular ion of dimer **18** is not seen in the mass spectrometer because of cleavage into monomer: calcd for $C_{22}H_{32}O_3NF$, m/e 409.2264; found, 409.2267.

ml), and sodium borohydride (0.83 g) was stirred at 25° for 22 hr. The clear solution was stirred with ice water for 2 hr, and the coloress precipitate thus obtained was filtered and recrystallized from a mixture of acetone and hexane, recovery 1.48 g (79%) of colorless crystalline 3β,17β-dihydroxy-6,6-difluoro-4-estrene (**8**): mp 90–110°; $[\alpha]^{24}D$ −32° (*c* 1.26, $CHCl_3$); ν_{max}^{Nujol} 3450, 3340, 3200 (OH), and 1165 cm^{-1} (C-F); ^{19}F nmr δ +5028 (d, J = 241, each member split J = 32), and +5990 Hz (d, J = 241); ^1H nmr δ 368 (m) (4-H) and 48 Hz (s) (18-H). Yields of 98% were recorded in subsequent batches.

Anal. Calcd for $C_{18}H_{26}F_2O_2$: C, 69.20; H, 8.39; F, 12.16. Found: C, 69.21; H, 8.78; F, 11.86.

17β-Hydroxy-6,6-difluoro-4-estren-3-one, 6,6-Difluoro-19-nortestosterone (9).—A solution of 3β,17β-dihydroxy-6,6-difluoro-4-estrene (**8**) (1.38 g), DDQ (1.38 g), and dry dioxane was stirred at 25° for 3 days. The yellow precipitate was filtered and discarded, and the filtrate was diluted with benzene and washed successively with 5% $NaHCO_3$, 5% NaOH, water, and brine. The residue left on evaporation of the dried benzene extract was chromatographed on Woelm neutral activity III alumina (50 g). The product, 6,6-difluoro-19-nortestosterone (**9**), was eluted with (1:1) hexane–benzene and recrystallized from a mixture of acetone and hexane, recovery 0.745 g (53%) of colorless crystals: mp 156–158°; $[\alpha]^{24}D$ −61° (*c* 1.31, $CHCl_3$); λ_{max}^{EtOH} 225–230 nm (ε 12,000) and 333 (40); ν_{max}^{Nujol} 3400 (OH), 1680 (3-CO) and 1160 cm^{-1} (C-F); ^1H nmr δ 379 (m) (4-H), 222 (t, J = 7) (17α-H), 134 (s) (OH), and 50 Hz (s) (18-H).

Anal. Calcd for $C_{18}H_{24}F_2O_2$: C, 69.65; H, 7.79; F, 12.24. Found: C, 69.88; H, 7.83; F, 12.65.

17β-Hydroxy-6,6-difluoro-4-estren-3-one 3-Ethylene Ketal (10).—A mixture of 6,6-difluoro-19-nortestosterone (**9**) (1.0 g), benzene (50 ml), oxalic acid dihydrate (0.5 g), and redistilled ethylene glycol (5.0 ml) was heated under reflux with a Dean–Stark trap for 1.5 hr, at which time the reaction was judged to be complete by tlc (3:1 ethyl acetate–cyclohexane; **9**, R_f 0.40; **10**, R_f 0.50) and ir (disappearance of 1680-cm^{-1} band). The benzene solution was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4,[20] and evaporated to leave the pure ketal **10** as a colorless crystalline solid (1.1 g, 96%): mp 128–130°; ν_{max}^{KBr} 3530, 3460 (OH); $[\alpha]^{25}D$ +7° (*c* 1.32, $CHCl_3$); ^1H nmr δ 361 (d, J = 4) (4-H), 240 (d, J = 2) (ketal), 219 (t, J = 8) (17α-H), and 47 Hz (s) (18-H).

Anal. Calcd for $C_{20}H_{28}F_2O_3$: C, 67.78; H, 7.96; mol wt, 354. Found: C, 67.64, 67.84; H, 7.66, 7.82; mol wt, 354.

The use of *p*-toluenesulfonic acid to catalyze the ketalization was unsatisfactory and caused extensive degradation of **9**.

6,6-Difluoro-4-estrene-3,17-dione 3-Ethylene Ketal (11). A. From 10.—Ketal **10** (2.3 g) was dissolved in pyridine, cooled to 0°, and treated with solid CrO_3[10] (2.4 g). After the mixture had been stirred at 25° for 20 hr, it was diluted with ethyl acetate (150 ml) and filtered through Celite. The filtrate was washed with water and brine, dried, and evaporated to leave 2.3 g of crude **11**: ^1H nmr ($CDCl_3$, TMS) δ 360 (d, J = 4) (4-H), 240 (m) (ketal), and 54 Hz (s) (18-H).

B. From 7.—A mixture of 6,6-difluoro-4-estrene-3,17-dione (1.0 g), redistilled ethylene glycol (2.5 ml), oxalic acid dihydrate (1.0 g), and benzene (50 ml) was heated under reflux using a Dean–Stark trap for 2 hr, the preferential ketalization of the 3-carbonyl being followed by tlc (2:1 ethyl acetate–cyclohexane; **11**, R_f 0.65; **7**, R_f 0.70) and the disappearance of the 1685 cm^{-1} carbonyl band in the ir spectrum. The benzene solution was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4, and evaporated to leave a colorless solid (1.1 g, 98%), consisting of a 6:1 mixture of the 3-monoketal **11** and 3,17-bisketal **25**: ^1H nmr δ 361 (q, J = 4) (4-H), 239 (d, J = 2) (3-ketal), 233 (d, J = 2) (17-ketal), 53 and 52 Hz (singlets) (18-H of mono- and bisketals). This material is satisfactory because the 3,17-dione **7** may be recovered by chromatography after the ethynylation step.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one 3-Ethylene Ketal (12). A. From 11.—A mixture of 6,6-difluoro-4-estrene-3,17-dione 3-ethylene ketal (33.0 g) and DMSO (400 ml) was stirred under N_2 at 25° and treated with a 20% suspension of sodium acetylide in xylene (250 ml). After 30 min, the mixture was poured into ice water, saturated with NaCl, and extracted with CH_2Cl_2. The extracts were washed with brine, dried, and evaporated to leave the crude product **12**. The same product was obtained when ketal **11** was treated with ethynylmagnesium bromide or acetylene and potassium *tert*-amylate, but the sodium acetylide method was the most convenient preparation.

B. From 13.—A pure sample of the final product 17β-hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (0.5 g) in a mixture of benzene (25 ml), oxalic acid dihydrate (0.5 g), and redistilled ethylene glycol (2.5 ml) was heated under reflux for 3 hr using a Dean–Stark trap, the progress of the reaction being followed by tlc (3:1 ethyl acetate–cyclohexane; **13**, R_f 0.57; **12**, R_f 0.62), and the disappearance of the 1680-cm^{-1} band in the ir spectrum. The benzene solution was washed with saturated $NaHCO_3$ and water, dried, and evaporated to leave the crude ketal **12** as a solid which was recrystallized from a mixture of $CHCl_3$ (5 ml), hexane (5 ml), and pyridine (1 drop). Pure ketal **12** formed colorless prisms (0.30 g): mp 170–171°; ν_{max}^{KBr} 3450 (OH) and 3310 cm^{-1} (C≡CH); $[\alpha]^{24}D$ −37° (*c* 0.65, $CHCl_3$); ^1H nmr δ 361 (d, J = 4) (4-H), 240 (d, J = 1) (ketal), 154 (s) (C≡CH), and 53 Hz (s) (18-H).

Anal. Calcd for $C_{22}H_{28}O_3F_2$: C, 69.71; H, 7.46; mol wt, 378. Found: C, 70.09; H, 7.58; mol wt, 378.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (13).—The ethynylated ketal **12** (from 33 g of **11**) was stirred with 90% acetic acid (500 ml) for 1 hr at 25°. The mixture was poured into water and extracted with chloroform. The extracts were washed with water and brine, dried over $MgSO_4$, and evaporated to leave crude **13**, two batches of which were combined and chromatographed on Woelm neutral alumina activity III (1000 g). The purified compound **13** was eluted with hexane and benzene mixtures and recrystallized from mixtures of acetone and hexane, yield 35.4 g (57% from **11**), mp 166–169°.

Pure samples of final product **13** were obtained on a small scale by preparative tlc on 2-mm silica gel plates[21] using 3:1 ethyl acetate–cyclohexane as the eluent, the product contained in the band R_f 0.50–0.70 being extracted with hot ethyl acetate; on a large scale, 10 g of **13** was dissolved in 2:1 cyclohexane–ethyl acetate and chromatographed on SilicAR CC-7 100–200 mesh silica gel[22] (400 g) using the same solvent mixture as eluent. The product (44.38 g), isolated from the early and middle fractions of several runs, was recrystallized from a mixture of cyclohexane (400 ml) and ethyl acetate (200 ml), recovery 36.99 g. The analytical sample formed colorless needles: mp 167–168°; ν_{max}^{KBr} 3475, 3265 (OH), and 1680 cm^{-1} (3-CO); λ_{max}^{EtOH} 330 nm (ε 37) and 228 (11,900); $[\alpha]^{24}D$ −113° (*c* 0.82, $CHCl_3$); ^1H nmr δ 383 (m), (4-H), 158 (s) (C≡CH), and 59 Hz (s) (18-H); ^{19}F nmr δ +5120 (d, J = 250) and +5965 Hz (d, J = 250).

Anal. Calcd for $C_{20}H_{24}F_2O_2$: C, 71.83; H, 7.23; mol wt, 334. found: C, 72.12, 71.96; H, 7.14, 7.24; mol wt, 334.

3β,17β-Dihydroxy-6,6-difluoro-17α-ethynyl-4-estrene (14).—A mixture of 17β-hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (**13**) (2.5 g), THF (100 ml), and lithium aluminum tri-*tert*-butoxide hydride (10.0 g) was stirred under N_2 at 25° for 3 days. The mixture was then stirred with 5% acetic acid (200 ml) for 4 hr at 25° and extracted continuously with chloroform. The crude diol was obtained as a colorless solid by evaporation of the dried extracts. It had ^1H nmr δ 368 (m) (4-H), 250 (m) (3α-H), 154 (s) (C≡CH), and 53 Hz (s) (18-H).

3β,17β-Dihydroxy-6,6-difluoro-17α-ethynyl-4-estrene-3,17-diacetate (15).—The crude diol **14** was acetylated by heating it in a mixture of pyridine (15 ml) and acetic anhydride (15 ml) at 100° for 20 hr. The crude product, isolated by pouring the reaction mixture into ice water followed by extraction with CH_2Cl_2, was chromatographed on Woelm neutral alumina activity III (70 g) using 2:1 hexane–benzene as the eluent. The diacetate product **15**, isolated from the early fractions, was recrystallized from hexane (5 ml), yield 1.47 g (47%). The analytical sample, obtained as colorless crystals after a further recrystallization, had mp 123–124°; ν_{max}^{KBr} 1745 cm^{-1} (OAc); $[\alpha]^{24}D$ −101° (*c* 0.37, $CHCl_3$); ^1H nmr δ 365 (m) (4-H), 157 (s) (C≡CH), 125, 123 (singlets) (3,17-OAc), and 55 Hz (s), (18-H); ^{19}F nmr δ +5131 (d, J = 230) and +6022 Hz (d, J = 230).

Anal. Calcd for $C_{24}H_{30}F_2O_4$: C, 68.55; H, 7.19; F, 9.03; mol wt, 420. Found: C, 68.79, 68.70; H, 6.80, 6.87; F, 9.10, 9.23; mol wt, 420.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one-17-acetate (16).—A mixture of 17β-hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (**13**) (4.0 g), pyridine (40 ml), and acetic anhydride

(20) $MgSO_4$ has been used to cause deketalization; *e.g.*, see J. J. Brown, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 2183 (1964).

(21) E. Merck AG, Darmstadt, Germany.

(22) Mallinckrodt Chemical Co.

(15 ml) was heated at 100° for 20 hr. The crude acetate, isolated by pouring the reaction mixture into ice water followed by dichloromethane extraction, was chromatographed on Woelm neutral alumina activity III (250 g), using 2:1 hexane–benzene as eluent. The product **16**, isolated from the middle fractions, was recrystallized from a mixture of acetone and hexane, yield 1.76 g (39%). After a further recrystallization, acetate **16** formed colorless prisms: mp 169–170°; ν_{max}^{KBr} 1745 (OAc) and 1690 cm^{-1} (3-CO); λ_{max}^{EtOH} 330 nm (ϵ 21) and 227 (9600); $[\alpha]^{24}D$ −111° (c 0.83, $CHCl_3$); ^1H nmr δ 378 (m) (4-H), 156 (s) (C≡CH), 122 (s) (17-OAc), and 55 Hz (s) (18-H).

Anal. Calcd for $C_{22}H_{26}F_2O_3$: C, 70.19; H, 6.96; mol wt, 376. Found: C, 70.91; H, 6.85; mol wt, 376.

3β,17β-Dihydroxy-17α-ethynyl-5-estrene-3,17-diacetate (**21**) was prepared in 54% yield from norethindrone (**20**) (125 g) by the literature procedure.[6,13]

3β,17β-Dihydroxy-5α-fluoro-17α-ethynylestran-6-one-3,17-diacetate (**22**) was prepared in 35% yield from 30 g of diacetate **21** according to Boswell.[3f]

3β,17β-Dihydroxy-5α,6,6-trifluoro-17α-ethynylestrane-3,17-diacetate (**23**).—A mixture of the 5α-fluoro 6-ketone **22** (1.0 g), dichloromethane (20 ml), water (0.5 ml), THF (3.5 ml), and SF_4 (46 g) was agitated at 18–22° for 10 hr in an autoclave. The organic layer was washed with water, 5% $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated to leave a residue which was chromatographed on Florisil (100 g). The trifluorodiacetate **23**, eluted with 10% acetone in hexane, was recrystallized from a mixture of acetone and hexane, yield 0.34 g (32%) of colorless crystals: mp 186.6–188.6°; ν_{max}^{Nujol} 1740 and 1210 cm^{-1} (OAc); $[\alpha]^{24}D$ −34° (c 1.48, $CHCl_3$); ^1H nmr δ 156 (s) (C≡CH), 122 (s) (OAc), and 53 Hz (s) (18-H); ^{19}F nmr δ +6339 (m) (6-F) and +10,025 Hz (m) (5α-F).

Anal. Calcd for $C_{24}H_{31}O_4F_3$: C, 65.60; H, 7.09; F, 12.95. Found: C, 65.69, 65.64; H, 7.30, 7.16; F, 13.32.

3β,17β-Dihydroxy-5α,6,6-trifluoro-17α-ethynylestrane (**24**).—A mixture of diacetate **23** (4.95 g), deaerated methanol (250 ml), anhydrous potassium carbonate (3.70 g), and deaerated water (70 ml) was stirred at 25° overnight. The product diol was precipitated with water and filtered, yield 3.56 g (88%). A pure sample was obtained by chromatography on Woelm neutral alumina activity III (75 g) using 10–20% ether in benzene as the eluent, followed by recrystallization from aqueous methanol. Compound **24** formed colorless crystals: mp 197–199°; ν_{max}^{Nujol} 3400 (OH) and 3300 cm^{-1} (C≡CH); ^1H nmr δ 154 (s) (C≡CH) and 52 Hz (s); ^{19}F nmr δ +6191 (d, J = 236), +6478 (d, J = 236) (6-F), and +9975 Hz (m) (5α-F).

Anal. Calcd for $C_{20}H_{27}F_3O_2$: C, 67.20; H, 7.60; F, 15.95. Found: C, 67.71; H, 7.82; F, 15.82, 16.00.

17β-Hydroxy-6,6-difluoro-17α-ethynyl-4-estren-3-one (**13**).—The trifluorodiol **24** (0.205 g) was oxidized with Jones' reagent,[8d] as described for compound **5**. The precipitated product (0.05 g, 23%), small colorless crystals, was taken up in benzene and passed down a column of Woelm neutral alumina, activity III, using benzene as the eluent. The product (0.04 g, 86%) was identified as **13** by comparison of melting point, infrared spectrum, and tlc behavior with those of the sample prepared by the first route.

6,6-Difluoro-5(10)-estrene-3,17-dione (**26**) and **17β-Hydroxy-6,6-difluoro-17α-ethynyl-5(10)-estren-3-one** (**27**).—A solution of 6,6-difluoro-4-estrene-3,17-dione (**7**) (1.0 g) in DMSO (20 ml) was treated under a nitrogen atmosphere with a 20% suspension of sodium acetylide in xylene (9 ml). After being stirred for 30 min at 25°, the reaction mixture was poured into ice water and extracted with dichloromethane. The dried extracts produced a residue which was chromatographed on Woelm neutral alumina activity III. Successive elution gave (a) 6,6-difluoro-5(10)-estrene-3,17-dione (**26**) (0.34 g) with 1:2 hexane–benzene and (b) 17β-hydroxy-6,6-difluoro-17α-ethynyl-5(10)-estren-3-one (**27**) (0.20 g) with benzene. Product **26** was recrystallized from hexane as a colorless solid: mp 196–197°; $\nu_{max}^{CHCl_3}$ 1740 (17-CO), 1720 (3-CO) and 1680 cm^{-1} (C=C); λ_{max} 287 nm (ϵ 140); $[\alpha]^{24}D$ +202° (c 1.30, dioxane); ^1H nmr δ 184 (m) (4-H) and 56 Hz (s) (18-H); ^{19}F nmr δ +2553 (d, J = 139) and +2815 Hz (d, J = 139).

Anal. Calcd for $C_{18}H_{22}F_2O_2$: C, 70.12; H, 7.19; F, 12.32. Found: C, 70.19; H, 7.20; F, 12.08.

Product **27** was recrystallized from hexane as colorless crystals: mp 166–168°; $\nu_{max}^{CHCl_3}$ 3600, 3400 (OH), 3300 (C≡CH), and 1720 cm^{-1} (3-CO); λ_{max}^{EtOH} 280 nm (ϵ 38); $[\alpha]^{24}D$ +109° (c 0.28, $CHCl_3$); ^1H nmr δ 182 (bm) (4-H) 156 (s) (C≡CH), 150 (s) (OH) and 54 Hz (s) (18-H).

Anal. Calcd for $C_{20}H_{24}F_2O_2$: C, 71.80; H, 7.23. Found: C, 71.99; H, 7.08.

17β-Hydroxy-17α-ethynyl-5(10)-estrene-3,6-dione (**28**).—A mixture of 17β-hydroxy-6,6-difluoro-17α-ethynyl-5(10)-estren-3-one **27** (0.10 g), methanol (100 ml), and concentrated HCl (0.5 ml) was stirred at 25° for 2 hr. The crude product, isolated by evaporation, was filtered through Florisil (25 g) using 10% acetone in hexane as eluent. Pure 3,6-dione **28** formed colorless crystals: mp 195–198°; $\nu_{max}^{CHCl_3}$ 3600 (OH), 3300 (C≡CH), 1715 (3-CO), and 1665 cm^{-1} (6-CO); λ_{max}^{EtOH} 248 nm (ϵ 9740) and 310 (90); $[\alpha]^{24}D$ −85° (c 0.33, $CHCl_3$).

Dehydrogenation–Dehydrofluorination of 6,6-Difluoro-4-estrene-3,17-dione (**7**).—A mixture of dione **7** (0.50 g) and 10% palladium on carbon (1.0 g) was sealed under N_2, and heated at 180° for 2 hr. The contents of the tube were extracted with dichloromethane (200 ml), evaporation of which left a gum (0.34 g). The principal components of this mixture were identified by high-resolution mass spectrometry as 6-fluoroequilenin (**29**) (62.5%), equilenin (**30**) (20.5%), and 3ξ-hydroxy-5,7,9(10)-estratrien-17-one (**31**) (17.0%).

6,6-Difluoro-17-methyl-4,16-*D*-homoestradiene-3,17a-dione (**32**).—6,6-Difluoro-4-estrene-3,17-dione 3-ethylene ketal (**11**) (4.0 g) was ethynylated in toluene with potassium *tert*-amylate and acetylene. The ethynylation mixture was hydrolyzed with 5% HCl in methanol (50 ml). The solvent was evaporated, and the residue was taken up in dichloromethane. The organic layer was washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated to leave a residue which was chromatographed on Woelm neutral alumina activity III (125 g). Elution with (a) hexane and benzene mixtures gave the D-homo steroid **32**, and (b) benzene gave the expected ethynyl derivative **13** (0.10 g). Recrystallization of crude **32** from a mixture of acetone and hexane gave pure compound as colorless crystals: mp 181–186°; ν_{max}^{Nujol} 1690 (3,17a-CO), and 1635 cm^{-1}, (C=C); λ_{max}^{EtOH} 237 nm (ϵ 17,300) and 317 (194); $[\alpha]^{24}D$ −104°; ^1H nmr δ 377 (m) (4, 16-H), 110 (s) (17-CH_3), and 55 Hz (s) (18-H); ^{19}F nmr δ +5150 (d, J = 251, each member split J = 30), and +6021 Hz (d, J = 251).

Anal. Calcd for $C_{20}H_{24}O_2F_2$: C, 71.83; H, 7.23. Found: C, 72.51; H, 7.54.

Registry No.—**4**, 27150-58-9; **5**, 27150-59-0; **6**, 27150-60-3; **7**, 27150-61-4; **8**, 27150-62-5; **9**, 27150-63-6; **10**, 27150-64-7; **11**, 27150-65-8; **12**, 27150-66-9; **13**, 25450-33-3; **14**, 27150-68-1; **15**, 27150-69-2; **16**, 27189-18-0; **23**, 27150-70-5; **24**, 27189-19-1; **26**, 27141-92-0; **27**, 27141-93-1; **28**, 27141-94-2; **32**, 27141-95-3.

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(23) W. H. Rooks II and R. I. Dorfman, *Contraception*, **1**, 403 (1970).

The Structure of Alstonisidine, a Novel Dimeric Indole Alkaloid from *Alstonia muelleriana* Domin

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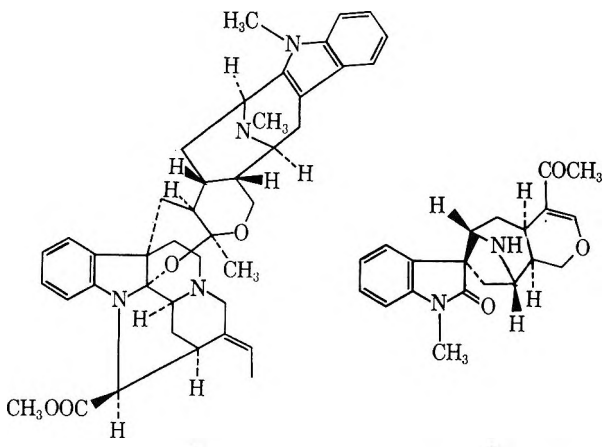
Alstonisidine, a "dimeric" indole alkaloid from the aerial bark of *Alstonia muelleriana* Domin, is assigned structure **5** on the basis of chemical reactions and spectral data. The two "monomeric" units of alstonisidine resemble macroline, **7**, and quebrachidine, **13** (stereochemistry is not assigned), and are linked in a novel manner. Possible biogenetic relationships with related alkaloids are discussed.

In their investigation of the alkaloids of the aerial bark of the Australian tree *Alstonia muelleriana* Domin, Elderfield and Gilman[2] isolated four compounds in pure form: villalstonine (**1**)[3,4] (= alkaloid B),[2a,b] alstonisine (**2**)[2c,5] (= alkaloid C),[2a,b] alstonerine (**3**),[6] and alstonisidine[2c] (= alkaloid A).[2a,b] Macralstonine (**4**)[7] has also recently been obtained.[8] We now report our work on a small sample of alstonisidine kindly made available by Professor Elderfield and propose structure **5**. This structure, while of a type not previously encountered, is in good accord with all evidence available, and is consonant with the likely biogenesis of related alkaloids.[9]



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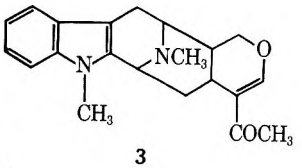

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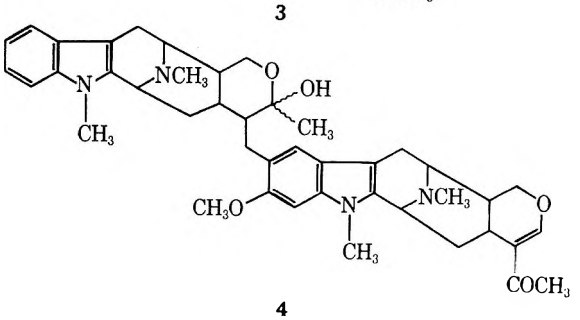

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Alstonisidine, $C_{42}H_{48}N_4O_4$, $[\alpha]D$ −234° (ethanol), shows λ_{max}^{EtOH} 230, 286, 294 nm (ϵ 41,600, 12,000, 12,100), λ_{min} 252 sh, 265 (ϵ 12,100), which is very similar to the uv spectrum of villalstonine (**1**),[4] and indicates the presence of indole and indoline chromophores. The ir spectrum lacks an N–H peak, but in dilute solution in carbon tetrachloride shows a weak, broad absorption at 3090 cm^{-1}, arising from a hydrogen-bonded alcoholic –OH group. Peaks at 1735, 1610, 1470, 1450, and 1380 cm^{-1} are assigned to carboxylic ester, indoline, indole, and C–CH_3 functions. The nmr spectrum shows a 7H multiplet centered at τ 2.95, arising from the indole and indoline groups, and indicates the absence of α or β protons on the indole nucleus.[10] The vinyl proton of an ethylidene group falls at τ 4.78 (q, J = 7 Hz), and the corresponding methyl signal at τ 8.28 (d, J = 7 Hz). A 3H singlet at τ 6.28 is assigned to an indolic NCH_3 group, and a 3H singlet at τ 6.37 to a carbomethoxy group. An aliphatic NCH_3 signal falls at τ 7.63. The highest field signal in the spectrum is a 3H singlet at τ 8.50, which is assigned to the amino-ketal quaternary methyl group of structure **5**. These assignments are similar to those for villalstonine (**1**).[4]

The high-resolution mass spectrum of alstonisidine substantiated the molecular formula obtained by microanalysis[2c] (M^+ at m/e 672.366; calcd for $C_{42}H_{48}N_4O_4$, 672.368) and, when considered in detail in combination with other data, leads to structure **5**. The base peak in the spectrum, at m/e 197.105 (calcd for $C_{13}H_{13}N_2$, 197.108), is due to the ion **6**, which is characteristic of alkaloids containing a unit derivable from macroline (**7**).[4,6,11,12] Two other characteristic fragments are also prominent: one group of peaks at m/e 182, 181, and 180 [compare, for example, villalstonine (**1**)[4]], and a peak at m/e 170.094 (calcd for $C_{12}H_{12}N$, ion **8**, 170.097). Two small peaks, at m/e 308.185 (calcd for $C_{20}H_{24}N_2O$, 308.189) and m/e 307.183 (calcd for $C_{20}H_{23}N_2O$, 307.181) correspond with two at the same values from villalstonine (**1**)[4] and macralstonidine (**9**)[12]

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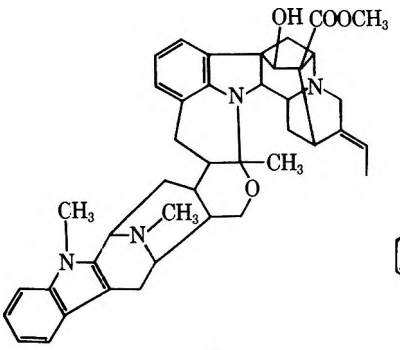
(12) E. E. Waldner, M. Hesse, W. I. Taylor, and H. Schmid, *ibid.*, **50**, 1926 (1967).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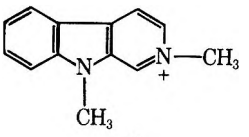
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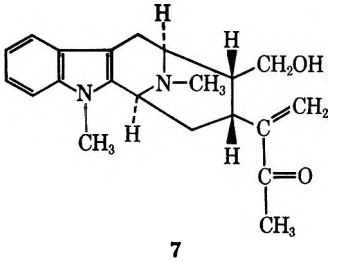
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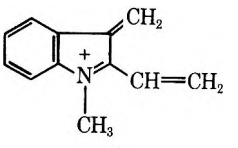
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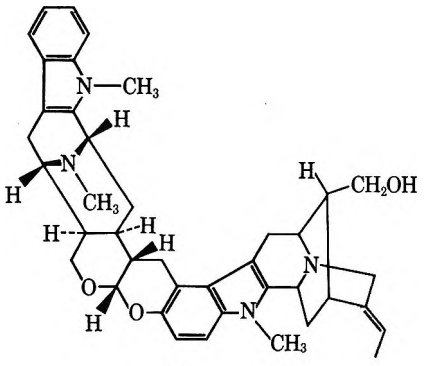
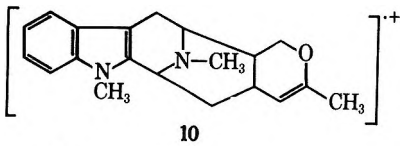

9

and are due to the fragments **10** and **11**. Fragment **10** arises by retro-Diels–Alder cleavage of alstonisidine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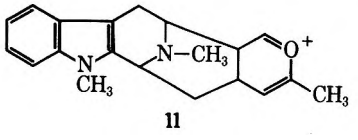
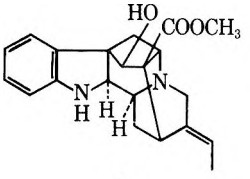

11

(**5**) (see Scheme I) and fragment **11** by loss of a hydrogen from **10** to its complementary fragment, giving the ion **12** at *m/e* 365.185 (calcd for $C_{22}H_{25}N_2O_3$, 365.187).

These data clearly prove the incorporation of an unsubstituted, ring-closed macroline unit into alstonisidine. The carbomethoxy, alcohol, and ethylidene functions are therefore associated with the indoline chromophore in the nonmacroline portion. The single quaternary C–CH_3 group of alstonisidine must, from its relatively low chemical shift, be associated with an amino-ketal or ketal function, as in villalstonine (**1**)[4] and macralstonidine (**9**).[12] At this point also, we may infer that, as in these two alkaloids, the amino-ketal or ketal function involving the quaternary C–CH_3 group forms part of the linkage between the macroline and nonmacroline portions of alstonisidine (see below).

Alstonisidine gives a mono-*O*-acetate (M^+ 714; calcd for $C_{44}H_{50}N_4O_5$, 714; ν_{max} 1740, 1735 cm^{-1}, no O–H remaining in the ir spectrum) with acetic anhydride–pyridine at 37°; this shows that, of the four oxygen atoms of the alkaloid, three are associated with the carbomethoxy and alcohol functions. That remaining is therefore the ethereal oxygen atom associated with the macroline portion and seen in the two fragment ions **10** and **11** discussed above. The quaternary C–CH_3 group must be associated with this oxygen, and hence also with a nitrogen of the nonmacroline portion, in an amino-ketal group. This is confirmed by the reduction of alstonisidine with excess lithium aluminum hydride to a triol (M^+ of triacetate at *m/e* 772; calcd for $C_{47}H_{56}N_4O_6$, 772), under conditions in which macralstonidine (**9**) is unaffected but villalstonine (**1**) gives the known villalstoninetriol.[4]

Insight into the structure of the nonmacroline portion of alstonisidine is given by the observation of a group of peaks at *m/e* 222, 221, and 220 in the mass spectrum. These are characteristic of indoline alkaloids in the ajmaline series, such as quebrachidine (**13**),[13] vincamajine (**14**),[14] and *O*-benzoylvincamajine (**15**)[15] (at *m/e* 326). These peaks represent the aliphatic portion of the indoline moiety (*m/e* 222.106, calcd for $C_{12}H_{16}NO_3$, 222.113; *m/e* 221.105, calcd for $C_{22}H_{15}NO_3$, 221.105; *m/e* 220.098, calcd for $C_{12}H_{14}NO_3$, 220.097). The $C_{12}H_{16}NO_3$ fragment has the structure **16**. The complementary fragment to **16**, which in quebrachidine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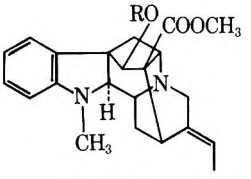
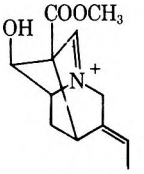
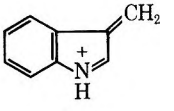

14, R = H
15, R = OCOPh


16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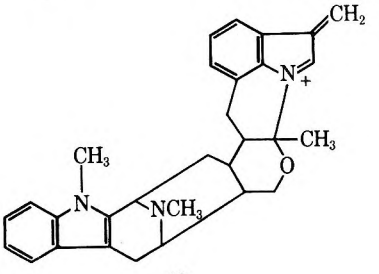
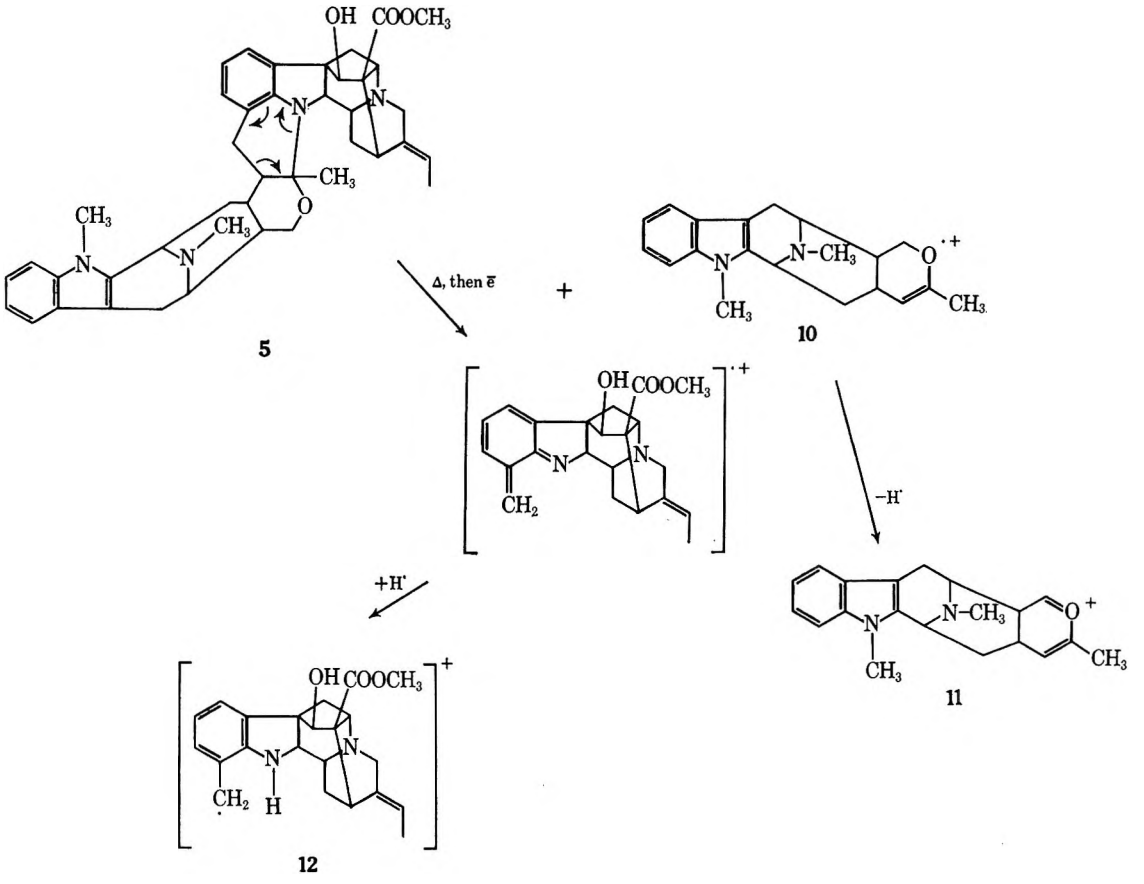

18

(13) M. Gorman, A. L. Burlingame, and K. Biemann, *Tetrahedron Lett.*, No. 1, 39 (1963).

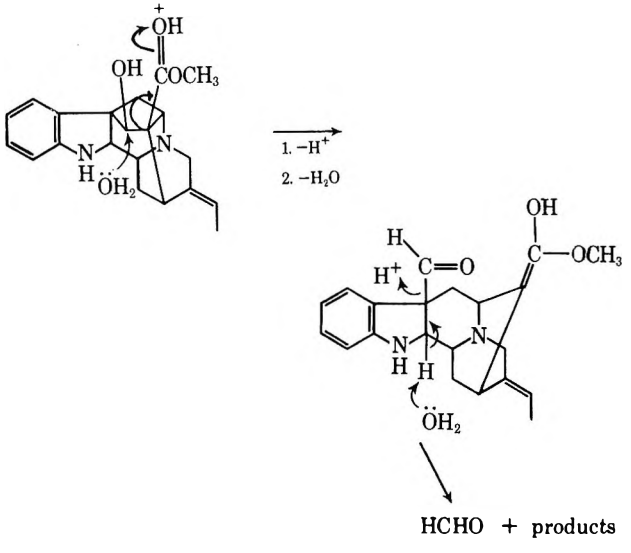
(14) M.-M. Janot, J. Le Men, J. Gosset, and J. Levy, *Bull. Soc. Chim. Fr.*, 1079 (1962); J. Trojanek and J. Hodkova, *Collect. Czech. Chem. Commun.*, **27**, 2981 (1962).

(15) B. Mukherjee, A. B. Ray, A. Chatterjee, and B. C. Das, *Chem. Ind. (London)*, 1387 (1969).

SCHEME I



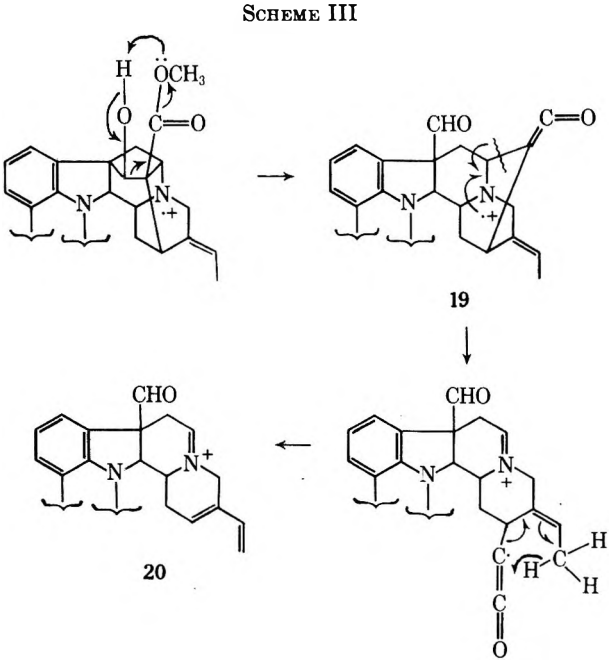
SCHEME II



is the well-known fragment **17**,[13,15,16] in the spectrum of alstonisidine falls at m/e 450.252 (calcd for $C_{30}H_{32}N_3O$, 450.254) and is assigned structure **18**.

Both alstonisidine and quebrachidine under reflux with 6 *N* HCl give formaldehyde, detected by the chromotropic acid test.[12,17] A possible mechanism for this reaction is shown in Scheme II for quebrachidine.[18] Further strong similarities between alstonisidine and quebrachidine are apparent from their mass spectra. Although alstonisidine is readily acylated (see above), there is virtually no loss of water or OH on electron impact. This is also true for quebrachidine. As well, both mass spectra show significant peaks at M − 31 and M − 32, of which the latter is the more intense. In alstonisidine, the M − 32 peak has m/e 640.342 (calcd for $C_{41}H_{44}N_4O_3$, 640.341), establishing that CH_3OH has been lost. This is in accord with adjacency of the $COOCH_3$ and OH groups. A possible mechanism is shown in Scheme III. Loss of methanol

SCHEME III



(16) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, "Alkaloids," Holden-Day, San Francisco, Calif., 1964, p 43.

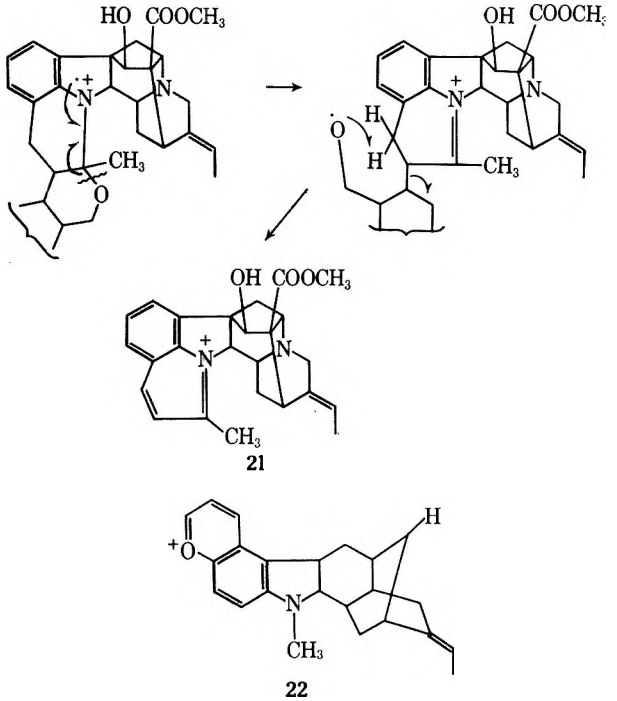
(17) F. Feigl, "Spot Tests," Elsevier, Amsterdam, 1956, p 331.

(18) Further investigations of this reaction are in progress.

from alstonisidine gives the fragment **19**, which undergoes bond cleavage as indicated. Loss of C_2HO as shown[19] gives the fragment **20**, which is seen as a small peak at *m/e* 599.342 (calcd for $C_{39}H_{43}N_4O_2$, 599.339).

Structure **5** for alstonisidine is further strongly supported by the presence of a prominent peak in the mass spectrum at *m/e* 403.202 (calcd for $C_{25}H_{27}N_2O_3$, 403.202). This peak is assigned structure **21** and its proposed origin is shown in Scheme IV. Cleavage

SCHEME IV



21

22

and bond rotation as shown, followed by further aromatization, give the relatively stable fragment **21**, which is strikingly analogous in structure and mode of formation to the ion **22** from macralstonidine **9**.[12]

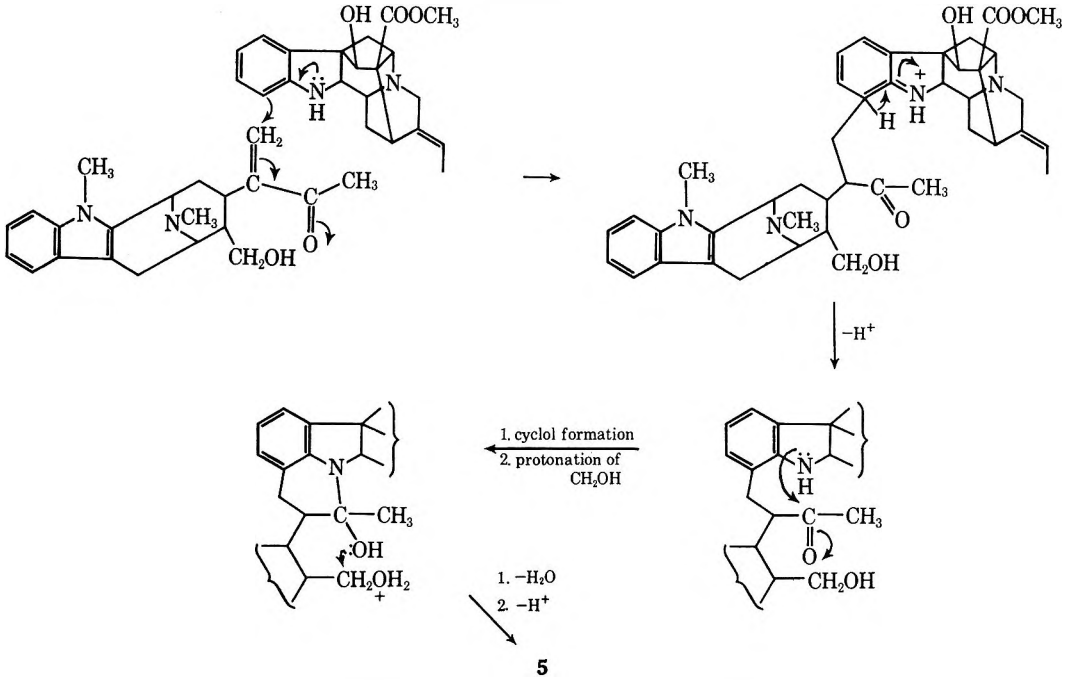
The structure **5** for alstonisidine is of considerable biogenetic interest. The work of Schmid and his coworkers[4,7,11,12] and the recent establishment of structure **3** for alstonerine[6] imply a central role for macroline **7** in the biogenesis of villalstonine (**1**),[4] macralstonine (**4**),[7] and macralstonidine (**9**).[12] Alstonisidine can be envisaged as arising (Scheme V) by electrophilic attack on the indoline aromatic ring of a quebrachidine-like species by the $CH_2{=}CC(=O)$ function of macroline (**7**). Subsequent ring closures would generate the amino-ketal function. It is noteworthy that *O*-benzoylvincamajine (**15**) has recently been obtained from the leaves of the closely related *A. macrophylla*.[15]

The stereochemistry of alstonisidine is being investigated crystallographically by Professor C. E. Nordman. Further chemical work in this area is in progress.

Experimental Section

Alstonisidine.—Alstonisidine (30 mg), obtained from Professor R. C. Elderfield, was recrystallized from methanol to give rods, mp 325° dec (uncorr). It was homogeneous on tlc,[8] and the ir spectrum was superimposable on that described by Gilman.[2a] Optical rotation and uv spectrum are also given by Gilman.[2a] The nmr data ($CDCl_3$) are given fully above. Mass spectrum was obtained by direct inlet at 325° on A.E.I. MS-902: *m/e* 674 (6.4), 673 (23), 672 (50), 658 (14), 657 (30), 641 (7), 640 (8.5), 625 (3.9), 614 (2.5), 514 (2), 484 (3.2), 470 (1), 463 (5.8), 462 (4.5), 450 (2.6), 429 (3.2), 405 (11.6), 404 (10.3), 403 (17), 370 (3.2), 307 (3.2), 269 (2.5), 268 (4.5), 267 (3.2), 239 (3.2), 238 (3.2), 237 (6.5) 235 (3.2), 223 (4.5), 222 (12.2), 221 (4.5), 220 (3.2), 210 (13), 209 (10.3), 208 (14), 199 (6.5), 198 (15.5), 197 (100), 195 (8.4), 194 (11.6), 190 (11), 184 (6.5), 183 (19.4), 182 (22.5), 181 (18.8), 180 (6.5), 171 (6.5), 170 (14.2), 168 (8.4), 167 (6.5), 158 (13), 144 (16.8). High-resolution mass spectra were obtained on a Consolidated Electrodynamics CEC High-Resolution Model 21-110.

SCHEME V



5

Detection of an Acylable OH Group in Alstonisidine.—A solution of alstonisidine (3 mg) in pyridine (0.6 ml) and acetic anhydride (0.6 ml) was held 1 hr at 37° and 12 hr at 20°. The reaction mixture was freed of solvent under reduced pressure and the

(19) *Cf.* ref 16, p 84.

residue taken up in chloroform (15 ml). This solution was extracted with 14% aqueous ammonia (1 ml), dried ($MgSO_4$), and concentrated. The product was homogeneous on tlc[8] ($R_{alstonisidine}$ 1.1): micro-ir ν^{KBr} 1740, 1735 (ester C=O), no -OH; micro-nmr τ ($CDCl_3$) new 3H singlet at τ 7.92 (CH_3COO-): mass spectrum M^+ at m/e 714.

Detection of an Amino-Ketal Group in Alstonisidine.—Lithium aluminum hydride (15 mg) was added to a solution of alstonisidine (2 mg) in tetrahydrofuran (1 ml). The mixture was heated under reflux for 8 hr, cooled, and quenched with wet tetrahydrofuran. Addition of 25% sodium hydroxide (10 ml) dissolved the inorganic precipitate, and the alkaline solution was then extracted with chloroform (10 ml). The chloroform extract was dried (K_2CO_3) and solvent removed. Tlc[8] showed no alstonisidine remaining. The product was treated with acetic anhydride (0.5 ml) and pyridine (0.5 ml) at 65° for 2 hr and at 20° for 60 hr. Solvents were removed under reduced pressure at 45°, and the residue was dissolved in chloroform. The solution was then washed with 5% ammonia and dried (K_2CO_3). Removal of solvent gave an oily residue which solidified on trituration with methanol: micro-ir ν^{KBr} 1740 cm^{-1}; M^+ 772 (calcd for $C_{47}H_{56}N_4O_6$, 772).

Treatment of macralstonidine with lithium aluminum hydride under the same conditions returned pure starting material. Villalstoninetriol was prepared by the published method.[4]

Chromotropic Acid Tests.—These were performed essentially as described for macralstonidine,[12] except that 4 mg of alstonisidine was used, and the colors were developed by adding chromotropic acid (1 mg) and 12 *N* sulfuric acid (2 ml) to 1–2-ml cuts of distillate. Blanks developed no color under these conditions, and the reaction with macralstonidine was used as a standard.

Registry No.—5, 27141-90-8; 5 monoacetate, 27248-70-0.

Acknowledgments.—We are greatly indebted to Drs. Norbert Neuss and John Occolowitz, Lilly Research Laboratories, for the indispensable high-resolution mass spectrometry, and to Gloria Cook and Mr. Forrest MacKellar for other spectral data. The MS-902 mass spectrometer at the University of Michigan was purchased with funds provided by the National Science Foundation. We gratefully acknowledge a Faculty Research Fellowship and Grant from the Horace H. Rackham School of Graduate Studies, University of Michigan (to P. W. Le Q.), and the award of a NASA Fellowship (to J. M. C.).

Preparation and Properties of Steroidal 17,20- and 20,21-Acetonides Epimeric at C-20. III. Dioxolone Derivatives of α-Hydroxy Acids[1]

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Received July 23, 1970

The common chromic anhydride–pyridine oxidation product of the 17,20α- and 17,20β-acetonido-21-ols **1a** and **1b** has been identified as the etienic acid acetonide (dioxolone) **2**. In a study of the reaction sequence involved in its formation, it was shown that the 20-methylene derivative **7** is not an intermediate, and that the 17,20-acetonido-21-aldehydes are the immediate precursors of **2**. A general method for the synthesis of dioxolones from α-hydroxy acids, using acetone–perchloric acid, was devised, and the preparation of eight examples from 17-hydroxyetianic and 20-hydroxypregnanoic acids in the 11-oxygenated Δ^4-3-keto series is described. All dioxolones are readily cleaved by dilute alkali, but are considerably more resistant to hydrolysis with 60% acetic acid at room temperature than isopropylidene derivatives of the corresponding glycols. Dioxolones from 17-hydroxyetianic and 17-deoxy- and 17-hydroxy-20-hydroxypregnanoic acids can be distinguished by their ir and nmr spectra.

We recently reported[2] that prolonged reaction of the 17,20α- and 17,20β-acetonido-21-ols **1a** and **1b** (Scheme I) with chromic anhydride in pyridine gives rise to not only the respective 21-aldehydes and 21-oic acids, but also a common neutral product with the empirical formula $C_{23}H_{30}O_5$. This substance has been identified as the etienic acid acetonide (dioxolone) **2**. In addition to presenting evidence for this structure, this paper includes a general procedure for the independent preparation of dioxolones not only from 17-hydroxyetianic acids, but also from homologous 20-hydroxypregnan-21-oic acids epimeric at C-20. Finally, some of the properties of the new derivatives will be discussed.

Structural assignment of the etiodioxolone **2** was based on the following considerations: (a) infrared spectroscopy indicated a new carbonyl band at 1782 cm^{-1} and retention of the isopropylidene group as evidenced by a characteristic doublet at 1385 and 1377 cm^{-1}; (b) its mass spectrum displayed a prominent molecular $(M)^+$ ion, m/e 386, as well as the m/e 328 ion, representing M less the elements of acetone [However, ions such as M − 15 (CH_3) and M − 15 − 60 (HOAc), which have been observed in both 17,20- and 20,21-acetonides, were not seen. Their absence is understandable in view of the greater complexity and, accordingly, lessened stability of the dioxolone ring.];[3] and (c) treatment of **2** with methanolic sodium hydroxide or methanolic hydrogen chloride gave the methyl etienate **3**.

An investigation was made of the mechanism of formation of **2** from **1a** and **1b**. A plausible sequence of reactions at C-21 would be $CH_2OH \rightarrow CHO \rightarrow COOH$, followed by decarboxylation. Subsequent oxidation of the resulting 20-methylene group to a carbonyl would afford the dioxolone **2**. Accordingly, the hypothetical 20-methylene intermediate **7** was prepared as follows. Treatment of the methyl etienate **4** with pyrrolidine in hot methanol[4] gave the crystalline 3-enamine. Its lithium aluminum hydride reduction, followed by buffered hydrolysis of the product, afforded the glycol **6** which was characterized by periodic acid oxidation to

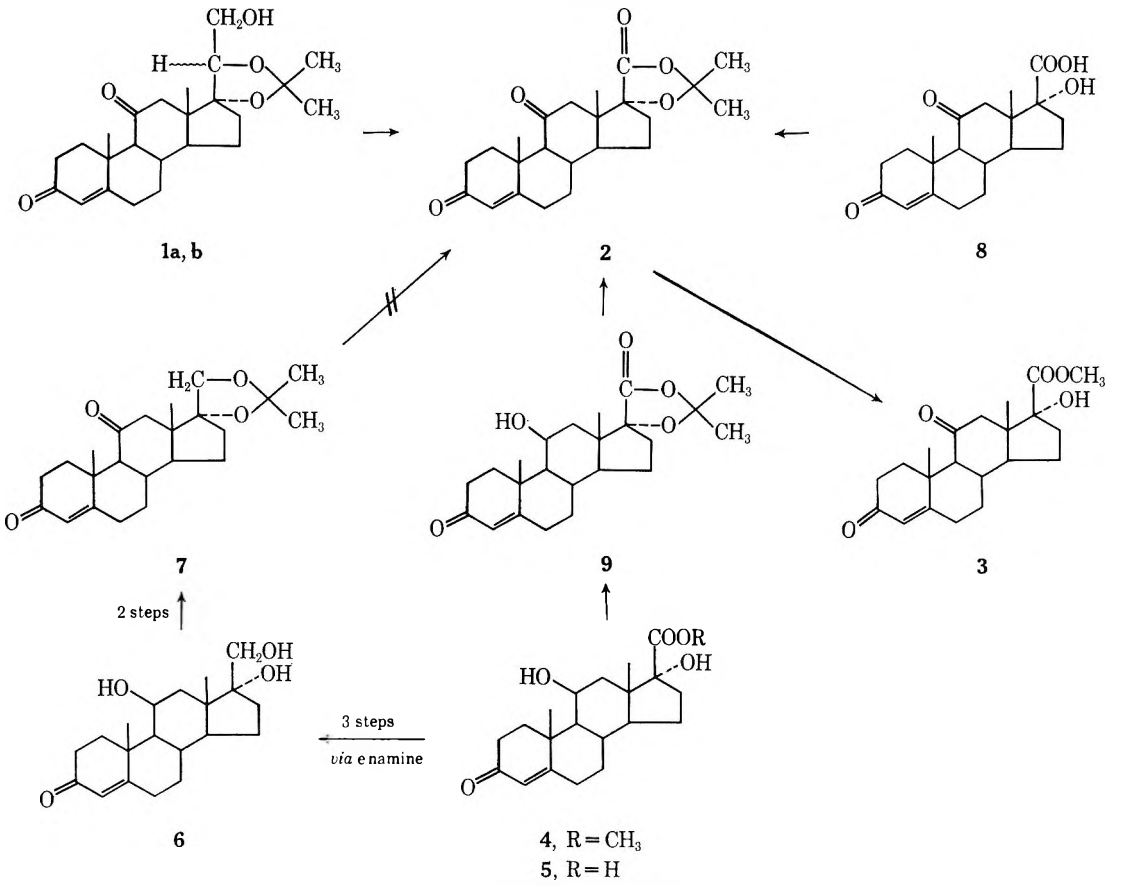
(1) This work was supported by a research grant, AM01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3513 (1969).

(3) A detailed study of the mass spectral characteristics of a number of cyclic derivatives of the steroid side chain, including acetonides and dioxolones, will be presented at a later date.

(4) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.*, **78**, 430 (1956).

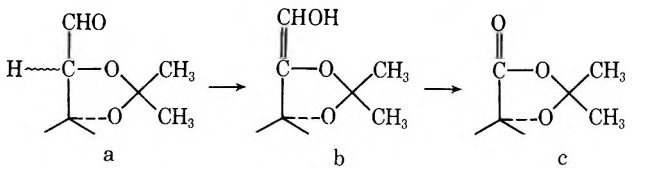
SCHEME I[a]



[a] In this and other schemes, the substituent at C-20 is α oriented in "a" compounds and β oriented in "b" compounds.

11β-hydroxyandrostenedione. To our knowledge, side-chain glycols of this type have not previously been prepared. Acetonation of **6** in the presence of *p*-toluenesulfonic acid (*p*-TSA)[5] provided an amorphous acetonide which was oxidized with chromic anhydride in pyridine to the crystalline 11-keto acetonide **7** in an overall yield of 87% from the glycol **6**. The acetonide **7** is not an intermediate in the formation of the dioxolone **2** since prolonged treatment with chromic anhydride in pyridine was without effect. A further investigation of the reaction sequence was made by the small-scale treatment with chromic anhydride–pyridine of 17,20β-acetonides with alcoholic, aldehydic, and carboxylic functions at C-21.[2] Paper chromatographic analysis of the reaction mixtures showed that only the alcohol and aldehyde can give rise to the dioxolone **2**. These results suggest that the 21-aldehyde (a, Scheme II) is the immediate precursor of the dioxolone c. In

SCHEME II



view of the relative ease of epimerization at C-20 of 17,20-acetonides with a carbonyl function at C-21,[2] the oxidative cleavage of the C-20/C-21 bond probably occurs *via* the chromate ester of the enolic form b. Such a mechanism has been proposed by Best, *et al.*, for the oxidative cleavage of cyclic ketones.[6]

The original preparation of acetonides from α-hydroxy acids was by Willstätter and Königsberger[7] who made such derivatives from glycolic, mandelic, and benzilic acids by the dropwise addition of sulfuric acid to an acetone solution at reduced temperature. Dioxolones of this type have received scant attention generally, and to our knowledge have not previously been described in the steroid field. It was therefore of interest to devise a general method for the preparation of such derivatives from steroidal α-hydroxy acids. Preliminary studies showed that *p*-TSA in acetone has no effect on 17-hydroxyetianic acids, and that reaction with 20-hydroxy-21-oic acids is slow and incomplete after 1 week at room temperature. However, conditions suitable for the acetonation of hindered 17,20-glycols, namely the use of perchloric acid as catalyst,[5] proved satisfactory. For example, treatment of the etienic acid **8** with acetone–perchloric acid for 6 hr provided in 68% yield a product identical with **2**. Similar acetonation of the 11β-hydroxyetienic acid **5** afforded the dioxolone **9** in a yield of 69%. The facile oxidation of **9** to **2** with chromic anhydride–pyridine illustrates the utility of the dioxolone ring as a protecting group in this reaction.

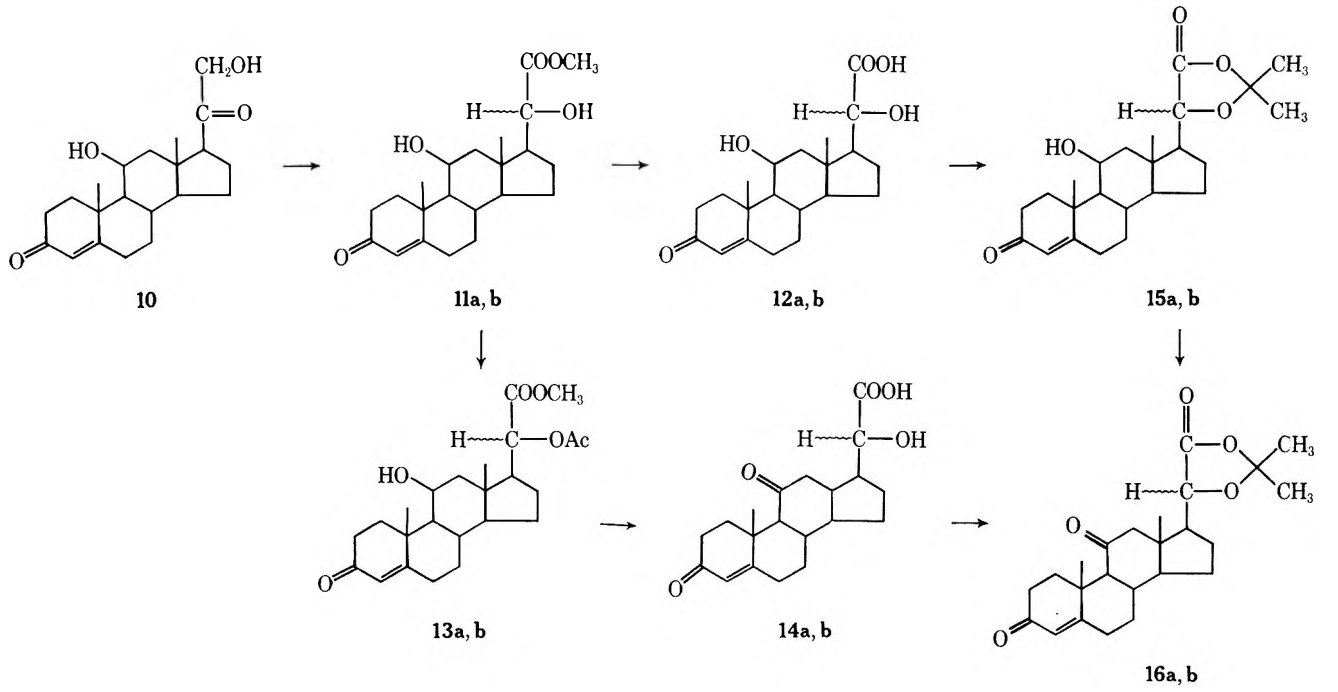
In order to obtain additional dioxolones in the 11-oxygenated Δ^4-3-keto series, the homologous C-20 epimeric acids derived from the 21-aldehydes of corticosterone and 11-dehydrocorticosterone were synthe-

(5) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).

(6) P. A. Best, J. S. Littler, and W. A. Walters, *J. Chem. Soc.*, 822 (1962).

(7) R. Willstätter and F. Königsberger, *Ber.*, **56**, 2108 (1923).

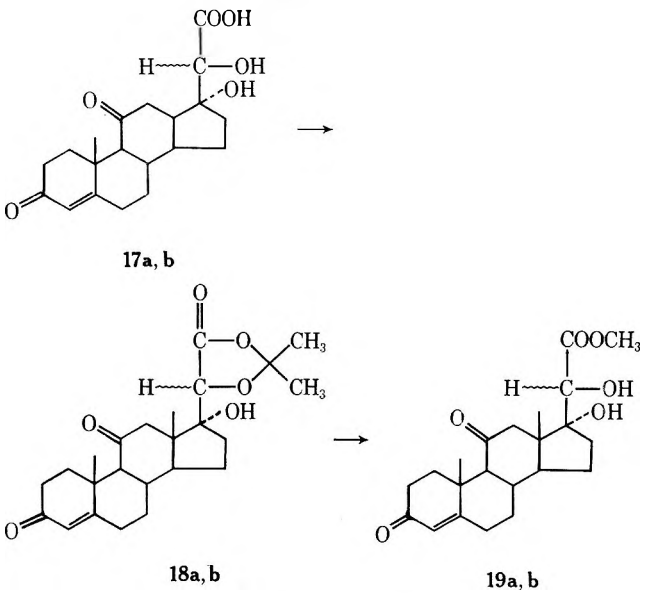
SCHEME III



sized. The glycolic acids from corticosterone (**10**, Scheme III) were prepared by rearrangement of the crude glyoxal in methanolic cupric acetate,[8] column chromatographic separation of the methyl esters **11a** and **11b**, followed by saponification to the free acids **12a** and **12b**. The glycolic acids from 11-dehydrocorticosterone were obtained by oxidation of the 11β-hydroxy methyl ester 20-acetates **13a** and **13b** with chromic anhydride–pyridine followed by saponification to the 11-keto acids **14a** and **14b**.[9] Configurational assignments at C-20 for the new glycolic acids and esters followed from their characteristic optical rotatory properties[8,10] and the identity of the oxidation product from **13b** with the known 11-keto methyl ester 20β-acetate.[10]. Acetonation of the two pairs of glycolic acids afforded the respective dioxolones **15a**, **15b**, **16a**, and **16b** in yields somewhat less than those obtained from the analogous 20,21-glycols.[5] Oxidation of the 11β-ols **15a** and **15b** with chromic anhydride–pyridine gave products identical with the acetonation products from **14a** and **14b**.

It was of interest to subject the glycolic acid pair from cortisone glyoxal[11] to the acetonation conditions since not only the 17-hydroxy-20,21-dioxolones, but also the 17,20-acetonido-21-oic acids and 20-hydroxy-17,21-dioxolones could be formed. However, treatment of **17a** and **17b** (Scheme IV) with acetone–perchloric acid afforded a single, neutral product in each case which was not affected by acetic anhydride–pyridine, and which possessed a carbonyl band close to 1800 cm^{-1}. They were therefore assigned the 17-hydroxy-20,21-dioxolone structures **18a** and **18b**, thus indicating the preferred reaction of acetone with the C-20 and carboxyl hydroxyls. Treatment of **18a** and **18b** with methanolic sodium hydroxide gave the respective

SCHEME IV



methyl 17,20-dihydroxy-21-oates **19a** and **19b**[11] unaccompanied by epimerization at C-20. This is not surprising since the steric factors believed responsible for the epimerization of 17,20α-acetonido-21-oates under these conditions[2] are not operative in 20,21-dioxolones.

In contrast to the isopropylidene derivatives of steroidal glycols, all dioxolones studied, by virtue of their lactonic nature, are readily hydrolyzed by dilute alklai to the parent α-hydroxy acids. However, dioxolones are considerably more resistant to room temperature hydrolysis with 60% aqueous acetic acid than 20,21-acetonides.[5] For example, under conditions where the latter are cleaved completely in 30 min, the 17-deoxydioxolones **16a** and **16b** required 24 hr and the 17-hydroxydioxolones **18a** and **18b** approximately 48 hr for complete hydrolysis. Because of the tertiary linkage at C-17, the etiodioxolones were considerably more

(8) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).
(9) Direct preparation of the epimeric glycolic acids from 11-dehydrocorticosterone 21-aldehyde was not possible because neither the methyl esters nor the methyl ester 20-acetates were separable chromatographically.
(10) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **29**, 2559 (1964).
(11) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, 1773 (1963).

TABLE I

INFRARED AND NMR SPECTRAL CHARACTERISTICS OF STEROIDAL DIOXOLONES

Compd	Type	Infrared bands (cm^{-1})				Chemical shifts (Hz)		
		Lactone carbonyl	*gem*-Dimethyl	1137–1120	938–879	C-18	C-19	Dioxolone methyls
9	11β-OH etiodioxolone	1784	1384, 1376	1136 (vs)	938 (vs)	77	90	94, 94
2	11-Keto etiodioxolone	1782	1385, 1377	1137 (vs)	936 (vs)	60	88	94, 97
15a	11β-OH, 20α,21-dioxolone	1789	1387, 1379	1120 (vs)	889 (vs)	62	90	95, 99
15b	11β-OH, 20β,21-dioxolone	1788	1386, 1378	1125 (vs)	886 (vs)	64	89	95, 97
16a	11-Keto, 20α,21-dioxolone	1786	1389, 1381	1121 (m)	884 (s)	45	88	95, 100
16b	11-Keto, 20β,21-dioxolone	1785	1384, 1376	1125 (vs)	884 (vs)	49	88	94, 96
18a	11-Keto, 17-OH, 20α,21-dioxolone	1795	1386, 1378	1126 (vs)	895 (s), 880 (s)	51	88	96, 102
18b	11-Keto, 17-OH, 20β,21-dioxolone	1790	1387, 1379	1130 (vs)	898 (vs), 879 (s)	52	88	95, 100

resistant, requiring refluxing for 3 hr to effect complete hydrolysis.

The infrared spectral properties of the α-hydroxy acid acetonides have been determined and the bands are presented in Table I. Justification for these assignments is based upon the constant occurrence of certain bands in these derivatives together with their absence in the corresponding α-hydroxy acids. All dioxolones exhibit a carbonyl band at 1795–1782 cm^{-1}, which is characteristic of saturated γ-lactones.[12] The symmetrical methyl deformation bands attributable to the *gem*-dimethyl group[13] appear as a doublet separated by 8 cm^{-1} and ranging from 1389 to 1384 and 1381 to 1376 cm^{-1}. In addition, a very strong band at 1274–1265 cm^{-1} (not listed in Table I) is common to all dioxolones. The presence of bands at 1137–1136 and 938–936 cm^{-1} serve to distinguish the etiodioxolones from 20,21-dioxolones in which these bands occur at somewhat lower frequencies (1130–1120 and 889–879 cm^{-1}). Differentiation between 17-deoxy- and 17-hydroxy-20,21-dioxolones rests on the observation that the 938–879-cm^{-1} band is distinctly split in the latter case.

Examination of the nmr spectra (Table I) shows four methyl resonances for each compound. Although dioxolones are not included in the tables compiled by Zürcher,[14] the following assignments can reasonably be made. The proton resonances of the C-19 methyl group, which is well removed from the dioxolone ring, fall within the expected narrow range of 88–90 Hz. Comparison of the C-18 methyl resonances among the 11β-ols and the 11-ketones show an average downfield shift of 14 Hz for the etiodioxolone *vs.* the homologous derivatives. This is ascribable to the fixed position of the dioxolone ring in the former case and its closer approach to the C-18 methyl group. The dioxolone methyl resonances, with one exception, appear as doublets within the limits of 94–102 Hz, but it is not possible to make individual assignments. The C-20 proton resonances in the pregnenoic acid derivatives fall within the range of 252–273 Hz, but it was not possible to distinguish between 20α and 20β protons.

Experimental Section

Melting points were taken on a Fisher–Johns apparatus and are uncorrected. Optical rotations were determined at 365 and 589 mμ (D line of sodium) in a Zeiss 0.005° photoelectric polarimeter. Measurements were made in methanol solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Ultraviolet spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. Infrared (ir) spectra were obtained as KBr pellets with a Beckman IR-8 instrument. The mass spectrum was obtained at the Morgan–Schaffer Corp., Montreal, Canada, with a Hitachi Perkin-Elmer RMU-6D spectrometer; the sample was introduced directly at an inital voltage of 70 V. Nmr spectra were determined in $CDCl_3$ solution by Spectratec, Washington, D. C. using a JEOL 60-MHz instrument with TMS as the internal standard of reference. Elemental analyses were by August Peisker-Ritter, Brugg, Switzerland.

Descriptions of our column and paper chromatographic techniques appear in papers previously cited.[10] Thin layer chromatography (tlc) was performed on plates coated with silica gel 1B-F. The processing of reaction mixtures from acetylations, lithium aluminum hydride reductions, and chromic anhydride–pyridine oxidations have also been previously described or cited.[2]

17,20-Isopropylidenedioxy-3,11-dioxoetiochol-4-en-20-oate (2) from 8.—To a solution of 17-hydroxy-3,11-dioxoetiochol-4-enic acid[15] (100 mg) in acetone (100 ml) was added 70% perchloric acid (0.25 ml). After 6 hr at room temperature, the solution was concentrated *in vacuo* to a small volume and partitioned between methylene chloride and water. The oily residue was chromatographed on a 13 × 550 mm silica gel column in ethyl acetate–isooctane (1:1), collecting 3 ml of effluent per 10 min. Crystallization of material obtained from fractions 53–90 gave prisms from methanol (67 mg, mp 243–244°; 9 mg, mp 240–241°) in a yield of 68%. The ir spectrum was identical with that of the common chromic anhydride–pyridine oxidation product from **1a** and **1b**: $[\alpha]_{365}$ +591°, $[\alpha]_D$ +120°; λ_{max} 238 mμ, ε 15,800.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.51; H, 7.90.

Methyl 17-Hydroxy-3,11-dioxoetiochol-4-enoate (3) from 2. A. With Methanolic Sodium Hydroxide.—To a solution of the etiodioxolone (20 mg) in methanol (9.5 ml) was added 1 *N* methanolic sodium hydroxide (0.5 ml). After 20 hr at room temperature, the reaction mixture was added to methylene chloride (50 ml). The solution was washed with water and concentrated to dryness. Crystallization from methanol gave 18 mg of prisms, mp 230–231.5°. A mixture melting point with **3**[16] was 230–232° and their ir spectra were identical.

B. With Methanolic Hydrogen Chloride.—Treatment of **2** (7 mg) in methanol (2.2 ml) with 5.2 *N* HCl in methanol (0.3 ml) for 48 hr at room temperature followed by silica gel chromatography of the product in ethyl acetate–isooctane (1:1) afforded 2.7 mg of prisms, mp 229–230°, which were identical in all respects with the methyl ester **3**.

17,20-Isopropylidenedioxy-11β-hydroxy-3-oxoetiochol-4-en-20-oate (9) from 5.—Acetonation of 11β,17-dihydroxy-3-oxoetiochol-4-enic acid (200 mg) was carried out for 6 hr as in the preparation of **2** from **8**. The oily residue was chromatographed on a 20 × 700 mm silica gel column in ethyl acetate–isooctane (1:1), collecting 4-ml fractions every 10 min. Crystallization of the residue from fractions 106–174 gave prisms from methanol (127 mg, mp 222.5–223°; 27 mg, mp 218–219°) in a yield of 69%. The analytical sample melted and resolidified at

(12) R. N. Jones and B. S. Gallagher, *J. Amer. Chem. Soc.*, **81**, 5242 (1959).

(13) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," New York, N. Y., 1958, p 24.

(14) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(15) H. L. Mason, W. Hoehn, and E. C. Kendall, *J. Biol. Chem.*, **124** 459 (1938).

(16) J. von Euw, C. Meystre, R. Neher, T. Reichstein, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1516 (1958).

approximately 200°, then melted again at 221–221.5°: $[\alpha]_{365}$ +36.9°, $[\alpha]_D$ +78.8°; λ_{max} 241 mμ, ε 16,050.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.11; H, 8.35.

2 from 9.—Oxidation of 17,20-isopropylidenedioxy-11β-hydroxy-3-oxoetiochol-4-en-20-oate (50 mg) with chromic anhydride (50 mg) in pyridine (6 ml) for 19 hr afforded 46 mg of prisms from methanol, mp 244.5–246°. The product did not depress the melting point of the acetonation product from **8** and their ir spectra were identical.

17β-Hydroxymethyl-11β,17-dihydroxyandrost-4-en-3-one (6) from 4.—To a solution of methyl 11β,17-dihydroxy-3-oxoetiochol-4-enoate[17] (1 g) in hot methanol (5 ml) was added 0.4 ml of pyrrolidine.[4] The enamine crystallized directly as yellow, prismatic needles (1080 mg, mp 167–178° dec) in a yield of 92%: ν_{max} 1640 and 1610 cm^{-1} ($\Delta^{3,5}$-pyrrolidinyl).[4]

A solution of methyl 3-(1-pyrrolidinyl)-11β,17-dihydroxyetiochola-3,5-dienoate (1 g) and an equal weight of lithium aluminum hydride were refluxed in tetrahydrofuran (135 ml) for 2 hr. After the cautious addition of ethyl acetate and water, most of the solvent was removed in a nitrogen stream. The residue was suspended in 50 ml of 50% aqueous methanol and the pH was adjusted to 4 by the dropwise addition of 1 *N* hydrochloric acid. Acetate buffer[18] (90 ml) was added, and the mixture was refluxed for 4 hr. The solvent was removed *in vacuo* and the product was recovered in the usual manner. Crystallization from ethyl acetate provided leaflets (385 mg, mp 157–158°; 195 mg, mp 155–156°) in a yield of 74%: $[\alpha]_{365}$ +56.2°, $[\alpha]_D$ +97.5°; λ_{max} 242 mμ, ε 14,900.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.80; H, 9.09.

Treatment of the glycol **6** (50 mg) with periodic acid in aqueous ethanol for 19 hr gave 34 mg (75%) of needles from ethanol, mp 198–200°; reported[19] for **11β-hydroxyandrostenedione**, mp 199–200°. The ir spectrum was identical with that of the reference compound.

17β-Hydroxymethyl-17-hydroxyandrost-4-ene-3,11-dione Acetonide (7) from 6.—Acetonation of 17β-hydroxymethyl-11β,17-dihydroxyandrost-4-en-3-one (100 mg) in the presence of *p*-TSA was carried out as described previously.[5] The product was homogeneous (R_f 0.16) by tlc in isooctane–ethyl acetate (3:2) but could not be obtained in crystalline form. Oxidation of the amorphous 17β-hydroxymethyl-11β,17-dihydroxyandrost-4-en-3-one acetonide was therefore performed with chromic anhydride (100 mg) in pyridine (11 ml) for 20 hr. The product crystallized as prisms from acetone–*n*-hexane (86.5 mg, mp 174.5–176°; 10 mg, mp 172–174°) in an overall yield from the glycol **6** of 87%: $[\alpha]_{365}$ +510°, $[\alpha]_D$ +110°; λ_{max} 238 mμ, ε 15,600; ν_{max} 1159 and 996 cm^{-1} (17,20-acetonide).[5]

Anal. Calcd for $C_{23}H_{34}O_4$: C, 74.16; H, 8.66. Found: C, 74.20; H, 8.62.

Methyl 11β,20α- and -20β-Dihydroxy-3-oxopregn-4-en-21-oates (11a and 11b) from 10.—Corticosterone (1384 mg, 4 mmol) was treated with methanolic cupric acetate for 120 hr as described previously.[8] The epimeric methyl ester mixture was chromatographed on 50 × 900 mm Celite column in toluene (120), isooctane (80), methanol (160), and water (40 ml). Fractions (12 ml) were collected every 10 min. Several mobile by-products which emerged between fractions 101 and 300 were discarded.

Methyl 11β,20β-Dihydroxy-3-oxopregn-4-en-21-oate (11b). Fractions 326–460.—Crystallization from aqueous methanol provided 516 mg (34%) of needles: mp 104–106°; $[\alpha]_{365}$ +27.6°, $[\alpha]_D$ +78.3°; λ_{max} 242 mμ, ε 15,700.

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; OCH_3, 8.24. Found: C, 69.49; H, 8,60; OCH_3, 8.02.

Treatment of **11b** (500 mg) with 1 ml each of acetic anhydride and pyridine for 18 hr afforded **methyl 20β-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (13b)** as prisms (469 mg) from methanol: mp 229–231°; $[\alpha]_{365}$ +91.3°, $[\alpha]_D$ +88.5°; λ_{max} 242 mμ, ε 15,900.

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.80; H, 8.24.

Saponification of **11b** (188 mg) in methanol (2 ml) with 1 *N* aqueous sodium hydroxide (1 ml) for 30 min at room temperature gave **11β,20β-dihydroxy-3-oxopregn-4-en-21-oic acid (12b)** as prismatic needles (160 mg) from ethyl acetate: mp 200–200.5°; $[\alpha]_{365}$ +22.8°, $[\alpha]_D$ +75.4°; λ_{max} 242 mμ, ε 15,100.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.30; H, 8.44.

Methyl 11β,20α-Dihydroxy-3-oxopregn-4-en-21-oate (11a). Fractions 551–850.—Crystallization from ethyl acetate provided prisms (253 mg, mp 182–183°; 54 mg, mp 173–175°) in a yield of 20%: $[\alpha]_{365}$ +145°, $[\alpha]_D$ +116°; λ_{max} 242 mμ, ε 15,500.

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; OCH_3, 8.24. Found: C, 70.02; H, 8.53; OCH_3, 7.95.

Conversion of **11a** (500 mg) to **methyl 20α-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (13a)** was carried out as in the preparation of **13b** from **11b**. The product crystallized as prisms (461 mg) from methanol: mp 201–202.5°; $[\alpha]_{365}$ +211°, $[\alpha]_D$ +137°; λ_{max} 242 mμ, ε 16,000.

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

Saponification of **11a** (188 mg) with methanolic sodium hydroxide as in the preparation of **12b** from **11b** gave **11β,20α-dihydroxy-3-oxopregn-4-en-21-oic acid (12a)** as needles (146 mg) from ethyl acetate: mp 201.5–202°; $[\alpha]_{365}$ +148°, $[\alpha]_D$ +122°; λ_{max} 242 mμ, ε 15,900.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.51; H, 8.36.

20α-Hydroxy-3,11-dioxopregn-4-en-21-oic Acid (14a) from 13a.—Oxidation of methyl 20α-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (400 mg) with an equal weight of chromic anhydride in pyridine (6 ml) for 16 hr afforded the 11-ketone which could be obtained only as a filterable solid from aqueous methanol: mp 70–72°; $[\alpha]_{365}$ +657°, $[\alpha]_D$ +166°.

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.89; H, 7.86.

The product was saponified and the free acid **14a** crystallized from methanol as leaflets (320 mg, mp 229–231°) in an overall yield of 93% from **13a**: $[\alpha]_{365}$ +623°, $[\alpha]_D$ +160°; λ_{max} 238 mμ, ε 14,600.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.60; H, 7.90.

20β-Hydroxy-3,11-dioxopregn-4-en-21-oic Acid (14b) from 13b.—Oxidation of methyl 20β-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (400 mg) as in the preparation of **14a** from **13a** gave 334 mg (84%) of the 11-ketone, mp 209–210°, which has been previously described.[10] Saponification gave the free acid **14b** as prisms from methanol: mp 199–201°; $[\alpha]_{365}$ +563, $[\alpha]_D$ +129°; λ_{max} 238 mμ, ε 15,000.

Anal. Calcd for $C_{21}H_{28}O_5 \cdot H_2O$: C, 66.64; H, 7.99. Found: C, 67.07; H, 7.80.

20α,21-Isopropylidenedioxy-11β-hydroxy-3-oxopregn-4-en-21-oate (15a) from 12a.—To a solution of 11β,20α-dihydroxy-3-oxopregn-4-en-21-oic acid (100 mg) in acetone (100 ml) was added 70% perchloric acid (0.25 ml). After 20 min solid sodium bicarbonate (300 mg) was added and the product was recovered in the usual manner. Crystallization from ether gave 98 mg (88%) of needles: mp 195–196°; $[\alpha]_{365}$ +122°, $[\alpha]_D$ +113°; λ_{max} 242 mμ, ε 15,900.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.72; H, 8.57.

20β,21-Isopropylidenedioxy-11β-hydroxy-3-oxopregn-4-en-21-oate (15b) from 12b.—Acetonation of 11β,20β-dihydroxy-3-oxopregn-4-en-21-oic acid (100 mg) was performed as in the preparation of **15a** from **12a**. The product crystallized from methanol as prismatic needles (79.5 mg, mp 239–240°; 9.5 mg, mp 236.5–237.5°) in a yield of 80%. The analytical sample had mp 241–242°; $[\alpha]_{365}$ +138°, $[\alpha]_D$ +106°; λ_{max} 242 mμ, ε 15,850.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.62; H, 8.52.

20α,21-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (16a) from 15a.—Oxidation of 20α,21-isopropylidenedioxy-11β-hydroxy-3-oxopregn-4-en-21-oate (50 mg) in pyridine (7 ml) with an equal weight of chromic anhydride for 17 hr afforded 37 mg (74%) of prisms from methanol: mp 193–194°; $[\alpha]_{365}$ +631°, $[\alpha]_D$ +166°; λ_{max} 238 mμ, ε 15,700.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.83; H, 8.07.

16α from 14a.—Acetonation of 20α-hydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg) in the usual manner provided 68 mg of prisms, mp 190–191°, which did not depress the melting point of **16a** prepared from **15a**, and their ir spectra were identical.

20β,21-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (16b) from 15b.—Oxidation of 20β,21-isopropylidenedioxy-11β-hy-

(17) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942).
(18) F. W. Heyl and M. E. Herr, *J. Amer. Chem. Soc.*, **75**, 1918 (1953).
(19) S. Bernstein, R. H. Lenhard, and J. H. Williams, *J. Org. Chem.*, **18**, 1166 (1953).

droxy-3-oxopregn-4-en-21-oate (50 mg) as in the preparation of **16a** from **15a** gave needles from methanol (35 mg, mp 208–210°; 9.1 mg, mp 204–206°) in a yield of 89%: $[\alpha]_{365}$ +579°, $[\alpha]_D$ +141°; λ_{max} 238 mμ, ε 15,200.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.65; H, 8.20.

16b from 14b.—Acetonation of 20β-hydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg) provided 68 mg of needles from methanol, mp 208–210°, which possessed an ir spectrum identical with that of **16b** prepared from **15b**.

20α,21-Isopropylidenedioxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (18a) from 17a.—Acetonation of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg)[11] for 3.5 hr and crystallization of the product from methanol gave 76 mg (69%) of leaflets, mp 269–271°. The analytical sample had mp 271–272°; $[\alpha]_{365}$ +395°, $[\alpha]_D$ +85.7°; λ_{max} 238 mμ, ε 15,500.

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.19; H, 7.74. Found: C, 69.32; H, 7.65.

Treatment of **18a** (10 mg) in methanol (2.5 ml) with an equal volume of 0.1 *N* methanolic sodium hydroxide for 2 hr followed by dilution with methylene chloride and washing with water afforded 7.7 mg of prisms from acetone–ether, mp 197–198°. A mixture melting point with **methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (19a)**[11] was 196–197.5°, and their ir spectra were identical.

20β,21-Isopropylidenedioxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (18b) from 17b.—Acetonation of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg)[11] for 3.5 hr and crystallization from methanol provided 45 mg of needles, mp 293.5–294°. Fractionation of the mother liquor on a small silica gel column in ethyl acetate–iscoctane (3:2) afforded an additional 35 mg of product, mp 293.5–294°, raising the yield to 72%: $[\alpha]_{365}$ +499°, $[\alpha]_D$ +107°; λ_{max} 238 mμ, ε 15,500.

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.19; H, 7.74. Found: C, 69.30; H, 7.68.

Treatment of **18b** (10 mg) with methanolic sodium hydroxide gave 8.4 mg of prisms from acetone–ether, mp 211.5–213°. The identity of this product with **methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (19b)**[11] was shown by mixture melting point and ir comparisons.

Registry No.—**2**, 27149-60-6; **3**, 3941-62-6; **6**, 3941-65-9; **7**, 27149-63-9; **9**, 27149-64-0; **11a**, 27149-65-1; **11b**, 27149-66-2; **12a**, 27149-67-3; **12b**, 27149-68-4; **13a**, 27149-69-5; **13b**, 27149-70-8; **14a**, 27149-71-9; **14b**, 27149-72-0; **15a**, 27150-71-6; **15b**, 27150-72-7; **16a**, 27150-73-8; **16b**, 27150-74-9; **18a**, 27189-20-4; **18b**, 27189-21-5; methyl 20α-acetoxy-3,11-dioxopregn-4-en-21-oate, 27150-75-0.

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Notes

Disulfides of 2-Mercaptocyclohexanol

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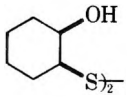
During the course of studies in our laboratory, we had need to prepare the disulfides **1** and **2** derived from *cis*- and *trans*-2-mercaptocyclohexanol, respectively. The trans,trans disulfide **2** has been reported by Mousseron[2] to be obtained by the reaction of sodium disulfide with *trans*-2-chlorocyclohexanol, while the cis,cis disulfide **1** has not been described in the literature.



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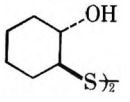
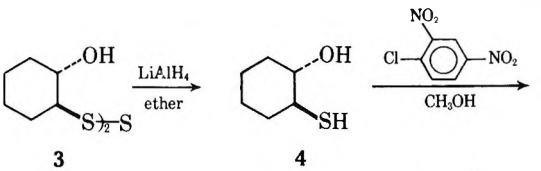
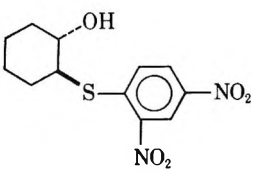


2

Repetition of Mousseron's procedure gave, as reported, a compound having a melting point of 156°. However, the molecular weight of this material, as determined by mass spectrometry, was found to be 294 rather than 262 as expected for the disulfide **2**. This difference of 32 mass units is indicative that Mousseron's product is the trisulfide **3** rather than the disulfide **2**. That this is the case was established by elemental analysis and by preparation, following a known procedure,[3] of the trisulfide **3**, which was shown to be identical with Mousseron's product. The trisulfide **3** has been reported[4] to possess a melting point of 157–158°. The all-trans stereochemistry of the trisulfide **3** was confirmed by reduction[5] with lithium aluminum hydride to give *trans*-2-mercaptocyclohexanol (**4**)[6] characterized as the known 2,4-dinitrophenyl thio ether derivative **5**.[4,6,7]



3 **4**



5

The trans,trans disulfide **2** was obtained by oxidation of *trans*-2-mercaptocyclohexanol (**4**)[6] with iodine. The disulfide **2** has a melting point of 82–83°, gives a molecular ion peak at *m/e* 262, and upon reduction with lithium aluminum hydride regenerates **4**.

(1) To whom inquiries should be sent.

(2) M. Mousseron, *Bull. Soc. Chim. Fr.*, 84 (1948).

(3) B. D. Vineyard, *J. Org. Chem.*, **31**, 601 (1966).

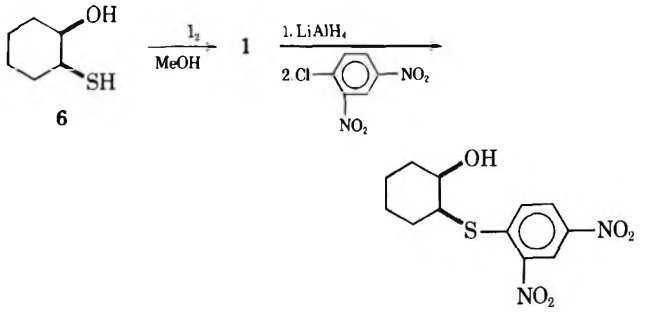
(4) J. Ebersberger, H. Holtschmidt, and R. Stroh, German Patent 1,098,937 (1961); *Chem. Abstr.*, **55**, 24680*h* (1961).

(5) M. Mousseron, R. Jacquier, M. Mousseron-Canet, and R. Zagoun, *Bull. Soc. Chim. Fr.*, 1042 (1952).

(6) C. C. J. Culvenor, W. Davis, and N. S. Heath, *J. Chem. Soc.*, 278 (1949).

(7) H. Behringer and W. Kley, *Justus Liebigs Ann. Chem.*, **595**, 160 (1955).

Oxidation of the known[7] *cis*-2-mercaptocyclohexanol (6) with iodine gave the cis,cis disulfide **1** melting at 85–88°. The molecular weight of the disulfide **1** was determined by mass spectrometry to be 262. The nonidentity of this material with the disulfide **2** was verified by depression of the mixture melting point and nonsuperposable ir and nmr spectra. The disulfide **1** was converted by reduction and derivatization to the known[7] *cis*-2-hydroxycyclohexyl 2,4-dinitrophenyl sulfide (**7**).



6 7

It is of interest to note that the nmr spectrum of the cis,cis disulfide **1** shows the C-1 carbinyl proton as a multiplet centered at τ 5.95 and appearing 0.50 ppm downfield from the corresponding carbinyl proton of the trans,trans disulfide **2**. This data establishes[8] that the hydroxyl group is axial and the disulfide group is equatorial in the disulfide **1**, while both function groups, as expected, are equatorial in the disulfide **2**.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained with Beckman IR-8 and IR-20A spectrophotometers. The nmr spectra were recorded at 60 MHz on a Varian A-60 spectrometer. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Solvents were removed *in vacuo* on a Buchler rotary evaporator.

trans,trans-**Bis(2-hydroxycyclohexyl) Trisulfide (3).**—A modified procedure for the preparation of trisulfides reported by Vineyard[3] was employed. *trans*-2-Mercaptocyclohexanol (**4**,[6] 14.9 g, 0.113 mol) was stirred with 0.5 ml of *n*-butylamine at room temperature. Recrystallized sulfur (2.5 g, 0.078 mol) was added over a 1-hr period after which the reaction mixture was stirred overnight. Benzene was added to the mixture and any solid material present was removed by filtration. The organic phase was washed with water, 6 *N* hydrochloric acid, 6 *N* sodium hydroxide, and water. After the mixture was dried over magnesium sulfate, the solvent was removed *in vacuo* to yield an oil. White crystals (2.0 g, 14%) were deposited from a solution of the oil in benzene–ligroin (bp 60–90°), mp 156–157° (lit.[4] 157–158°). This material was identical (mixture melting point, ir, nmr, mass spectrum) with material prepared following Mousseron's procedure:[2] ir (KBr) 3280 cm^{-1} (OH); nmr (DMSO-d_6) τ 5.15–5.34 (d, 2 H, OH), 6.35–6.91 (m, 2 H, CHOH), 7.05–7.65 (m, 2 H, CHS), and 7.70–9.20 (m, 16 H, methylene); molecular ion, *m/e* 294.

Anal. Calcd for $C_{12}H_{22}O_2S_3$ (294.5): C, 48.9; H, 7.53; S, 32.7. Found: C, 48.8; H, 7.66; S, 32.4.

The trisulfide **3** was reduced with lithium aluminum hydride in ether to give, as previously reported,[5] *trans*-2-mercaptocyclohexanol (**4**) in 40% yield: bp 95–97° (15 mm) [lit.[6] bp 100° (18 mm)]. The 2,4-dinitrophenyl thio ether of **4** was prepared[9] in a yield of 56%, mp 133–134° (lit.[4,6,7] mp 135°).

trans,trans-**Bis(2-hydroxycyclohexyl) Disulfide (2).**—To 4.4 g (0.033 mol) of *trans*-2-mercaptocyclohexanol (**4**), prepared according to Culvenor, *et al.*,[6] was added dropwise a solution containing 5.0 g of iodine/100 ml of methanol until a permanent brown color was obtained, following which the reaction mixture was stirred at room temperature for 16 hr. Saturated aqueous sodium bisulfite was added dropwise until a colorless mixture resulted. The methanol was evaporated *in vacuo* and the remaining aqueous phase was extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated *in vacuo* to yield a pale yellow oil. The oil was taken up in hot ethyl acetate–*n*-hexane, whereupon a white solid crystallized upon cooling. The solid (2.4 g, 55%) was collected by filtration and air-dried: mp 83–84°; ir ($CHCl_3$) 3400 (OH), no absorption at 2500–2600 cm^{-1} (no SH); nmr ($CDCl_3$) τ 6.15–6.70 (m, 4 H, CHOH), 6.90–7.50 (m, 2 H, –CHS–), and 7.60–8.80 (m, 16 H, methylene); molecular ion, *m/e* 262.

Anal. Calcd for $C_{12}H_{22}O_2S_2$ (262.4): C, 54.9; H, 8.45; S, 24.4. Found: C, 54.8; H, 8.43; S, 24.2.

The disulfide **2** was reduced[5] with lithium aluminum hydride in ether to the trans compound **4**, which was characterized as the 2,4-dinitrophenyl thio ether derivative **5**,[9] mp 133–134° (lit.[4,6,7] mp 135°).

cis,cis-**Bis(2-hydroxycyclohexyl) Disulfide (1).**—*cis*-2-Mercaptocyclohexanol (**6**, 18.6 g, 0.14 mol), prepared according to procedure of Behringer and Kley,[7] was treated with iodine in methanol as was done in the preparation of the disulfide **2**. The pale yellow oil obtained was eluted through a silica gel column using benzene followed by chloroform. A small amount of white crystals formed within the oil: these crystals were collected and used as seed crystals in the subsequent recrystallization of **1**. The remaining oil was dissolved in hot ethyl acetate, to which ligroin (bp 60–90°) was added to the cloud point. After the solution was cooled to room temperature and seeded, white crystals of **1** were slowly deposited. The crystals were collected by filtration and air-dried (3.0 g, 18%): mp 82–85°; ir 3550 (OH), no absorption at 2500–2600 cm^{-1} (no SH); nmr ($CDCl_3$) τ 5.8–6.1 (m, 2 H, CHOH), 7.9–7.2 (m, 2 H, –CHS–), 7.58 (s, 2 H, OH), 7.9–8.9 (m, 16 H, methylene); molecular ion, *m/e* 262; with **2**, mmp 73–85°.

An analytical sample was prepared by recrystallization from ethyl acetate–ligroin (bp 60–90°), mp 85–88°.

Anal. Calcd for $C_{12}H_{22}O_2S_2$ (262.4): C, 54.9; H, 8.45. Found: C, 54.9; H, 8.60.

Reduction of the disulfide **1** with lithium aluminum hydride following the procedure reported[5] for the trans disulfide gave *cis*-2-mercaptocyclohexanol (**6**), as established by comparison of infrared spectra, in a yield of 70%. Following a previously reported procedure,[7] **6** was converted to *cis*-2-hydroxycyclohexyl 2,4-dinitrophenyl sulfide (**7**) in a yield of 33%, mp 141–143° (lit.[7] mp 143°).

Registry No.—**1**, 27040-92-2; **2**, 27040-93-3; **3**, 27040-94-4.

Acknowledgment.—Partial support is acknowledged to the U. S. Public Health Service, National Cancer Institute, Grant No. CA 10653.

(8) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 117.

(9) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience, New York, N. Y., p 532, 1957.

Hydroformylation of 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose

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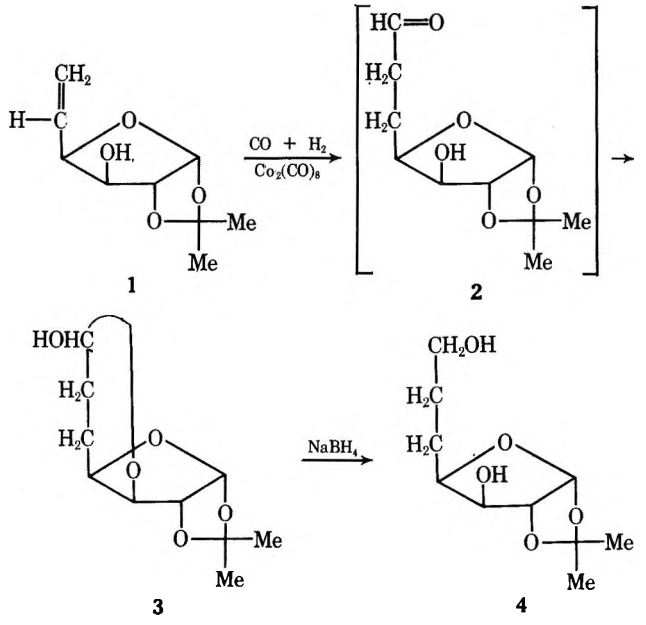
Hydroformylation of unsaturated sugar derivatives has posed a problem of great difficulty.[1] This difficulty

(1) (a) A. Rosenthal and D. Abson, *J. Amer. Chem. Soc.*, **86**, 5356 (1964). (b) A. Rosenthal, D. Abson, T. D. Field, H. J. Koch, and R. E. J. Mitchell, *Can. J. Chem.*, **45**, 1525 (1967); A. Rosenthal, *Advan. Carbohyd. Chem.*, **23**, 59 (1968).

arises from the fact that the initial products, namely the anhydrodeoxyaldoses, subsequently undergo hydrogenation to afford anhydrodeoxyalditols. In this communication we present a novel approach to this problem by designing a starting material having a free hydroxyl on a carbon atom of the ring which is subsequently capable of cyclizing with the *aldehydo* group to form a hemiacetal and thus possibly prevent the hydrogenation stage of the oxo reaction.

When 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (**1**)[2] was allowed to react with carbon monoxide and hydrogen in the presence of preformed dicobalt octacarbonyl at 105° for 45 min, a mixture of three main components and traces of two additional compounds was obtained. The major component **3**, isolated in 51% yield, crystallized from the reaction mixture; ether–petroleum ether was used as solvent. The nuclear magnetic resonance (nmr) spectrum of **3**,



when compared with the spectra of 5-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose and various 6-deoxyhexose derivatives,[3] conclusively shows that the formyl group is attached to position 6. If the hydroformylation had proceeded in such a manner as to add the formyl group at C-5 yielding a 6-deoxy derivative, the protons at C-6 would have appeared as a doublet at about τ 8.9. Instead, the 5,6-dideoxy protons of **3** gave a multiplet equal to four protons at τ 7.8–8.6. The nmr of **3** showed the absence of a formyl hydrogen and showed the presence of two hemiacetal hydrogens at τ 4.82 and 5.32 assigned to H-7e and H-7a, respectively.[1,4] Irradiation of either of these signals altered the signals at τ 7.8–8.6. Presumably, the free aldehyde group of the hydroformylation product **2** immediately cyclized with the free hydroxyl group on C-3 to give an α,β mixture of anomers possessing the tricyclic structure **3**. Further proof that **3** was a dialdose was provided by converting it into a crystalline phenylhydrazone derivative which possessed an isopropylidene group on C-1 and C-2. Reduction of **3** with sodium borohydride gave an aldose derivative with retention of the isopropylidene group. This new aldose had the same R_f as one of the minor components present in the hydroformylation product mixture. Presumably, the dialdose **2** underwent partial reduction during the hydroformylation reaction. The remaining products of the hydroformylation reaction could not be separated into pure compounds.

In order to study the effect of the free hydroxyl on C-3 of **1** in controlling the hydroformylation reaction compound **1** was converted into its 3-*O*-acetate derivative. The latter was then subjected to an oxo reaction. Surprisingly, a very complex mixture of products was obtained which could not be separated by chromatography. The unblocked oxo product mixture also could not be separated by paper chromatography.

(2) (a) H. Ohle and E. Dickhäuser, *Ber.* **58**, 2593 (1925); (b) J. K. N. Jones, and J. L. Thompson, *Can. J. Chem.*, **35**, 955 (1957); (c) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961); (d) D. Horton and W. N. Turner, *Tetrahedron Lett.*, 2531 (1964); (e) D. Horton and W. N. Turner, *Carbohyd. Res.*, **1**, 444 (1966).

(3) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, **28**, 3551 (1963), and references therein.

(4) P. W. K. Woo, H. W. Dion, and L. F. Johnson, *J. Amer. Chem. Soc.*, **84**, 1066 (1962).

Experimental Section

General Considerations.—Nmr spectra were obtained in deuteriochloroform solution (unless otherwise stated) with tetramethylsilane as the internal standard (set at τ 10) using a Varian A-60 spectrometer.[5] Mass spectra were obtained with an AEI MS9 spectrometer. All melting points (micro hot stage) are corrected. Silica gel G was used in the tlc with methyl ethyl ketone–water azeotrope as developer. Elemental analyses were performed by the Microanalytical Laboratory, University of British Columbia.

Hydroformylation of 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (1) to Yield 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-α,β-D-7,3-pyranose (3).—A solution of compound **1** (1.40 g) and dicobalt octacarbonyl (0.30 g) in dry purified benzene (50 ml) was shaken with carbon monoxide (1100 psi) and hydrogen (1100 psi) in a high-pressure autoclave at a temperature of 105° for 45 min. The reaction mixture was transferred to a beaker and heated at 60–70° to decompose the catalyst. The reaction mixture was added to a short column of Celite–Norit and eluted with 99:1 benzene–ethanol. Evaporation of the eluent gave a syrup which was crystallized several times from ether–petroleum ether, bp 35–60°, to afford 0.82 g of the major compound **3** in 51% yield: mp 103–104°; $[\alpha]^{24}D$ +18° (*c* 1, water) which changed to +36° after 1.5 hr; R_f 0.81; nmr τ^{CDCl_3} 4.1 (t, H-1), 4.82 (t, H-7e), 5.32 (t, H-7a), 5.53 (overlapping peaks, H-2), 5.8 (s, H-3), 5.9 (m, H-4), 6.6 (broad peak, OH), 7.8–8.6 (m, equal to 4 hydrogens, assigned to H-5,6), 8.5, 8.7 (CMe_2). Irradiation at τ 4.82 and 5.32 altered the signals at τ 7.8–8.6.

Anal. Calcd for $C_{16}H_{16}O_6$: C, 55.60; H, 7.40; mol wt, 216. Found: C, 55.55; H, 7.10; *m/e* 201 [the base peak in the mass spectrum is at $M^+ - 15$ (loss of CH_3)].

The mother liquor consisted of a mixture of components one of which was the reduced compound **4** (about 5%). The remaining components could not be separated by chromatography.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose Phenylhydrazone.—To a solution of the sugar **3** (0.090 g) in 1 drop of water was added 4 drops of a solution of phenylhydrazine hydrochloride (0.20 g) in water (3 ml) containing sodium acetate (0.30 g). The reaction mixture was warmed on a steam bath for 1 min and then cooled in an ice–water bath to afford the crystalline phenylhydrazone derivative (0.056 g), in 49% yield: mp 146–149°; $[\alpha]^{24}D$ −32° (*c* 0.7, chloroform).

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.74; H, 7.18; N, 9.10. Found: C, 62.82; H, 7.25; N, 8.92.

7-*O*-Acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-α,β-D-7,3-pyranose.—Compound **3** (0.040 g) was acetylated with acetic anhydride and pyridine at 0° under the usual conditions for 48 hr. After the pyridine and acetic anhydride were evaporated under reduced pressure, the product was passed through a short column of silica gel using ethyl ether as eluent to afford 0.032 g (60%) of a syrup, $[\alpha]^{24}D$ +54° (*c* 3,

(5) s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

chloroform). The product consisted of both α and β anomers as evidenced by tlc and nmr: τ^{CDCl_3} 3.95 and 4.45 (m, assigned to H-7e and H-7a), 4.15 (t, H-1), 5.30 (t, H-2), 8.20 (m, equal to four hydrogens on C-5 and C-6); the mixture could not be separated by tlc.

5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hepto-1,4-furanose (4).—Compound **3** (0.045 g) in methanol (20 ml) was reduced with sodium borohydride at 0° for 24 hr. After the reaction mixture was neutralized with acetic acid (2 ml), water (10 ml) was added and the mixture then passed consecutively through columns of Amberlite IR-120 (H^+) and Dowex A-4 (OH^-). The eluent was evaporated to dryness and benzene–ethanol was distilled from the syrup (0.035 g, 75%): $[\alpha]^{24}D$ +2° (*c* 2, ethanol); R_f 0.46; nmr τ^{D_2O} 6.25 (t, H-7), 8.10 (m, equal to 4 hydrogens, assigned to hydrogens on C-5 and C-6). Compound **4** had the same R_f as one of the components of the hydroformylation product mixture.

Reaction of 3-*O*-Acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose with Carbon Monoxide and Hydrogen.—The 3-*O*-acetate derivative of **1** was subjected to the usual oxo conditions[1] at 135° for 2 hr. The oxo product mixture could not be separated by chromatography. An aliquot of the oxo mixture was deacetylated with methanolic sodium methoxide and then deisopropylidenated[3] with Amberlite IR-120 (H^+) to yield a very complex mixture of free sugars which could not be separated by paper chromatography using 4:1:5 butanol–ethanol–water as developer.

Registry No.—**3** (7*R*), 27039-90-3; **3** (7*S*), 26988-37-4; **3** phenylhydrazone, 26988-64-7; **4**, 26988-65-8; 7-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-α-D-7,3-pyranose, 26988-66-9; 7-*O*-acetyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-heptodialdo-1,4-furanose-β-D-7,3-pyranose, 26988-67-0.

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The Stereoselective Total Synthesis of Racemic Nootkatone

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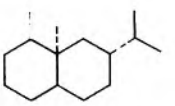
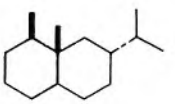
Received September 4, 1970

Considerable effort has been devoted over the past decade to the exploration of potential synthetic routes to compounds in the eremophilane–valencane family of sesquiterpenes.[1,2] A major problem in this connection has been the stereochemical control of the vicinal methyl groupings which characterize the members of this family. Several years ago we devised a straightforward solution to this problem based upon the stereoselective condensation of cyclohexanone derivatives with *trans*-3-penten-2-one.[1c] This report describes our application of that synthetic concept to the total synthesis of nootkatone (**11**), a sesquiterpene constituent of citrus fruit.[3]

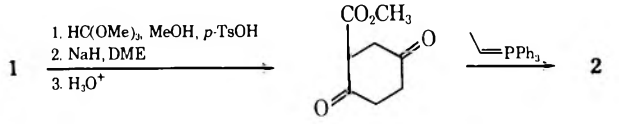


eremophilane skeleton



valencane skeleton

The requisite starting material for our synthesis, keto ester **2**, could be obtained directly in one step by treatment of dimethyl γ-ketopimelate (**1**)[4] with ethylidenetriphenylphosphorane in dimethyl sulfoxide (DMSO).[5] Evidently the basic reaction medium promotes Dieckmann cyclization of the γ-ketopimelate either prior to Wittig condensation or as a subsequent step. The unsaturated keto ester **2** could also be prepared through reaction of the diketo ester **12** with the ethylidene phosphorane in DMSO. Keto ester **12** was readily obtained from dimethyl γ-ketopimelate (**1**) *via* ketal formation, Dieckmann cyclization, and hydrolysis. This latter route to the keto ester **2**, though longer than the direct condensation–cyclization scheme, proceeded in higher overall yield.



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The stereochemically critical step of the synthesis, condensation of keto ester **2** with *trans*-3-penten-2-one, was effected in *tert*-amyl alcohol with potassium *tert*-amylate as the base. Aldol cyclization of the resulting Michael addition product in methanolic sodium methoxide then gave the bicyclic keto ester **3**, a 3:1 mixture of cis and trans CH_3, CO_2CH_3 isomers, and a 1:1 mixture of *Z* and *E*[6] double bond isomers according to the nmr spectrum. These conditions for the Michael–aldol sequence were selected on the basis of studies on related condensations.[1c,7] The desired cis isomer **3** could be readily separated from the mixture and purified through crystallization. Material thus secured still contained the *Z* and *E* double bond isomers[6] in nearly equal amounts.

Epoxidation of the ethylidene grouping of the dienone ester **3** followed by boron trifluoride etherate promoted rearrangement[8] of the resulting epoxide mixture (syn, anti, and α,β stereoisomers) led to a 2:1 mixture of

(1) (a) D. Herbst and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 4337 (1960); (b) R. F. Church, R. E. Ireland, and D. R. Shridhar, *J. Org. Chem.*, **27**, 707 (1962); (c) J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); (d) R. M. Coates and J. E. Shaw, *ibid.*, 47 (1968); (e) R. M. Coates and J. E. Shaw, *ibid.*, 515 (1968); (f) C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968); (g) E. Piers and R. J. Keziere, *ibid.*, 583 (1968); (h) R. M. Coates and J. E. Shaw, *ibid.*, 5405 (1968); (i) S. Murayama, D. Chan, and M. Brown, *ibid.*, 3715 (1968); (j) H. Roebke, "Addition of Organocopper Reagents to Conjugated Ketones," Ph.D. Thesis, Northwestern University, 1968; (k) E. Piers, R. W. Britton, and W. Dewaal, *Can. J. Chem.*, **47**, 4307 (1969).

(2) Total syntheses of nootkatone have recently been reported by two groups: M. Pesaro, G. Bozatto, and P. Schudel, *Chem. Commun.*, 1152 (1968); H. C. Odom and A. R. Pinder, *ibid.*, 26 (1969). The approach used by the latter group is similar to that used in our synthesis of isonootkatone (ref 1c) except for the use of a 2-methylcyclohexanone rather than a 2-carbomethoxyl derivative in the stereochemically critical condensation with *trans*-2-penten-3-one. However, recent developments indicate that this step of the Odom–Pinder synthesis is markedly influenced by certain unknown experimental factors which drastically change the stereochemical outcome. The synthesis has therefore been retracted pending clarification of these factors: H. C. Odom, A. K. Torrence, and A. R. Pinder, "Synthetic Studies in the Eremophilane Sesquiterpene Group," presented at the Symposium on Synthesis and Substitutes for the Food Industry, American Chemical Society, Division of Agricultural and Food Chemistry, 158th National Meeting of the American Chemical Society, Sept 8-12, 1969, New York, N. Y., Abstract 48.

(3) W. D. Macleod, Jr., *Tetrahedron Lett.*, 4779 (1965).

(4) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Amer. Chem. Soc.*, **74**, 1401 (1952).

(5) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

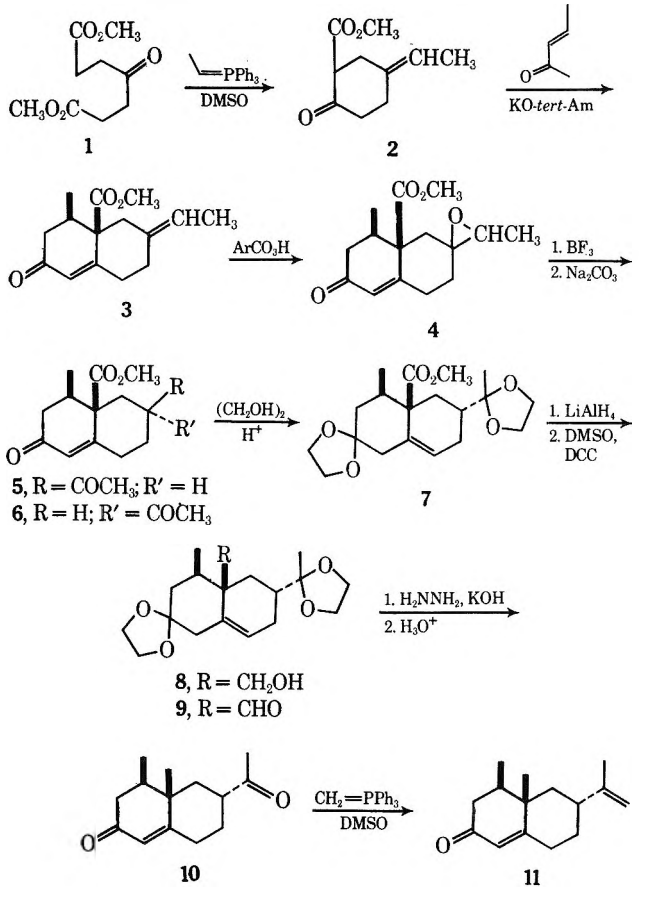
(6) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *ibid.*, **90**, 509 (1968).

(7) T. M. Warne, Jr., "Total Synthesis of (±)-Isonootkatone," Ph.D. Thesis, Northwestern University, 1969.

(8) *Cf.* H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

β- and α-acetyl derivatives **5** and **6**. Assuming that the epoxide rearrangement proceeds with inversion of the oxirane-linked cyclohexane carbon, this finding indicates that a similar mixture of β- and α-epoxide stereoisomers must be produced upon epoxidation of olefin **3**. This result would not have been expected on the basis of steric considerations.

The less stable predominant β-acetyl isomer **5** could be isolated and purified by crystallization from the mixture. Basic treatment effected its conversion to the more stable α isomer **6**. Ketalization of this material then gave the bis-ketal derivative **7**. Attempts to convert the β-acetyl isomer **5** to ketal **7** directly were not successful. Only partial equilibration of the side chain could be realized and a mixture of stereoisomeric ketals resulted.



Reduction of the bis-ketal ester **7** with lithium aluminum hydride in ether and Moffatt oxidation[9] of the resulting alcohol **8** led to the aldehyde **9** in high overall yield. Wolff–Kishner reduction of this aldehyde and subsequent hydrolysis of the bis-ketal product afforded the dione **10**. Initially we examined a number of schemes of the type $CO_2CH_3 \rightarrow CH_2OH \rightarrow CH_2Y \rightarrow CH_3$ for effecting the methoxycarbonyl to methyl conversion in compounds related to keto ester **6**. In all cases the final step, reduction of the neopentyl sulfonic ester or halide by a variety of methods, gave little or none of the desired product.[7]

The final synthetic operation, conversion of the dione **10** to racemic nootkatone (**11**), was accomplished through a selective Wittig reaction using methylenetriphenylphosphorane in DMSO.[5] The spectral properties of material thus secured exactly matched those of authentic nootkatone.

(9) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).

Experimental Section[10]

Methyl 4-Ethylidene-2-oxocyclohexanecarboxylate (**2**). **A.** ***Via*** **Condensation of Dimethyl γ-Ketopimelate with Ethylidenetriphenylphosphorane.**—A solution of 2.00 g of dimethyl γ-ketopimelate (**1**)[4] in 22 ml of DMSO was added dropwise to a solution of ethylidenetriphenylphosphorane prepared from 9.20 g of triphenylethylphosphonium bromide and 1.01 g of 56% NaH dispersion, from which the mineral oil had been removed by pentane washing, in 94 ml of DMSO.[5,10a] The mixture was stirred at room temperature for 4 hr and the product was isolated *via* pentane extraction.[10b] Filtration through 10 g of silica gel with benzene and distillation of the filtrate afforded 0.71 g (40%) of keto ester **2**: bp 75° (bath temperature) (0.05 mm); $\delta_{TMS}^{CCl_4}$ 12.05 and 12.08 [enol OH (*Z* and *E* isomers)], 5.41 (vinyl CH, J = 6.2 Hz), 3.78 and 3.82 (CH_3O–), and 1.62 ppm (vinyl CH_3, J = 6.2 Hz).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.1; H, 7.7.

B. ***Via*** **Diketo Ester 12.**—A solution of 2.02 g of dimethyl γ-ketopimelate and 0.2 g of *p*-toluenesulfonic acid in 18.0 ml of trimethyl orthoformate and 12 ml of methanol was heated at 50° with stirring for 72 hr.[10a] The solution was poured into aqueous sodium bicarbonate and the product was isolated with ether[10b] affording 2.42 g (98%) of the ketal diester: bp 90° (0.10 mm); λ_{max}^{film} 5.75 μ; $\delta_{TMS}^{CCl_4}$ 3.58 (CO_2CH_3) and 3.08 ppm (OCH_3).

Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.22; H, 8.12. Found: C, 53.0; H, 8.0.

A 1.98-g sample of the ketal in 20 ml of 1,2-dimethoxyethane was stirred with NaH (0.41 g of 57% oil dispersion washed with pentane to remove the oil) at 50° for 9 hr.[10a] Most of the solvent was removed under reduced pressure, the residue was acidified with ethereal acetic acid, and the product was isolated with ether[10b] affording 1.53 g (99%) of ketal keto ester: bp 112° (0.2 mm); λ_{max}^{film} 6.01 and 6.08 μ; $\delta_{TMS}^{CCl_4}$ 11.95 (enol H), 3.69 (CO_2CH_3), and 3.12 ppm (OCH_3).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.8; H, 7.6.

A 40-g sample of ketal keto ester comparable to that described above was stirred at room temperature for 12 hr with 250 ml of acetone, 35 ml of water, and 1 ml of concentrated HCl.[10a] The solution was concentrated under reduced pressure and the product was isolated with benzene[10b] affording 25.7 g (82%) of solid diketo ester **12**: mp 34–37°; λ_{max}^{KBr} 5.82, 6.01 and 6.15 μ; $\delta_{TMS}^{CCl_4}$ 12.10 (enol H) and 3.76 ppm (CO_2CH_3).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.7; H, 6.0.

To a solution of ethylidenetriphenylphosphorane, prepared as described above from 55 g of ethyltriphenylphosphonium bromide and 5.9 g of 57% NaH oil dispersion in 345 ml of DMSO, was added a solution of 10.0 g of diketo ester **12** in 100 ml of DMSO.[10a] The solution was stirred for 4 hr and the product was isolated with pentane[10b] affording 8.50 g (79%) of keto ester **2**, bp 75° (0.05 mm).

Condensation of Keto Ester 2 with ***trans*****-3-Penten-2-one.**—To a solution of 2.00 g of keto ester **2** in 10 ml of KO-*tert*-Am in *tert*-AmOH (from 0.05 g of K) at −10° was added portionwise with stirring, 1.35 g of *trans*-3-penten-2-one.[10a] The solution was allowed to stand at 0° for 18 hr and the product was isolated with ether.[10b] The material thus obtained was treated with 10 ml of 2.3 *M* methanolic NaOMe at room temperature for 22 hr to effect aldol cyclization.[10a] Isolation *via* extraction with ether[10b] afforded 2.04 g (75%) of pale yellow solid keto ester **3** (a mixture of *Z* and *E* isomers): λ_{max}^{KBr} 5.80, 6.01 μ; $\delta_{TMS}^{CCl_4}$ 5.92 (vinylic CH), 5.35 (vinylic CH, quartet, J = 6.2 Hz), 3.71 (OCH_3), 1.60 and 1.70 ppm [vinylic CH_3 (*Z* and *E* isomers) doublet, J = 6.2 Hz].

Purification *via* short-path distillation, recrystallization from hexane, and, finally, sublimation gave material of mp 93–102°.

(10) (a) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132) was used to maintain a nitrogen atmosphere. (b) The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated brine solution, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. (c) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.6; H, 8.2.

Conversion of the Dienone Ester 3 to the Enedione Ester 6.—A solution of 1.02 g of dienone ester **3** in 20 ml of DME and 10 ml of water was stirred at room temperature with 0.83 g of 97% *m*-chloroperoxybenzoic acid for 5 hr. The product was isolated with ether[10b] (10% KOH wash to remove acidic material) affording 1.02 g of crude epoxide **4**, a mixture of stereoisomers. This material was dissolved in 50 ml of benzene and 1.0 ml of boron trifluoride etherate was added *via* hypodermic syringe.[8,10a] After 1.5 min aqueous sodium bicarbonate was added, and the product was isolated with benzene[10a] to give 0.88 g (88%) of a colorless semisolid mixture of acetyl epimers **5** and **6** (2:1 according to the integrated nmr spectrum). The major isomer **5** was purified by recrystallization from hexane–ether to give a white solid: mp 148–148.5°; λ_{max}^{KBr} 5.80, 5.88, and 6.00 μ; $\delta_{TMS}^{CCl_4}$ 5.96 (vinylic CH), 3.62 (OCH_3), and 2.30 ppm (CH_3CO).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.0; H, 7.5.

A 0.44-g sample of the aforementioned 2:1 mixture of enediones **5** and **6** was stirred at room temperature with 25 ml of MeOH, 1 ml of water, and 0.03 g of sodium carbonate for 5 hr.[10a] Isolation with benzene[10b] afforded 0.44 g (99%) of oily enedione **6**: λ_{max}^{film} 5.78, 5.85, and 6.01 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic CH), 3.73 (CH_3O), 2.17 (CH_3CO), and 0.98 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.4; H, 7.8.

Conversion of the Enedione Ester 6 to the Bis-Ketal Aldehyde 9.—A solution of 0.44 g of enedione ester **6** in 40 ml of benzene containing 6 ml of ethylene glycol and 0.13 g of *p*-toluenesulfonic acid was stirred at reflux with a Dean–Stark trap for 12 hr.[10a] Solid sodium bicarbonate was added and the product was isolated with benzene[10b] affording 0.58 g (95%) of bis-ketal ester **7**: λ_{max}^{film} 5.78 μ; $\delta_{TMS}^{CCl_4}$ 5.58 (vinylic CH), 3.82 ($-OCH_2CH_2O-$), 3.63 (CH_3O), 1.20 (CH_3), and 0.95 ppm (CH_3, unresolved doublet).

The above material in 50 ml of ether was treated with 0.50 g of lithium aluminum hydride and the mixture was stirred at reflux for 24 hr. Water (0.5 ml), 15% aqueous NaOH (0.5 ml), and water (1.5 ml) were added in turn, stirring was continued for 0.5 hr, and the mixture was filtered. Removal of ether under reduced pressure left 0.50 g (95%) of bis-ketal alcohol **8**: λ_{max}^{film} 3.0 and 9.51 μ; $\delta_{TMS}^{CDCl_3}$ 5.60 (vinyl H, unresolved triplet), 3.87 ($-OCH_2CH_2O-$), 1.24 (CH_3), and 0.98 ppm (CH_3, unresolved doublet).

The above alcohol in 3 ml of DMSO was treated with 0.12 ml of pyridine, 0.06 ml of trifluoroacetic acid, and 0.94 g of dicyclohexylcarbodiimide in 3 ml of benzene.[9,10a] After stirring for 18 hr at room temperature, the mixture was poured into 25 ml of ethyl acetate, and a solution of 0.42 g of oxalic acid in 4 ml of MeOH was added. After 0.5 hr, the mixture was filtered and the filtrate was washed with water, aqueous sodium bicarbonate, and saturated brine and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure left 0.46 g (93%) of bis-ketal aldehyde **9**: λ_{max}^{film} 3.7 and 5.81 μ; $\delta_{TMS}^{CCl_4}$ 9.75 (CHO), 5.68 (vinyl H, unresolved triplet), 3.91 ($-OCH_2CH_2O-$), 1.27 (CH_3), and 1.10 ppm (CH_3, unresolved doublet).

Conversion of the Bis-Ketal Aldehyde 9 to the Enedione 10.—A solution of 0.46 g of bis-ketal aldehyde **9** in 25 ml of ethylene glycol and 3.5 ml of 85% hydrazine hydrate was heated at 120° with stirring for 1 hr.[10a] The solution was allowed to cool, 1.5 g of KOH was added, and the temperature was increased to 205° and maintained near that point for 2 hr. The solution was allowed to cool and the product isolated with ether.[10b] The resulting material in solution with 10 ml of acetone, 1 ml of water, and 3 drops of concentrated HCl was stirred at reflux for 1 hr.[10a] Extraction with benzene[10b] followed by short-path distillation at 130° (0.01 mm) afforded 0.24 g (78%) of pale yellow enedione. Further purification by preparative layer chromatography (silica gel) and short-path distillation yielded the analytical sample: λ_{max}^{film} 5.85 and 6.00 μ; $\delta_{TMS}^{CCl_4}$ 5.93 (vinylic CH), 2.07 (CH_3CO), 1.04 (angular CH_3), and 0.93 ppm (CH_3 doublet, J = 6 Hz).

Anal. Calcd for $C_{14}H_{20}O$: C, 76.33; H, 9.15. Found: C, 76.1; H, 9.3.

A solution of methylenetriphenylphosphorane was prepared as previously described from 0.48 g of NaH and 7.65 g of methyl triphenylphosphonium bromide in 40 ml of DMSO. A 2.60-ml sample was removed *via* syringe and added to 248 mg of enedione **10** in 2 ml of DMSO. The mixture was stirred at room temperature for 4 hr, and the product was isolated with pentane[10b] and chromatographed on silica gel to give 55 mg of (±)-nootkatone: mp 44–45°; λ_{max}^{film} 5.98 (CO), 6.16 (C=C), and 11.3 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 5.60 (H-4), 4.66 (C=CH_2, doublet, J = 1 Hz), 1.66 (vinyl CH_3), 1.10 (angular CH_3), and 0.95 ppm (CH_3, doublet, J = 6 Hz). The spectral characteristics of the synthetic material were identical with those of the natural material.[3]

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.39; H, 10.16.

An early fraction amounting to 8 mg was obtained with hexane elution. This material exhibited spectral properties suggestive of the expected bis condensation product of dione **10**.

Registry No.—**1** dimethyl ketal, 27024-77-7; ketal keto ester [bp 112° (0.2 mm)], 27024-78-8; **2**, 27024-79-9; **3** (cis), 27024-80-2; **3** (trans), 27024-81-3; **5**, 27024-82-4; **6**, 27024-83-5; **7**, 27024-84-6; **8**, 27024-85-7; **9**, 27024-86-8; **10**, 27024-87-9; **11**, 20071-81-2; **12**, 27024-89-1.

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Lincomycin. XII.[1] The Preparation of Methyl *N*-Methyl-α-thiolincosaminide

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Cleavage of the antibiotic lincomycin in refluxing hydrazine hydrate led to the isolation of methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (methyl α-thiolincosaminide) (MTL) (**1**) in good yield.[2] Treatment of this sugar with triphenylphosphine dichloride afforded methyl 7(*S*)-chloro-7-deoxy-α-thiolincosaminide which when coupled with various 4-alkyl-L-prolines gave a series of potent antibacterial and antimalarial agents.[3] Further chemical transformations of methyl α-thiolincosaminide (**1**) to form methyl *N*-methyl-α-thiolincosaminide (**8**) and methyl *N*,*N*-dimethyl-α-thiolincosaminide (**2**) are now described.

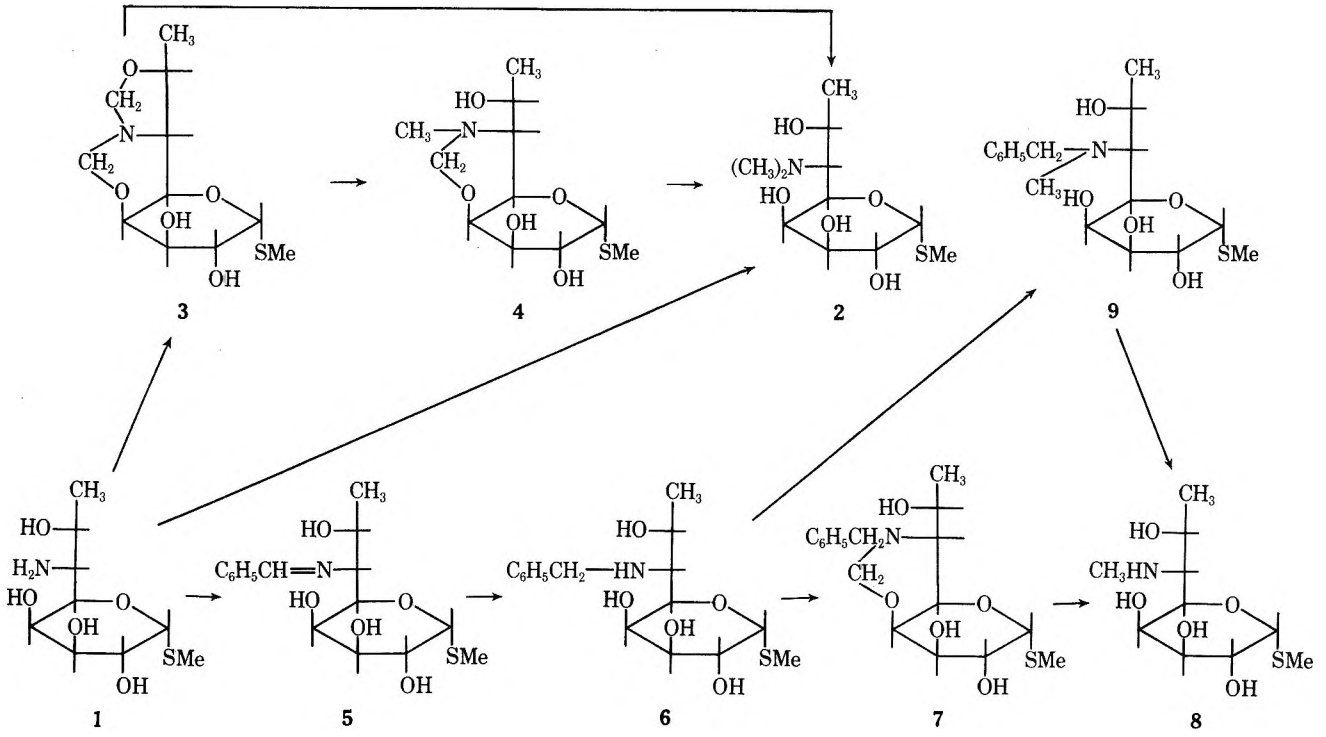
Reductive alkylation of methyl α-thiolincosaminide (**1**) with excess formaldehyde readily formed *N*,*N*-dimethyl sugar **2**. In the presence of but 1 molar equiv of formaldehyde, reductive alkylation gave no evidence of the mono-*N*-methyl sugar **8**, but only a lowered yield of **2** and unreacted amino sugar **1**.

Examination by tlc (thin layer chromatography) of partially completed reductive alkylations revealed the presence of two new compounds both less polar than starting sugar **1** as well as *N*,*N*-dimethyl sugar **2**. These compounds could not be detected after further reduction. After separation by chromatography, the least polar of these intermediates was shown to be the initial condensation product of **1** with 2 mol of formaldehyde. This compound was assigned structure **3** on

(1) Previous paper in this sequence: R. D. Birkenmeyer and F. Kagan, *J. Med. Chem.*, **13**, 616 (1970).

(2) W. Schroeder, B. Bannister, and H. Hoeksema, *J. Amer. Chem. Soc.*, **89**, 2448 (1967).

(3) B. J. Magerlein and F. Kagan, *J. Med. Chem.*, **12**, 780 (1969).



the basis of elemental and nmr data. The assignment of the bond to oxygen at C-4 was made after examination of models indicated that attachment to the axial hydroxyl at C-4 was favored over the equatorial hydroxyls at C-3 or C-2. The formation of the bicyclic structure **3** is analogous to the facile condensation of 2-amino-1,3-diols with carbonyl compounds to yield 1-aza-3,7-dioxabicyclo[3.3.0]octanes.[4] 1-Aza-3,7dioxabicyclo[3.3.0]octanes are reported to undergo hydrogenolysis to form dialkylamino alcohols[4] which is analogous to the hydrogenolysis of **3** to *N*,*N*-dimethyl sugar **2**.

The second compound isolated from the incomplete reduction was assigned structure **4**. Elemental analyses and nmr data were consistent with a *N*-methyl compound bearing a methylene bridge, such as **4**. The attachment of the methylene bridge is shown to the ring hydroxyl by analogy with *N*-benzyl compound **7**, whose structure is discussed below. Hydrogenolysis of either **3** or **4** afforded methyl *N*,*N*-dimethyl-α-thiolincosaminide (**2**).

The foregoing suggested that a successful synthesis of the desired mono-*N*-methyl compound **8** could be achieved provided the amino group of **1** could be suitably blocked to allow reaction with only 1 equiv of formaldehyde. Accordingly, **1** was converted to benzylidine derivative **5** which on careful hydrogenation over platinum formed methyl *N*-benzyl-α-thiolincosaminide (**6**) in high yield. Benzyl derivative **6** readily coupled with formaldehyde to form a less polar compound assigned structure **7**. Elemental analyses and nmr data indicated a cyclic structure containing a methylene group. The choice of attachment of the methylene bridge is shown to the ring hydroxyl rather than to the 7-hydroxyl since chlorination with triphenylphosphine–carbon tetrachloride[5] gave a monochloride in which the 8-methyl signal in the nmr was shifted downfield as noted with other 7-chloro compounds of this type.[1]

Hydrogenolysis of **7** over palladium yielded methyl *N*-methyl-α-thiolincosaminide (**8**) and varying amounts of dimethyl compound **2**. The presence of the latter compound probably is due to partial decomposition of **7** or debenzylated **7**, since the hydrogenolysis reaction required an acidic solution.

In an alternate, but less successful procedure to prepare **8** from **6**, compound **6** was formylated with ethyl formate and reduced with $LiAlH_4$ to give impure *N*-benzyl-*N*-methyl **9** in low yield. Hydrogenolysis of crude **9** gave methyl *N*-methyl-α-thiolincosaminide (**8**) identical with that prepared by the previous method.

Attempts to condense either methyl N-methyl-α-thiolincosaminide (**8**) or methyl *N*-benzyl-α-thiolincosaminide (**6**) with 4-*n*-propylhygric acid by the method previously described[3] were unsuccessful.

Experimental Section

Melting points were taken in Pyrex capillaries and are corrected. Infrared spectra, recorded on a Perkin-Elmer Model 21 spectrophotometer, and nuclear magnetic resonance spectra, recorded on a Varian high-resolution, 60-MHz instrument, were consistent with the structures shown. M^+ values were determined using a Varian MAT CH4 mass spectrometer equipped with a direct insertion probe. Optical rotations were taken in the solvent noted ($c \sim 1$). Silica gel used for chromatography was silica gel 0.05–0.20 mm for chromatography, E. Merck A. G. Distibutors, Brinkman Industries, Inc., Westbury, N. Y.

Methyl *N*-Benzylidene-α-thiolincosaminide (5).—With vigorous stirring 24.7 ml of benzaldehyde was added to a suspension of 50.0 g of methyl α-thiolincosaminide in 990 ml of water containing 5 ml of 5% sodium hydroxide solution. The solid rapidly dissolved and crystals precipitated in a few minutes. The solution was filtered and the residue washed with water and dried. There was thus obtained 46.7 g (69.1%) of **5**, mp 206–207°, λ_{max}^{EtOH} 248 nm (ε 16,000), $[\alpha]D$ +178° (MeOH).

Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.28; H, 6.79; N, 4.10; S, 9.39. Found: C, 56.31; H, 6.61; N, 4.08; S, 9.36.

Methyl *N*-Benzyl-α-thiolincosaminide (6).—A solution of 46.7 g of **5** in 800 ml of methanol containing 8 g of PtO_2 in 100 ml of ethanol was shaken under hydrogen pressure (3 atm) for 4.5 hr. The catalyst was removed by filtration and the solvent distilled

(4) M. Senkus, *J. Amer. Chem. Soc.*, **67**, 1515 (1945); W. H. Edgerton, J. R. Fisher, and G. W. Moersch, *ibid.*, **79**, 6487 (1957).

(5) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).

under vacuum. The crystalline residue was dissolved in 100 ml of warm methanol and diluted with 400 ml of ethyl acetate. The crystals which formed were collected by filtration and dried. They weighed 30.7 g (65%) and melted at 155–157°. The analytical sample, prepared by two recrystallizatios from methanol, melted at 157–159° and gave $[\alpha]_D$ +235° (MeOH).

Anal. Calcd for $C_{16}H_{25}NO_5S$: C, 55.95; H, 7.34; N, 4.08; S, 9.34. Found: C, 55.73; H, 7.31; N, 4.20; S, 9.52.

Methyl *N*-Benzyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (7).—A solution of 11.6 g of *N*-benzyl sugar **6** and 4 ml of formalin in 200 ml of methanol was maintained at 26° for 30 min. Evaporation of the solvent gave a residue of 11.8 g which was chromatographed over 1.2 kg of silica gel using chloroform–methanol (4:1) for elution. A fraction of 11.8 g of oil was recovered. A portion was dissolved in acetone, clarified, and evaporated to a glassy solid, $[\alpha]_D$ +175° (MeOH).

Anal. Calcd for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94; M^+, 355. Found: C, 57.33; H, 6.92; N, 3.93; M^+, 355.

Methyl *N*-Methyl-α-thiolincosaminide (8).—**7** (6 g) was dissolved in 160 ml of methanol and the solution was acidified with 6 *N* hydrochloric acid. Pd/C (10%) (6 g) suspended in 40 ml of 95% ethanol was added. The resulting mixture was shaken for 5 hr under 2 atm of hydrogen pressure. A few drops of acid were added to acidify the solution and hydrogenation continued for 12 hr. The catalyst was removed by filtration and the solvent distilled *in vacuo* after the mixture was made basic with triethylamine. The residue, 7.1 g, was chromatogaphed over 700 g of silica gel. Elution with methanol afforded 1.2 g of dimethyl compound **2**, which was recrystallized from methanol to give 700 mg of crystals, mp 174–176°. The more polar fraction was recrystallized from methanol to yield 900 mg of monomethyl compound **8**, mp 187–189°. Stripping the column with methanol–ammonium hydroxide (5%) followed by recrystallization gave an additional 330 mg of **8**, mp 186–188°. A portion of **8** was recrystallized from methanol. It now melted at 180–182° and gave $[\alpha]_D$ +267° (H_2O).

Anal. Calcd for $C_{10}H_{21}NO_5S$: C, 44.92; H, 7.92; N, 5.24; S, 12.00. Found: C, 45.20; H, 7.54; N, 5.34; S, 11.62.

Methyl *N*-Benzyl-*N*-methyl-α-thiolincosaminide (9).—A mixture of 3 g of **6** and 100 ml of ethyl formate was heated for 2.5 hr at 100° in a stirred autoclave. After cooling, the solution was removed and evaporated to yield an oil. Tlc showed no starting amine **6**, while infrared data indicated stong amide and ester bands. The oil was dissolved in 60 ml of tetrahydrofuran and added to a mixture of 3 g of $LiAlH_4$ in 50 ml of tetrahydrofuran. The mixture was heated at reflux for 20 hr. Water was added and the supernant was decanted from the precipitated salts and evaporated. The residue was crystallized from methanol–acetone to give 200 mg of crude crystals, mp 155–175°. Recrystallization from the same solvent gave 120 mg of **9**, mp 165–175. The nmr spectrum in DMSO was satisfactory. This material was not purified further but used as described below.

Methyl *N*,*N*-Dimethyl-α-thiolincosaminide (2) and Methyl *N*-Methyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (4).—A solution of 10.8 g of methyl α-thiolincosaminide and 4.9 ml of formalin (37%) in 50 ml of water was maintained at room temperature for 30 min. The solution was lyophilized. The amorphous solid was dissolved in 150 ml of methanol and shaken under hydrogen over 1 g of 10% Pd/C for 18 hr. Two grams of catalyst was added and shaking continued for 18 hr. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The residue was dissolved in water, the solution was clarified, and the filtrate was lyophilized. Chromatography over silica gel using chloroform–methanol, 4:1, for elution gave chiefly two oily fractions which crystallized on standing. These fractions were triturated with ethyl acetate to yield the following crops of crystals. The less polar fraction afforded 2.6 g (18.9%) of crystalline **2**, mp 173–179°; the more polar fraction, 1.15 g (82%) of **4**, mp 166–176°. Each fraction showed only one spot on tlc.

The dimethyl compound (**2**) was recrystallized twice from methanol to afford an analytical sample, mp 177–179°, $[\alpha]_D$ +270° (MeOH).

Anal. Calcd for $C_{11}H_{23}NO_5S$: C, 46.95; H, 8.34; N, 4.98. Found: C, 46.96; H, 8.37; N, 5.02.

The more polar fraction after recrystallization from methanol melted at 184–186° and gave $[\alpha]_D$ +254° (MeOH).

Anal. Calcd for $C_{11}H_{21}NO_5S$: C, 47.29; H, 7.58; N, 5.01. Found: C, 47.46; H, 7.91; N, 4.93.

Methyl *N*-Methyl-α-thiolincosaminide (8) by Hydrogenolysis of 9.—The crude crystals of **9** from above were dissolved in 25 ml of methanol and shaken under hydrogen over 200 mg of 10% Pd/C for 7 hr. The catalyst was removed by filtration and the filtrate evaporated. The residue was crystallized from methanol–acetone to give 40 mg of **8**, mp 179–184°, whose infrared spectrum was identical with that of a known sample of **8**.

Methyl 4,6:6,7-Di-*O*,*N*-methylene-α-thiolincosaminide (3).—A solution of 10 g of methyl α-thiolincosaminide in 50 ml of water and 5 ml of formalin was stirred for 10 min. The solution was lyophilized. Chromatography over silica gel (chloroform–methanol, 4:1) gave a 5-g fraction of glassy solid, $[\alpha]_D$ +239° (H_2O).

Anal. Calcd for $C_{11}H_{19}NO_5S$: C, 47.63; H, 6.90; N, 5.05. Found: C, 47.58; H, 6.98; N, 5.21.

Methyl *N*,*N*-Dimethyl-α-thiolincosaminide (2). A. From Methyl 4,6:6,7-Di-*O*,*N*-methylene-α-thiolincosaminide (3).—Methyl 4,6:6,7-di-*O*,*N*-methylene-α-thiolincosaminide (**3**) (500 mg) was shaken over 200 mg of 10% Pd/C for 17 hr under hydrogen pressure. Tlc indicated about equal amounts of dimethyl compound **2** and monomethyl compound **4**. Fresh Pd/C (200 mg) was added and the mixture again shaken for 20 hr. A final addition of 150 mg of PtO_2 was made and shaking continued for 4 hr longer. The catalyst was removed by filtration and the solvent distilled *in vacuo*. The residue was crystallized from methanol to yield 145 mg of **2**, mp 169–172°, identical by infrared absorption with a known sample of **2**.

B. From Methyl *N*-Methyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (4).—**4** (200 mg) was hydrogenolyzed over 100 mg of 10% Pd/C in the manner described above. Evaporation of the solvent after filtration afforded a crystalline residue which when recrystallized from methanol yielded 50 mg of **4**, mp 170–173°. This product was identical by infrared data with known **4**.

Chlorination of Methyl *N*-Methyl-4,6-*O*,*N*-methylene-α-thiolincosaminide (4).—A solution of 0.75 g of **4** and 2.2 g of triphenylphosphine in 10 ml of acetonitrile and 9 ml of carbon tetrachloride was stirred at ambient temperature for 17 hr. Methanol (2 ml) was added and the solvents were evaporated. Chromatography over silica gel afforded 400 mg of oily chlorination product showing only one spot on tlc ($CHCl_3$–MeOH, 6:1). The nmr spectrum in $CDCl_3$ showed a three-proton doublet centered at δ 1.5 (3 H-8). The nmr spectrum of **4** possessed a three-proton doublet centered at δ 1.2 (3 H-8).

Registry No.—**2**, 22939-47-5; **3**, 27093-10-3; **4**, 27093-11-4; **5**, 22939-44-2; **6**, 22939-45-3; **7**, 27141-08-8; **8**, 22939-46-4; **9**, 27093-15-8.

Acknowledgment.—The author acknowledges with gratitude the technical assistance of R. J. Reid.

The Photochemical Acid Type II Reaction of Organic Esters[1a]

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The recent report by Nicholls and Leermakers[2] which established the occurrence of a type II photochemical elimination reaction in butyric and valeric acids, and the absence of such a reaction for butyramide, valeramide, and *N*,*N*-dimethylbutyramide prompts us to communicate our results concerning a closely related reaction. The reaction to which we refer is a type II elimination in the alkyl group of the acid portion of organic esters (acid type II reaction). The

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. (b) National Science Foundation Undergraduate Research Participant, 1969.

(2) C. H. Nicholls and P. A. Leermakers, *J. Org. Chem.*, **35**, 2754 (1970).

TABLE I
COMPETITIVE TYPE II REACTIONS OF ORGANIC ESTERS

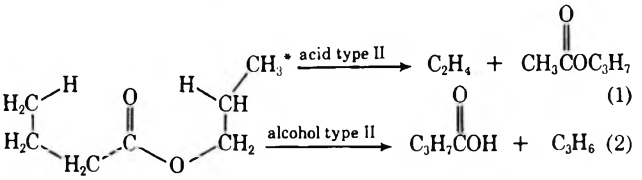
Ester	Acid type II			Alcohol type II			Φ(acid type II)/[a] Φ(alcohol type II)
	No.[b]	Type H	Olefin	No.	Type H	Olefin	
Isopropyl butyrate	3	1[c]	C_2H_4	6	1[c]	C_3H_6	0.129 ± 0.006
n-Propyl butyrate	3	1	C_2H_4	2	2[d]	C_3H_6	0.058 ± 0.002
Isobutyl butyrate	3	1	C_2H_4	1	3[e]	*i*-C_4H_8	0.022 ± 0.001
Ethyl valerate	2	2[d]	C_3H_6	3	1	C_2H_4	2.80 ± 0.12
n-Butyl valerate	2	2	C_3H_6	2	2	1-C_4H_8	0.200 ± 0.011
Isobutyl valerate	2	2	C_3H_6	1	3	*i*-C_4H_8	0.140 ± 0.008

[a] A minimum of three determinations for each value. [b] The number of γ-hydrogen atoms available. [c] Primary. [d] Secondary. [e] Tertiary.

type II elimination in the alkyl group of the alcohol portion of organic esters (alcohol type II reaction) is well established.[3] The acid type II reaction of organic esters was first postulated by Ausloos[4] in 1958 based upon the experimental observation that, in the gas-phase photolysis of methyl butyrate, the yield of ethylene, which is a major product, is only slightly reduced by the presence of molecular oxygen, while essentially all of the other hydrocarbon products disappear. Norrish, *et al.*,[5,6] later reached the same conclusion based upon a similar experimental observation. The experiments described here not only put the occurrence of the acid type II reaction of organic esters on a firmer basis but also provide additional insight into this reaction.

Results

When methyl butyrate vapor undergoes mercury ($^3P_1$) sensitized decomposition in the presence of 10% nitric oxide, the yields of ethylene and methyl acetate are identical within experimental error (±10%). In order to eliminate the analytical difficulties associated with the relative analysis of two substances of very different boiling points and polarities, we have examined the acid type II reaction relative to the alcohol type II reaction in esters which are capable of undergoing both reactions. This competition is shown in reactions 1 and 2 for *n*-propyl butyrate. In the absence of prod-



(1)

(2)

ucts originating from free radicals, the ratio of C_2H_4/C_3H_6 may be equated to the ratio of the quantum yield of reaction 1 relative to that of reaction 2. In the mercury sensitized photolysis of the esters shown in Table I, in the presence of nitric oxide and at conversions of 0.5%, saturated hydrocarbons and olefins, other than those expected from reactions 1 and 2, constitute less than 0.1% of the total yield of the expected olefins. The last column in Table I gives the ratio of the quantum yield for the acid type II reaction relative to that for the alcohol type II reaction for each of the six esters.

Discussion

The observation of ethylene and methyl acetate in equivalent yields from the photolysis of propyl acetate substantiates the occurrence of the alcohol type II reaction. The data presented in Table I indicate that the alcohol type II reaction is the favored reaction. This is most clearly demonstrated by the ratio of 0.200 obtained for *n*-butyl valerate. In this ester both the number and type of γ hydrogens are the same for each reaction. The remainder of the data also support this conclusion. The only case in which the ratio observed is greater than 1 is that of ethyl valerate. In this particular ester a secondary hydrogen atom is transferred in the acid type II reaction while a primary hydrogen atom is transferred in the alcohol type II reaction. The data in Table I indicate that, although the number of γ-hydrogen atoms available for each reaction has a slight effect upon the competition, the major factor is the strength of the C–H bond which is broken. The importance of this factor in the alcohol type II reaction has been recognized previously by Ausloos, *et al.*,[7,8] who observed a primary isotope effect in the photolysis of ethyl acetate-d_1 and also a preferential transfer of a secondary rather than a primary hydrogen atom in the photolysis of *sec*-butyl acetate and formate. Similar effects have also been recognized by Ausloos, *et al.*,[9,10] and Nichol and Calvert[11] among others, in the type II reaction of ketones. These observations are perhaps not unexpected if one makes the reasonable assumption that C–H bond breaking is occurring in the transition state. This assumption is supported by the molecular orbital calculations of Boer, *et al.*,[12] who concluded that, although olefin formation is not important in the transition state, C–H bond breaking is occurring in the transition state.

The observation that the competition between the alcohol type II and the acid type II reactions of organic esters is dependent upon structural differences in the alkyl groups is, we believe, presumptive evidence that the same excited state is involved in both reactions. Therefore it appears that the relative quantum yields are related directly to the relative rate constants for the partitioning of that excited state between the alternate paths indicated by reactions 1 and 2. Since spin conservation normally holds for Hg($^3P_1$) sensitized

(3) J. G. Calvert and J. N. Pitts, "Photochemistry," Wiley, New York, N. Y., 1966, p 435.
(4) P. Ausloos, *Can. J. Chem.*, **36**, 383 (1958).
(5) P. Borrell and R. G. W. Norrish, *Proc. Roy. Soc., Ser. A*, **262**, 19 (1961).
(6) R. G. W. Norrish and R. P. Wayne, *ibid.*, **284**, 1 (1965).
(7) P. Ausloos and R. E. Rebbert, *J. Phys. Chem.*, **67**, 163 (1963).
(8) R. P. Borkowski and P. Ausloos, *J. Amer. Chem. Soc.*, **83**, 1053 (1961).
(9) P. P. Borkowski and P. Ausloos, *J. Phys. Chem.*, **65**, 2257 (1961).
(10) P. Ausloos, *ibid.*, **65**, 1616 (1961).
(11) C. H. Nichol and J. G. Calvert, *J. Amer. Chem. Soc.*, **89**, 1790 (1967).
(12) F. P. Boer, T. W. Shannon, and F. W. McLafferty, *ibid.*, **90**, 7239 (1968).

reactions, the excited state involved in the present system is most likely a triplet, presumably n–π^*.

Experimental Section

Each of the six esters used in this study was synthesized by the reaction of the appropriate acid chloride and alcohol. After being refluxed for 24 hr, the reaction mixture was distilled through a Vigreux column. After a number (usually three to four) of careful distillations in which only the middle half of the distillate was taken, no impurities were observed by gas chromatography using both diisodecyl phthalate and Hallcomid columns.

Mercury sensitized photolyses were conducted in a cylindrical quartz cell containing a drop of mercury. The light source was a Hanovia 87A-45 low-pressure mercury vapor lamp. Since the envelope of this lamp is Vycor, the radiation is pure 253.7 nm and contains none of the 184.9-nm mercury line. The reaction is entirely mercury sensitized since the long wavelength cutoff of absorption by aliphatic esters is 240 nm. The pressure of the esters was generally 2–5 Torr and nitric oxide was added to remove products of free-radical reactions. The data given in Table I were determined at conversions of 0.5% in the presence of 10% nitric oxide.

Hydrocarbon products were analyzed using a 30 ft long, 0.25 in. o.d. column packed with 20% squalane on 60–80 mesh Chromosorb P, operated at ambient temperature and a helium flow of 70 ml/min. Methyl acetate was analyzed using a 10 ft long 0.25 in. o.d. column packed with 10% diisodecyl phthalate on 60–80 mesh Chromosorb P, operated at 80° and a helium flow of 30 ml/min.

Registry No.—Isopropyl butyrate, 638-11-9; *n*-propyl butyrate, 105-66-8; isobutyl butyrate, 539-90-2; ethyl valerate, 539-82-2; *n*-butyl valerate, 591-68-4; isobutyl valerate, 10588-10-0.

Acknowledgment.—We would like to thank Professor S. J. Weininger for his interest in this work.

The Preparation and Certain Reactions of 3-Formyl-4*H*-flavene

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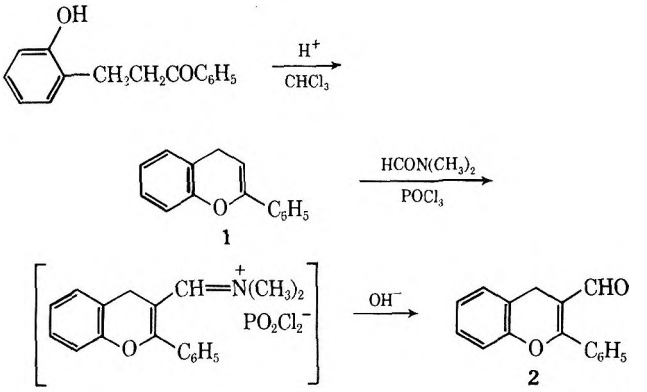
Received July 8, 1970

Recently we described[1] a convenient method for the preparation of 4*H*-flavene (2-phenyl-4*H*-1-benzopyran) (**1**). The present paper describes the formylation of **1** to give 3-formyl-4*H*-flavene (**2**) and the reaction of **2** with some active methyl compounds.

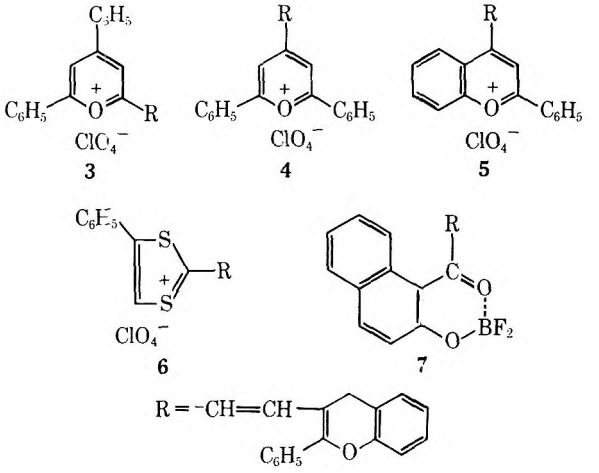
The Vilsmeier reagent reacts with **1** to give an intermediate iminium salt (not characterized) which was hydrolyzed to give **2**, as shown in Scheme I. It is interesting that the aldehyde **2** is stable, in contrast to **1**, which is quite unstable and decomposes to a tar in several hours. We have found that it is not necessary to isolate **1** but, instead, to treat the chloroform reaction mixture containing **1** directly with the Vilsmeier reagent.

The aldehyde **2** was allowed to react with some charged heterocyclic compounds which contained active methyl groups to give the compounds listed in Scheme II. Only compounds which contain very reactive methyl

SCHEME I

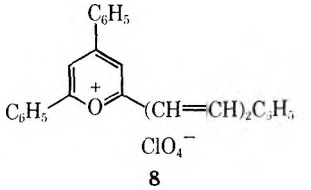


SCHEME II



groups react with **2**. No reaction took place between **2** and 1-ethyl-2-methylquinolinium perchlorate or 1,2-dimethylnaphtho[1,2-*d*]thiazolium perchlorate under the conditions employed for the preparation of the compounds in Scheme II.

The dyes listed in Scheme II show absorption at longer wavelengths than the corresponding simple styryl dyes. For example, in acetonitrile solution, 2,4-diphenyl-6-(4-phenyl-1,3-butadienyl)pyrylium perchlorate[2] (**8**) shows absorption at λ_{max} 490 mμ (ϵ 30,200)



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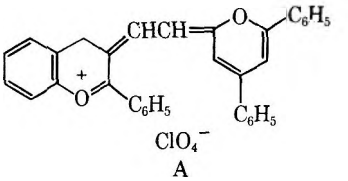
while **3** shows λ_{max} 539 mμ (ϵ 28,900). It is evident that the oxygen atom of the flavene nucleus has affected the absorption of **3**, and therefore canonical forms such as A must be considered. However, comparison of the



A

(1) J. A. VanAllan, G. A. Reynolds, and T. H. Regan, *J. Org. Chem.*, **32**, 1897 (1967).

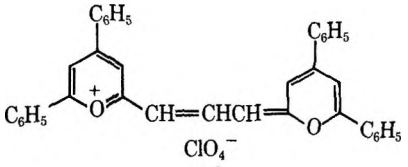
(2) R. Wizinger and K. Wagner, *Helv. Chim. Acta*, **34**, 2290 (1951).

TABLE I
PHYSICAL PROPERTIES AND ANALYTICAL DATA

Compd no.	Method of prepn	Mp, °C	Yield, %	Solvent of recrystn	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Found, % C	Found, % H	Found, % Cl	Absorption, λ_{max} ($\epsilon \times 10^{-3}$) in $CHCl_3$
2		65–66	56	Ligroin (bp 63–75°)	$C_{16}H_{12}O_2$	81.3	5.1		81.1	5.3		295 (11.8)
3	A	260–261	42	Acetic anhydride	$C_{34}H_{25}ClO_6$	72.1	4.5	6.3	71.9	4.7	6.4	274 (16.3), 352 (35.4), 539 (39.9)
4	A	264–265	53	*Acetonitrile*	$C_{34}H_{25}ClO_6$	72.1	4.5	6.3	71.9	4.6	6.6	269 (23.1), 406 (21.3), 313 (9.8), 523 (55.3)
5	A	253–254	67	Acetic anhydride	$C_{32}H_{23}ClO_6$	71.3	4.3	6.6	71.0	4.5	6.7	249 (21.1), 390 (19.7), 263 (17.0), 562 (45.5)
6	A	85–86	61	Acetic anhydride	$C_{26}H_{19}ClO_5S_2$	61.0	3.7	12.5	60.6	4.0	12.4	~240 (18.4), 525 (33.3), ~280 (7.2)
7	A	214–215	20	Alcohol	$C_{28}H_{19}BF_2O_3$	74.4	4.2	8.4	74.1	4.4	8.6	238 (29.0), ~380 (7.2), 340 (14.2), ~520 (34.0), 540 (46.4)
8	...[a]	207–209		Acetonitrile	$C_{27}H_{21}ClO_5$	70.2	4.6	7.7	70.0	4.3	7.5	264 (13.8), ~368 (22.0), 345 (28.0), 490 (30.2)
9		125–126		Acetic anhydride	$C_{37}H_{27}ClO_6$	73.0	4.5	5.8	72.9	4.7	6.0	267 (27.5), 452 (3.0), 308 (30.0), 482 (3.0), 249 (27.0), 527 (1.0), 388 (25.5), 720 (76.0), ~413 (11.0), 790 (99.0)
11	A	297	87	Acetic anhydride	$C_{28}H_{22}ClNO_5$	69.0	4.8	2.9	69.2	5.2	2.7	270 (19.2), 385 (21.6), 325 (11.6), 550 (90.5)
12	A	287	88	Acetonitrile	$C_{28}H_{22}ClNO_5$	69.0	4.8	2.9	68.7	4.8	2.7	268 (29.8), 570 (40.4), 353 (28.4)

[a] Reference 2.

spectrum of **3** with that of the symmetrical pyrylium cyanine dye **9** [λ_{max} 790 mμ (ϵ 99,000)] demonstrates that A is not an important resonance contributor in the dye **3**.



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In order to determine the effect of the basicity of the heteroatom on the absorption spectra, the dyes **11** and **12** were prepared by the reaction sequence shown in Scheme III.

The nitrogen containing dyes **11** and **12** showed absorption at approximately 30-mμ longer wavelength than the corresponding oxygen dyes **3** and **4** (see *Table I*).

Several attempts were made to prepare 3-formylflavylium perchlorate by treatment of **1** with triphenylmethyl perchlorate, but the only product that was identified in the reaction mixture was triphenylmethane.

Experimental Section

The physical properties of the compounds are collected in Table I.

3-Formyl-4*H*-flavene (2).—A mixture of 5 g (0.22 mol) of 2-hydroxydihydrochalcone, 0.5 g of *p*-toluenesulfonic acid, and 50 ml of chloroform was refluxed for 2 hr while the water which is formed in a Dean-Stark water separator was collected. The cooled solution was shaken with dilute aqueous sodium bicarbonate, and the organic phase was dried (magnesium sulfate) and filtered from the drying agent. The filtrate was added to a cooled mixture of 4.5 ml of dimethylformamide and 2.3 ml of phosphorus oxychloride, and the resulting mixture was stirred for 2 hr at room temperature. The reaction mixture was mixed with 50 ml of 5% aqueous sodium hydroxide, and the mixture was stirred for 1 hr. The organic phase was separated, washed with water, and dried (magnesium sulfate), and the chloroform was removed by means of a rotary evaporator. The oily residue solidified on standing. The nmr spectrum[3] of **2** in deuteriochloroform showed absorptions at δ 3.69, singlet (2 H) for the methylene protons, a multiplet at δ 7.19–7.52 (9 H) for the aromatic protons, and a singlet at δ 9.62 for the aldehyde proton. A sample of **2** was converted to the dinitrophenylhydrazone, mp 237–238°.

Anal. Calcd for $C_{22}H_{16}N_4O_5$: C, 63.6; H, 3.6; N, 13.5. Found: C, 64.0; H, 3.8; N, 13.5.

Method A.—The dyes listed in Table I were prepared by the following procedure. A mixture of 1 mmol of **2** and 1 mmol of the appropriate methyl-substituted heterocyclic compound in 25 ml of acetic anhydride was refluxed for 30 min. The colored reaction mixture was chilled and the solid was collected. In some cases it was necessary to dilute the reaction mixture with ether to obtain the product.

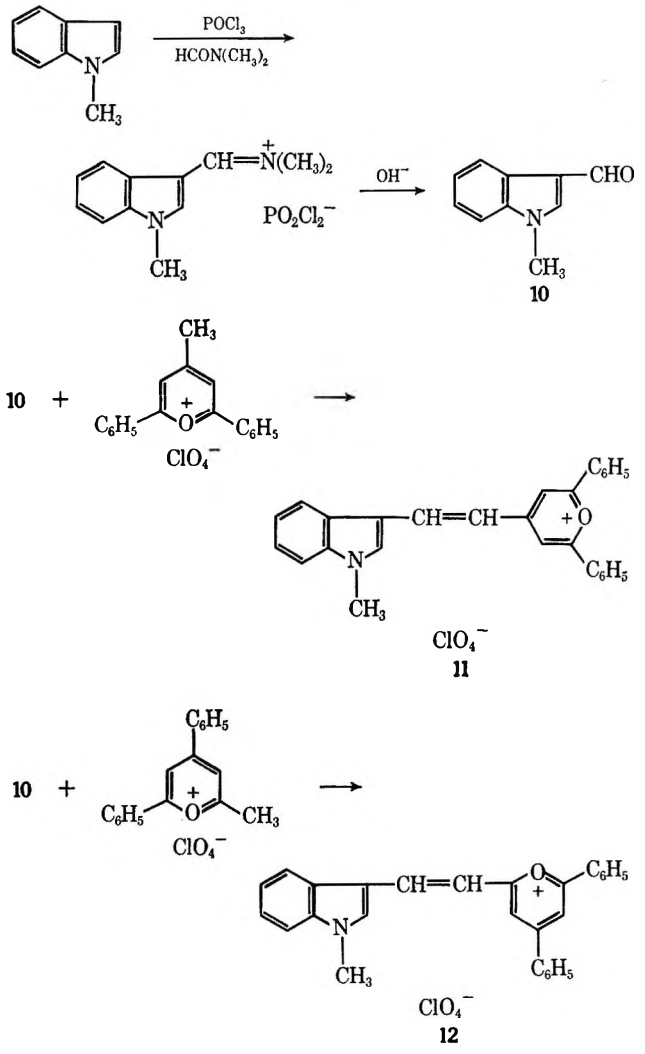
3-Formyl-1-methylindole (10).—A solution of 6 g of dimethylformamide, 7.2 ml of phosphorus oxychloride, 10 g of 1-methylindole, and 50 ml of chloroform was stirred at room temperature for 1 hr. The reaction mixture was washed with water, 50 ml of 5% aqueous sodium hydroxide was added to it, and the stirring was continued for an additional hour. The chloroform layer was separated, washed with water, and dried (magnesium sulfate). The solvent was removed to yield 11 g of the aldehyde, mp 62–64° (reported[4] mp 65°).

4,6-Diphenyl-2-[3-(4,6-diphenyl-2*H*-pyran-2-ylidene)propenyl]-pyrylium Perchlorate (9).—A mixture of 3.5 g of 2-methyl-4,6-diphenylpyrylium perchlorate, 6 ml of triethyl orthoformate, 50 ml of acetic acid, and 5 ml of pyridine was refluxed for 0.5 hr and then chilled. The solid was collected and recrystallized from acetic acid and then again from acetic anhydride to yield 1.2 g of **9**.

(3) The nmr spectrum was measured at 60 MHz on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

(4) H. Wieland, W. Kronz, and H. Mittasch, *Justus Liebigs Ann. Chem.*, **513**, 1 (1934).

SCHEME III



Registry No.—**2**, 27179-40-4; **2** 2,4-DNP, 27179-41-5; **3**, 27179-42-6; **4**, 27179-43-7; **5**, 27179-44-8; **6**, 27179-45-9; **7**, 22181-72-2; **8**, 6802-23-9; **9**, 27179-48-2; **11**, 27179-49-3; **12**, 27179-50-6.

Acknowledgment.—We are indebted to Dr. T. H. Regan and Mr. R. L. Young for the determination and interpretation of the nmr spectrum.

Reaction of 2-Thiouracils with Formaldehyde under Acidic Conditions

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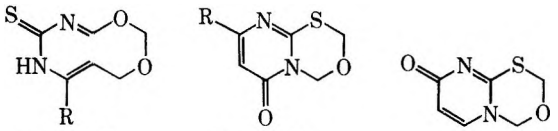
Received September 26, 1969

The reaction of 6-methyl- and 6-phenyl-2-thiouracil with formaldehyde under acidic conditions has previously been investigated. Structures **1b** and **1c** were assigned to the products.[1] The basis for this assignment was the observation that the same products were obtained also by reaction of the 5-hydroxymethyl derivatives of these thiouracils with formaldehyde under the same reaction conditions.[1] Thus it appeared that substitution at position 5 of the 2-thiouracil ring had been incontrovertibly demonstrated. Since these results were not in agreement with the available evidence, which indicated that the sulfur atom could be a very reactive center,[2-5] we reinvestigated these reactions and included 2-thiouracil because of its biological significance.

First we ascertained that 2-thiouracil itself reacts with formaldehyde under acidic conditions giving the pyrimidooxathiazine **2a**. Confirmation of the assigned structure seemed necessary not only in order to exclude possible isomeric formulas **1a** and **3**, but also because the reaction product crystallized from water giving two crystalline forms, aggregates of orthorhombic needles and monocline crystals. This was accomplished by X-ray analysis (see Experimental Section). The two crystalline forms were shown to represent a single substance having the assigned structure (**2a**).



1a, R = H
b, R = CH_3
c, R = C_6H_5

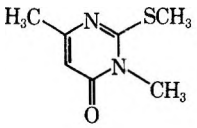
2a, R = H
b, R = CH_3
c, R = C_3H_7

3

Nmr, ir, and uv data were fully compatible with this assignment. In particular the nmr spectra of the two crystalline forms were identical and fully compatible with structures **2a** and **3**, since position 5 of the original 2-thiouracil ring was shown to be unsubstituted.

The ir spectra in Nujol mull were different because of the different crystal-packing effects while spectra in chloroform solutions were identical; all these spectra showed the presence of the carbonyl bands.

Uv spectra of both crystalline forms of **2a** in water were identical and very similar to the uv spectra of the pyrimidothiazine **5** (methanol), 3,6-dimethyl-2-methylthiopyrimidin-4-one (**4**) (methanol),[6] and the thiazolopyrimidine **5** (water), displaying a maximum in the range 285–295 mμ and two very close maxima in the range 224–245 mμ. Because of this we concluded that all the above-mentioned substances had the same *o*-quinoid chromophore shown to be present in **2a**; structures **5** and **6** were previously supported only by ir analysis.[4]



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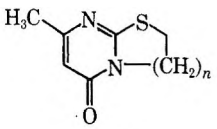
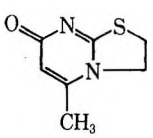


5, $n = 2$
6, $n = 1$



7

The presence of two very close maxima in the uv spectrum of **4** in methanol at about 230 and 240 mμ

(1) L. Monti and C. Pacini, *Gazz. Chim. Ital.*, **78**, 638 (1948).

(2) B. Stanovnik and M. Tisler, *Arzneim.-Forsch.*, **14**, 1004 (1964).

(3) H. F. Andrew and C. K. Bradsher, *J. Heterocycl. Chem.*, **4**, 577 (1967).

(4) N. G. Pashkurov and V. S. Reznik, *Khim. Geterotsikl. Soedin.*, 1918 (1968).

(5) I. Wempen, and J. J. Fox, *J. Org. Chem.*, **34**, 1020 (1969).

(6) P. Galimberti, V. Gerosa, and M. Melandri, *Ann. Chim. (Rome)*, **48**, 457 (1958).

has been interpreted as resulting from a tautomeric equilibrium in which the N–CH_3 bond is being broken and a new O–CH_3 bond is being formed.[6,7] Although the uv spectra of **2a** and **6** in water were very similar to that reported for **4** in methanol, this tautomerism cannot operate in the case of **6**. Moreover on changing the solvent to methanol or ethanol the two very close maxima of **2a** and **6** overlapped. Hence the tautomerism most likely does not apply in the case of **4** either.

Starting from 6-methyl- and 6-propyl-2-thiouracil the expected homologs of **2a** were obtained. Structures **2b** and **2c** have been assigned to these compounds on the basis of the following considerations.

Firstly uv spectra of **2b** and **2c** in various solvents were quite similar to the corresponding spectra of **2a**. Secondly, the presence of a *p*-quinoid chromophore characteristic of an isomer of the type **3** was ruled out by comparing the uv spectra of **2b** and **2c** with those of the thiazolopyrimidine **7** in various solvents. The structure of **7** has been previously supported only by ir analysis.[4] Finally the chromophore characteristic of **1a** has been excluded because the ir spectra of **2b** and **2c** showed the presence of a carbonyl group and their nmr spectra demonstrated the presence of a proton bound to the carbon atom adjacent to this carbonyl.

Now that the structure of the product **2b** has been established the role played by the acidity of the medium can be understood. Under conditions of weak acidity 5-hydroxymethyl-2-thiouracils are preferentially formed, as reported in the literature.[1,8] Under conditions of strong acidity the sulfur atom becomes the reactive center and pyrimidooxathiazines like **2a–c** are formed with the unstable 5-hydroxymethyl derivatives serving as intermediates.

The appearance of the new reactive center is also evidenced when uracil and 2-thiouracil respectively are allowed to react with formaldehyde in the presence of concentrated hydrochloric acid. Uracil is reported to form the 5-chloromethyl derivative.[9] Under the same reaction conditions we have now obtained the hydrochloride of the pyrimidooxathiazine **2a** in good yield from 2-thiouracil.

Experimental Section

Melting points were determined in a Büchi capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 225 spectrophotometer. Ultraviolet spectra were determined on a Hitachi Perkin-Elmer Model 124 spectrophotometer and nmr spectra on a Varian A-60 spectrophotometer with tetramethylsilane as internal reference. Eastman Chromogram 6060 sheets (silica gel with fluorescent indicator) were used for thin layer chromatography and were developed with ligroin–methyl alcohol–ethyl acetate (2:5:2).

Crystal Structure Determination.—On the basis of procession photographs, taken with Co Kα radiation, the plate-like crystals were found to belong to the monoclinic system. The cell parameters were $a = 11.66 \pm 0.02$ Å, $b = 8.71 \pm 0.02$ Å, $c = 7.32 \pm 0.02$ Å, $\beta = 110.2 \pm 0.3°$, $U = 697.4$ Å^3 with eight formula units per unit cell. The systematic extinctions, $0k0$ for k odd and $h0l$ for l odd, indicated the centrosymmetric space group C_{2h}^5-$P2_1/c$. Intensity data were collected by the equiinclination Weissenberg technique, using Fe-filtered Co Kα radiation. Levels $hk0$ and $h0l$ through $h5l$ were recorded by the multiple film technique. The intensities of 513 independent reflections were measured by visual comparison with a calibrated scale. The usual Lorentz and polarization factors and the spot-shape correction for nonzero levels were applied. No correction for absorption or extinction was made. The observed structure amplitudes were placed in a common scale by Weissenberg cross-level data. The structure was solved by the heavy-atom method and refined by the block-diagonal isotropic method to $R = 0.097$, the atomic parameters of the hydrogen atoms being not allowed to vary.[10] See Table I.

TABLE I

FINAL FRACTIONAL COORDINATES OF THE ATOMS[a]

Atom	x	y	z
S	0.5680 (3)	0.5092 (5)	0.2761 (5)
O(1)	0.9861 (7)	0.3592 (13)	0.2918 (13)
O(2)	0.7226 (7)	0.6540 (11)	0.1313 (12)
N(1)	0.6465 (8)	0.2327 (14)	0.2743 (14)
N(2)	0.7925 (8)	0.4197 (14)	0.2804 (14)
C(1)	0.6777 (11)	0.3747 (16)	0.2764 (15)
C(2)	0.7314 (12)	0.1250 (18)	0.2843 (19)
C(3)	0.8465 (10)	0.1554 (17)	0.2861 (18)
C(4)	0.8849 (11)	0.3137 (18)	0.2880 (18)
C(5)	0.8208 (12)	0.5862 (19)	0.2812 (23)
C(6)	0.6193 (12)	0.6809 (17)	0.1876 (19)
H(2)	0.7049	0.0045	0.2893
H(3)	0.9088	0.0622	0.2853
H(5-1)	0.8284	0.6380	0.4208
H(5-2)	0.9059	0.6063	0.2570
H(6-1)	0.5431	0.7684	0.3016
H(6-2)	0.5452	0.7268	0.0640

[a] Estimated standard deviations are in parentheses for the nonhydrogen atoms. The esd's were derived from the residuals and the diagonal elements of the inverse matrix of the last least-square cycle.

All calculations were performed on an IBM 7044 computer using programs of Immirzi[11] and Albano, *et al.*[12] A program of our own design (unpublished) was used to calculate best molecular planes according to Schomaker, *et al.*[13] The atomic scattering factors used were those given in the "International Tables for X-Ray Crystallography"[14] for sulfur, those of Berghuis, *et al.*,[15] for nitrogen, and those of Hanson, *et al.*,[16] for oxygen, carbon, and hydrogen.

The results of this analysis showed that the crystals consisted of discrete molecules of the isomer **2a**. A perspective drawing of the molecule is shown in Figure 1. The S and C(5) atoms are coplanar with the pyrimidine ring within 0.05 Å. The conformation of the oxathiazine ring is well described by the torsion angles around its bonds: C(1)–N(2), 0.3; N(2)–C(5), −49.8; C(5)–O(2), 81.8; O(2)–C(6), −56.3; C(6)–S, 5.1; S–C(1), 20.9°.

The needle-like crystals are orthorhombic with cell dimensions, determined from precession photographs, $a = 7.08 \pm 0.02$ Å, $b = 4.02 \pm 0.01$ Å, $c = 24.29 \pm 0.04$ Å, $U = 691.3$ Å^3. The crystals appeared to be disordered and the observed extinctions did not allow a sure determination of the space group. However, since we were interested in the overall geometry of the molecule, the space group analysis has not been carried out. The projection of the structure onto (010) is centrosymmetric and belongs

(7) For a conclusive discussion on the uv spectra of uracil derivatives, see J. Pitha, *J. Org. Chem.*, **35**, 903 (1970); and for 2-thiouracil derivatives, see J. Reiter, P. Sohár, and J. Lipták, *Tetrahedron Lett.*, **17**, 1417 (1970).

(8) G. Poetsch and R. Behrend, *Justus Liebigs Ann. Chem.*, **448**, 89 (1926).

(9) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Amer. Chem. Soc.*, **82**, 991 (1960).

(10) Listings of atomic parameters, bond lengths, and angles and deviation of the atoms from planarity will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

(11) A. Immirzi, *Ric. Sci.*, **10**, 846 (1967).

(12) V. Albano, A. Domenicano, and A. Vaciago, *Gazz. Chim. Ital.*, **96**, 922 (1966).

(13) V. Schomaker, J. Waser, R. E. Marsh, and G. Bergman, *Acta Crystallogr.*, **12**, 600 (1959).

(14) "International Tables for X-Ray Crystallography," Vol. 3, Kynoch Press, Birmingham, England, 1962.

(15) J. Berghuis, I. J. M. Haanappell, M. Potters, B. O. Loopstra, C. H. Gillavry, and A. L. Veenedaal, *Acta Crystallogr.*, **8**, 478 (1955).

(16) H. P. Hanson, F. Herman, J. D. Lea, and S. Skilman, *ibid.*, **17**, 1040 (1964).

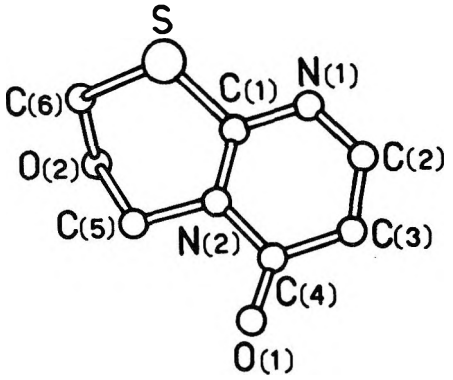


Figure 1.—A sketch of the molecule with a numbering scheme. The hydrogen atoms are not shown.

to the plane space group *pmg*. A two-dimensional analysis, carried out on the basis of 116 independent *h*0*l* reflections using the heavy-atom method, allowed the location of all the nonhydrogen atoms. After three cycles of isotropic block-diagonal least-squares refinement the *R* factor was 0.21. This value suggests that the deduced model is essentially correct, as shown by the Fourier projection calculated on the basis of these data. Since the geometry of the molecule was univocally determined, no attempt was made to locate the hydrogen atoms in order to inprove the refinement.

Thus the results showed that the orthorhombic needles and the monocline crystals were two crystalline modifications of a single substance having the assigned structure **2a**.

6*H*-Pyrimido[2,1-*d*][1,3,5]oxathiazin-6-one (2a).—The procedure reported in literature[1] for the homolog **2b** has been followed. 2-Thiouracil (18 g) was dissolved in a mixture of 40 ml of water, 130 ml of concentrated sulfuric acid, and 30 ml of 35% formaldehyde. The solution was allowed to stand at room temperature for 24 hr and was stirred occasionally. After dilution with 800 ml of water, the pH was adjusted to about 8 with diluted ammonia. The precipitate that formed was collected by filtration and crystallized from water. A mixture of monoclinic crystals, mp 132°, and fibrous aggregates of orthorhombic needles, mp 131.5°, was obtained. The monoclinic crystals could be converted into needles by recrystallization from aqueous solutions. The two crystalline forms had identical nmr[17] and uv spectra: λ_{max}^{hexane} 298 mμ (ε 7496), 228 (6283); λ_{max}^{water} 293, 240, 226 at pH 6.5; $\lambda_{max}^{95\%\ ethanol}$ 296.5 (240 mμ sh), 228; $\lambda_{max}^{methanol}$ 296 (240 sh), 229; $\delta_{TMS}^{CDCl_3}$ 7.78 (d, 1 H, CH), 6.21 (d, 1 H, CH), 5.58 (s, 2 H, CH_2), 5.31 (s, 2 H, CH_2). The ir spectra were different: *e.g.*, monoclinic crystals, ν_{max}^{Nujol} 1690 and 1666 (C=O); needles, ν_{max}^{Nujol} 1678 and 1664 (C=O); $\nu_{max}^{CHCl_3}$ 1680 cm^{-1} (C=O) for both forms.

The R_f values obtained by thin layer chromatography for both these crystalline forms were identical.

Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.34; H, 3.55; N, 16.46; O, 18.80; S, 18.84. Found: C, 42.21; H, 3.59; N, 16.46; O, 19.01; S, 18.76.

The hydrochloride of the base described above has been obtained from 2-thiouracil itself in a 55% yield; the procedure followed was that reported for chloromethylating uracil;[9] and the product was precipitated by addition of acetone to the reaction mixture. After recrystallization from alcohol–ether, the compound had mp 187° with decomposition, depending on the heating speed. This hydrochloride can also be obtained from chloroform solutions of the base by precipitation with hydrogen chloride.

Anal. Calcd for $C_6H_7ClN_2O_2S$: C, 34.88; H, 3.41; N, 13.55; Cl, 17.15; S, 15.51. Found: C, 34.92; H, 3.50; N, 13.48; Cl, 17.03; S, 15.64.

6*H*-8-Methylpyrimido[2,1-*d*][1,3,5]oxathiazin-6-one (2b).—The procedure reported for **2a** was followed starting from 6-methyl-2-thiouracil. After recrystallization from water, the yield was 84%; mp 140° (lit.[1] mp 140–141°); λ_{max}^{hexane} 294 mμ (ε 6915), 228 (6409); $\lambda_{max}^{95\%\ ethanol}$ 293.5, 240 (230 mμ sh); λ_{max}^{water} 290, 243.5 (225.5 sh); $\delta_{TMS}^{CD_3SO}$ 6.00 (s, 1 H, CH), 5.46 (s, 2 H, CH_2), 5.40 (s, 2 H, CH_2), 2.08 (s, 3 H, CH_3); $\nu_{max}^{CHCl_3}$ 1679 cm^{-1} (C=O).

Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.37; N, 15.20. Found: C, 45.45; H, 4.20; N, 15.32.

(17) J. P. Kokko, L. Mandell, and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 1042 (1962).

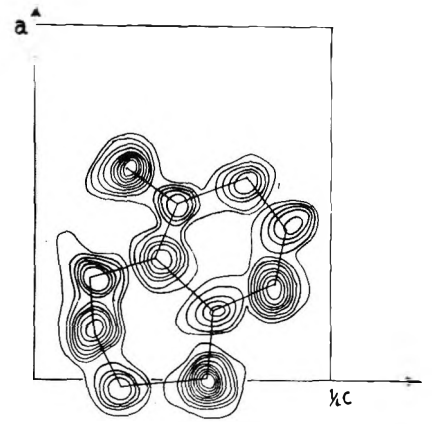


Figure 2.—Fourier projection of the electron density onto (010). Contours are drawn at intervals of 2 e $Å^{-2}$ for the S atom and of 1 e $Å^{-2}$ for the O, N, and C atoms.

6*H*-8-Propylpyrimido[2,1-*d*][1,3,5]oxathiazin-6-one (2c).—The procedure reported for **2a** was followed starting from 6-propyl-2-thiouracil. After recrystallization from water, the product had mp 97°; λ_{max}^{hexane} 295 mμ (ε 6770), 229 (ε 6498); λ_{max}^{water} 288, 242 (221.5 sh); $\lambda_{max}^{95\%\ ethanol}$ 294.5, two overlapping maxima 235; $\delta_{TMS}^{CDCl_3}$ 6.0 (s, 1 H, CH), 5.5 (s, 2 H, CH_2), 5.26 (s, 2 H, CH_2), and with approximated first order 2.37 (tr, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 0.87 (tr, 3 H, CH_3); $\nu_{max}^{CHCl_3}$ 1675 cm^{-1} (C=O).

Anal. Calcd for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20. Found: C, 50.87; H, 5.60; N, 13.28.

8-Methyl-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (5)[4] had λ_{max}^{water} 292 mμ, 247; $\lambda_{max}^{95\%\ ethanol}$ 295 (240 sh), 228; $\lambda_{max}^{methanol}$ 294, 243.5, 229. The hydrochloride precipitated from a chloroform solution of the base with hydrogen chloride had mp 268–270° (uncor).

Anal. Calcd for $C_8H_{11}N_2ClOS$: C, 43.93; H, 5.07; N, 12.81. Found: C, 43.69; H, 4.98; N, 12.90.

7-Methyl-2*H*,5*H*-thiazolo[3,2-*a*][1,3]pyrimidin-5-one (6)[4] had λ_{max}^{water} 284.5 mμ (243 and 227 mμ sh); $\lambda_{max}^{95\%\ ethanol}$ 285.5, 227; $\lambda_{max}^{methanol}$ 285 (240 mμ sh), 228.

5-Methyl-2*H*,7*H*-thiazolo[3,2-*a*][1,3]pyrimidin-7-one (7)[4] had λ_{max}^{water} 262 mμ, 229; $\lambda_{max}^{95\%\ ethanol}$ (257 sh), 229.5; $\lambda_{max}^{methanol}$ 264, 228.5.

Registry No.—**2a**, 27092-97-3; **2a** HCl, 27092-98-4; **2b**, 27092-99-5; **2c**, 27093-00-1; **5** HCl, 27093-01-2; 2-thiouracil, 156-82-1; formaldehyde, 50-00-0.

Acknowledgment.—The authors are very indebted to Dr. E. Trivellone for preliminary nmr spectroscopy and to Mrs. A. Andreassi for her cooperation. This work has been partly supported by Italian National Research Council.

Cyclization of Some 2-(Haloacylamino)pyrimidines

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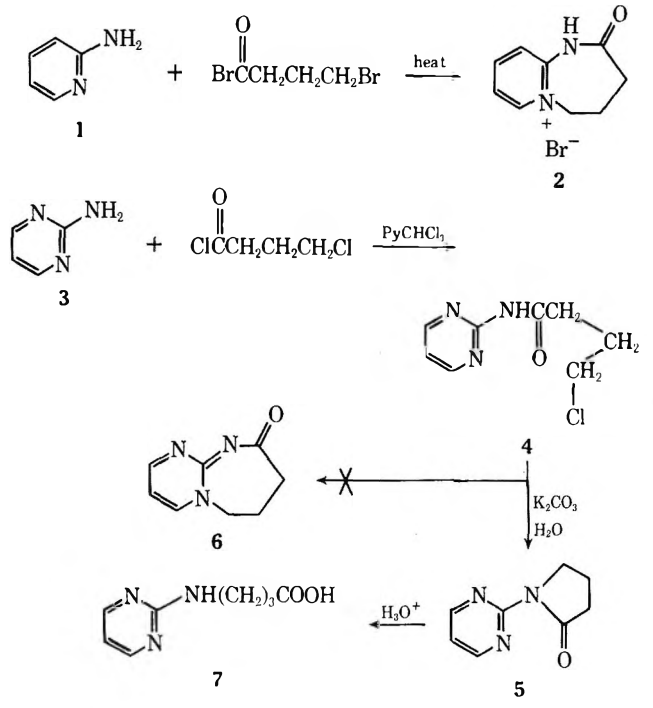
Fozard and Jones[2] reported that heating 2-aminopyridine (**1**) with 4-bromobutyryl bromide led to the formation of 2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[1,2-*a*]-diazepinium bromide (**2**, Scheme I). When we at-

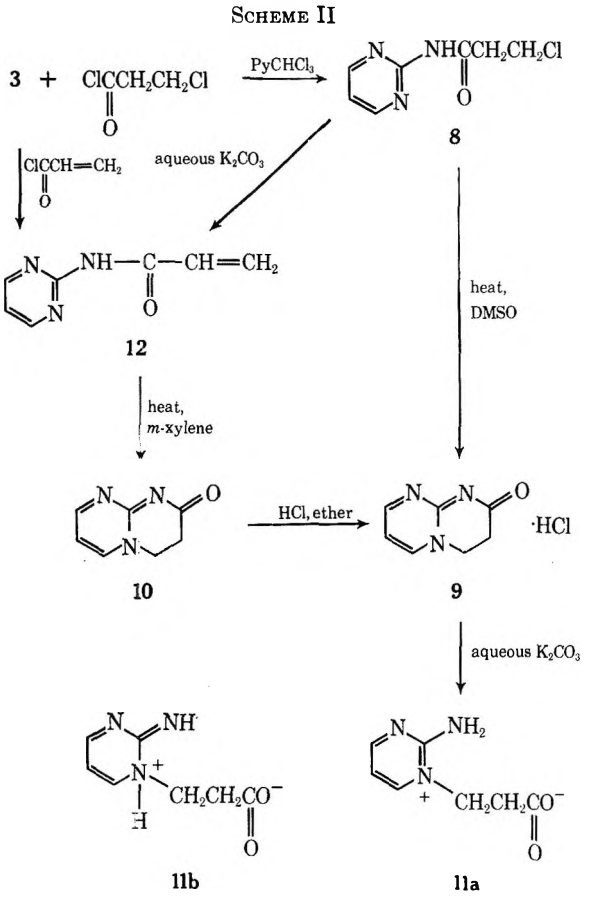
(1) To whom inquiries should be addressed.

(2) A. Fozard and G. Jones, *J. Chem. Soc.*, 2763 (1964).

SCHEME I



SCHEME II



tempted reaction of 2-aminopyrimidine (**3**) with either 4-iodobutanoic acid[3] or 4-chlorobutyryl chloride under similar conditions,[2] only the respective hydrohalide salts of **3** were isolated. The precursor haloamide, 2-(4-chlorobutyryl)aminopyrimidine (**4**), however, could be readily prepared by treating **3** with 4-chlorobutyryl chloride in chloroform–pyridine solution. Heating **4** at 140° in an oil bath afforded only intractable tars. Reaction of **4** with aqueous potassium carbonate or ethanol–triethylamine solution or sodium hydride in refluxing xylene led to 1-(2-pyrimidinyl)-2-pyrrolidine (**5**) rather than the pyrimido[1,2-*a*]diazepinone **6**. It was unusual that the potassium carbonate method, which gave the highest yield, succeeded at all since cyclizations of haloamides generally proceed under anhydrous conditions in the presence of a strong base as sodium hydride or potassium *tert*-butoxide.[4] The structure of **5** was assigned on the basis of (1) the nmr spectrum, which showed two of the three pyrimidine ring protons as being equivalent and the presence of three adjacent methylene groups; (2) 5.84-μ ir absorption, attributed to the pyrrolidone carbonyl group; (3) acid hydrolysis to the amphoteric 2-(3-carboxypropyl)aminopyrimidine (**7**); and (4) the mass spectrum, which showed a fragmentation pattern common to pyrrolidones.[5] An attempt to prepare **5** from 2-chloropyrimidine and 2-pyrrolidone in the presence of sodium hydride was not successful.

Treatment of **3** with 3-chloropropionyl chloride in chloroform–pyridine solution at 0–5° led exclusively to 2-(3-chloropropionyl)aminopyrimidine (**8**, Scheme II).[6] Treatment of **8** with an equimolar amount of aqueous potassium carbonate solution caused dehydrochlorination to 2-acryloylaminopyrimidine **12**. This structure was supported by (1) the olefinic absorption and the equivalence of two of the three pyrimidine ring protons as exhibited in its nmr spectrum, and (2) an alternate synthesis by reaction of **3** with acryloyl chloride (Scheme II).

Heating **8** in chloroform, dimethylformamide, or dimethyl sulfoxide produced 3,4-dihydro-2*H*-pyrimido-[1,2-*a*]pyrimidin-2-one hydrochloride (**9**). We are aware of only one other report on the synthesis of this class of compound. Hurd and Hayao[7] prepared the 6,8-dimethyl analog by fusion of 4,6-dimethyl-2-aminopyrimidine with 3-bromopropionic acid.[8] The nmr spectrum of **9** exhibited the three pyrimidine ring hydrogens as multiplets at δ 9.3–9.1, 9.0–8.8, and 7.9–7.6. Brown[9] observed similar multiplet absorptions for the nonequivalent protons in 1-alkyl-2-alkylimino-1,2-dihydropyrimidines. Attempts to isolate the free base **10** from **9** were unsuccessful.[10] With either equimolar or excess aqueous potassium carbonate solution, **9** was hydrolyzed to 2-amino-1-(2-carboxyethyl)pyrimidinium betaine **11a**. The absence of a significant bathochromic shift[11] in the uv spectrum in 0.001 *N* sodium hydroxide [λ_{max} 263 nm (ϵ 2780), 305 (3180)] from the spectral absorptions in methanol [266 nm (ϵ 3490), 310 (2920)], and the absence of any absorption around 345 nm which could be attributed to an imino moiety[11] led

(3) F. L. M. Pattison, J. B. Stothers, and R. G. Woolford, *J. Amer. Chem. Soc.*, **78**, 2255 (1956).

(4) M. S. Manhas and S. J. Jeng, *J. Org. Chem.*, **32**, 1246 (1967).

(5) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 5536 (1964).

(6) At room temperature, a mixture of **8** and the pyrimidopyrimidine **9** was obtained; the isomers were separable by sublimation.

(7) C. D. Hurd and S. Hayao, *J. Amer. Chem. Soc.*, **77**, 117 (1955).

(8) Compound **9** was also obtained by fusion of **3** with 3-chloropropionic acid.

(9) D. J. Brown, B. T. England, and J. S. Harper, *J. Chem. Soc. C*, 1165 (1966).

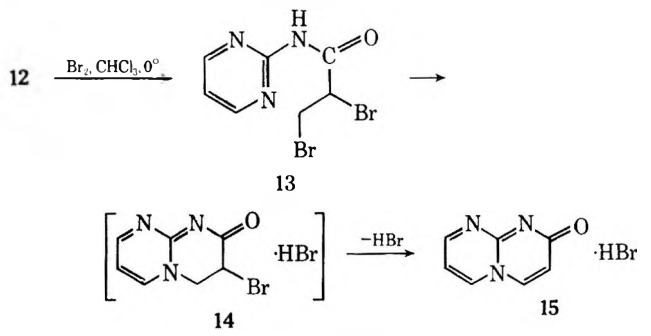
(10) The pyridopyrimidone analog was isolable by neutralization of its hydrochloride salt. *Cf.* R Adams and I. J. Pachter, *J. Amer. Chem. Soc.*, **74**, 4906 (1952).

(11) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963).

to the exclusion of the imino tautomer **11b**. Also our structural assignment of **11a** was based on the similarity of the uv[10] and ir[7] spectra to the corresponding 2-amino-1-(2-carboxyethyl)pyridinium betaine. The free base **10** was finally obtained by heating **12** in *m*-xylene. On treatment with ether–hydrogen chloride, **10** was converted to **9**.

Bromination of **12** gave 2-(2,3-dibromopropionyl)-aminopyrimidine (**13**, Scheme III). At room tempera-

SCHEME III



ture, the bromination procedure led to a solid which tlc analysis showed to be a binary mixture, the major component being **13**, minor component **14**. On heating of this mixture in dimethylformamide, 2*H*-pyrimido-[1,2-*a*]pyrimidin-2-one hydrobromide (**15**) was prepared. An attempt to obtain **15** by fusion of **3** with 1,3-dibromopropionic acid was not successful. Heating **13** in dimethylformamide at 100–110° for about 45 min gave a high yield of **15**. A characteristic feature of the nmr spectrum of **15** was the AB pattern with the more shielded doublet centered at δ 6.85 and the less shielded doublet at δ 8.40. The latter resonance also showed secondary splitting due to coupling with the peri hydrogens at the 4 and 6 positions.[12,13]

Experimental Section[14]

2-(3-Chloropropionyl)aminopyrimidine (8).—**3** (10 g, 0.105 mol) and 8.4 ml (8.3 g, 0.105 mol) of pyridine were added to 50 ml of chloroform. To this mixture at 0–5°, 9.2 ml (13.4 g, 0.105 mol) of 3-chloropropionyl chloride in 50 ml of chloroform was added dropwise over a 1-hr period. After dilution with 150 ml of chloroform, the solution was allowed to warm to room temperature and was washed with 300 ml of 5% aqueous potassium carbonate. The aqueous layer was then extracted with chloroform until the pink coloration was removed. The dried ($MgSO_4$) combined extracts were filtered, reduced *in vacuo* below 40° to 75 ml, and cooled. White crystals (5.5 g, 28.3%) of **8** precipitated: mp 280–285° dec; $\nu_{C=O}$ 5.98 μ; nmr (TFA) 3.30 (t, 2 H, CH_2CO), 3.96 (t, 2 H, CH_2Cl), 7.78 (t, 1 H, 5 proton of pyrimidine ring), 9.08 (d, 2 H, 4,6 protons of pyrimidine ring).

Anal. Calcd for $C_7H_8ClN_3O$: C, 45.29; H, 4.35; Cl, 19.10; N, 22.64. Found: C, 45.45; H, 4.47; Cl, 19.34; N, 22.48.

2-(4-Chlorobutyryl)aminopyrimidine (4).—Using 4-chlorobutyryl chloride in the above procedure gave a 72% yield of **4** as a white solid after two recrystallizations from 2-propanol: mp 97–99°; $\nu_{C=O}$ 5.95 μ; nmr ($CDCl_3$) 2.26 (m, 2 H, CH_2), 3.04 (t, 2 H, CH_2CO), 3.72 (t, 2 H, CH_2Cl), 7.04 (t, 2 H, 5 proton on pyrimidine ring), 8.66 (d, 2 H, 4,6 protons on pyrimidine ring), 10.06 (s, 1 H, NH).

Anal. Calcd for $C_8H_{10}ClN_3O$: C, 48.12; H, 5.01; Cl, 17.50; N, 21.05. Found: C, 48.41; H, 4.98; Cl, 17.50; N, 21.28.

2-Acryloylaminopyrimidine (12).—To 2.0 g (0.015 mol) of potassium carbonate in 50 ml of water was added 2.7 g (0.015 mol) of amide **8**, and the mixture heated on a steam bath until all solids dissolved. The cooled soluion (pH about 7) was saturated with sodium chloride and extracted with chloroform. The dried (Na_2SO_4) extracts were filtered and evaporated at reduced pressure to yield 1.4 g (63%) of an off-white solid. Purification by sublimation (90°, 0.5 mm) or recrystallization (1-butanol–benzene) gave **12**: mp (partial) 125–126°, resolidification and decomposition 195–200°; $\nu_{C=O}$ 5.99 μ; nmr ($CDCl_3$) 7.40–5.76 (m, 4 H, three vinylic and one for 5 position on pyrimidine ring), 8.62 (d, 2 H, 4,6 protons on pyrimidine ring) 10.70 (s, 1 H, NH).

Anal. Calcd for $C_7H_7N_3O$: C, 56.36; H, 4.74; N, 28.17. Found: C, 56.33; H, 4.74; N, 28.09.

Compound **12** was also prepared in lower yield (27%) by reacting equimolar quantities of **3**, acryloyl chloride, and triethylamine in acetonitrile essentially according to the procedure described for compound **8**.

2-(2,3-Dibromopropionyl)aminopyrimidine (13).—A solution of **12** (1.25 g, 0.0084 mol) in 200 ml of chloroform at 0° was treated with a chloroform (30 ml) solution of bromine (1.36 g, 0.0085 mol) dropwise over a 2-hr period. The resulting mixture became colorless after 48 hr of refrigeration and was filtered to afford 0.65 g of a pale yellow solid. Tlc examination (silica gel, 30:70 chloroform:methanol) showed this solid to be mainly **13** contaminated with **14**. The reaction filtrate was evaporated below room temperature under reduced pressure to about 15 ml, chilled overnight, and filtered to afford 1.18 g (45.4%) of **13** as a white solid: mp 135–140° bubbling, resolidification on further heating, 290° dec; $\nu_{C=O}$ 5.91 μ; nmr (TFA) 4.29–3.67 (m, 2 H, CH_2), 4.92 (q, 1 H, CH), 7.84 (t, 1 H, 5 proton on pyrimidine ring), 9.18 (d, 2 H, 4,6 protons on pyrimidine ring).

Anal. Calcd for $C_7H_7Br_2N_3O$: C, 27.21; H, 2.29; Br, 51.73; N, 13.60. Found: C, 27.22; H, 2.47; Br, 51.53; N, 13.45.

1-(2-Pyrimidinyl)-2-pyrrolidone (5).—**4** (6 g, 0.03 mol) was dissolved in a solution of 4.14 g (0.03 mol) of potassium carbonate in 200 ml of water by briefly heating on a steam bath. The cooled solution (pH 7–8) was extracted with chloroform, and the extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude residue recrystallized from hot ether to yield 3.7 g (76%) of a white solid: mp 107.5–110°; $\nu_{C=O}$ 5.84 μ; nmr ($CDCl_3$) 2.12 (m, 2 H, CH_2), 2.56 (t, 2 H, CH_2CO), 3.96 (t, 2 H, CH_2N), 6.82 (t, 1 H, 5 proton on pyrimidine ring), 8.46 (d, 2 H, 4,6 protons on pyrimidine ring).

Anal. Calcd for $C_8H_9N_3O$: C, 58.90; H, 5.52; N, 25.77; mol wt, 163. Found: C, 58.95; H, 5.54; N, 26.09; mol wt, 163 (mass spectrometric).

2-(3-Carboxypropyl)aminopyrimidine (7).—To 15 ml of a 10% solution of sulfuric acid was added 0.6 g (0.0037 mol) of **5**, and the solution was heated at 100° for 24 hr. Adjustment of the pH to 6 precipitated a white solid. The mixture was evaporated to dryness and the residue extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residual solids were recrystallized from absolute alcohol–ether to afford 0.44 g (65.6%) of **7**, mp 120–124°. Sublimation at 96° (0.1 mm) gave the analytical sample, mp 124.5–126°.

Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.04; H, 6.08; N, 23.21; mol wt, 181. Found: C, 53.31; H, 6.25; N, 23.10; mol wt, 181 (mass spectroscopic).

3,4-Dihydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-one Hydrochloride (9).—To 5 ml of dimethyl sulfoxide was added 0.5 g (0.0027 mol) of **8**, and the mixture heated 10 min on a steam bath and then cooled. The solids were filtered off and washed with fresh dimethyl sulfoxide followed by chloroform to give a nearly quantitative yield of **9**: mp 290–291° dec; $\nu_{C=O}$ 5.74 μ; uv λ_{max}^{MeOH} 233 nm (ϵ 6000), 268 (3300), 300 (2360); nmr (TFA) 3.44 (t, 2 H, CH_2), 5.10 (t, 2 H, CH_2), 7.76 (q, 1 H, pyrimidine ring), 8.96 (q, 1 H, pyrimidine ring), 9.20 (q, 1 H, pyrimidine ring).

Anal. Calcd for $C_7H_8ClN_3O$: C, 45.29; H, 4.35; Cl, 19.10; N, 22.64. Found: C, 45.45; H, 4.35; Cl, 19.29; N, 22.50.

3,4-Dihydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-one (10).—To 5 ml of *m*-xylene was added 0.36 g (0.0024 mol) of **12**. As the temperature was increased, the olefin slowly dissolved until *ca.* 120° a white solid began to separate which gradually yellowed while the temperature was maintained between 120 and 130° for 0.5 hr. Cooling gave a quantitative yield of crude **10**. Recrystallization (DMF) gave 0.29 g (58%) of **10**: mp 210–211°; ir strong bands at 6.18, 6.50, 6.59, 6.79, 6.96, 7.34, 7.92, 8.68,

(12) K. D. Bartle, D. W. Jones, and R. S. Matthews, *Tetrahedron*, **25**, 2701 (1969).

(13) W. W. Paudler and H. L. Blewitt, *ibid.*, **21**, 353 (1965).

(14) Spectra were obtained on the following instruments: infrared on a Perkin-Elmer Infracord 137 (KBr pellets), ultraviolet on a Bausch and Lomb Spectronic 505, nmr on a Varian A-60A [chemical shifts reported downfield from Me_4Si as an internal standard in parts per million (δ)], mass spectra at 70 eV on a CEC 21-103C. Brinkman silica gel F-254 was employed for tlc.

8.99, 12.02, 12.78, 13.27 μ; uv λ_{max}^{MeOH} 265 nm (ϵ 23,000), 314 (5070).

Anal. Calcd for $C_7H_7N_3O$: C, 56.36; H, 4.74; N, 28.17. Found: C, 56.20; H, 4.31; N, 28.04.

Solution of **10** in methanol–hydrogen chloride–ether gave **9**.

2-Amino-1-(2-carboxyethyl)pyrimidinium Betaine (11a).—To a solution of 0.75 g (0.0054 mol) of potassium carbonate in 25 ml of water was added 1.0 g (0.005 mol) of **9**. The nearly neutral solution was evaporated to dryness and the residue extracted with hot chloroform. The chloroform extracts were evaporated at reduced pressure. Recrystallization of the residue (ethanol–ether) gave 0.3 g of a light yellow solid, mp 171–172.5°.

2*H*-Pyrimido[1,2-*a*]pyrimidin-2-one Hydrobromide (15).—A mixture of 5 ml of dimethylformamide and 1.0 g (0.0032 mol) of **13** was slowly heated in an oil bath whereupon solution occurred. Near 80° a solid began to separate and heating was continued at 100–110° for *ca.* 45 min. The cooled mixture was filtered and the residue washed with dimethylformamide followed by chloroform. Recrystallization (TFA–methanol) gave 0.53 g (72.6%) of **15**: mp (darkening) 280°, bubbling 310° dec; $\nu_{C=O}$ 5.75 μ; uv λ_{max}^{MeOH} 240 nm (ϵ 9464), 320 (5986); λ_{max} (0.001 *N* NaOH) 247 (14,280), 275 (14,570), 313 (46,280); nmr (TFA) 6.85 (d, 1 H, 3 proton), 8.10–7.84 (m, 1 H, 7 proton), 8.40 (d, 1 H, 4 proton), 9.76–9.40 (m, 2 H, 6,8 protons).

Anal. Calcd for $C_7H_6BrN_3O$: C, 36.86; H, 2.66; Br, 35.04; N, 18.43. Found: C, 36.87; H, 3.09; Br, 35.03; N, 18.43.

If the resulting solid formed at 80° was filtered off and washed with chloroform, tlc analysis showed the presence of only a small amount of **15**, the major component being the intermediate **14**.

Registry No.—**4**, 27179-31-3; **5**, 27179-32-4; **7**, 27179-33-5; **8**, 27179-34-6; **9**, 27248-73-3; **10**, 27179-35-7; **11**, 27179-36-8; **12**, 27179-37-9; **13**, 27179-38-0; **15**, 27179-39-1.

Cyclic Lactams. II.[1] 1,7-Dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione and 3,6-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-1,4-dione from 4-Methyl-1-tetralone-4-acetic Acid

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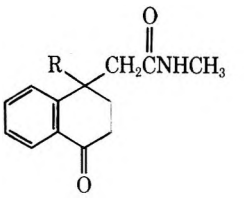
In a model study related to preparation of some benzomorphan analgesics,[3] we attempted to prepare the basic nucleus of this system from 4-methyl-1-tetralone-4-acetic acid. Various routes to this hexahydro-2,6-methano-3-benzazocine nucleus have been explored in considerable detail.[4-7] Walker and Alkalay[7] reported a successful ring closure to this skeleton from the *N*-methylamide of 4-phenyl-1-tetralone-4-acetic acid (**2**) by intramolecular displacement of the halide of the intermediate α-bromo ketone **4**. Because of the problems encountered in separation of the diastereomeric α-bromo ketones, and only partially successful cyclization using methanol–sodium methoxide, we sought to investigate the possibility of a solvolytic displacement process which would lead to benzazocine **5**. The isolation of the azabicyclo[4.3.0]nonane derivative from this process is reported.



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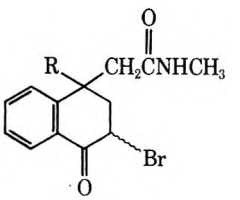
2, R = Ph



3, R = CH_3
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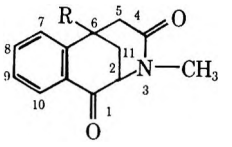
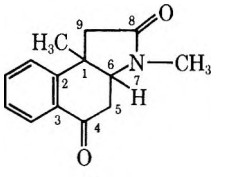
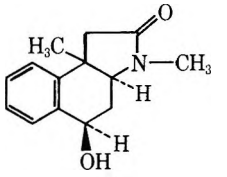


5, R = CH_3
6, R = Ph

The necessary 4-methyl-1-tetralone-4-acetic acid was available from the Friedel–Crafts alkylation of γ-methyl-γ-(carbethoxymethyl)butyrolactone and subsequent cyclization.[8] The amide formation process was very inefficient when the mixed anhydride formed from ethyl chcroformate was treated with anhydrous methylamine. However, formation of the *N*-hydroxysuccinimide ester using dicyclohexylcarbodiimide followed by treatment with aqueous methylamine resulted in the desired amide in excellent yield. Bromination was performed in acetic acid–chloroform, or in benzene–tetrahydrofuran, with the latter method being preferable. The intermediate mixture of α-bromo ketones (**3**) was refluxed in dimethylformamide to attempt intramolecular displacement. Only a single ketone amide was isolated which was identified as 1,7-dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione (**7**), based on nmr evidence, reduction, and subsequent preparation of **5** by a related method.



7



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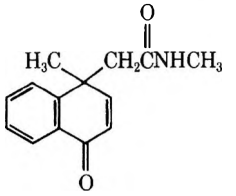

9

The nmr spectrum of the isolated product showed, in addition to the expected tetralone aromatic protons, singlets for methyl groups and methylene protons adjacent to the carboxamide function, a triplet, and a doublet at δ 3.83 and 2.90 (J = 4 Hz), integrating for one and two protons, respectively. The position of the

(1) Previous paper: W. L. Nelson, D. D. Miller, and R. S. Wilson, *J. Heterocycl. Chem.*, **6**, 131 (1969).

(2) Taken in part from the Ph.D. thesis of K. F. Nelson, submitted to the Graduate School, University of Washington, July 1970.

(3) K. F. Nelson, Ph.D. Thesis, University of Washington, 1970.

(4) E. L. May and L. J. Sargent in "Analgetics," Medicinal Chemistry Monographs, Vol. 5, G. deStevens, Ed., Academic Press, New York, N. Y., 1965, pp 123–177.

(5) N. B. Eddy and E. L. May in "Synthetic Analgesics," International Series of Monographs in Organic Chemistry, Vol. 8, D. H. R. Barton and W. von Doering, Ed., Pergamon Press, London, 1966, pp 115–137.

(6) G. deStevens, *Pure Appl. Chem.*, **19**, 89 (1969).

(7) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966), and references therein.

(8) W. Herz and A. Caple, *J. Amer. Chem. Soc.*, **84**, 3517 (1962).

doublet suggested structure **7** where the C-5 protons would be expected downfield with respect to the C-11 methylene protons in alternate structure **5**. The single coupling constant of 4 Hz may result from a combination of averaging of chemical shifts of the C-5 protons and the fact that the coupling constant may be large with respect to the difference in chemical shifts of these protons.

Deuterium exchange simplified the spectrum and provided data consistent only with **7**. The C-5 and C-9 protons are exchanged reducing the signal of H-6 to a singlet. Structure **5** is inconsistent with exchange of the methylene protons which would be exchangeable in **7**. Further evidence for **7** was obtained from the borohydride reduction product **8**, which showed quartets for H-4 and H-6 at δ 4.62 and 3.50, respectively, J = 4 and 10 Hz. The observation of one large coupling constant (J_{45} and J_{65}) is consistent with axial and pseudoaxial disposition of H-6 and H-4, compatible with either a cis- or trans-1,6 ring junction in **7**.

The formation of **7** is best rationalized in terms of an intermediate α,β-unsaturated ketone, **9**, resulting from elimination of hydrogen bromide, followed by intramolecular conjugate addition of the amide nitrogen. These results are probably a consequence of the poor nucleophilic character of the amide nitrogen under reaction conditions where elimination could readily occur.[9]

When the mixture of α-bromo ketones (**3**) was subjected to reaction conditions favoring formation of a better nucleophile, the anion of the amide nitrogen (sodium methoxide–methanol), benzazocine **5** was isolated, a result of the direct displacement of the halogen rather than elimination, followed by conjugate addition.

The nmr spectrum of **5** showed the C-11 protons at δ 2.33 (multiplet, W_h = 6 Hz), and H-2 at δ 3.97 (distorted quartet, J = 4 and 3 Hz), consistent with the expected methylene and methine resonances, respectively. Deuterium exchange removed only the C-5 signal leaving the other resonances intact as expected.

Experimental Section[13]

4-Methyl-1-tetralone-4-*N*-methylacetamide (1). **A. Mixed Anhydride Method.**—To a cooled solution (0°) of 2.18 g (10 mmol) of 4-methyl-1-tetralone-4-acetic acid[8] dissolved in 150 ml of chloroform was added a solution of 1.60 g (14.8 mmol) of ethyl chloroformate in 25 ml of chloroform. This mixture was heated slowly to 40° and maintained at this temperature for 2 hr. After cooling at 0°, 620 mg (20 mmol) of anhydrous methylamine was bubbled into the solution. The amount was determined by weight difference. The solution was stirred for 2 hr while being allowed to warm to room temperature and then heated at 40° for an additional 2 hr. The white, granular precipitate that formed was removed by filtration. This solid was washed several times with chloroform and the chloroform extracts were combined and dried ($MgSO_4$). The chloroform was removed leaving 5.0 g of a brown oil. Thin layer chromatography on silica gel G (Brinkman) with a chloroform–methanol mixture (5:1) showed two major peaks with R_f 0.6 and 0.5. Careful column chromatography on a 150-g silica gel (Brinkman) column separated the two components.

The second component was the amide isolated as a colorless solid, 462 mg (20% of theory): mp 103–104° (acetone–ether); λ_{max}^{KBr} 3.08, 3.42, 3.50, 6.05 (C=O) (very broad), 6.34, 6.50, 6.95, 7.13, 7.80, 9.60, 13.15; $\delta_{TMS}^{CDCl_3}$ 1.55 (s, CCH_3), 2.20 (m, 4 methylene protons at C-2 and C-3), 2.58 (s, $CH_2C(=O)N$), 2.70 (d, NCH_3, with J = 5 Hz), 7.22 (q, broad, NH, coupling constant undiscernible), 7.50 (m, 3 aromatic protons), 8.00 (d, distorted, 1 aromatic proton with J = 7 Hz).

B. *N*-Hydroxysuccinimide Method.—A suspension of 1.00 g (4.6 mmol) of the tetralone acid and 946 mg (4.6 mmol) of dicyclohexylcarbodiimide in 20 ml of dioxane was cooled to 15°. To this cooled solution was added 527 mg (4.6 mmol) of *N*-hydroxysuccinimide, prepared by the method of Anderson.[14] This mixture was stirred overnight at room temperature. Dicyclohexylurea was removed by suction filtration and the dioxane evaporated affording the *N*-hydroxysuccinimide ester as a colorless oil: λ_{max}^{film} 3.38, 3.50, 5.45, 5.55, 5.73, 5.90, 6.18, 6.50, 6.65, 6.80, 7.25, 7.70, 7.90, 8.20, 8.50, 8.87, 9.25, 9.70, 11.10, 11.30, 12.20, 12.75, 15.20, and 15.65.

Without further purification the *N*-hydroxysuccinimide ester was dissolved in 25 ml of 1,2-dimethoxyethane and with stirring 2 ml of aqueous 40% methylamine was added. Dimethoxyethane may be substituted for dioxane in the esterification procedure to reduce the procedure to a single manipulation. After 24 hr the solvents were evaporated; the resulting oil was partitioned between 50 ml of ether and 50 ml of water. The ether solution was then washed with 20 ml of saturated brine solution, dried ($MgSO_4$), and filtered, and the ether was evaporated yielding 857 mg of 1 (81% of theory), mp 103–104° (acetone–ether).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.57; H, 7.34; N, 6.40.

1,7-Dimethyl-2,3-benzo-7-azabicyclo[4.3.0]nonane-4,8-dione (**7**).—To a refluxing solution of 8.30 g (35.9 mmol) of tetraloneacetamide 1 in 75 ml of glacial acetic acid was added dropwise a solution of 5.73 g (36 mmol) of bromine in 10 ml of acetic acid. The solution was refluxed for 10 min, cooled, and then thoroughly partitioned between water and ethyl acetate. The ethyl acetate fractions were combined, washed with water, aqueous 10% sodium bicarbonate solution, water, and saturated brine solution, and dried ($MgSO_4$). The solvent was evaporated, leaving 2.04 g (18% of theory) of crude α-bromo ketone: λ_{max}^{neat} 3.00 (broad), 3.30, 3.42, 3.47, 5.88, 6.06, 6.25, 6.45, 6.85, 7.17, 7.50, 7.69, 8.03, 8.62, 9.09, 9.66, 10.00, and 13.00.

The crude bromo ketone was dissolved in 60 ml of dimethylformamide and refluxed overnight. The dimethylformamide was evaporated affording an oil which contained several components as determined by thin layer chromatography. Column chromatography on 120 g of silica gel using 7:3 chloroform–ethyl acetate as eluent gave a total of 880 mg of **7**, mp 156–157° (60% yield based on crude α-bromo ketone), which was eluted in the fifth and sixth 100-ml portion of solvent: λ_{max}^{KBr} 3.35, 3.38, 5.82, 6.11, 6.25, 6.37, 6.82, 7.00, 7.15, 7.53, 7.90, 8.00, 8.88, 9.23, 9.53, 10.00, 10.40, 10.90, 11.10, 11.90, 12.20, 12.65, 13.00, 14.30, 14.90, and 15.65; $\delta_{TMS}^{CDCl_3}$ 1.59 (s, CCH_3), 2.70 (s, $CH_2C(=O)N$), 2.80 (s, NCH_3), 2.97, (d, CH_2CH, J = 4 Hz), 3.87 (CH, J = 4 Hz), 7.50 (m, 3 aromatic protons), 7.87 (d, distorted, 1 aromatic proton, J = 7 Hz).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.10; H, 6.58; N, 6.12.

To 50 mg (0.218 mmol) of **7** dissolved in 3.0 ml of dioxane was added 2.0 ml of deuterium oxide and 100 mg of sodium methylate. This mixture was stirred at room temperature overnight, neutralized with aqueous 10% hydrochloric acid, and thoroughly extracted with ethyl acetate. The ethyl acetate extracts were combined and dried ($MgSO_3$) and the solvent was evaporated affording deuterated **7**: $\delta_{TMS}^{CDCl_3}$ 1.59 (s, CCH_3), 2.80 (s, NCH_3), 3.87 (s, CHN), 7.50 (m, 3 aromatic protons), and 7.87 (d, distorted, 1 aromatic proton, J = 7 Hz).

1,7-Dimethyl-8-hydroxy-2,3-benzo-7-azabicyclo[4.3.0]-nonane-

(9) The intramolecular conjugate addition of the amide function would be expected to occur from a developing axial position on intermediate **9**, probably affording the cis-1,6 product, similar to reported preponderant axial conjugate additions of cyanide anion,[10,11] and certain carbanions.[12] The alternate structure with a trans-1,6 ring juncture cannot be eliminated.

(10) W. Nagata and I. Kikkawa, *Chem. Pharm. Bull.*, **11**, 289 (1963).

(11) M. P. Mertes, A. A. Ramsey, P. E. Hanna, and D. D. Miller, *J. Med. Chem.*, **13**, 789 (1970).

(12) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).

(13) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR-5A and IR-20 spectrophotometers. Nmr spectra were determined with Varian A-60 and T-60 spectrometers using tetramethylsilane as internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Microanalyses were conducted by Drs. G. Weiler and F. B. Stauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(14) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **86**, 1339 (1964).

4-one (**8**).—To 100 mg (0.437 mmol) of **7** and in 10 ml of absolute methanol was added 17 mg (0.437 mmol) of sodium borohydride and 1.0 mg of sodium hydroxide and the mixture was stirred at room temperature overnight. The reaction mixture was partitioned between 50 ml of ethyl acetate and 100 ml of water. The water layer was extracted with additional ethyl acetate (three 25-ml portions). The combined ethyl acetate fractions were washed with water and saturated brine solution and dried ($MgSO_4$). Removal of the solvent afforded 45 mg (22.3% of theory) of a colorless oil: λ_{max}^{neat} 2.94, 3.38, 3.44, 6.05, 6.80, 7.00, 7.23, 7.70, 7.87, 8.05, 8.47, 9.10, 9.35, 9.50, 9.80, 10.02, 13.30, 14.10, 14.60, 15.30, and 15.80 μ; $\delta_{TMS}^{CDCl_3}$ 1.43 (s, CH_3), 2.43 (m, C-5 CH_2), 2.67 (s, $CH_2C(=O)N$), 2.95 (s, NCH_3), 3.50 (q, CHN, J = 4 and 10 Hz), 4.62 (q, CHO, J = 4 and 10 Hz), and 7.25 (m, 4 aromatic protons).

3,6-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-1,4-dione (**5**).—Bromination of ketone amide **1** was more efficiently performed using a mixture of benzene and tetrahydrofuran as cosolvents. To a solution of 1.55 g (5.0 mmol) of **1** in 100 ml of benzene and 25 ml of tetrahydrofuran was added over 30 min a solution of 850 mg (5.3 mmol) of bromine in 10 ml of tetrahydrofuran. After the addition was complete and the bromine color disappeared, the solution was diluted with ethyl acetate, washed with 5% aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$), and evaporated affording crude α-bromo ketone **3**, 1.05 g (67% of theory), identical spectrally with the product obtained from the acetic acid method.

To a solution of sodium methoxide in methanol prepared by adding 0.92 g (0.004 g-atom) of sodium to 25 ml of absolute methanol was added 0.825 g (2.3 mmol) of crude α-bromo ketone **3** in 10 ml of methanol. The mixture was refluxed for 2 hr during which time sodium bromide precipitated. The mixture was partitioned between water and ethyl acetate and extracted with several portions of ethyl acetate. The organic layers were combined, washed with saturated brine, dried ($MgSO_4$), and evaporated affording a brown oil which was chromatographed on 40 g of silica gel eluted with chloroform. The benzazocinedione (**5**) was obtained in fractions 5–8 (100-ml fractions). A total of 350 mg (67% of theory), mp 163–164° (benzene–petroleum ether), was collected: λ_{max}^{KBr} 3.38, 3.42, 3.48, 5.92, 6.05, 6.25, 6.85, 7.18, 7.41, 7.56, 7.71, 7.83, 8.07, 8.59, 9.03, 9.48, 10.05, 10.30, 12.23, 12.78, 13.03, 13.74, and 14.08; $\delta_{TMS}^{CDCl_3}$ 1.52 (s, CCH_3), 2.39 (m, $W_h \simeq 6$ Hz, CH_2CH), 2.55 (s, broadened, $CH_2C(=O)N$), 2.95 (s, NCH_3), 3.97 (q, distorted, J = 4 and 3 Hz, CHN), 7.45 (m, 3 aromatic protons), 8.02 (d, distorted, 1 aromatic proton).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.61; H, 6.64; N, 6.38.

Deuterium exchange was performed in a manner similar to that described for exchange on **7**. Only the signal at δ 2.55 disappeared.

Registry No.—**1**, 27093-03-4; 1 *N*-hydroxysuccinimide ester, 27093-04-5; **3**, 27093-05-6; **5**, 27093-06-7; **7**, 27141-07-7; **8**, 27093-07-8; 4-methyl-1-tetralone-4-acetic acid, 27093-08-9.

Acknowledgment.—This investigation was supported by Grant GM-13,782 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and by the State of Washington Initiative 171 Funds for Research in Biology and Medicine.

Synthesis of 2-Acetyl-1,4,5,6-tetrahydropyridine, a Constituent of Bread Aroma

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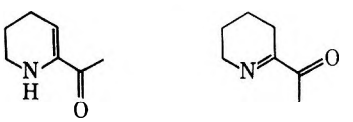
Of the aromas associated with man's food, that of baked bread is one of the most perishable. Efforts to stabilize the taste of fresh bread have met with little success mainly because the compounds responsible for this unique aroma remained unknown. Recent analysis of a methylene chloride extract of freshly baked bread led to the isolation of a compound with an overpowering odor of crackers.[1] This aroma principle was identical with a substance produced in low yield by heating proline with dihydroxyacetone[2] or glycerol,[1] and structural studies suggested the presence of 2-acetyl-1,4,5,6-tetrahydropyridine (**1**).[3] To confirm this and to further evaluate the organoleptic properties of this important compound, we have developed a rational synthesis.

Hydrogenation of 2-acetylpyridine (**3**) over a rhodium-on-alumina catalyst yielded 2-(1-hydroxyethyl)-piperidine (**4**) in 78% yield.[4] Oxidation of the alcohol **4**



1

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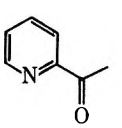

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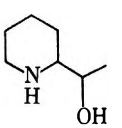

4

with Celite suspended silver carbonate[5] in benzene solution did not give the anticipated saturated ketone but the desired enamino ketone **1** directly. This one-step procedure should be useful for the preparation of other α-amino-α,β-unsaturated ketones from 1,2-amino alcohols. The nuclear magnetic resonance spectrum of synthetic material was identical with that of the natural bread aroma constituent,[3] but a series of resonances previously[3] attributed to decomposition products are in fact caused by the imino tautomer **2** (see Experimental Section). Oxidation of the amino alcohol **4** for a short period of time gave a mixture of tautomers with ultraviolet absorption (pentane) at 312 nm (ϵ 2020) judged by nmr analysis to contain approximately two-thirds of the imine **2** and one-third of the enamine **1**. Further heating in benzene produced a new mixture with ϵ 3360 containing approximately two-thirds of the enamine **1** and one-third of the imine **2**. Consequently imine **2** is the initial product of oxidation while the enamine **1** represents the more stable tautomer. Infrared spectra confirmed the identities of synthetic and natural material and are in full accord with the presence of tautomers. Mixtures rich in imine form show intense absorption at 1695 cm^{-1}, while the enamine tautomer gives rise to bands at 1670 and 1650 cm^{-1}. Synthetic 2-acetyl-1,4,5,6-tetrahydropyridine (**1**) has the organoleptic properties characteristic of the bread constituent. In agreement with earlier findings the substance is exceptionally sensitive to air, but we have stored the corresponding

(1) I. R. Hunter, M. K. Walden, W. H. McFadden, and J. W. Pence, *Cereal Sci. Today*, **11**, 493 (1966).

(2) L. Wiseblatt and H. F. Zoumut, *Cereal Chem.*, **40**, 162 (1963).

(3) I. R. Hunter, M. K. Walden, J. R. Scherer, and R. E. Lundin, *ibid.*, **46**, 189 (1969). We are indebted to Dr. R. Teranishi for sending us a preprint of this paper.

(4) This reduction was mentioned in an article by M. Freifelder, *J. Org. Chem.*, **29**, 2895 (1964), but no details were given.

(5) H. Fetizon and M. Golifier, *C. R. Acad. Sci.*, **267**, 900 (1968).

hydrochloride with little change in a sealed ampoule for three months.

Experimental Section

Microanalyses were performed in the laboratory of Dr. F. Gautschi, Firmenich et Cie., Geneva. Boiling points are uncorrected. Vapor phase chromatography was performed on a F & M 720 instrument. The following spectrometers were used: nmr, Varian T-60 and HA-100; ir, Perkin-Elmer Models 237 and 247; uv, Cary Model 14; mass spectrum, Hitachi RMU6D.

Hydrogenation of 2-Acetylpyridine (3).—A solution of 8.4 g (69 mmol) of 2-acetylpyridine in 75 ml of absolute ethanol was hydrogenated in the presence of 1.5 g of 5% rhodium on alumina. Absorption was complete after uptake of 6490 cm^3 of H_2 [22° (760 mm), 3.9 equiv]. The mixture was filtered through Celite, evaporated, and distilled to give 6.94 g (78%) of alcohol **4**: bp 48° (0.1 mm) [lit.[6] bp 101–102° (23 mm)]; ir ($CHCl_3$) 2400–3650 cm^{-1}; nmr (CCl_4) δ 1.0 (3 H, d, J = 7 Hz), 0.8–3.2 (9 H, m), 3.3 (1 H, s, disappears on exchange with D_2O), 3.4 (1 H, s, disappears on exchange with D_2O), 3.4 (1 H, m).

Oxidation of Alcohol 4.—A stirred suspension of silver carbonate on Celite (prepared[5] from 50 g of Celite, 60 g of silver nitrate, and 37 g of sodium bicarbonate), 7.0 g (54 mmol) of alcohol **4**, and 400 ml of benzene was heated at reflux for 20 hr under nitrogen. Filtration, evaporation *in vacuo*, and distillation afforded 3.84 g (57%) of approximately a 2:1 mixture of ketones **1** and **2** (nmr): bp 35–40° (0.1 mm); vpc (2-ft TCEP and 6-ft silicon gum rubber) 1 peak; ir ($CHCl_3$) 1650, 1670, 1695, 3430 cm^{-1}; uv (EtOH) 308 nm (ϵ 2450); uv (pentane) 312 nm (ϵ 3360); nmr (100 MHz, C_6D_6) enamine tautomer δ 1.5 (2 H, m), 1.9 (2 H, m), 2.0 (3 H, s), 2.8 (2 H, t, J = 2.5 Hz), 4.3 (1 H, broad, disappears on exchange with D_2O), 5.2 (1 H, t, J = 2.5 Hz); nmr imine tautomer δ 1.2 (4 H, m), 2.2 (2 H, m), 2.3 (3 H, s), 3.4 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 125 (58), 43 (100).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 67.25; H, 9.29.

Hydrochloride of 1 and 2.—To an ice-cold solution of 603 mg (4.8 mmol) of the amines **1** and **2** in 20 ml of dry ether was added dropwise a slight excess of HCl in dry ether. The solid was filtered, washed with ether, and dried in a desiccator at 10 mm to give 664 mg (86%) of the hydrochloride: mp 112–119°; ir ($CHCl_3$) 1675, 1690, 1735, 2000–3600 cm^{-1}.

Regeneration of the Free Base.—A mixture of 427 mg (2.64 mmol) of the hydrochloride, 20 ml of methylene chloride, and 2 g of sodium bicarbonate was stirred at room temperature for 20 min. Filtration followed by evaporation and distillation of the residue yielded 217 mg (66%) of the amines **1** and **2**, bp ~35° (0.1 mm).

Registry No.—**1**, 25343-57-1; **1** HCl, 27300-26-1; **2**, 27300-27-2; **2** HCl, 27300-28-3.

Acknowledgment.—We are indebted to Firmenich et Cie., Geneva, for generous financial support.

(6) G. R. Clemo, R. Raper, and H. J. Vipond, *J. Chem. Soc.*, 2095 (1949).

Further Evidence for the Validity of the Overlap Indicator Method. Correlation of pK_a's of Corresponding Aniline and 2-Nitroaniline Derivatives

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Katritzky and coworkers[1] and Arnett and coworkers[2,3] have recently reported that good linear enthalpy–free-energy correlations serve to support the validity of the Hammett overlap indicator method[4] for estimating pK_a's of very weak bases. In the former instance,[1] ionization constants of a number of aniline indicators were determined over a range of temperatures,[5] and ΔF values were shown to be linear with enthalpies of ionization. The latter reports[2,3] involved comparisons of pK_a's for a variety of amine types with partial molal heats of transfer from carbon tetrachloride or tetrachloroethane to fluorosulfuric or sulfuric acid solvents.

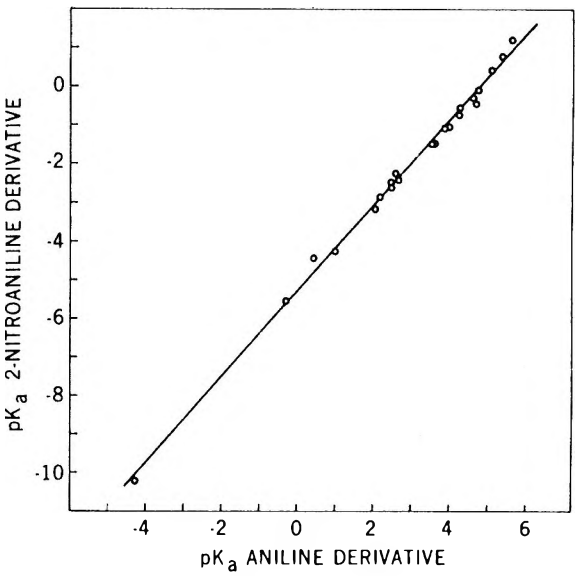

Figure 1.—Variation in pK_a's of 2-nitroaniline derivatives with those of correspondingly substituted anilines.

We wish now to describe an extended pK_a range linear free-energy correlation which serves as additional supporting evidence to confirm the reliability of more recent H_0 acidity function extrapolations for primary aniline indicators and therefore the overlap indicator method in general. Our evidence differs in nature from Arnett's and Katritzky's in that they compared related thermodynamic properties of same materials, whereas we correlate same properties of related materials.[6]

We have compared literature values for pK_a's of ortho- meta-, para-, and polysubstituted anilines (reaction series A) with those of corresponding 2- (or 6-) nitroaniline derivatives (series B) in water at 25 ± 3°; the data are listed in Table I. A plot (Figure 1) shows excellent linear correlation between the two series; least-squares analysis leads to the equation

$$\text{p}K_a\,(\text{series B}) = -5.32 + 1.11\ \text{p}K_a\,(\text{series A}) \qquad (1)$$

r (correlation coefficient) = 0.998
s (standard deviation) = 0.16 pK unit

For the more basic compounds, the pK_a determinations in both series were carried out in standard buffer solutions; at intermediate basicities, the pK_a's in

(1) P. D. Bolton, C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **92**, 1567 (1970).

(2) E. M. Arnett and J. J. Burke, *ibid.*, **88**, 4308 (1966).

(3) E. M. Arnett, R. P. Quirk, and J. J. Burke, *ibid.*, **92**, 1260 (1970).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940; E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 233 (1963).

(5) C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

(6) In a sense, the present correlation represents an application of a generalization regarding constant effects of ortho substituents first suggested by H. H. Jaffé, *Science*, **118**, 246 (1953); *Chem. Rev.*, **53**, 191 (1953).

TABLE I
pK_a's OF CORRESPONDING ANILINE AND 2-NITROANILINE DERIVATIVES IN WATER AT 25 ± 3°

No.	Substituent	Aniline pK_a	ref	2- (or 6-) Nitroaniline pK_a	ref	ΔpK_a, exptl − calcd (eq 1)
1	Unsubstituted	4.60	a	−0.29	b	0.10
2	4-CH_3O–	5.34	a	0.77	c	−0.14
3	4-CH_3–	5.08	a	0.43	c	−0.09
4	4-F–	4.65	a	−0.44	c	0.30
5	4-Cl–	3.98	a	−1.03	c	0.14
6	4-Br–	3.86	a	−1.05	c	0.03
7	4-CF_3–	2.57	d	−2.25	c	−0.21
8	4-CH_3OCO–	2.46	e	−2.61	c	0.03
9	4-NO_2–	1.00	b	−4.27	l	0.06
10	4-CH_3CO–	2.19	f	−2.85	c	−0.03
11	4-HO–	5.60	f	1.20	g	−0.28
12	3-CH_3–	4.73	a	−0.09[h]	i	0.04
13	3-CH_3O–	4.23	a	−0.72[h]	i	0.11
14	3-Cl–	3.52	a	−1.48[h]	i	0.08
15	3-Br–	3.58	a	−1.48[h]	i	0.15
16	3-NO_2–	2.46	a	−2.49[h]	i	−0.09
17	3-HO–	4.25	f	−0.55[h]	j	−0.03
18	2-Cl–	2.65	a	−2.41	b	0.04
19	2-NO_2–	−0.29	b	−5.56	b	−0.09
20	2,4-Cl_2–	2.05	k	−3.16	k	0.12
21	4-CH_3-2-NO_2–	0.43	c	−4.45	k	−0.39
22	2,4-$(NO_2)_2$–	−4.27	l	−10.23	b	0.15

[a] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [b] Reference 1. [c] J. O. Shreck, C. K. Hancock, and R. M. Hodges, *J. Org. Chem.*, **30**, 3504 (1965). [d] J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Amer. Chem. Soc.*, **72**, 408 (1950). [e] R. A. Robinson and A. I. Biggs, *Aust. J. Chem.*, 10, 128 (1957). [f] J. M. Vandenbelt, C. Henrich, and S. G. Vanden Berg, *Anal. Chem.*, **25**, 726 (1954). [g] H. G. Hansson, *Acta Chem. Scand.*, **16**, 1956 (1962). [h] 3-Substituted 6-nitroanilines. [i] C. K. Hancock, R. A. Brown, and J. P. Idoux, *J. Org. Chem.*, **33**, 1947 (1968). [j] J. W. Eastes, M. H. Aldridge, and M. J. Kamlet, *J. Chem. Soc. B*, 922 (1969). [k] E. Hogfeldt and J. Bigeleisen, *J. Amer. Chem. Soc.*, **82**, 15 (1960). [l] Reference 5.

series A were in standard buffers and those in series B in H_0 solutions; at the lower pK_a's, the overlap indicator method was used to determine basicities in both series. The excellent linearity, extending from the buffer range completely through the H_0 range, therefore serves to confirm both the accuracy of the latter measurements and the validity of the method. Considering the diverse sources of the data, and the fact that determinations in the H_0 range involved hydrochloric, perchloric, and sulfuric acid solutions, it is significant that the measured pK_a for 2,4,6-trinitroaniline (22B of Table I), which involves the greatest H_0 extrapolation, fits the correlation equation to within a single standard deviation, and that only one value (a relatively older measurement for 21B) differs from the calculated by as much as two standard deviations.

It is also worth comment that the 1.11 slope in the correlation equation implies that the base-weakening effect of the 2-nitro group in series B is not quite constant (*i.e.*, no straightforward additivity of substituent effects) but rather increases slightly the greater the electron-withdrawing ability of additional substituents. We rationalize this on the basis that intramolecular amine → nitro hydrogen bonding in 2-nitroanilines serves toward stabilization of the free bases relative to the corresponding anilinium ions and that inductive or mesomeric electron withdrawal from the amine nitrogens tends toward an increase in the strength of these amine → nitro hydrogen bonds.[7]

It should be noted that the 2- (or 6-) nitro substituents in series B are always unhindered and most likely essentially coplanar. The correlation would probably break down in situations where the nitro were adjacent to a second ortho substituent which might tend to force it toward noncoplanarity, *e.g.*, in 3-substituted 2-nitroanilines.

(7) Jaffé's generalization[6] would have required a 1.00 slope in eq 1. The slightly higher observed value, attributable to the hydrogen-bonding effect, represents a refinement of the earlier statements but not a significant or inexplicable difference.

Synthesis and Cyclization of *S*-(2-Propynyl)-L-cysteine S-Oxide and S-Dioxide

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1-Alkenylcysteine *S*-oxides and *S*-dioxides in the presence of base undergo an internal addition of the amino function to the double bond to yield cyclic sulfoxides and sulfones.[1] It was of interest to determine if acetylenic cysteine *S*-oxides and *S*-dioxides would react in a similar manner. McDowell and Stirling[2] have shown that in the addition of a secondary amine to 1-alkynyl-, 2-alkynyl-, or the corresponding allenyl-*p*-tolyl sulfone, the same addition product is formed in each case with the double bond appearing α,β to the sulfur. These investigators also obtained evidence from kinetic studies that 2-alkynyl sulfones first isomerize to allenes which then add amine in a rate-determining step.

S-(2-Propynyl)-L-cysteine *S*-dioxide (**1**) was prepared by oxidation of *S*-(2-propynyl)-L-cysteine with hydrogen peroxide in acetic acid at 50°. Oxidation with the same reagent under milder conditions yielded a mixture of diastereomeric sulfoxides which were separated by fractional crystallization into (+)-*S*-(2-propynyl)-L-cysteine *S*-oxide, $[\alpha]^{26}D$ +72.5° (water), and the (−) *S*-oxide, $[\alpha]^{25}D$ −110° (water). With the expectation of comparing the cyclization of 1-propynyl and 2-propynyl derivatives, the oxidation of *S*-1-propynyl-L-cysteine[3] was attempted. Neither sulfoxide nor sulfone could be obtained by reaction with hydrogen peroxide in acetic acid or with aqueous sodium metaperiodate. Cystine and starting material were the only recoverable products. We have no explanation for the failure of 1-propynylcysteine to form sulfoxides or sulfones under conditions where the 1-propenyl and the 2-propynylcysteines oxidize.[4]

(1) J. F. Carson, L. E. Boggs, and R. E. Lundin, *J. Org. Chem.*, **33**, 3739 (1968); J. F. Carson, R. E. Lundin, and L. E. Boggs, *ibid.*, **34**, 1996 (1969).
(2) S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc. B*, 351 (1967).
(3) J. F. Carson and L. E. Boggs, *J. Org. Chem.*, **30**, 895 (1965).
(4) Truce and Markley[5] have recently reported the preparation of aliphatic 1-propynyl sulfoxides and sulfones by oxidation of the corresponding sulfides with *m*-chloroperbenzoic acid in chloroform at 0° with no difficulty.
(5) W. E. Truce and L. D. Markley, *ibid.*, **35**, 3275 (1970).

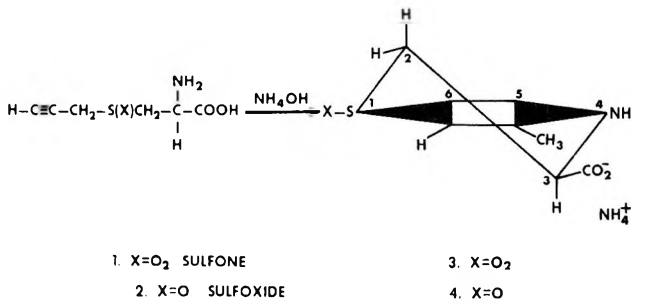
TABLE I

NMR SPECTRAL DATA FOR 3-(*R*)-CARBOXY-5-METHYL-2,3-DIHYDRO-4*H*-1,4-THIAZINE *S*-DIOXIDE (3) AND OXIDE (4) AT 100 MHz

Sulfone (3)[a]		CH_3	H-2 (a)	H-2 (e)	H-3 (a)	H-6	NH	NH_4^+
Dimethyl-d_6 sulfoxide, 60°	δ[b]	s[d] 1.87	t 2.72	d of t 3.22	q 3.92	s 4.81	s 6.32	s 6.78
	J[c]		$J_{22'}$ = 13.5 (g)	$J_{22'}$ = 13.0 (g)	J_{23} = 13.5 (aa)			
			J_{23} = 13.5 (aa)	J_{23} = 3.0 (ae)	J_{23} = 3.0 (ae)			
				J_{26} = 3.0 (LR)				
D_2O, 31°	δ'[b]	s 0.74	q 2.05	q 2.21	q 3.10			
	J		$J_{22'}$ = 13.3 (g)	$J_{22'}$ = 13.3 (g)	J_{23} = 11.7 (aa)			
			J_{23} = 11.7 (aa)	J_{23} = 3.6 (ae)	J_{23} = 3.6 (ae)			
D_2O + trifluoroacetic acid (D), 31°	δ'	s 1.12	q 2.73	q 2.92	q 3.50			
	J		$J_{22'}$ = 15.5 (g)	$J_{22'}$ = 15.5 (g)	J_{23} = 8.0 (aa)			
			J_{23} = 8.0 (aa)	J_{23} = 3.6 (ae)	J_{23} = 3.6 (ae)			
Sulfoxide (4)								
D_2O, 31°	δ'	s 0.78	t 1.15	q 1.97	q 2.75			
	J		$J_{22'}$ = 13.8 (g)	$J_{22'}$ = 13.8 (g)	J_{23} = 13.8 (aa)			
			J_{23} = 13.8 (aa)	J_{23} = 2.7 (ae)	J_{23} = 2.7 (ae)			

[a] Chemical shifts and coupling constants for the sulfone in dimethyl sulfoxide are first order; all other data were obtained by an ABX approximation. [b] Chemical shifts (δ) are in ppm from tetramethylsilane as internal standard; δ' refers to *tert*-butyl alcohol as internal standard. [c] Coupling constants (J) are in Hz. [d] s = singlet, t = triplet, q = quartet, d of t = doublet of triplets.

S-(2-Propynyl)-L-cysteine *S*-dioxide (1) and the corresponding (+) *S*-oxide (2) cyclize in dilute ammonium hydroxide solution to the ammonium salts of 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-dioxide (3) and of the corresponding *S*-oxide (4), respectively. Cyclization of the sulfone was accomplished in ammonium hydroxide solution at 25° or in sodium hydroxide solution followed by absorption on a cation exchanger and elution with ammonium hydroxide. The (+) sulfoxide requires carefully controlled conditions for cyclization (0.5 *N* ammonium hydroxide at 0–5° for 18–24 hr) to avoid excessive resin formation. Attempts to cyclize the (−) sulfoxide or mixtures rich in the (−) isomer under the same conditions yielded only dark resinous materials from which no cyclic compound could be isolated. Apparently, only one cyclic sulfoxide with $[\alpha]^{25}D$ *ca.* +1° (water) with configuration undetermined at sulfur is produced and predominately from the (+) sulfoxide isomer. The compounds are unusual as amino acids in that they crystallize as stable ammonium salts. Attempts to prepare the free cyclic amino acids led to hygroscopic amorphous materials.



1. X=O2 SULFONE
2. X=O SULFOXIDE
3. X=O2
4. X=O

The structures of the cyclic sulfone (3) and of the sulfoxide (4) were established by elemental analysis and nmr spectra as shown in Table I. Integrations were consistent with the assignments. The coupling constants between the 2 and 3 protons of the sulfone (3) in dimethyl-d_6 sulfoxide (J_{23} = 13.5 and 3.0 Hz) and of the sulfoxide (4) in D_2O (J_{23} = 13.8 and 2.7 Hz) are consistent with a trans-diaxial relation between the 3 proton and one of the 2 protons. If the compounds are present in the half-chair form, they must have the conformation as shown with H-3 axial and carboxylate equatorial rather than the inverted one with H-3 equatorial and carboxylate axial.

J_{23}(aa) for the sulfone (Table I) decreases as solvent is changed from dimethyl sulfoxide to D_2O to D_2O + trifluoracetic acid (13.5, 11.7, and 8.0 Hz, respectively). The decrease of J_{23}(aa) in D_2O on acidification may be a consequence of changing carboxylate anion to unionized carboxyl. This is consistent with the general rule that vicinal coupling constants decrease with increasing electronegativity of substituents.[6] In the absence of appropriate models, however, the possibility of small conformational changes cannot be eliminated. The magnitude of J_{23}(aa) favors a half-chair rather than a boat conformation. In the latter case, a dihedral angle of approximately 120° between the diaxial 2 and 3 protons would be expected to produce a much smaller coupling constant.[7]

In the ir (KBr pellet) the sulfoxide stretching frequency of sulfoxide (4) occurs at the unusually low value 995 cm^{-1}. In thiane sulfoxides an equatorial sulfoxide usually absorbs at a higher frequency than the axial isomer. This rule is applicable to the 3-carboxy-1,4-thiazane *S*-oxides with equatorial sulfoxides absorbing at 1040–1060 cm^{-1} and axial sulfoxides at 1025–1040 cm^{-1} in the solid state.[8] If the rule applies in the present case, the low sulfoxide ir frequency suggests an axial or pseudoaxial conformation for the sulfoxide. This must be speculative since the conformation is now a half-chair with unsaturation in the ring; the other isomer is not available and hydrogen bonding to the sulfoxide may be important.

Experimental Section[9]

S-(2-Propynyl)-L-cysteine *S*-Dioxide (1).—A mixture of 21.0 g (0.132 mol) of *S*-propargyl-L-cysteine[3] in 750 ml of acetic acid

(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 283.

(7) Similar arguments were used to establish the conformation of shikimic acid as a half-chair in D_2O; see ref 6, pp 296–297, and L. D. Hall, *J. Org. Chem.*, **29**, 297 (1964).

(8) J. F. Carson, L. E. Boggs, and R. E. Lundin, *ibid.*, **35**, 1594 (9970).

(9) Infrared spectra were determined as potassium bromide disks with a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were taken on a Varian Associates HR-100 spectrometer to which had been added an internal

was stirred at 50° for 7 hr while 65 ml of 30% hydrogen peroxide was added in 10-ml portions per hour. The yellow-orange solution was held overnight at room temperature and then concentrated *in vacuo* to a yellow oil. Crystallization from 100 ml of water and 100 ml of ethanol yielded 9.62 g of sulfone. From the mother liquor there was obtained an additional 1.45 g (combined yield 44%). Treatment of an aqueous solution with carbon and recrystallization from 50% ethanol yielded pure *S*-(2-propynyl)-L-cystene *S*-dioxide (1): dec 152°; $[\alpha]^{25}D$ −0.98° (*c* 2.8, H_2O); ir 3270 (HC≡C–), 1605 (ionized carboxyl), and 1135 cm^{-1} (sulfone).

Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33. Found: C, 37.7; H, 4.67; N, 7.33.

S-(2-Propynyl)-L-cysteine S-Oxide (2).—To a solution of 18 g (0.113 mol) of *S*-propargyl-L-cysteine in 1000 ml of acetic acid, there was added 13.0 ml of 32% hydrogen peroxide in 2-ml portions per hour, while the solution was stirred for 8 hr at 25°. The opalescent reaction solution was stirred overnight at room temperature, filtered from a trace of insoluble material, and concentrated *in vacuo* to an oil. Crystallization from 50 ml of water yielded 3.53 g, $[\alpha]^{26}D$ ~0° (water). Crystallization of the mother liquor from ethanol–water with increasing proportions of ethanol yielded the further fractions: 2.77 g, $[\alpha]^{26}D$ −16°; 6.65 g, $[\alpha]D$ −24.7°; 4.27 g, $[\alpha]D$ −41.0° (combined yield 87%). Several recrystallizations of the most levorotatory fraction from aqueous ethanol yielded 450 mg of (−)-*S*-(2-propynyl)-L-cysteine *S*-oxide as prismatic plates: dec 198° (colors 150°); $[\alpha]^{26}D$ −110.1° (*c* 2, water); ir 3190 (s) (HC≡C–), 1630 (s) (ionized carboxyl), and 1005 cm^{-1} (s) (sulfoxide).

Anal. Calcd for $C_6H_9NO_3S$: C, 41.12; H, 5.18; N, 7.99. Found: C, 40.9; H, 5.18; N, 8.03.

Five recrystallizations of the first fraction with $[\alpha]D$ ~0° from water–ethanol (1:4) or aqueous acetone yielded 590 mg of (+)-*S*-(2-propynyl)-L-cysteine *S*-oxide as soft fibrous needles: dec 189°; $[\alpha]^{26}D$ +72.5° (*c* 2, water); ir 3200 (m) (HC≡C–) 1660 (s), 1580 (s) (ionized carboxyl), and 1025 cm^{-1} (s) (sulfoxide).

Anal. Calcd for $C_6H_9NO_3S$: C, 41.12; H, 5.18; N, 7.99. Found: C, 40.7; H, 5.14; N, 7.94.

Cyclization of S-(2-Propynyl)-L-cysteine S-Dioxide (1).—A solution of 4.86 g (0.0254 mol) of 1 in 1 l. of 2 *N* ammonium hydroxide was kept at room temperature under nitrogen for 2 days. The pale yellow solution was concentrated *in vacuo* to a solid, redissolved in 100 ml of water, and passed through a column of Dowex 50 (H^+) (200 cm^3). The column was eluted with 1300 ml of 2 *N* ammonium hydroxide and the ammonical eluate concentrated *in vacuo* to a solid. Crystallization from 4 ml of water and 30 ml of ethanol yielded 3.39 g of crystalline product. An additional 1.12 g was obtained from the mother liquor (combined yield 85%). Recrystallization from the same solvent system yielded pure 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-dioxide ammonium salt (**3**) as tiny crystals: dec 185°; $[\alpha]^{26}D$ −0.1° (*c* 4.5, water); ir 3360 (s), 3000–3200 (broad), 1580 (s) (ionized carboxyl), and 1125 cm^{-1} (s) (sulfone).

Anal. Calcd for $C_6H_{12}N_2O_4S$: C, 34.60; H, 5.89; N, 13.45; S, 15.40. Found: C, 34.6 ; H, 5.84; N, 13.2; S, 15.4.

Conversion of the Ammonium Salt (3) to the Hyrochloride.—The ammonium salt (**3**) (4.89 g, 0.0235 mol) was dissolved in 100 ml of cold 3 *N* hydrochloric acid and concentrated *in vacuo* to a solid. Ammonium chloride was removed by crystallization from cold acetone–H_2O (8:1). A yield of 1.12 g (89%) was obtained. The amino acid hydrochloride was obtained from the mother liquor by crystallization from ethanol–acetone (1:15). A yield of 3.86 g of crystalline 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-dioxide hydrochloride was obtained: dec 173° (sharp); ir 1740 (un-ionized carboxyl) and 1125 cm^{-1} (sulfone).

Anal. Calcd for $C_6H_{10}NO_4SCl$: C, 31.65; H, 4.43; N, 6.15; Cl, 15.57. Found: C, 32.3; H, 4.67; N, 6.17; Cl, 15.3.

Cyclization of S-(2-Propynyl)-L-cysteine S-Oxide (2) to 4.—A solution of 3.56 g of the sulfoxide ($[\alpha]D$ +1.4°) containing 61% of the (+) isomer and 39% of the (−) isomer in 600 ml of water containing 6 ml of reagent ammonium hydroxide was kept at +3° for 18 hr. The pale amber solution was concentrated *in vacuo* (<20°) to *ca.* 100 ml, decolorized with carbon, and further concentrated *in vacuo* to a solid. Crystallization from 3 ml of water and 18 ml of ethanol yielded 1.50 g of prisms. An additional 0.61 g was obtained from the mother liquor.

The yield of crude product was 88% based on reaction of the (+) isomer. Recrystallization from ethanol–water (5:1) yielded pure 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-oxide ammonium salt (**4**) as small colorless prisms: dec 182–184° (darkens, 177°); $[\alpha]^{25}D$ +1.0 (*c* 2.4, water); ir 3340 (m), 3000–3100 (broad), 1605 (s) (ionized carboxyl), and 992 cm^{-1} (s) (sulfoxide).

Anal. Calcd for $C_6H_{12}N_2O_3S$: C, 37.49; H, 6.29; N, 14.58; S, 16.68. Found: C, 37.5; H, 6.38; N, 14.6; S, 16.8.

Fractional crystallization from aqueous ethanol or aqueous acetone showed no variation in rotation at the D line and a second sulfoxide could not be obtained. A hydrochloride could not be prepared and addition of acid to the ammonium salt led to decomposition. When cyclization was attempted with pure (−) isomer, only dark resins were obtained.

Registry No.—**1**, 27199-03-7; (+)-**2**, 27199-04-8; (−)-**2**, 27199-05-9; **3**, 27199-06-0; **3** HCl, 27199-07-1; **4**, 27199-08-2.

Acknowledgment.—We thank Robert Lundin for nmr spectra and L. M. White and Geraldine Secor for elemental analysis.

A Facile Quantitative Reduction of Sulfoxides

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Received September 17, 1970

The recent literature indicates an interest in finding an effective method for the reduction of sulfoxides to sulfides.[1] However, no general method is available which accomplishes the reduction in high yields under mild conditions with common laboratory reagents. A recent report[2] showing the effectiveness of sodium borohydride–transition metal salt systems in the reduction of nitro, amide, and nitrile groups has prompted us to report our findings in sulfoxide reductions.

In connection with our previous work[3] on the novel reduction–dehydration of thioxanthone sulfoxide to thioxanthone and thioxanthenol by sodium borohydride, we found that the same products resulted when the hydroxide ion was replaced by cobalt chloride.[4] However, it was not clear whether the latter reduction again proceeded through a dehydration step or occurred by a simple sulfoxide reduction. Thus, we began an investigation into the effect of this reducing system on sulfoxides.

As shown in Table I, the sodium borohydride–cobalt chloride system reduced dialkyl, arylalkyl, and diaryl sulfoxides, as well as the conformationally restricted[5]

field-frequency lock built at this laboratory. Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

(1) (a) I. Granoth, A. Kalir, and Z. Pelah, *J. Chem. Soc. C*, 2424 (1969), and references cited therein; (b) H. Alper and E. C. H. Keung, *Tetrahedron Lett.*, 53 (1970); (c) K. Naumann, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 2788 (1969); (d) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heynengen, *J. Org. Chem.*, **35**, 2430 (1970).

(2) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Lett.*, 4555 (1969).

(3) A. L. Ternay and D. W. Chasar, *J. Org. Chem.*, **32**, 3814 (1967).

(4) D. W. Chasar, Ph.D. Thesis, Case Western Reserve University, Cleveland, Ohio, 1968; *Diss. Abstr.*, **30**, 116B (1969).

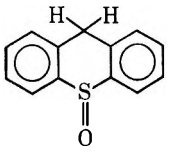
(5) A. L. Ternay, L. Ens, J. Herrmann, and S. Evans, *J. Org. Chem.*, **34**, 940 (1969).

TABLE I

Sulfoxide	Yield of sulfide, %[a]
$(CH_3CH_2CH_2CH_2)_2S(O)$ (5)	98
$C_6H_5S(O)CH_3$ (6)	98
$(C_6H_5)_2S(O)$ (4)	95
Thioxanthene sulfoxide (1)	100
$(C_6H_5CH_2)_2S(O)$ (2)	10
$(CH_2)_4S(O)$ (3)	0

[a] Isolated yields after column chromatography.[6]

thioxanthene sulfoxide **1**, in excellent yields. Thin layer chromatography of the crude products indicated quantitative reduction of the sulfoxide in each of these compounds.[6]



1

However, dibenzyl sulfoxide (**2**) and tetramethylene sulfoxide (**3**) afforded little or no sulfide on reduction. In both reductions, the recovery of crude product was low, suggesting possible cleavage reactions[7] leading to volatile products. In the reduction of **2**, some **2** still remained even after extended reaction times, but the major components of the recovered material were two high melting unidentified solids. No sulfide or sulfoxide could be detected (tlc) in the crude product from the reduction of **3**. Both **2** and **3** have also been shown to give poor yields of sulfide by other reduction procedures.[1b,8]

(6) While reduction proceeded quantitatively, an unidentified impurity (<1%) was usually present in the sulfide. This was easily removed by column chromatography.

(7) H. H. Szmant in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, Chapter 16; T. J. Wallace, H. Pobiner, J. E. Hofmann, and A. Schriesheim, *J. Chem. Soc.*, 1271 (1965).

(8) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).

The investigations of Brown, *et al.*,[9a] and Brown[9b] on the reaction of transition metal ions with sodium borohydride suggest that these reductions may proceed by catalytic hydrogenation. However, it is conceivable that the sulfoxide oxygen coordinates with the metal ion, thus weakening the sulfur–oxygen bond and rendering it more liable to borohydride reduction.[10] Our work toward this end is continuing as well as the applicability of this reducing system to other sulfur-containing functional groups.

Experimental Section

The sulfoxides were either obtained commercially (Aldrich Chemical Co.) or were prepared by oxidation of the corresponding sulfide with *m*-chloroperbenzoic acid according to the procedure of Johnson and McCants.[12] The products were identified by direct comparison of their infrared spectra and tlc behavior with those of authentic sulfides. Thin layer chromatography was performed on precoated glass plates of silica gel using chloroform as eluent and iodine vapor as the visual aid. Column chromatography was accomplished on silica gel (100 mesh) using chloroform as eluent.

Reduction of Diphenyl Sulfoxide (4).—In a typical experiment, sodium borohydride (3.8 g, 0.10 mol) was slowly added to a cooled (10–15°) stirred solution of **4** (2.0 g, 0.01 mol) and cobalt chloride hexahydrate (4.8 g, 0.02 mol) in 200 ml of 95% ethanol. Gas evolved and a black precipitate formed. After complete addition, the mixture was stirred for 2 hr at room temperature. Water (25 ml) was added and the mixture was heated on a steam bath for 5–10 min and then poured into water (300 ml). This mixture was extracted with ether (four 75-ml portions), the extracts were combined and dried ($MgSO_4$), and the solvent was evaporated under vacuum to afford essentially pure sulfide.[6]

Registry No.—**1**, 10133-81-0; **2**, 621-08-9; **3**, 1600-44-8; **4**, 945-51-7; **5**, 2168-93-6; **6**, 1193-82-4.

(9) (a) H. C. Brown, H. I. Schlesinger, A. E. Finholt, J. R. Gilbreath, H. R. Hoekstra, and E. K. Hyde, *ibid.*, **75**, 215 (1953); (b) C. A. Brown, *J. Org. Chem.*, **35**, 1900 (1970).

(10) This mechanism would be analogous to that proposed for the reduction of alkoxysulfonium salts by sodium borohydride.[11]

(11) C. R. Johnson, *J. Org. Chem.*, **32**, 3233 (1967)

(12) C. R. Johnson and D. McCants, *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

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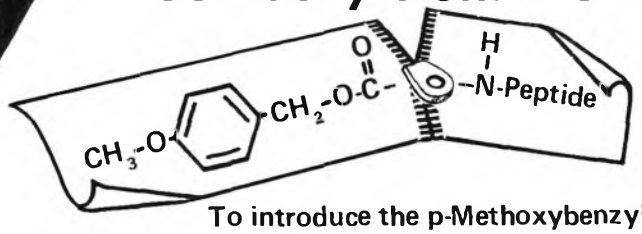

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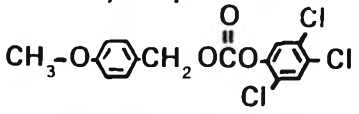

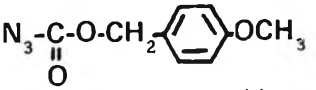

p-Methoxybenzyl 2, 4, 5-trichlorophenyl carbonate and p-methoxybenzyloxycarbonyl azide are the reagents of choice to introduce this moiety, which is so easily and selectively split off with trifluoroacetic acid.[1,2]

(1) F. and K. Hunger, Ber. 95, 1, 11 (1962). (2) E. Klieger, Ann., 724, 204 (1969).

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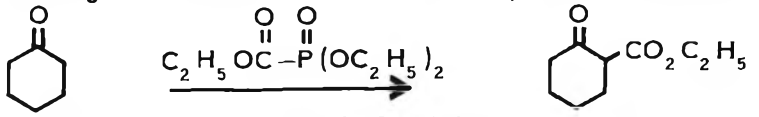

(1) L.F. Fieser and M. Fieser, Reagents for Organic Synthesis, Wiley, New York 1967.

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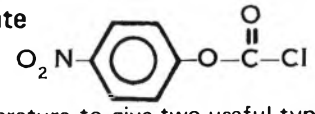

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(1) R.L. Letsinger and K.K. Ogilvie, J. Org. Chem., 32, 296 (1967).

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