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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 2

JANUARY 26, 1973

Formation and Reactions of Ketene Diphenyl Dithioacetals Derived from Aldoses[1,2]

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Received August 3, 1972

Acetonation of D-xylose diphenyl dithioacetal (**4**) gives the 2,3:4,5-diisopropylidene acetal (**5**), which suffers elimination of acetone by action of methylsulfinyl carbanion to yield 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diphenyl dithioacetal (**6**). This product, its 3-methyl ether (**7**), its 3-*p*-nitrobenzoate (**8**), and the corresponding D-erythro analogs (**1–3**), on treatment with concentrated hydrochloric acid and subsequent acetylation, gave mixtures from which 5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thio-D-*erythro*- and -D-*threo*-pentono-1,4-lactones (**10** and **11**) were isolated. Extended heating of compound **2** in 1 *M* aqueous ethanolic hydrochloric acid gave a low yield of a crystalline compound, tentatively identified as either 2,5-bis(phenylthio)-6*H*-pyran (**9**) or 2-phenylthio-5-(phenylthiomethyl)furan (**14**). *p*-Nitrobenzoylation of compound **1** gave, in addition to the 3-*p*-nitrobenzoate (**3**) having the same stereochemistry at C-3, some of the 3 epimer (**8**). An improved preparation of compound **4** is recorded.

Despite Fischer's statements[4,5] that diphenyl dithioacetals of aldoses could not be made, several examples have been reported in recent years.[2,6–9] These derivatives appear to be formed more slowly and are less labile to hydrolysis than the dialkyl analogs,[2,9] but their conformational behavior and the reactions of the polyhydroxyalkyl chain appear essentially the same.[2,7–9]

The action of any one of several powerful bases on the 2,3:4,5-diisopropylidene acetal of D-arabinose diphenyl dithioacetal was found to cause elimination of acetone to give 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diphenyl dithioacetal[10] (**1**), characterized as its 3-methyl ether (**2**) and 3-*p*-nitrobenzoate (**3**). These products are formally derivatives of a carbohydrate ketene, the unknown 2-deoxy-D-*erythro*-pent-1-enose. It was found[2,11] that compound **2** is exceptionally inert to common reactions of alkenes or of dithioacetals, although it was decomposed by aqueous acid. A formally related compound, tetrakis(phenylthio)ethylene, has been reported[12] to be inert toward singlet oxygen, whereas a number of simple ketene dithioacetals are highly susceptible to electrophiles.[13]

Uncertainty about the stereochemistry of the products of acid-catalyzed degradation of **2** prompted a parallel study on reactions of the 3 epimer of **2**. This report describes an improved preparation of D-xylose diphenyl dithioacetal (**4**) and its conversion, by way of the 2,3:4,5-diisopropylidene acetal (**5**), into the D-threo analogs (**6–8**, respectively) of **1–3** (Scheme I). Also reported are the isolation and spectroscopic identification of two lactones (**10** and **11**) and other products, resulting from acid hydrolysis of both stereochemical series of ketene dithioacetal derivatives.

Discussion

Preparation of Compounds 4–8.—An improved direct preparation of crystalline D-xylose diphenyl dithioacetal[2] (**4**) involved treatment of D-xylose with benzenethiol and saturated aqueous hydrogen chloride for 4 hr at 0°, and shaking the cold, diluted mixture with ether; a 53% of crystalline **4** was obtained in reactions on a 50-g scale. Acetonation of **4** in the presence of copper(II) sulfate and sulfuric acid gave, in good yield, a distillable diisopropylidene acetal considered to be the 2,3:4,5 isomer (**5**) by analogy with the corresponding diethyl dithioacetal,[14] and by

(1) Supported, in part, by Grant No. GM-11976 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md. 20014 (The Ohio State University Research Foundation, Project 1820).

(2) Previous paper in this series: D. Horton and J. D. Wander, *Carbohyd. Res.*, **13**, 33 (1970).

(3) To whom correspondence should be addressed.

(4) E. Fischer, *Ber.*, **27**, 673 (1894).

(5) E. Fischer, "Untersuchungen über Kohlenhydrate und Fermente (1884–1908)," Julius Springer Verlag, Berlin, 1909, p 89.

(6) Z. El-Hewehi, *Chem. Ber.*, **91**, 2039 (1958).

(7) D. Horton, J. B. Hughes, J. M. J. Tronchet, W. N. Turner, and J. D. Wander, Abstracts, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 12–17, 1965, p 21D.

(8) E. Zissis, A. L. Clingman, and N. K. Richtmyer, *Carbohyd. Res.*, **2**, 461 (1966).

(9) D. Horton and J. D. Wander, *ibid.*, **15**, 271 (1970).

(10) So named by inserting the unsaturation locant and infix "1-en" into the name of the saturated analog. The name used previously,[2] 1,2-dideoxy-4,5-*O*-isopropylidene-1,1-bis(phenylthio)-D-*erythro*-pent-1-enitol, although not incorrect, renders less obvious the direct relationship of **1** to the aldose dithioacetals.

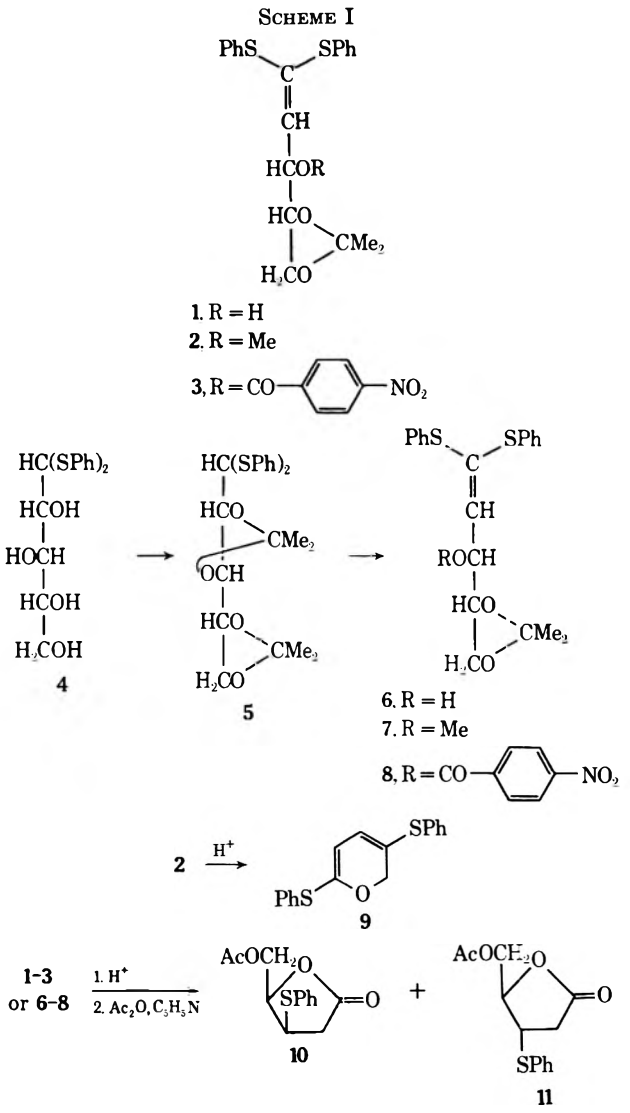
(11) J. D. Wander, Ph.D. Dissertation, The Ohio State University, 1970, pp 206–213, 238–258; *Diss. Abstr.*, Order No. 70-26,384.

(12) W. Adam and J.-C. Liu, *J. Amer. Chem. Soc.*, **94**, 1206 (1972).

(13) F. A. Carey and J. R. Neergaard, *J. Org. Chem.*, **36**, 2731 (1971).

(14) H. Zinner and J. Milbradt, *Carbohyd. Res.*, **3**, 389 (1967).

SCHEME I



the fact that the conversion product **6**, formed from **5** under basic conditions, has an *O*-isopropylidene group at positions 4 and 5. The mass spectrum of **5** (see Experimental Section) showed a major ion at m/e 101, presumably a 2,2-dimethyl-1,3-dioxolanium ion resulting from C-3–C-4 bond cleavage in **5**; a similar fragmentation (between C-4 and C-5) has been observed[15] with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Treatment of compound **5** with methylsulfinyl carbanion in methyl sulfoxide leads, as with the D-arabino analog,[2,7] to abstraction of H-1 with synchronous or subsequent elimination of the 2,3-*O*-isopropylidene group as acetone; the resultant anion, on treatment with water, gives the syrupy, chromatographically homogeneous 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diphenyl dithioacetal (**6**) in 62% yield. Treatment of the anion of **6** with methyl iodide gave the corresponding 3-methyl ether (**7**), also a liquid. A crystalline, levorotatory *p*-nitrobenzoate (**8**) (mp 90–92°) was prepared from **6** by the conventional procedure,[2] and its nmr spectrum (Table I) permitted detailed assignments. The site of acylation was identified as O-3 by the low-field appearance of a doublet of doublets assignable only to H-3 (τ 3.70; $J_{2,3}$ = 8.5, $J_{3,4}$ = 5.6 Hz); the pattern shifted

(15) D. C. DeJongh and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 67 (1964).

TABLE I

NMR SPECTRAL DATA (60 MHz, $CDCl_3$) FOR KETENE DITHIOACETAL DERIVATIVES **6**, **7**, AND **8**

	Chemical shifts, ppm							
Compd	H-2	H-3	H-4	H-5	H-5′	Ph	CMe_2	Other
6	3.85	5.17	5.72	—	6.26	2.73	8.57, 8.65	7.30[a]
7	4.16	5.43	5.67	—	6.32	2.74	8.56, 8.65	6.66[b]
8	4.01	3.70	5.42	—	6.26	2.66–2.85	8.52, 8.63	1.78[c]

[a] OH resonance: $J_{2,3}$ = 8.8, $J_{3,4}$ = 5.8 Hz. [b] OMe resonance $J_{2,3}$ = 8.9, $J_{3,4}$ = 6.0 Hz. [c] *p*-Nitrophenylene resonances: $J_{2,3}$ = 8.5, $J_{3,4}$ = 5.6 Hz.

to lower field by acylation would have been more complex had the acyl group been located at O-4 or O-5. This evidence therefore establishes the structure formulated for compound **8**, and thus also for compounds **5**, **6**, and **7**.

A very minor, dextrorotatory side product (mp 100–102°) from the *p*-nitrobenzoylation of **6** was found to be identical with the 3 epimer of **8** (**3**) previously prepared,[2] by *p*-nitrobenzoylation of 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diphenyl dithioacetal[2] (**1**). The *p*-nitrobenzoylation of **1** was repeated and it was found that, in addition to the dextrorotatory D-erythro derivative **3** (mp 102–103°) already reported[2] there was formed a lesser proportion of the levorotatory D-threo derivative **8** (mp 91–92°). As the nmr spectra of compounds **1**, **2**, **6**, and **7** showed no evidence whatsoever of epimeric contamination, it must be concluded that epimerization of the *p*-nitrobenzoates **3** and **8** occurs either in pyridine solution or on the silicic acid column, possibly by a process involving brief separation and internal return of the *p*-nitrobenzoate anion; further work would be necessary to clarify this point.

Reactivity of the Ketene Dithioacetal 2.—Compound **2** was remarkably stable toward reagents that normally react with alkenes or with dithioacetals. It was recovered unchanged upon attempted cleavage of the dithioacetal group by Raney nickel[16] or by mercuric chloride,[17] even in the presence of an overwhelming excess of the reagent. It was not appreciably hydrolyzed by the action of 1 equiv of bromine in acetic acid,[18] although a substantial excess of bromine led to decomposition of **2** with formation of diphenyl disulfide[19] and other, unidentified products. Diphenyl disulfide was also produced in fair yield from **2** by ozonolysis at ~25° or by dissolution in acetic anhydride–sulfuric acid; complex mixtures again accompanied this product.

Extended oxidation of **2** with peroxypropionic acid[20] led to methyl phenyl sulfone,[21] whereas extended exposure of **2** to alkaline hydrogen peroxide in acetone gave benzenesulfonic acid. The product of oxidation with peroxyacetic acid detonated spontaneously during isolation.

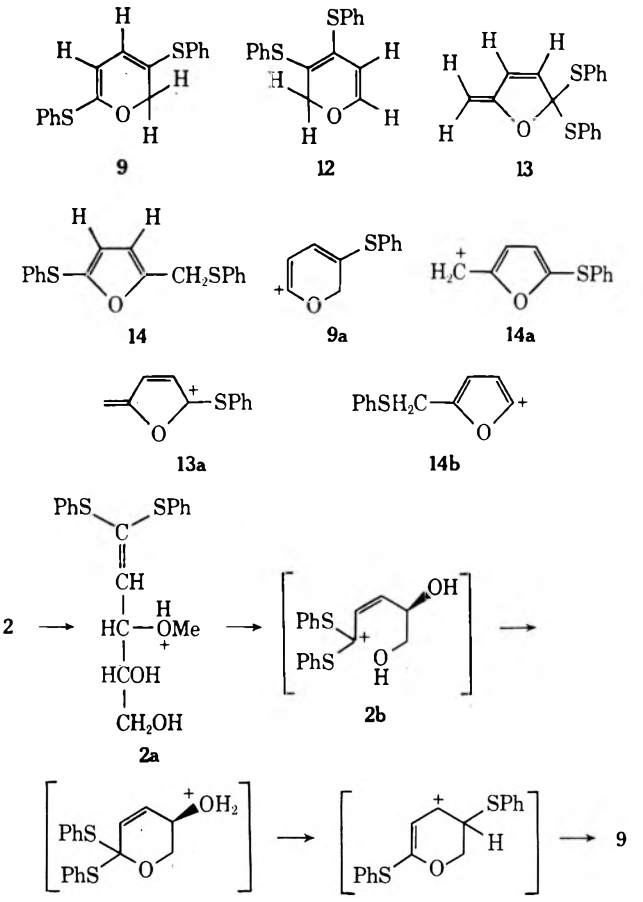
Hydrolysis of **2** in 1 *M* aqueous ethanolic hydrochloric acid for 24 hr at reflux gave a dark mixture of products from which a crystalline, optically inactive solid (mp

(16) M. L. Wolfrom and J. V. Karabinos, *ibid.*, **66**, 909 (1944).
(17) M. L. Wolfrom, *ibid.*, **51**, 2188 (1929).
(18) F. Weygand, H. J. Bestmann, and H. Ziemann, *Chem. Ber.*, **91**, 1040 (1958).
(19) E. Dreher and R. Otto, *Justus Liebigs Ann. Chem.*, **154**, 178 (1870).
(20) D. L. MacDonald and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **74**, 2087 (1952).
(21) A. Michael and G. M. Palmer, *Amer. Chem. J.*, **6**, 254 (1884).

53°) was isolated in low yield; its analysis and mass spectrum indicated the molecular formula $C_{17}H_{14}OS_2$, and detailed inspection of the mass spectral and nmr data led to tentative[11] formulation of this product as 2,5-bis(phenylthio)-6*H*-pyran (**9**). The partial structure $C_5H_4O(SPh)_2$ was readily recognized from three mass spectral ions: *m/e* 298 ($M\cdot^+$), 189 (base peak, $M\cdot^+ - \cdot SPh$), and 109 (PhS^+), and from the nmr spectrum, which shows a ten-proton multiplet for two phenyl groups, a two-proton singlet at τ 6.08 ($-CH_2O-$), and an AB system (τ 3.75, 3.96; J_{AB} = 3.1 Hz) indicative of two vicinal, vinyl protons. Assuming conventional hydrolytic cleavage of the acetal group from **2**, followed by protonation at O-3 and loss of methanol to give an allylic carbonium ion stabilized by the thio groups, cyclization to give furan or pyran derivatives could take place by attack of either O-4 or O-5 at C-1. Bearing in mind the proclivity of RS groups to migrate *via* episulfonium ions under acidic conditions,[22] it is possible to formulate numerous plausible isomers of the structure $C_5H_4O(SPh)_2$, although the nmr data appear to exclude all but four of these, namely structures **9**, **12**, **13**, and **14**. Structure **12** is not attractive because the ions formed by loss of PhS· from **12** would not be expected to possess the extreme stability manifested by *m/e* 189, and furthermore the separation of the vinyl proton resonances is not so large as would be anticipated from the effect of the oxygen atom in structure **12**. The mass spectral fragment $PhSCH_2^+$ (*m/e* 123) was shown[2] earlier to exhibit considerable stability, so that the absence of this fragment from the observed mass spectrum appears to militate against structure **14**; it is observed, however, that the benzyl cation (*m/e* 91, $PhCH_2^+$) dominates the mass spectrum of benzylthiobenzene,[23] whereas the phenylthiomethyl cation (*m/e* 123) is exceedingly minor. As the benzyl cation and the furylmethyl cation (**14a**) could be expected to exhibit generally similar stabilities, structure **14** cannot be excluded at the present. Whereas structures **9** and **14** accord with all experimental data, the magnetic equivalence of the methylene protons in **13** would be an improbable but not impossible circumstance. Strong support for structure **9** or **14** and against structure **13** is provided by the mass spectral peak at *m/e* 161, identified as the transition *m/e* 189 → 28 by the metastable peak at *m/e* 137.5. Loss of C_2H_4 from *m/e* 189 is out of the question for either structure, and no mechanism can be drawn for loss of CO from **13a**; in contrast the ions **9a** and **14b** can readily extrude this fragment. The route from **2** to 2,5-bis(phenylthio)-6*H*-pyran (**9**) can be supposed to follow the process shown in Scheme II, whereas a similar process with the roles of the hydroxyl groups reversed would lead to 2-phenylthio-5-(phenylthiomethyl)furan (**14**). Unambiguous assignment of the structure of $C_5H_4O(SPh)_2$ will require studies on suitable reference compounds.

Conversion of Compounds 1, 2, 3, 6, 7, and 8 into the Lactones 10 and 11.—Dissolution of compound **7** in concentrated hydrochloric acid at ~25°, isolation of the organic product after 20 min, and subsequent acetylation with acetic anhydride–pyridine gave a mixture that was resolved by chromatography to give

SCHEME II



22% of crystalline 2-deoxy-3-*S*-phenyl-3-thio-D-*threo*-pentono-1,4-lactone (**10**) and 13% of the syrupy D-erythro isomer (**11**) of **10**. Essentially similar results were obtained when compounds **1**, **2**, **3**, **6**, or **8** were substituted for **7** as starting material, with compounds **10** and **11** being isolated in about 3:2 proportion in an overall yield of 25–35% (appreciable manipulative losses probably occurred during chromatographic separation).

The structures of the lactones **10** and **11** were assigned from various lines of evidence. The empirical formula $C_{13}H_{14}O_4S$ of the crystalline isomer **10** was also the molecular formula, as the mass spectrum showed a molecular ion at *m/e* 266. The liquid product **11** had a mass spectrum identical with that of **10** except for relative peak intensities, indicating that **11** is a diastereoisomer of **10**; the nonidentical, nonzero specific rotations observed for the two products supported this diastereoisomeric relationship. The nmr spectrum of each product showed a five-proton multiplet for the phenyl group, a three-proton singlet for an acetoxyl group, and separated multiplets accounting for six proton resonances having couplings appropriate only for the saturated, four-carbon-atom sequence $WCH_2C(H,X)C(H,Y)CH_2Z$, in which W, X, Y, and Z are not magnetically active nuclei. The ir spectra of the products show, in addition to typical acetate C=O absorption at 5.72 μm, a second carbonyl band at 5.62 μm, typical[24] of 1,4-lactones. Accordingly, the two products were formulated as diastereoisomeric 3,5-disubstituted 4-hydroxypentanoic 1,4-lactones hav-

(22) B. Berrang and D. Horton, *Chem. Commun.*, 1038 (1970).
(23) F. Taboury, *Bull. Soc. Chim. Fr.*, **31**, 1183 (1904).
(24) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, San Francisco, Calif., 1962, p 44.

TABLE II

COMPARATIVE NMR SPECTRAL DATA (100 MHz, $CDCl_3$) FOR 10, 11, AND SEVERAL RACEMIC 4-HYDROXY-3-THIOPENTANOIC 1,4-LACTONE DERIVATIVES

	Chemical shifts, ppm						Coupling constants, Hz						
Compd	H-2	H-2′	H-3	H-4	H-5	H-5′	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
15	6.94	7.47	6.14	5.54	8.57		17.9	8.9	8.6	6.7	6.5		
16	6.84	7.38	5.89	5.34	8.54		17.7	8.8	7.9	6.3	6.3		
17	6.98	7.44	6.70	5.63	8.51		17.1	8.1	8.8	7.0	6.3		
18	6.87	7.42	6.53	5.53	8.55		17.9	8.0	8.1	6.4	6.4		
19	7.04	7.50	6.75	5.65	8.59		17.0	7.8	9.6	7.4	6.2		
11	7.08	7.31	5.83	5.14	5.55	5.55	17.7	8.4	8.4	6.9	4.3	4.3	*a*
10	7.19	7.65	6.20	5.44	5.66	5.90	17.0	8.0	6.9	5.6	2.9	4.4	11.8
20	6.93	7.52	6.19	5.25	8.59		17.5	7.5	4.1	5.3	6.4		
21	*b*	*b*	*b*	*b*	*b*		17.4[c]	8.0[c]	5.0[c]	*b*	*b*		

[a] Not available owing to the fortuitous magnetic equivalence of H-5 and H-5′. [b] Not reported. [c] Data from ref 25; measured at 56.4 MHz.

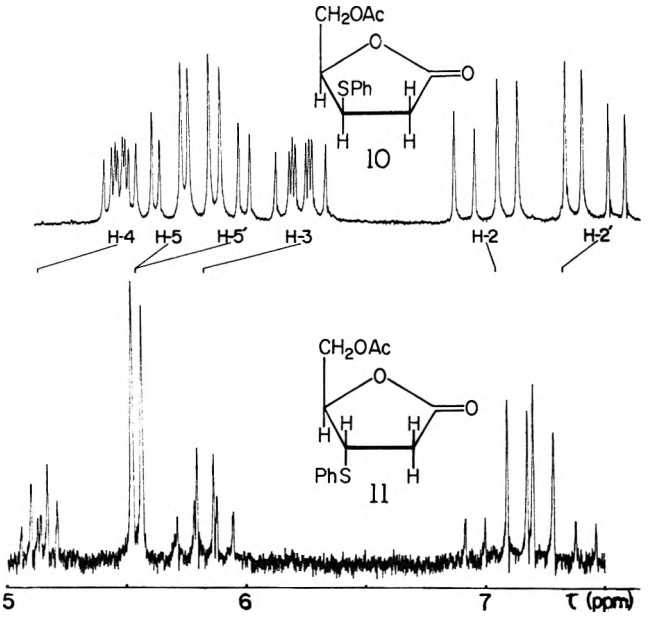


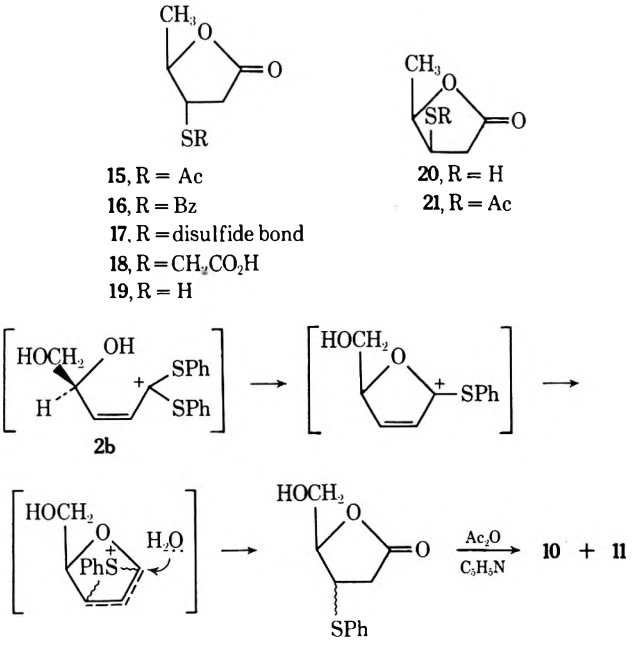
Figure 1.—Central portion of the nmr spectra (100 MHz, $CDCl_3$) of (a) 5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thio-D-*threo*-pentono-1,4-lactone (**10**) and (b) the D-erythro analog (**11**).

ing one acetoxyl and one arylthio group. As the mass spectra exhibit peaks at *m/e* 73 ($AcOCH_2^+$) but not at *m/e* 123 ($PhSCH_2^+$) (see ref 2) there is good evidence to assign the 5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thiopentono-1,4-lactone skeleton structure to the two products. Support for this assignment is found in the nmr spectra (Figure 1) of the diastereoisomers; the H-3 signals are observed at fields that are atypically high for acetoxymethylene protons [but are within the range observed (Table II) for substituted thiomethylene groups], whereas H-5 and H-5′ resonate within the range of chemical shift (τ 5–6) characteristic of acetoxymethyl groups in carbohydrate derivatives. As the products (a) are optically active, (b) are not enantiomorphs, and (c) are formed in a ratio not influenced by the stereochemistry at C-3 of the starting material, it may be inferred that the stereochemistry at C-4 of the two lactones is the same as that in the precursors. Thus it remains only to differentiate specifically the two isomers as D-erythro (trans) and D-threo (cis).

Although attempts at direct determination of relative stereochemistry in **10** and **11** [as by comparing relative intensities of the *m/e* 84 ($M\cdot^+ - PhSCH_2OAc$) fragment] proved indecisive, the assignment was assisted by nmr spectral comparison with several 4-hydroxy-3-thiopentanoic-1,4-lactones (**15–21**) that have been described in the literature[25,26] (see Table II). Although the values of $J_{2,2}$ and $J_{2,3}$ remain essentially constant for both the cis and trans numbers of the series, the other coupling values vary characteristically between the two series; $J_{2',3}$ in the known (racemic) derivatives exceeds 8 Hz in the trans isomers whereas it is several hertz smaller in the cis isomers, and $J_{3,4}$ (trans isomers) surpasses $J_{3,4}$ (cis isomers). The crystalline lactone ($J_{2',3} = 6.9$, $J_{3,4} = 5.6$ Hz) is thus presumed to be the cis isomer (5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thio-D-*threo*-pentono-1,4-lactone, **10**) and the liquid one ($J_{2',3} = 8.4$, $J_{3,4} = 6.9$ Hz) the trans isomer (5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thio-D-*erythro*-pentono-1,4-lactone, **11**). These structures await confirmation by classical degradative methods.

The sequence of steps leading to compounds **10** and **11** could possibly follow a route such as that shown in Scheme III, from an intermediate **2b** already formulated in the sequence leading to compound **9**, although experimental evidence for the steps is not available. The formation of these products probably

SCHEME III



(25) G. Fuchs, *Ark. Kemi*, **29**, 379 (1968).
(26) G. Fuchs, *Acta Chem. Scand.*, **22**, 1052 (1968).

depends on competing processes that are influenced by the reaction conditions.

Examination of molecular models indicates that, in compound **10**, the phenyl group is sterically constrained away from C-5; this conformational restriction and the shielding effect of the π-electron cloud of the phenyl group may be the reason for the higher field position observed for H-2′ and certain other resonances in **10** as compared with **11**.

Experimental Section[27]

Improved Preparation of D-Xylose Diphenyl Dithioacetal (4).—D-Xylose (50 g) was dissolved in concentrated hydrochloric acid (100 ml) that had previously been saturated at 10° with hydrogen chloride. The solution was cooled to 0° and stirred with benzenethiol (85 g) for 4 hr at 0°. The homogeneous solution was poured into ice–water (1 l.) and shaken with ether (~100 ml) to promote crystallization. The mixture was kept overnight at 0° and the white, crystalline product was filtered off and recrystallized from ethanol–water to give pure **4**, yield 55 g (53%), mp 100–101°, $[\alpha]^{22}D$ −8° (*c* 0.4, ethanol) (lit.[2] mp 101–101.5°, $[\alpha]D$ −8° in ethanol).

2,3:4,5-Di-*O*-isopropylidene-D-xylose Diphenyl Dithioacetal (5).—A mixture of compound **4** (40 g), anhydrous copper(II) sulfate, dry acetone (500 ml), and sulfuric acid (0.2 ml) was stoppered securely and shaken vigorously for 70 hr at ~25°. The mixture was filtered and the filtrate was stirred for 20 min with anhydrous sodium carbonate (8 g). Filtration and evaporation of the filtrate gave **5** as a chromatographically homogeneous syrup that could be kept without decomposition for several weeks at 0°: yield 30 g (51%); R_f 0.83 [1:9:10 isopropyl alcohol–benzene–petroleum ether (bp 30–60°)]; bp (bath) 140° (0.1 mm); $[\alpha]^{24}D$ −33° (*c* 1.2, chloroform); mass spectrum *m/e* 432 (0.3, $M\cdot^+$), 417 (0.05, $M^+ - \cdot CH_3$), 323 (4.5, $M^+ - PhS\cdot$), 265 (6.5), 244 [6.0, $(PhSCH{=}CHSPh)\cdot^+$], 207 (12.5), 135 (24.5, $PhSC^-{=}CH_2$), 123 (17, $PhSCH_2^+$), 110 (100, $PhSH\cdot^+$), 109 (36, PhS^+), 101 (13, $C_5H_9O_2^+$), 91 (17, $C_7H_7^+$), 78 (17, PhH^+), 77 (16, Ph^+), 43 (67, Ac^+).

Anal. Calcd for $C_{23}H_{28}O_4S_2$: C, 63.88; H, 6.46; S, 14.82. Found: C, 64.06; H, 6.70; S, 15.13.

2-Deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose Diphenyl Dithioacetal (6).—The acetal **5** (14 g) was dissolved (with external cooling to maintain the temperature below 40°) in dry dimethyl sulfoxide (120 ml) in which sodium (5 g) had previously been dissolved. After 10 min, the red-brown solution was agitated vigorously with a mixture of cold water (1 l.) and benzene (300 ml). The organic phase was washed twice with water, dried (sodium sulfate), and evaporated to an orange-yellow, chromatographically homogeneous syrup: yield 7.5 g (62%); R_f 0.30 (1:9:10 isopropyl alcohol–benzene–petroleum ether). A sample was further purified on a 20 × 1 cm column of silica gel (1:1 ether–petroleum ether) to give **6** as a pale yellow syrup, $[\alpha]^{24}D$ −61° (*c* 1.1, chloroform); for nmr, see Table I.

2-Deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*threo*-pent-1-enose Diphenyl Dithioacetal (7).—Sodium (5 g) was dissolved in dry dimethyl sulfoxide (150 ml), and compound **6** (10 g) was added with stirring and external cooling to 25°; after a few minutes methyl iodide (30 g) was added dropwise with continued cooling. After 3 min the resulting slurry was poured into a well-agitated mixture of water (1.5 l.) and benzene (300 ml). The benzene extract was washed with water, dried (sodium sulfate), and evaporated to a yellow-orange syrup, yield 6 g (65%). Purification of 1 g of the product on a 25 × 1 cm column of silica gel (1:2 ether–petroleum ether) gave **7** as a pale-yellow syrup, R_f 0.45 (1:9:10 isopropyl alcohol–benzene–petroleum ether), $[\alpha]^{25}D$ −66° (*c* 1.4, chloroform); for nmr, see Table I.

2-Deoxy-4,5-*O*-isopropylidene-3-*O*-(*p*-nitrobenzoyl)-D-*threo*-pent-1-enose Diphenyl Dithioacetal (8).—A solution of **6** (700 mg) and *p*-nitrobenzoyl chloride (3 g) in freshly distilled pyridine (20 ml) was stirred overnight at ~25° and then poured into water (500 ml) at 0°. The crude **8** that precipitated was dissolved in benzene and purified on a column of silica gel (dichloromethane as eluent). The product crystallized slowly from methanol to give pure **8**: yield 380 mg (40%); mp 90–92°; $[\alpha]^{22}D$ −47° (*c* 1.2, chloroform); R_f 0.43 [1:9:10 isopropyl alcohol–benzene–petroleum ether); nmr, see Table I; X-ray powder diffraction data 9.76 (vs) (1), 9.00 (w), 8.20 (w), 6.88 (m), 6.60 (w), 5.65 (m), 5.33 (m), 4.82 (s) (2), 4.41 (m), 4.28 (m), 3.75 (s) (3), 3.56 (m), 3.30 (m), 3.03 (m), 2.76 (w).

Anal. Calcd for $C_{27}H_{25}NO_6S_2$: C, 61.95; H, 4.78; N, 2.68; S, 12.24. Found: C, 61.73; H, 4.88; N, 2.80; S, 12.33.

In another preparation, the methanolic mother liquors were concentrated to give additional **8** and, in later fractions, a low yield (~3%) of a different, dextrorotatory product crystallizing as white needles, mp 100–102°; the physical constants of this second product were the same as those of the 3 epimer **3**.

2-Deoxy-4,5-*O*-isopropylidene-3-*O*-*p*-nitrobenzoyl-D-*erythro*-pent-1-enose Diphenyl Dithioacetal (3).—The conditions previously described[2] for *p*-nitrobenzoylation of 2-deoxy-4,5-*O*-isopropylidene-D-*erythro*-pent-1-enose diphenyl dithioacetal (**1**) were essentially followed, but the crude product remained in contact with aqueous pyridine and with silica gel for a longer period. A solution of **1** (700 mg) and *p*-nitrobenzoyl chloride (3 g) in dry pyridine was stirred overnight at ~25° and the resultant slurry was poured into ice–water (300 ml). The precipitate that formed was filtered off, dried, and extracted with benzene at 10°. The orange-colored extract was purified on a 20 × 1 cm column of silica gel with dichloromethane as eluent to give a pure *p*-nitrobenzoate fraction, which was fractionally recrystallized from ethanol by cooling very slowly to 0°. The early fractions were fine, white needles of the D-erythro ester **3**, yield 250 mg (26%), mp 102–103°, $[\alpha]^{23}D$ +38° (*c* 1, chloroform), identical with **3** previously reported[2] by melting point, $[\alpha]D$, nmr spectrum, and X-ray diffractogram.

Later fractions yielded clusters of white prisms of the D-threo ester **8**, yield 120 mg (12%), mp 91–92°, identical with authentic **8** by mixture melting point, $[\alpha]D$, nmr spectrum, and X-ray diffractogram.

Additional crystalline fractions obtained behaved as mixtures of **3** and **8**.

Reactions of 2-Deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*erythro*-pent-1-enose Diphenyl Dithioacetal (2). A. Raney Nickel.—A solution of **2** (2 g) in 80% aqueous ethanol (40 ml) was refluxed for 48 hr with 4 tablespoonfuls of neutral, W-4 Raney nickel. The reaction solution was found (tlc and nmr) to contain mainly starting material, contaminated with several minor products.

B. Mercuric Chloride.—Compound **2** (3 g) in acetone (65 ml) was stirred vigorously for 24 hr at 40° with mercuric chloride (25 g) and cadmium carbonate (15 g), and the mixture was filtered. Evaporation of the filtrate, extraction of the residue with dichloromethane, and washing the extract with aqueous potassium iodide gave a solution that contained (tlc and nmr) several components but mainly **2**; no free aldehyde was formed and little loss of phenyl groups had occurred (nmr).

C. Bromine.—Treatment of **2** (2 g) with bromine (1.5 g) in 70% aqueous acetic acid for 5 min at ~25° by the general procedure of Weygand and coworkers[18] gave an almost quantitative return of **2**. When a large excess (15 g) of bromine was used there was obtained, as the only product soluble in organic solvents, diphenyl disulfide, yield 500 mg (55%), mp 59–60° (undepressed on admixture with an authentic sample[19]). Treatment of **2** (1 g) with bromine (3 ml) in methanol (15 ml) gave a black, apparently polymeric material.

D. Ozone.—A stream of ozonized oxygen was passed for ~30 min at −78° through a solution of **1** (2 g) in methanol (25 ml). Evaporation of the solution gave a product that by tlc and nmr appeared to be mainly starting material.

E. Acetolysis.—To a mixture of acetic anhydride (20 ml) and sulfuric acid (4 ml) kept below 10° was added **2** (2 g), and after 5 min the mixture was poured onto ice and treated with

(27) Solutions were evaporated under diminished pressure below 50°. Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Tlc was effected with 250-μm layers of silica gel G (Merck) activated at 110°, and column chromatography with silica gel 7734 (Merck). Ir spectra were recorded with a Perkin-Elmer Model 137 or a Perkin-Elmer Model 457 spectrophotometer. Nmr spectra were recorded at 60 or 100 MHz with Varian A-60 or HA-100 nmr spectrometers, respectively, tetramethylsilane (τ 10.00) being used as the internal standard. Mass spectra were recorded with an AEI MS-9 instrument at a source temperature of 250°, an ionizing potential of 70 eV, and an accelerating potential of 8 kV. X-Ray powder diffraction data give interplanar spacings in angstroms for Cu Kα radiation. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities. The camera diameter was 114.59 mm. Microanalyses were performed by W. N. Rond.

sodium hydrogen carbonate. Extraction of the mixture with ether gave diphenyl disulfide, yield 0.5 g (55%), mp and mmp 59–60°.

F. Peroxy Acids.—A solution of **2** (2 g) in ~2 *M* peroxypropionic acid in propionic acid (20 ml) was kept for 4 hr at ~25°, the excess peroxy acid was decomposed with manganese dioxide, and the dichloromethane-soluble product was purified by column chromatography on silica gel to give methyl phenyl sulfone: yield 0.3 g (35%); mp 85–86° (lit.[21] mp 88°); nmr $CDCl_3$) τ 2.55–2.00 (5 protons, Ph), 6.98 (3-proton singlet, Me).

Hydrogen peroxide (30%, 5 ml) was added to a solution of **2** (1 g) in acetic acid (20 ml), and after 1 hr at ~25° the mixture was treated with manganese dioxide. After cessation of effervescence the solid was filtered off. Evaporation of the solution in a rotary evaporator left a residue that detonated spontaneously.

When a solution of **2** (2 g) in acetone (10 ml) was treated with hydrogen peroxide (30%, 5 ml) for 3 months at 5°, a precipitate was formed that was identified as benzenesulfonic acid, mp and mmp 42–43°.

Acid Degradation of 2 to an Unsaturated Bis(phenyl thioether) $C_4H_5O(SPh)_2$ (9 or 14).—A solution of **2** (2 g) in 2 *M* hydrochloric acid (50 ml) and ethanol (50 ml) was heated for 24 hr under reflux on a steam bath. The malodorous mixture was concentrated to ~50 ml and then extracted with dichloromethane. The extract was washed with water, dried (magnesium sulfate), and evaporated, and the resultant syrup was kept overnight at ~25° with acetic anhydride (5 ml) and pyridine (5 ml). The mixture was evaporated at ~25° and two 2-ml portions of toluene were evaporated from the residue. A solution of the residue in methanol (5 ml) was kept for 30 min at −80° to give a solid that was filtered at 0° and recrystallized from cold methanol (2 ml) to give a white solid: yield 50 mg (5%); mp 50–52° [52.3–53.2° after sublimation at 150° (bath) (4 Torr)]; $[\alpha]^{26}D$ 0° (c 1.6, chloroform); λ_{max}^{EtOH} 246 nm (ϵ 44,000) and 211 (sh, 23,000); λ_{max}^{KBr} 3.3 (CH), 6.3, 6.8, 7.0, 8.1, 8.2, 8.4, 8.8, 8.9, 9.3, 9.9, 10.4, 10.6, 12.6, 13.6, 14.5 μm (aryl); nmr (100 MHz, $CDCl_3$) τ 2.85–3.00 (10-proton multiplet, 2 Ph), 3.75 and 3.96 (1-proton doublets, $J_{3,4}$ = 3.1 Hz, H-3, H-4), 6.08 (2-proton singlet, CH_2); X-ray powder diffraction data 7.91 (m), 5.75 (w), 5.48 (w), 4.72 (m), 4.55 (vs), (1), 4.33 (w), 4.00 (s) (2), 3.62 (w), 3.43 (s) (3), 3.07 (m); mass spectrum *m/e* 298 (0.9, $M\cdot^+$), 189 [100, $M\cdot^+$ − PhS· (m* 119.8, calcd 119.9)], 161 [5.0, 189 − CO (m* 137.5, calcd 137.2)], and 109 [4.4, $M\cdot^+$ − 189 (m* 39.6, calcd 39.3)].

Anal. Calcd for $C_{17}H_{14}OS_2$: C, 68.46; H, 4.70; S, 21.47. Found: C, 68.23; H, 4.57; S, 21.17.

A slightly better yield (90 mg, 9%) of this product was obtained by passing the initial dichloromethane extract through a column (2.5 × 10 cm) of silica gel. Diphenyl disulfide (0.2 g) was eluted first by dichloromethane, followed by $C_5H_4O(SPh)_2$; slower-moving components from the column were poorly defined, apparently polymeric products.

Degradation of 2-Deoxy-4,5-*O*-isopropylidene-3-*O*-methyl-D-*threo*-pent-1-enose Diphenyl Dithioacetal (7) and Analogs (1, 2, 3, 6, and 8) to the Lactones 10 and 11.—A solution of **7** (800 mg) in concentrated hydrochloric acid (10 ml) was kept for 20 min at ~25° and then diluted with water and extracted with dichloromethane. The extract was washed with water, dried (sodium sulfate), and evaporated to a yellow syrup that by tlc contained many components. Acetic anhydride (5 ml) and dry pyridine (5 ml) were added and after 18 hr at ~25° the solvent and reagents were evaporated off at 40°. The residual syrup was purified by elution with dichloromethane through a 50 × 1 cm column of silica gel to give a fraction having R_f 0.33 (1:9:10 isopropyl alcohol–benzene–petroleum ether). This fraction was repeatedly rechromatographed on a similar column, with ether–petroleum ether as eluent, to give two chromatographically homogeneous products having R_f 0.49 and 0.60 (1:2 ether–petroleum ether).

The faster migrating compound (R_f 0.60), assigned the structure 5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thio-D-*threo*-pentono-1,4-lactone (**10**), recrystallized as white needles: yield 120 mg (22% based on **7**); mp 61–62°; $[\alpha]^{21}D$ +53° (*c* 1, chloroform); λ_{max}^{EtOH} 253 nm (ϵ 5200), 215 (sh, 21,000); λ_{max}^{KBr} (Perkin–Elmer 457 ir spectrophotometer) 3.23 (ArH), 3.33 (CH), 5.62 (C=O, 1,4-lactone), 5.72 (AcO), 6.31 (aryl), 7.10 ($-CH_2CO-$), 7.20, 7.30 (Ac), 8.18 (asymmetric Ac–O stretch), 8.50 (symmetric Ac–O stretch), 9.25, 9.60, 10.45, 11.50, 12.05, 13.35, and 14.45 μm (aryl); nmr, see Table II; mass spectrum *m/e* 266 (6, $M\cdot^+$), 193 (0.8, $M\cdot^+ - \cdot CH_2OAc$), 157 (2.5, $M\cdot^+ - \cdot SPh$), 137 (0.7, $PhSCHCH_3^+$), 136 (3.1), 135 (3.5), 110 (100, $PhSH\cdot^+$), 109 (23, PhS^+), 84 (14, $M\cdot^+ - PhSCH_2OAc$), 78 (8, $PhH\cdot^+$), 77 (12, Ph^+), 73 (5, $AcOCH_2^+$), 43 (86, Ac^+); X-ray powder diffraction data 10.10 (s) (2, 2), 5.71 (w), 5.20 (m), 5.06 (s) (2, 2), 4.75 (s) (3, 3), 4.23 (vs) (1, 1), 3.96 (vs) (1, 1), 3.81 (w), 3.70 (m), 3.40 (s) (3, 3), 3.06 (m), 2.57 (w), 2.34 (vw).

Anal. Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30; S, 12.04. Found: C, 58.76; H, 5.37; S, 11.90.

The slower migrating component, R_f 0.49, assigned the structure 5-*O*-acetyl-2-deoxy-3-*S*-phenyl-3-thio-D-*erythro*-pentono-1,4-lactone (**11**), was obtained as a colorless syrup: yield 70 mg (13% based on **7**); $[\alpha]^{22}D$ +35° (*c* 1.2, chloroform); λ_{max}^{film} 3.22 (CH), 3.39 (CH_2), 5.60 (C=O of 1,4-lactone), 5.74 (AcO), 6.32, 6.90 (aryl), 7.10, 7.28, 8.11 (asymmetric Ac–O stretch), 8.53 (symmetric Ac–O stretch), 9.52, 10.58, 13.43, 14.46 μm (aryl); nmr, see Table II; mass spectrum *m/e* 266 (16), 193 (2), 157 (1.2), 137 (3), 136 (22, $M\cdot^+ - CH_2{=}CHPh$), 135 (12, $M\cdot^+ - \cdot CHCHSPh$), 110 (90), 109 (26), 84 (15), 78 (8), 77 (15), 73 (6), 43 (100).

The following relative yields were obtained when other ketene dithioacetal derivatives were used as starting materials [starting material, yield of 10 (%), yield of 11 (%)]: **1**, 15, 6; **2**, 8, 5; **3**, 15, 6; **6**, 21, 13; **8**, 16, 12.5.

Registry No.—**3**, 28697-90-7; **5**, 37107-87-2; **6**, 37107-88-3; **7**, 37107-89-4; **8**, 37107-90-7; **9**, 37107-91-8; **10**, 37112-32-6; **11**, 37112-33-7; **14**, 37157-02-1.

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Branched-Chain N-Sugar Nucleosides. 1. Nucleosides of Branched-Chain Cyanomethyl, Aminoethyl, and *N,N*-Dimethylcarbamoylmethyl Allo Sugars. 6-*N,N*-Dimethylamino-9-[3′-*C*-(*N,N*-dimethylcarbamoylmethyl)-3′-deoxy-β-D-allofuranosyl]purine[1]

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The synthesis of two novel branched-chain N-sugar nucleosides is described. Condensation of diethyl cyanomethylphosphonate with 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (1) by a Wittig reaction afforded, after stereoselective reduction of the unsaturated sugars over palladium on charcoal, 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2) in 78% yield. Compound 2 was reduced over rhodium on Al_2O_3 to yield an amino sugar 3 (isolated as its acetamido derivative 4). Compound 2 was also converted by alkaline hydrogen peroxide hydrolysis into the branched-chain 3-*C*-carbamoylmethyl-3-deoxy sugar 5 in 70% yield. Compound 2 was hydrolyzed selectively to the 1,2-monoisopropylidene derivative 6, which was converted *via* benzoylation, hydrolysis with trifluoroacetic acid, and then acetylation into the 1,2-diacetate 7. Fusion of 7 with 6-chloropurine afforded the blocked allo nucleoside 8 in 69% yield. Treatment of the latter with methanolic aqueous dimethylamine gave the novel branched-chain allo sugar nucleoside 9 containing a 3′-*C*-(*N,N*-dimethylcarbamoylmethyl) branched chain in 45% yield. Sodium metaperiodate oxidation of 9 followed by sodium borohydride reduction of the aldehydo nucleoside gave the branched-chain ribo nucleoside 10. Compound 7 was also converted into the benzamido nucleoside 11. Treatment of 11 with lithium aluminum hydride afforded 9-[3′-*C*-(2′-aminoethyl)-3′-deoxy-β-D-allofuranosyl]adenine (12).

The occurrence of unique and unusual amino, deoxy, and branched-chain sugars in some of the antibiotics has stimulated increased interest in the distribution of unusual carbohydrates in nature, and an extensive list of unusual sugars has resulted from chemical investigations on bacterial cell walls, capsular materials, and other naturally occurring macromolecules.[2a] A classification of the sugar-containing antibiotics in addition to a discussion of the chemistry of those members whose complete structures were known to 1969 has been made.[2b] The chemistry and biochemistry of branched-chain sugars from 1969 to the present have just been reviewed.[3]

The discovery that nucleosides with branched-chain sugars can exhibit cytostatic and virostatic activity has heightened the interest in the development of general methods for the synthesis of branched-chain sugars.[3] The isolation of nucleoside antibiotics containing carbamoyl and peptide groups (gougerotin and puromycin[4]) has probably helped to stimulate a continued interest in the synthesis of analogs of these substances. With the recent report of the synthesis of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (virazole) by Witkowski of I. C. N. and the finding that it has significant and reproducible activity against a broad spectrum of DNA and RNA viruses,[5] there might be expected to be a further continued interest in nucleosides containing the carbamoyl group. In this connection, it is interesting to note that adenosine 5′-carboxamides are reported to affect blood circulation when administered orally or parenterally.[6] Recently, appropriately blocked amino acids and peptides have been coupled to a purine 5′-amino-5′-deoxy nucleoside derivative[7] and to a nucleoside containing a free carboxylic acid moiety to afford novel nucleoside peptides.[8] Reasons for the preparation of this class of compounds have been outlined.[7]

The objective of the research outlined in this and in the following paper was to develop a general synthetic procedure for the substitution of the 3′-hydroxyl on adenosine and related nucleosides by cyanomethyl, carbamoylmethyl, *N,N*-dimethylcarbamoylmethyl, aminoethyl, and a peptide branched chain.

In the preliminary communication,[9] we have reported the synthesis of 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2) and its subsequent utilization in the synthesis of a nucleoside containing a branched-chain cyano sugar 8. We now wish to describe in detail this synthesis and, in addition, to outline the utilization of 8 in the synthesis of other novel branched-chain N-sugar nucleosides.

Condensation of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[10] (1) with diethyl cyanomethylphosphonate in the presence of sodium hydride followed by hydrogenation over 10% palladium on charcoal according to a procedure already published[11] afforded the key intermediate in our synthesis, namely, 3-*C*-cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2), in over 80% yield. The assignment of configuration of 2 was deduced from its nuclear magnetic resonance spectrum. Based on the fact that trans H_2–H_3 of the furanose sugars have small cou-

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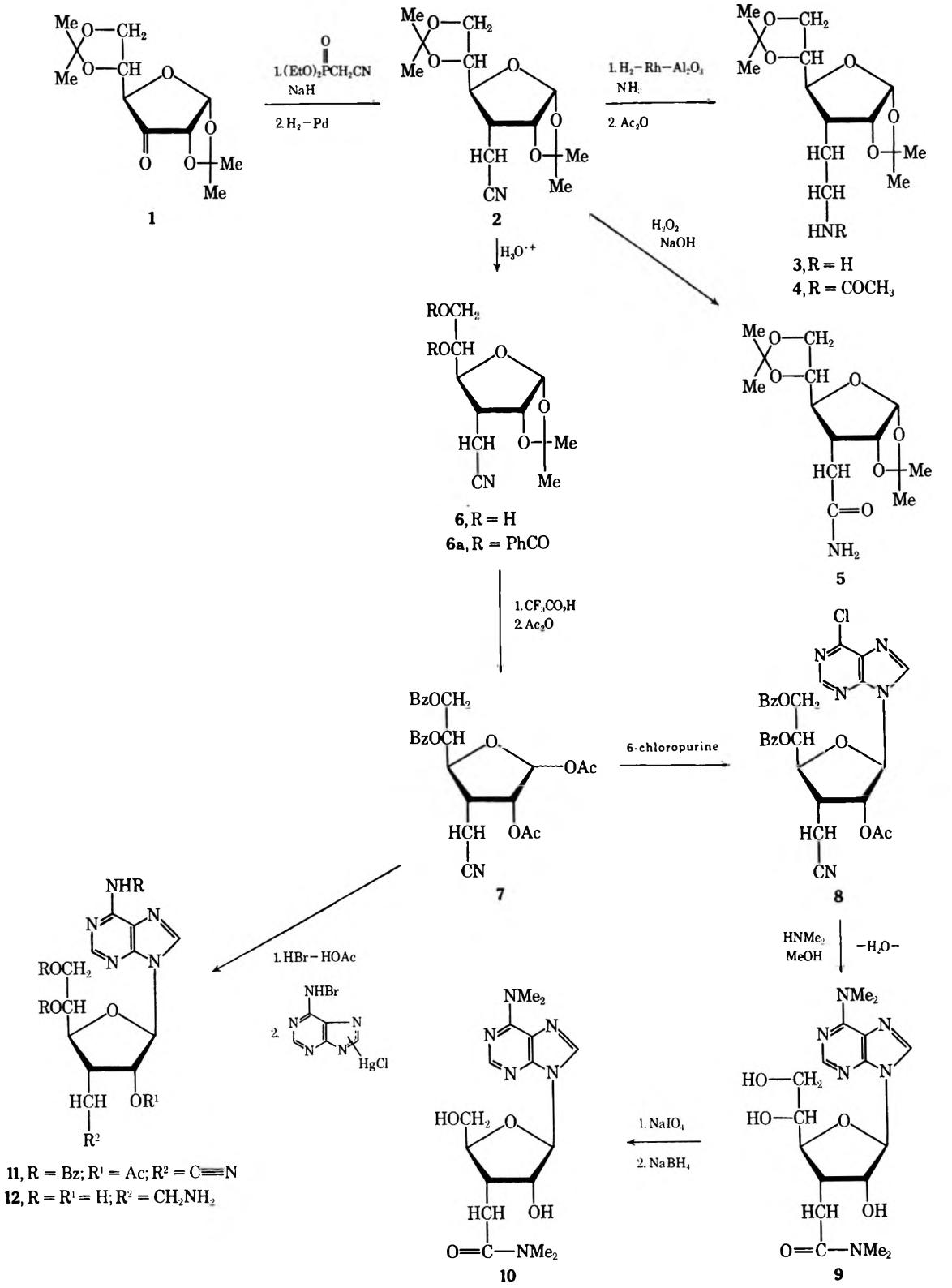

plings of less than 0.5 Hz whereas cis H_2–H_3 have couplings greater than 2.5 Hz,[12] the fact that H-2 of compound 2 exhibited a triplet at τ 5.18 having $J_{2,3}$ = 3.6 Hz (irradiation of the H-1 signal at τ 4.2 collapsed the H-2 signal to a doublet of J = 3.6 Hz) showed that H-2 and H-3 must be in the cis orientation and, therefore, compound 2 must have the allo configuration. The stereoselectivity of the reduction of the unsaturated sugars obtained in the Wittig reaction of 1 makes the synthesis of the key intermediate 2 very useful.

Because the primary objective of our research was to prepare structural analogs of puromycin,[4,13] we first converted 2 into the branched-chain amino sugar 3 by reduction over 5% rhodium on aluminum followed by acetylation to afford 3-*C*-(2′-acetamidoethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4) in 80% yield. When an attempt was made to utilize 4 in the synthesis of a branched-chain amino sugar nucleoside

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by a known sequence of reactions[14] the synthesis was unsuccessful owing to the fact that, on deisopropylidenating **4**, the acetamido group participated and formed what was presumed to be a N-heterocyclic sugar.[15] Another course open to us appeared to be *via* the conversion of the cyanomethyl sugar into a carbamoylmethyl sugar. Hydrolysis of **2** with hydrogen peroxide in the presence of sodium hydroxide proceeded smoothly to afford crystalline 3-*C*-carbamoylmethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5**) in 70% yield. The latter compound also could not be directly utilized in nucleoside synthesis. This fact, coupled with the knowledge that the chemistry of nucleosides containing a carbamoyl group (as exemplified by the nucleoside antibiotic gougerotin[4,16]) has posed a problem of great complexity led us to direct our principal efforts towards the direct utilization of **2** in the synthesis of a structural analog of puromycin.

Selective hydrolysis of the 5,6-isopropylidene group of **2** was achieved with aqueous methanol containing sulfuric acid. The reaction was conducted at room temperature for 4 hr, giving the monoisopropylidene derivative **6** in almost quantitative yield. The reaction was monitored by thin layer chromatography (tlc) on silica gel and was stopped when **2** was consumed. It was essential to keep the reaction under careful surveillance because of the possibility of further hydrolysis. Compound **6** was converted into the crystalline 5,6-di-*O*-benzoate ester **6a** (which was purified by column chromatography) and its structure was confirmed by nmr spectroscopy. Acetolysis of the dibenzoate ester with an 80% solution of trifluoroacetic acid at room temperature for 0.75 hr (careful monitoring of reaction by tlc) removed the 1,2-*O*-isopropylidene group and did not hydrolyze the cyano group. The hydrolysis product obtained by use of trifluoroacetic acid was immediately acetylated with acetic anhydride and pyridine to afford crystalline 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-allofuranose (**7**) in 54% yield based on **6**. The β-anomeric configuration of **7** was assigned on the basis of the fact that H-1 exhibited a singlet in its nmr spectrum.[12] The β anomer **7** was condensed with 6-chloropurine by direct fusion at 160° without catalyst[17] to afford, after column chromatography on silica, the blocked nucleoside **8** as a solid foam in 69% yield. Treatment of the latter with 25% aqueous dimethylamine and methanol[13c] at room temperature for 4 hr afforded, after column chromatography on silica, an unblocked crystalline nucleoside **9** in 45% yield. This nucleoside exhibited a strong carbonyl absorption in its infrared spectrum at 6.30 μ but did not possess a cyano band. Its nmr spectrum clearly showed that deacylation was complete and that the compound **9** had four methyl groups (one NMe_2 from the expected substitution of the 6-chloro atom by the NMe_2). This evidence, coupled with the fact that the molecular weight of compound **9** was 394, strongly supported the unexpected result that the nucleoside now contained an *N*,*N*-dimethylcarbamoyl group in place of the cyano group. It is tentatively suggested that the C-2′ hydroxyl (after unblocking) might have participated[18] in forming an imine from the cyano group, and the imine was subsequently hydrolyzed to yield a five-membered cyclic lactone. The latter might be expected to undergo ready aminolysis with the dimethylamine to yield the unusual branched-chain nucleoside 6-*N*,*N*-dimethylamino-9-(3′-*C*-*N*,*N*-dimethylcarbamoylmethyl-3′-deoxy-β-D-allofuranosyl)purine (**9**). The assignment of β-anomeric configuration to **9** was based on the following: (1) ultraviolet (uv) absorption data of **9** substantiates the site of glycosylation[19] at N-9; (2) the trans rule[20] indicates that **9** has a β configuration; the allo nucleoside **9** exhibits a negative Cotton effect that is consistent with the proposals advanced[21,22] for purine β-D-nucleosides. Although the nmr measurement of **9** was of little value in confirming the β-anomeric configuration, the magnitude of $J_{1',2'} = 4$ Hz is consistent with the $J_{1',2'}$ coupling constant of other branched-chain β-allo nucleosides.[14,23]

Sodium metaperiodate oxidation of the allo nucleoside **9** yielded an aldehydo nucleoside that was immediately reduced with sodium borohydride to give, after column chromatography on silica, in 68% yield the expected ribo nucleoside **10**. Although the nmr spectrum was consistent with structure **10** (the nmr spectrum showed one primary and one secondary hydroxyl group and four methyl groups) the nucleoside failed to crystallize.

The cyanomethyl branched-chain sugar **7** was also used to prepare a nucleoside having a cyano group following a classical nucleoside synthesis.[24] Thus, treatment of **7** with anhydrous hydrogen bromide in dichloromethane readily afforded the bromo sugar (not characterized because of instability), which was immediately condensed with chloromercuri-6-benzamidopurine in anhydrous toluene under reflux conditions to afford, after silica column chromatography, 6-benzamido-9-(2′-*O*-acetyl-5′,6′-di-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-allofuranosyl)purine (**11**) in 60% yield. Treatment of the latter with lithium aluminum hydride in tetrahydrofuran gave a mixture of compounds. The major component **12**, which was insoluble in water, was further purified by passage through a column of Dowex 1X resin. This component, isolated in 30% yield, gave a positive ninhydrin test and its nmr spectrum showed that the cyanomethyl group was reduced to an aminoethyl group. However, owing to complexing of the amino sugar nucleoside **12** with inorganic ions which could not be removed, its elemental analysis was not satisfactory.

Experimental Section

General Considerations.—Nmr spectra were obtained in chloroform-*d* solution (unless otherwise stated) with tetramethyl-

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silane as the internal standard (set at τ 10) by using a Varian T-60 or Varian HA-100 spectrometer (peak multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet). Ir spectra were obtained with a Perkin-Elmer Model 457 spectrophotometer. Molecular weight was obtained by mass spectroscopy using an A.E.I.-M.S.9 spectrometer. All melting points (micro hot state) are corrected. Silica gel G was used for tlc and silica gel Grace (60–200 mesh, deactivated with 10% water) was used for column chromatography. Elemental analyses were performed by the microanalytical laboratory, University of British Columbia.

Wittig Reaction of 1,2:5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (1) to Yield 3-*C*-Cyanomethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (2).—To a suspension of sodium hydride (2.33 g) in anhydrous 1,2-dimethoxyethane (100 ml) was carefully added a solution of diethyl cyanomethylphosphonate (17.4 g) in 1,2-dimethoxyethane (100 ml). When the evolution of gas had ceased the mixture was filtered (all operations were performed in a drybox under a nitrogen atmosphere) and the solution was then cooled to 0°. To the cold solution of the carbanion a solution of the ketose 1 (16.9 g) in 1,2-dimethoxyethane (300 ml) was added with stirring and external cooling. The reaction was then allowed to warm to room temperature. After 4 hr the reaction mixture was removed from the drybox, diluted with 100 ml of water, and extracted with 3 × 250 ml of ether. The combined ether extracts were washed with water (3 × 20 ml), dried over sodium sulfate, filtered, and evaporated under reduced pressure to afford a syrup which appeared to be homogeneous as evidenced by tlc on silica gel G with 19:1 benzene–methanol (R_f 0.68). Hydrogenation of the syrup in ethanol over 10% palladium on charcoal gave 14.5 g (78%) of product 2 which was recrystallized from ether–petroleum ether (bp 35–60°): mp 109°; $[\alpha]^{22}D$ +91° (*c* 2, chloroform); ir 4.5 μ (C≡N); τ^{CDCl_3} 4.18 (d, $J_{1,2}$ = 3.6 Hz, H-1), 5.23 (t, $J_{2,3}$ = 3.6 Hz, H-2), 8–7.5 (m, H-3). Irradiation of the H-1 signal at τ 4.2 collapsed the H-2 signal to a doublet.

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.30; H, 7.47; N, 4.94. Found: C, 59.26; H, 7.35; N, 4.81.

3-*C*-(2′-Acetamidoethyl)-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (4).—The branched-chain sugar 2 (1 g) dissolved in absolute ethanol (70 ml) saturated with ammonia was hydrogenated over 5% rhodium on alumina at room temperature and 60 psi for 20 hr. The catalyst was removed by filtration and the solvent was evaporated under diminished pressure. The resulting syrup was acetylated with a mixture of acetic anhydride (3.5 ml) and pyridine (3.5 ml) for 24 hr. The product was worked up in the usual way to afford 0.92 g of compound 4 (80%): ir 6.15 and 6.55 μ (C=O); τ^{CDCl_3} 5.26 (t, H-2), 4.23 (d, $J_{1,2}$ = 3 Hz, H-1), 3.20 (NH); $[\alpha]D$ 41° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.20; N, 4.25. Found: C, 58.27; H, 8.44; N, 4.00.

3-*C*-Carbamoylmethyl-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (5).—To a solution of 2 (0.566 g) in ethanol (6 ml) was added hydrogen peroxide (0.8 ml) and 6 *N* sodium hydroxide[25] (0.8 ml). After the reaction mixture was left to stand at 50° for 6 hr, the solution was evaporated under reduced pressure to yield a syrup which was extracted with dichloromethane. The dichloromethane extract was evaporated under diminished pressure to yield a solid which was recrystallized from ether to yield 0.400 g (70%) of 5: mp 138°; $[\alpha]^{21}D$ +86° (*c* 1.3, chloroform); ir 2.9 (NH_2), 6.1 μ (C=O); τ^{CDCl_3} 4.1 (NH_2), 4.23 (d, $J_{1,2}$ = 4 Hz, H-1), 5.27 (t, H-2).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.8; H, 7.69; N, 4.47. Found: C, 55.7; H, 7.91; N, 4.57.

3-*C*-Cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (6).—To a solution of 6.5 g of 2 in 300 ml of methanol was added 30 ml of 1 *N* sulfuric acid. The reaction mixture was left stand at room temperature for 4 hr, then neutralized with solid sodium hydrogen carbonate, and extracted with chloroform (3 × 200 ml). The combined chloroform extracts were dried over sodium sulfate, filtered, and evaporated under diminished pressure to afford 5.5 g of 6 (quantitative yield): $[\alpha]^{25}D$ +99° (c 1.7, chloroform); ir 2280 cm^{-1} (C≡N); τ^{CDCl_3} 8.17 (s, 3 H), 8.33 (s, 3 H, isopropylidene).

Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.01; H, 7.21; N, 5.56.

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5,6-Di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (6a).—To a solution of 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (2) (60 g) in anhydrous benzene (30 ml) was added dropwise a mixture of benzoyl chloride (32 ml) and pyridine (4.5 ml). After standing for 14 hr at room temperature, the reaction mixture was filtered through a short column of grade II alumina (25 g) and the column was washed was washed with benzene (150 ml). Evaporation of the combined eluents gave 6a, which was crystallized from ether–petroleum ether (bp 30–60°) to give 10.0 g (90%) of product: mp 71–72°; $[\alpha]^{24}D$ +48.2° (*c* 1.3, chloroform).

Anal. Calcd for $C_{25}H_{25}NO_7$: C, 66.60; H, 5.57; N, 3.10. Found: C, 66.33; H, 5.54; N, 2.95.

1,2-Di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-allofuranose (7).—An amount of 8 g of 6a was allowed to react with an 80% solution of trifluoroacetic acid (70 ml) for 0.75 hr, followed by neutralization with solid sodium hydrogen carbonate. The resulting mixture was extracted with methylene chloride. Evaporation of the combined methylene chloride extracts, after drying over sodium sulfate, gave 5.9 g of syrup. An aliquot of this syrup (5 g) was acetylated with acetic anhydride (20 ml) and pyridine (20 ml) and the product was worked up in the usual way to yield 5.4 g (54% yield based on 6) of product 7. An analytical sample of 7 was prepared by chromatographing it on neutral alumina using an 8:1 mixture of dichloromethane–ether as developer. The product, crystallized from ether, had mp 110°; $[\alpha]^{23}D$ −31° (*c* 2, chloroform); ir (KBr) 4.48 μ (C≡N); τ^{CDCl_3} 3.77 (s, H-1).

Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.08; N, 2.81. Found: C, 63.00; H, 4.97; N, 2.65.

An attempted acetolysis[14] of the dibenzoate ester 6a gave a complex mixture of products; the major component did not possess nitrogen.

6-Chloro-9-(2′-*O*-acetyl-5′,6′-di-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-allofuranosyl)purine (8).—A thoroughly dried, finely powdered mixture of 1 g (2.02 mmol) of 1,2-di-*O*-acetyl-5,6-di-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-allofuranose and 0.350 g (2.27 mmol) of anhydrous 6-chloropurine was heated in an oil bath at 160° at 30 Torr for 5 min followed by further heating at 160° at 1 Torr for 40 min. The melt was extracted with 50 ml of dichloromethane and the extract was then filtered. Evaporation of the filtrate gave 1.24 g of syrup, which was chromatographed on a silica column (70 g) using 1:1 benzene–ethyl acetate as developer. The faster moving component (0.150 g) was starting material, whereas the second fraction (0.700 g, 69% yield) was the blocked nucleoside 8. This nucleoside was a solid foam which could not be crystallized: ir 4.5 μ (C≡N); $[\alpha]^{22}D$ −13° (*c* 1.7, $CHCl_3$); τ^{CDCl_3} 7.2 (d, CH_2CN), 6.6–6.4 (m, H-3′), 3.9 (d, $J_{1',2'}$ = 2 Hz, H-1′), 1.3 and 1.76 (s, H-2 and H-8).

Anal. Calcd for $C_{29}H_{24}N_5O_7Cl$: C, 59.19; H, 4.10; N, 11.87. Found: C, 59.46; H, 4.35; N, 11.47.

6-*N*,*N*-Dimethylamino-9-(3′-*C*-*N*,*N*-dimethylcarbamoylmethyl-3′-deoxy-β-D-allofuranosyl)purine (9).—To a solution of 20 ml of methanol and 10 ml of aqueous 25% dimethylamine was added 0.450 g of the blocked nucleoside 8 and the mixture was left to stand at room temperature for 4 hr. After removal of the solvent under diminished pressure, the residue was partitioned between water (20 ml) and dichloromethane (10 ml). The dichloromethane layer was washed with water (10 ml). The combined aqueous extracts were evaporated under diminished pressure to yield a syrup. This syrup was chromatographed on a column of silica (12 g) using 9:1 dichloromethane–methanol as developer to afford 0.160 g (45% yield) of the unblocked nucleoside 9. An analytical sample of 9 was prepared by rechromatographing 9 on silica using water as developer. The nucleoside 9 was crystallized from ethanol–ether: mp 178–179°; ir 6.30 μ (C=O); λ_{max} (MeOH) 275 mμ (ε 20,000); CD max (MeOH) 275 mμ (θ −11,000); $[\alpha]^{23}D$ −66° (*c* 1.8, methanol); τ^{D_2O} 4.76 (t, H-2′), 3.74 (d, $J_{1',2'}$ = 4 Hz, H-1′), 1.56, 1.74 (s, H-2 and H-8); $\tau^{DMSO\text{-}d_6}$ 5.38 (t, primary OH), 4.23 and 4.50 (d, due to secondary OH's) (these signals disappear on addition of D_2O); τ^{CDCl_3} 7.10 and 6.95 (two methyls), 6.57 (singlet, equal to two methyl groups); mol wt (mass spectroscopy) 394.

Anal. Calcd for $C_{17}H_{26}O_5N_6$: C, 51.79; H, 6.64; N, 21.31. Found: C, 51.69; H, 6.71; N, 21.28.

Metaperiodate Oxidation and Reduction of 9 to Yield 6-*N*,*N*-Dimethylamino-9-(3′-*C*-*N*,*N*-dimethylcarbamoylmethyl-3′-deoxy-β-D-ribofuranosyl)purine (10).—To a solution of the allo

nucleoside 9 (0.275 g, 0.7 mmol) in 21 ml of water and 14 ml of ethanol was added with stirring 0.5 ml of saturated sodium hydrogen carbonate and a 5% aqueous solution of sodium metaperiodate (0.150 g, 0.7 mmol). The reaction mixture was left standing at room temperature in the dark for 2.5 hr. To the resulting solution was added with stirring sodium borohydride (0.212 g) and the mixture was stirred for 3 hr. Excess sodium borohydride was decomposed by addition of glacial acetid acid. The reaction mixture was evaporated under reduced pressure and the residue was treated with 3 × 5 ml of methanol followed by evaporation. The residue was extracted with dichloromethane and filtered, and the filtrate was evaporated to a syrup. Chromatography of this residue on silica (32 g) with 92:8 dichloromethane–methanol gave 0.170 g (68%) of a nucleoside **10**. This product appeared to be homogeneous by paper chromatography with 40:19:11 *n*-butyl alcohol–ethanol–water (R_f 0.68) or by tlc on silica with 9:1 dichloromethane–methanol (R_f 0.42): $[\alpha]^{25}D$ −35° (c 1.37, water); ir 3.2 (OH), 6.5 μ (C=O); uv λ_{max} 275 mμ (ε 14,300, water); τ^{CDCl_3} 7.10 and 6.97 (s, NMe_2), 6.55 (s, equal to 6 H of NMe_2), 4.5 (two OH groups), 4.07 (d, $J_{1',2'}$ = 3 Hz, H-1'), 1.82 (H-2 and H-8).

Anal. Calcd for $C_{16}H_{24}N_6O_4 \cdot {}^1/_2H_2O$: C, 51.30; H, 6.68; N, 23.06. Found: C, 50.86; H, 6.43; N, 22.40.

The analysis varied depending on the temperature at which the sample was dried under vacuum. The compound lost dimethylamine on heating.

6-Benzamido-9-(2'-*O*-acetyl-5',6'-di-*O*-benzoyl-3'-*C*-cyanomethyl-3'-deoxy-β-D-allofuranosyl)purine (11).—A solution of 1 g of 1,2-*O*-acetyl-5,6-di-*O*-benzoyl-3-cyanomethyl-3-deoxy-β-D-allofuranose (**7**) in dichloromethane (50 ml) kept at 0° was kept saturated with anhydrous hydrogen bromide for 15 min and the flask was then lightly stoppered and kept at 0° for 1 hr and finally at room temperature for 15 min. The solvents were removed under diminished pressure and two portions of anhydrous toluene were then added and removed under reduced pressure to yield a syrup. This syrup, dissolved in anhydrous toluene (40 ml), was immediately added to a thoroughly dried mixture (by distilling, at atmospheric pressure, anhydrous toluene from it) of 0.950 g (2.0 mmol) of chloromercuri-6-benzamidopurine, Celite (0.300 g) in anhydrous toluene (30 ml). The mixture was heated to the reflux temperature and refluxing was continued for 0.75 hr. The hot mixture was filtered and the filtrate was then evaporated under reduced pressure. The residue was extracted with dichloromethane (120 ml), and the extract was washed with two 20-ml portions of 30% KI and two 20-ml portions of water. Concentration of the dried ($MgSO_4$) dichloromethane layer gave a residue which was chromatographed on a silica column (60 g) using 1:1 benzene–ethyl acetate as developer to give 0.900 g (60%) of purified **11**: ir 4.50 μ (C≡N); τ^{CDCl_3} (100 MHz) 7.26 (d, CH_2CN), 0.8 (NH); $[\alpha]^{22}D$ −37° (c 1.5, $CHCl_3$).

Anal. Calcd for $C_{36}H_{30}N_6O_8$: C, 64.07; H, 4.45; N, 12.47. Found: C, 63.76; H, 4.72; N, 12.08.

9-(3'-*C*-Aminoethyl-3'-deoxy-β-D-allofuranosyl)adenine (12).—To a suspension of lithium aluminum hydride (210 mg, 5.5 mmol) in tetrahydrofuran (150 ml) was added dropwise a solution of 6-benzamido-9-(2'-*O*-acetyl-5',6'-di-*O*-benzoyl-3'-*C*-cyanomethyl-3'-deoxy-β-D-allofuranosyl)purine (**11**) (826 mg, 1.23 mmol) in THF. After the reaction mixture was left stand at room temperature for 0.5 hr and then refluxed for 2 hr, the excess reducing reagent was destroyed by the slow addition of water (10 ml), ethanol (10 ml), and 5 *N* ammonium hydroxide (10 ml). The resulting precipitate was removed by filtration and washed with ethanol (50 ml). The residue, obtained by evaporation of the combined filtrate and washings, was partitioned between dichloromethane (10 ml) and water (7.5 ml). Examination of the dichloromethane extract showed that it contained no nucleoside nor any substance giving a positive test with ninhydrin. The water extract was evaporated to dryness and the remaining material (700 mg) was taken up in ethanol and left to stand at 0° overnight. From this solution was obtained 200 mg of crystalline product having an ultraviolet spectrum similar to that of adenosine. The ultraviolet spectrum of the mother liquor indicated that it contained a negligible amount of nucleoside.

The above crystalline material was dissolved in 2% acetic acid (2 ml) and chromatographed on 5 ml of Dowex 50W-X2 (NH_4^+ form) resin. The column was first washed with 100 ml of water and then with 5% ammonium hydroxide to afford, after crystallization of the main component from methanol, a homogeneous nucleoside **12** (0.080 g, 30% yield): mp 170–171°; uv λ_{max} 261 mμ (ε 15,000, H_2O); τ^{DMSO-d_6} 1.66, 1.82 (2 s, 2 H, H-2, H-8), 2.70 (b, 2 H, NH_2), 4.10 (d, 1 H, H-1'), 4.2–4.6 (b, 2 H, NH_2), 5.28 (t, 1 H, H-2'); $[\alpha]^{25}D$ −59° (c 1, H_2O).

Anal. Calcd for $C_{13}H_{20}N_6O_4$: C, 48.14; H, 6.18; N, 25.91. Found: C, 44.45; H, 5.41; N, 21.69. The sample contained some inorganic material which could not be removed by use of resins.

Registry No.—**2**, 30694-90-7; **4**, 37108-14-8; **5**, 37108-15-9; **6**, 37108-16-0; **6a**, 37108-17-1; **7**, 37406-75-0; **8**, 37108-18-2; **9**, 37108-19-3; **10**, 37108-20-6; **11**, 37108-21-7; **12**, 37108-22-8.

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Branched-Chain N-Sugar Nucleosides. 2. Nucleosides of 3-C-Cyanomethyl-, Carboxamidomethyl-, and N,N-Dimethylcarboxamidomethyl-3-deoxyribofuranose. Synthesis of a Homolog of the Amino Sugar Nucleoside Moiety of Puromycin[1]

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The synthesis of novel N-containing branched-chain ribo sugar nucleosides is described. Periodate oxidation of 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene-α-D-allofuranose (1) followed by sodium borohydride reduction of the resulting aldehydo sugar afforded 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (2) in 90% yield. Utilizing a parallel set of reactions to those described in the previous paper,[2a] the 6-chloro-3'-(cyanomethyl)ribofuranosylpurine nucleoside 6 was prepared. Treatment of the latter with dimethylamine–water–methanol gave 6-N,N-dimethylamino-9-[3'-deoxy-3'-C-(N,N-dimethylcarbamoylmethyl)-β-D-ribofuranosyl]purine (7) in 72% yield. Sublimation of the latter compound afforded the novel γ-lactone nucleoside, 6-N,N-dimethylamino-9-[3'-C-(carboxymethyl-2',3'-γ-lactone)-3'-deoxy-β-D-ribofuranosyl]purine (8) in 73% yield. Treatment of 8 with liquid ammonia yielded the branched-chain 3'-carbamoylmethyl ribo nucleoside 9 in quantitative yield. Reaction of the lactone 8 with ethyl glycinate in N,N-dimethylformamide afforded a nucleoside peptide 6-N,N-dimethylamino-9-[3'-C-(carbomethyl-N-glycine ethyl ester)-3'-deoxy-β-D-ribofuranosyl]purine (10) in 72% yield. Selective de-O-acylation of 6 at −10° yielded the 3'-C-cyanomethyl ribo nucleoside 11 in 67% yield. Catalytic hydrogenation of 11 in the presence of acetic anhydride and ethanol followed by de-O-acetylation of the blocked nucleoside gave, in about 90% yield, crystalline 6-N,N-dimethylamino-9-[3'-(2''-acetamidoethyl)-3'-deoxy-β-D-ribofuranosyl]purine (12).

In the previous report[2a] from this laboratory the synthesis of 6-N,N-dimethylamino-9-(3'-C-N,N-dimethylcarbamoylmethyl-3'-deoxy-β-D-allofuranosyl)-purine from a cyanomethyl nucleoside was described. Attempts to degrade the allo carbamoyl nucleoside to a ribo nucleoside by classical procedures[2b,3] failed to give a crystalline product, although its structure was supported by nmr, ir, and mass spectrometry. Although lithium aluminum hydride reduction of the 3-C-cyanomethyl allo nucleoside gave the expected 3-C'-aminoethyl allo nucleoside (as evidenced by its nmr spectrum), the amino sugar nucleoside could not be freed from inorganic ions. As a consequence, a new approach for the synthesis of an ethyl homolog of the amino sugar nucleoside moiety of puromycin[4] was sought. This paper deals mainly with this synthesis and, in addition, the preparation of a branched-chain 3'-C-carbamoylmethyl and a nucleoside peptide analog are described. The reasons for the synthesis of these novel classes of branched-chain N-sugar nucleosides were presented in the preceding paper.[2a] Other authors[5] have also given reasons for the great interest in the potential biological activity of puromycin analogs.

Periodate oxidation of the previously described 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene-α-D-allofuranose (1) followed by immediate sodium borohydride reduction of the resulting aldehydo sugar afforded crystalline 3-C-cyanomethyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (2) in 90% yield. The latter compound was readily converted into its 5-O-benzoate ester 3 in 80% yield. Acetolysis of the 1,2-O-isopropylidene group of 3 with a 90% solution of trifluoroacetic acid at room temperature followed by acetylation yielded crystalline 1,2-di-O-acetyl-5-O-benzoyl-3-C-cyanomethyl-3-deoxy-β-D-ribofuranose (4) in 78% yield and the 2,3-γ-lactone 4a (about 5% yield). The β-anomeric configuration of 4 and 4a was assigned on the same basis as described previously.[2a]

Treatment of the cyanomethyl branched-chain ribo sugar 4 with anhydrous hydrogen bromide in dichloromethane afforded the bromo sugar, which was immediately condensed with chloromercuri-6-benzamidopurine in anhydrous toluene to afford, after silica gel column chromatography, amorphous 6-benzamido-9-(2'-O-acetyl-5'-O-benzoyl-3'-C-cyanomethyl-3'-deoxy-β-D-ribofuranosyl)purine (5) in 40% yield.

Fusion of the β anomer 4 with 6-chloropurine at 160° afforded, after column chromatography on silica gel, the crystalline 6-chloropurine nucleoside (6) in 66% yield. Treatment of 6 with 25% aqueous dimethylamine and methanol at room temperature for 4 hr readily de-O-acetylated 6 and aminated the cyanomethyl group to yield 6-N,N-dimethylamino-9-(3'-deoxy-3'-C-N,N-dimethylcarbamoylmethyl-β-D-ribofuranosyl)purine (7) in 72% yield, identical (nmr and mass spectrum) with compound 10 described in the previous paper.[2a] Compound 7 was readily acetylated to yield a diacetyl derivative which failed to crystallize. Attempts to remove all traces of moisture from 7 by drying under vacuum at about 60° led to a gradual decrease in its nitrogen content, indicating deamination. Surprisingly, the allo homolog of 7, described in the previous report,[2a] was stable when heated under similar conditions. Sublimation of 7 at temperatures of 180–210° led to complete dehydroamination, resulting in the formation, after crystallization, of the novel branched-chain 2',3'-γ-lactone nucleoside 8 in 73% yield. Its ir spectrum (1770 cm^{-1}, lactone), nmr, molecular weight (319), and elemental analysis were in complete accord with the structure 8. The lactone 8 was readily reconverted in quantitative yield into the N,N-dimethylcarbamoylmethyl nucleoside 7 by treatment with dimethylamine at 0° for 4 hr. When the γ-lactone 8 was allowed to react with anhydrous liquid ammonia for 6 hr, then the branched-chain 3'-C-carbamoylmethyl ribo nucleoside 9 was produced in 95% yield. Surprisingly, the carbamoylmethyl-

(1) Preliminary communication: Abstracts, Third International Congress of Heterocyclic Chemistry, Sendai, Japan, Aug 1971, p 106.

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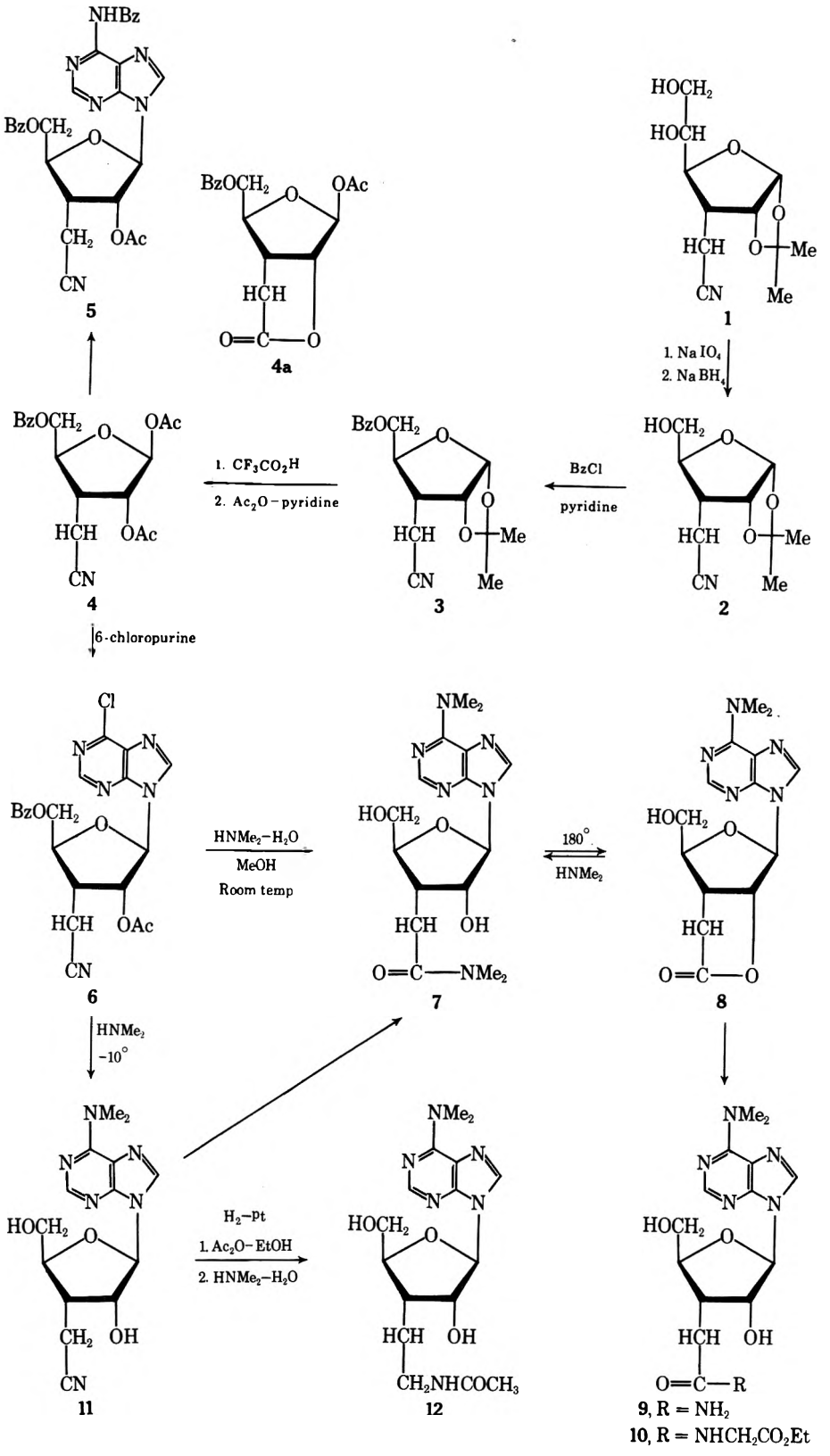
(3) A. Rosenthal and M. Sprinzl, *Can. J. Chem.*, **47**, 4477 (1969).

(4) J. J. Fox, K. A. Watanabe, and A. Block, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966).

(5) L. V. Fisher, W. W. Lee, and L. Goodman, *J. Med. Chem.*, **13**, 775 (1970), and references cited therein.



nucleoside **9** had much greater thermal stability than the *N*,*N*-dimethylcarbamoylmethyl nucleoside **7**. Again, nmr and ir fully supported structure **9** and, in addition, a very satisfactory elemental analysis of crystalline **9** was obtained. The great utility of the γ-lactone nucleoside **8** was demonstrated by its ready conversion into the crystalline nucleoside peptide **10**, by treatment with ethyl glycinate in anhydrous *N*,*N*-dimethylformamide at room temperature for 30 hr.

Lithium aluminum hydride reduction of the carbamoylmethyl ribo nucleoside **9** gave only a trace amount of a branched-chain aminoethyl ribo nucleoside **12**. As a consequence, efforts were then directed toward finding a procedure for preferentially de-O-acylating the blocked cyanomethyl ribo nucleoside **6** without hydrolyzing or aminating the cyano group. Treatment of **6** with anhydrous liquid ammonia gave, on work-up, a complex mixture of products. Use of methanolic sodium methoxide for de-O-acylating also

proved to be unsatisfactory because a complex mixture of nucleosides was obtained. Selective de-O-acylation of **6** was finally achieved by treatment of the 6-chloropurine cyano nucleoside **6** with anhydrous dimethylamine at −10° for 20 days. Concomitant replacement of the 6-chloro substituent on purine by the *N,N*-dimethylamino group also took place to afford, after chromatography and crystallization, 6-*N,N*-dimethylamino-9-(3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (**11**) in 67% yield. Treatment of **11** with methanolic aqueous dimethylamine at room temperature for 12 hr gave the *N,N*-dimethylcarbamoylmethyl nucleoside **7** in quantitative yield.

Catalytic reduction of the branched-chain cyanomethyl ribo nucleoside **11** over platinum in the presence of acetic anhydride and ethanol gave a mixture of two acetylated amino nucleosides in about 90% yield which were separated by column chromatography on silica gel. The faster moving component was the triacetate of the branched-chain amino ethyl ribo nucleoside **12**, whereas the slower moving component (in about equal yield) was the 5′-*O*-acetyl derivative of **12** (on the basis of its nmr spectrum in DMSO-d_6: one doublet at τ 4.18, assigned to C-2′ OH, disappeared on addition of D_2O). Treatment of either component with aqueous dimethylamine readily afforded crystalline 6-*N,N*-dimethylamino-9-[3′-(2″-acetamidomethyl)-3′-deoxy-β-D-ribofuranosyl]purine (**12**). Interestingly, the presence of the ethanol and acetic anhydride in the hydrogenation mixture did not prevent acetylation of the hydroxyl groups. Catalytic reduction of **6** or **11** in the absence of acetic anhydride gave a complex mixture of products which were very difficult to separate.

Experimental Section

3-*C*-Cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (2).—To a well-stirred solution of 3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (**1**)[2a] (1.5 g) in ethanol (40 ml) was added a saturated solution of sodium hydrogen carbonate (2 ml) followed by sodium metaperiodate solution (1.32 g in 70 ml of water). After the solution was stirred for 3 hr the excess sodium metaperiodate was destroyed by the addition of a few drops of ethylene glycol. The resoluting aldehydo sugar was immediately reduced with sodium borohydride (0.120 g). After the solution had stood for 4 hr, acetone (0.5 ml) was added and the mixture was stirred for an additional 0.5 hr. After the residue was removed by filtration, the filtrate was extracted with methylene chloride (4 × 100 ml). The combined extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure to yield 1 g (90%) of **2**. Crystallization of this product from ether gave pure **2**: mp 70°; $[\alpha]^{22}D$ +97° (*c* 1.1, chloroform); τ^{CDCl_3} 4.23 (d, $J_{1,2}$ = 4 Hz, H-1), 5.34 (t, $J_{2,3}$ = 4 Hz, H-2).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.4; H, 7.05; N, 6.57. Found: C, 56.6; H, 6.99; N, 6.67.

5-*O*-Benzoyl-3-*C*-cyanomethyl-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (3).—To a solution of 4.55 g of **2** in 25 ml of anhydrous pyridine was added 2 ml of benzoyl chloride. After the reaction mixture was kept at room temperature for 24 hr, a mixture of ice and water was added causing precipitation of solid **3**. Recrystallization of this solid from ethanol and then from ether–petroleum ether (bp 30–65°) gave 5.4 g (80%) of pure **3**: mp 110°; $[\alpha]^{22}D$ +59° (*c* 1.8, chloroform); τ^{CDCl_3} 4.1 (d, $J_{1,2}$ = 4 Hz, H-1), 5.22 (t, H-2); ir 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.26; H, 6.03; N, 4.45. Found: C, 64.11; H, 5.93; N, 4.31.

1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-ribofuranose (4) and 1-*O*-Acetyl-5-*O*-benzoyl-3-*C*-(carboxymethyl-2,3-γ-lactone)-3-deoxy-β-D-ribofuranose (4a).—The benzoate **3** (4.40 g) was hydrolyzed with 90% trifluoroacetic acid (50 ml) for 10 min and the resulting syrup was acetylated with acetic anhydride (15 ml) and pyridine (15 ml) for 18 hr. The product, worked up as described previously,[2a] was crystallized from ethanol to give 2 g of pure β anomer **4**. The mother liquor was evaporated to dryness and the residue was chromatographed on 120 g of silica gel using 3:1 benzene–ethyl acetate as developer to afford a fast-moving fraction **4a** (0.4 g, 5%) and 1.9 g (38%) of a 3:7 mixture of α,β anomers of **4**. Pure **4** had mp 117°; $[\alpha]^{22}D$ −21.9° (*c* 1.5, chloroform); ir 2250 cm^{-1} (C≡N); τ^{CDCl_3} 3.83 (s, H-1), 4.7 (d, H-2).

Anal. Calcd for $C_{18}H_{19}NO_7$: C, 59.82; H, 5.31; N, 3.81. Found: C, 59.56; H, 5.17; N, 3.53.

4a was recrystallized from ethanol: mp 137°; $[\alpha]^{24}D$ −96° (*c* 1.6, chloroform); ir (Nujol), 1700, 1780 cm^{-1} (C=O); τ^{CDCl_3} 3.6 (s, 1 H, H-1), 5.0 (d, 1 H, H-2), 5.5–5.9 (m, 3 H, H-5 and H-4), 6.7–7.5 (m, CH_2CO_2 and H-3), 8.0 (s, 3 H, Ac).

Anal. Calcd for $C_{16}H_{16}O_7$: C, 60.00; H, 5.04. Found: C, 59.80; H, 5.18.

6-Benzamido-9-(2′-*O*-acetyl-5′-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (5).—Hydrogen bromide was bubbled into a 0° solution of 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-*C*-cyanomethyl-3-deoxy-β-D-ribofuranose (**4**) (0.500 g) in anhydrous dichloromethane (25 ml) for 15 min. The reaction mixture was kept at 0° for 1 hr and then at room temperature for 15 min. The solution was then evaporated to a syrup and the last traces of hydrogen bromide were removed by coevaporation with dry toluene. The resultant syrup was redissolved in toluene (10 ml) and added to a suspension of chloromercuri-6-benzamidopurine (0.658 g) and Celite (0.500 g) in toluene (50 ml) which had been previously dried by distilling off 20 ml of toluene from the mixture. When the addition was completed the mixture was refluxed for 1 hr and then worked up as previously described.[2a] The material resulting from this procedure (0.508 g) was chromatographed on silica gel using benzene–ethyl acetate–ethanol (5:5:1) as developer to afford nucleoside **5** (0.298 g, 40% yield) as an amorphous foam: $[\alpha]^{25}D$ +3.1° (*c* 1.2, chloroform); ir film 2250 cm^{-1} (C≡N); τ^{CDCl_3} 0.75–1.00 (b, 1 H, HNC=O), 1.46 (s, 1 H, H-2 or H-8), 7.26 (d, 2 H, $-CH_2C{\equiv}N$), 7.83 (s, 3 H, $O{=}CCH_3$).

Anal. Calcd for $C_{23}H_{24}N_6O_6$: C, 62.22; H, 4.48; N, 15.55. Found: C, 61.99; H, 4.80; N, 15.50.

6-Chloro-9-(2′-*O*-acetyl-5′-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (6).—A thoroughly dried, finely powdered mixture of 0.72 g of **4** and 0.33 g of anhydrous 6-chloropurine was heated in an oil bath at 160° at 30 Torr for 5 min followed by further heating at 160° at 1 Torr for 40 min. The melt was extracted with 40 ml of dichloromethane and the extract was then filtered. Evaporation of the filtrate gave a residue which was chromatographed on 45 g of grade II silica using 2:1 benzene–ethyl acetate as developer to afford 0.600 g (66%) of nucleoside. Crystallization of this solid from ethanol gave pure nucleoside **6**: mp 136.5–137°; $[\alpha]^{22}D$ +16° (*c* 1.5, chloroform); ir (Nujol) 2250 cm^{-1} (C≡N); τ^{CDCl_3} 1.75 and 1.50 (H-2 and H-8), 3.96 (d, 1 H, $J_{1',2'}$ = 1 Hz, H-1′), 7.2 (d, 2 H, CH_2CN), 7.78 (s, 3 H, OAc).

Anal. Calcd for $C_{21}H_{18}N_5O_5Cl$: C, 55.33; H, 3.98; N, 15.35. Found: C, 55.00; H, 3.60; N, 15.14.

6-*N,N*-Dimethylamino-9-[3′-deoxy-3′-*C*-(*N,N*-dimethylcarbamoylmethyl)-β-D-ribofuranosyl]purine (7).—To a solution of 6-chloro-9-(2′-*O*-acetyl-5′-*O*-benzoyl-3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (**6**) (0.102 g in 7 ml of methanol) was added dropwise a 25% aqueous solution of dimethylamine (2 ml). After the reaction mixture was allowed to stand for 4 hr, the solvent was evaporated and the residue was chromatographed on a column of tlc silica gel using dichloromethane–methanol (93:7) as developer to afford the amide nucleoside **7** (0.064 g, 72% yield) as a syrup which crystallized after standing for over a month, mp 82–84°. This compound was homogeneous on paper (R_f 0.68, butanol–ethanol–water, 40:19:11), and on silica tlc (R_f 0.42, dichloromethane–methanol, 9:1): τ^{CDCl_3} 1.80 (s, 2, H-2 and H-8), 6.10 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1′), 4.43 (s, 2-3, C-5′ OH and C-2′ OH), 5.3 (two d, 2, $J_{2',3'}$ = 3.5 Hz, H-2′), 5.7–6.3 (m, 3, H-4′ and C-5′ CH_2), 6.53 [s, 6, $N(Me)_2$], 6.96, 7.08 [2 τ s, 6, $O{=}CN(Me)_2$], 7.1–7.6 (m, 3, H-3′, CH_2CO); on addition of D_2O, the peak at τ 4.43 disappeared and the singlet at 1.80 became two singlets; uv (two max) 275 mμ (H_2O); ir (film) 3200–3500 (OH), 1640 cm^{-1} (C=O). The nmr spectrum of **7** was the same as that of compound **10** described in the previous paper. The analysis given is that of **10**.[2a]

Anal. Calcd for $C_{16}H_{24}N_6O_4 \cdot {}^1/_2H_2O$): C, 51.30; H, 6.65; N, 22.50. Found: C, 50.86; H, 6.43; N, 22.40; mol wt 364 (mass spectroscopy).

Attempts to dry the compound under reduced pressure at about 50° led to a slow conversion of **7** into the lactone **8**.

6-*N*,*N*-Dimethylamino-9-[2′,5′-di-*O*-acetyl-3′-*C*-(*N*,*N*-dimethylcarbamoylmethyl)-3′-deoxy-β-D-ribofuranosyl]purine.—A solution of **7** (0.050 g) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was stored at room temperature for 20 hr. The reaction mixture was then diluted with ice water (10 ml) and extracted with chloroform (3 × 20 ml). After the chloroform extracts were dried over sodium sulfate and evaporated, the residue was chromatographed on a column of tlc silica to yield 0.055 g (40%) of the title nucleoside as a syrup, $[\alpha]^{25}D$ −25° (*c* 1, chloroform).

Anal. Calcd for $C_{20}H_{28}N_6O_6$: C, 53.64; H, 6.29; N, 18.74. Found: C, 53.90; H, 6.31; N, 18.65.

6-*N*,*N*-Dimethylamino-9-[3′-*C*-(carboxymethyl-2′,3′-γ-lactone)-3′-deoxy-β-D-ribofuranosyl]purine (8).—Sublimation of 6-*N*,*N*-dimethylamino-9-(3′-*C*-*N*,*N*-dimethycarbamoylmethyl-3′-deoxy-β-D-ribofuranosyl)purine (**7**) (0.030 g) at 210° (0.1 Torr) afforded after crystallization from ethyl acetate the title lactone nucleoside (**8**) (0.019 g, 73%): mp 198–199° (with sublimation); $[\alpha]^{22}D$ − 57.5° (*c* 1.1, chloroform); uv max 274 mμ (ε 14,500, methanol); CD max 274 (θ −10,000, methanol); ir (KBr) 1770 cm^{-1} (C=O); τ^{CDCl_3} 1.73, 2.23 (2 s, 2H, H-2, H-8), 6.48 [s, 6H, $N(Me)_2$]; $\tau^{DMSO\text{-}d_6}$ 4.93 (t, 1 H, C-5′ OH). The hydroxyl absorption disappeared on addition of D_2O; molecular weight from mass spectrum 319.

Anal. Calcd for $C_{14}H_{17}N_5O_4$: C, 52.65; H, 5.37; N, 21.93. Found: C, 52.43; H, 5.54; N, 21.83.

Amidation of Lactone 8 to Yield Amide Nucleoside 7.—6-*N*,*N*-Dimethylamino-9-[3′-*C*-(carboxymethyl-2′,3′-γ-lactone)-3′-deoxy-β-D-ribofuranosyl]purine (**8**) (0.030 g) was dissolved in dimethylamine (3 ml) and allowed to stand at 0° for 4 hr. After evaporation of the dimethylamine from the reaction mixture the branched-chain *N*,*N*-dimethylcarbamoylmethyl nucleoside (**7**) (0.034 g, quantitative yield) was recovered having an ir and nmr identical with those of the product obtained by treatment of **6** with aqueous dimethylamine. The product crystallized after standing at room temperature for over a month.

6-*N*,*N*-Dimethylamino-9-[3′-*C*-(carbamoylmethyl)-3′-deoxy-β-D-ribofuranosyl]purine (9).—The lactone nucleoside **8** (0.030 g) was allowed to react with liquid ammonia (3 ml) for 6 hr and the ammonia was then allowed to slowly evaporate. The resultant residue was crystallized from ethanol to afford the amide nucleoside **9** (0.030 g, 95%): mp 207°; $[\alpha]^{23}D$ − 29.9° (c 0.5, water); ir (Nujol) 1650 cm^{-1} (C=O); $\tau^{DMSO\text{-}d_6}$ 2.60, 3.13 (b, 2 H, O=CNH_2), 4.08 (d, 1 H, C-2′ OH(, 4.83 (t, 1 H, C-5′ OH); uv max 275 mμ (ε 14,000, H_2O); CD max 275 (θ −6000).

Anal. Calcd for $C_{14}H_{20}N_6O_4$: C, 49.99; H, 5.99; N, 24.98. Found: C, 49.59; H, 5.94; N, 24.72.

6-*N*,*N*-Dimethylamino-9-[3′-*C*-(carbomethyl-*N*-glycine ethyl ester)-3′-deoxy-β-D-ribofuranosyl]purine (10).—The lactone **8** (0.040 g) was dissolved in a mixture of *N*,*N*-dimethylformamide (0.75 ml) and ethyl glycinate (0.25 ml) and stirred at room temperature for 30 hr. The volatile material was removed by distillation (50°, 0.1 Torr) and the remaining residue column was chromatographed on tlc silica gel using dichloromethane–methanol (9:1) as developer to afford after crystallization from ethyl acetate the title peptide nucleoside (**10**) (0.038 g, 72%): mp 155–157°; $[\alpha]^{25}D$ − 49° (*c* 1.3, chloroform); uv λ_{max} 275 mμ (ε 14,600, water); CD λ_{max} 275 mμ (θ −8500, water); ir (KBr) 1730 (C=O ester), 1650 cm^{-1} (C=O amide); τ^{CDCl_3} 1.83, 2.00 (2 s, 2 H, H-2, H-8), 7.18 (b, 1 H, NH), 4.10 (d, 1 H, H-1), 8.70 (t, 3 H, CH_3 of ethyl ester).

Anal. Calcd for $C_{18}H_{26}N_6O_6$: C, 51.10; H, 6.21; N, 19.89. Found: C, 50.92; H, 6.19; N, 19.61.

6-*N*,*N*-Dimethylamino-9-(3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (11).—6-Chloro-9-(2′-*O*-acetyl-5′-*O*-benzoyl-3′-(*C*-cyanomethyl)-3′-deoxy-β-D-ribofuranosyl)purine (**6**) (0.268 g) was dissolved in anhydrous dimethylamine (30 ml) and stored at −10° for 20 days. The dimethylamine was then evaporated and the residue was triturated with ether (5 ml). The material remaining after the ether was decanted was taken up in ethanol and allowed to stand at 0° for 24 hr. A portion of the title nucleoside (0.094 g) crystallized directly out of this solution and a further 0.060 g (67% yield) was obtained by chromatography of the mother liquor on a column of tlc silica gel using dichloromethane–ethanol (93:7) as developer. Recrystallization of the nucleoside from ethanol or sublimation gave pure **11**: mp 206°; $[\alpha]^{25}D$ −39.4° (*c* 0.6, ethanol); uv λ_{max} 275 mμ (ε 15,800, water); CD λ_{max} 275 (θ −6100, water); ir (KBr) 2230 cm^{-1} (C≡N); $\tau^{DMSO\text{-}d_6}$ 1.70, 1.76 (2 s, 2 H, H-2, H-8), 3.98 (d, 1 H, H-1′), 6.80 [s, 6 H, $N(Me)_2$].

Anal. Calcd for $C_{14}H_{18}N_6O_3$: C, 52.82; H, 5.70; N, 26.40. Found: C, 52.64; H, 5.64; N, 26.42.

6-*N*,*N*-Dimethylamino-9-[3′-deoxy-3′-*C*-(*N*,*N*-dimethylcarbamoylmethyl)-β-D-ribofuranosyl]purine (7) from 11.—6-*N*,*N*-Dimethylamino-9-(3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (**11**) (0.020 g) was dissolved in a mixture of methanol (4 ml) and 25% aqueous dimethylamine (2 ml). After the reaction mixture was left to stand at room temperature for 12 hr the solvent was evaporated to yield **7** (0.023 g, quantitative yield) as a syrup which crystallized after standing at room temperature. The product was identical by ir and nmr with the product obtained by treatment of **6** with a methane–water–dimethylamine mixture except for an additional HO peak in its nmr at τ 7.3. The product was not stable, mp 82–85°.

Anal. Calcd for $C_{16}H_{24}N_6O_4 \cdot H_2O$: C, 50.35; H, 6.82; N, 21.95. Found: C, 49.86; H, 6.58; N, 21.31.

6-*N*,*N*-Dimethylamino-9-[3′-(2″-acetamidoethyl)-3′-deoxy-β-D-ribofuranosyl]purine (12).—6-*N*,*N*-Dimethylamino-9-(3′-*C*-cyanomethyl-3′-deoxy-β-D-ribofuranosyl)purine (**11**) (0.030 g) was dissolved in a mixture of acetic anhydride (2 ml) and absolute ethanol (2 ml) and hydrogenated over platinum oxide (20 mg) at 60 psi for 4 hr. The catalyst was then removed by filtration and the solvent was evaporated to afford 0.040 g of syrup. Examination of this product by tlc showed that it contained two components, R_f 0.18 and 0.10 in dichloromethane–ethyl acetate–ethanol (5:5:1). These two components were separated by column chromatography on tlc silica gel using the above developer, to afford 0.017 g of the faster component [$\tau^{DMSO\text{-}d_6}$ 2.14 (broad t, 1 H, NH), 7.85, 8.04, 8.20 (3 s, 9 H, 3 Ac), no hydroxyl signals] and 0.019 g (about 90% total yield of two components) of the slower component [$\tau^{DMSO\text{-}d_6}$ 2.22 (broad t, 1 H, NH), 4.18 (d, 1 H, C-2′ OH), 7.98, 8.17 (2 s, 6 H, 2 Ac)]. Upon addition of D_2O the doublet at τ 4.18 disappeared. The slower moving component was dissolved in 25% aqueous dimethylamine (1 ml) solution and allowed to stand for 3 hr at room temperature. After evaporation of the solvent, the remaining material crystallized on trituration with dichloromethane. Reaction of the faster moving component under the same conditions afforded the identical product. Recrystallization of these products from isopropyl alcohol–water gave pure **12** (0.023 g, 63%): mp 193–194°; $[\alpha]^{25}D$ −1.0° (*c* 0.9, ethanol); $\lambda_{max}^{H_2O}$ 274 mμ (ε 23,900); $\tau^{DMSO\text{-}d_6}$ 1.56, 1.76 (2 s, 2 H, H-2, H-8), 2.19 (t, 1 H, NH), 4.0 (s, 1 H, H-1′), 8.23 (s, 3 H, NAc).

Anal. Calcd for $C_{16}H_{24}N_6O_4 \cdot {}^1/_2H_2O$: C, 51.47; H, 6.74; N, 22.47. Found: C, 51.38; H, 6.38; N, 22.07.

Registry No.—**2**, 37108-29-5; **3**, 37108-30-8; **4**, 37108-31-9; **4a**, 37108-32-0; **5**, 37108-33-1; **6**, 37157-03-2; **7**, 37108-20-6; **8**, 37108-35-3; **9**, 37108-36-4; **10**, 37108-37-5; **11**, 37108-38-6; **12**, 37108-11-5; 6-*N*,*N*-dimethylamino-9-[2′,5′-di-*O*-acetyl-3′-*C*-(*N*,*N*-dimethylcarbamoylmethyl)-3′-deoxy-β-D-ribofuranosyl]-purine, 37108-12-6.

Acknowledgment.—The authors thank the National Research Council of Canada for financial assistance.

Some Derivatives of 1,6-Anhydroglucosamine and Their Use as Aglycons in Disaccharide Synthesis[1]

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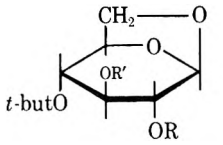
2-Acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-D-glucopyranose (*N*-acetyllactosamine) and 2-acetamido-2-deoxy-4-*O*-(β-D-glucopyranosyl)-D-glucopyranose (*N*-acetylcellobiosamine) have been synthesized. 2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (VII) proved to be an excellent aglycon for the Koenigs–Knorr reaction.

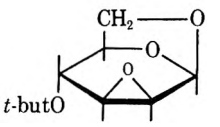
A number of naturally occurring substances contain glucosamine to which various hexose units are linked in position 4. Such sequences are found, *inter alia*, in blood group active oligosaccharides,[2,3] in bacterial cell-wall components,[4,5] and in chitin.[6] In view of the low reactivity of the C-4 hydroxyl in the C-1 conformation of glucopyranose, attempts to synthesize glycosides involving this position have met with limited success. Thus, condensation of acetobromogalactose with 2-acetamido-1,3,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranose gave only 4% of octaacetyl lactosamine.[7] Heyns, *et al.*,[8] employed an open-chain derivative of glucosamine as aglycon for the synthesis of *N*-acetylglucosamine-(1→4)-*N*-acetylglucosamine. This approach required a sequence of deblocking reactions which eventually resulted in a mixture of α and β isomers.

In recent publications we described a new aglycon, *viz.*, 2,3-di-*O*-acetyl-1,6-anhydro-β-D-glucopyranose,[9] and its utilization in the synthesis of oligosaccharides of the lactose type.[9-11] The selective substitution involves protection of the C-4 hydroxyl by the *tert*-butyl group and subsequent deblocking of I. We now wish to report the preparation of an analogous derivative of glucosamine which was found to be a most suitable aglycon for the synthesis of amino disaccharides. This was achieved by introduction of the amino function into levoglucosan already blocked at C-4.

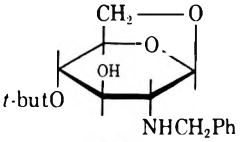
Catalytic deacylation of 2,3-di-*O*-acetyl-1,6-anhydro-4-*O*-*tert*-butyl-β-D-glucopyranose (I)[9] was followed by tosylation of II under controlled conditions, which gave, after column chromatography, a 72% yield of the 2-tosyl derivative III. The selective substitution is in accordance with the observation of Černý, *et al.*,[12] that tosylation of 1,6-anhydroglucose gives almost exclusively the 2,4-ditosyl derivative. The structure of III was, indeed, proved by removal of the *tert*-butyl group and isolation of 1,6-anhydro-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose.[13] Displacement of the tosyloxy group in III afforded 1,6:2,3-dianhydro-4-*O*-*tert*-butyl-β-D-mannopyranose (IV) in 90% yield.



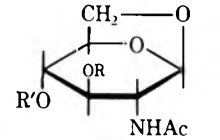
I, R = R′ = Ac
II, R = R′ = H
III, R = Ts; R′ = H



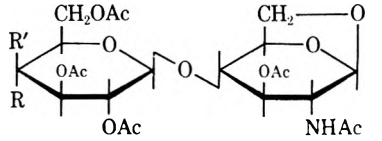
IV



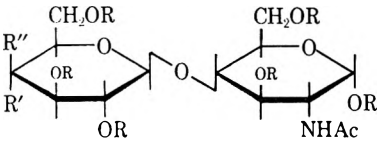
V



VI, R = Ac; R′ = *t*-but
VII, R = Ac; R′ = H
VIII, R = H; R′ = *t*-but
IX, R = R′ = H



X, R = H; R′ = OAc
XI, R = OAc; R′ = H



XII, R = Ac; R′ = H; R″ = OAc
XIII, R = Ac; R′ = OAc; R″ = H
XIV, R = R″ = H; R′ = OH

Epoxides attached to the rigid 1,6-anhydro system are known to undergo scission by a nitrogen nucleophile to lead predominantly to trans-diaxial substitution.[14] This was advantageously effected by benzylamine to give accordingly 1,6-anhydro-2-benzylamino-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (V) in 79% yield. Hydrogenolysis of V followed by acetylation afforded 2-acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (VI, 73%). A synthesis of 4-methylated glucosamine derivatives proceeding *via* an epoxide has been reported previously.[15]

Since the *O*-acyl and *tert*-butyl groups can be selectively removed by mild alkaline or acid treatment to obtain at will VIII or VII, respectively, compound VI

(1) This work was supported by the National Institutes of Health, PL 480, Agreement No. 06-015-1.

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appears to be an excellent starting material for the synthesis of both 1→3 and 1→4 glycosides.

Removal of the *tert*-butyl group by 80% trifluoroacetic acid gave the desired 2-acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (VII) in 83% yield. Catalytic deacylation led to the known 2-acetamido-1,6-anhydro-2-deoxy-β-D-glucopyranose (IX).[16,17]

The new aglycon VII was successfully applied to the synthesis of *N*-acetyllactosamine and *N*-acetylcellobiosamine. The Koenigs–Knorr reaction of VII with acetobromogalactose afforded the disaccharide X in high yield. Acetolysis of the 1,6-anhydro ring led to the known octaacetate XII.[7] Kuhn and Kirschenlohr[18] synthesized the disaccharide by the cyanohydrin method from 3-*O*-β-D-galactopyranosyl-D-arabinose prepared by degradation of lactose.

Analogously, condensation of VII with acetobromoglucose yielded *N*-acetylcellobiosamine XIV *via* the anhydro derivative XI and the octaacetate XIII. A disaccharide to which this structure was tentatively assigned was obtained by partial acid hydrolysis of Type XIV pneumococcal polysaccharide.[19]

We have shown previously that introduction of the electrophilic *N*-dichloroacetyl group into hexosamines leads to stable and highly reactive bromides which permit the smooth synthesis of hexosaminylsaccharides.[20,21] The scheme outlined in the present report appears to offer an approach to similar bromides of hexosyl hexosamines, namely, by introducing the electrophile into the intermediate primary amine resulting from the hydrogenation of V.

Experimental Section[22]

1,6-Anhydro-4-*O*-*tert*-butyl-β-D-glucopyranose (II).—To a solution of I[9] (3.0 g) in absolute methanol (60 ml) was added 3 drops of methanolic 1 *N* sodium methoxide, and the mixture was kept at room temperature for 4 hr. The solution was neutralized with Dowex 50W-X8, H^- form and the filtrate was evaporated *in vacuo*. The residue was crystallized from ether and a little hexane: yield 1.80 g (84%); mp 104–105°; $[\alpha]^{25}D$ −57.0°.

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.20; H, 8.34.

1,6-Anhydro-4-*O*-*tert*-butyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (III).—To an ice-cold solution of II (1.82 g) in pyridine (10 ml) was added dropwise with stirring a solution of toluene-*p*-sulfonyl chloride (2.37 g, 1.5 equiv) in pyridine (14 ml). The reaction mixture was stored in the refrigerator at 5° for 3 days. Tlc (ethyl acetate–methylene chloride, 15:85) showed one major spot and an upper faint spot, presumably of the ditosylate. The reaction mixture was concentrated *in vacuo* at room temperature to half its volume. Methylene chloride was added, and the solution was washed successively with cold water, saturated sodium hydrogen carbonate, and water, dried, and evaporated. The residue was passed through a silica gel column and the product was obtained by elution with ethyl acetate–methylene chloride (1:9), yield 2.23 g (72%). After crystallization from ethyl acetate–hexane, it melted at 125–126°, $[\alpha]^{25}D$ −38.5°.

Anal. Calcd for $C_{17}H_{24}O_7S$: C, 54.83; H, 6.50; S, 8.59. Found: C, 54.93; H, 6.43; S, 8.57.

A sample of III (100 mg) was dissolved in 80% aqueous trifluoroacetic acid (3 ml). After standing for 20 min at room temperature, no starting material was present [tlc, ethyl acetate–methylene chloride (1:3)]. The residue resulting from evaporation of the reagent solidified on cooling and crystallized when triturated wih cold ether: yield 71 mg (83%); mp 115–117°; $[\alpha]^{25}D$ −47.5°; reported[8] for 1,6-anhydro-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose, mp 117–119°, $[\alpha]^{25}D$ −48 ± 1°.

1,6:2,3-Dianhydro-4-*tert*-butyl-β-D-mannopyranose (IV).— A solution of the tosylate III (4.3 g) in chloroform (60 ml) was cooled to 5°, and 1 *N* methanolic sodium methoxide (23 ml) was added. The reaction mixture was stirred at 5° for 2 hr and at room temperature overnight. Water was added to dissolve the precipitated salts and the aqueous phase was extracted twice with chloroform. The combined extracts were washed with water, dried, and evaporated. Crystallization from hexane gave 2.09 g (90%) of IV, mp 81–82°, $[\alpha]^{25}D$ −35.0°.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.98; H, 7.91.

1,6-Anhydro-2-benzylamino-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (V).—The epoxide IV (2.0 g) was dissolved in a mixture of dimethylformamide (14 ml) and freshly distilled benzylamine (6 ml) and the solution was heated with stirring at 110–115° for 40 hr. Tlc [ethyl acetate–methylene chloride (15:85)] showed the disappearance of starting material. The solvent and excess of reagents were distilled off at reduced pressure. The crystalline residue was triturated with water, dissolved in hot ethanol, and decolorized with charcoal. Tlc (ethyl acetate) showed one spot and only traces of a second compound moving close to the product. The filtrate was taken to dryness, and the residue was crystallized from 50% aqueous ethanol: yield 2.42 g (79%); mp 176–177°; $[\alpha]^{25}D$ −41.7°. The nmr spectrum showed signals at τ 2.66 (five aromatic protons) and 8.78 (nine *tert*-butyl protons).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.55; H, 8.32; N, 4.52.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (VI).—The preceding compound (3.1 g) was hydrogenated in 95% ethanol (100 ml) with prewashed 10% palladium on charcoal (2 g) at 40° and 50 psi. After 48 hr, the suspension was filtered through a Celite bed and the filtrate was concentrated *in vacuo*. The solid residue, dried over phosphorus pentoxide, was dissolved in pyridine (8 ml), and acetic anhydride (3 ml) was added. After standing overnight at room temperature, the reaction mixture was concentrated to dryness *in vacuo* and the last traces of acylating agent were removed by distilling with several portions of toluene. Crystallization from ethyl acetate–hexane yielded 2.23 g (73%), mp 131–133°. Recrystallized from the same solvents, VI had mp 133–134°, $[\alpha]^{25}D$ −41.9°, ir spectrum (KBr) 5.77 (ester), 6.05, and 6.5 μ (amide). The nmr spectrum showed signals at τ 7.84 (three *O*-acetyl protons), 7.95 (three *N*-acetyl protons), and 8.72 (nine *tert*-butyl protons).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.82; H, 7.88; N, 4.51.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-glucopyranose (VII).—Preliminary experiments showed that 10–20% trifluoroacetic acid in methylene chloride as described previously[9] did not remove the *tert*-butyl group of VI satisfactorily. Even after 6 hr, starting material was still present. Heating in 70% aqueous acetic acid at 90° for 20 min caused substantial deacetylation.

A solution of VI (1.42 g) in 80% aqueous trifluoroacetic acid (15 ml) was kept at room temperature and the course of disappearance of VI was followed by tlc [ethyl acetate–methanol (9:1)]. The reaction was complete in 20 min. The solution was concentrated *in vacuo* at room temperature and the residue was codistilled with several portions of toluene. The remainder was crystallized from ethyl acetate and a few drops of hexane, and recrystallized from ethyl acetate. The yield of pure VII amounted to 950 mg (83%), mp 147–148°, $[\alpha]^{25}D$ −71.0°. Tlc [ethyl acetate–methanol (9:1)] showed R_{VI} 0.70. The nmr spectrum showed signals at τ 7.86 (three *O*-acetyl protons) and 7.95 (three *N*-acetyl protons).

Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.97; H, 6.17; N, 5.71. Found: C, 49.10; H, 5.97; N, 5.68.

A sample of VII was de-O-acetylated as described above for compound II. The residue resulting from the evaporation of the methanolic solution to dryness was crystallized from methanol–ether (2:1) to yield 85% of 2-acetamido-2-deoxy-1,6-anhydro-β-D-glucopyranose (IX): tlc [benzene–methanol (7:3)] R_{VII}

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(22) Optical rotations were determined in 1% chloroform solutions unless stated otherwise.

0.76; mp 193–194°; $[\alpha]^{25}D$ −47° (*c* 1.2, water) (reported mp 190–191°, $[\alpha]^{25}D$ −45.2°,[16] and mp 190°, $[\alpha]D$ −45.2[17]).

2-Acetamido-1,6-anhydro-2-deoxy-4-*O*-*tert*-butyl-β-D-glucopyranose (VIII).—Deacetylation of VI (150 mg) as above, followed by crystallization from ethyl acetate–ether–hexane afforded 102 mg (78%) of VIII: mp 139–140°; $[\alpha]D$ −25.3°; tlc [ethyl acetate–methanol (9:1)] R_{VI} 0.88; nmr τ 7.98 (three *N*-acetyl protons) and 8.74 (nine *tert*-butyl protons).

Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.70; H, 8.24; N, 5.25.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (X).—Tetra-*O*-acetyl-α-D-galactosyl bromide (1.03 g, 2.5 mmol) was dissolved in dry ethylene chloride (40 ml), the aglycon VII (0.37 g, 1.51 mmol) and mercuric cyanide (0.63 g, 2.5 mmol) were added, and the mixture was stirred at 40°, with protection from light, until no more aglycon was detectable on tlc (3 days). The cooled solution was poured into a mixture of ice–water and chloroform, and the organic layer was shaken thoroughly with 5% sodium hydrogen carbonate and washed with water. The residue obtained after evaporation of the solvent was dissolved in methylene chloride (5 ml) and chromatographed on a column (40 mm i.d.) of silica gel (E. Merck, 60, 70–230 mesh, 70 g). The compound eluted by a mixture of methylene chloride–ethyl acetate (3:7) weighed 0.72 g (83%) and was crystallized twice from 2-propanol: mp 187–188°; $[\alpha]^{25}D$ −79.4° (*c* 2, chloroform) tlc (ethyl acetate) R_{VII} 1.9. The ir spectrum (KBr) showed bands at 11.2 (β-glycoside) and 11.45 μ (galactopyranose ring).

Anal. Calcd for $C_{24}H_{33}NO_{15}$: C, 50.08; H, 5.78. Found: C, 50.02; H, 5.88.

2-Acetamido-3-*O*-acetyl-1,6-anhydro-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (XI).—Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.5 mmol) in ethylene chloride (40 ml) was treated with aglycon VII (1.51 mmol) and mercuric cyanide (2.5 mmol) as described for X. Elution from the silica gel column with methylene chloride–ethyl acetate (2:8) gave 0.76 g (87%) of the chromatographically pure compound. After crystallization from ethyl acetate–ether (1:4) and recrystallization from 2-propanol–isopropyl ether (1:2) it had mp 118–119°; $[\alpha]^{25}D$ −77.5° (*c* 2, chloroform); tlc (ethyl acetate) R_{VII} 1.84, R_X 0.97; ir (KBr) 11.2 μ (β-glycoside).

Anal. Calcd for $C_{24}H_{33}NO_{15}$: C, 50.08; H, 5.78. Found: C, 50.30; H, 5.69.

2-Acetamido-2-deoxy-1,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranose (XII).—Opening of the 1,6-anhydro ring in X (115 mg) was effected by treating with acetic anhydride (7 ml), glacial acetic acid (3 ml), and concentrated sulfuric acid (0.05 ml) at 15° for 24 hr. Anhydrous sodium acetate (0.3 g) was added, and the suspension was taken to dryness by coevaporation *in vacuo* with toluene. The residue was extracted with chloroform, and the extract was washed with water, dried over sodium sulfate, and evaporated at reduced pressure. The residue was chromatographed on a silica gel column (10 g, 15 mm i.d.). The fraction eluted by ethyl acetate–methylene chloride (8:2) was crystallized from alcohol–ether and recrystallized from 2-propanol–isopropyl ether: yield 66 mg (45%); mp 223–225°; $[\alpha]^{25}D$ +57.9°; tlc [benzene–methanol (9:1)] R_X 0.9 (reported mp 224–225°, $[\alpha]^{18}D$ +57.7°[7]).

2-Acetamido-2-deoxy-1,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranose (XIII).—Acetolysis of XI (230 mg) as described for X yielded after column chromatography 124 mg (46%) of XIII. Crystallization from alcohol–ether (1:1) and recrystallization from ethyl acetate–isopropyl ether (9:1) gave the pure octaacetyl derivative: mp 229–230°; $[\alpha]^{26}D$ + 46.4°; tlc [benzene–methanol (9:1)] R_{XII} 0.93, R_{XI} 0.99.

Anal. Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80. Found: C, 49.68; H, 6.00.

2-Acetamido-2-deoxy-4-*O*-(β-D-glucopyranosyl)-D-glucopyranose (XIV).—Catalytic deacetylation of the preceding compound (XIII, 100 mg) gave the free disaccharide XIV, which was crystallized from methanol–ether (8:2) and recrystallized from 2-propanol: yield 39 mg (69%); mp 168–170°; $[\alpha]^{24}D$ +12.9 ± 1° (*c* 1, water); tlc [benzene–methanol (1:2)] $R_{lactose}$ 0.8; ir (KBr) 6.0, 6.45 (amide group), and 11.2 μ (β linkage).

Anal. Calcd for $C_{14}H_{25}NO_{11}\cdot 2H_2O$: C, 40.09; H, 6.97. Found: C, 40.10; H, 7.03.

Registry No.—II, 36949-97-0; III, 36949-98-1; IV, 36949-99-2; V, 37042-48-1; VI, 37042-49-2; VII, 37042-50-5; VIII, 37042-51-6; IX, 37042-52-7; X, 36954-61-7; XI, 36954-62-8; XII, 36954-63-9; XIII, 36954-64-0; XIV, 36954-65-1.

Levoglucosenone (1,6-Anhydro-3,4-dideoxy-Δ³-β-D-Pyranosen-2-one). A Major Product of the Acid-Catalyzed Pyrolysis of Cellulose and Related Carbohydrates

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Levoglucosenone (1,6-anhydro-3,4-dideoxy-Δ³-β-D-pyranosen-2-one) was isolated as the major component of the tar fraction from the acid-catalyzed pyrolysis of cellulose, D-glucose, or levoglucosan (1,6-anhydro-β-D-glucopyranose). Its structure was determined and a mechanism describing its formation from levoglucosan is proposed.

Until the early 1950's studies of the pyrolysis of cellulose and cellulosic fuels, neat and treated with various fire retardants, were largely confined to determination of such gross fractions as gas, tar, and char and to simple observation of how the combustibility of the sample varied with the relative proportions of these fractions. Such studies clearly established that high "tar" yields favor high flammability.[1,2]

As early as 1918, Pictet and Sarasin[3] isolated as a major constituent of the tar fraction a substance they named "levoglucosan." This constituent was subsequently identified by Josephson[4] as 1,6-anhydro-β-D-glucopyranose (I).

Unfortunately, many of the more recent studies of the combustion behavior of cellulose have tended to equate levoglucosan and tar. Since high levoglucosan yield—and, consequently, high tar yield—favors high flammability, it was assumed that reducing the levoglucosan yield—and, therefore, presumably the tar yield—would lower flammability. In particular, since both acidic and basic retardants were found to lower drastically the levoglucosan yield on pyrolysis of treated cellulose, such materials have frequently been

(1) S. Coppick in "Flameproofing Textile Fabrics," R. W. Little, Ed., ACS Monograph 104, 1947, p 41.

(2) K. Tamaru, *Bull. Chem. Soc. Jap.*, **24**, 164 (1951).

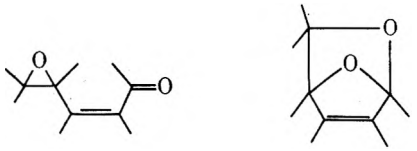
(3) A. Pictet and J. Sarasin, *Helv. Chim. Acta*, **1**, 87 (1918).

(4) K. Josephson, *Chem. Ber.*, **62B**, 313 (1929).

considered more or less interchangeable in their potentials as fire retardants.

Recently Tsuchiya and Sumi[5] demonstrated that with acidic retardants a new unidentified compound replaced levoglucosan as the major constituent of a still significant tar fraction. Subsequently they and their colleagues[6] demonstrated that the decrease in levoglucosan yield was not necessarily related to the effectiveness of flame retardants, with results implying that the overall tar yield is a more important criterion for flammability than is the yield of levoglucosan. Further, they purified a sample of the new compound and, using infrared (ir), nuclear magnetic resonance (nmr), and mass spectral analyses, identified it as *cis*-4,5-epoxy-2-pentenal (II).

Working independently during the same period, Wodley[7] pyrolyzed both cellulose and levoglucosan with acidic retardants and reported a major unknown tar constituent with the empirical formula $C_5H_6O_2$. On the basis of ir, nmr, and mass spectrometric results essentially the same as those reported for II, Lipska and McCasland[8] assigned to this compound the structure 1,5-anhydro-2,3-dideoxy-β-D-pent-2-enofuranose (III).



II

III

The two proposed structures have a number of common features and most likely represent the same compound. Since we believed the determination of the correct structure of this compound to be important to the understanding of the thermal behavior of cellulose, *i.e.*, of the reaction mechanisms which should be the basis of fire-retardant technology, we undertook a further study to elucidate this structure. This paper reports the results of that investigation.

Experimental Section

Preparation of 1,6-Anhydro-3,4-dideoxy-Δ³-β-D-pyranosen-2-one. A.—One gram of acidic additive ($NH_4H_2PO_4$, NaH_2PO_4, or $NaHSO_4$) was thoroughly mixed with 10 g of powdered cellulose (Cellex MX, Bio-Rad Laboratories, Richmond, Calif.). The sample was then introduced into a Pyrex tube, 1.5 × 10 in., which was connected to a Dry Ice–acetone trap and vacuum pump. The tube was evacuated and introduced into a preheated furnace positioned about 10° from the horizontal in order to allow liquid products to flow readily out of the hot zone and thus minimize secondary reactions. After 45 min at 300° the system was brought to room temperature and air was introduced. The nonaqueous fraction (about 500 mg total) of the mixture of liquid products was extracted essentially quantitatively into about 50 ml of methylene chloride, washed with water, and dried over anhydrous sodium sulfate. The volume of the above solution was reduced tenfold by evaporation of the methylene chloride at room temperature and reduced pressure. The major product was purified by preparative gas chromatography (gc) using a 10% Carbowax 20M on Chromosorb W copper column (0.25 in. × 3 ft) at 175° with helium carrier. Injector and detector temperatures were maintained at 235°. The pure compound was collected in an ice-cooled Pyrex tube covered with aluminum foil.

B.—A 50–100 mg sample of cellulose, D-glucose (Calbiochem, La Jolla, Calif.) or levoglucosan (prepared and purified by the procedure of Ward[9]) was placed in a small Pyrex tube (0.25 × 3 in.) and covered with a layer of clean glass wool 0.125 in. thick. On top of this layer was placed a second one, 0.5 in. thick, containing 100 mg of the additive. The tube was introduced into the system detailed above; pyrolysis conditions and work-up procedure were the same as previously described.

Analyses.—Both the preparative column and a 5% SE-30 on Chromosorb W glass column at 100° were used for analytical gc. Carbon and hydrogen analyses by the ultramicro method[10] and molecular weight by osmometry with chloroform as solvent were determined at the Microchemical Analytical Laboratory, University of California, Berkeley. Additional molecular weight data were obtained using the Rast freezing point lowering of camphor method.[11] Mass and infrared spectra were obtained on the neat material. For ultraviolet spectra, solvents were *n*-hexane spectrograde (Matheson Coleman and Bell) and ethanol (95%), distilled immediately before analysis. Proton nmr (pmr) and carbon-13 nmr (^{13}C nmr) spectra were obtained in $CDCl_3$ for the unknown. The ^{13}C nmr spectrum of levoglucosan was determined in water. Refractive index, optical activity, and optical rotatory dispersion (ORD) were also measured.

Instrumentation.—Two gc instruments were used: a Packard Model 7831 with a flame ionization detector and a splitter of ratio 50:1 when used preparatively and an Aerograph Model 1520 with thermal conductivity detector. The pmr spectra were obtained on a Varian HA-60 nmr spectrometer equipped with a variable-temperature probe and on a Varian HA-100 equipped with a proton decoupler. A 14-kG instrument (home built, Department of Chemistry, University of California, Berkeley) was used for the ^{13}C nmr spectrum of the unknown, and a Varian HA-100 nmr spectrometer for the spectrum of levoglucosan. Other instruments used were a Microlab Model 301 osmometer, a Consolidated Electrodynamics Corp. Model 21103B mass spectrometer, Perkin-Elmer Model 337 and Unicam Model SP-800 spectrophotometers, a Bausch and Lomb 33-45-58 refractometer, a Zeiss LEP-A2 polarimeter, and a Cary Model 60 recording spectropolarimeter.

Results

The gas chromatogram of the methylene chloride extract showed the presence of a major product constituting about 90% of the solute. This product, after collection from either preparative gas chromatograph, was shown to be pure both by reinjection into the same column and by using the other column and separation conditions.

As collected, the compound was a faintly greenish-yellow liquid ($n^{25}D$ 1.5084) which darkened during several days' storage, even under refrigeration. Elemental analysis of both a freshly prepared sample and one stored for 10 days showed essentially identical results: C, 57.04; H, 4.85.

The initial molecular weight obtained by the Rast method, 165, appeared unreasonably high. Quantitative determination by gc of the compound in the camphor mixture showed that its amount was reduced to about 75% of the original on melting the mixture (1 min at 180°, in order to obtain maximum homogeneity) and that heating the mixture further in the melting point determination reduced the amount to 50%. This, and the fact that no smaller products were detected by gc, indicated that the material was polymerizing on heating. Repetition of the melting point determination on the same sample gave a molecular weight of about 250.

(5) Y. Tsuchiya and K. Sumi, *J. Appl. Polym. Sci.*, **14**, 2003 (1970).
(6) D. P. C. Fung, Y. Tsuchiya, and K. Sumi, *Wood Sci.*, **5**, 38 (1972).
(7) F. A. Wodley, *J. Appl. Polym. Sci.*, **15**, 835 (1971).
(8) A. E. Lipska and G. E. McCasland, *ibid.*, **15**, 419 (1971).
(9) R. B. Ward in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, p 394.
(10) C. W. Koch and E. E. Jones, *Mikrochim. Acta*, **4**, 734 (1963).
(11) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longman Group Limited, London, 1970, p 1037.

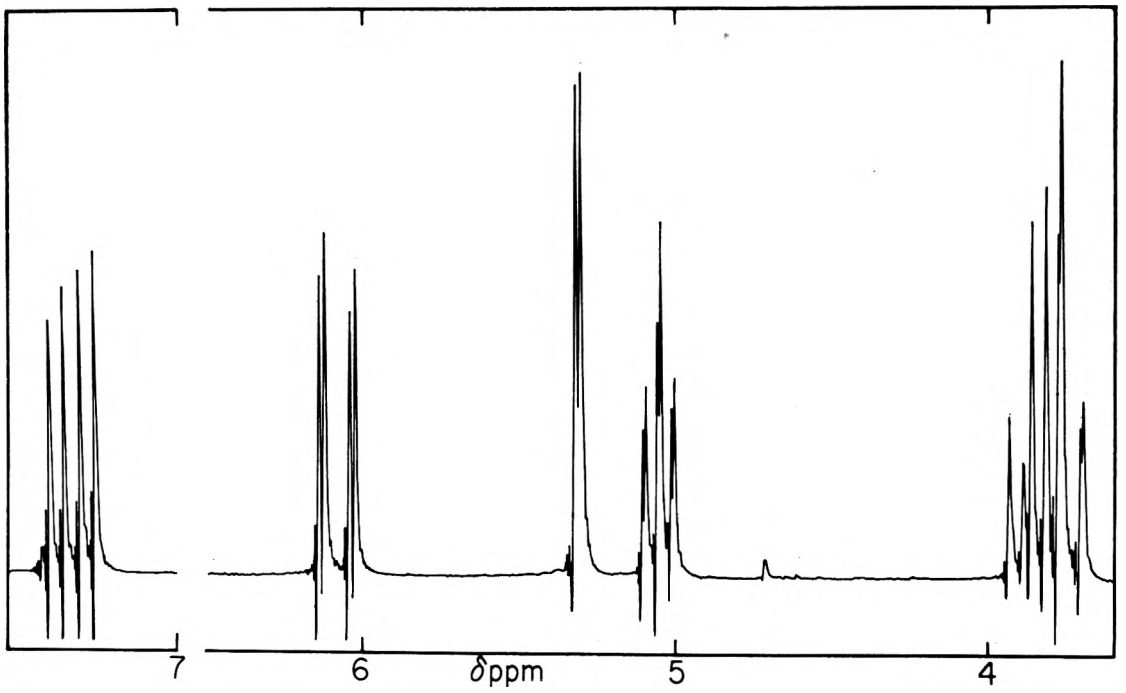


Figure 1.—100-MHz pmr spectrum of levoglucosenone in $CDCl_3$: δ in parts per million from internal TMS.

By osmometry, a freshly prepared sample and one which was kept refrigerated in the dark for 2 days (in which no detectable color change was observed) each gave a molecular weight of 131. A sample which was kept under similar conditions but for 10 days, and during this period was exposed to light several times at room temperature, showed a distinct color darkening and gave a molecular weight of 139.

Mass spectroscopic analysis showed the major fragment at m/e 39. The main peaks (>25% of the base mass) were m/e (rel intensity) 98 (52), 96 (43), 68 (61), 53 (58), 42 (43), 41 (39), 39 (100), 29 (75), 27 (42), 26 (28).

The infrared spectrum of the neat compound exhibited absorptions at the following frequencies: 2990, 2900, 1720, 1700, 1610, 1380, and 1100 cm^{-1}.

Ultraviolet spectra showed an absorption of λ_{max} 211 mμ (log $\epsilon^{1\%}_{1\,cm}$ 2.82) in n-hexane and λ_{max} 218 mμ (log $\epsilon^{1\%}_{1\,cm}$ 2.78) in 95% ethanol. In both solvents there was a second, much smaller, absorption, λ_{max} 275 mμ (log $\epsilon^{1\%}_{1\,cm}$ 1.5). The maximum at the shorter wavelength in both solvents obeyed the Beer–Lambert law for concentrations smaller than 10^{-4} M. It was difficult to determine accurately this behavior for the weaker absorption at the longer wavelength.

The 100-MHz pmr spectrum of a deuteriochloroform solution at room temperature is shown in Figure 1. Integration of the proton signals showed the presence of six nonequivalent protons. The pmr spectrum displayed no temperature dependence over the range of 25–65°. In addition, no change in the spectrum was observed when it was determined in the presence of deuterium oxide, even after 30 min at 30°.

A pmr spectrum in deuteriochloroform of the methylene chloride extract which, based on gc, consisted of the major product to an extent of about 90%, revealed the presence of the same peaks as in the purified compound.

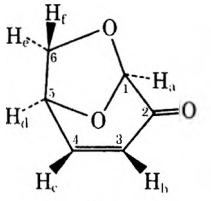
The 14-kG proton-noise decoupled cmr spectrum of the pure compound in deuteriochloroform is shown in Figure 2a. The spectrum shows six different carbons each of which appears as a sharp singlet.

The compound was highly optically active, with a specific rotation of $[\alpha]^{25}D$ −460° (c 1.0, $CHCl_3$). No change in activity was observed as a function of time.

The ORD determination showed that the shorter wavelength uv band is optically active and exhibits a positive Cotton effect curve (Figure 3).

Discussion

On the basis of these results the correct structure of the compound is 1,6-anhydro-3,4-dideoxy-Δ^3-β-D-pyranosen-2-one (levoglucosenone) (IV).



IV

We wish to show how this structure follows from the results and to suggest a mechanism which describes the formation of IV from I.

The formation of IV is qualitatively independent of the acid used as an additive. In our experiments the same compound was isolated whether $NH_4H_2PO_4$, NaH_2PO_4, or $NaHSO_4$ was added. This fact eliminated the possibility that the compound contained elements other than carbon, hydrogen, and oxygen, and hence on the basis of the elemental analysis, the compound has the empirical formula $(C_2H_2O)_n$ (calcd C, 57.14; H, 4.76).

The increased molecular weight on standing (with no change in elemental analysis) implies that even the lowest value observed, 131, was high as a result of some polymerization. With n = 3 in the empirical formula, *viz.*, the molecular formula $C_6H_6O_3$, the molecular

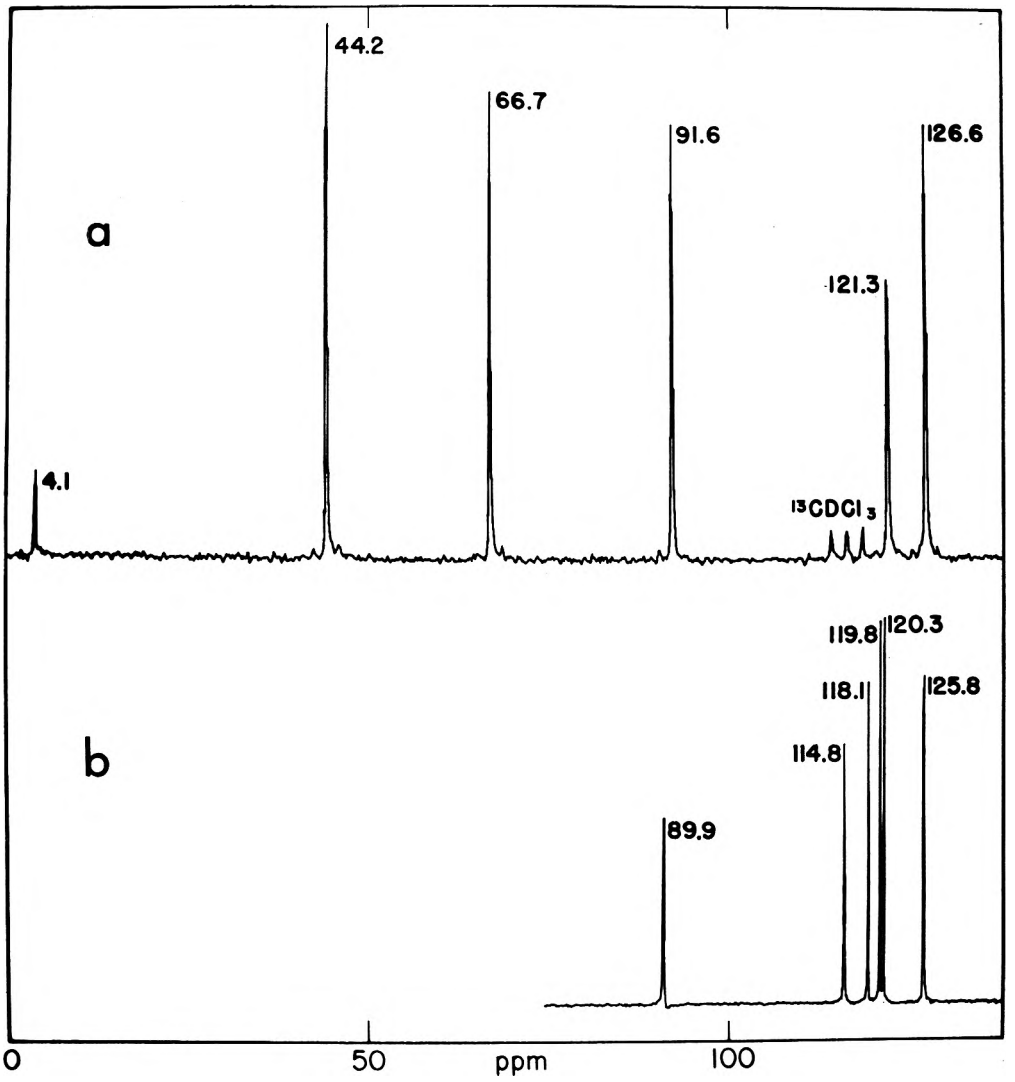


Figure 2.—Proton-noise decoupled ^{13}C nmr spectra (chemical shifts calculated from external CS_2): (a) levoglucosenone; (b) levoglucosan.

weight is 126. Then, the presence of 8, 19, and 47% by weight of an assumed dimer would cause an increase in the average molecular weight to 131, 139, and 165, respectively. This last value, resulting from heating during the Rast procedure, is in good agreement with quantitative gc determination.

Of the major peaks in the mass spectrum, the highest value of m/e is 98, with isotope peaks at P + 1 and P + 2 corresponding to the formula $C_5H_6O_2$. However, the spectrum does show small (~0.1%) peaks at higher m/e, including 126, not clearly attributable to impurities. In any case, mass spectra do not necessarily show significant parent peaks, and without additional data the value 98 only serves to set a lower limit on the molecular weight.

The infrared spectrum shows the presence of a CH_2 group (2900, 2990 cm^{-1}), C=C (1380, 1610), COC (1100), and most significantly a carbonyl group, probably conjugated to a double bond (1700, 1720). This carbonyl absorption is in conflict with the reported ir interpretation for III.

Strong support for the presence of a conjugated system emerges from the ultraviolet spectrum. The wavelengths of the two maxima and the values of the molar absorptivity are characteristic of α,β-unsaturated carbonyl compounds. The bathochromic shift observed for the higher maximum when going from a

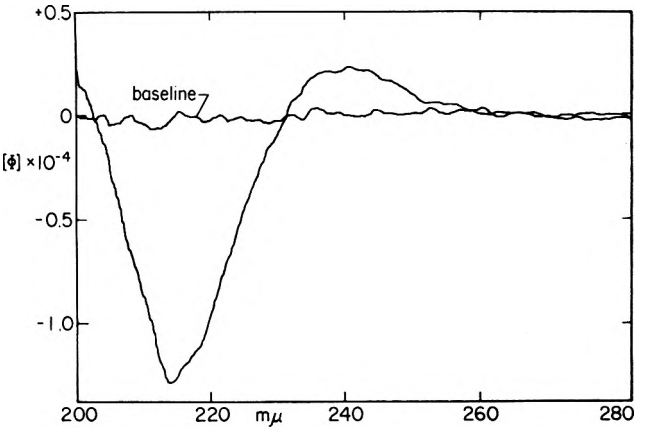


Figure 3.—ORD spectrum of levoglucosenone in n-hexane (concentration 2×10^{-3} g/100 ml).

nonpolar (n-hexane) to a polar one (95% ethanol) is normal behavior for the $\pi \rightarrow \pi^*$ transition in α,β-unsaturated carbonyl compounds. Such compounds are also known to dimerize under the influence of heat or light.[12]

The pmr spectrum (Figure 1) together with the above data permitted us to write a structure for the molecular

(12) D. J. Trecker in "Organic Photochemistry," Vol. 2, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1969, p 72.

formula $C_6H_6O_3$. The assignments of H_a through H_d are straightforward; those of H_e and H_f are based on their coupling constants with H_d and the dihedral angles (about 30° and 80°, respectively) as shown in a Dreiding model. The observed coupling constants agree well with values calculated for similar angles.[13] The entire spectrum interpretation is shown in Table I.

TABLE I
INTERPRETATION OF THE 100-MHz PMR SPECTRUM OF IV

Proton	δ^a	$J_{H,H}$,[b] Hz
H_a	5.31	a,b = 1.7[c]
H_b	6.09	b,c = 10.1; a,b = 1.7[c]
H_c	7.34	b,c = 10.1; c,d = 4.8
H_d	5.05	c,d = 4.8; d,e = 4.8; d,f = 1.0
H_e	3.87	d,e = 4.8; e,f = 6.6
H_f	3.74	d,f = 1.0; e,f = 6.6

[a] Chemical shifts in parts per million from internal TMS. [b] Absolute values of proton–proton coupling constants in hertz. [c] Long-range coupling constant (through four bonds) as found in similar α,β-unsaturated cyclic carbonyl systems (see, *e.g.*, ref 13, p 312).

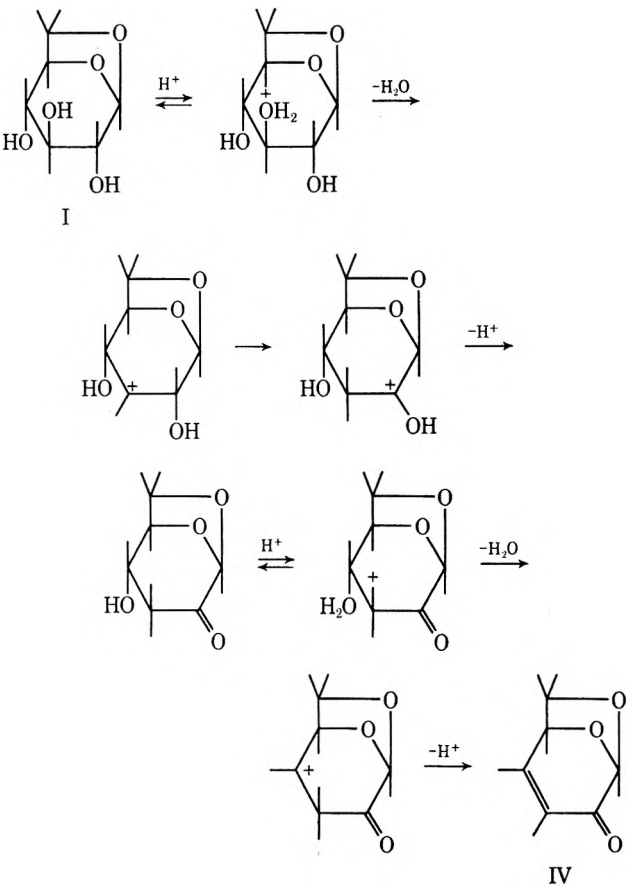
The values given were verified by proton–proton decoupling experiments.

The proton-noise decoupled ^{13}C nmr spectrum (Figure 2a) shows the presence of six different carbons. The signal at δ 4.1 ppm (upfield from CS_2) is in good agreement with the chemical shift of the carbonyl carbon in α,β-unsaturated ketones somewhat shielded by the two oxygens on the α' carbon.[14] Carbons 3 and 4 appear as olefinic carbons conjugated to a carbonyl group at 66.7 and 44.2 ppm, respectively.[15] Carbon 1 appears at 91.6 ppm and is in good agreement both with the acetal carbon of β-pyranosides[16] and with carbon 1 of I (Figure 2b). Carbons 5 and 6 appear at δ 121.3 and 126.6, respectively, in the region of the reported chemical shifts for the corresponding carbons in a pyranose ring.[17] Carbon 6 appears at somewhat lower field than in glucose because of the deshielding effect accompanying the transformation from a hydroxyl to an ether group.[17] In an off-center resonance proton decoupling experiment on I only one signal (at 125.8 ppm) appeared as a triplet; all the others were doublets. This permitted us to assign the triplet to carbon 6 and indicated that the 126.6 peak in IV was likewise carbon 6.

The ^{13}C nmr data for carbons 1, 5, and 6 in IV reflect the similarity between the latter and I. Moreover, the ^{13}C chemical shift of carbon 1 in IV indicated that this carbon still had the same configuration as in I, *i.e.*, the β configuration; α-anomeric carbon appears at higher field, around 100 ppm.[17]

IV was formed as a major product in the acid-catalyzed pyrolysis of cellulose. In addition, when cellulose, D-glucose, and levoglucosan were pyrolyzed in the absence of additives and the products were passed through an acidic filter while still in the vapor phase, IV was found to be the major product. In all these cases little or no I was found. On the other hand, when the filter contained no additives, the major constituent of the tar fraction was I, whether the sample pyrolyzed was cellulose, glucose, or levoglucosan itself. Results to date neither establish nor contradict a route by way of I for the formation of IV from the other carbohydrates. Further work is in progress.

The following mechanism can be drawn for the acid-catalyzed transformation of I to IV.



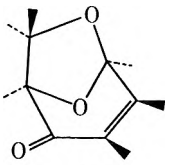
According to the proposed mechanism, asymmetric carbons C_1 and C_5 are not involved in the transformation process; thus if one starts with levoglucosan ($[\alpha]^{25}D$ −55° (*c* 0.5, H_2O)) the product levoglucosenone must also be optically active.[18] The results of the optical activity measurement were consistent with the mechanism on this point.

The third step in the proposed mechanism shows a 1,2-hydride shift from carbon 2 to the carbenium[19] center at carbon 3. This is justified by the formation of a more stable hydroxycarbenium ion from the secondary ion initially formed at carbon 3.

An alternate 1,2-hydride shift forming a hydroxycarbenium ion is possible from carbon 4, but in the former case (from carbon 2) the ion has additional stability owing to the proximity of oxygen. Carbenium ions may be stabilized by oxygen on adjacent carbon by overlap of the filled 2p orbital of the oxygen with the empty 2p orbital of the sp^2-hybridized carbon; models show that the carbon-6 oxygen is spatially in a favorable position to so stabilize the carbon-2 carbenium center. Possibly the alternate route also occurs to some degree; this would result in the formation of 1,6-

(13) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 281.
(14) J. B. Stothers and P. C. Lauterbur, *Can. J. Chem.*, **42**, 1563 (1964).
(15) D. H. Marr and J. B. Stothers, *ibid.*, **43**, 596 (1965).
(16) D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4463 (1971).
(17) G. A. Olah and A. M. White, *ibid.*, **91**, 5801 (1969).
(18) According to the proposed mechanism, 1,6-anhydrohexoses of the D family would yield levoglucosenone, while L-anhydrohexoses would result in the formation of its mirror image.
(19) For definition see G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972).

anhydro-2,3-dideoxy-Δ^2-β-D-pyranosen-4-one (isolevoglucosenone), a structural isomer of IV. A search for this compound in the pyrolysate is in progress.



V

According to the above mechanism, the transformation of I to IV does not involve a configuration change at asymmetric carbon 5. Models show that the enone of the D series is of a right-handed chirality. If IV is of this configuration, its skewed transoid α,β-unsaturated carbonyl system, which is inherently dissymmetric, should be manifested in a positive Cotton effect in the ORD spectrum.[20] The results showed this to be the case.

In addition to the elucidation of the structure of IV, two further questions require discussion. (1) Is IV a direct product of the pyrolysis process or a secondary compound formed during purification? (2) Is IV the same product isolated by the two other groups?

With respect to question 1, it is exceedingly unlikely that the mild conditions used during the work-up process before injection into the gc would alter a compound formed during the severe pyrolysis process. Isolation of the same compound using two different column packings and operating conditions strongly indicate that the product was not formed in the gc. Furthermore, a pmr spectrum obtained on the methylene chloride extract indicated that the identified end product is the major component of the tar mixture.

With respect to question 2, the principal preparation procedure of all three groups was quite similar. Although no direct comparison of the products was possible, our pmr spectrum and the comparable (*i.e.*, major) peaks of the mass spectrum corresponded closely to those observed for II[21] and III.[22] Furthermore, although we did not see the ir spectrum for III, that of II was fundamentally equivalent to that for IV. Finally, a sample of our material injected into the gc used by Lipska showed a retention time consistent with that found for III. Thus it is unlikely that more than one compound is involved.

Registry No.—I, 498-07-7; II, 25073-23-8; III, 37112-30-4; IV, 37112-31-5.

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(20) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 194.

(21) D. P. C. Fung, personal communication.

(22) A. E. Lipska, personal communication.

Terpenoids. LXVIII.[1] 23ξ-Acetoxy-17-deoxy-7,8-dihydroholothurinogenin, a New Triterpenoid Sapogenin from a Sea Cucumber[2]

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A new triterpenoid sapogenin was isolated and found to be 3β,20ξ-dihydroxy-23ξ-acetoxylanost-9(11)-ene-18-carboxylic acid lactone (18 → 20) (**5**). The functionality at C-23 is unprecedented in sapogenins from the sea cucumber.

Sapogenins from sea cucumbers have been very actively investigated in recent years. Structure proof of many of these compounds has been carried out.[1,5-12] All of these sapogenins have been found to be triterpenoids with a lanostane skeleton. These have included 22,25-oxidoholothurinogenin (**1a**) and its deoxy analog **1b** from *Actinopyga agassizi*[6] obtained by rigorous acid cleavage of saponins obtained from the Cuvier glands. Milder hydrolytic conditions[7] led to the isolation of 12β-methoxy-7,8-dihydroholothurinogenins of which **2** is an example. Enzymatic hydrolysis has led to a 12α-hydroxy analog. Using vigorous acid hydrolysis of the saponins from other sea cucumbers our group and others have found lanostane derivatives

(1) For part LXVII see P. Roller, B. Tursch, and C. Djerassi, *J. Org. Chem.*, **35**, 2585 (1970).

(2) Financial assistance from the National Institutes of Health (Grant No. GM-06840) and a fellowship from the Rutgers University Research Council to I. R. is gratefully acknowledged.

(3) On sabbatical leave (1971–1972) from Rutgers, The State University of New Jersey, Newark, N. J.

(4) Faculté des Sciences, Université Libre de Bruxelles, Brussels, Belgium.

(5) For a recent review see J. S. Grossert, *Chem. Soc. Rev.*, **1**, 1 (1972).

(6) J. D. Chanley, T. Mezzetti, and H. Sobotka, *Tetrahedron*, **22**, 1857 (1966).

(7) J. D. Chanley and C. Rossi, *ibid.*, **25**, 1897, 1911 (1969).

(8) B. Tursch, I. S. de Souza Guimaraes, B. Gilbert, R. T. Aplin, A. M. Duffield, and C. Djerassi, *ibid.*, **23**, 761 (1967).

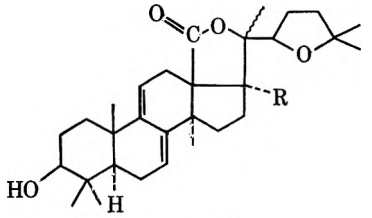
(9) G. Habermehl and G. Volkwein, *Justus Liebigs Ann. Chem.*, **731**, 53 (1970).

(10) P. Roller, C. Djerassi, R. Cloetens, and B. Tursch, *J. Amer. Chem. Soc.*, **91**, 4918 (1969).

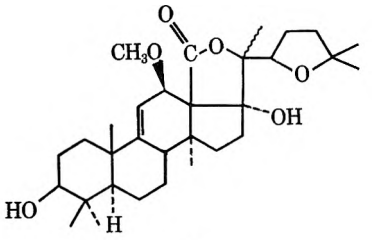
(11) B. Tursch, R. Cloetens, and C. Djerassi, *Tetrahedron Lett.*, 467 (1967).

(12) G. B. Elyakov, T. A. Kuznetsova, and Yu. N. Elkin, *ibid.*, 1151 (1969).

with a heteroannular diene system with variations in the side chain of which griseogenin[8] (**3**) is a representative example. Elyakov[12] has reported the isolation of two sapogenins containing homoannular diene systems (**4**).



1a, R = OH
b, R = H



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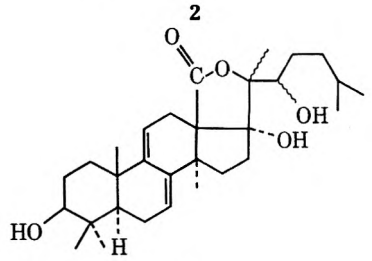

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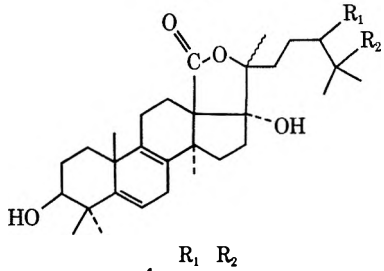
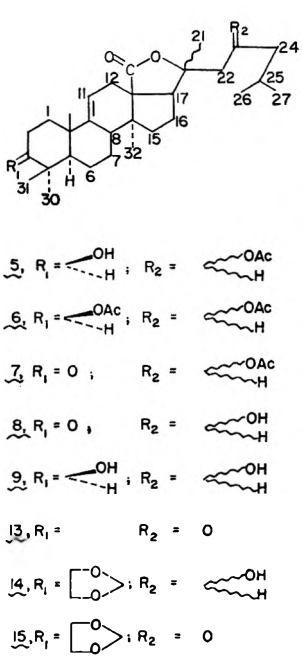


	R_1	R_2
4a,	═	═
4b,	H	OH

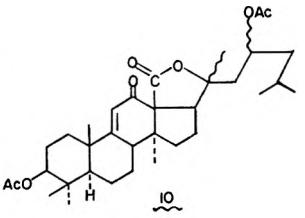
We report here the isolation and structure proof of a new sapogenin, 23ξ-acetoxy-17-deoxy-7,8-dihydroholothurinogenin (**5**), isolated from the dried skins of *Stichopus chloronotus* Brandt found in the bay of Telukdalam, Nias Island, Indonesia. This sapogenin is highly unusual in having an acetoxy group at the 23 position and a double bond at the 9(11) position without a 12 alkoxy or hydroxy group.

High-resolution mass spectrometry established the empirical formula $C_{32}H_{50}O_5$ for **5**, and the ir spectrum showed absorption at 1760 cm^{-1} characteristic of a five-membered lactone.[1,6-11] The presence of acetate was demonstrated by an ir absorption band at 1735 cm^{-1}, a methyl peak at δ 2.02 in the nmr, and by the loss of acetic acid in the mass spectrum of **5**. There is essentially no uv absorption of **5**, thus showing the absence of a heteroannular diene system.

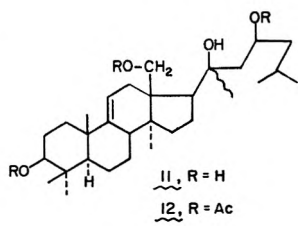
Treatment of **5** with acetic anhydride in pyridine yielded diacetate **6**. Oxidation of **5** with Jones reagent led to 23ξ-acetoxy-17-deoxy-7,8-dihydro-3-holothurinogenone (**7**). Hydrolysis of keto acetate **7** with hydroxide in methanol led to the keto alcohol **8** and hydolysis of (**5**) itself gave 23ξ-hydroxy-17-deoxy-7,8-dihydroholothurinogenin (**9**).



5, R_1 = 3β-OH, α-H ; R_2 = 23ξ-OAc
6, R_1 = 3β-OAc, α-H ; R_2 = 23ξ-OAc
7, R_1 = O ; R_2 = 23ξ-OAc
8, R_1 = O ; R_2 = 23ξ-OH
9, R_1 = 3β-OH, α-H ; R_2 = 23ξ-OH
13, R_1 = ; R_2 = O
14, R_1 = ; R_2 = 23ξ-OH
15, R_1 = ; R_2 = O



10



11, R = H
12, R = Ac

The nmr spectrum of **5** showed the presence of seven methyl groups in addition to an acetate methyl. The number and overall similarity of the position of the methyl absorptions to previously reported work[6-11] suggests the presence of a lanostane skeleton.

The β configuration of the C-3 hydroxyl group is indicated by the position of the nmr absorption at δ 3.19 in compound **5** and 3.20 in compound **9**. The 3α-proton signal in a large number of 3β-lanostane alcohols is known to occur at δ 3.18–3.30,[1,8,9,13-15] whereas the 3β proton in 3α alcohols is downfield from this.

Reduction of ketone **7** with sodium borohydride regenerated **5**. It has been reported previously that reduction of the 3-ketone function in lanostane derivatives with sodium borohydride leads to the 3β alcohol.[6] The location of the hydroxyl group is also very strongly indicated by the properties of the ketones **7**, **8**, and **13**. The nmr spectra of **7** and **8** show that the methyl groups at C-30 and -31 have been deshielded by the adjacent carbonyl when compared to the corresponding alcohols **5** and **9**. The C-30 and -31 methyls appear at δ 1.06 as a singlet in **7** and at 1.08 as a singlet in **8** and **13** whereas in the parent alcohols the 30 and 31 methyl groups appear upfield from δ 1.0 and appear as a doublet of methyl groups. This feature has been reported previously for 19-nor-4,4-dimethyl-5α-androstan-17β-ol-3-one.[16] The CD spectrum of **7**, $[\theta]_{302}$ −1552 (Figure 1), is essentially identical in appearance and amplitude with that of $\Delta^{9(11)}$-lanosten-3-one, $[\theta]_{302}$ −1556 (measured in our laboratory). The CD spec-

(13) N. Entwistle and A. D. Pratt, *Tetrahedron*, **24**, 3949 (1968).
(14) J. Fried, P. Grabowich, E. F. Sabo, and A. I. Cohen, *ibid.*, 2297 (1964).
(15) For a comparison of some 3α- and 3β-lanostane derivatives see H. K Adam, T. A. Bryce, I. M. Campbell, and N. J. McCorkindale, *Tetrahedro Lett.*, 1461 (1967).
(16) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectros copy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, 167.

trum indicates also the 5α configuration which has been found in all other sea cucumber sapogenins.

The location of the double bond was established by the following findings. There is a single olefinic proton in the nmr spectra of **8**, **9**, **10**, and **13**. The olefinic proton in **5** and **6** is masked because the proton at C-23 is superimposed upon it. There are three possible positions (Δ^5, Δ^7, or $\Delta^{9(11)}$) where the double bond could be located. From the CD spectrum (Figure 1) of **7** the 5,6 position could be excluded since the Cotton effect would be expected to be positive.[17] The 9,11 position was the most reasonable because of the very close resemblance of the CD spectrum of **7** with that of $\Delta^{9(11)}$-lanosten-3-one. The Cotton effect of Δ^7-lanosten-3-one is negative,[17] but its amplitude is different.[18] Very significant evidence for the $\Delta^{9(11)}$ position is found in the ORD spectrum of **10** prepared by chromic acid oxidation of **6** in refluxing acetic acid[19] (Figure 1). There is a very close resemblance to the spectrum of 12-oxolanost-9(11)-en-3β-yl acetate.[20] This similarity suggests a $\Delta^{9(11)}$ olefin with an 8β-hydrogen, 13β-carboalkoxy, and 14α-methyl group, since the ORD spectrum of a 6-oxo-7-ene chromophore would be expected to be opposite in sign.[21] The appearance of the olefinic proton signal in the nmr spectrum of **10** is very similar to that of the proton at C-11 in 12-oxolanost-9(11)-en-3β-yl acetate. There is a sharp doublet at δ 5.75 (J = 2 Hz) for the olefinic proton of **10** resulting from coupling with the axial 8β proton. The doublet disappears upon irradiation at δ 3.33 of the C-8 proton. This compares closely with the nmr spectra of the 12-oxo derivative of arborinol[18] and 12-oxolanost-9(11)-en-3β-yl acetate which show a sharp doublet (J = 2 Hz) for the olefinic proton resulting from coupling to the 8β proton.

The position of the acetoxy group in the side chain of **5** was established in the following manner. Both hydroxyl groups of **9** were shown to be secondary by acetylation and by nmr spectral analysis. This could also be clearly deduced by the nmr spectra of compounds **8** and **10**. Compound **9** upon treatment with acetic anhydride in pyridine yielded 23ξ-acetoxy-17-deoxy-7,8-dihydroholothurinogenin 3β-acetate (**6**), which was reduced with lithium aluminum hydride to the tetraol **11**. Tetraol **11** upon treatment with acetic anhydride–pyridine yielded a triacetate **12**, one of the hydroxyl groups not being acetylated because it is tertiary. The nmr spectrum of the triacetate **12** shows for the 18-CH_2OAc an AB quartet (J = 11 Hz, geminal coupling) which has been reported previously.[1,6] Treatment of the tetraol **11** with lead tetraacetate yields only starting material indicating that the acetoxy group in **5** is not at position 2 or 22.

Oxidation of **9** with Jones reagent led to the dione **13**, whose ir spectrum showed carbonyl absorption at 1755 (lactone) and at 1710 cm^{-1}. The carbonyl absorption at 1710 was larger than the lactone carbonyl absorption whereas in the mono ketone **8** the lactone carbonyl was slightly larger suggesting that the 1710-cm^{-1} band was being enhanced[22] by a new carbonyl group which is located in a six-membered ring or in the side chain. Dione **13** in neutral ethanol had essentially no uv spectrum but when the solution was made 0.01 M in potassium hydroxide an absorption appeared (λ_{max} 252 nm (ε 8300)). A 1,3 diketone was considered as a possible structure but was eliminated for the following reasons. 1,3-Diketolanostane derivatives are known[23] and have λ_{max} 256 nm (ε 11,000) in neutral ethanol and λ_{max} 286 nm (ε 24,000) in ethanol made 0.01 M in sodium hydroxide. Lanostane-1,3-dione and lanost-8-ene-1,3-dione readily form 3-acetoxylanost-2-en-1-one derivatives upon treatment with acetic anhydride in pyridine, whereas **13** did not form such a derivative. The strongest evidence that the acetoxy group is not in ring A comes from an examination of the properties of the 3-ethylene ketal **15**. The base peak in the mass spectrum of **15** is at m/e 99 indicating ring A is not substituted at position 1 or 2.[24] The ir spectrum of **15** shows carbonyl absorption at 1760 (lactone C=O) and at 1710 cm^{-1} indicating more clearly than could be seen in the spectrum of **13** that the carbonyl group is in the side chain or in a six-membered ring. Compound **15** showed essentially no uv absorption in neutral ethanol, but when the solu-

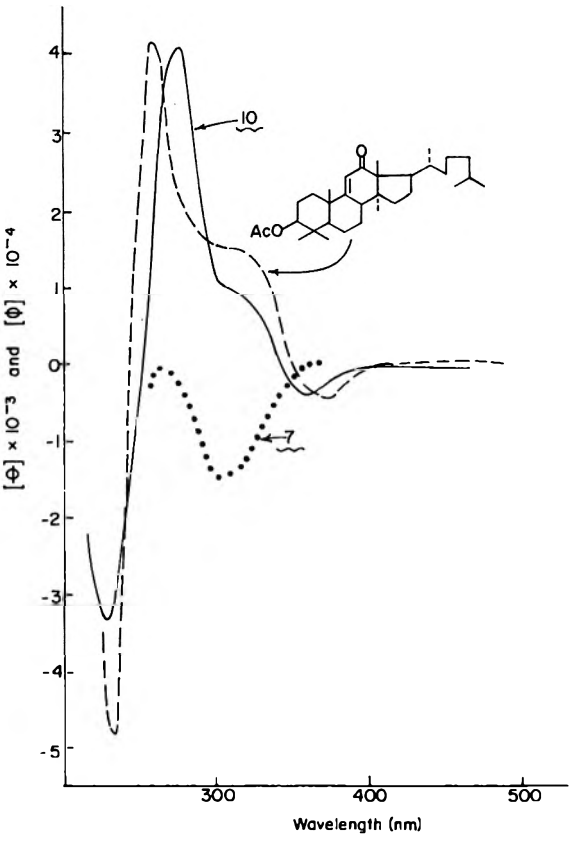


Figure 1.—CD spectrum of **7**, [θ]; ORD spectrum of **10** and 12-oxolanost-9(11)-en-3β-yl acetate, [φ].

(17) C. Djerassi, O. H. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, **80**, 4001 (1958).

(18) For the ORD spectrum of $\Delta^{9(11)}$-lanosten-3-one see H. Vorbrüggen, S. C. Pakrashi, and C. Djerassi, *Justus Liebigs Ann. Chem.*, **668**, 57 (1963).

(19) H. R. Bentley, J. A. Henry, D. S. Irvine, and F. S. Spring, *J. Chem. Soc.*, 3673 (1953).

(20) We wish to thank Dr. Richard Muccino of this laboratory for a sample of this compound.

(21) C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6377 (1956); J. A. Beisler and Y. Sato, *J. Org. Chem.*, **36**, 3946 (1971).

(22) R. N. Jones, D. A. Ramsay, D. S. Keir, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 80 (1952).

(23) D. H. R. Barton, P. J. L. Daniels, J. F. McGhie, and P. J. Palmer, *J. Chem. Soc.*, 3675 (1963).

(24) (a) Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 3722 (1964); (b) H. Audier, J. Bottin, A. Diara, M. Fétizon, P. Foy, M. Golfier, and W. Vetter, *Bull. Soc. Chim. Fr.*, 2292 (1964).

tion was made 0.01 *M* in potassium hydroxide an absorption appeared at λ 252 nm (ε 8300). Clearly the chromophore is not a lanostene-1,3-dione since the 3 position is tied up as an ethylene ketal and hence cannot be implicated.

Substitution at the 7 position could be excluded in the following manner. Ketone **15** and diketone **13** were dissolved in ethanol and made 0.01 *M* in potassium hydroxide. Each was then recovered and the ir spectrum taken. In each case no conjugated carbonyl absorption was present. The ir spectrum was essentially identical with the starting material ir. This excludes an 8-en-7-one.[23] A 6-one should not have uv absorption.

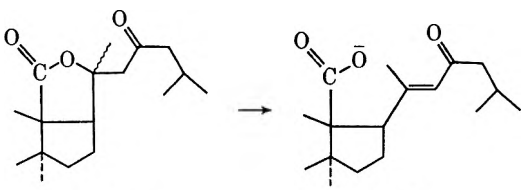
Ring D can be excluded for several reasons. The ir carbonyl absorption of **15** and **13** indicates that there is no carbonyl group in a five-membered ring. Furthermore the lack of chemical shift for the 32-methyl group downfield from δ 0.88 in **13** is indicative of the absence of a 15 ketone.[14,25] If the acetoxy group in **5** were in the 16 position, it would have to possess the α orientation. This can be seen from a comparison (Table I) of the molecular rotations of **5** *vs.* **9** and from

TABLE I
MOLECULAR ROTATIONS OF ACETATES AND ALCOHOLS

Compound	$[M]_D$ ($CHCl_3$)	$[M]_{acetate} - [M]_{alcohol}$
5	−102	−96
9	−6.40	
7	−189	−114
8	−75	

7 *vs.* **8**. The more negative value of the rotation of the acetates would indicate a 16α substituent.[26-28] The chemical shift for the 32-methyl group of **5** and all of its derivatives is upfield from δ 1.0. This is inconsistent with the 1–3 interaction of a 16α-oxygen and 32-methyl group.[6,7,29]

The location of the acetoxy group of **5** is thus limited to either the 23 or 24 positions. The 24 position can be excluded from the nmr spectrum of **13**. The nmr spectrum of 3β-acetoxylanost-8-en-24-one has been reported[30] with the 26- and 27-methyl group having signals at δ 1.03 and 1.14, respectively. This is inconsistent with the spectrum of **13**, in which the 26- and 27-methyl groups display a doublet centered at δ 0.93. Confirmation that the acetoxy group is at the 23 position is provided by the uv spectrum of **13** and **15** in basic ethanol and by the mass spectrum of some of the derivatives of **5**. The uv spectrum of **13** and **15**



13 or 15 16

in basic ethanol can be readily rationalized in terms of a base-catalyzed β elimination as shown above. The λ_{max} 252 nm of **16** is in reasonable agreement with the reported value of 248 nm for 5α-cholesta-9(11),20(22)-diene-3β,6α-diol-23-one.[31]

The mass spectal fragmentations shown in Table II

TABLE II
DIAGNOSTIC PEAKS IN THE MASS SPECTRA OF TRITERPENOID LACTONES

	Compound				
	5	7	8	9	13
M^+	514.36133	512	470.34131	472.352539	468
$M - C_4H_9$			413.26929	415.282227	411
$M - C_4H_9 + CO$					383
M − side chain	353.28829[a]	369	369.24365	371.260254	325[b]

[a] Loss of side chain and loss of water. [b] Loss of side chain and loss of CO_2.

are readily rationalized by structure **5**. Compounds **8** and **9** show loss of C_4H_9 and loss of the side chain ($C_6H_{13}O$). Both of these fragments would be expected to be the typical products[32] of α fission of a C-23 alcohol. In **5** and **7** there is a loss of $C_8H_{15}O_2$ which represents loss of the side chain containing an acetoxy group. The diketone **13** shows loss of C_4H_9 and C_4H_9 + CO. This can be represented as α fission at the carbonyl followed by loss of CO, typical fragments that would be expected from a C-23 ketone.[32]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. All optical rotations were determined using chloroform as solvent. Infrared spectra were obtained using a Perkin-Elmer Model 421 grating spectrophotometer. Ultraviolet spectra were measured in 95% ethanol and in the cases mentioned in 95% ethanol made 0.01 *M* in potassium hydroxide on a Cary 14 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian HA-100 or XL-100 spectrometer using deuteriochloroform as solvent. Tetramethylsilane was used as internal reference and line positions are given in the δ scale. Microanalyses were carried out by Messrs. E. Meier and J. Consul. Low-resolution mass spectra (70 eV) were carried out on AEI MS-9, Atlas CH-4, and Varian MAT 711 instruments with direct inlet systems. High-resolution spectra were determined on the MS-9 and MAT-711 instruments.

Gas–liquid chromatography (glpc) was carried out on a Hewlett-Packard 402 high efficiency instrument with glass columns packed with 3% of OV-25 on Gas-Chrom Q (100–120 mesh) from Applied Science Laboratories, Inc. Column chromatography was carried out using Davison 50–200 mesh activated silica gel and E. Merck neutral, activity grade II, aluminum oxide. Analytical thin layer chromatography (tlc) was carried out on 5 × 20 cm, 250-μ silica gel HF_{254} plates. When necessary, substances were made visible by exposure to iodine vapors or by spraying with ceric sulfate solution (2% in 1 *M* sulfuric acid) followed by heating on a hot plate. Preparative-scale tlc was carried out or 20 × 20 cm, 1000-μ silica gel HF_{254} plates.

We thank Dr. L. J. Durham for the nmr spectra, Mr. R. Ross, Mr. R. Conover, and Miss A. Wegeman for the mass spectra, and Mrs. R. Records for the ORD spectra.

Isolation of the Saponin from *Stichopus chloronotus*.[33]—Dried skins (500 g) from *Stichopus chloronatus* were stirred in a blender

(25) A. I. Cohen, D. Rosenthal, G. W. Krakower, and J. Fried, *Tetrahedron*, **21**, 3171 (1965).
(26) F. C. Chang and C. K. Chiang, *Chem. Commun.*, 1156 (1968).
(27) A. Bowers, T. G. Halsall, and G. C. Sayer, *J. Chem. Soc.*, 3070 (1954).
(28) W. Klyne and W. M. Stokes, *ibid.*, 1979 (1954).
(29) For the interaction of a 16α-hydroxy or acetoxy group on the 32-methyl substituent in cucurbitanes see D. Lavie, B. S. Benjaminov, and Y. Shvo, *Tetrahedron*, **20**, 2585 (1964).
(30) D. H. R. Barton, D. M. Harrison, G. P. Moss, and D. A. Widdowson, *J. Chem. Soc. C*, 775 (1970).
(31) Y. M. Sheikh, B. M. Tursch, and C. Djerassi, *J. Amer. Chem. Soc.* **94**, 3278 (1972).
(32) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967
(33) This experiment was carried out by Dr. R. J. Liedtke.

with 2 l. of 75% ethanol and allowed to stand overnight. This was filtered through Celite and then extracted a second time with 2 l. of 50% ethanol and filtered. The combined filtrates were evaporated at reduced pressure on a rotary evaporator. The residue was dissolved in 1 l. of water and carefully washed with benzene. The aqueous layer was extracted with 1-butanol (1 l.). The 1-butanol was evaporated, and the residue was dissolved in water (500 ml) and washed with ethyl ether. The saponin was removed from the aqueous layer by extraction into butanol. After evaporation of the butanol there was obtained 22 g of crude saponin. This was found to be toxic to guppies.

Isolation of 23ξ-Acetoxy-17-deoxy-7,8-dihydroholothurinogenin (5).—Saponin (21 g) was dissolved in 1 l. of 2.5 *N* hydrochloric acid and heated on a steam bath for 3 hr. After cooling the mixture was extracted with chloroform. The chloroform was washed with water and sodium bicarbonate, dried (magnesium sulfate), and evaporated to give 15 g of semisolid. Chromatography on silica gel (700 g) using gradient elution with benzene–ether and several recrystallizations gave 1.1 g of **5** in greater than 90% purity by glpc. Nonhomogeneous materials showed a single spot by tlc identical with pure genin **5**: mp 223–224° (from methanol); $[\alpha]^{20}D$ −20° (*c* 0.74); ir (KBr) 3430 (broad), 1760 (lactone C=O), 1735 (ester C=O), 1450, 1370, 1240, 1170, 1030, 940 cm^{-1}; essentially no uv absorption above 210 nm; nmr δ 0.83 (3, s, CH_3-32), 0.87 (3, s, CH_3-31), 0.91 (6, d, *J* = 6 Hz, CH_3-26, 27), 0.98 (CH_3-30), 1.15 (3, s, CH_3-19), 1.40 (3, s, CH_3-21), 2.03 (3, s, $OCOCH_3$), 2.95 (1, broad, CH-8), 3.19 (1, broad, CH-3), 5.17 (2, broad, CH-11 and CH-23); mass spectrum *m/e* (rel intensity) 514 (23, M^+), 512 (3), 499 (3, M − CH_3), 496 (2, M − H_2O), 481 (2, M − CH_3 + H_2O), 454.34204 (4, M − CH_3COOH requires 454.34448), 439.31958 (8, M − CH_3COOH + CH_3 requires 439.32104), 421.31128 (9, M − CH_3COOH + H_2O + CH_3 requires 421.31055), 395.32910 (25, M − CO_2 + CH_3COOH + CH_3 requires 395.33130), 353.24829 (3, M − side chain ($C_8H_{15}O_2$) + H_2O requires 353.24780), 95 (16), 81 (24), 69 (28), 55 (25), 43 (100).

Anal. Calcd for $C_{32}H_{50}O_5$: C, 74.65; H, 9.80; mol wt, 514.36572. Found: C, 74.69; H, 9.60; mol wt (mass spectrometry), 514.36133.

Preparation of 23ξ-Acetoxy-17-deoxy-7,8-dihydroholothurinogenin 3β-Acetate (6).—Compound **5** (0.650 g) was treated with 1:1 pyridine–acetic anhydride at room temperature and worked up in the usual way. The crude reaction product was chromatographed on silica gel and recrystallized from methanol–water to give 0.602 g of **6**: mp 192–194°; $[\alpha]^{20}D$ −3.28 (*c* 0.6); ir (KBr) 1760 (lactone C=O), 1735 (ester C=O), 1460, 1370, 1240, 1170, 1130, 1030 cm^{-1}; essentially no uv absorption above 210 nm; nmr δ 0.85 (6, s, CH_3-31, 32), 0.90 (3, s, CH_3-30), 0.91 (6, d, *J* = 6 Hz, CH_3-26, 27), 1.17 (s, CH_3-19), 1.40 (s, CH_3-21), 2.02 (6, s, $OCOCH_3$), 2.95 (1, broad, CH-8), 4.50 (1, M, CH-3), 5.18 (2, broad, CH-11 and CH-23); mass spectrum *m/e* (rel intensity) 556 (71, M^+), 554 (7), 541 (7, M − CH_3), 496 (23, M − AcOH), 481 (24, M − AcOH + CH_3), 437 (64, M − AcOH + CO_2 + CH_3), 436 (7, M − 2 AcOH), 421 (51, M − 2 AcOH + CH_3), 353 (7, M − side chain + CH_3COOH), 325 (18), 127 (37), 109 (62), 81 (42), 69 (50), 55 (97), 43 (100).

Anal. Calcd for $C_{34}H_{52}O_6$: C, 73.33; H, 9.42. Found: C, 73.60; H, 9.23.

23ξ-Acetoxy-17-deoxy-7,8-dihydro-3-holothurinogenone (7).—Compound **5** (20 mg) was dissolved in 15 ml of acetone and cooled to 0°. Jones reagent (CrO_3, 10 g, and sulfuric acid, 8.0 g, diluted to 37 ml with water) was added slowly with stirring until an orange color persisted. The excess oxidizing agent was destroyed by adding 2-propanol and work-up in the usual manner, and recrystallization from methanol–water gave 15 mg of **7**: mp 217–218°; $[\alpha]^{20}D$ −37° (*c* 0.4); CD (dioxane) $[\theta]_{302}$ −1552; ir (KBr) 1760 (lactone C=O), 1735 (ester C=O), 1710 (C=O in six-membered ring), 1460, 1435 (methylene adjacent to C=O in a six-membered ring), 1375, 1280, 1245, 1165, 1140, 1110, 1010, 935 cm^{-1}; nmr δ 0.86 (3, s, CH_3-32), 0.93 (6, d, *J* = 6 Hz, CH_3-26, 27), 1.06 (6, s, CH_3-30, 31), 1.34 (3, s, CH_3-19), 1.40 (3, s, CH_3-21), 3.0 (1, m, CH-8), 5.22 (2, broad, CH-11 and CH-23); mass spectrum *m/e* (rel intensity) 512 (82, M^+), 510 (9), 497 (4, M − CH_3), 452 (49, M − AcOH), 437 (34, M − AcOH + CH_3), 407 (24), 393 (100, M − AcOH + CO_2 + CH_3), 369 (7, M − side chain ($C_8H_{15}O_2$)), 323 (19), 295 (29), 281 (27), 269 (24), 255 (15), 171 (13), 157 (12), 145 (18), 127 (32), 109 (35), 95 (27), 81 (35), 69 (37), 55 (40), 43 (61).

Anal. Calcd for $C_{32}H_{48}O_5$: C, 74.95; H, 9.44. Found: C, 74.90; H, 9.17.

Reduction of Ketone 7.—Ketone **7** (10 mg) in 6 ml of dioxane and 0.4 ml of water was allowed to react with 15 mg of sodium borohydride at room temperature for 4 hr. Work-up in the usual manner, gradient elution chromatography on alumina (benzene–ether), and recrystallization gave 3 mg of material identical with **5** by ir, mass spectrum, mp, mmp, and tlc.

23ξ-Hydroxy-17-deoxy-7,8-dihydro-3-holothurinogenone (8).—Keto acetate **7** (25 mg) was hydrolyzed by refluxing with 5% potassium hydroxide in methanol, worked up in the usual way to give 20 mg of crude product, and recrystallized (methanol–water) to give pure **8**: mp 174–176°; $[\alpha]^{20}D$ −16° (*c* 0.3); ir (KBr) 3450, 1755 (lactone C=O), 1705 (C=O at C_3), 1460, 1380, 1260, 1160, 1110, 1030, 940, 800 cm^{-1}, shows essentially no uv absorption above 210 nm; nmr δ 0.88 (3, s, CH_3-32), 0.92 (6, d, *J* = 6 Hz, CH_3-26, 27), 1.08 (6, s, CH_3-30, 31), 1.34 (3, s, CH_3-19), 1.53 (3, s, CH_3-21), 3.98 (1, m, CH-23), 5.27 (1, m, CH-11); mass spectrum *m/e* (rel intensity) 470 (100, M^+), 468 (19), 455 (7, M − CH_3), 452 (4, M − H_2O), 437 (7, M − CH_3 + H_2O), 413.26929 (12, M − C_4H_9 by high-resolution mass spectrum), 407 (8), 393.31665 (20, M − CH_3 + CO_2 + H_2O), 384.26538 (23, M − $C_5H_{10}O$ (ring A cleavage[34] or side chain cleavage), 369.24365 (35, M − $C_6H_{13}O$ (side chain)), 325.25024 (14, M − $C_6H_{13}O$ + CO_2), 69 (43), 57 (50), 55 (45), 43 (40).

Anal. Calcd for $C_{30}H_{46}O_4$: mol wt, 470.33961. Found: mol wt (mass spectrometry), 470.34131.

Oxidation of 23ξ-Acetoxy-17-deoxy-7,8-dihydroholothurinogenin 3β-Acetate (6).—Compound **6** (200 mg) was dissolved in 25 ml of acetic acid, heated to reflux, and stirred. Over the course of 1 hr chromic acid (100 mg) in 25 ml of acetic acid was added. After addition was complete the reaction mixture was refluxed for 1 hr. The acetic acid was then largely evaporated at reduced pressure. The residue was worked up in the usual manner, chromatographed on 20 g of alumina using gradient elution with benzene–ether, and recrystallized from methanol–water to give 65 mg of pure **10**: mp 259–260°; ORD (dioxane, *c* 0.27) $[\phi]_{361}$ −3615, $[\phi]_{350}$ −3081, $[\phi]_{273}$ +41,300, $[\phi]_{230}$ −33,044; ir (KBr) 1760 (lactone C=O), 1735 (ester C=O), 1675 (conjugated C=O), 1470, 1370, 1240, 1170, 1130, 1095, 1020 cm^{-1}; uv λ_{max} 251 nm (ε 10,565), position and ε not changed when made 0.01 *M* in potassium hydroxide; nmr δ 0.86 (3, s, CH_3-31), 0.88 (3, s, CH_3-32), 0.91 (6, d, *J* = 6 Hz, CH_3-26, 27), 0.94 (3, s, CH_3-30), 1.34 (3, s, CH_3-19), 1.44 (3, s, CH_3-21), 2.04 (6, s, $OCOCH_3$), 2.96 (1, t, *J* = 6 Hz, CH-17), 3.33 (1, broad m, CH-8), 4.50 (1, broad m, CH-3), 5.20 (1, broad m, CH-23), 5.75 (1, d, *J* = 2 Hz); mass spectrum *m/e* (rel intensity) 570 (16, M^+), 510 (100, M − AcOH), 495 (6, M − AcOH + CH_3), 451 (30, M − AcOH + CO_2 + CH_3), 427 (8, M − side chain), 367 (3, M − side chain + AcOH), 359 (30), 341 (18), 269 (43), 69 (30), 55 (35), 43 (66).

Anal. Calcd for $C_{34}H_{50}O_7$: C, 71.53; H, 8.83. Found: C, 71.69; H, 8.55.

Lithium Aluminum Hydride Reduction of Diacetate 6.—Diacetate **6** (20 mg) was allowed to react with lithium aluminum hydride in refluxing tetrahydrofuran for 5 hr, discharged with ethyl acetate, and worked up with saturated sodium sulfate in the usual way. Recrystallization (tetrahydrofuran–hexane) gave 17 mg of **11**: mp 223–226°; ir (KBr) 3400, 1460, 1370, 1180, 1100, 1050, 1030, 970, 860, 790 cm^{-1}; mass spectrum *m/e* (rel intensity) 476 (3, M^+), 458 (10, M − H_2O), 443 (4, M − H_2O + CH_3), 440 (18, M − H_2O + H_2O), 428.364258 (13, M − CH_2 + H_2O requires 428.365234), 425.339355 (10, M − CH_3 + H_2O + H_2O requires 425.341797), 413,342773 (43, M − CH_2O + CH_3 + H_2O requires 413.341797), 357.277100 (71, M − $C_6H_{13}O$ (cleavage between C_{20} and C_{22}) + H_2O), 357.279297, 299.237061 (55, $C_{21}H_{31}O$ requires 299.237305), 145 (92), 85 (100), 43 (90).

Anal. Calcd for $C_{30}H_{52}O_4$: mol wt, 476.38656. Found: mol wt (mass spectrometry), 476.38647.

Acetylation of the Tetraol 11.—Tetraol **11** (220 mg) was acetylated by heating with acetic anhydride–pyridine (1:1) on a steam bath for 2 hr and worked up in the usual manner. Chromatography on alumina using gradient elution (benzene–ether) gave 190 mg of crude triacetate as an oil and recrystallization (hexane) gave **12** as a white solid: mp 137–139°; $[\alpha]^{20}D$ + 59° (*c* 0.5); ir (KBr) 1735 (ester C=O), 1460, 1370, 1240, 1025, 980 cm^{-1}; nmr δ 0.88 (6, s, CH_3-31, 32), 0.90 (3, s, CH_3-30), 0.94 (6, d, *J* = 6 Hz, CH_3-26, 27), 1.13 (3, s, CH_3-19), 1.35 (3, s, CH_3-21), 2.05 (3, s, $OCOCH_3$), 2.06 (6, s, $OCOCH_3$), AB quartet at 3.90 and at 4.46 (1 each, *J* = 11 Hz, CH_2-18), 4.50 (1, m,

(34) R. H. Shapiro and C. Djerassi, *Tetrahedron*, **20**, 1987 (1964).

CH-3), 5.22 (2, m, CH-11 and CH-23); mass spectrum *m/e* (rel intensity) 602 (2, M^+), 584 (10, M − H_2O), 527 (4, M − CH_3COOH + CH_3), 524 (60, M − CH_3COOH + H_2O), 511 (4, M − CH_2OAc + H_2O), 464 (40, M − CH_3COOH + CH_3CO-OH + H_2O), 459 (5, M − $C_8H_{15}O_2$ (cleavage between C_{20} and C_{22}), 451 (100, M − CH_2OAc + CH_3COOH + H_2O), 449 (60, M − CH_3COOH + CH_3COOH + CH_3 + H_2O), 399 (12, M − $C_8H_{15}O_2$ (cleavage between C_{20} and C_{22}) + CH_3COOH), 225 (65), 109 (50), 69 (48), 43 (67).

Anal. Calcd for $C_{36}H_{58}O_7$: C, 71.71; H, 9.70. Found: C, 72.03; H, 9.72.

Hydrolysis of Triacetate 12.—The triacetate 12 (20 mg) was hydrolyzed by refluxing with 5% potassium hydroxide in methanol, worked up in the usual way, and recrystallized (hexane) to give 15 mg of material identical (tlc, ir, mp and mmp) with tetraol 11.

Attempted Cleavage of Tetraol 11 with Lead Tetraacetate.—Tetraol 11 (20 mg) dissolved in 5 ml of acetic acid to which 40 mg of lead tetracetate was added, was allowed to react at room temperature for 24 hr. The acetic acid was lyophilized, water added (30 ml), and the water lyophilized. The residue was extracted with dichloromethane and the dichloromethane washed with water, dried, and evaporated. The ir spectrum of the residue shows no carbonyl absorption and tlc shows only starting material. Chromatography on alumina was carried out to give 14 mg of material which after recrystallization (tetrahydrofuran–hexane) was identical with starting tetraol 11 by tlc, mp, mmp, and ir spectra.

23ξ-Hydroxy-17-deoxy-7,8-dihydroholothurinogenin (9).—Compound 5 (20 mg) was refluxed with 5% potassium hydroxide in methanol for 30 min, worked up in the usual way, and recrystallized (methanol–water) to give 11 mg of diol 9: mp 233–236°; $[\alpha]^{20}D$ − 1.35 (*c* 0.4); ir (KBr) 3450, 1760 (lactone C=O), 1460, 1370, 1260, 1090, 1020, 940, 800 cm^{-1}; nmr δ 0.82 (3, s, CH_3-32), 0.87 (3, s, CH_3-31), 0.91 (6, d, *J* = 6 Hz, CH_3-26, 27), 0.98 (3, s, CH_3-30), 1.15 (3, s, CH_3-19), 1.50 (3, s, CH_3-21), 2.95 (1, m, CH-8), 3.20 (1, m, CH-3), 5.17 (1, m, CH-11); mass spectrum *m/e* (rel intensity) 472 (100, M^+), 470 (15), 457 (12, M − CH_3), 454 (5, M − H_2O), 439 (13, M − CH_3 + H_2O), 421.307129 (10, M − H_2O + 2H + CH_3 requires 421.310547), 415.282227 (10, M − C_4H_9 (cleavage between C_{23} and C_{24}) requires 415.284668), 413.339111 (8, M − CO_2 + CH_3 requires 413.341797), 411.323730 (7, M − CO + CH_3 + H_2O requires 411.326172), 395.331543 (13, M − CO_2 + CH_3 + H_2O requires 395.331299), 386.281738 (9 ($C_{25}H_{38}O_3$), cleavage between C_{22} and C_{23} with loss of one hydrogen requires 386.281982), 371.260254 (17, M − loss of side chain ($C_6H_{13}O$) requires 371.258545), 353.248291 (31, M − loss of side chain ($C_6H_{13}O$) + H_2O requires 353.247803), 309.256348 (8, M − loss of side chain ($C_6H_{13}O$) + H_2O + CO_2 requires 309.258057), 267 (12), 95 (30), 69 (55), 55 (44), 43 (48).

Anal. Calcd for $C_{30}H_{48}O_4$: mol wt, 472.354980. Found: mol wt (mass spectrometry), 472.352539.

23-Oxo-17-deoxy-7,8-dihydro-3-holothurinogenone (13).—The diol 9 (15 mg) was oxidized with Jones reagent as described for 7 and the product recrystallized (methanol–water) to give 13 mg of 13: mp 190–192°; $[\alpha]^{20}D$ −17° (*c* 0.3); CD (dioxane) $[\theta]_{300}$ − 1665; ir (KBr) 1755 (lactone C=O), 1710 (ketone at C_3 and at C_{23}), 1465, 1450, 1370, 1280, 1160, 1110, 1010, 940 cm^{-1}; uv, essentially no absorption in neutral ethanol; uv λ_{max} 252 (ε 8300) in ethanol 0.01 *M* in potassium hydroxide; nmr δ 0.88 (3, s, CH_3-32), 0.93 (6, d, *J* = 6 Hz, CH_3-26, 27), 1.08 (6, s, CH_3-30, 31), 1.36 (3, s, CH_3-19), 1.50 (3, s, CH_3-21), 2.98 (2, s, CH_2-22), 5.25 (1, m, CH-11); mass spectrum *m/e* (rel intensity) 468 (100, M^+), 453 (13, M − CH_3), 411 (3, M − C_4H_9), 407 (50), 383 (10, M − C_4H_9 + CO), 325 (30, M − side chain ($C_6H_{11}O$) + CO_2), 323 (50), 85 (50), 57 (55), 43 (63).

Anal. Calcd for $C_{30}H_{44}O_4$: C, 76.86; H, 9.47. Found: C, 76.97; H, 9.34.

Preparation of Ethylene Ketal Derivative of 7.—23-Acetoxy 3-ketone 7 (12 mg) was dissolved in 100 ml of benzene and 0.20 ml of ethylene glycol and 10 mg of *p*-toluenesulfonic acid (monohydrate) added and refluxed for 18 hr using a Dean–Stark trap. The reaction mixture was then poured into saturated potassium carbonate solution. The benzene layer was separated and washed with saturated potassium carbonate, water, dried (magnesium sulfate), and evaporated. After partial evaporation the ir spectrum (benzene) showed absorption at 1755 (lactone C=O) and at 1730 (ester C=O) but none at 1700 cm^{-1}. The residue after evaporation was dissolved in 10 ml of methanol and 500 mg of potassium hydroxide added and refluxed for 30 min. The reaction mixture was poured into water and extracted with ether. The ether was dried and evaporated, and the residue chromatographed on 2 g of basic activity grade II alumina using gradient elution chromatography with benzene–ether. Recrystallization (methanol) gave 5 mg of 14: mp 229–233; $[\alpha]^{20}D$ −10° (*c* 0.4); ir (benzene) 3600, 1760 (lactone C=O), 1550, 1250, 1080, 800 cm^{-1}; mass spectrum *m/e* (rel intensity) 514 (30, M^+), 512 (3), 499 (6, M − CH_3), 457 (7, M − C_4H_9), 415 (65), 413 (13, M − side chain ($C_6H_{13}O$)), 397 (42), 329 (100), 99 (60).

Anal. Calcd for $C_{32}H_{50}O_5$: mol wt, 514. Found: mol wt (mass spectrometry), 514.

Oxidation of Ethylene Ketal Derivative 14.—Ethylene ketal 14 (5 mg) was dissolved in 0.5 ml of pyridine and added to 1.0 ml of pyridine to which 20 mg of chromic acid had been previously added. The reaction mixture was stirred at room temperature for 18 hr and then poured into ether and water. The water was extracted with ether and the combined ether washed with water, dried, and evaporated. The residue was chromatographed on 3 g of basic alumina (activity II) using gradient elution chromatography with benzene–ether and recrystallized (benzene–hexane) to give 2 mg of 15: mp 233–236°; ir (KBr) 1760 (lactone C=O), 1710 (side chain C=O), 1450, 1370 (ketal 1160, 1135, 1110, 1060), 1010, 940 cm^{-1}; essentially no uv in neutral ethanol, uv λ_{max} 252 (ε 8320) when in 0.01 *M* potassium hydroxide in ethanol; mass spectrum *m/e* (rel intensity) 512 (8, M^+), 497 (3, M − CH_3), 413 (25), 329 (11), 99 (100).

Anal. Calcd for $C_{32}H_{48}O_5$: mol wt, 512. Found: mol wt (mass spectrometry) 512.

Recovery of the Uv-Absorbing Material.—3-Ethylene ketal 23-one 15 (0.5 mg) was dissolved in 5 ml of ethanol containing 0.01 *M* potassium hydroxide (uv λ_{max} 252 (ε 8300)) and the solution poured into water and extracted with chloroform. The chloroform was washed well with water, dried, and evaporated. The ir spectrum of the residue was essentially identical with starting material ir with no carbonyl absorption below 1710 cm^{-1}. The same experiment was carried out with diketone 13 to give the same results.

Registry No.—**5**, 36872-76-1; **6**, 36872-77-2; **7**, 36872-78-3; **8**, 36872-79-4; **9**, 36872-80-7; **10**, 36872-81-8; **11**, 36871-79-1; **12**, 36871-80-4; **13**, 36871-81-5; **14**, 36871-82-6; **15**, 36871-83-7.

Geissovelline, a New Alkaloid from *Geissospermum vellosii*

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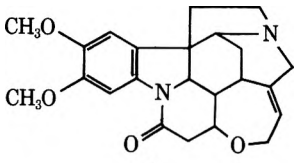
Geissovelline, $C_{23}H_{30}N_2O_4$, is a new dihydroindole alkaloid from the bark extract of Brazilian *Geissospermum vellosii*. Based on the chemistry of the unusual functional groups, *e.g.*, a tertiary nitrogen which interacts transannularly with an α,β-unsaturated ketone carbonyl, structure **3** is proposed for geissovelline and is supported by complete analyses of proton and carbon-13 nmr spectra of deacetylgeissovelline (**28**). The reactions of this alkaloid are unparalleled. Deacetylgeissovelline is readily pyrolyzed to 1-ethyl-6,7-dimethoxycarbazole. Lead tetraacetate oxidation of deacetylgeissovelline prior to pyrolysis, on the other hand, leads to compound **6**.

A detailed procedure for the separation of the alkaloid-rich bark extract of Brazilian *Geissospermum vellosii* into various fractions using liquid–liquid extraction at different pH's has been described.[2] Further purification of the weakly basic fraction B or fraction 1[3] by chromatography on alumina has resulted in the isolation of a new crystalline alkaloid, geissovelline, and the structure determination and chemistry of this new alkaloid is the subject of the present report.

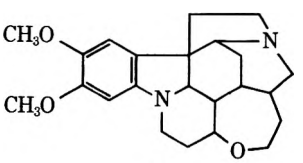
Structure Determination.—Geissovelline, a moderately basic alkaloid (pK_a = 6.7), has the molecular formula $C_{23}H_{30}N_2O_4$ and shows the presence of two OCH_3, one NCH_3, and two CCH_3 groups. The infrared spectrum of geissovelline shows no OH or NH absorption but exhibits a strong amide carbonyl band at 1659 cm^{-1}. Its ultraviolet spectrum is typical of an *N*-acyldialkoxyindoline and yet noticeably different from the spectrum of brucine (**1**) (Figure 1). However, when geissovelline is protonated, its ultraviolet absorption is comparable to that of **1** (which is unaffected



1

by acid), suggesting the presence of a second chromophore in geissovelline which is transparent in acid.

When geissovelline is treated with 1 *N* acid, acetic acid and deacetylgeissovelline, $C_{21}H_{28}N_2O_3$, are produced. The ultraviolet spectrum of deacetylgeissovelline resembles that of a 5,6-dialkoxyindoline but there are appreciable differences in the peak intensities when one compares it with the spectrum of a typical model compound such as dihydrobrucidine (**2**) (Figure 2). Both deacetylgeissovelline and **2**, however, show similar ultraviolet spectra in acid. In the infrared

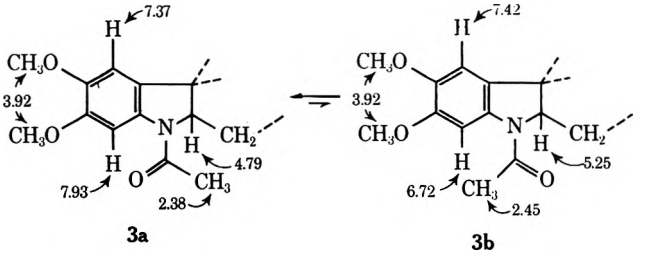


2

spectrum of deacetylgeissovelline a new band has appeared at 3338 cm^{-1} for the indoline NH and the amide carbonyl absorption has disappeared. Geissovelline is regenerated when deacetylgeissovelline is treated with acetic anhydride in pyridine.

Singlet peaks at δ 6.25 and 7.22 in the nmr spectrum of deacetylgeissovelline are ascribed to two aromatic protons which are para to each other and ortho and meta, respectively, to the indoline NH. The remaining two positions of the aromatic ring are occupied by the two methoxyl substituents as shown by nmr signals at δ 3.76 and 3.81.

In geissovelline the indoline NH is acetylated. The nmr spectrum of geissovelline (Figure 3), however, is complex owing to the presence of the *N*-acetyl group, as the rate of rotation for the amide *N*-carbonyl bond is slow enough at 25° that absorptions for two conformers are observed. The *N*-acetyl protons, for example, appear as 2:1 singlets at δ 2.38 and 2.45 for the cisoid and transoid conformers, respectively. At 100° the interconversion of the two conformers is faster and the *N*-acetyl peaks coalesce to a single peak at δ 2.38. A comparison of the nmr spectra of geissovelline and deacetylgeissovelline indicates that a proton is present on the α carbon of the indoline ring. This proton, which appears as doublets of doublets (J = 12 and 6.5 Hz) at δ 4.79 and 5.25 for the two geissovelline conformers (**3a** and **3b**) and as a single absorption at δ 4.26 for deacetylgeissovelline, is coupled with two protons on adjacent carbons. No β hydrogens are present on the indoline ring, as geissovelline is not oxidized to an *N*-acetyl-5,6-dimethoxyindole with lead tetraacetate and is recovered unchanged. It is therefore concluded that the two protons are on a methylene group that is also attached to the α position of the indoline ring.



3a **3b**

The singlet at δ 1.90 in the nmr spectrum of geissovelline (δ 1.86 for deacetylgeissovelline) is ascribed to an *N*-methyl group, as this signal is shifted paramagnetically about 1 ppm after protonation. One of the two

(1) National Institutes of Health Predoctoral Fellow, 1959–1962, University of California, Berkeley.

(2) H. Rapoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Amer. Chem. Soc.*, **80**, 1601 (1958).

(3) H. Rapoport and R. E. Moore, *J. Org. Chem.*, **27**, 2981 (1962).

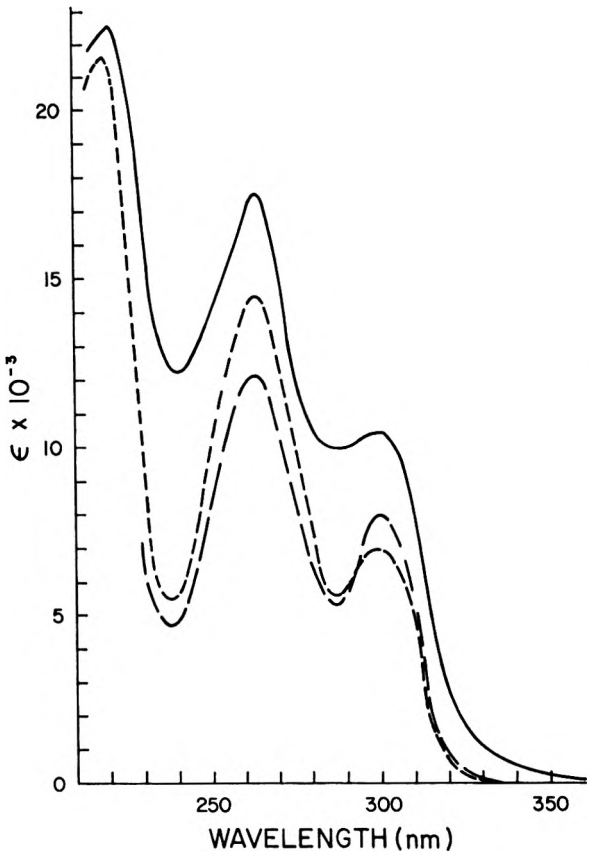


Figure 1.—Comparison of the ultraviolet spectra of geissovelline in ethanol (——) and 0.01 *N* ethanolic hydrochloric acid (- - - -) and brucine in ethanol (— —).

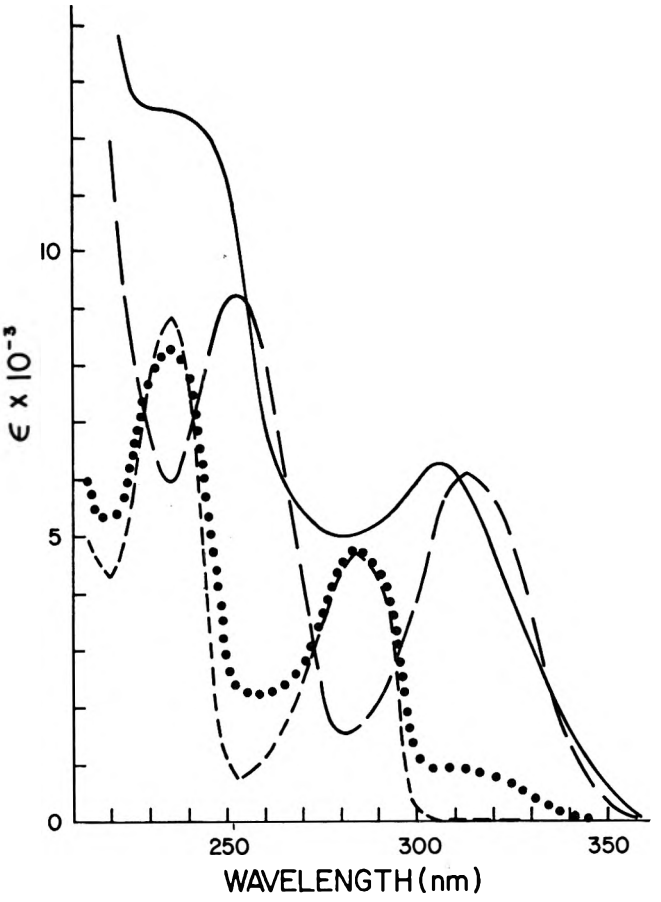
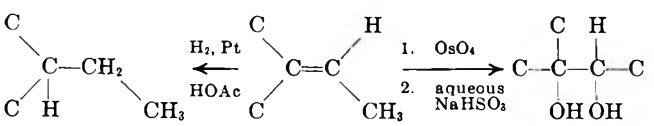


Figure 2.—Comparison of the ultraviolet spectra of deacetylgeissovelline in ethanol (——) and 0.1 *M* ethanolic hydrochloric acid (- - -), and dihydrobrucidine in ethanol (— —) and 0.1 *N* ethanolic hydrochloric acid (· · · ·). The shoulder at 310 nm in curve · · · · is due to incomplete protonation of the indoline nitrogen of dihydrobrucidine in 0.1 *N* ethanolic hydrochloric acid.

CCH_3 groups of geissovelline is the indoline *N*-acetyl group and the other an ethylidene group, as shown from a doublet at δ 1.71 (J = 7.7 Hz) for the methyl protons and two 1:3:3:1 quarters at δ 6.52 and 6.45 for the olefinic proton of the two geissovelline conformers **3a** and **3b**, respectively.

The presence of the olefinic double bond was demonstrated chemically when it was found that geissovelline catalytically absorbs 1 mol of hydrogen and reacts with 1 mol of osmium tetroxide. The dihydrogeissovelline obtained from catalytic hydrogenation exhibits its CCH_3 absorption as a perturbed triplet at δ 0.9 and apparently is a mixture of *C*-ethyl epimers as indicated by its melting point range. Kuhn–Roth oxidation of the dihydrogeissovelline now gave propionic acid, proving that the ethylidene group had been converted to an ethyl group. The dihydroxydihydrogeissovelline resulting from cis hydroxylation exhibits its methyl absorption as a doublet at δ 1.08 and also appears to be a mixture of epimers from its melting point range. No hydrogen is attached to the carbon bearing the ethylidene group, as no other olefinic proton signals are observed in the nmr spectrum of geissovelline. Furthermore, a nitrogen or oxygen cannot be attached to the ethylidene double bond, as the chemical shift of the olefinic proton in such an environment should resonate at higher field. Carbons must therefore be attached to the ethylidene double bond.



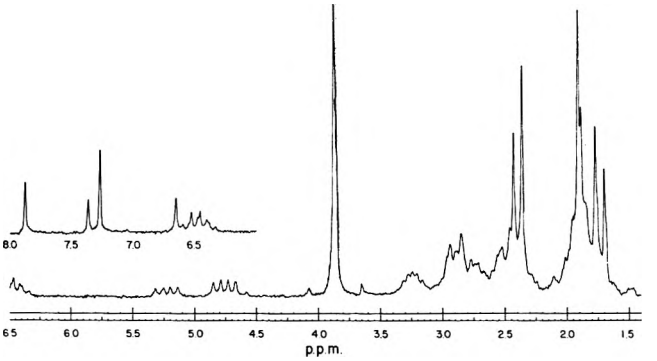
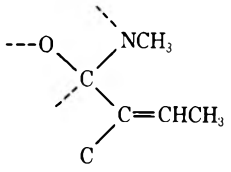


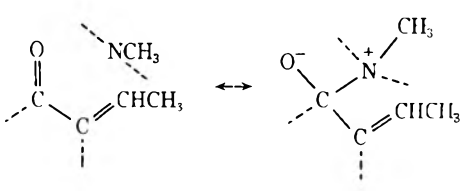
Figure 3.—The 100-MHz proton nmr spectrum of geissovelline in chloroform-*d*.

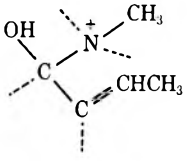
Treatment of geissovelline with sodium borohydride produces the same dihydrogeissovelline obtained by catalytic hydrogenation. Similarly, deacetylgeissovelline is reduced to a deacetyldihydrogeissovelline which is identical with the acid hydrolysis product of dihydrogeissovelline. Surprisingly, the CCH_3 protons of the ethylidene group could be exchanged for deuterium when geissovelline was treated with sodium ethoxide in ethanol-*O*-*d*. To account for both the reduction of the olefinic double bond by borohydride and the acidity of the methyl protons of the ethylidene group, a carbonyl group had to be in conjugation with the olefinic double bond. The ultraviolet spectrum of geissovelline

had already suggested the presence of a second chromophore, but, if this chromophore was due to an α,β-unsaturated ketone, it was not apparent why such a system should become transparent to uv on acidification. In addition the infrared spectrum of deacetylgeissovelline did not show an absorption band typical of an α,β-unsaturated ketone. Structures in which the ketone carbonyl was masked were considered but all were finally eliminated. A carbinolamine structure, for example, could be immediately ruled out, as geissovelline showed no OH absorption in the infrared. An azaketal structure could also be rejected, as it was not compatible with the ultraviolet spectral properties.



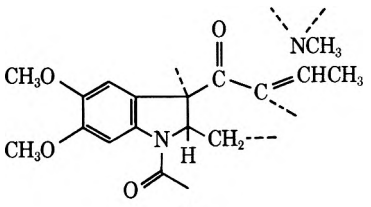
The masked carbonyl structures were completely rejected when the carbon-13 nmr spectrum of geissovelline revealed the presence of two carbonyl absorptions. The signal at δ 167.1 was clearly due to the amide carbonyl, but the signal at δ 184.3 could only be attributed to an α,β-unsaturated ketone. In the infrared spectrum of deacetylgeissovelline the absorption nearest the normal carbonyl region was a strong band at 1608 cm^{-1}. An absorption of such low frequency is shown only by carbonyls of relatively long bond length such as found in carboxylate anions where the nonbonding electrons interact with the carbonyl carbon. Perhaps the ketone carbonyl bond of geissovelline was longer for a similar reason, but it is the nonbonding pair of electrons on the nitrogen which interacts which the carbonyl carbon. Such a transannular nitrogen–carbonyl interaction has been observed before.[4,5] The transannular nitrogen–carbonyl structure[6] explains the weaker basicity of geissovelline (pK_a = 6.7)[7] and the disappearance of the ultraviolet absorption in acidic medium. The nitrogen is not available for protonation owing to its transannular interaction with the carbonyl. Instead the less basic carbonyl oxygen is protonated, resulting in loss of the α,β-unsaturated ketone chromophore. Also consistent with the unavailability of the electron pair on





the nitrogen is the nonreactivity of geissovelline with methyl iodide or cyanogen bromide in aprotic solvents.

Reaction of geissovelline with lithium aluminum hydride in diethyl ether produced a mixture of epimers in which the *N*-acetyl had been reduced to an *N*-ethyl group and the olefinic double bond was hydrogenated. More vigorous treatment with lithium aluminum hydride in refluxing tetrahydrofuran led to reduction of the ketone carbonyl; the resulting mixture of epimeric alcohols was found to be readily oxidized by air, apparently forming indoles. To account for the possible formation of indoles the α,β-unsaturated ketone function was most likely attached to the β position of the indoline ring (**3c**).



3c

Further evidence for its attachment to the β position of the indoline ring came from the following experiment. Oxidation of deacetylgeissovelline with lead tetraacetate did not lead to an indolenine but rather to a water-soluble product which had an ultraviolet spectrum characteristic of an indole. Pyrolysis of the water-soluble indole at 180° lead to a new compound, $C_{21}H_{26}N_2O_3$, which had lost only two hydrogens compared with deacetylgeissovelline over the course of the two reactions. Examination of the nmr spectrum of the pyrolysis product immediately revealed that the α,β-unsaturated ketone group had been expelled from the β position of the indoline ring[8] during the oxidation, as the indolic NH had become acylated during the pyrolysis. A sharp singlet at δ 8.00 showed that the aromatic proton ortho to the nitrogen was again experiencing the anisotropy of a carbonyl group attached to the nitrogen. A 1:3:3:1 quartet at δ 7.15 showed that the olefinic proton of the ethylidene group was cis to the amide carbonyl[9] in the pyrolysis product and therefore probably cis to the ketone group in geissovelline. Also shown in the nmr spectrum was a doublet of doublets at

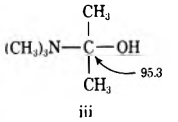
(4) N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956); N. J. Leonard and M. Oki, *J. Jap. Chem.*, **10**, 1003 (1956); N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Amer. Chem. Soc.*, **80**, 4858 (1958).

(5) Transannular nitrogen–carbonyl interactions are exhibited by the *Strychnos* alkaloids novacin and vomicin. For a review see H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademe-Verlag, Berlin, 1961.

(6) It has recently been reported [T. T. Nakashima and G. E. Maciel, *Org. Magn. Resonance*, **4**, 321 (1972)] that 11-methyl-11-azabicyclo[5.3.1]undecan-4-one is best represented by formula i in aprotic solvents such as cyclohexane and by ii in proton solvents such as 90% chloroform in cyclo-

i ii

hexane. The conclusion is based on the carbon-13 chemical shift (parts per million relative to cyclohexane) of C-4 in the two solvents. The chemical shift for C-4 of ii agrees with the one estimated from additivity considerations for a similar carbon in the model system iii.



iii

(7) V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **32**, 1851 (1949).

(8) Indolenines having *Strychnos* and *Aspidosperma* structural skeletons are readily reduced and rearranged by a retro-Mannich reaction to indoles when treated with sodium or potassium borohydride: G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, 792 (1960); K. Biemann and G. Spiteller, *Tetrahedron Lett.*, 299 (1961).

(9) The appreciable difference in chemical shift of an olefinic proton cis to a carbonyl function compared with one trans is demonstrated by the geometrical isomers tiglic acid (δ 7.06) and angelic acid (δ 6.27).

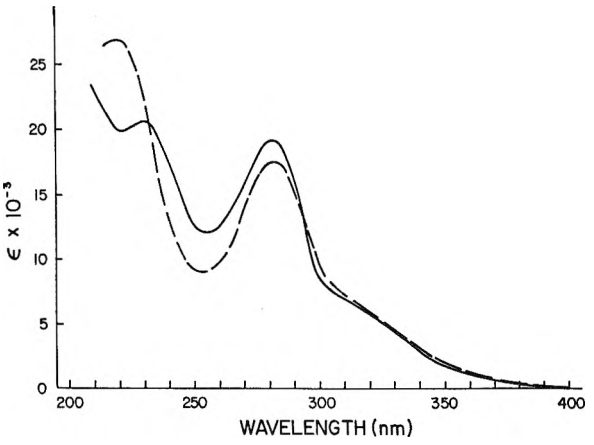
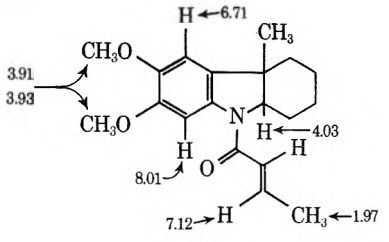


Figure 4.—Comparison of the ultraviolet spectra of compound **6** (—) and *N*-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (**5**) (– – –).

δ 4.53 which suggested that the pyrolysis product had regained a proton on the α carbon of an indoline ring. This possibility was quickly ruled out, as the ultraviolet spectrum of the pyrolysis product did not resemble that of *N*-crotonyl-1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole (**4**). It made more sense mechanistically that the pyrolysis product should possess an indole ring. Comparison of the ultraviolet spectra of the pyrolysis product and a suitable synthetic model compound, *N*-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (**5**) (Figure 4) showed indeed that the pyrolysis product had the partial structure **6a**.



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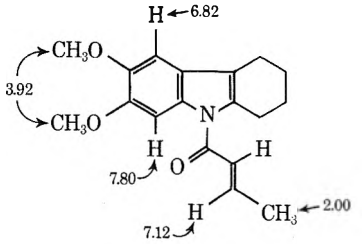
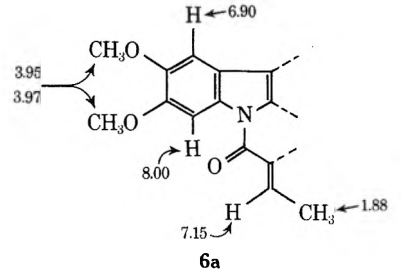
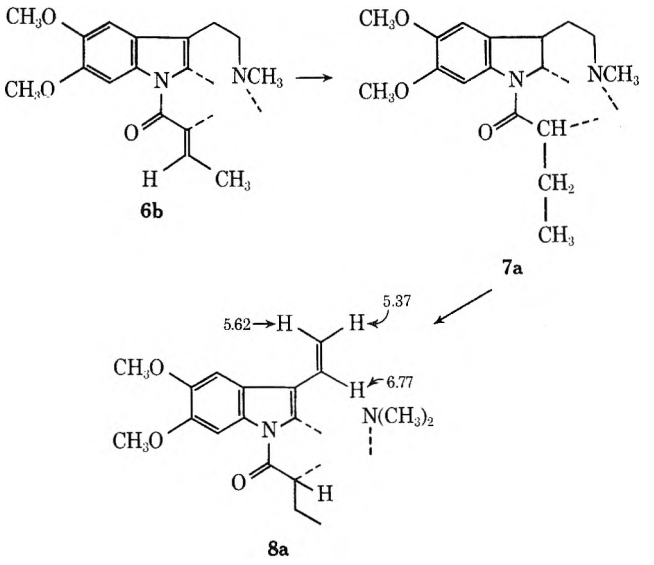


5



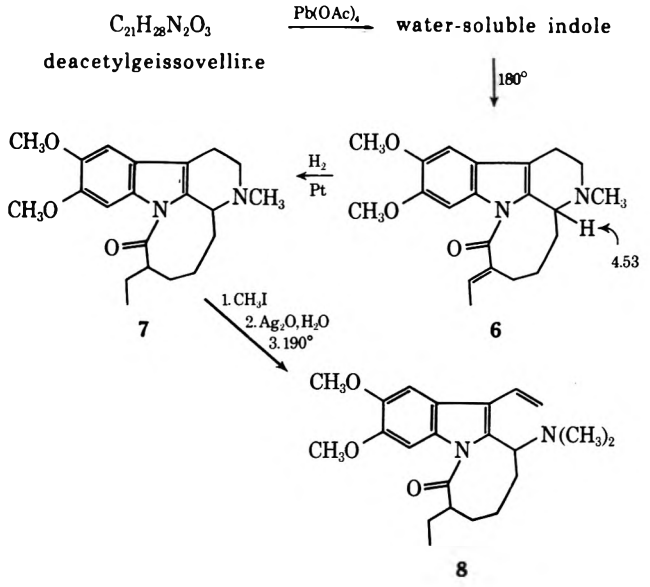
6a

Assuming that geissovelline has the tryptamine structure, *i.e.*, the basic nitrogen is separated from the β carbon of the indoline ring by two carbon atoms, and that this structure is retained after pyrolysis of the lead tetraacetate oxidation product of deacetylgeissovelline, then Hofmann degradation of the pyrolysis product **6b** might lead to a compound having a vinyl group attached to the β position of the indole ring. The ethylidene double bond in **6b** was first catalytically hydrogenated so that isomerization and other side reactions would be minimized during the Hofmann elimination reaction. As predicted, Hofmann degradation of **7a** led to a β-vinyl indole **8a**. The nmr spectrum of the product

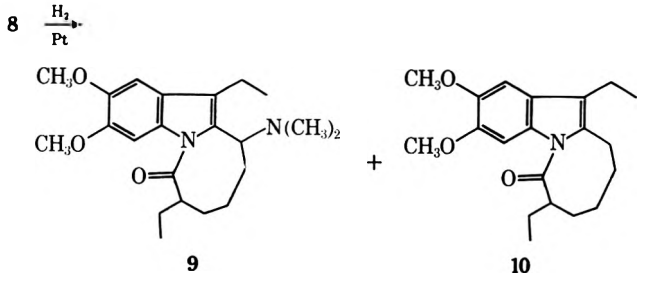


exhibited doublets of doublets at δ 5.37 (J = 12 and 2 Hz, 5.62 (J = 18 and 12 Hz), and 6.77 (J = 18 and 12 Hz) for the vinyl protons. Many of the signals in the spectrum were doubled either to cisoid and transoid vinyl conformers or to *C*-ethyl epimers. As the aromatic proton meta to the indole nitrogen appeared to be more strongly influenced by the anisotropy of the vinyl group (singlet peaks at δ 6.87 and 7.13) than the ortho aromatic proton (singlet peaks at δ 8.04 and 8.09), the vinyl group had to be attached to the β position on the indole ring in the Hofmann degradation product. The nmr signal for the *N*-methyl protons was also doubled (singlet peaks at δ 2.20 and 2.36) and this suggested that the dimethylamino group was very close to the vinyl group. The closest that one can place the dimethylamino group with respect to the vinyl substitutent is to attach it to a benzylic carbon at the α position of the indole ring. Only three carbons remain unassigned now for a complete structure and must be used to construct a ring. The three carbons, which can only be methylenes as the sole CCH_3 group has already been accounted for, connect the benzylic carbon at the α position of the indole ring and the carbon bearing the ethyl group (in **7a** and **8a**) or the ethylidene group (in **6b**). Structures **6b**, **7a**, and **8a** can now be expanded to **6**, **7**, and **8**.

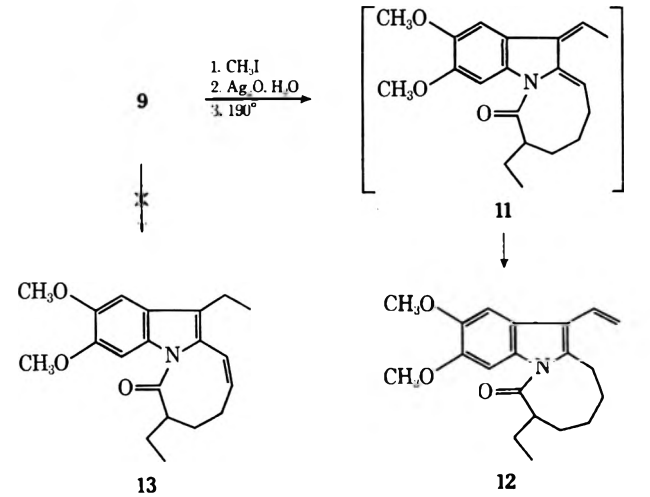
The doublet of doublets at δ 4.53 in the nmr spectrum of the pyrolysis product is readily explained by structure **6**. In deacetylgeissovelline a methylene had been attached at the α position of its indoline ring, but it appeared that the basic nitrogen had reacted with this carbon, most likely during the pyrolysis of the water-soluble indole when it was benzylic. Difficult to explain with structure **6** was the seemingly facile formation of a strained eight-membered ring by acylation of the indole nitrogen during the pyrolysis.



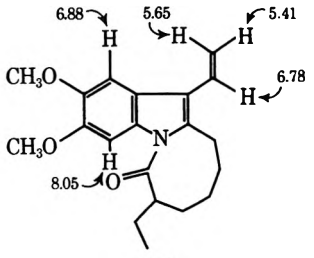
To secure structure **6** for the pyrolysis product, an exhaustive Hofmann degradation was carried out. Compound **8** was first catalytically hydrogenated to a mixture of a basic compound **9** and a nonbasic compound which exhibited no *N*-methyl absorption in its nmr spectrum. Loss of the dimethylamino group is rationalized only by hydrogenolysis from a benzylic position such as that present in **8**. The nonbasic compound must therefore have structure **10**.



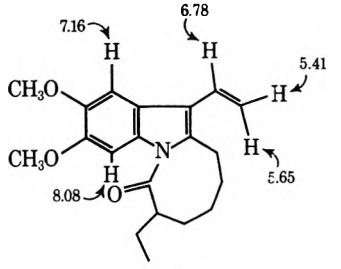
Hofmann degradation of **9** led to a product which nmr analysis showed to be the β-vinylindole **12**. Pyrolysis of the methohydroxide of **9** did not lead to **13**, as the hydroxide ion attacked the more acidic benzylic proton and eliminated trimethylamine to give the intermediate **11**. A 1,5-sigmatropic proton shift in **11** then leads to the more stable **12**. The nmr spectrum of **12** showed the identical pattern of peaks for the olefinic and aromatic protons as for **8**. The aromatic signals were



again doubled and this clearly had to be attributed to cisoid and transoid conformations of the vinyl group (**12a** and **12b**). In the nmr spectrum of **8** the doubling



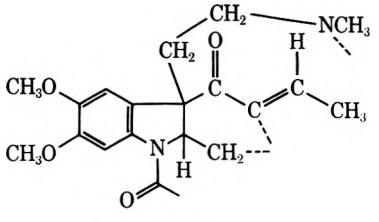
12a



12b

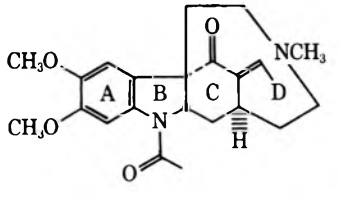
of the aromatic and dimethylamino signals must therefore have been due to vinyl conformers rather than to *C*-ethyl epimers.

We were not able to rationalize a complete structure for geissovelline from **6** and therefore concluded that a rearrangement had occurred during the conversion of deacetylgeissovelline to **6**. What was learned about the structure of geissovelline was (1) the olefinic proton was cis to the ketone carbonyl group and (2) the tryptamine structure was present. The partial structure of geissovelline could now be expanded to **3d**.

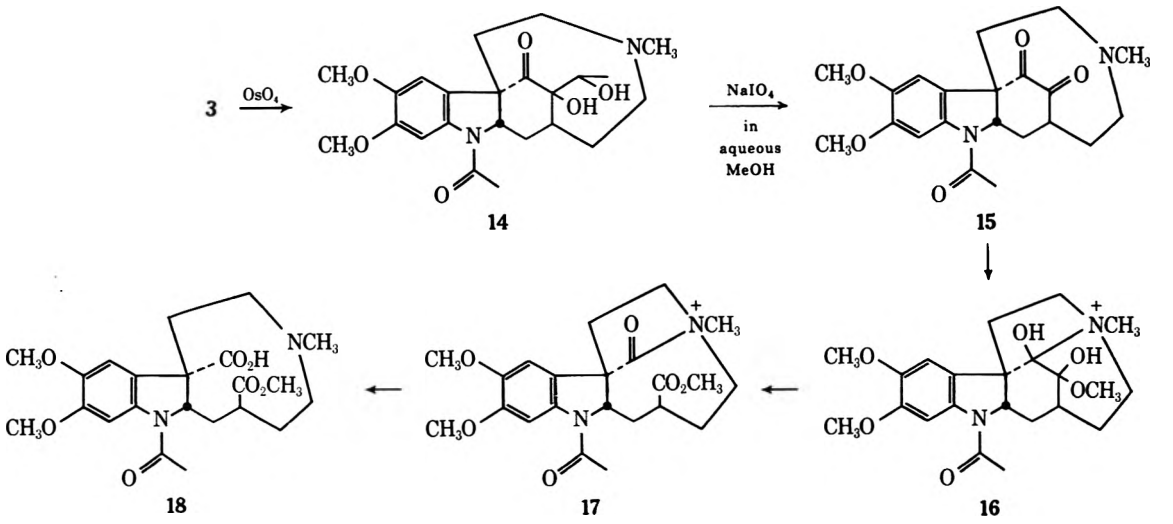


3d

Two methylenes and one methine remained unassigned and had to be put together to construct two additional rings. Only six structures (nonionic) could be written for geissovelline. One of these structures was not considered further, as the transannular nitrogen–carbonyl interaction resulted in a strained four-membered ring. Four of the remaining five structures were eliminated when an oxidative degradation of geissovelline revealed that a methine is attached to the olefinic double bond and that the *N*-methyl group cannot be on a carbon β to the olefinic double bond. By this process of elimination geissovelline was proposed to have the remaining structure **3** and furthermore the stereo-

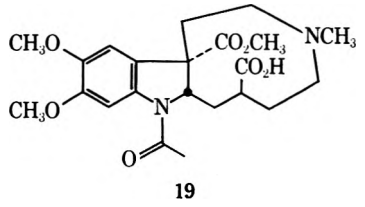


3

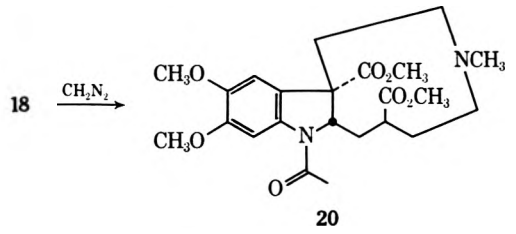


chemistry depicted from molecular model considerations.[10]

The oxidative degradation of geissovelline was carried out as follows. Hydroxylation of **3** with osmium tetroxide to the diol **14** followed by oxidation with sodium metaperiodate in aqueous methanol produced acetaldehyde and a product $C_{22}H_{30}N_2O_7$ which had incorporated a molecule of methanol during the oxidation as shown by nmr and Zeisel analyses. The α diketone was most likely formed first, but subsequent nucleophilic addition of methanol and protonation of **15** led to **16**, which underwent further oxidation to **17**. Hydrolysis of the labile quaternary amide **7** then resulted in the product **18**. It was possible that the periodate oxidation product had instead structure **19**, resulting from hydration and protonation of ketone **15**, oxidation to a quaternary amide, and reaction with

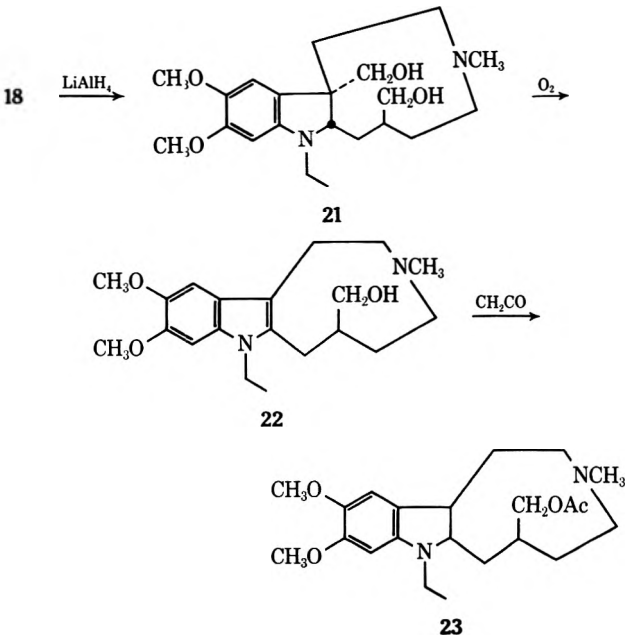


methanol. Evidence for ester, amide, and carboxyl carbonyls in **18** was shown by both the infrared and carbon-13 spectra. Compound **18** readily formed the dimethyl ester **20** on treatment with diazomethane.



Treatment of **18** with sodium ethoxide in ethanol-*O*-*d* resulted in exchange of the *N*-acetyl protons and the acidic proton, as shown by the disappearance of their nmr signals. It could not be determined whether a proton on the carbon α to the ester carbonyl had been exchanged, as the remainder of the nmr spectrum looked essentially the same before and after exchange. Compound **18** did appear to be fairly stable to the strong alkaline conditions, and this suggested that the *N*-methyl group was not on a carbon β to the carbomethoxy group.

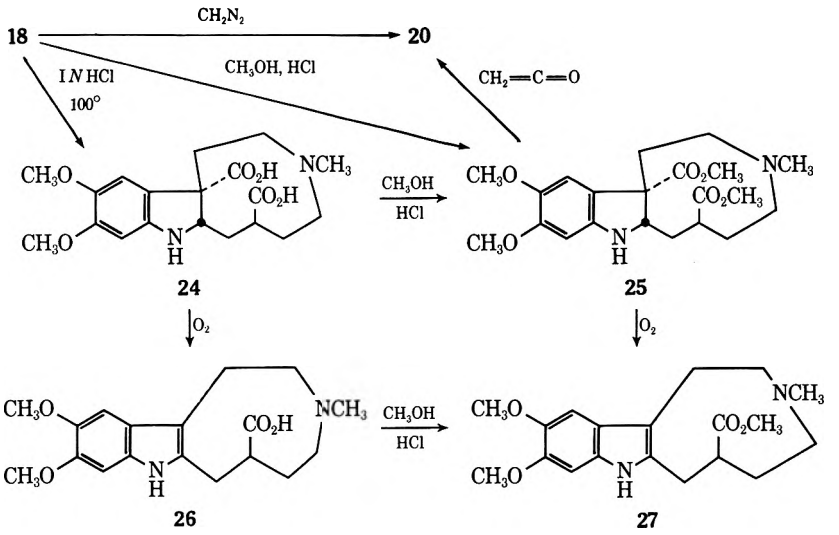
Reduction of **18** with lithium aluminum hydride gave the *N*-ethylindcline **21**, which was rapidly converted to the indole **22** by an oxidative decarbonylation.



The nmr spectrum of **22** showed a sharp doublet at δ 3.7 (J = 6 Hz) assigned to a methylene flanked by a methine and a hydroxy group which upon acetylation with ketene **23** showed the expected 0.5-ppm paramagnetic shift. The nmr evidence showed that a methine was adjacent to the ester carbonyl in **18** and therefore to the olefinic double bond in geissovelline (**3**).

Acid hydrolysis of the amide and ester of **18** gives an indoline which must have structure **24**, since it can be converted to **20** by Fischer esterification followed by acetylation with ketene. Fischer esterification of **18** or **24** yields the same indoline **25**. Compound **24** is readily

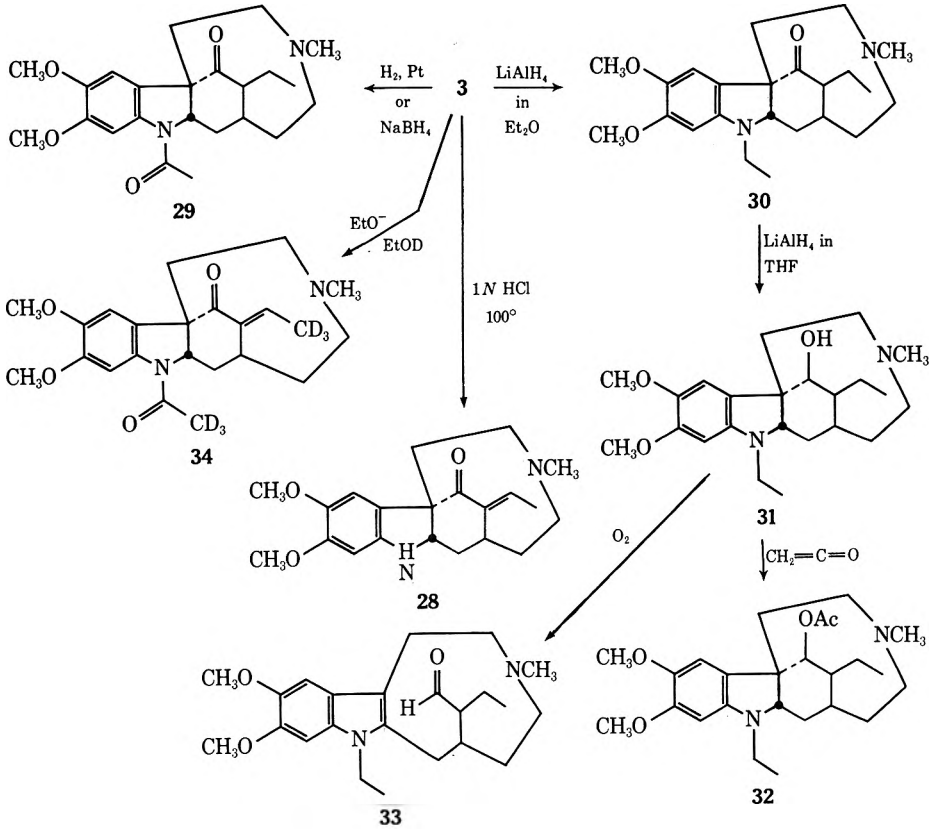
(10) Geissovelline appears to be related to the alkaloids condyfoline [D. Schumann and H. Schmid, *Helv. Chim. Acta*, **46**, 1966 (1963)] and condylocarpine [K. Biemann, A. L. Burlingame, and D. Stauffacher, *Tetrahedron Lett.*, 527 (1962); A. Sandoval, F. Walls, J. N. Schoolery, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, 409 (1962)].



oxidized by air to an indole, presumably by an oxidative decarboxylation to **26**. Compound **25** also undergoes a facile oxidation to indole **27**, which is identical with the Fischer esterification product of **26**. The carbomethoxy group at the β position of the indoline ring of **25** appears to be easily hydrolyzed, possibly owing to a transannular assistance by the nitrogen.

Structure **3** is consistent with all of the chemistry of geissovelline. Acid hydrolysis of **3** gives deacetylgeissovelline (**28**). Catalytic hydrogenation or sodium borohydride reduction of **3** leads readily to an epimeric mixture of dihydrogeissovellines (**29**). Reduction of the ketone group, however, is sluggish; geissovelline is rapidly reduced to **30** with lithium aluminum hydride and to **31** only with more vigorous conditions. Compound **31** forms a monoacetate **32** with ketone and is oxidized by air to an indole, possibly **33** as suggested by carbonyl absorption at 1725 cm^{-1}. Reaction of **3** with sodium ethoxide in ethanol-*O*-*d* results in geissovelline-d_6 (**34**).

The mass spectrum of geissovelline is also compatible with structure **3** for the alkaloid. The largest fragment ion produced upon electron impact of **3** corresponds to the loss of 71 mass units and the elements of C_4H_9N from the molecular ion. The transition is accompanied by a metastable ion at m/e 268.7. The M − 71 ion is shifted six mass units higher in the mass spectrum of geissovelline-d_6 (**34**), showing that both the ethylidene and *N*-acetyl methyl groups are retained. The mass spectrum of deacetylgeissovelline (**28**) also exhibits a prominent M − 71 ion which may be identical with the m/e 285 ion resulting from loss of ketene from the M − 71 ion of **3**. The M − 71 ion is conspicuously missing in the mass spectrum of dihydrogeissovelline (**29**), suggesting that fragmentation leading to the M − 71 ion is initiated by fission of the allylic C–C bond in ring D of **3**.



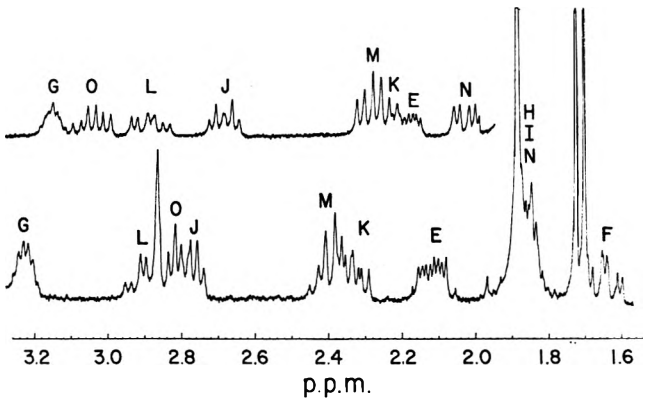
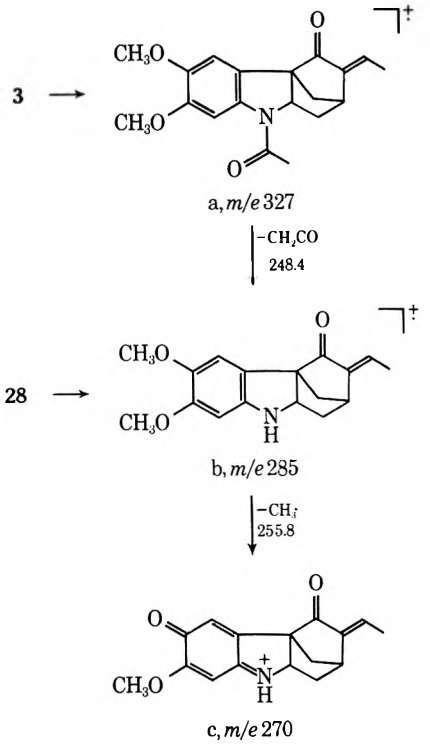
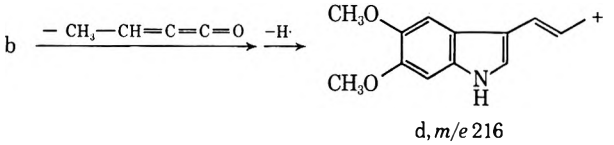


Figure 5.—High-field region of the 300-MHz proton nmr spectrum of deacetylgeissovelline in chloroform-*d* (lower trace) and pyridine-d_5 (upper trace).

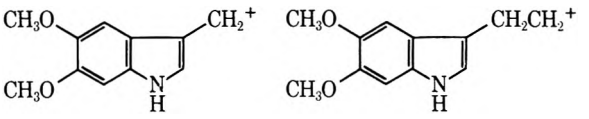
Two possible structures for the M − 71 ions of **3** and **28** are a and b, respectively.



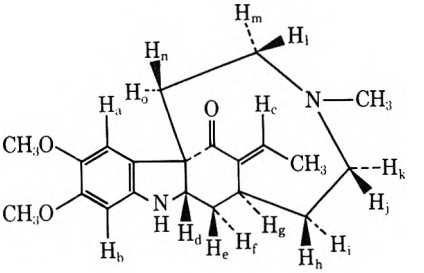
In the mass spectrum of **28** the largest fragment ion is found at *m/e* 216 and has the elemental composition $C_{13}H_{14}NO_2$. The *m/e* 216 ion is also present in the mass spectrum of **3**, is shifted to *m/e* 217 in the mass spectrum of **34**, and is missing in the mass spectrum of **29**. The *m/e* 216 ion has about the same relative intensity as the *m/e* 285 ion (b) in both the mass spectra of **3** and **28**, suggesting that the *m/e* 216 ion might be formed from b. No metastable ions could be found to account for the origin of the *m/e* 216 ion. The *m/e* 216 ion could be the results of a two-step degradation of ion b and have structure d.



Formation of the ions at *m/e* 58, 70, 216, 270, 285, 312, 313, 327, and 339 in the mass spectrum of **3** appears to be initiated by cleavage of the allylic C–C bond in ring D, whereas ions at *m/e* 122, 124, and 138 may result from initial cleavage of the allylic C–C bond in ring C. All of these ions are absent in the mass spectrum of **29**. Formation of the ions at *m/e* 190 (e) and 204 (f) in the mass spectrum of **3** is independent of initial allylic C–C cleavage, as these ions are also found in the mass spectrum of **29**.



Nmr Studies of Deacetylgeissovelline.—To confirm the proposed structure for geissovelline, the 300-MHz proton nmr spectrum of deacetylgeissovelline (**28a**)



28a

(Figure 5) was determined and completely analyzed. In chloroform-*d* H_d is found at δ 4.26 as a doublet of doublets showing vicinal coupling to H_e and H_f. The coupling constants, J_{de} = 6.5 and J_{df} = 11.5 Hz, are consistent with the approximate dihedral angles of 60 and 180°, respectively, observed in a model of deacetylgeissovelline.

Irradiation of H_d removes the small splitting from an octet at δ 2.08, assigned to H_e, and the large splitting from the triplet of doublets at δ 1.61 for H_f. The resulting doublets of doublets now show only the geminal interaction of H_e and H_f (J_{ef} = 13 Hz) and the vicinal coupling of H_e and H_f to H_g ($J_{eg} = J_{fg}$ = 4 Hz). Again the coupling constants are compatible with the approximate dihedral angles of 60° in a model of **28a**.

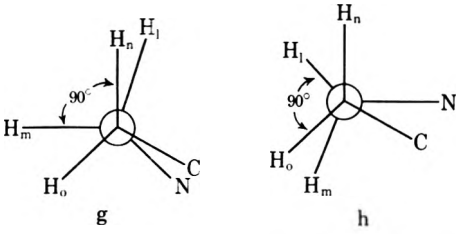
The sextet at δ 3.20 is attributed to H_g and irradiation of this proton also reduces the H_e signal to a doublet of doublets and the H_f signal to a triplet in which the geminal coupling of H_e and H_g and the vicinal interactions of H_e and H_f to H_d remain.

The H_h and H_i resonances are located in a complex three-proton multiplet at *ca.* δ 1.8 as shown by the appreciable change in its shape when H_g is irradiated. Conversely, irradiation of the multiplet at δ 1.8 causes the sextet for H_g to collapse to a 1:2:1 triplet ($J_{eg} = J_{fg}$ = 4 Hz). The sextet for H_g is a quartet of 1:2:1 triplets where the quartet is the X part of a typical ABX spectrum and the lines of the quartet are separated by about 4 Hz. Irradiation of the multiplet at δ 1.8 also causes a doublet of triplets at δ 2.74, assigned to H_j, and a multiplet at δ 2.31 for H_k to simplify, the resulting doublets showing only the geminal coupling of H_j and H_k (J_{jk} = 13.5 Hz). A reasonably close match between the experimental spectrum of H_g, H_h, H_i, H_j, and H_k and the calculated spectrum was achieved with the aid of generalized multispin programs LAOCOON I and II.

The parameters which agreed best with the experimentally observed line frequencies and intensities are $\nu_g = 962.47$, $\nu_h = 550.0$, $\nu_i = 568.0$, $\nu_j = 828.63$, and $\nu_k = 695.98$ for the chemical shifts and $J_{gh} = 8.46$, $J_{gi} = 3.56$, $J_{gj} = 0.0$, $J_{gk} = 0.0$, $J_{hi} = -13.0$, $J_{hj} = 5.46$, $J_{hk} = 8.93$, $J_{ij} = 5.54$, $J_{ik} = 6.03$, and $J_{jk} = -13.02$ Hz for the spin–spin coupling constants.

The *N*-methyl protons absorb at rather high field (δ 1.86), showing that the *N*-methyl group is located in the shielding region of the π-electron cloud of the α,β-unsaturated ketone system. In this conformation the nonbonding pair of electrons on the nitrogen is oriented toward the carbonyl carbon and this supports the existence of a transannular nitrogen–carbonyl interaction already indicated from infrared evidence.

The signals for H_l, H_m, H_n, and H_o appear as complex multiplets in the spectrum determined in chloroform-*d* but are seen very clearly in pyridine-d_5 (upper trace of Figure 6) as triplets of doublets at δ 2.84 and 3.03 and doublets of doublets at δ 1.99 and 2.24. Since two of the protons exhibit doublets of doublets, the vicinal coupling constant between these two protons must be zero and therefore the dihedral angle about 90°. Examining the many conformational possibilities for **28a**, only two (g and h) fulfill this requirement and show at the same time a transannular nitrogen–carbonyl interaction. In both g and h H_o is located near the



deshielding region of the aromatic ring while H_l interacts sterically with H_j. The two paramagnetically displaced triplets of doublets must therefore be attributed to H_o and H_l and the doublets of doublets at higher field to H_m and H_n. Hence protons H_l, H_m, H_n, and H_o in **28a** have the conformation depicted by g. The proton absorbing at highest field (δ 1.99) should be H_n, since it is in a methylene attached only to carbon. Proton H_n then shows a geminal coupling of -13 Hz to H_o and vicinal coupling of 6 Hz to H_l. The H_m proton should resonate at lower field (δ 2.24) as it is in a methylene attached to a nitrogen. A geminal coupling of -13 Hz is shown for H_m and H_l and a vicinal interaction of 7 Hz between H_m and H_o. After the coupling constants in the various multiplets were compared assuming that H_n absorbs at highest field, the triplets of doublets at δ 3.03 and 2.84 were assigned to H_o and H_l, respectively. A reasonable solution of the more complex experimental spectrum of protons H_l, H_m, H_n, and H_o in chloroform-*d* is obtained by calculating a spectrum with the parameters $\nu_l = 863.2$, $\nu_o = 845.9$, $\nu_m = 714.2$, and $\nu_n = 553.8$ Hz for the chemical shifts and $J_{mn} = 0$, $J_{no} = -14.8$, $J_{ln} = 6.6$, $J_{mo} = 7.0$, $J_{ml} = -14.5$, and $J_{lo} = 13.0$ Hz for the spin–spin coupling constants.

The H_o proton lies in the deshielding region of the aromatic ring and is the most paramagnetically displaced methylene proton, whereas H_f is shielded by the aromatic ring and is the most diamagnetically shifted

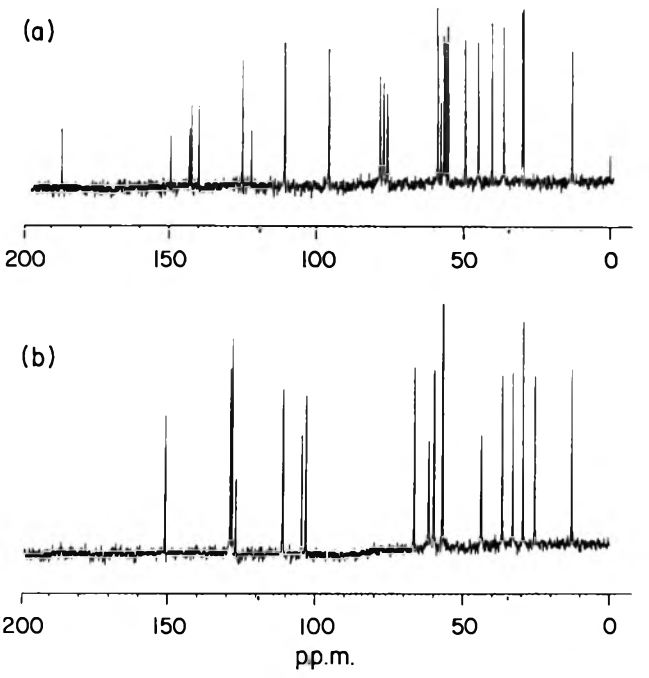
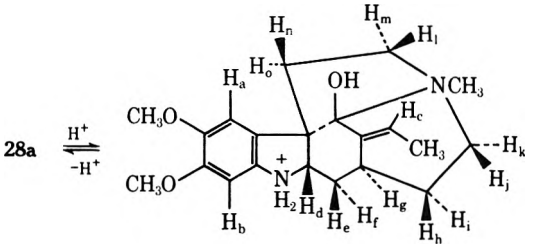


Figure 6.—The Fourier transform 25.2-MHz carbon-13 nmr spectrum of deacetylgeissovelline in (a) chloroform-*d* and (b) 0.1 *N* DCl in D_2O.

methylene proton. For the methylene groups attached to the basic nitrogen, H_l and H_j absorb at lower field than H_m and H_k owing to a nonbonded interaction between H_l and H_j. The H_g proton is found of fairly low field owing to van der Waals deshielding by the *C*-methyl group. Finally, the H_d proton is found at much lower field compared with other alkaloids owing probably to deshielding by the ketone carbonyl.

Since a transannular nitrogen–carbonyl interaction exists in deacetylgeissovelline, acidification results in protonation of the carbonyl oxygen rather than the tertiary nitrogen. The indoline nitrogen is also protonated at pH 0.



In 1 *N* DCl in D_2O the protons on carbons attached to the positively charged nitrogens are strongly deshielded. The *N*-methyl signal has shifted paramagnetically about 1 ppm (Table I), as have the signals for the four *N*-methylene protons H_j, H_k, H_l, and H_m which exhibit a very complex multiplet centered at about δ 3.65. The signal for H_d, however, is shifted only 0.54 ppm to lower field, as H_d no longer experiences deshielding by the ketone carbonyl. The aromatic proton ortho to the indoline nitrogen is strongly affected by the electron-withdrawing character of the positively charged nitrogen and is paramagnetically shifted 1.15 ppm. The aromatic proton meta to the indoline nitrogen, on the other hand, is more strongly affected by the removal of deshielding by the ketone carbonyl and is diamagnetically shifted 0.31

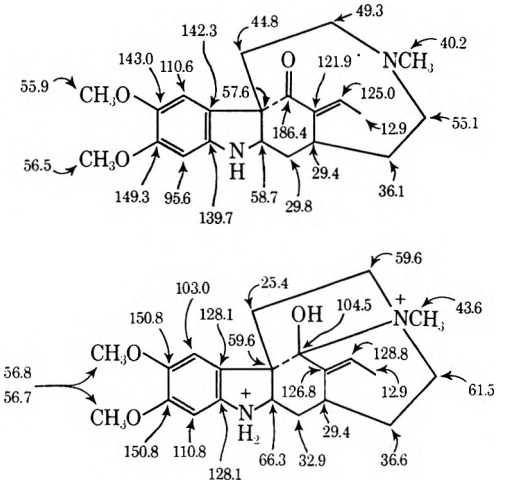
TABLE I
COMPARISON OF PROTON CHEMICAL SHIELDING PARAMETERS OF DEACETYLGEISSOVELLINE IN DIFFERENT SOLVENTS

	Chemical shift, δ				
Protons	$CDCl_3$	C_5D_5N	C_6F_6	C_6D_6	0.1 *N* DCl in D_2O
OCH_3	3.76	3.65	3.64	3.68	3.66
	3.81	3.72	3.70	3.76	3.70
NCH_3	1.86	1.88	1.80	1.81	2.83
CCH_3	1.68	1.62	1.73	1.61	1.44
NH[a]	3.27	5.36	*b*	*c*	4.62[d]
H_a	7.22	7.71	*b*	7.26	6.91
H_b	6.25	6.47	*b*	6.14	7.40
H_c	6.43	6.68	*b*	6.47	5.88
H_d	4.26	4.52	4.25	4.12	4.80
H_e	2.08	2.13	2.13	1.91	2.46[e]
H_f	1.61	1.71	1.58	1.52	1.86
H_g	3.21	3.11	3.25	3.07	3.23
H_h	1.83	1.71	1.93	1.70	1.64[e]
H_i	1.89	1.71	1.93	1.70	1.98[e]
H_j	2.76	2.64	2.77	2.60	3.65[f]
H_k	2.32	2.20	2.35	2.18	3.65[f]
H_l	2.88	2.84	2.91	2.72	3.65[f]
H_m	2.38	2.24	2.33	2.25	3.65[f]
H_n	1.85	1.99	1.70	1.70	2.39[e]
H_o	2.82	3.03	2.69	2.82	2.61[e]

[a] Concentration dependent. [b] Not determined. [c] Not observed. [d] HDO peak. [e] Tentative assignment. [f] Center of complex 4 H multiplet.

ppm. The quartet for H_c and the doublet for the CCH_3 group are found at higher field, as these protons no longer feel the anisotropic and electron-withdrawing effects of the ketone carbonyl.

The 25.15-MHz proton-noise decoupled Fourier transform carbon-13 nmr spectrum of deacetylgeissovelline is shown in Figure 6. All 21 carbon signals of deacetylgeissovelline are resolved in $CDCl_3$, whereas only 18 lines are visible in 0.1 *N* DCl in D_2O. In $CDCl_3$ the off-resonance continuous-wave (cw) decoupled spectrum shows seven singlets, five doublets, five 1:2:1 triplets, and four 1:3:3:1 quartets, confirming the presence of seven quaternary, five methylene, five methine, and four methyl carbons, respectively, in the structure of deacetylgeissovelline. In acid the peaks for the two aromatic quaternary carbons attached to methoxyl, the two aromatic quaternary carbons at the indoline ring junction, and a methylene and a quaternary carbon at the β position of the indoline ring accidentally overlap, resulting in three lines instead of six. All of the methyl and methine carbon signals could be readily assigned,



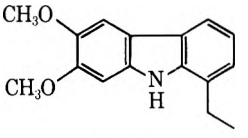
but most of the methylene and quaternary carbon assignments must remain tentative.

In the cw spectrum of deacetylgeissovelline the three doublets at 125.0, 110.6, and 95.6 ppm with residual splittings (J_r) of 26.6, 24.9, and 27.5 Hz are assigned to the olefinic methine carbon and the aromatic methine carbons meta and ortho to the indoline NH, respectively, as the separations of the corresponding methine proton signals from the applied decoupling frequency (δ 14) are 7.57, 6.78, and 7.75 ppm.[11] In 0.1 *N* DCl in D_2O these methine carbons are found at 128.8, 103.0, and 110.8 ppm, respectively, as shown from comparison of the magnitudes of J_r and the proton shift separations.

The most important feature of the carbon-13 spectrum in $CDCl_3$ is the peak at δ 186.4 attributed to the α,β-unsaturated carbonyl carbon. In 0.1 *N* DCl in D_2O the carbonyl signal disappears and a new signal is produced at higher field (δ 104.5) for $HOCN^+$.[6]

The CH_2 signals at lowest field (δ 49.3 and 55.1 in $CDCl_3$ and 59.6 and 61.5 in 0.1 *N* DCl) most likely are assigned to the methylene carbons attached to the tertiary nitrogen. All of the carbons attached to the deuterated nitrogens have shifted paramagnetically. The aromatic carbons ortho and para to the deuterated indoline nitrogen shift downfield to a greater extent than the meta carbons. Finally the methylene carbon attached to the β carbon of the indoline ring is influenced by the anisotropy of the carbonyl group and shifts diamagnetically upon deuteronation.

Pyrolysis of Deacetylgeissovelline and Derivatives.—Structure **3** suggested that it might be possible to degrade geissovelline to a 3-ethyl-6,7-dimethoxycarbazole. Dehydrogenation or pyrolysis of **3** produced a mixture of uncharacterized *N*-acetylindolines, but no carbazole or *N*-acetylcarbazole. Pyrolysis of **28**, on the other hand, produced ca. 20% yield of 1-ethyl-6,7-dimethoxycarbazole (**35**), but not the expected 3-ethyl isomer (**36**) as shown by synthesis.[12]



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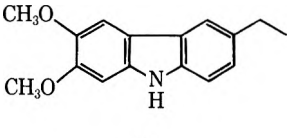
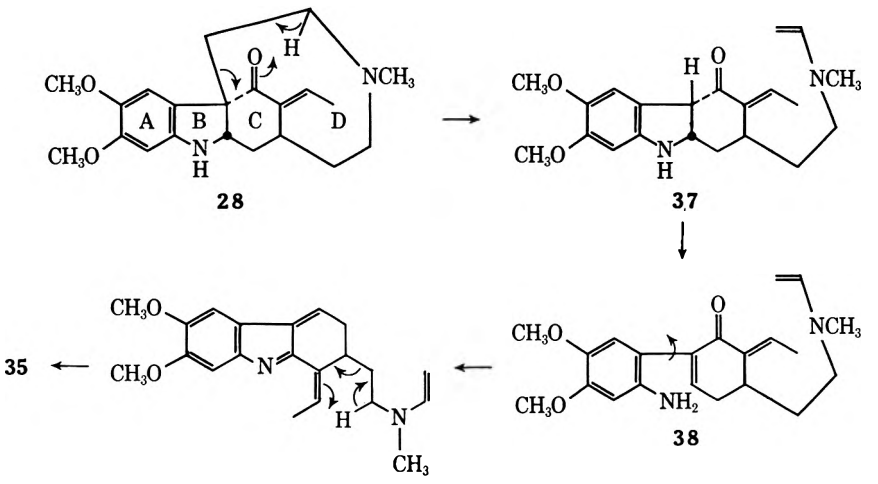


36

The degradation of **28** is probably initiated by cleavage of ring D at the β position of the indoline ring, abstraction of a *N*-methylene proton, and enolization of the ketone. Subsequent tautomerization to ketone **37** and β-elimination of the indoline nitrogen gives the α,β-unsaturated ketone **38**. Regeneration of the indoline ring from condensation of the amine and ketone groups to **39**[13] followed by tautomerism and elimination of divinylmethylamine results in **35**.

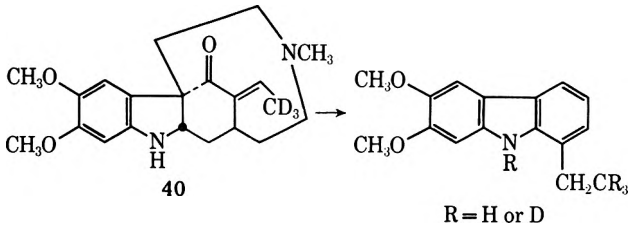
Pyrolysis of deacetylgeissovelline-d_3 (**40**) resulted in a mixture of 17% **35**, 19% mono-, 23% di-, 33% tri-, and 8% tetradeuterated 1-ethyl-6,7-dimethoxycarbazoles and mass spectrometry showed that the deuterium was predominately in the ethyl side chain. If one consid-

(11) R. R. Ernst, *J. Chem. Phys.*, **45**, 3845 (1966); M. Tanabe, T. Hamasaki, D. Thomas, and L. Johnson, *J. Amer. Chem. Soc.*, **93**, 273 (1971).
(12) R. E. Moore and H. Rapoport, *J. Org. Chem.*, **32**, 3335 (1967).
(13) This β elimination followed by amine–ketone condensation is similar to the rearrangement observed with certain β-amino acids: M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 3877 (1972).



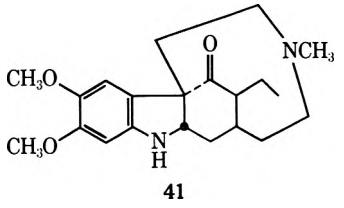
28 37 38 39 35

ers the acidity of the olefinic methyl group of **28**, it is not too surprising that scrambling of the deuterium occurs during the pyrolysis, for example by exchange



40 R = H or D

with the indoline NH. The presence of deuterium in the ethyl side chain of the carbazole shows that the ethyl group has originated from the ethylidene group. Dehydrogenation of deacetyldihydrogeissovelline (**41**) with 30% palladium on charcoal at 275° also resulted in the formation of **35**.

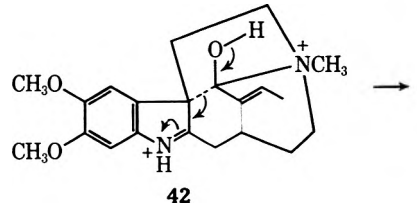


41

As shown above, when **28** is oxidized first with lead tetraacetate and then pyrolyzed at 180°, a 40% yield of **6** is obtained. The intermediate water-soluble product

$$28 \xrightarrow[2.\ 180°]{1.\ Pb(OAc)_4} 6$$

of the lead tetraacetate oxidation, which exhibits an ultraviolet spectrum typical of an indole, may have structure **43**, arising presumably from a retroaldol type



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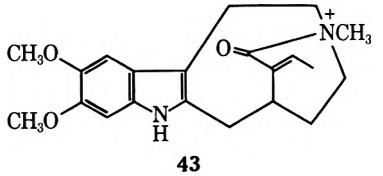
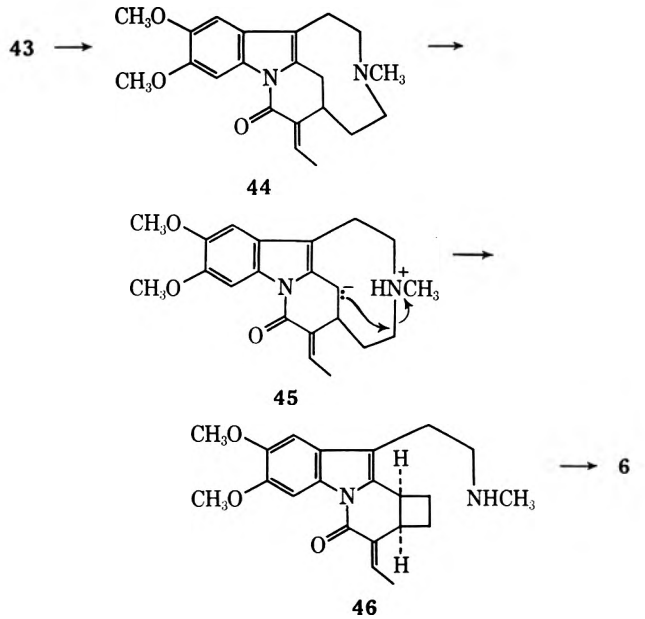


43

reaction of the bis-protonated indolenine **42**. Pyrolysis of the resulting unstable quaternary amide leads to internal acylation of the indole nitrogen and the product **44**.[14] Examination of a model of **44** in the conformation appearing to have the least torsional and ring strain and steric interaction of groups shows that one of the protons on the methylene attached to the α carbon of the indole ring is very close to the nonbonding pair of electrons of the basic nitrogen. This hydrogen is benzylic and therefore acidic enough to be abstracted by the nitrogen during the pyrolysis. The resulting carbanion **45** would then be in a position to nucleophilically attack the nearby *N*-methylene carbon to displace a secondary amino group and form the cyclobutane compound **46**. A model of **44** indicates that the two reacting carbons are close enough to each other for such a reaction, although unprecedented, to conceivably take place. Rupture of the cyclobutane ring and its subsequent reaction with the secondary amino group finally leads to **6**.



43 44 45 46 6

The ethylidene group of **28** appears to have no effect on the course of the reaction, as lead tetraacetate oxidation

(14) J. Harley-Mason and C. G. Taylor, *Chem. Commun.*, 1384 (1969).

of **41** followed by pyrolysis of the oxidation product leads similarly to a 45% yield of **7**.

$$41 \xrightarrow[2.\ 180°]{1.\ Pb(OAc)_4} 7$$

Experimental Section[15]

Isolation of Geissovelline (3).—The chloroform-soluble portion of 65 g of fraction B[2] was applied to an alumina (Woelm, neutral, 600 g) column. Elution with 6 l. of chloroform removed 4.5 g of yellow oil followed by 5 g of red oil. The yellow oil was dissolved in 50% hexane–benzene and rechromatographed on alumina (Woelm, neutral, 120 g), developing the chromatogram with 250 ml of 50% benzene–hexane, 1-l. portions of 75 and 90% benzene–hexane, 500 ml of benzene, and 500 ml of 25% chloroform–benzene. Elution was continued with 2 l. of 50% chloroform–benzene and evaporation of the solvent gave 2.5 g of a gum which produced 1.45 g of crystalline geissovelline on trituration with ether. From a similar chromatography of 73 g of fraction 1,[3] obtained from further separation of the pH 7 ether extract as previously described, on alumina (Woelm, neutral, 2.2 kg) was obtained 8 g of crystalline geissovelline.

The crude geissovelline was crystallized once from chloroform–ether and twice from ethanol and sublimed at 155° (0.01 mm) to give a white, crystalline powder: mp 189–190°; $[\alpha]^{25}D$ −125° (c 1.15, $CHCl_3$); pK_a (50% EtOH–H_2O) = 6.7; uv max (95% EtOH) 217 nm (ε 22,600), 262 (17,500), 299 (10,500); uv max (0.01 *N* ethanolic HCl) 216 nm (ε 21,600), 262 (14,500), 297 (7000); ir (KBr) 1614 (C=O), 1659 cm^- (amide C=O); proton nmr ($CDCl_3$) δ 1.71 (d, 3, *J* = 7.7 Hz, C=CHCH$_3$), 1.90 (s, 3, NCH_3), 2.38 and 2.45 (two singlets, 3, $NCOCH_3$ for conformers **3a** and **3b**, respectively), 3.22 (m, 1, C=CCH), 3.92 (s, 6, aromatic OCH_3), 4.79 and 5.25 (two dd, 1, *J* = 12 and 6.5 Hz, NCH for conformers **3a** and **3b**, respectively), 6.45 and 6.52 (quartet, 1, *J* = 7.7 Hz, C=CHCH$_3$ for conformers **3b** and **3a**, respectively), 6.72 and 7.93 (two singlets, 1, aromatic proton ortho to indoline N for conformers **3b** and **3a**, respectively), 7.37 and 7.42 (two singlets, 1, aromatic proton meta to indoline N for conformers **3a** and **3b**, respectively); proton nmr (HI salt in SO_2) δ 1.77 (d, 3, *J* = 7 Hz, C=CH–CH$_3$), 2.47 (s, 3, $NCOCH_3$), 3.12 (s, 3, $^+NCH_3$), 3.81 (s, 6, aromatic OCH_3), 5.59 (m, 1), 6.19 (q, 1, *J* = 7 Hz, C=CHCH$_3$), 7.54 (s, 1, aromatic proton meta to indoline N), 7.81 (s, 1, aromatic proton ortho to indoline N); carbon-13 nmr ($CDCl_3$) δ 12.8 (olefinic CH_3), 15.1, 22.9 (NCO-CH_3), 24.0, 29.0, 29.2, 29.4 29.6, 29.9, 30.9, 31.6, 33.4, 40.0 (NCH_3), 40.4, 44.9, 50.0, 55.5, 55.8, 56.0, 56.2, 61.7, 62.2, 100.4, 102.1, 108.7, 110.2, 124.3, 125.5, 126.1, 127.1, 132.8, 134.0, 138.7, 145.9, 148.3, 167.1 (amide C=O), 184.3 (ketone C=O); low-resolution mass spectrum (70 eV) *m/e* (rel intensity) 398 (100), 383 (8), 370 (14), 355 (27), 339 (9), 327 (89), 313 (12), 312 (15), 285 (14), 270 (14), 216 (13), 204 (17), 190 (20), 166 (6), 146 (8), 138 (12), 124 (14), 122 (10), 70 (22), 58 (34), 57 (24), 44 (73), 43 (41), 42 (25); high-resolution mass spectrum (70 eV) *m/e* 398.2202 ($C_{23}H_{30}N_2O_4$), 370.2241 ($C_{22}H_{30}N_2O_3$), 355.2020 ($C_{21}H_{27}N_2O_3$), 339.1464 ($C_{20}H_{21}NO_4$), 327.1473 ($C_{19}H_{21}NO_4$), 312.1227 ($C_{18}H_{18}NO_4$), 285.1354 ($C_{17}H_{19}NO_3$), 270.1127 ($C_{16}H_{16}NO_3$), 216.1017 ($C_{13}H_{14}NO_2$), 204.1017 ($C_{12}H_{14}NO_2$), 190.0862 ($C_{11}H_{12}NO_2$), 146.0602 (C_9H_8NO), 138.1279 ($C_9H_{16}N$), 124.1125 ($C_8H_{14}N$), 122.0970 ($C_8H_{12}N$).

Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.3; H, 7.6; N, 7.0; (2) OCH_3, 15.5; (1) NCH_3, 3.8; (2) CCH_3, 7.5. Found: C, 69.5; H, 7.6; N, 6.9; OCH_3, 15.7; NCH_3, 3.5; CCH_3, 6.6.

Deacetylgeissovelline (28).—A solution of 1 g of geissovelline in 30 ml of 1 *N* hydrochloric acid was heated on the steam bath in a nitrogen atmosphere for 4 hr. The solution was neutralized with sodium bicarbonate and extracted with chloroform under nitrogen. The chloroform was dried and evaporated to give a gum which readily crystallized from ether. Sublimation at 145–150° (0.01 mm) produced 0.82 g (92%) of deacetylgeissovelline as a pale yellow crystalline powder: mp 158–159.5°; $[\alpha]^{28}D$ −6° (c 1.07, chloroform); pK_a (50% EtOH–H_2O) = 7.0; uv max (95% EtOH) 230 nm (ε 12,500), 305 (6260); uv max (0.1 *N* ethanolic HCl) 254 nm (ε 8770), 283 (4710); ir (KBr) 1608 (C=O), 1659 (C=C), 3338 cm^{-1} (NH); proton nmr ($CDCl_3$) δ 1.68 (d, 3, *J* = 7.7 Hz, C=CHCH$_3$), 1.86 (s, 3, NCH_3), 3.27 (b, 1, NH), 3.76 (s, 3, aromatic OCH_3), 3.81 (s, 3, aromatic OCH_3), 4.26 (dd, 1, *J* = 6.5 and 11.5 Hz, NCH), 6.25 (s, 1, aromatic H ortho to indoline N), 6.43 (q, 1, *J* = 7.7 Hz, C=CH-CH_3), 7.22 (s, 1, aromatic H meta to indoline N); carbon-13 nmr ($CDCl_3$) δ 12.9 (CCH_3), 29.4 (CH), 29.8 (CH_2), 36.1 (CH_2), 40.2 (NCH_3), 44.3 (CH_2), 49.3 (NCH_2), 55.1 (NCH_2), 55.9 (OCH_3), 56.5 (OCH_3), 57.6 (quaternary C), 58.7 (NCH), 95.6 (aromatic CH β to indoline N), 110.6 (aromatic CH γ to indoline N), 121.9 (olefinic C), 125.0 (olefinic CH), 139.7 (aromatic CN), 142.3 (aromatic C), 143.0 (aromatic CO), 149.3 (aromatic CO), 186.4 (C=O); carbon-13 nmr (1 *N* DCl in D_2O) δ 12.9 (CCH_3), 25.4 (CH_2), 29.4 (CH), 32.9 (CH_2), 36.6 (CH_2), 43.6 (^+NCH), 56.7 (OCH_3), 56.8(OCH_3), 59.6 (CH_2 and quaternary C), 61.5 (CH_2), 66.3 (^+NCH), 103.0 (CH), 104.5 (^+NCOH), 110.8 (aromatic CH), 126.8 (olefinic C), 128.1 (two aromatic C), 128.8 (CH), 150.8 (two aromatic CO); mass spectrum (70 eV) *m/e* (rel intensity) 356 (100), 341 (10), 328 (8), 327 (10), 313 (19), 285 (70), 270 (42), 256 (17), 216 (82), 204 (34), 190 (32), 146 (16), 124 (22), 110 (17), 58 (17), 57 (16), 44 (32).

Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.8; H, 7.9; N, 7.9; (1) CCH_3, 4.2. Found: C, 70.6; H, 7.8; N, 8.0; CCH_3, 4.1.

To regenerate geissovelline a solution of 15 mg of deacetylgeissovelline in 0.2 ml of pyridine and 0.1 ml of acetic anhydride was heated on the steam bath for 1 hr. The solution was made slightly basic with dilute ammonium hydroxide and extracted with chloroform. The giessovelline crystallized from ether and was sublimed at 155° (0.01 mm): mp and mmp 189–191°; $[\alpha]^{24}D$ −123° (c 1.19 chloroform).

Dihydrogeissovelline (29). A. Catalytic Hydrogenation of Geissovelline.—A solution of 125 mg of geissovelline in 5 ml of glacial or 5% ethanolic acetic acid was hydrogenated at atmospheric pressure using 50 mg of platinum oxide catalyst. Fresh catalyst was added periodically until absorption of hydrogen ceased. The acetic acid was removed *in vacuo* and the residual oil was shaken with aqueous sodium bicarbonate solution and chloroform. Evaporation of the chloroform and sublimation of the residual oil gave a white, crystalline solid, mp 50–70°. The melting point of the dihydrogeissovelline was not improved after several recrystallizations from carbon disulfide. The same product was obtained when geissovelline was catalytically hydrogenated in 0.5 *M* methanolic NaOH. Dihydrogeissovelline had the following properties: pK_a (50% EtOH–H_2O) = 8.4; uv max (95% EtOH) 260 nm (ε 14,100), 300 (8500); uv max (0.01 *N* ethanolic HCl) 262 nm (ε 15,600), 298 (7350); uv max (0.1 *N* ethanolic KOH) 262 nm (ε 14,800), 302 (16,000); proton nmr ($CDCl_3$) δ 0.9 (m, 3, CH_2CH_3), 2.04 (s, 3, NCH_3), 2.38 and 2.45 (two singlets, 3, $NCOCH_3$ for conformers **29a** and **29b**, respectively), 3.84 and 3.90 (two singlets, 6, aromatic OCH_3 for conformers **29b** and **29a**, respectively), 4.68 and 5.12 (two triplets, 1, NCH for conformers **29a** and **29b**, respectively), 6.72 and 7.92 (two singlets, 1, aromatic proton ortho to indoline N for conformers **29b** and **29a**, respectively), 7.00 and 7.12 (two singlets, 1, aromatic proton meta to indoline N for conformers **29a** and **29b**, respectively); mass spectrum (70 eV) *m/e* (rel intensity) 400 (54), 385 (11), 372 (11), 357 (11), 343 (11), 314 (11), 313 (35), 290 (21), 204 (11), 190 (14), 126 (22), 59 (100), 44 (25), 43 (20).

Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 69.0; H, 8.1. Found: C, 68.6; H, 7.9.

B. Sodium Borohydride Reduction of Geissovelline.—Sodium borohydride (250 mg) was added in five portions over 10 hr to a solution of 100 mg of geissovelline in 20 ml of 0.05 *N* ethanolic sodium hydroxide. After standing overnight dilute aqueous hydroxide was added, the ethanol was removed *in vacuo*, and the mixture was extracted with chloroform. The chloroform was evaporated to give dihydrogeissovelline, identical with the product produced by catalytic hydrogenation.

Deacetyldihydrogeissovelline (41). A. From Deacetylgeissovelline.—Deacetylgeissovelline (200 mg) in 6 ml of glacial acetic acid was hydrogenated at atmospheric pressure using 60 mg of platinum oxide. The mixture was filtered and evaporated *in vacuo* and the residual oil was distributed between dilute ammonium hydroxide and chloroform. The chloroform layer was separated and evaporated and the residue was sublimed at

(15) All melting points were determined on a Kofler hot stage and are uncorrected; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley; pK_a measurements were determined in 50% ethanol–water. Proton nmr spectra were determined on Varian A-60, HA-100, HR 220, and HR 300 spectrometers; carbon-13 nmr spectra were recorded on a XL-100 spectrometer equipped with Fourier transform; all chemical shifts are reported as δ units relative to TMS (δ 0) as an internal standard in organic solutions or an external standard in aqueous solutions. Low-resolution mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D spectrometer; high-resolution mass measurements were made on a CEC-21-110B instrument.

150° (0.01 mm) to give deacetylhydrogeissovelline: mp 50–60°; uv max (EtOH) 303 nm (ε 4980), sh 235 (11,100); uv max (0.1 *N* ethanolic HCl) 280 nm (ε 4730), 230 (8700); proton nmr ($CDCl_3$) δ 0.9 (m, 3, CCH_3), 2.00 (s, 3, NCH_3), 3.70 (b, 1, NH), 3.79 (s, 6, OCH_3), 4.18 (t, 1, NCH), 6.28 (s, 1, aromatic H ortho to indoline N), 6.93 (s, 1, aromatic H meta to indoline N).

Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.4; H, 8.4; (1) CCH_3, 4.2. Found: C, 70.7; H, 8.6; (1) CCH_3, 2.6.

The volatile acids from the Kuhn–Roth oxidation showed the presence of acetic and propionic acids by paper chromatography.

B. From Dihydrogeissovelline.—A solution of 35 mg of dihydrogeissovelline in 2 ml of 1 *N* hydrochloric acid was heated on the steam bath in a nitrogen atmosphere for 5 hr. The solution was made basic with sodium bicarbonate and extracted with chloroform under nitrogen. The chloroform was evaporated and the residual gum was sublimed at 150° (0.01 mm) to give deacetyldihydrogeissovelline, mp 60–80°.

Dihydroxydihydrogeissovelline (14).—Osmium tetroxide (100 mg) was added to a solution of 100 mg of geissovelline in 1.5 ml of pyridine and 1.5 ml of benzene. After standing overnight at room temperature the dark brown mixture was shaken with 7.5 ml of benzene, 10 ml of methanol, 1.8 g of sodium sulfite, 1.5 g of sodium bicarbonate, and 20 ml of water for 24 hr to decompose the osmate ester. The mixture was filtered through Celite and the Celite was washed with benzene and then with benzene–methanol. The combined filtrate and washings were concentrated *in vacuo* and extracted several times with benzene. Evaporation of the benzene gave 93 mg (86%) of dihydroxydihydrogeissovelline as a white, crystalline solid: mp 100–110°; $[\alpha]^{20}D$ −120° (c 0.69, chloroform); pK_a (50% EtOH–H_2O) = 6.7; uv max (95% EtOH) 258 nm (ε 13,750), 229 (8620); uv max (0.01 *N* ethanolic HCl) 262 nm (ε 14,100), 301 (7150); ir (KBr) 1655 (amide C=O), 3300–3600 cm^{-1} (OH); proton nmr ($CDCl_3$), δ 1.08 (d, 3, *J* = 6.1 Hz, $CH(OH)CH_3$), 2.13 (s, 3, NCH_3), 2.33 and 2.45 (two singlets, 3, $NCOCH_3$ for conformers **14a** and **14b**, respectively), 3.84 and 3.88 (two singlets, 6, aromatic OCH_3 for conformers **14b** and **14a**, respectively), 4.32 (quartet, 1, *J* = 6.1 Hz, $CH(OH)CH_3$), 4.64 and 5.07 (two triplets, 1, NCH for conformers **14a** and **14b**, respectively), 6.72 and 7.92 (two singlets, 1, aromatic proton ortho to indoline N for conformers **14b** and **14a**, respectively), 7.00 and 7.12 (two singlets, 1, aromatic proton meta to indoline N for conformers **14a** and **14b**); mass spectrum (70 eV) *m/e* (rel intensity) 432 (46), 415 (71), 404 (8), 387 (20), 373 (8), 359 (10), 341 (12), 331 (19), 328 (21), 327 (17), 325 (21), 303 (22), 289 (14), 204 (24), 190 (27), 158 (14), 155 (14), 149 (14), 142 (19), 141 (24), 85 (72), 83 (100), 81 (33), 71 (31), 69 (67), 57 (57), 55 (53), 45 (29), 43 (64), 41 (93).

Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.9; H, 7.5; N, 6.5. Found: C, 64.0; H, 7.5; N, 6.8.

The diol could be recrystallized twice from chloroform to give a small quantity of white needles, mp 170–176°. The bulk of the material, mp 110–130°, which remained in the mother liquors could not be improved in melting point by recrystallization.

Geissovelline-d_6 (34).—Sodium (100 mg) was dissolved in 5 ml of absolute deuterium ethoxide (90 atom %) and 100 mg of geissovelline was added. After standing at room temperature for 4 hr, the yellow solution was concentrated and distributed between deuterium oxide and chloroform. The chloroform was separated and evaporated to give a gum which readily crystallized in ether. Electronic integration of the nmr spectrum of the geissovelline-d_6 indicated the presence of 5.1 deuterons (95% exchange); mass spectrum (70 eV) *m/e* (elemental composition) 404 ($C_{23}H_{24}D_6N_2O_4$), 386 ($C_{22}H_{24}D_3N_2O_4$), 376 ($C_{22}H_{24}D_6N_2O_3$), 358 ($C_{21}H_{24}D_3N_2O_3$), 345 ($C_{20}H_{15}D_6NO_4$), 333 ($C_{19}H_{15}D_6NO_4$), 319 ($C_{18}H_{13}D_6NO_4$), 318 ($C_{18}H_{12}D_6NO_4$), 289 ($C_{17}H_{15}D_4NO_3$), 274 ($C_{16}H_{12}D_4NO_3$), 217 ($C_{13}H_{13}DNO_2$), 205 ($C_{12}H_{13}DNO_2$), 191 ($C_{11}H_{11}DNO_2$), 169 ($C_{10}H_{13}D_3NO$), 147 (C_9H_7DNO), 141 ($C_9H_{13}D_3N$), 127 ($C_8H_{11}D_3N$), 125 ($C_8H_9D_3N$), 70 (C_4H_8N), 58 (C_3H_8N), 57 (C_3H_7N), 46 (C_2D_3O), 44 (C_2H_6N), 43 (C_2H_5N), 42 (C_2H_4N).

Deacetylgeissovelline-d_3 (40).—Geissovelline-d_6 (100 mg) was hydrolyzed to **40** using the procedure described above for the preparation of **28**. Electronic integration of the nmr spectrum of **40** showed the presence of 2.5 deuterons (93% exchange).

***N*-Ethyldeacetyldihydrogeissovelline (30).**—A solution of 100 mg of geissovelline in 5 ml of chloroform was added to a solution of 100 mg of lithium aluminum hydride in 50 ml of ether. After standing at room temperature for 3 hr, the mixture was treated with ethyl acetate to decompose the excess hydride and then shaken with 25 ml of 10% sodium hydroxide solution. The ether was separated, dried (Na_2SO_4), and evaporated and the residue was sublimed at 150° (0.01 mm) to give *N*-ethyldeacetylhydrigeissovelline as a yellow gum which could not be induced to crystallize: uv max (95% EtOH) 251 nm (ε 9800), 328 (5220); uv max (0.5 *N* ethanolic HCl) 235 nm (9850), 282 (4900); proton nmr ($CDCl_3$) δ 0.88 (t, 3, *J* = 7.5 Hz, CCH_2CH_3), 1.21 and 1.24 (two triplets, 3, *J* = 7 Hz, NCH_2CH_3 for conformers **30a** and **30b**, respectively), 2.01 (s, 3, NCH_3), 3.24 (quartet, 2, *J* = 7 Hz, NCH_2CH_3), 3.78 and 3.84 (two singlets, 6, aromatic OCH_3 for conformers **30b** and **30a**, respectively), 4.06 (dd, 1, *J* = 7.5 and 9 Hz, NCH), 6.02 and 6.03 (two partially resolved singlets, 1, aromatic H ortho to indoline N for conformers **30b** and **30a**, respectively), 6.83 and 6.94 (two singlets, 1, aromatic H meta to indoline N).

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.5; H, 8.9; N, 7.3; (2) CCH_3, 7.8. Found: C, 71.3; H, 8.6; N, 7.3; CCH_3, 3.8.[16]

The volatile acids from the Kuhn–Roth oxidation showed the presence of acetic acid and propionic acids by paper chromatography.

Reduction of *N*-Ethyldeacetyldihydrogeissovelline with Lithium Aluminum Hydride in Tetrahydrofuran.—A mixture of 50 mg of *N*-ethyldeacetyldihydrogeissovelline and 200 mg of lithium aluminum hydride in 10 ml of freshly distilled tetrahydrofuran was refluxed in a dry nitrogen atmosphere for 24 hr. The excess hydride was decomposed with ethyl acetate, the solvent was removed under reduced pressure, and the residue was distributed between 10% sodium hydroxide solution and chloroform. Evaporation of the chloroform gave a mixture, probably *C*-ethyl epimers of **31**, **33**, and unreduced **30**, as a yellow gum which darkened on exposure to air: ir (KBr) 1725, 3400–3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 2.01 (NCH_3 for unreacted *N*-ethyldeacetyldihydrogeissovelline), 2.28 (NCH_3), 2.45 (NCH_3).

Treatment of the crude reduction product with ketene in benzene for 5 min gave a gum which was distributed between benzene and dilute hydrochloric acid. The aqueous layer was shaken with air, neutralized with sodium bicarbonate, and extracted with benzene and the benzene was evaporated to give a mixture of **30** and **32** as a gum: nmr (CS_2) δ 1.92 (NCH_3 for unreduced *N*-ethyldeacetyldihydrogeissovelline), 2.02 ($OCOCH_3$), 2.27 (NCH_3), 5.23 (d, 1, *J* = 6 Hz, CHCHOAC).

Lead Tetraacetate Oxidation of Deacetylgeissovelline. Isolation of Compound 6.—A solution of 100 mg (0.28 mmol) of deacetylgeissovelline in 0.1 ml of glacial acetic acid and 10 ml of benzene was shaken with 135 mg (0.30 mmol) of lead tetraacetate for 1 min. The mixture was filtered through $MgSO_4$, the dark yellow filtrate (and $CHCl_3$ wash of the $MgSO_4$) was evaporated *in vacuo* at room temperature, and the residue was sublimed rapidly at 180–200° (0.1 mm) to give 30–40 mg of compound **6** as a light yellow, waxy solid: uv max (95% EtOH) 230 nm (ε 20,600), 281 (19,200), sh 320 (5710); ir (KBr) 1625, 1637 (conjugated C=C), 1690 cm^{-1} (amide C=O); proton nmr ($CDCl_3$) δ 1.88 (d, 3, *J* = 7.5 Hz, $COC{=}CHCH_3$), 2.41 (s, 3, NCH_3), 3.95 (s, 3, aromatic OCH_3), 3.97 (s, 3, aromatic OCH_3), 4.53 (dd, 1, *J* = 13 and 3 Hz, NCCHN), 6.90 (s, 1, aromatic H meta to indole N), 7.15 (quartet, 1, *J* = 7.5 Hz, $CO{-}C{=}CHCH_3$), 8.00 (s, 1, aromatic H ortho to indole N); mass spectrum (70 eV) *m/e* 354.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.2; H, 7.4. Found: C, 71.3; H, 7.6.

Lead Tetraacetate Oxidation of Deacetyldihydrogeissovelline. Isolation of Compound 7.—A mixture of 170 mg of deacetyldihydrogeissovelline in benzene, 0.2 ml of acetic acid, and 210 mg of lead tetraacetate was shaken for 1 min. The mixture was filtered through magnesium sulfate and the filtrate and $CHCl_3$ wash of the $MgSO_4$ were evaporated *in vacuo*. The foamy residue was rapidly heated at 180° (0.1 mm) in a sublimation apparatus and compound **7** was collected on the cold finger as a yellow, waxy solid. The unsublimed portion was redissolved in chloroform, the chloroform was evaporated, and the residue again heated in the sublimation apparatus for an additional yield of compound **7**. The total yield of compound **7** was 75 mg (45%): uv max (95% EtOH) 261 nm (ε 17,000), 295 (7400); proton nmr ($CDCl_3$) δ 1.0 (m, 3, CH_2CH_3), 2.41 (s, 3, NCH_3), 3.93 (s, 3, aromatic OCH_3), 3.95 (s, 3, aromatic OCH_3), 6.88 (s, 1, aromatic H meta to indole N), 7.94 (s, 3, aromatic H ortho to indole N); mass spectrum (70 eV) *m/e* 356.

Compound **7** could also be obtained by catalytic hydrogenation

(16) The yield of acetic acid from Kuhn–Roth oxidation of an *N*-ethyl group is generally very low.

of 6 with 1 molar equiv of hydrogen in ethanol using a platinum catalyst.

1,2,3,4-Tetrahydro-11-methyl-6,7-dimethoxycarbazolenine.—A solution of 2.05 g (0.01 mol) of 3,4-dimethoxyphenylhydrazine hydrochloride and 1.11 g (0.01 mol) of 2-methylcyclohexanone in 100 ml of 50% methanol–benzene was heated to reflux in a nitrogen atmosphere, 2 ml of pyridine was added, and the mixture was refluxed for 15 min and then evaporated *in vacuo*. The residue was dissolved in 50 ml of glacial acetic acid, the mixture was heated for 10 min on the steam bath and then evaporated, and the residue was distributed between ether and dilute hydrochloric acid. The aqueous layer was neutralized with ammonium hydroxide and extracted with ether, the ethereal layer was evaporated, and the residual oil was treated with picric acid. The precipitated picrate was washed thoroughly with warm ethanol and then distributed between ether and aqueous ethanolamine. After the ethereal layer was washed free of ethanolamine picrate, it was dried (Na_2SO_4) and evaporated to give a gum which crystallized readily from *n*-hexane. After repeated vacuum sublimation and recrystallization from *n*-hexane, 0.71 g (28%) of the pure carbazolenine as pale yellow crystals was obtained: mp 72.5–73.5°; uv max (95% EtOH) 219 nm (ϵ 21,400), 290 (6800); uv max (0.1 *N* ethanolic HCl) 223 nm (ϵ 24,400) sh 245 (15,400), 330 (5190); proton nmr ($CDCl_3$) δ 1.28 (s, 3, C-11 methyl), 3.91 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 6.88 (s, 1, aromatic H on C-8), 7.23 (s, 1, aromatic H on C-5).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8. Found: C, 73.1; H, 7.7.

9-Crotonyl-1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole (4).—A solution of 250 mg of 1,2,3,4-tetrahydro-11-methyl-6,7-dimethoxycarbazolenine in ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of platinum oxide catalyst. When hydrogen was no longer absorbed, the mixture was filtered and the filtrate was evaporated to give 1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole as a colorless gum which was air sensitive and could not be induced to crystallize.

A stirred solution of 90 mg (1.05 mmol) of crotonic acid in 10 ml of acetone and 0.1 ml of water was cooled to 0° and 0.15 ml of triethylamine and 100 mg (0.92 mmol) of ethyl chloroformate in 5 ml of acetone was added. Stirring was continued at 0° for 1 hr, 200 mg (0.81 mmol) of 1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole in acetone was then added all at once, and the mixture was stirred at room temperature for an additional 3 hr. The acetone was evaporated and the residue was distributed between 1 *N* potassium hydroxide solution and ether. Evaporation of the ether gave a gum that slowly crystallized from *n*-hexane. After two recrystallizations from *n*-hexane and sublimation at 130° (0.1 mm), light yellow crystals of 9-crotonyl-1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole (4) were obtained: mp 143–145°; uv max (95% EtOH) 212 nm (ϵ, 22,400), 295 (10,400), 316 (12,500); ir (KBr) 1658 cm^{-1} (amide C=O); proton nmr ($CDCl_3$) δ 1.13 (s, 3, C-11 methyl), 1.97 (dd, 3, J = 7.5 and 1.5 Hz, $COCH{=}CHCH_3$), 3.91 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 4.03 (m, 1, C-10 proton), 6.33 (doublet of quartets, 1, J = 15 and 1.5 Hz, $CO\text{-}CH{=}CHCH_3$), 6.71 (s, 1, aromatic H on C-5), 7.12 (doublet of quartets, 1, J = 15 and 7.5 Hz, $COCH{=}CHCH_3$), 8.01 (b, 1, aromatic H on C-8).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.4; H, 8.0. Found: C, 72.2; H, 7.9.

1,2,3,4-Tetrahydro-6,7-dimethoxycarbazole.—A mixture of 3.8 g of 4-aminoveratrole, 3.4 g of 2-chlorocyclohexanone, and 2.5 g of anhydrous sodium acetate in 100 ml of absolute ethanol was refluxed for 6 hr in a nitrogen atmosphere. Sodium chloride precipitated during the first hour of reflux. The mixture was evaporated *in vacuo*, the residue was distributed between water and ether, and the ethereal layer was washed with 0.5 *M* hydrochloric acid and water, dried ($MgSO_4$), and evaporated slowly under a stream of nitrogen to give 1.7 g (30%) of indole which was sublimed at 90° (0.1 mm): mp 108–110° (lit.[17] mp 105–106°); uv max (95% EtOH) 229 nm (ϵ 28,100), sh 280 (5200), 303 (8850); proton nmr ($CDCl_3$) δ 1.85 (m, 4, C-2 and C-3 CH_2), 2.63 (m, 4, C-1 and C-4 CH_2), 3.80 (s, 3, aromatic OCH_3), 3.89 (s, 3, aromatic OCH_3), 6.68 (s, 1, aromatic H on C-5), 6.94 (s, 1, aromatic H on C-8), 7.66 (b, 1, indole NH).

9-Crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (5).—A solution of 500 mg of 1,2,3,4-tetrahydro-6,7-dimethoxycarbazole in 18 ml of 50% sulfuric acid was placed in a porous cup and reduced electrolytically for 48 hr using a 6-V battery and lead electrodes (1 × 10 cm separated by 3 cm). After 48 hr an aliquot remained clear on dilution with water. The solution was diluted with water, washed with ether, made basic with sodium bicarbonate and sodium sulfite, and extracted again with ether to remove the product. The ether was evaporated and the residue, which darkened on exposure to air, was distilled (short-path) at 110° (0.3 mm.) to give 280 mg of 1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole as a light yellow oil.

A solution of 130 mg of crotonic acid in 10 ml of acetone and 0.1 ml of water was cooled to 0° and 0.2 ml of triethylamine was added followed by 150 mg of ethyl chloroformate in acetone. Triethylamine hydrochloride precipitated and the mixture was stirred at 0° for 1 hr. The 280 mg of 1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole in acetone was added all at once and the mixture was stirred for 3 hr at room temperature, concentrated *in vacuo*, and distributed between 1 *N* potassium hydroxide solution and ether. The ethereal layer was washed with dilute hydrochloric acid and then with aqueous sodium sulfite, dried (Na_2SO_4), and evaporated to give 312 mg of 9-crotonyl-1,2,3,4-10,11-hexahydro-6,7-dimethoxycarbazole as a yellow gum.

A mixture of 177 mg of 9-crotonyl-1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 10 ml of benzene, 0.1 ml of acetic acid, and 300 mg of lead tetraacetate was stirred for 5 min. The benzene solution was decanted and washed with aqueous sodium sulfite solution, dried (Na_2SO_4), and evaporated. The product, which crystallized from chloroform–ether, was sublimed at 155° (0.4 mm) and recrystallized several times from chloroform–ether to give 100 mg of 9-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (5) as light yellow crystals: mp 128–130°; uv max (95% EtOH) 220 nm (ϵ 26,800), 281 (17,500), sh 320 (5800); proton nmr ($CDCl_3$) δ 1.85 (m, 4, C-2 and C-3 CH_2), 2.00 (dd, 3, J = 7.5 and 1.5 Hz, $COCH{=}CH\text{—}CH_3$), 2.62 (m, 2, C-4 CH_2), 2.86 (m, 2, C-1 CH_2), 3.92 (s, 6, aromatic OCH_3), 6.57 (doublet of quartets, 1, J = 15 and 1.5 Hz, $COCH{=}CHCH_3$), 6.82 (s, 1, aromatic H on C-5), 7.12 (doublet of quartets, 1, 15 and 7.5 Hz, $COCH{=}CHCH_3$), 7.80 (s, 1, aromatic H on C-8).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.2; N, 4.7. Found: C, 72.1; N, 4.5.

Hofmann Degradation of Compound 7.—A solution of 75 mg of compound 7 in 2.5 ml of methanol and 2.5 ml of methyl iodide was refluxed under argon for 2 hr. Evaporation of the solvent gave the methiodide of compound 7 as a brown resin which was dissolved in 5 ml of water and shaken with 70 mg of freshly prepared silver oxide for 30 min. The mixture was filtered, the filtrate was washed with chloroform and evaporated, and the methohydroxide of compound 7 was pyrolyzed in a sublimation apparatus at 190° (0.1 mm). Compound 8 was deposited on the cold finger as a yellow gum (55 mg) which could not be induced to crystallize: uv max (95% EtOH) 224, 261, 295 nm; proton nmr ($CDCl_3$) δ 1.08 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.20 and 2.36 (two singlets, 3, NCH_3 for conformers **8b** and **8a**, respectively), 3.93 (s, 6, aromatic OCH_3), 5.37 (dd, 1, J = 12 and 2 Hz, vinyl methylene H trans to indole ring), 5.62 (dd, 1, J = 18 and 2 Hz, vinyl methylene H cis to indole ring), 6.77 (dd, 1, J = 12 and 18 Hz, vinyl methine H), 6.87 and 7.13 (two singlets, 1, aromatic H meta to indole N for conformers **8a** and **8b**, respectively), 8.04 and 8.09 (two singlets, 1, aromatic H ortho to indole N for conformers **8a** and **8b**, respectively).

A solution of 55 mg of compound 8 in ethanol was hydrogenated at atmospheric pressure using 5 mg of platinum oxide catalyst. When absorption of hydrogen had ceased, the mixture was filtered, the filtrate was evaporated, and the residue was distributed between dilute phosphoric acid and chloroform. Evaporation of the chloroform left 10 mg of a brown gum, compound **10**, which could not be induced to crystallize: proton nmr (CS_2) δ 1.0 (m, 3, $CHCH_2CH_3$), 1.22 (m, 3, $=CCH_2CH_3$), 3.71 (s, 6, aromatic OCH_3), 6.64 (s, 1, aromatic H meta to indole N), 7.77 (s, 1, aromatic H ortho to indole N); mass spectrum (70 eV) *m/e* 329. The aqueous portion was made basic with ammonium hydroxide and extracted with chloroform. Evaporation of the chloroform and sublimation of the residual gum gave 40 mg of compound 9 as a light, yellow solid: mass spectrum (70 eV) *m/e* 372.

A solution of 40 mg of compound 9 in 1 ml of methanol and 1 ml of methyl iodide was refluxed under argon in the presence of a small amount of anhydrous potassium carbonate for 2 hr. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residual glass, the methiodide of compound 9, was dissolved

(17) R. J. S. Beer, L. McGrath, A. Robertson, A. B. Woodier, and J. S. E. Holker, *J. Chem. Soc.*, 2061 (1949).

in water and the solution was shaken with 4 mg of freshly prepared silver oxide for 30 min. Filtration of the mixture and evaporation of the chloroform-washed filtrate gave the methohydroxide of **9** as a brown glass. Pyrolysis in a sublimation apparatus at 190° (0.1 mm) led to an orange-brown solid which was distributed between dilute phosphoric acid and chloroform. Evaporation of the chloroform gave 12 mg of compound **12** as a light brown gum: proton nmr ($CDCl_3$) δ 5.41 (dd, 1, J = 12 and 2 Hz, vinyl methylene H trans to indole ring), 5.65 (dd, 1, J = 18 and 2 Hz, vinyl methylene H cis to indole ring), 6.78 (dd, 1, J = 12 and 18 Hz, vinyl methine H), 6.88 and 7.16 (two singlets, 1, aromatic H meta to indole N for conformers **12a** and **12b**), 8.05 and 8.08 (two singlets, 1, aromatic H ortho to indole N for conformers **12a** and **12b**; mass spectrum (70 eV) m/e 327.

Periodate Oxidation of Dihydrodihydrogeissovelline. Isolation of Compound 18.—A solution of 259 mg (0.60 mmol) of dihydroxydihydrogeissovelline (**14**) in 2 ml of methanol and 4 ml of water was treated with a solution of 256 mg (1.20 mmol) of sodium metaperiodate in 8 ml of water over a period of 24 hr at 0–5°. After standing for an additional 24 hr at 0–5°, the mixture was extracted with chloroform. Evaporation of the chloroform gave 105 mg (40%) of a colorless gum which slowly crystallized. Recrystallization from chloroform–ether (seeding) gave pure compound **18**: mp 175–177° after drying at 90° (0.2 mm); uv max (95% EtOH) 269 mm (ϵ 11,300), 303 (7600); ir (KBr) 1615 (carboxylic acid C=O), 1653 (amide C=O), 1725 (ester C=O), 2400–3600 cm^{-1} (carboxylic acid OH); proton nmr ($CDCl_3$) δ 2.27 (s, 3, NCH_3), 2.57 (s, 3, $NCOCH_3$), 3.60 (s, 3, CO_2CH_3), 3.87 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 5.62 (m, 1, NCH), 6.62 (s, 1, aromatic H meta to indoline N), 6.95 (b, 1, aromatic H ortho to indoline N), 9.92 (b, 1, CO_2H); carbon-13 nmr ($CDCl_3$) δ 25.8 ($NCOCH_3$), 32.0, 33.6, 41.4, 44.0 (NCH_3), 45.6 (CH), 49.6, 52.1 (CO_2CH_3), 56.3 (CH_2 and two aromatic OCH_3), 58.2 (quaternary C), 75.7 (NCH), 100.2 (aromatic CH), 106.4 (aromatic CH), 126.8 (aromatic quaternary C), 134.7 (aromatic quaternary C), 146.2 (aromatic $COCH_3$), 149.2 (aromatic $COCH_3$), 169.8 (C=O), 173.5 (C=O), 177.8 (C=O); mass spectrum (70 eV) m/e (rel intensity) 434 (17), 419 (6), 415 (4), 406 (7), 391 (14), 375 (100), 303 (12), 290 (22), 204 (25), 190 (13), 144 (15), 142 (18), 141 (11), 138 (15), 87 (10), 85 (55), 83 (82), 58 (20), 57 (40), 44 (20), 43 (18).

Anal. Calcd for $C_{22}H_{30}N_2O_7$: C, 60.8; H, 7.0; N, 6.5; (3) OCH_3, 21.3; (1) NCH_3, 3.5. Found: C, 60.9; H, 7.2; N, 6.5; OCH_3, 19.6; NCH_3, 3.1.

To a solution of 100 mg of sodium in 2.5 ml of absolute deuterium ethoxide (90%) was added a solution of 50 mg of **18** in 2.5 ml of absolute deuterium ethoxide. The mixture was allowed to stand at room temperature under nitrogen for 1.5 hr, diluted with 5 ml of deuterium oxide (99.5%), and extracted with chloroform. The chloroform extract was washed with a small amount of D_2O, dried over anhydrous magnesium sulfate, and evaporated to dryness to give tetradeuterated **18** which showed no signals at δ 2.57 ($NCOCH_3$) or 9.92 (CO_2H) in the proton nmr spectrum ($CDCl_3$).

Hydrolysis and Oxidation of Compound 18.—A solution of 100 mg of **18** in 5 ml of 2 *N* hydrochloric acid was heated on the steam bath under a nitrogen atmosphere for 1 hr. Evaporation *in vacuo* gave compound **24** as a water-soluble glass: uv max (0.01 *N* ethanolic HCl) 239 nm (ϵ 5200), 282 (4500); ir (KBr) 1620, 1725 (carboxylic acid C=O), 2600–3600 cm^{-1}.

A solution of compound **24** in 10 ml of 0.01 *N* ethanolic HCl was shaken periodically for 1 hr with air. The oxidation was monitored by ultraviolet spectroscopy and after 20 min the spectrum had changed from an indoline to that of an indole. Evaporation *in vacuo* gave **26** as a water-soluble glass [uv max (95% EtOH) 302 nm (ϵ 8800)] which was dissolved in methanol saturated with dry hydrogen chloride and allowed to stand in a stoppered flask at room temperature for 24 hr. The methanolic HCl was evaporated *in vacuo* and the residue was distributed between aqueous sodium bicarbonate and chloroform. Evaporation of the chloroform gave **27** as a yellow gum which darkened rapidly on contact with air: uv max (95% EtOH) sh 260, 302 nm; proton nmr[18] ($CDCl_3$) δ 1.92 (NCH_3), 2.53 (NCH_3), 3.61 (OCH_3), 3.75 (OCH_3), 3.81 (OCH_3), 3.84 (OCH_3), 3.89 (OCH_3), 6.71 (aromatic H), 6.81 (aromatic H), 7.01 (aromatic H). Compound **27** was also obtained by a similar air oxidation of **25** (see below).

Compound 20. A. From Compound 18.—A solution of 17 mg of compound **18** in ether was treated with excess diazomethane at 0° for 1 hr. Evaporation of the ether gave compound **20** as a colorless gum: uv max (95% EtOH) 266, 302 nm; ir ($CHCl_3$) 1650 (amide C=O), 1730 cm^{-1} (ester C=O); proton nmr ($CDCl_3$) δ 2.34 (s, 3, NCH_3), 2.42 (s, 3, $NCOCH_3$), 3.63 (s, 3, CO_2CH_3), 3.74 (s, 3, CO_2CH_3), 3.87 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 5.55 (m, 1, NCH), 6.60 (s, 1, aromatic H meta to indoline N), 7.30 (b, 1, aromatic H ortho to indoline N); mass spectrum (70 eV) m/e 448.

B. From Compound 24. A solution of compound **24** in absolute methanol saturated with dry hydrogen chloride was allowed to stand for 24 hr under nitrogen. Evaporation of the methanolic HCl gave compound **25** [uv max (95% EtOH) 282 nm] as a light yellow air-sensitive gum. Compound **25** was also obtained when **18** was treated similarly.

A solution of compound **25** in benzene was treated with ketene and allowed to stand for 5 min. The mixture was introduced onto a short alumina column. The column was washed thoroughly with benzene and the product was eluted with 50% chloroform–benzene and chloroform. The resulting gum was distributed between benzene and 0.5 *M* sodium dihydrogen phosphate solution and the aqueous layer was neutralized with dilute ammonium hydroxide and extracted with benzene. Evaporation of the benzene gave compound **20**.

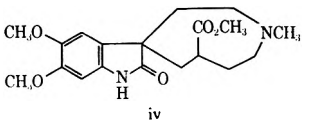
Compound 22.—A solution of 50 mg of compound **18** in ether–chloroform was added to a solution of 100 mg of lithium aluminum hydride in ether and the mixture was allowed to stand at room temperature for 3 hr. The excess hydride was decomposed with ethyl acetate, the mixture was shaken with 10% sodium hydroxide solution, and the ethereal layer was separated, dried, and evaporated. The yellow gum, a mixture of **21** and **22**, was distributed between benzene and dilute hydrochloric acid and the aqueous layer was separated, allowed to stand in contact with air for 20 min, neutralized with aqueous sodium bicarbonate, and extracted with benzene. Evaporation of the benzene gave compound **22** as a yellow gum: uv max (95% EtOH) 231, sh 280, 304 nm; proton nmr (CS_2) δ 1.3 (t, 3, J = 7.5 Hz, NCH_2CH_3), 2.4 (s, 3, NCH_3), 3.7 (d, 2, J = 6 Hz, CH_2OH), 3.9 (s, 6, aromatic OCH_3), 4.1 (quartet, 2, J = 7.5 Hz, NCH_2CH_3), 6.8 (s, 1, aromatic H meta to indole N), 7.0 (s, 1, aromatic H ortho to indole N).

Compound 23.—A solution of compound **22** in benzene was treated with ketene. The product was washed into dilute hydrochloric acid and the aqueous layer was neutralized with sodium bicarbonate and extracted with benzene. Evaporation of the benzene and sublimation of the residue gave compound **23** as a light yellow gum: uv max (95% EtOH) 231, sh 280, 304 nm; proton nmr (CS_2) δ 1.30 (t, 3, J = 7.5 Hz, NCH_2CH_3), 2.11 (s, 3, $OCOCH_3$), 2.39 (s, 3, NCH_3), 3.93 (s, 6, aromatic OCH_3), 4.10 (quartet, 2, J = 7.5 Hz, NCH_2CH_3), 4.19 (d, 2, J = 7 Hz, CH_2OAc), 6.80 (s, 1, aromatic H meta to indole N), 6.96 (s, 1, aromatic H ortho to indole N).

Pyrolysis of Deacetylgeissovelline to 1-Ethyl-6,7-dimethoxycarbazole (35).—Deacetylgeissovelline (100 mg) was pyrolyzed at 280° in a nitrogen atmosphere for 0.5 r. The product was sublimed at 0.01 mm, the yellow solid was distributed between ether and 1 *N* hydrochloric acid, the ether was dried and evaporated, and the residue was sublimed at 140° (0.2 mm) to give 15 mg (21%) of crude 1-ethyl-6,7-dimethoxycarbazole. After several recrystallizations from absolute ethanol, the carbazole (prisms) melted at 136–138° with resolidification to needles: mp and mmp 159–160° (lit.[12] mp 157.5–158°); uv max (95% EtOH) 210 nm (ϵ 28,000), 235 (44,300), sh 250 (19,400), 262 (15,600), 303 (17,500), 335 (5190), 340 (5280); ir (KBr) 3477 cm^{-1} (NH); proton nmr ($CDCl_3$) δ 1.38 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.88 (quartet, 2, J = 7.5 Hz, CH_2CH_3), 3.90 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 6.92 (s, 1, aromatic H on C-8), 7.19 (m, 2, aromatic protons on C-2 and C-3), 7.51 (s, 1, aromatic H on C-5), 7.81 (t, 1, aromatic H on C-4), 7.94 (b, 1, NH); mass spectrum (70 eV) m/e (rel intensity) 255 (100), 240 (64), 212 (10), 197 (18), 184 (13), 183 (25), 182 (19).

Under the same conditions 25 mg of deacetylgeissovelline-d_3 (**40**) was pyrolyzed to 2 mg of a mixture of un-, mono-, di-, tri-, and tetrasubstituted 1-ethyl-6,7-dimethoxycarbazoles: mass

(18) It was not determined whether the complexity (*i.e.*, doubling) of the nmr spectrum was due to a slow interconversion of conformers or to a mixture of oxidation products such as the indole **27** and oxindole iv.



iv

spectrum (20 eV) *m/e* (rel intensity) 260 (7), 259 (38), 258 (100), 257 (80), 256 (62), 255 (54).

Pyrolysis of geissovelline at 280° produced a white solid which had a uv spectrum corresponding to that of geissovelline and not a carbazole or a *N*-acetylcarbazole.

9-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole.—A mixture of 300 mg of 1,2,3,4-tetrahydro-6,7-dimethoxycarbazole, 0.5 g of anhydrous sodium acetate, and 3 ml of acetic anhydride was refluxed for 3 hr under nitrogen. The solvent was evaporated and the residue was distributed between chloroform and water. Evaporation of the chloroform gave 9-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole, which was crystallized from ether and sublimed (0.1 mm): mp (136–137° (lit.[19] mp 136°); uv max (95% EtOH) 260 nm (ε 23,500), 285 (9380); proton nmr ($CDCl_3$) δ 1.80 (m, 4, C-2 and C-3 CH_2), 2.48 (s, 3, $NCOCH_3$), 2.52 (m, 2, C-1 or C-4 CH_2), 2.77 (m, 2, C-1 or C-4 CH_2), 3.89 (s, 6, aromatic OCH_3), 6.76 (s, 1, aromatic H on C-5), 7.91 (s, 1, aromatic H on C-8).

9-Acetyl-6,7-dimethoxycarbazole.—A mixture of 200 mg of 9-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole and 300 mg of 30% palladium/charcoal in 5 ml of *n*-hexyl ether was refluxed and stirred for 3 hr under nitrogen. The mixture was filtered hot and the cooled filtrate was diluted with petroleum ether (bp 30–60°). The product crystallized slowly. Three recrystallizations from ethanol gave colorless needles of 9-acetyl-6,7-dimethoxycarbazole: mp 123–124° after drying at 80° (0.1 mm); uv max (95% EtOH) 224 nm (ε 44,200), sh 240 (25,200), 295 (15,600), sh 303 (14,400), 324 (11,600).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6. Found: C, 71.3; H, 5.5.

(19) G. K. Hughes, F. Lions, J. J. Maunsell, and L. E. A. Wright, *J. Proc. Roy. Soc. N. S. W.*, **71**, 428 (1938).

Dehydrogenation of Deacetyldihydrogeissovelline (41).—An intimate mixture of 225 mg of deacetyldihydrogeissovelline and 225 mg of 30% palladium/charcoal was heated at 275° in a nitrogen atmosphere for 0.5 hr. The cooled mixture was extracted with methanol, the methanol was evaporated, the residue was distributed between ether and 1 *N* hydrochloric acid, the dried ethereal layer was evaporated, and the residual gum was sublimed at 140° (0.3 mm) to give 27 mg of crude 1-ethyl-6,7-dimethoxycarbazole (**35**).

Registry No.—**3**, 36954-68-4; **4**, 36950-24-0; **5**, 36954-69-5; **6**, 36950-25-1; **7**, 36950-26-2; **8**, 36950-27-3; **9**, 36950-28-4; **10**, 36950-29-5; **12**, 36950-30-8; **14**, 36950-31-9; **18**, 36954-70-8; **20**, 36954-71-9; **22**, 36954-72-0; **23**, 36950-32-0; **27**, 36954-73-1; **28**, 36954-74-2; **29**, 36954-75-3; **30**, 36954-76-4; **34**, 36994-22-6; **41**, 36994-23-7; 1,2,3,4-tetrahydro-11-methyl-6,7-dimethoxycarbazolenine, 36950-33-1; 1,2,-3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 36950-34-2; 9-crotonyl-1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 36950-35-3; 9-acetyl-6,7-dimethoxycarbazole, 36950-36-4.

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6-Alkyl Penicillins and 7-Alkyl Cephalosporins

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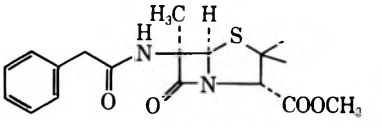
Several 6-alkyl penicillins and 7-alkyl cephalosporins have been prepared. The syntheses of two unique cephalosporins are also discussed.

Although a 6-substituted penicillin has been known for some time,[1] the first generally useful synthetic method for the preparation of 6-substituted penicillins and 7-substituted cephalosporins was published only recently.[2] Since this publication, several papers[3] have appeared describing the synthesis of other 6-alkyl penicillins[4] and 7-alkyl cephalosporins as well as of 6-methoxypenicillins and 7-methoxycephalosporins. These interesting results prompt us to describe some further work we have carried out in this area.

6α-Methylpenicillin V *p*-methoxybenzyl ester (**3**) has been synthesized by the method previously reported (Scheme I). A convenient base for generating the anion of **1** was sublimed potassium *tert*-butoxide. Hydrogenolysis of ester **3** in dioxane–water using 10% palladium on calcium carbonate liberated the free acid, **4**. The stereochemical course of this alkylation has been discussed earlier.[2] Methylation occurs from the sterically less hindered α face of the 6 anion to give the thermodynamically less favored product. The stereochemistry has already been proven by X-ray diffraction analysis on 6-amino-6-α-methylpenicillanic acid methyl ester,[2] and has been corroborated by single-crystal X-ray diffraction analysis[5] on 6α-methyl-6-phenylacetamidopenicillanic acid methyl ester (**5**).



5

In agreement with the assigned stereochemistry is the finding that double irradiation of the C_6 methyl group[6] produces a 24% nuclear Overhauser effect on the C_5 proton.

(1) R. Reiner and R. Zeller, *Helv. Chim. Acta*, **51**, 1905 (1968).

(2) E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).

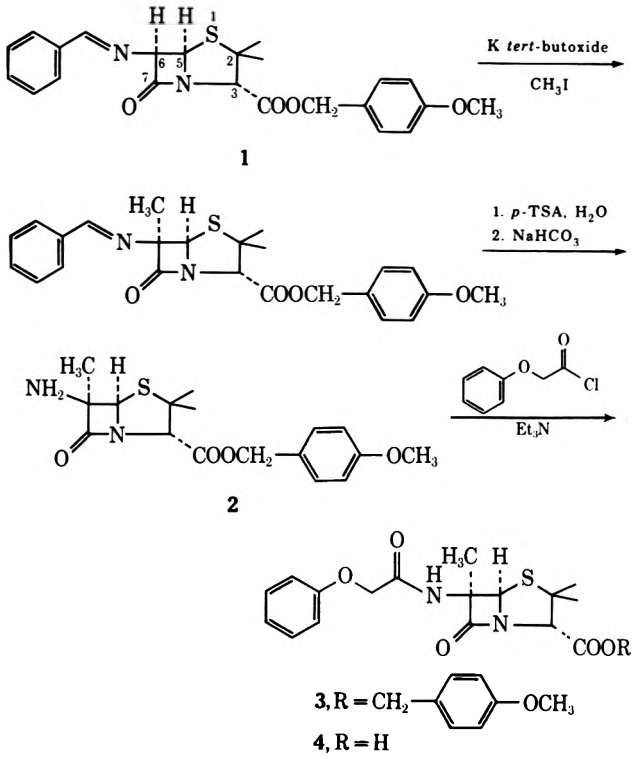
(3) (a) D. Cama, W. J. Leanza, T. R. Beatti, and B. G. Christensen, *ibid.*, **94**, 1408 (1972); (b) S. Karaday, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *ibid.*, **94**, 1410 (1972); (c) R. A. Firestone, N. Scheleshovv, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(4) The stereospecific alkylation of a penicillin at C-6 using a nitrogen ylide has been published previously: G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *J. Amer. Chem. Soc.*, **93**, 2342 (1971).

(5) We wish to thank Professor Jack Z. Gougoutas and Mrs. B. Toeplitz for providing us with this data: Crystallization of **5** from dichloromethane–hexane solvent mixtures gave orthorhombic crystals of space group $P2_12_12_1$ which were used for the analysis (a = 9.75, b = 20.53, c = 9.52 Å, Z = 4, D_0 = 1.277 g/cm³). The R factor before refinement is 0.23 for the 1173 observed reflections. A full account of the refined structure will be published in a separate report.

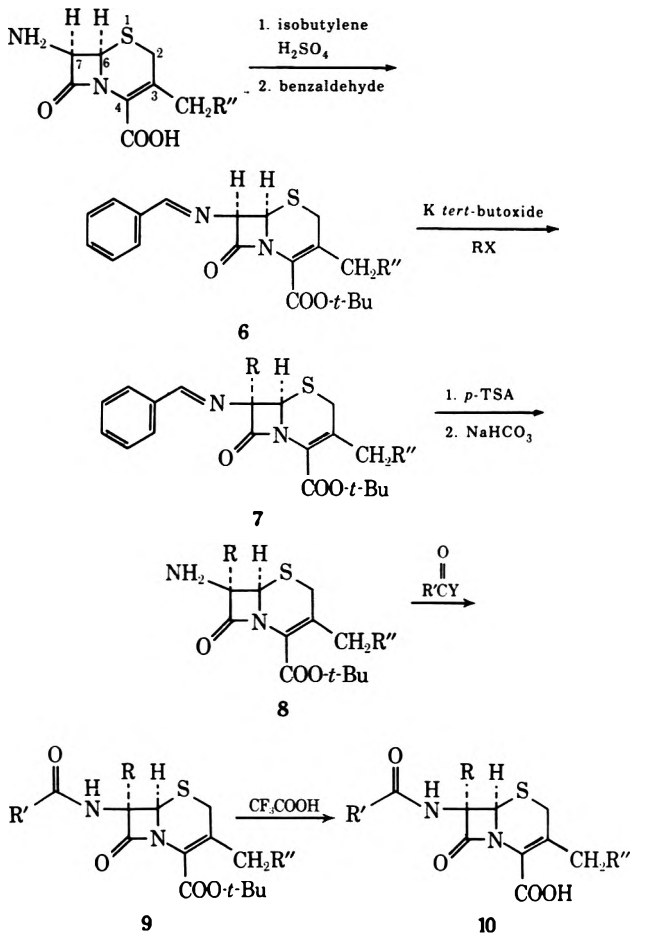
(6) This technique has been used by Firestone, *et al.*,[3c] to determine stereochemistry in a similar series of compounds.

Scheme I

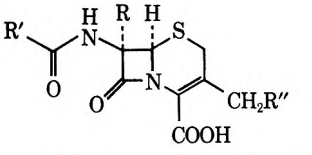


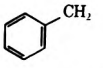
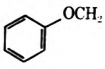
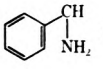
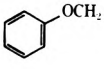
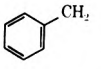
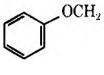
We have also synthesized several cephalosporins by the method described for 6-methylpenicillin V *p*-methoxybenzyl ester. The sequence of reactions is depicted in Scheme II.

Scheme II



In a typical reaction sequence, the *N*-benzylidene Schiff base **6** is dissolved in anhydrous glyme and cooled to −30°. This solution is then treated with 1 equiv of potassium *tert*-butoxide before an alkylating agent, such as methyl iodide, is added. The ensuing reaction mixture is worked up to give the 7-alkylated Schiff base **7** (R = CH_3; R″ = H). The latter is then treated with excess *p*-toluenesulfonic acid (*p*-TSA) and water in ethyl acetate to give the *p*-TSA salt of the free amine **8** (R = CH_3; R″ = H). The amine is liberated with sodium bicarbonate. This amine can then be acylated in the usual manner to give compounds of type **9**. The free acid, **10**, is liberated by treating the *tert*-butyl ester with trifluoroacetic acid. Utilizing the above scheme (Scheme II), the following compounds were prepared.



	R′	R	R″
11		CH_3	H
12[2]		CH_3	H
13	 (D)	CH_3	H
14	CH_3		H
15			H
16			H
17			OAc
18		CH_3	OAc

By analogy with the addition of the alkylating agent to the α side of the molecule in Schiff bases in penicillins,[2] all additions of alkylating agents to the *N*-benzylidene Schiff bases of cephalosporin esters have been assumed to yield products with similar stereochemistry. To obtain corroborative proof for the α addition of alkylating agents to these Schiff bases, the nuclear Overhauser[7] effect (NOE) of 7-amino-7α-methyldeacetoxycephalosporanic acid *tert*-butyl ester (**8**) (R = CH; R″ = H) was studied. It was found that double irradiation of the C-7 methyl group produced a 22% NOE on the C-6 proton. Similarly, when the C-7 methyl of the methyl ester of compound **11** was doubly irradiated, an NOE of 21% on the C-6 proton was observed. The magnitude of this NOE is possible only if we are dealing with the 7α-methylcephalosporins.

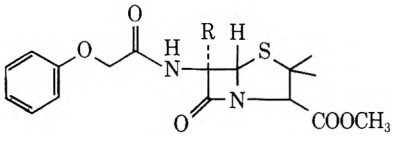
(7) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, N. Y., 1971.

When compounds **4**, **11–13**, and **18** were tested *in vitro*, the biological results[8] indicated that none of these new, substituted penicillin and cephalosporins were more active than their unsubstituted parent against both gram-positive and gram-negative organisms.[9] Against gram-positive organisms, the substituted compounds exhibited no more than 20% of the activity of the parent, whereas, against gram-negative organisms, these compounds were generally inactive at levels up to 200 μg/ml. Interestingly, though, 7-methoxycephalosporin C is reported to be more active toward gram-negative organisms than is cephalosporin C itself.[16] Similarly, 7-methoxycephalothin has been reported[3] to exhibit a spectrum *in vitro* that is similar to that of cephalothin, and to inhibit a number of cephalosporin-resistant organisms.

Since the biological activity in β-lactam antibiotics has been attributed[10,11] directly to an enzymatically catalyzed nucleophilic attack on the β-lactam, in the cephalosporins, a methyl group at the 7 position might tend to stabilize the β-lactam, and hence cause the substantial decrease in biological activity observed. Therefore, a C-7 substituent of greater electronegative character than methyl would make the β-lactam more susceptible to nucleophilic attack. The presence of a more reactive β-lactam might then result in greater biological activity for the whole molecule. In order to demonstrate the change in stability of the β-lactam of these types of compounds, we submitted penicillin V methyl ester,[12] 6-methylpenicillin V methyl ester, and 6-acetylpenicillin V methyl ester to basic hydrolysis[13] (Table I).

TABLE I
FIRST-ORDER RATE CONSTANTS

Compd	K, hr^{-1}, basic solutions (pH 8.0)
19	1.9×10^{-2}
20	0.5×10^{-2}
21	4.5×10^{-2}

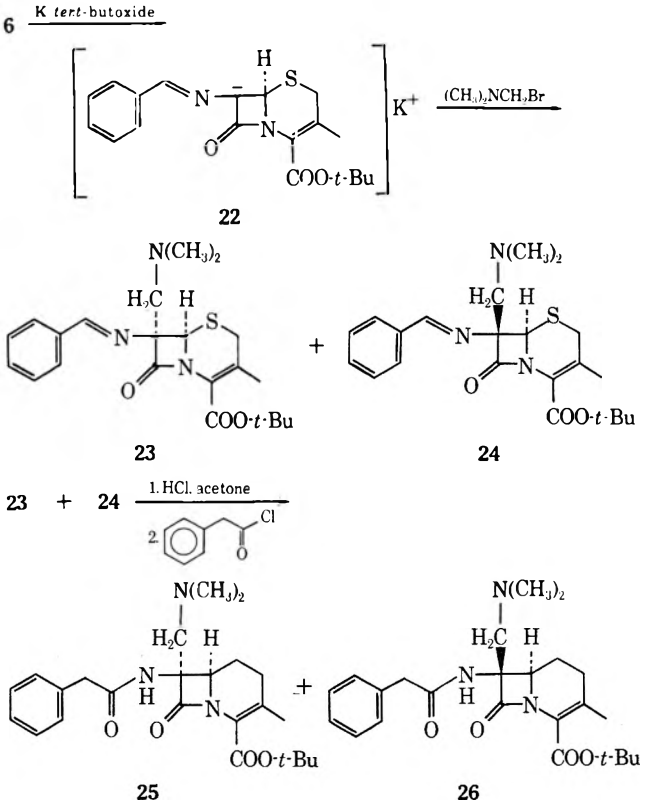


19, R = H
20, R = CH_3
21, R = $OCOCH_3$

As predicted, compound **21** was found to be more susceptible to basic hydrolysis than were the other two. However, when compounds **14–17** were submitted to *in vitro* assay, the biological results[8] indicated that, rather than enhancement of microbiological activity for these 7-acetylcephalosporins over the corresponding 7-methylcephalosporins, a pronounced decrease of activity was observed.

An alkylation with a Mannich-type[14] base was also carried out (Scheme III). Dimethylbromomethyl-

SCHEME III

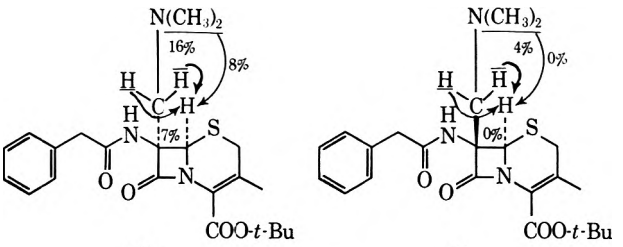


amine[15] was added to the anion **22** in solution and allowed to react for 45 min at room temperature. An approximate 1:1 mixture of α and β isomers of the substituted Schiff bases **23** and **24** resulted. This mixture was then treated with aqueous hydrochloric acid–acetone to give the corresponding free amines. These were acylated to give both the α and β isomers of 7-dimethylaminomethyl-7-phenylacetamidodeacetoxycephalosporanic acid *tert*-butyl ester (**25** and **26**). At this point, the mixture was separated into its two components. As has been shown previously, the C-7 substitutions occur almost stereospecifically from the α face of the molecule. In this case, however, we are dealing with a "reversible alkylation"[14] and, hence, a 1:1 mixture of α and β isomers is not an unlikely result. We were able to make stereochemical assignments to the two components by studying their NOE's. The values for the NOE observed for both **25** and **26** are depicted in Chart I. Because of hindered rotation, the two methylene protons of the dimethylaminomethyl side chain had different chemical shifts and, hence, NOE's could be assigned for each of the two protons.

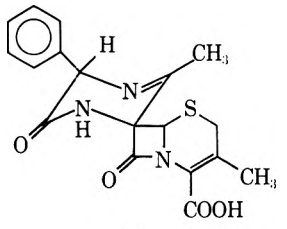
In the course of studying these 7-substituted cephalosporins, we obtained two new and chemically unique structures. The first, **27**, arose when we attempted

(8) The full *in vitro* spectra of these compounds will be reported elsewhere.
(9) F. Pansy, H. Basch, W. Tambor, G. Maestone, R. Semar, and R. Donovick, *Antimicrob. Ag. Chemother.*, 399 (1966).
(10) J. L. Strominger and D. J. Tipper, *Amer. J. Med.*, **30**, 708 (1965).
(11) J. L. Strominger, K. Izaki, M. Matsuhasi, and D. J. Tipper, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **26**, 9 (1967).
(12) G. Gomis, M. Isquierdo, and A. Turado, *Bull. Soc. Chim. Fr.*, 420 (1968).
(13) The lability of β-lactams toward nucleophiles has been studied before: R. J. Washkuhn and J. R. Robinson, *J. Pharm. Sci.*, **60**, 1168 (1971); R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **71**, 2124 (1949); **72**, 2771 (1950); **73**, 3172 (1972).
(14) R. O. C. Norman, "Principles of Organic Synthesis," Methuen London, 1968, p 248.
(15) H. Bohme, E. Mundles, and O. E. Herboth, *Chem. Ber.*, **90**, 2003 (1957).

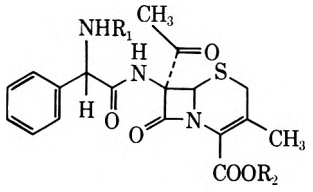
Chart I



to deprotect 7α-acetyl-7-*tert*-butoxycarbonyl-D-phenylglycylaminodeacetoxycephalosporanic acid *tert*-butyl

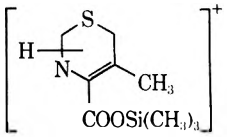


ester (**28**) with trifluoroacetic acid in order to prepare 7α-acetyl-7-phenylglycylaminodeacetoxycephalosporanic acid (**29**). Evidence for structure **27** was



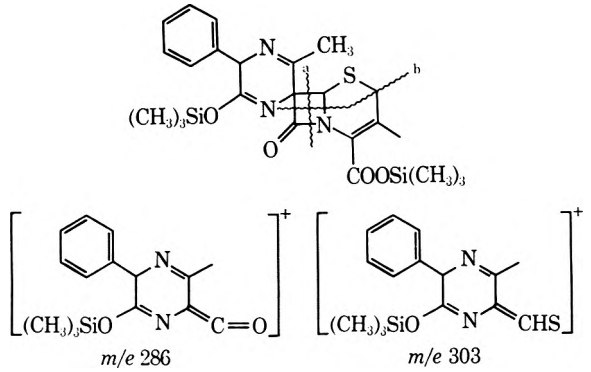
28, R_1 = COO-*t*-Bu; R_2 = *t*-Bu
29, $R_1 = R_2 = H$

obtained by submitting its trimethylsilyl derivative to mass-spectral analysis. The low-resolution spectrum yielded a molecular ion at *m/e* 515 corresponding to the ditrimethylsilylation of **27**. The typical β-lactam type fragmentation at *m/e* 230 corresponding to the following fragment is observed.



m/e 230

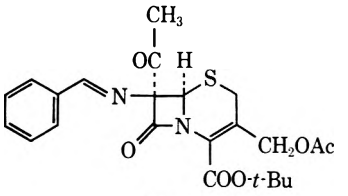
The β-lactam can be cleaved in two ways to give, *via* fragmentation a, the ion *m/e* 286 and, *via* fragmentation b, the ion *m/e* 303. Both of these ions are present



m/e 286 *m/e* 303

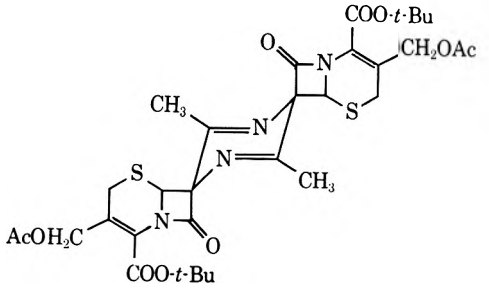
in the spectrum. Electrophoretic studies of compound **27** indicated that it was monoacidic, as evidenced by its charge of -1 at pH 4.0.

The second new and interesting material was formed when *N*-benzylidene-7-α-acetyl-7-aminocephalosporanic acid *tert*-butyl ester (**30**) was treated with dilute,



30

aqueous hydrochloric acid. Instead of the expected free amine, the following dimer (**31**) was the major



31

component of the reaction mixture. The nuclear magnetic resonance spectrum of this compound agreed with the structure assigned. Furthermore, electrophoretic studies showed **31** to be a neutral compound.

From the preceding observations, it is apparent that, in the presence of simple alkyl groups adjacent to the β-lactam carbonyl, the antimicrobial activities of these compounds are lowered and their overall microbiological spectra of inhibition are limited. Also it is apparent that the mere presence of an electron-withdrawing group at that position is not, *per se*, sufficient to improve or maintain the activity of the parent, unsubstituted compound. Whether the methoxy group has a unique effect[16] not generally shared by other electronegative groups is a point which must be established.

Experimental Section

Melting points (corrected) were taken on a Kofler hot stage. Proton nmr spectra were recorded on a Varian T-60 spectrometer. Nuclear Overhauser effects were studied on a Varian XL-100-15 spectrometer on deoxygenated, sealed $CDCl_3$ solutions. Chemical shifts are relative to TMS. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Elemental analyses were performed at the Squibb Institute. Preparative thin layer chromatography was carried out on Quantum PQIF silica gel plates.

***N*-Benzylidene-6-aminopenicillanic Acid *p*-Methoxybenzyl Ester (1).**—6-Aminopenicillanic acid *p*-methoxybenzyl ester (13.3 g, 0.04 mol) was dissolved in 50 ml of benzene; 4.2 g (0.04 mol) of benzaldehyde and 10 g of $MgSO_4$ were added. This mixture was stirred at room temperature for 16 hr before the $MgSO_4$ was removed by filtration. The organic solution was evaporated to dryness *in vacuo* to give 13.7 g (82% yield) of a yellow oil: nmr ($CDCl_3$) 517 (d, J = 2.0 Hz, 1, CH=N), 439 (m, 9, aromatic), 338 (d, J = 4 Hz, 1, C_5 H), 321 (d of d, J = 2 and 4 Hz, 1, C_6 H), 309 (s, 2, CH_2Ph), 264 (s, 1, C_3 H), 225 (s, 3,

(16) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971).

OCH_3), 96 (s, 3, C_2CH_3), 84 Hz (s, 3, C_2CH_3); ir ($CHCl_3$) 1782 (β-lactam), 1738 (ester), 1638 cm^{-1} (imine).

N-Benzylidene-6-amino-6α-methylpenicillanic Acid p-Methoxybenzyl Ester.—Compound 1 (170 mg, 0.4 mequiv) was dissolved in anhydrous glyme (12 ml, distilled from $LiAlH_4$) and cooled to −40°. Methyl iodide (2 ml) was added, followed by the addition of 43.2 mg (0.4 mequiv) of sublimed potassium *tert*-butoxide. The reaction was allowed to proceed under nitrogen atmosphere at −40° for 3 hr. The mixture was then diluted to 100 ml with $CHCl_3$ and washed several times with 50-ml portions of distilled water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 166 mg (95% yield) of a clear oil: nmr ($CDCl_3$) 520 (s, 1, CH=N), 439 (m, 9, aromatic), 321 (s, 1, C_5H), 308 (s, 2, CH_2Ph), 260 (s, 1, C_3H), 227 (s, 3, OCH_3), 106 (s, 3, C_6CH_3), 89 (s, 3, C_2CH_3), 81 Hz (s, 3, C_2CH_3).

6-Amino-6α-methylpenicillanic Acid p-Methoxybenzyl Ester (2).—*N*-Benzylidene-6-amino-6α-methylpenicillanic acid *p*-methoxybenzyl ester (2.58 g, 5.9 mequiv) was dissolved in 75 ml of EtOAc at room temperature. *p*-Toluenesulfonic acid monohydrate, 1.61 g, (8.5 mequiv), and 1.61 ml (0.09 equiv) of distilled water were added. Precipitation of a white solid started almost immediately. The reaction was allowed to proceed for 3 hr before the white solid was filtered off and dried *in vacuo* to give 2.47 g of the salt (80% yield), mp 171–174°. The latter was treated with dilute aqueous $NaHCO_3$ to liberate the crystalline free amine **2**, which was recrystallized from EtOAc–hexane to give 1.33 g (65% yield) of **2**: mp 84–87°; nmr ($CDCl_3$) 426 (q, 4, aromatic), 314 (s, 1, C_6H), 308 (s, 2, CH_2Ph), 265 (s, 1, C_3H), 223 (s, 3, OCH_3), 118 (s, 6, C_6CH_3, C_2CH_3), 83 Hz (s, 3, C_2CH_3); ir ($CHCl_3$) 3380 cm^{-1} ($-NH_2$). *Anal.* Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.53; H, 6.50; N, 7.80.

6α-Methyl-6-phenoxyacetamidopenicillanic Acid p-Methoxybenzyl Ester (3).—Compound **2** (1.33 g, 3.8 mequiv) was dissolved in 50 ml of dry $CHCl_3$ and treated with 652 mg (3.8 mequiv) of phenoxyacetyl chloride and 384 mg (3.8 mequiv) of triethylamine for 4 hr at ice-bath temperature. $CHCl_3$ (150 ml) was then added and this organic solution was washed twice with 50-ml portions of 0.1 *N* HCl and twice with 50-ml portions of distilled water before being dried ($MgSO_4$) and evaporated to dryness *in vacuo*. **3** (1.89 g) was isolated as a colorless oil: nmr ($CDCl_3$) 425 (m, 9, aromatic), 324 (s, 1, C_5H), 305 (s, 2, CH_2Ph), 267 (s, 2, OCH_2CO), 263 (s, 1, C_3H), 226 (s, 3, OCH_3), 108 (s, 3, C_6CH_3), 85 (s, 3, C_2CH_3), 80 Hz (s, 3, C_2CH_3).

6α-Methyl-6-phenoxyacetamidopenicillanic Acid (4).—Compound **3** (570 mg) was dissolved in a 10 ml dioxane–2 ml water mixture; 1.2 g of 10% palladium on calcium carbonate catalyst was added. This mixture was hydrogenolyzed at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. This occurred after 4 hr, and 14 ml of hydrogen had been taken up (53% of theoretical). The catalyst was removed by filtration through Celite. The filtrate was diluted with 75 ml of $CHCl_3$ and washed twice with 15 ml of saturated aqueous $NaHCO_3$. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness to give 345 mg of colorless oil, mainly starting material (**3**). The aqueous $NaHCO_3$ (30 ml) was acidified to pH 1 with 5 *N* aqueous HCl. This solution was extracted with five 50-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo* to yield 168 mg of amorphous material: mass spectrum M^+ *m/e* 364; nmr ($CDCl_3$) 473 (s, 1, COOH), 427 (m, 5, aromatic), 326 (s, 1, C_5H), 372 (s, 2, OCH_2CO), 119 (s, 3, C_6CH_3), 91 and 89 Hz (s, 6, C_2CH_3); ir ($CHCl_3$) 3330 and 2616 (COOH), 1780 cm^{-1} (β-lactam).

***N*-Benzylidene-7-aminodeacetoxycephalosporanic Acid *tert*-Butyl Ester (6) (R = H).**—Concentrated sulfuric acid (30 ml) was added to 600 ml of dioxane in a 1-l. pressure bottle and chilled in an ice bath until the solution began to freeze. Liquid isobutylene (200 ml) and 30.0 g of 7-aminodeacetoxycephalosporanic acid were then added. The pressure bottle was stoppered, clamped in frame, and shaken overnight at room temperature. The reaction mixture was rechilled in ice prior to opening of the pressure bottle. The solution was poured into a stirred, ice-cold solution of 150 g of $NaHCO_3$ in 2.5 l. of water and extracted with three 800-ml portions of $CHCl_3$. The organic extracts were washed with water and saturated NaCl, dried ($MgSO_4$), and stripped to dryness *in vacuo*, yielding 25 g (66% yield) of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester as a yellow, crystalline solid. These 25 g (92.5 mequiv) were immediately dissolved in 450 ml of benzene. Benzaldehyde (9.8 g, 92.5 mequiv) and 50 g of anhydrous $MgSO_4$ were then added. This mixture was stirred for 2 hr at room temperature before it was filtered and evaporated to dryness *in vacuo*. The yellow, crystalline product was recrystallized from benzene to yield a total of 30.8 g of **6** (R″ = H) (93% yield), mp 118–119°. *Anal.* Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.37; H, 6.40; N, 7.65.

***N*-Benzylidene-7-amino-7α-methyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (7) (R = CH_3; R″ = H).**—Compound **6** (500 mg, 1.4 mequiv) was dissolved in 25 ml of anhydrous glyme and cooled to −30° before 156 mg (1.4 mequiv) of potassium *tert*-butoxide was added. The anion was allowed to form under nitrogen for a few minutes, and then 2 ml of methyl iodide was added. The reaction was allowed to proceed at −30° and under nitrogen for 20 min. The mixture was diluted with 100 ml of $CHCl_3$ and washed with 50 ml of distilled water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 512 mg of slightly yellow crystals (97% crude yield) (recrystallized from CH_2Cl_2–hexane): mp 138–140°; nmr ($CDCl_3$) 526 (s, CH=N–), 451 (s, 5, aromatic), 388 (s, 1, C_6H), 216 (d, J = 19 Hz, 1, C_2H), 184 (d, J = 18 Hz, 1, C_2H), 124 (s, 3, $\geq CH_3$), 110 (s, 3, C_7CH_3), 96 Hz (s, 9, *t*-Bu). *Anal.* Calcd for $C_{20}H_{24}N_2O_3S$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.38; H, 6.33; N, 7.41.

7-Amino-7α-methyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (8) (R = CH_3; R″ = H).—Compound **7** (R = CH_3; R″ = H) (5.72 g, 15.4 mequiv) was dissolved in 140 ml of EtOAc at room temperature, and then 2.93 g (15.4 mequiv) of *p*-toluenesulfonic acid and 28 ml of water were added. In 2 min, a white precipitate began to form. The reaction was continued for another 2 hr before the white solid was removed by filtration. The latter was redissolved in 100 ml of $CHCl_3$ and shaken well with 100 ml of 5% $NaHCO_3$. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give 1.63 g of white, crystalline **8** (R = CH_3; R″ = H) (36.3% yield), recrystallized from benzene: mp 132–133°; nmr ($CDCl_3$) 278 (s, 1, C_6H), 212 (d, J = 18 Hz, 1, C_2H), 195 (d, J = 18 Hz, 1, C_2H), 122 (s, 5, NH_2 and $\geq CH_3$), 112 (s, 3, C_7CH_3), 92 Hz (s, 9, *t*-Bu); ir (Nujol) 3390 (NH_2), 1780 (β-lactam), 1750 cm^{-1} (*t*-Bu ester). *Anal.* Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.67; H, 6.89; N, 9.71.

7α-Methyl-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (9) (R = CH_3; R″ = H).—Compound **8** (R = CH_3; R″ = H) (310 mg, 1.08 mequiv) was dissolved in 25 ml of anhydrous $CHCl_3$. Phenylacetyl chloride (170 mg, 1.09 mequiv) and 110 mg (1.09 mequiv) of triethylamine were added. The reaction was allowed to proceed for 4 hr at room temperature under nitrogen before being diluted with 100 ml of $CHCl_3$. The organic layer was washed first with 50 ml of 0.1 *N* HCl and then with 50 ml of water, dried ($MgSO_4$), and evaporated to dryness to give 413 mg of oil (94% yield): nmr ($CDCl_3$) 436 (s, 5, aromatic), 410 (s, 1, NH), 284 (s, 1, C_6H), 213 (s, 2, $PhCH_2CO$), 200 (d, J = 19 Hz, 1, C_2H), 179 (d, J = 19 Hz, C_3H), 123 (s, 3, $\geq CH_3$), 107 (s, 3, C_7CH_3), 89 Hz (s, 9, *t*-Bu).

7α-Methyl-7-phenylacetamidodeacetoxycephalosporanic Acid (11).—Compound **9** (R = CH_3; R′ = C_6H_5; R″ = H) (783 mg) was treated with 3 ml of trifluoroacetic acid (TFA) at room temperature for 5 min. Excess TFA was removed by evaporation before the residue was dissolved in 50 ml of $CHCl_3$. This solution was extracted with two 10-ml portions of saturated $NaHCO_3$. The combined $NaHCO_3$ layers were acidified with 5 *N* HCl to pH 1 and extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried ($MgSO_4$), and evaporated to dryness to give 437 mg of white crystals **11** (48% yield), recrystallized from EtOAc: mp 99–105°; mass spectrum M^+ *m/e* 346; nmr ($CDCl_3$) 436 (s, 5, aromatic), 389 (s, 1 NH), 284 (s, 1, C_6H), 215 (s, 2, $PhCH_2CO$), 192 (s, 2, SCH_2), 128 (s, 3, $\geq CH_3$), 120 Hz (s, 3, C_7CH_3); ir (Nujol) 3290, 2590 (COOH), 1770 (β-lactam), 1715 (COOH), 1700 (amide I), 1550 cm^{-1} (amide II). Analysis of this compound was not possible, since the molecule seemed to retain about one molecule of solvent. Any prolonged heating *in vacuo*, even at 60°, decomposed the material.

7α-Methyl-7-phenylglycylaminodeacetoxycephalosporanic Acid (13).—*N*-*tert*-Butoxycarbonylphenylglycine (705 mg, 2.7 mequiv) was dissolved in 20 ml of anhydrous tetrahydrofuran (THF) and stirred at −5°. Triethylamine (272 mg, 2.7 mequiv) and 370 mg (2.7 mequiv) of isobutyl chloroformate were added and the stirring was continued for 30 min. Compound **8** (R =

CH_3; R'' = H) (819 mg, 2.7 mequiv) in 15 ml of anhydrous TFA was added. The temperature of the reaction was allowed to rise to 23°, and stirring was continued for another 2 hr. The mixture was poured into 50 ml of ice-cold water and 50 ml of $CHCl_3$. The pH was raised to 7.5 and, after shaking, the layers were separated. The aqueous layer was extracted once more with 50 ml of $CHCl_3$. The organic layers were combined, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give 1.48 g (99% yield) of the deprotected acid **13**: nmr ($CDCl_3$) 441 (s, 5, aromatic), 390 (s, 1, CONH), 348 (d, J = 6 Hz, 1, PhNCHCO), 311 [d, J = 6 Hz, 1, $NHCOOC(CH_3)_3$], 284 (s, 1, C_6H), 192 (d, J = 4 Hz, 2, SCH_2), 123 (s, 3, $\geqslant CH_3$), 109 (s, 3, C_7CH_3), 91 and 83 Hz each (s, 9, *t*-Bu); ir ($CHCl_3$) 3410 (NH), 1775 (β-lactam), 1720 and 1710 (esters), 1690 (amide I), 1480 cm^{-1} (amide II). The latter was treated with 5 ml of TFA at 0° for 5 min. The solution was evaporated to dryness *in vacuo*, and the residue was triturated several times with ether to leave 540 mg of an off-white, amorphous powder (TFA salt of **13**, 70% yield): nmr (CD_3OD) 452 (m, 5, aromatic), 185 (s, 2, SCH_2), 123 (s, 3, $\geqslant CH_3$), 99 Hz (s, 3, C_7CH_3); ir (Nujol) 3400, 2600 (COOH), 1760 (β-lactam), 1680 (amide I and carboxylate, 1540 cm^{-1} (amide II). Compound **13** was liberated by dissolving its TFA salt in 20 ml of water and passing this solution through 50 g of IR 4B ion-exchange resin. The aqueous extracts were lyophilized to give 259 mg of **12**: mp 150–154° dec; nmr (DMSO-d_6) 441 (m, 5, aromatic), 200 (s, 2, SCH_2), 124 (s, 3, $\geqslant CH_3$), 95 Hz (s, 3, C_7CH_3).

N-Benzylidene-7α-acetyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (7) (R = $COCH_3$; R'' = H).—The procedure for the preparation of **7** (R = CH_3; R'' = H) was followed, except that the equivalents of acetyl chloride, rather than of methyl iodide, were used to quench the anion. Compound **7** (R = $COCH_3$; R'' = H) was prepared in this manner as white crystals (95% yield), recrystallized from EtOAc–hexane: mp 138–139°; nmr ($CDCl_3$) 533 (s, 1, CH=N), 460 (m, s, aromatic), 327 (s, 1, C_7H), 213 (d, J = 18 Hz, 1, C_2H), 180 (d, J = 18 Hz, 1, C_2H), 142 (s, 3, $COCH_3$), 124 (s, 3, $\geqslant CH_3$), 93 (s, 9, *t*-Bu).

Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.91; H, 6.29; N, 6.93.

7-Acetamido-7α-acetyldeacetoxycephalosporanic Acid (14).—The procedure for the preparation of **9** (R = CH_3; R'' = H) was followed, except that acetyl chloride was used as the acylating agent and **7** (R = $COCH_3$; R'' = H) was the starting Schiff base. The *tert*-butyl ester of **14** was isolated in 66% yield as white crystals recrystallized from EtOAc: mp 168–169°; nmr ($CDCl_3$) 470 (s, 1, NH), 331 (s, 1, C_6H), 210 (d, J = 16 Hz, 1, C_2H), 188 (d, J = 18 Hz, 1, C_2H), 139 (s, 3, $COCH_3$), 129 and 127 (2, s, 6, $\geqslant CH_3$ and CH_3CONH), 90 Hz (s, 9, *t*-Bu); ir (Nujol) 3250 (NH), 1778 (β-lactam), 1720 (ester), 1611 cm^{-1} (amide).

Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.33; H, 6.26; N, 7.91. Found: C, 54.16; H, 6.11; N, 7.82.

By following the procedure for synthesis of free acid **11**, **14** was prepared in 67% yield, recrystallized from EtOAc: mp 181–183°; nmr (CD_3OD) 333 (s, 1, C_6H), 2.5 (d, J = 18 Hz, 1, C_2H), 192 (d, J = 16 Hz, 1, C_2H), 135 (s, 3, $COCH_3$), 126 Hz [s, 3, CH, CONH (?)] [s, 3, $\geqslant CH_3$ (?)].

Anal. Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.10; H, 5.00; N, 9.17.

7α-Acetyl-7-phenylacetamidodeacetoxycephalosporanic Acid (15).—The procedure for the preparation of **14** was followed, except that phenylacetyl chloride was used as the acylating agent. The *tert*-butyl ester of **15** was isolated as white crystals recrystallized from EtOAc: mp 155–156°; nmr ($CDCl_3$) 457 (s, 1, NH), 430 (s, 5, aromatic), 328 (s, 1, C_6H), 218 (s, 2, CH_2CO), 205 (d, J = 18 Hz, 1, C_2H), 195 (d, J = 18 Hz, 1, C_2H), 131 (s, 3, $COCH_3$), 125 (s, 3, $\geqslant CH_3$), 89 Hz (s, 9, *t*-Bu).

Anal. Calcd for $C_{22}H_{26}N_2O_5S$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.18; H, 6.21; N, 6.48.

Free acid **15** was isolated and recrystallized from EtOAc–hexane: mp 129–130°; nmr ($CDCl_3$) 530 (s, 1, COOH), 451 (s, 1, NH), 438 (s, 5, aromatic), 327 (s, 1, C_6H), 219 (s, 2, CH_2CO), 195 (s, 2, CH_2S), 131 Hz (s, 6, CH_3CO and $\geqslant CH_3$).

Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.94; H, 5.10; N, 7.20.

7α-Acetyl-7-phenoxyacetamidodeacetoxycephalosporanic Acid (16).—Compound **7** (R = $COCH_3$; R'' = H) (1 g, 2.5 mequiv) was dissolved in 5 ml of $CHCl_3$ and cooled in an ice bath. Phenoxyacetyl chloride (426 mg, 2.5 mequiv) and 1 drop of water were added. The reaction was allowed to proceed at 3° for 16 hr before being diluted with 100 ml of $CHCl_3$. This organic solution was washed with 50 ml of dilute aqueous $NaHCO_3$ and 50 ml of dilute aqueous HCl with two 50-ml portions of water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo* to give 1.0 g of the crystalline *tert*-butyl ester of **16** (97% crude yield) recrystallized from isopropyl alcohol–hexane: mp 165–166°; nmr ($CDCl_3$) 459 (s, 1, NH), 429 (m, 5, aromatic), 328 (s, 1, C_6H), 276 (s, 2, OCH_2), 200 (s, 1, SCH_2), 141 (s, 3, $COCH_3$), 131 (s, 3, $\geqslant CH_3$), 91 Hz (s, 9, *t*-Bu).

Anal. Calcd for $C_{22}H_{26}N_2O_6S$: C, 59.18; H, 5.87; N, 6.28. Found: C, 58.90; H, 5.92; N, 6.23.

The free acid **16** was liberated from its *tert*-butyl ester as described previously for compound **11**. Compound **16** was obtained as an amorphous material (72% yield): nmr ($CDCl_3$) 545 (s, 1, COOH), 469 (s, 1, NH), 430 (m, 5, aromatic), 338 (s, 1, C_6H), 279 (s, 2, CH_2O), 200 (broad singlet, 2, CH_2S), 143 (s, 3, $COCH_3$), 137 Hz (s, 3, $\geqslant CH_3$); ir ($CHCl_3$) 3250, 2580 (COOH), 1775 (β-lactam), 1720 (COOH), 1690 (amide I), 1600 (aromatic), 1550 cm^{-1} (amide II).

N-Benzylidene-7-aminocephalosporanic Acid *tert*-Butyl Ester (6) (R'' = OAc).—The procedure for the preparation of **6** (R'' = H) was followed using 7-aminocephalosporanic acid to give a 38.5% yield of **6**: nmr ($CDCl_3$) 518 (d, J = 3 Hz, 1, CH=N), 456 (m, 5, aromatic), 326 (d of d, J = 3 and 6 Hz, 1, C_7H), 309 (d, J = 6 Hz, 1, C_6H), 305 (d, J = 14 Hz, 1, CHOAc), 284 (d, J = 14 Hz, CHOAc), 218 (d, 18 Hz, 1, C_2H), 196 (d, J = 18 Hz, 1, C_2H), 123 (s, 3, $OCOCH_3$), 93 Hz (s, 9, *t*-Bu); ir ($CHCl_3$) 1778 (β-lactam), 1735 (ester), 1720 (acetate), 1640 cm^{-1} (imine).

7α-Acetyl-7-phenylacetamidocephalosporanic Acid (17).—The procedure for the preparation of **15** was followed, substituting **6** (R'' = OAc) for **6** (R'' = H). The *tert*-butyl ester of **17** was isolated in 36% crude yield from **6** (R'' = OAc) crystallized from EtOAc–hexane: mp 135–136°; nmr ($CDCl_3$) 440 (s, 5, aromatic), 330 (s, 1, C_6H), 306 (d, J = 12.0 Hz, 1, CHOAc), 288 (d, J = 12.0 Hz, 1, CHOAc), 219 (s, 2, CH_2Ph), 216 (d, J = 18.0 Hz, 1, C_2H), 192 (d, J = 18.0 Hz, 1, C_2H), 131 (s, 3, C_7COCH_3), 124 (s, 3, $OCOCH_3$), 88 Hz (s, 9, *t*-Bu).

Anal. Calcd for $C_{24}H_{28}N_2O_7S$: C, 59.01; H, 5.78; N, 5.74. Found: C, 59.21; H, 6.02; N, 5.57.

Free acid **17** was prepared in 85% crude yield recrystallized from MeOH–$CHCl_3$: mp 169–170°; nmr (CD_3OD) 436 (s, 5, aromatic), 333 (s, 1, C_6H), 308 (d, J = 14 Hz, 1, CHOAc), 289 (d, J = 14 Hz, 1, CHOAc), 222 (d, J = 18 Hz, 1, C_2H), 198 (d, J = 18 Hz, 1, C_2H), 127 (s, 3, C_7COCH_3), 123 Hz (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{20}H_{20}N_2O_7S$: C, 55.55; H, 4.66; N, 6.48. Found: C, 55.43; H, 4.80; N, 6.18.

7α-Methyl-7-phenoxyacetamidocephalosporanic Acid (18).—The procedure for the preparation of **17** was followed, using methyl iodide as the alkylating agent and phenoxyacetyl chloride as the acylating agent. The *tert*-butyl ester of **18** was isolated and purified by preparative thin layer chromatography on silica gel (4% acetone in $CHCl_3$) (19% yield from **6**, R'' = OAc): mass spectrum m/e 476; nmr ($CDCl_3$) 426 (m, 5, aromatic), 306 (d, J = 13 Hz, 1, CHOAc), 294 (d, J = 13 Hz, 1, CHOAc), 290 (s, 1, C_6H), 269 (s, 2, OCH_2), 214 (d, J = 18 Hz, 1, C_2H), 192 (d, J = 18 Hz, 1, C_2H), 124 (s, 3, $OCOCH_3$), 114 (s, 3, C_7CH_3), 94 Hz (s, 9, *t*-Bu).

Free acid **18** was obtained in 43% yield from its *tert*-butyl ester: nmr ($CDCl_3$) 425 (m, 5, aromatic), 312 (d, J = 15 Hz, 1, CHOAc), 292 (d, J = 15 Hz, 1, CHOAc), 293 (s, 1, C_6H), 273 (s, 2, CH_2O), 203 (broad singlet, 2, CH_2S), 125 (s, 3, $OCOCH_3$), 115 Hz (s, 3, C_7CH_3).

6α-Methyl-6-phenoxyacetamidopenicillanic Acid Methyl Ester (20).—*N*-Benzylidene-6-amino-6α-methylpenicillanic acid methyl ester[1] (2.9 g, 8.5 mequiv) was dissolved in 50 ml of $CHCl_3$ and stirred with 1.45 g (8.5 mequiv) of phenoxyacetyl chloride and 2 drops of water for 2 hr at room temperature. The reaction mixture was then diluted with 150 ml of $CHCl_3$ and washed with 50 ml of 0.1 *N* HCl, 50 ml of dilute $NaHCO_3$, and two 50-ml portions of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to leave an oil. This oil was purified on preparative silica gel thin layer chromatography using chloroform as the eluent. Compound **20** (707 mg) was isolated as an oil (23% yield): nmr ($CDCl_3$) 430 (m, 6, aromatic and NH), 328 (s, 1, C_5H), 272 (s, 2, OCH_2CO), 266 (s, 1, C_3H), 226 (s, 3, OCH_3), 110 (s, 3, C_6CH_3), 91 Hz [s, 6, $C_2(CH_3)_2$]; ir ($CHCl_3$) 3320 (amide), 1780 (β-lactam), 1740 (ester), 1685 (amide I), 1600 (aromatic), 1520 cm^{-1} (amide II).

6α-Acetyl-6-phenoxyacetamidopenicillanic Acid Methyl Ester (21).—*N*-Benzylidene-6-aminopenicillanic acid methyl ester (3.39 g, 10.3 mequiv) was dissolved in 100 ml of glyme and cooled to −40° under nitrogen, 1.16 g (10.3 mequiv) of potassium *tert*-butoxide was added, and the anion was allowed to form for 3 min. Acetyl chloride (810 mg, 10.3 mequiv) was added and the reaction was allowed to proceed at −40° for 5 min. The reaction mixture was diluted with 150 ml of $CHCl_3$ and washed with three 100-ml portions of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 3.6 g of *N*-benzylidene-6α-acetylpenicillanic acid methyl ester as an oil which did not crystallize (93% crude yield): nmr ($CDCl_3$) 527 (s, 1, CH=N), 457 (m, 5, aromatic), 353 (s, 1, C_5 H), 263 (s, 1, C_3 H), 225 (s, 3, OCH_3), 139 (s, 3, $COCH_3$), 91 and 87 Hz [2, s, 6, $C_2(CH_3)_2$]. This oil (3.37 g, 9.35 mequiv) was dissolved in 100 ml of $CHCl_3$ and cooled to 0°, and then 1.6 g (9.35 mequiv) of phenoxyacetyl chloride and 0.5 ml of water were added. After the reaction was completed (45 min), 150 ml of $CHCl_3$ was added to the reaction mixture and this solution was washed with 100 ml each of 0.1 *N* HCl, dilute $NaHCO_3$, and water. The organic extract was dried ($MgSO_4$) and evaporated to dryness to leave 3.45 g of yellow oil, which was purified by preparative silica gel thin layer chromatography using 10% hexane in $CHCl_3$ as the eluent. Compound 21 was isolated as an oil (523 mg) that could not be crystallized: nmr ($CDCl_3$) 475 (s, 1, NH), 421 (m, 5, aromatic), 360 (s, 1, C_5 H), 277 (s, 2, OCH_2CO), 269 (s, 1, C_3 H), 226 (s, 3, OCH_3), 139 (s, 3, $COCH_3$), 87 Hz [s, 6, $C_2(CH_3)_2$]; ir ($CHCl_3$) 3330 (amide), 1785 (β-lactam), 1745 (ester), 1685 (amide I), 1600 (aromatic), 1500 cm^{-1} (amide II).

7α-Acetyl-7-*tert*-butoxycarbonylphenylglycylaminodeacetoxycephalosporanic Acid *tert*-Butyl Ester (28).—The procedure for the preparation of 13 was followed, except that 8 (R = $COCH_3$; R″ = H) was used as the starting free amine. The crude yield of 28 was 95%. The product, however, failed to crystallize and was, therefore, purified by preparative thin layer chromatography on silica gel using $CHCl_3$ as the eluent. After this purification, 28 was isolated as an oil in 51% yield: nmr ($CDCl_3$) 440 (m, 5, aromatic), 341 (d, J = 7 Hz, 1, PhCNHCO), 324 (s, 1, C_6 H), 317 (d, J = 7 Hz, 1, NHCOO-*t*-Bu), 198 (d, J = 18 Hz, 1, C_2 H), 177 (d, J = 18 Hz, 1, C_2 H), 137 (s, 3, $COCH_3$), 124 (s, 3, $\geq CH_3$), 90 (s, 9, *t*-Bu), 85 Hz (s, 9, *t*-Bu).

Compound 27.—Compound 28 (50 mg, 0.9 mequiv) was dissolved in 2 ml of TFA and allowed to stand at room temperature for 2 min. Excess TFA was removed *in vacuo* to leave 25 mg of a brown glass: mass spectrum M^+ *m/e* 515, 286, 303; nmr (D_2O–CF_3COOH) 451 (s, 5, aromatic), 318 (s, 1, C_6 H), 199 (d, J = 18 Hz, 1, C_2 H), 174 (d, J = 18 Hz, 1, C_2 H), 141 (s, 3, $COCH_3$), 124 Hz (s, 3, $\geq CH_3$); electrophoresis, Eh value[17] −53.

Dimer 31.—Compound 7 (R = $COCH_3$; R″ = OAc) (100 mg, 0.25 mequiv) was dissolved in 2 ml of acetone and stirred with 1 ml of 0.1 *N* HCl for 10 min at room temperature. The reaction mixture was poured into ice water and extracted twice with 50 ml of $CHCl_3$. The combined $CHCl_3$ extracts were washed with distilled water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*, to give 76 mg of a clear glass: nmr ($CDCl_3$) 309 (s, 2, CH_2OAc), 294 (s, 1, C_6 H), 219 (d, J = 18 Hz, 1, C_2 H), 198 (d, J = 18 Hz, 1, C_2 H), 148 (s, 3, $\geq CH_3$), 124 (s, 3, $OCOCH_3$), 92 Hz (s, 9, *t*-Bu); electrophoresis, Eh value[17] 0.

7α-Dimethylaminomethyl-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (25) and the 7β Isomer (26).—Compound 6 (R″ = H) (4 g, 11.2 mequiv) was dissolved in 200 ml of anhydrous glyme and cooled to −30°, and then 1.25 g (11.2 mequiv) of potassium *tert*-butoxide was added under nitrogen. The anion was allowed to develop for about 10 min before 1.54 g (11.2 mequiv) of dimethylbromomethylamine was added. The reaction mixture was allowed to come to room temperature over a 2-hr period before being poured into 100 ml of distilled water. This mixture was then extracted three times with 75-ml portions of $CHCl_3$. The organic extracts were combined, washed with water, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give 4.4 g of oil. This oil was taken up in 50 ml of acetone and shaken with 100 ml of 0.1 *N* HCl for 25 min. Distilled water (250 ml) was added, and this acidic solution was washed with 200 ml of $CHCl_3$. The acidic aqueous layer was brought to pH 7.5 with dilute $NaHCO_3$ and then extracted four times with 100-ml portions of $CHCl_3$. The organic extracts were combined, washed with 150 ml of water, dried ($MgSO_4$), and evaporated to dryness to give 2.15 g of oil 8 [R = α- and β-$CH_2N(CH_3)_2$, R″ = H, yield 46%]. The oil (6.85 mequiv) was dissolved in 50 ml of dry $CHCl_3$ and treated with 1.01 g (6.55 mequiv) of phenylacetyl chloride and 6.65 mg (6.55 mequiv) of triethylamine at room temperature, under nitrogen, for 35 min. The reaction mixture was diluted with 100 ml of $CHCl_3$, then washed with 100 ml of 0.1 *N* HCl followed by 100 ml of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 2.64 g of yellow oil. Thin layer chromatography on silica gel (Eastman chromagram plates, 6060 silica gel) showed that the oil consisted of two major and at least three minor components. It was, therefore, purified by preparative thin layer chromatography on silica gel, using $CHCl_3$ as the eluent. By this method of purification, 410 mg of 25 [14% yield, mass spectrum *m/e* 446; nmr ($CDCl_3$) 438 (s, 5, aromatic), 283 (s, 1, C_6 H), 209 (s, 3, CH_2CON), 190 (d, J = 6 Hz, 4, C_2 CH_2 and CH_2N), 143 (s, 6, $N(CH_3)_2$), 126 (s, 3, $\geq CH_3$), 91 Hz (s, 6, *t*-Bu)], and 421 mg of 26 [14.4% yield; mass spectrum M^+ *m/e* 446; nmr ($CDCl_3$) 440 (s, 5, aromatic), 316 (s, 1, C_6H), 217 (s, 2, CH_2CON), 202 (s, J = 10 Hz, 1, C_2 H), 183 (d, J = 10 Hz, 1, C_2 H), 173 (d, J = 14 Hz, 1, $CHN(Me)_2$), 153 (d, J = 14 Hz, 1, $CHN(Me)_2$), 128 (s, 6, $N(CH_3)_2$), 120 (s, 3, $\geq CH_3$), 96 Hz (s, 9, *t*-Bu)] were isolated as oils.

Stability Studies.—Two sets of solutions of 19, 20, and 21, *ca.* 3 mg/ml, were prepared: (a) 1:1 glyme/citrate buffer, pH 8.0; (b) 1:1 glyme/citrate buffer, pH 3.0. The citrate buffers were prepared from 0.1 *M* citric acid solution adjusted to the proper pH values with NaOH pellets. The penicillin solutions were kept in stoppered flasks at 50°.

Samples were assayed at various times by iodometric titration. A 1-ml aliquot was hydrolyzed for 30 min with 1 ml of 1 *N* NaOH, then acidified with 1 ml of 1 *N* HCl. Phthalate buffer (5 ml, pH 4.5) and 10.0 ml of 0.01 *N* iodine solution were added, and the solution was allowed to stand for 30 min. Excess iodine was titrated with 0.01 *N* sodium thiosulfate. Phthalate buffer (5 ml) and 10.0 ml of iodine solution were added to a second 1-ml aliquot, which was then allowed to stand for 30 min. Excess iodine was titrated with the thiosulfate solution. The percentage assay was calculated from these titer values.

Registry No.—1, 36954-77-5; 2, 36954-78-6; 3, 36954-79-7; 4, 36954-80-0; 6 (R″ = H), 36954-81-1; 6 (R″ = OAc), 36954-82-2; 7 (R = CH_3; R″ = H), 33627-23-5; 7 (R = $COCH_3$; R″ = H), 36954-84-4; 8 (R = CH_3; R″ = H), 36954-85-5; 9 (R = CH_3; R″ = H), 36954-86-6; 11, 36994-24-8; 12, 32956-88-0; 13, 37156-99-3; 14, 36954-88-8; 14 (*t*-Bu ester), 36954-89-9; 15, 36954-90-2; 15 (*t*-Bu ester), 36954-91-3; 16, 36954-92-4; 16 (*t*-Bu ester), 36954-93-5; 17, 36954-94-6; 17 (*t*-Bu ester), 36954-95-7; 18, 36954-96-8; 18, (*t*-Bu ester), 36954-97-9; 20, 36954-98-0; 21, 36954-99-1; 25, 36955-00-7; 26, 36955-01-8; 27, 36955-02-9; 28, 36955-03-0; 31, 36955-04-1; *N*-benzylidene-6-amino-6α-methylpenicillanic acid *p*-methoxybenzyl ester, 36955-05-2; *N*-benzylidene-6α-acetylpenicillanic acid methyl ester, 36955-06-3.

Acknowledgment.—We are indebted to Mr. Octavian Kocy and Mrs. Clara Smith for the electrophoretic data. We are also indebted to Mr. Harold Basch for biological data, to Dr. Harold Jacobson and Mrs. Veronica Valenti for the hydrolysis study, and to Mr. Joseph Alicino for the elemental analyses. We are especially thankful to Professor Jack Strominger, who has followed our work with great interest.

(17) Eh value is the ratio of the migration of the compound in centimeters to the distance between caffeine and picric acid multiplied by 100.

Steroidal Adducts. V.[1] Further Studies of the Reactions of Steroidal Dienes with Tetracyanoethylene

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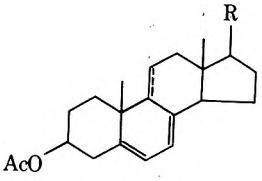
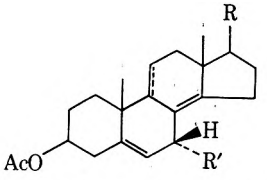
Two new compounds from reactions of ergosteryl acetate 1 with tetracyanoethylene are assigned structures 8 and 9 from analytical and spectral data. Mass spectra of the reaction products are described. Reactions in this series are considered in the light of steric effects on ene and Diels–Alder reactions.

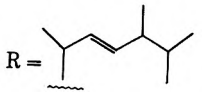
In a recent paper of this series,[4] some reactions of tetracyanoethylene with ergosteryl acetate (1), 9(11)-dehydroergosteryl acetate 2, and related steroids were described. While the chief products from compounds 1 and 2 were the ene adducts 3 and 4, both were accompanied, for the 9(11)-dehydro compound to a major extent, by the dehydrogenated adduct 5. Compound 5 was also produced by mild thermal decomposition of 4 in the presence of tetracyanoethylene. This compound was suggested to arise from an intermediate pentaene 6, whose origin from 4 was inferred from the isolation of tetracyanoethane from the reaction and by trapping 6 as its maleic anhydride adduct 7. The formation of 5 from 2, then, involves dehydrogenation *via* ene-adduct decomposition, and its origin from 1 requires two dehydrogenation steps.

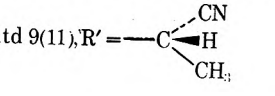


1, satd 9(11)
2, Δ 9(11)

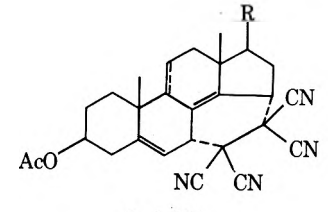


3, satd 9(11), R′ = —C(CN)$_2$CH(CN)$_2$
4, Δ 9(11), R′ = —C(CN)$_2$CH(CN)$_2$

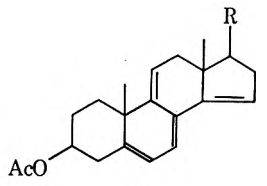




11, satd 9(11), R′ = —C(CN)H—CH$_3$



5, Δ 9,11
8, satd 9(11)



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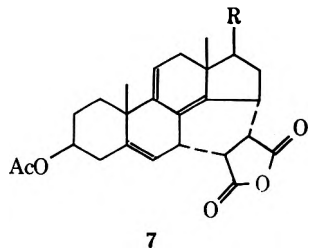

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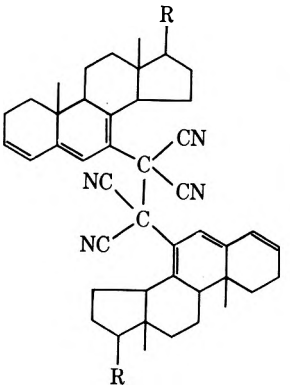
We now report the isolation of two further new compounds from reaction mixtures of ergosteryl acetate 1 and tetracyanoethylene, discuss spectral properties of the adducts, consider the role of steric effects in these reactions, and suggest a pathway for the formation of 5 from 1.

Adduct 5 was formed in best yield when the ene adduct 4 was placed in chloroform–nitromethane at 0° in contact with additional tetracyanoethylene. We therefore attempted to prepare the analogous compound 8 from 3 under the same conditions. However, no 8 was thus obtained from 3, but, when ergosteryl acetate 1 was treated with 2 equiv of tetracyanoethylene under much more vigorous conditions (benzene at 75°), two new crystalline products, accompanied by extensive decomposition, were obtained. The first analyzed for $(C_{31}H_{41}N_2)_n$, and had $[\alpha]_D$ + 140°. Its uv spectrum showed λ_{max} 306, 313 nm (ε 53,000, 48,000), which is reasonably consistent with a $\Delta^{3,5,7}$ triene.[5] The nmr spectrum showed three vinyl protons per steroid nucleus in addition to those of the side chain, two of them as an AB quartet. Although it is not certain that the material is completely homogeneous (separation of mixed isomeric bis steroids is frequently difficult), the data available are consistent with the compound 9, $C_{62}H_{82}N_4$, being a major component of the material, yet with some isomeric octaenes probably present as well. Repeated attempts to observe a molecular ion in the mass spectrum of the compound were unsuccessful, the highest peak observed being at *m/e* 504, corresponding to a species such as 10. The close relationship of the new compound to adduct 3 was emphasized by its formation when 3 was heated alone in methanol, benzene, acetic acid, chloroform–nitromethane, or ether. Structure 9 can be envisaged



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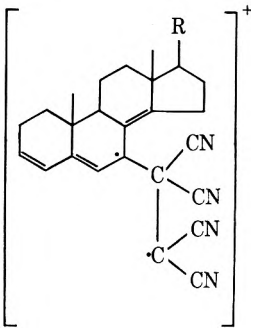


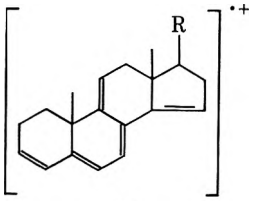
10

(1) Part IV: D. E. Burke and P. W. Le Quesne, *J. Org. Chem.*, **36**, 2397 (1971).
(2) Kent State University.
(3) University of Michigan; to whom inquiries should be addressed.
(4) A. L. Andrews, R. C. Fort, Jr., and P. W. Le Quesne, *J. Org. Chem.*, **36**, 83 (1971).
(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 17.

as arising from two molecules of **3** by radical cleavage and combination reactions, elimination of two molecules of acetic acid, and double-bond shifts.

The second new compound was the desired adduct **8**. It was obtained together with **5**, which it closely resembles in physical properties. Separation of these compounds also was difficult, but repeated crystallization gave samples of **8** contaminated with ~10% of **5**. This estimate was made from consideration of uv, nmr, and mass spectral data (see below). This material had $[\alpha]_D$ −223°. The uv spectrum of **8** had λ_{max} 220, 284 nm (ϵ 4655, 504), which is in accord with that of **3** [λ_{max} 213 nm (ϵ 8080)] contaminated with a little **5** [λ_{max} 284 nm (ϵ 8550)].[4] The nmr spectrum of **8** showed the three vinyl protons as two multiplets, one at τ 4.4, integrating for slightly more than one proton owing to the superposition of the corresponding 2 H signal from **5**,[4] and the other from the two side-chain protons, at ~τ 4.7. The eight methine protons of **8** appear upfield from the vinyl protons in three groups: τ 5.3 (1 H, m, C-3α), 6.8 (2 H, m, C-7β and C-15β), and in a group of twelve protons between τ 7.0 and 8.0 which also contains the acetate methyl group at τ 7.98 and the two allylic ring methylene protons at C-4. The ten nonallylic ring methylene protons fall between τ 7.98 and 8.78. The C-18 and C-19 signals of **8** appear as superimposed signals at τ 9.1. This is in accord with τ 9.05 found for **3**[4] and τ 9.1 reported for **11**,[6] and reaffirms the presence of a $\Delta^{5,8(14)}$-diene system.

Strong confirmation of structure **8** comes from comparison of its mass spectrum with those of **5** and related steroids. On electron impact adduct **5** undergoes retro Diels–Alder loss of tetracyanoethylene and elimination of acetic acid to give a peak at *m/e* 374. An apparently identical fragment is found (as the base peak) in the spectrum of the ene adduct **4** in which the molecular ion loses acetic acid and tetracyanoethane, giving an ion of probable structure **12**. The formation of **12** on electron impact from **4** is analogous to the ground state dehydrogenation mentioned above. Subsequent decomposition of ion **12** is the same in



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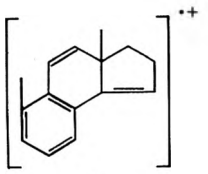
both cases; the side chain (*m/e* 125) is lost giving an ion at *m/e* 249, which is analogous to ions at *m/e* 253 and 251 in the spectra of ergosteryl acetate **1** and 9(11)-dehydroergosteryl acetate **2**, respectively. Loss of methane (C-19) follows to give an ion at *m/e* 233, or butadiene from ring A to give ion **13** at *m/e* 195, which loses methane to give ion **14** at *m/e* 179.

Similarly, on electron impact both **8**, by retro Diels–Alder loss of tetracyanoethylene and elimination of acetic acid, and **3**, by loss of tetracyanoethane and acetic acid, give a base peak at *m/e* 376. This ion then produces the same fragmentation pattern in both



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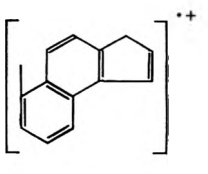


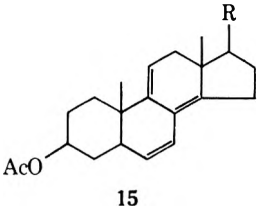
14

these spectra, and this pattern is the same, except that the peaks are at 2 mass units higher, as that from the *m/e* 374 ion from **5** and **4**. This strikingly confirms the analogous structures of **5** and **8**.

In the spectra of **3** and **4** the peaks corresponding to the loss of tetracyanoethane (*m/e* 376 for **3** and 374 for **4**) are accompanied by peaks at *m/e* 378 and 376, 18 and 9%, respectively, the intensities of the former. Since the peak at *m/e* 378 in ergosteryl acetate, which corresponds to the loss of acetic acid, was accompanied under analogous conditions on our instrument by a peak at *m/e* 380 of 7% its intensity, we believe that the *m/e* 376 and 378 peaks from **4** and **3** arise, in part at least, from retro ene reactions, analogous to the McLafferty rearrangement, as adumbrated previously.[4] Predominantly, however, the ene adducts on electron impact characteristically lose tetracyanoethane and the Diels–Alder adducts (*e.g.*, **5**, **8**, and **16**) tetracyanoethylene.

These mass spectra are similar to that of ergosteryl acetate **1** which strongly resembles the spectrum of ergosterol itself.[7-9] The steroid 9(11)-dehydroergosteryl acetate (**2**) on electron impact shows, because of the 9(11) double bond, much reduced ring-C cleavage compared with that in ergosteryl acetate **1**, which therefore reduces the abundance of ring A–B fragments at *m/e* 158, 143, and 128. The ions representing loss of acetic acid, angular methyl groups, and side chain are analogous but of two mass units less.

The mass spectrum of 3β-acetoxyergosta-6,8(14),-9(11),22-tetraene (**15**) and its Diels–Alder adduct **16**



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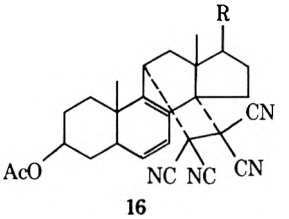


16

are very similar. Both, as expected,[10,11] lose acetic acid less readily than the Δ^5 steroids discussed above, and a metastable ion at *m/e* 202.6 documents the loss of acetic acid after the loss of side chain or side chain plus tetracyanoethylene. The prominent ion **17** at *m/e* 311 readily loses methane with aromatization of ring C, to give an ion at *m/e* 295; the ion resulting from loss of acetic acid from **17** itself loses ring A (butadiene) or methane from C-18 to give ions at *m/e* 197 and 235. A strong tendency to cleavage in ring B is

(6) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, **24**, 5215 (1968).

(7) S. S. Friedland, G. H. Lane, Jr., R. T. Longman, K. E. Train, and M. J. O'Neil, Jr., *Anal. Chem.*, **31**, 169 (1959).

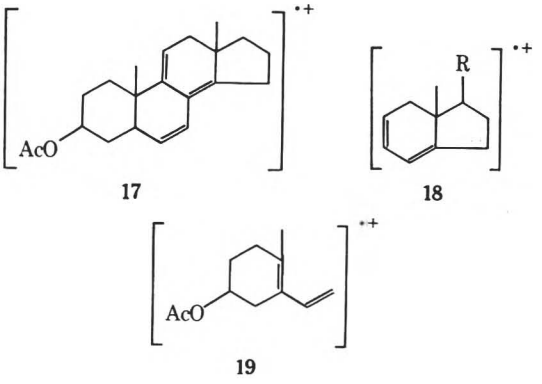
(8) J. Jaurégiberry, J. H. Law, J. A. McCloskey, and E. Lederer, *Biochemistry*, **4**, 347 (1965).

(9) F. R. Smith and E. D. Korn, *J. Lipid Res.*, **9**, 405 (1968).

(10) G. Galli and S. Maroni, *Steroids*, **10**, 189 (1967).

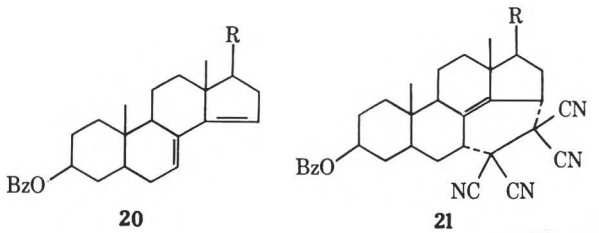
(11) H. J. M. Fitches in "Advances in Mass Spectrometry," Vol. 2, R. M. Elliot, Ed., Pergamon Press, New York, N. Y., 1963, p 428.

evinced by fission of the tetraene molecular ion into fragments **18** (*m/e* 257) and **19** (*m/e* 179).

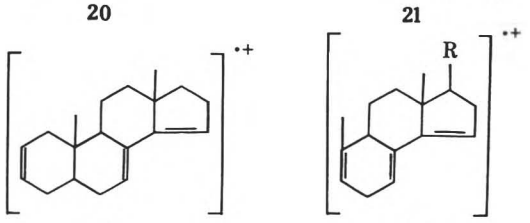


17 **18** **19**

The steroid 3β-benzoyloxyergosta-7,14,22-triene (**20**) and its Diels–Alder adduct **21** also show virtually identical behavior on electron impact. In analogy to the

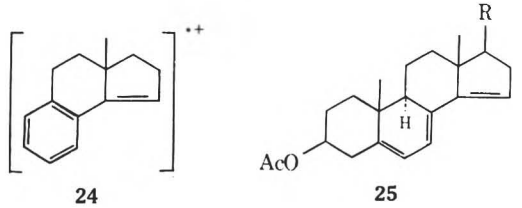


20 **21**



22 **23**

compounds above, benzoic acid is not lost readily owing to the absence of a Δ^5 double bond. The ion **22** (*m/e* 253), resulting after loss of benzoic acid and the side chain, undergoes loss of methane (probably C-18) to give an ion at *m/e* 237, or butadiene from ring A to ion **23** at *m/e* 199, which in turn losses methane from C-19 to give the aromatic ion **24** at *m/e* 183. Al-



24 **25**

though one must be cautions in attributing unique structures to polyene radical cations such as these, it seems clear that the overall patterns of fragmentation are characteristic of the locations of single or grouped alkene linkages in these compounds and are thus useful in structure determination.

The data accumulated suggest that steric factors exert major control of the reactions between steroidal lkenes and tetracyanoethylene. The fact that no Diels–Alder adduct was obtained with ergosteryl acetate or 9(11)-dehydroergosteryl acetate suggests that tetracyanoethylene is too bulky to achieve the required transition state geometry. The literature of steroid addition reactions of this kind[12] shows that all nonacetylenic dienophiles giving Diels–Alder adducts with $\Delta^{5,7}$ and $\Delta^{5,7,9(11)}$ steroids possess cis vinyl hydrogens or a cis diazo function. The bulk of cis vinyl nitrile groups is, from molecular models, great enough that the approach of tetracyanoethylene to **1** to give a Diels–Alder adduct is hindered not only by the 9α hydrogen but by the 1α and 12α hydrogens as well. That **1** does not give a $\Delta^{8,9}$ ene adduct isomeric with **3** is probably also a consequence of the bulk of the nitrile groups; the transition state for this reaction is appreciably hindered by the 15α hydrogen (*cf.* ref 6). (Steric effects, however, are not the only factors in all reactions of this kind; the difference in reactivity of benzyne and tetrafluorobenzyne with the $\Delta^{5,7}$ diene system[13] is of interest here.)

For steric reasons too, the decomposition of the 7α-tetracyanoethyl ene adducts to tetracyanoethane and a dehydrogenated steroid preferentially involves the accessible 15α hydrogen. The formation of **5** in minute yield from **1** and tetracyanoethylene could involve initial decomposition of **3** to give 3β-acetoxyergosta-5,7,14,22-tetraene (**25**) which, if not trapped as **8**, might, lacking the 15α hydrogen, undergo an ene reaction involving the 9α hydrogen, dehydrogenation at the 9(11) bond, and final trapping as **5**.

Further work on steric aspects of these reactions and on the dehydrogenations is in progress.

Experimental Section

General experimental directions are as for ref 4.

3β-Acetoxy-7α,15α-tetracyanoethanoergosta-5,8(14),22-triene (8) and the Bis Steroid 9.—Ergosteryl acetate (**1**) (13.6 g, 0.031 mol) and tetracyanoethylene (8.0 g, 0.062 mol) were held in benzene solution at 75° for 2.5 hr. The dark solution was filtered, giving tetracyanoethane (1.6 g, 0.012 mol), identified by comparison with authentic material. Addition of heptane precipitated slightly impure tetracyanoethylene (1.9 g), identified by its melting point, ir spectrum, and orange color reaction with xylene. Replacement of chloroform by ether gave fine white crystals of the bis steroid **9**, recrystallized for analysis from benzene–ethyl acetate: mp 198° with prior sintering, giving a red melt; vacuum mp 202°; $[\alpha]^{20}D$ +140° (c 1.0, $CHCl_3$); uv $\lambda_{max}^{CHCl_3}$ 306, 313 nm (ε 53,000, 48,000); nmr τ 3.56, 3.73, 3.95, 4.10 (4 H, AB q, J = 10 Hz, vinyl H's) 4.47 (2 H, m, vinyl H), 4.80–5.70 (4 H, m, C-22,23 H's), 6.32–6.85 (2 H, m). *Anal.* Calcd for $(C_{31}H_{41}N_2)_2$: C, 84.30; H, 9.35; N, 6.34. Found: C, 84.08, 84.19; H, 9.37, 9.46; N, 6.28, 6.35. Mass spectrum: *m/e* (rel intensity) 504 (0.3), 479 (1.5), 376 (100), 361 (14), 251 (94), 236 (15), 235 (12), 209 (8), 197 (32), 155 (19), 143 (10), 128 (7). Addition of heptane to the ether mother liquor caused precipitation of impure **8** (2.5 g, mp 160–180°), contaminated with **5**. Two careful recrystallizations from benzene–heptane and two from ethyl acetate gave the analytical sample of substantially pure **8** (0.53 g): mp 195–196° (melt cooling to a yellow solid); $[\alpha]^{20}D$ −223° (c 1.0, $CHCl_3$); uv $\lambda_{max}^{cyclohexane}$ 220, 284 nm (ε 4655, 504); nmr τ 4.37 (>1 H, m, C-6 H), 4.72 (2 H, m, C-22,23 H's), 5.30 (1 H, m, C-3α H), 6.75 (2 H, m, C7β,15β H's), 7.0–7.9 (5 H, m, C-9,17,20,24,25 H's), 7.97 (3 H, s, CH_3COO–, 7.9–8.7 (12 H, m, ring $-CH_2$'s), 9.10 (3 H, s, probably C-18), 9.07 (3 H, s, probably C-19). *Anal.* Calcd for $C_{36}H_{44}N_4O_2$: C, 76,56; H, 7.85; N, 9.92. Found: C, 76.66; H, 7.78; N, 9.82.

Gentle reflux of adduct **3** (360 mg) in methanol (7 ml) for 1 hr gave a yellow suspension from which colorless needles of **9** (68 mg) identical with that obtained above, were filtered off. Replacement of the methanol solvent by benzene, acetic acid, chloro-

(12) For a summary see A. L. Andrews, Ph.D. Thesis, Kent State University, 1971, p 12.

(13) I. F. Eckhard, H. Heaney, and B. A. Marples, *J. Chem. Soc. C*, 2098 (1969).

form–nitromethane, or ether gave the same result. Mass spectral data in *m/e* (rel intensity) follow.

Compound **2**: ion chamber 143°; M+ 436 (9), 376 (100), 361 (13), 251 (41), 235 (12), 209 (16), 197 (9), 181 (10), 158 (2), 155 (10), 143 (6), 128 (4); metastable ion 347.

Compound **3**: ion chamber 134°; 436 (7), 378 (18), 376 (100), 361 (14), 253 (12), 251 (67), 237 (9), 235 (19), 209 (12), 197 (22), 181 (12), 155 (21), 143 (13), 128 (13).

Compound **4**: ion chamber 200°; 436 (2), 434 (14), 376 (9), 374 (100), 359 (10), 249 (64), 235 (25), 233 (19), 209 (10), 207 (11), 195 (7), 179 (11).

Compound **5**: ion chamber 185°; M+ 562 (0.3), 502 (0.6), 434 (9), 374 (100), 359 (15), 249 (60), 233 (28), 207 (18), 179 (18), 153 (4); metastable ions 165.7, 345.

Compound **8** (containing some **5**): ion chamber 200°; 504 (16), 434 (5), 376 (100), 374 (23), 36 (8), 251 (19), 249 (21), 235 (7), 233 (5), 209 (8), 207 (5), 197 (5), 195 (7), 181 (6), 179 (6), 155 (6), 153 (6); metastable ions 324, 345.

Compound **15**: ion chamber 135°; M+ 436 (38), 376 (26), 361 (17), 311 (71), 295 (24), 257 (14), 251 (100), 235 (19), 209 (24), 197 (33), 181 (21), 155 (24), 179 (17), 119 (8), 55 (76); metastable ions 202.6, 222.

Compound **16**: ion chamber 190°; M+ 564 (3), 504 (5.5), 436 (31), 376 (33), 361 (17), 311 (45), 295 (23), 258 (12), 251 (100), 235 (21), 209 (27), 197 (31), 181 (17), 179 (14), 155 (19), 119 (5), 55 (70); metastable ions 202.6, 222.

Compound **20**: ion chamber 180°; M+ 500 (42), 485 (19), 375 (39), 374 (100), 363 (4), 359 (4), 253 (14), 237 (6), 211 (3), 199 (6), 183 (5), 157 (9), 55 (60); metastable ions 170.5, 222, 280, 322, 345, 471.

Compound **21**: ion chamber 220°; M+ 628 (2), 613 (0.2), 500 (13), 485 (12), 375 (21), 374 (58), 253 (6), 237 (4), 183 (3), 157 (6), 55 (100); metastable ions 280, 471.

Registry No.—**2**, 1060-56-6; **3**, 21549-35-9; **4**, 21549-36-0; **5**, 26885-77-8; **8**, 36959-76-9; **9**, 36959-77-0; **15**, 36959-78-1; **16**, 36959-79-2; **20**, 36959-80-5; **21**, 36959-81-6; tetracyanoethylene, 670-54-2.

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Stereochemistry of Some Δ^1-Butenolide Syntheses

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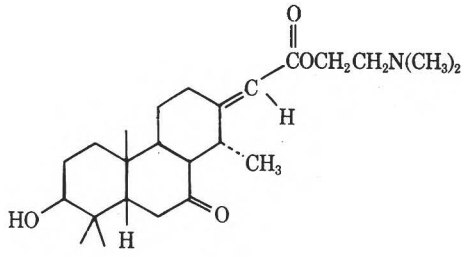
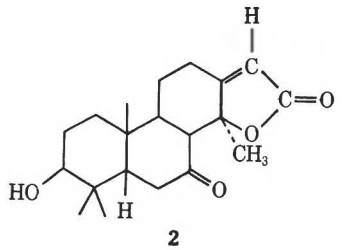
Alkylation of *trans*-1- and *trans*-2-decalone with ethyl bromoacetate *via* the pyrrolidine enamine and subsequent ester hydrolysis and dehydration (Ac_2O) gave equatorially fused butenolides. The Reformatsky products from 3(*a*)-acetoxy-*trans*-2-decalone, ethyl bromoacetate, zinc, and trimethyl borate were saponified and ring closed to give isomeric β-hydroxy γ-lactones which could be dehydrated to the axially fused butenolide. Similar reactions with 3(*e*)-acetoxy-*trans*-2-decalone gave the other two isomeric β-hydroxy-γ-lactones which on dehydration gave the equatorially fused butenolide. Stereochemical assignments were made on the basis of nmr spectra.

Interest in the preparation of conformationally rigid butenolide analogs of cassaine (**1**) such as **2** made

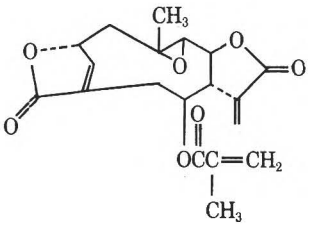


1



2

necessary the investigation of the stereochemistry of some Δ^1-butenolide syntheses. Of the large number of syntheses for the Δ^1-butenolides most have been applied only to nonfused ring systems.[2] However, in recent years several butenolide syntheses have been used for fused ring systems involved in naturally occurring compounds.[3-10] Further interest in the chemistry of butenolides has been generated by the discovery of naturally occurring fused butenolides with tumor-inhibitor activity such as elephantopin (**3**).[11]



3

The butenolide syntheses investigated were selected because they appeared to have applicability in the synthesis of the desired cassaine analogs. *trans*-Decalin was chosen as the model because it is conformationally rigid and the B–C rings of cassaine are a trans-fused decalin ring system. Thus, synthetic approaches to 2-

(1) This research was supported by Faculty Research Grants and by Assistant Professor Research Grants from the University of Missouri—Kansas City, Mo.

(2) Y. S. Rao, *Chem. Rev.*, **64**, 353 (1964); P. E. Sonnet, *Chem. Ind. (London)*, 1296 (1967).

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(6) H. Minato and T. Nagaski, *J. Chem. Soc.*, 377 (1966).

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(8) S. W. Pelletier, A. L. Chappell, and S. Probhakar, *J. Amer. Chem Soc.*, **90**, 2889 (1968).

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(10) Z. Horii, M. Ito, I. Minami, M. Yamauchi, M. Hanaoka, and I Momose, *Chem. Pharm. Bull.*, **18**, 1967 (1970).

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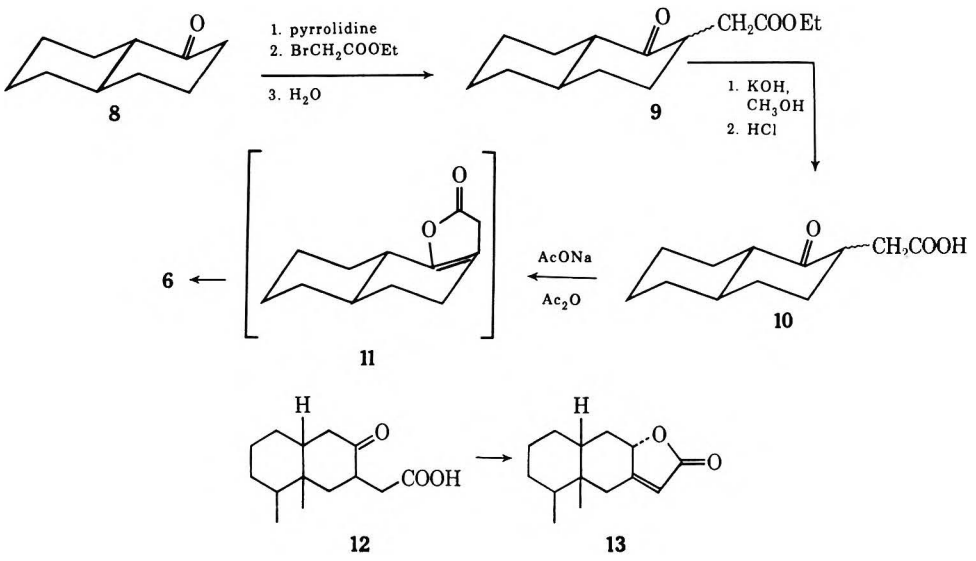
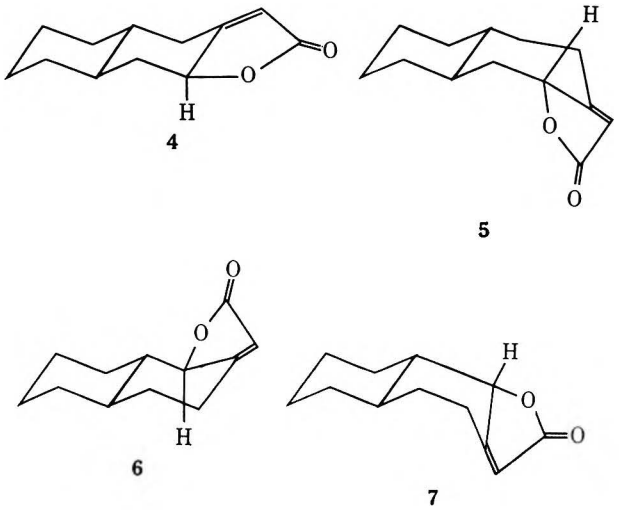
SCHEME I



8 9 10 11 12 13

[3(*e*)-hydroxy-2-decalylidine]acetic acid γ-lactone (**4**), 2-[3(*a*)-hydroxy-2-decalylidine]acetic acid γ-lactone (**5**), 2-[1(*e*)-hydroxy-2-decalylidine]acetic acid γ-lactone (**6**), and 2-[1(*a*)-hydroxy-2-decalylidine]acetic acid γ-lactone (**7**) were explored. Butenolides **4** and **6** are fused in an equatorial manner, while **5** and **7** are axially fused since the lactone oxygen is equatorial in **4** and **6** and axial in **5** and **7**.



4 5 6 7

The first synthetic approach is outlined in Scheme I and is essentially that of Minato and Nagaski.[6] The equatorially fused butenolides **4** and **6** were obtained utilizing *trans*-2-decalone and *trans*-1-decalone (**8**), respectively.

The equatorial nature was assigned on the basis of nmr spectra. The C-3 proton of **4** appeared at δ 4.65 as a four-line multiplet with further fine splitting. The larger coupling constants were observed as 9 Hz for the axial–axial coupling and 6 Hz for the axial–equatorial coupling with the C-4 protons.[12] The fine splitting was shown by spin–spin decoupling to be due to coupling with the vinyl proton of the butenolide ring. The C-1 proton of **6** was observed at δ 4.39 as a doublet (J = 8 Hz) with further fine splitting. The doublet nature is due to coupling with the axial proton at C-9. The fine splitting is due to coupling with the vinyl proton. No evidence of the axially fused isomers **5** or **7** was observed in their respective reaction sequences. This would be expected, since the lactonization must involve the enol (example **11**), which on isomerization would give the more stable equatorial arrangement. The equatorially fused butenolide was obtained by Piers, *et al.*,[9] in their synthesis of ermophilenolide, which involved lactonization of **12** to **13**. The synthetic approach outlined in Scheme I is an excellent route to the equatorial isomers, since a ketone with no other functionality is the starting material and the yields are reasonable.

The second synthetic approach studied is outlined in Scheme II. The Reformatsky reaction of 3(*e*)-acetoxy-*trans*-2-decalone (**14**) with ethyl bromoacetate was conducted according to the procedure of Rathke and Lindert,[13] which employs trimethyl borate as a Lewis acid to reduce the basicity of the reaction. This procedure gave improved yields over conventional Reformatsky conditions. Column chromatography of the reaction mixture gave approximately a 2:1 ratio of the equatorial addition product **15** to axial addition product **16**. A very small amount of the diol **17** was also obtained, which on acetylation with acetic anhydride gave **15**. The stereochemistry at C-2 of **16** and **17** was assigned by comparison of chemical shifts of hydroxyl protons in deuterated dimethyl sulfoxide.[14] The hydroxyl proton of **16** is 9.4 Hz downfield from the hydroxyl proton of **15**, which is consistent with an equatorial hydroxyl in **16** and an axial hydroxyl in **15**. The magnitude of the difference is considerably less than reported.[14] Further support for this assignment will be presented below. The protons at C-3 had peak widths at one-half height of 18 and 17 Hz for **15** and **16**, respectively, which is consistent for axial protons and thus an equatorial acetate.

The Reformatsky product **16** on base hydrolysis and acidification gave the hydroxy lactone **18**. Treatment of **18** with thionyl chloride in pyridine produced the butenolide **4**. Base hydrolysis and acidification of **15** yielded an insoluble acid **19**. The acid **19** could be

(12) D. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965.

(13) M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1970).

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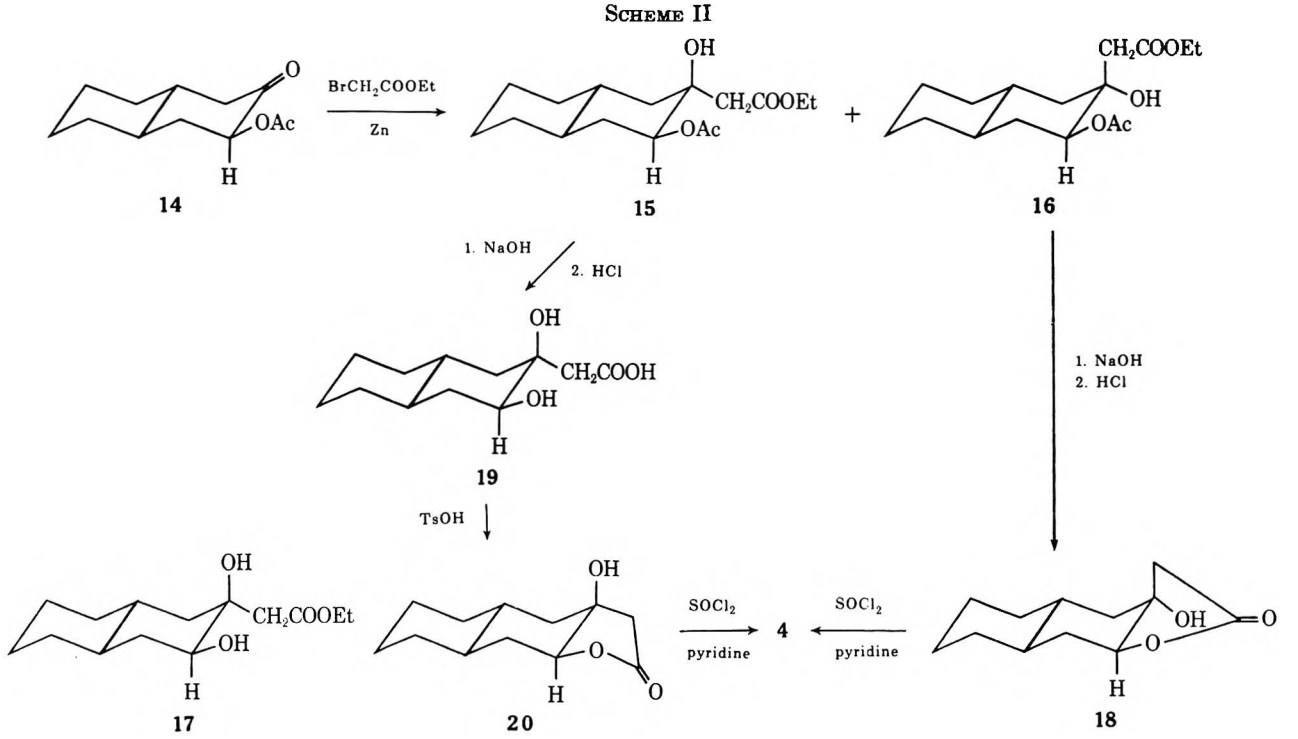
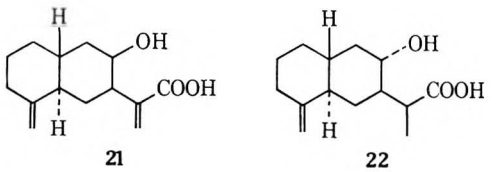
SCHEME II



converted to hydroxy lactone **20** by refluxing in benzene with a trace of *p*-toluenesulfonic acid. The hydroxy lactone **20** was converted to butenolide **4** by treatment with thionyl chloride in pyridine.

The assigned stereochemistry of the two hydroxy lactones **18** and **20** is supported in two ways. First, Minato and Horibe[15] observed that the cis configuration **21** underwent facile lactonization while the trans configuration **22** required heating to the melting point *in vacuo*.[16] A similar order of reactivity was observed for **18** and **20**. The cis configuration **18** lactonized spontaneously while the trans configuration **20** required refluxing benzene with *p*-toluenesulfonic acid. Secondly, the chemical shift of the hydroxyl proton in deuterated dimethyl sulfoxide of **18** was 12 Hz downfield from that of **20**, which is consistent with an equatorial hydroxyl group in **18** and an axial hydroxyl in **20**.[14]



21 **22**

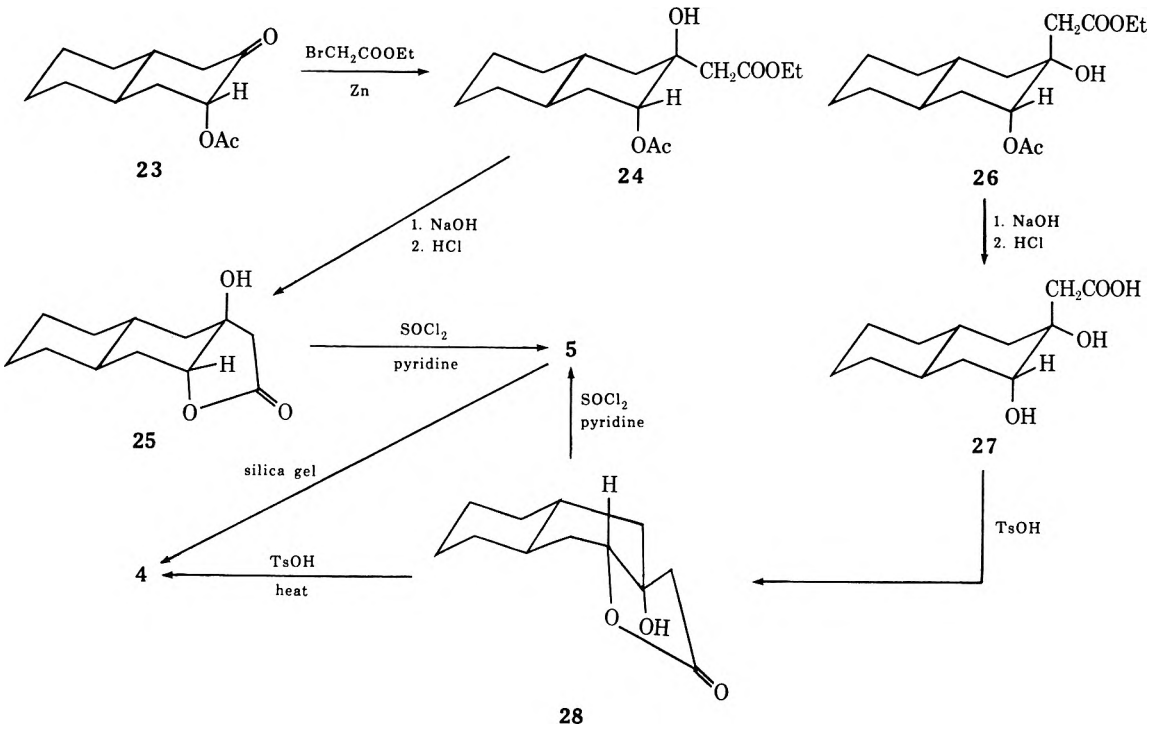
The Reformatsky reaction of 3(*a*)-acetoxy-*trans*-2-decalone (**23**) with ethyl bromoacetate gave a mixture from which **24** could be separated by column chromatography. The proton at C-3 had a peak width at one-half height of 8 Hz (δ 4.80), which is consistent for an equatorial proton and thus an axial acetate. Hydrolysis of **24** in base followed by acidification gave the lactone **25**. The infrared spectrum exhibited a carbonyl stretching at 1780 cm^{-1},[17] while in the nmr the C-3 proton had a peak width of 6 Hz. Both pieces of data support the assigned structure. Treatment of **25** with pyridine and thionyl chloride gave **5** (Scheme III). The infrared spectrum of **5** exhibited carbonyl stretching at 1778 and 1754 cm^{-1} which correspond to reported values for Δ^1-butenolides.[17] The nmr spectrum of **5** showed the C-3 proton as a triplet (J = 7 Hz) with further fine splitting and the vinyl proton as a multiplet ($W_{1/2}$ = 5 Hz) located at δ 5.72. Observance of the C-3 proton signal as a triplet suggests that the one ring of the decalin has flipped to a twist form. If the C-3 proton is approximately 25° from the 4β proton and thus about 145° from the 4α proton, the predicted coupling constant is about 7 Hz, according to the Karplus rule. The twist confirmation just described to fit the nmr data appears to be the most stable one based on Framework Molecular Models[18] of the system.

The butenolide **5** was chromatographed using preparative layer silica gel plates to purify it for analysis, but the epimerized butenolide **4** was obtained.

Attempts to obtain **26** by chromatography of the Reformatsky reaction mixture were unsuccessful. Therefore, the crude reaction mixture was hydrolyzed in base and then acidified. The acid solution was extracted with chloroform to give **25**. A white solid which was not chloroform soluble was filtered and found to be the acid **27**. The axial nature of the C-3 hydroxy group was shown by nmr spectroscopy. The C-3 proton had a peak width of 6 Hz. When the acid **27** was refluxed in benzene with *p*-toluenesulfonic acid, the hydroxy lactone **28** was obtained. A triplet at δ 4.47 (J = 8 Hz) was assigned to the C-3 proton. The observance of a triplet for the C-3 proton signal indicated that the one ring of the decalin system was in the twist form as observed with **5**. Treatment of **28** with thionyl chloride in pyridine gave the axially fused butenolide **5**. When the acid **27** was accidently heated with *p*-toluenesulfonic acid in the dry state, epimerized butenolide **4** was isolated.

(15) H. Minato and I. Horibe, *Chem. Commun.*, 531 (1965).
(16) K. Naemura and M. Nakazaki, *Tetrahedron Lett.*, 33 (1969).
(17) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962.
(18) Framework Molecular Models, Prentice-Hall, Englewood Cliffs N. J.

SCHEME III



The stereochemical assignment at C-2 for **24**, **25**, **26**, and **27** was based on the reactions of these compounds. The lactone **25** must be a cis fused lactone because of the ease with which it underwent lactonization. Since the oxygen of the lactone is axial, the acetic acid portion is equatorial. Further, the decalin moiety of **25** appears to be in the chair–chair conformations, which is only possible with the stereochemistry shown. The acid **27** would not be expected to lactonize spontaneously. The carboxyl and the hydroxyl group which lactonize are trans diaxial and thus one ring of decalin must go to a twist form, as was observed, for this reaction to occur.

Further studies of the stereochemistry of Δ^1-butenolides are currently underway and will be presented in a later paper.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Infracord or Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 spectrometer using deuteriochloroform as the solvent unless otherwise specified. Data are reported in parts per million (δ) using TMS as internal standard. Melting points were obtained on a Thomas-Hoover Unimelt and are uncorrected. For column and dry column chromatography, E. Merck silica gel containing 15% water (based on R_f of *p*-dimethylaminoazobenzene with benzene as solvent) was used. E. Merck silica gel plates, 2 mm thick, 20 × 20 cm, were used for preparative thin layer chromatography. Microanalyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

2-(3-Keto-*trans*-2-decalyl)acetic Acid.—*trans*-2-Decalone (10.0 g) was allowed to react with pyrrolidine (7.0 g) in benzene (100 ml) to give the enamine which was used without further purification. The enamine was alkylated with ethyl bromoacetate (11.0 g), using the procedure of Stork, *et al.*,[19] followed by hydrolysis of the enamine to give ethyl 2-(3-keto-*trans*-2-decalyl)acetate. The keto ester was hydrolyzed with 5% KOH to give 4.34 g (35% based on *trans*-2-decalone) of 2-(3-keto-*trans*-2-decalyl)-acetic acid: mp 92–94° (lit. mp 75–77°, 91.5–92° upon solidification and remelting);[20] ir 1730, 1710 cm^{-1} (C=O); nmr δ 11.70 (s, 1).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.51; H, 8.62. Found: C, 68.30; H, 8.79.

2-(3(*e*)-Hydroxy-2-decalylidine)acetic Acid γ-Lactone (4).—2-(3-keto-*trans*-2-decalyl)acetic acid (2.0 g) was heated at reflux with acetic anhydride for 3.5 hr using the procedure of Minato and Nagaski[6] to give 1.78 g of a light brown oil. The oil was chromatographed on silica gel (150 g) using a nylon dry column (2.5 × 54 cm) and developed with benzene. The segment of the column 5 to 23 cm from the origin was extracted with $CHCl_3$ to give 1.32 g (72%) of **4** as white crystals. An analytical sample was obtained by recrystallization from chloroform–hexane: mp 75–76°; ir (CCl_4) 1785, 1750 (C=O), 1650 cm^{-1} (C=C); nmr (CCl_4) δ 4.65 (m, 1, J = 10, 6, 1.5 Hz, C-3 H), 5.55 (t, 1, J = 1.5 Hz, CH=C).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.01; H, 8.34. Found: C, 74.92; H, 8.36.

2-(1-Keto-*trans*-2-decalyl)acetic Acid (10).—A mixture of *cis*- and *trans*-1-decalone was epimerized to give 6.8 g (45%) of *trans*-1-decalone (**8**) on distillation, mp 28–31 (lit.[21] mp 31–32°). *trans*-1-Decalone (**8**) (6.5 g) was alkylated with ethyl bromoacetate *via* the pyrrolidine enamine as above to give 3.7 g (41% based on **8**) of **10**: mp 153–154° after recrystallization from benzene; ir ($CHCl_3$) 1710 cm^{-1} (C=O); nmr δ 11.68 (s, 1).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.51; H, 8.62. Found: C, 68.90; H, 8.82.

2-[1(*e*)-Hydroxy-2-decalylidine]acetic Acid γ-Lactone (6).—The keto acid **10** (1.2 g) was cyclized as above to give 1.2 g of brown oil. The oil was chromatographed using the dry column technique with 1.5 × 50 cm nylon column packed with silical gel (100 g) and developed with $CHCl_3$. The section 10 to 18 cm from the top was extracted with $CHCl_3$–CH_3OH to give 650 mg as a fairly pure sample of **6**. An analytical sample was prepared by chromatography on a preparative thin layer plate developed with chloroforom. The major band was scraped off and extracted with 2% methanol in chloroform. The solvent was removed *in vacuo* and the residue was dissolved in 2 ml of $CHCl_3$ and filtered with a sintered glass funnel. Evaporation of the solvent gave an oil which crystallized on standing: mp 40–41°; ir (neat) 2920, 2850 (CH), 1795, 1745 (C=O), 1645 cm^{-1} (C=C); nmr δ 4.39 (q, 1, J = 8, 1.6 Hz, C-1 H), 5.80 (t, 1, J = 1.6 Hz, CH=C).

(19) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(20) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *ibid.*, **83**, 606 (1961).

(21) C. D. Gutsche and H. H. Peter, *ibid.*, **77**, 5971 (1955).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.36; H, 7.91. Found: C, 75.40; H, 8.09.

3(*a*)-Acetoxy-*trans*-2(*a*)-decalol.—A solution of decalin 2,3-oxide (9.4 g) and glacial acetic acid (100 ml) was heated on a steam bath for 4 hr and then allowed to stand overnight at room temperature. The solution was evaporated *in vacuo*. The remaining oil was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo*, leaving 12.8 g (97%) of a viscous, colorless oil which was oxidized without further purification, nmr δ 2.03 (s, $CH_3C{=}O$), 3.80 (m, $W_{1/2}$ = 9.6 Hz, 2(*e*)H), 4.82 (m, $W_{1/2}$ = 7.2 Hz, 3(*e*)H).

3(*a*)-Acetoxy-*trans*-2-decalone (23).—3(*a*)-Acetoxy-*trans*-2(*a*)-decalol (10.0 g) was oxidized with Jones reagent while cooling in an ice bath. Stirring was continued for 2 hr after addition. Isopropyl alcohol was added and then the solvents were removed *in vacuo*. Water was added to dissolve the inorganic salts and then extracted with chloroform. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo*, leaving 9.3 g (94%) of fairly pure **23**: ir (salts) 1745, 1735 (C=O), 1225 cm^{-1} (CO); nmr δ 2.07 (s, $CH_3C{=}O$), 4.82 (m, $W_{1/2}$ = 7.2 Hz, 3(*e*)H). **23** was analyzed as its 2,4-dinitrophenylhydrazone, mp 189–190° from ethyl acetate–ethanol.

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.32; H, 5.80; N, 14.39.

3(*e*)-Acetoxy-*trans*-2-decalone (14).—A solution of **23** (1.0 g) and glacial acetate (5 ml containing 2 drops of 48% HBr) was allowed to stand at room temperature for 2 days. The solution was evaporated *in vacuo* to give an oil which was dissolved in chloroform. The chloroform solution was washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated to give 0.92 g of a yellow oil which crystallized on standing. Recrystallization from hexane gave 0.8 g of **14**: mp 57–58° (lit.[22] mp 64–65°); ir (CCl_4) 1740, 1730 (C=O), 1235 cm^{-1} (CO); nmr (CCl_4) δ 2.07 (s, 3), 5.10 (m, 1, $W_{1/2}$ = 20.4 Hz, C-3 H).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.55; H, 8.74.

Reformatsky Reaction with 3(*e*)-Acetoxy-*trans*-2-decalone (14).—3(*e*)-Acetoxy-*trans*-2-decalone (14) (16.3 g) was allowed to react with ethyl bromoacetate (13.05 g) and zinc (5.1 g of 30–60 mesh without purification) in the presence of trimethyl borate (30 ml) and tetrahydrofuran (30 ml) for 60 hr according to the procedure of Rathke and Lindert.[13] Work-up gave 17.3 g of a yellow oil. The oil was chromatographed on silica gel (400 g) using chloroform as solvent and 10-ml fractions were collected. Fractions 121–310 contained 6.57 g of ethyl 2-[3(*e*)-acetoxy-2(*a*)-hydroxy-2(*e*)-decalyl]acetate (**15**): ir (neat) 3690 (OH), 1735, 1720 (C=O), 1240 cm^{-1} (CO); nmr δ 1.28 (t, 3, J = 7 Hz, CH_3CH_2), 2.07 (s, 3), 2.32 (d, 1, J_{gem} = 15 Hz, CH_2CO), 2.62 (d, 1, J_{gem} = 15 Hz, CH_2CO), 4.17 (q, 2, J = 7 Hz, CH_3CH_2), 4.70 (m, 1, $W_{1/2}$ = 17 Hz, C-3 H); nmr (DMSO) hydroxyl proton is 125.6 Hz downfield from strongest peak in DMSO (0.00985 molar ratio). Fractions 311–370 contained 3.43 g of a mixture of **15** and **16**. Fractions 371–405 contained 3.00 g of ethyl 2-[3(*e*)-acetoxy-2(*e*)-hydroxy-2(*a*)-decalyl]acetate (**16**): ir (neat) 3480 (OH), 1730, 1718 cm^{-1} (C=O); nmr δ 1.30 (t, 3, J = 7 Hz, CH_3CH_2), 2.03 (s, 3), 2.50 (d, 1, J_{gem} = 15 Hz, CH_2CO), 2.87 (d, 1, J_{gem} = 15 Hz, CH_2CO), 4.22 (q, 2, J = 7 Hz, CH_3CH_2), 4.83 (m, 1, $W_{1/2}$ = 18 Hz, C-3 H); nmr (DMSO) hydroxyl proton is 135.0 Hz downfield from strongest peak in DMSO. Fractions 402–430 contained 1.30 g of a mixture of **16** and **17**. Fractions 431–460 contained 90 mg of an oil which crystallized on standing. Recrystallization from hexane gave 80 mg of ethyl 2-[3(*e*), 2(*a*)-dihydroxy-2(*e*)-decalyl]-acetate (**17**) as white crystals: mp 92–93°; ir (CCl_4) 3590, 3510 (OH), 1710 (C=O), 1185 cm^{-1} (CO); nmr (CCl_4) δ 1.28 (t, 3, J = 7 Hz, CH_3CH_2), 2.20 (d, 1, J_{gem} = 15 Hz, CH_2CO), 2.82 (d, 1, J_{gem} = 15 Hz, CH_2CO), 3.17 (q, 1, J = 10, 5 Hz, C-3 H), 4.15 (q, 2, J = 7 Hz, CH_3CH_2).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.70; H, 9.42.

2-[2(*a*),3(*e*)-Dihydroxy-2(*e*)-decalyl]acetic Acid (19).—The ester **15** (1.32 g) was heated on a steam bath with sodium hydroxide (10%, 20 ml) for 6 hr and allowed to stand for 48 hr. The solid which formed was dissolved on addition of water. The basic solution was extracted with chloroform and the chloroform extracts were discarded. The aqueous solution was acidified with hydrochloric acid (10%) to give a solid which was extracted with three portions of chloroform, although the solid was not very soluble in chloroform. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated to give 402 mg (43%) of **19**, mp 175–177°. An analytical sample was recrystallized from methanol–benzene: mp 176–177°; ir (KBr) 3510, 3460 (OH), 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.11; H, 8.79.

2-[2(*a*),3(*e*)-Dihydroxy-2(*e*)-decalyl]acetic Acid γ-Lactone (20).—A solution of **19** (60 mg) in benzene (20 ml) containing a trace of *p*-toluenesulfonic acid was heated at reflux for 7 hr. The solvent was removed *in vacuo* to give a white solid, mp 160–162°. Recrystallization from benzene–hexane gave **20**: mp 164–164.5°; ir ($CHCl_3$) 3595, 3430 (OH), 1780 cm^{-1} (C=O); nmr δ 2.52 (s, 2, CH_2CO), 4.05 (q, 1, J = 6, 11 Hz, C-3 H); nmr (DMSO) at 0.012 molar ratio the hydroxyl proton is 150 Hz downfield from the strongest peak of DMSO.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.42; H, 8.75.

Dehydration of 2-[2(*a*),3(*e*)-Dihydroxy-2(*e*)-decalyl]acetic Acid γ-Lactone (20).—Thionyl chloride (1 ml) was dissolved in pyridine (2 ml) and added to a solution of **20** (90 mg) in pyridine (3 ml). The reaction mixture turned black and became hot. It was then heated on a steam bath for 10 min. The reaction mixture was evaporated *in vacuo*. Water (10 ml) was added to the residue and extracted with three portions of chloroform. The chloroform solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give a reddish-brown oil. The nmr spectrum was identical with the spectrum of **4** except for a singlet at δ 1.27 and peaks for pyridine. No further purification was performed.

2-[2(*e*),3(*e*)-Dihydroxy-2(*a*)-decalyl]acetic Acid γ-Lactone (18).—A mixture of **16** (540 mg) and 10% aqueous sodium hydroxide (10 ml) was heated on a steam bath for 1.25 hr, at which time solution was complete. The basic solution was acidified with 10% hydrochloric acid and allowed to stand at room temperature for 2 hr and then extracted with three portions of chloroform (15 ml). The chloroform solution was washed with an aqueous sodium bicarbonate solution, dried ($MgSO_4$), filtered, and evaporated to give 217 mg (57%) of oil which crystallized on standing. Recrystallization from benzene–hexane gave an analytical sample of **18**: mp 88.5–89.5; ir ($CHCl_3$) 3610, 3430 (OH), 1775 cm^{-1} (C=O); nmr δ 2.25 (d, 1, J_{gem} = 17 Hz, CH_2CO), 2.72 (d, 1, J_{gem} = 17 Hz, CH_2CO), 4.30 (m, 1, $W_{1/2}$ = 19 Hz, C-3 H); nmr (DMSO) at 0.0115 molar ratio the hydroxyl proton is 162 Hz downfield from the strongest peak of DMSO.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.51; H, 8.74.

Dehydration of 2-[2(*e*)-Dihydroxy-2(*a*)-decalyl]acetic Acid γ-Lactone (18).—The procedure for this reaction was identical with that for **20** and 80 mg of **18** was used. Work-up gave an oil (60 mg) which crystallized on standing. The nmr spectrum was identical with the spectrum of **4**. No further purification was performed.

Reformatsky Reaction with 3(*a*)-Acetoxy-*trans*-2-decalone (23).—The reaction was conducted on 16.3 g of **23** using the same procedure as for **14**. Work-up of the reaction gave 18.7 g of yellow oil. The oil (3.77 g) was chromatographed using the dry column technique with silica gel (200 g) in a nylon column (3.5 × 45 cm) and developed with chloroform. The section 6 cm from the bottom and 25 cm long was extracted with chloroform containing 10% methanol. Evaporation of the solvent yielded 1.88 g of ethyl 2-[2(*a*)-hydroxyl-3(*a*)-acetoxy-2(*e*)decalyl]acetate (**24**): ir (neat) 3480 (OH), 1725, 1710 (C=O), 1230 cm^{-1} (CO); nmr (CCl_4) δ 1.23 (t, 3, J = 7 Hz, CH_3CH_2), 2.03 (s, 3), 2.34 (s, 2, CH_2CO), 4.11 (q, 2, J = 7 Hz, CH_3CH_2), 4.80 (m, 1, $W_{1/2}$ = 8 Hz, C-3 H).

2-[2(*a*),3(*a*)-Dihydroxy-2(*e*)-decalyl]acetic Acid γ-Lactone (25).—Ethyl 2-[2(*a*)-hydroxy-3(*a*)-acetoxy-2(*e*)-decalyl]acetate (**24**) (500 mg) was heated at reflux with 10% sodium hydroxide (5 ml) for 1 hr. The basic solution was extracted with chloroform and the chloroform was discarded. The basic solution was acidified with 10% hydrochloric acid and extracted with chloroform. The chloroform was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give an oil (250 mg) which crystallized Recrystallization from benzene–hexane gave 175 mg (83%) of colorless crystal (**25**): mp 113–114°; ir (CCl_4) 3615, 3450 (OH) 1780 (C=O), 1220 cm^{-1} (CO); nmr δ 2.40 (d, 1 J_{gem} = 16 Hz, CH_2CO), 2.75 (d, 1, J_{gem} = 16 Hz, CH_2CO), 4.33 (m, 1, $W_{1/2}$ = 6 Hz, C-3 H).

(22) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2111 (1958).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.49; H, 8.53.

2-[3(*a*)-Hydroxy-2-decalylidine]acetic Acid γ-Lactone (5).—The hydroxy lactone **25** (300 mg) was dissolved in pyridine and a solution of thionyl chloride in pyridine was added. The mixture became hot during the addition and was allowed to stand for 20 min. It was evaporated *in vacuo*. Water was added and extracted with chloroform. The chloroform extract was dried ($MgSO_4$), filtered, and evaporated *in vacuo*, which gave a red oil. The oil was chromatographed on silica gel (40 g) developed with chloroform and 75-ml fractions were collected. Fractions 3 and 4 contained 175 mg of a fairly pure sample of **5**: ir (CCl_4) 1778, 1754 (C=O), 1642 cm^{-1} (C=C); nmr δ 5.72 (m, 1, $W_{1/2}$ = 5 Hz), 5.12 (triplet with further fine splitting, 1, J = 7 Hz, C-3 H). In an attempt to purify the sample for analysis, it was chromatographed twice on preparative thin layer chromatography (Brinkman, silica gel, 20 × 20 cm). The first time it was developed two times with chloroform; the second, three times with 50% benzene–chloroform. This treatment completely epimerized the sample to the equatorial butenolide **4**.

2-[2(*e*),3(*a*)-Dihydroxy-2(*a*)decalyl]acetic Acid (27).—The reaction mixture from the Reformatsky reaction with 3(*a*)-acetoxy-*trans*-2-decalone (**23**) (5.69 g) was hydrolyzed by heating overnight on a steam bath with 10% sodium hydroxide (30 ml). A precipitate formed which was soluble on addition of water. The basic solution was extracted with chloroform and the chloroform extract was discarded. The aqueous solution was acidified with 10% HCl and allowed to stand for 3 hr, during which time a precipitate formed. The aqueous mixture was extracted with chloroform. The chloroform was washed with sodium bicarbonate solution, dried ($MgSO_4$), filtered, and evaporated to give 2.42 g of **25**, mp 108–111°. The acidic aqueous solution from above was filtered to give 530 mg of **27**, mp 109–115°. Recrystallization of **27** from methanol–chloroform did not improve the melting point, which was quite variable. It was then recrystallized from acetone and again the melting point was variable. However, if placed in an oil bath at 113° it melted immediately, but if the bath was 111° the range was 111–115°: ir (KBr) 3400–2500 (broad series of peaks), 1705 cm^{-1} (C=O); nmr (CD_3COCD_3) 2.6 (2, s, CH_2CO), 3.77 (m, 1, $W_{1/2}$ = 6 Hz, C-3 H), 4.33 (m, 3, $W_{1/2}$ = 24 Hz, OH).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.10; H, 9.03.

Lactonization of 2-[2(*e*),3(*a*)-decalyl]acetic Acid (27).—The acid **27** (30 mg) was heated on a steam bath overnight in benzene containing a trace of *p*-toluenesulfonic acid. Solvent was removed *in vacuo*, leaving 2-[2(*e*),3(*a*)-dihydroxy-2(*a*)-decalyl]acetic acid γ-lactone (**28**) as an oily brown solid: nmr (CD_3COCD_3) δ 2.38 (d, 1, J_{gem} = 16 Hz, CH_2CO), 2.72 (d, 1, J_{gem} = 16 Hz, CH_2CO), 3.37 (m, 1, OH) 4.47 (t, 1, J = 8 Hz, C-3 H). When the reaction was repeated using 200 mg of **27**, the benzene accidentally evaporated. The residue was epimerized butenolide **4**.

Attempts to purify **28** by recrystallization resulted in hydrolysis of the lactone to **27**. Treatment of **28** (30 mg) with pyridine and thionyl chloride according to the procedure for **20** gave a brown oil (20 mg). The nmr spectrum of this oil showed the presence of axially fused butenolide **5**.

Registry No.—**4**, 37107-56-5; **5**, 37107-57-6; **6**, 37107-58-7; **10**, 37107-59-8; **14**, 37107-60-1; **15**, 37107-61-2; **16**, 37107-62-3; **17**, 37107-63-4; **18**, 37107-64-5; **19**, 37107-65-6; **20**, 37107-66-7; **23** dinitrophenylhydrazone, 37107-67-8; **24**, 37107-68-9; **25**, 37107-69-0; **27**, 37107-70-3; **28**, 37107-71-4; 2-(3-keto-*trans*-2-decalyl)acetic acid, 37107-72-5; 3(*a*)-acetoxy-*trans*-2(*a*)-decalol, 29121-93-5.

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Deoxy Oligonucleotide Synthesis *via* the Triester Method

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The β-cyanoethyl β′,β′,β′-trichloroethyl phosphate group is used in the triester method of deoxy oligonucleotide synthesis. The utility of this protecting function, and the triester method, is indicated by the synthesis of a number of deoxy di-, tri-, and tetranucleotides, including dCpdCpdTp, dTpdCpdTp, dTpdCpdTpdCp, and dApdTpdTpdCp. The tetranucleotides were prepared by block condensation from two dinucleotide units.

There are compelling biochemical reasons for the synthesis of oligonucleotides of known sequence. The two general chemical approaches, the diester and the triester methods, differ in that in the first the phosphate groups carry an acidic hydrogen while in the second they are fully esterified and, hence, neutral. The diester method is, at present, the better developed; Khorana, *et al.*, have synthesized a gene for alanine transfer ribonucleic acid by the combination of this method and biochemical procedures.[2] The triester method offers three advantages over the diester method: the product can be rapidly purified by chromatography on silica gel, making large-scale synthesis possible; the yields do not fall rapidly with chain length; and the phosphate backbone, being fully esterified, is not susceptible to attack by the condensating agent during each condensation step. Triester methods of oligonucleotide synthesis have been explored using β,β,β-trichloroethyl,[3,4] phenyl,[5] *o*-chlorophenyl,[6] and β-cyanoethyl[7] as phosphate protecting groups.

During an attempt to synthesize DNA codons *via*

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(1) (a) J. C. Catlin was Recipient of a Fulbright-Hays Travel Grant. (b) Requests for reprints should be sent to Professor F. Cramer, Max-Planck-Institut für Experimentelle Medizin, Abteilung Chemie, 34 Göttingen/Germany, Hermann-Rein-Str. 3. (c) Abbreviations of oligonucleotides according to IUPAC–IUB recommendations, 1970. See, *e.g.*, *Eur. J. Biochem.*, **15**, 203 (1970): dT = thymidine, dC = deoxy cytidine, dA = deoxyadenosine, dG = deoxyguanosine, dN = any deoxy nucleoside, dbz^{6}A = N^6-benzoyldeoxyadenosine, dac^{2}G = N^2-acetyldeoxyguanosine, dan^{4}C = N^4-anisoyldeoxycytidine, dbz^{4}C = N^4-benzoyldeoxycytidine, [(MeO)Tr] dA = 5′-monomethoxytrityldeoxyadenosine, [$(MeO)_2$Tr] dA = 5′-dimethoxytrityldeoxyadenosine, pdA = deoxyadenosine 5′-phosphate, dAp = deoxyadenosine 3′-phosphate, dAp(CNEt) = deoxyadenosine 3′-phosphate β-cyanoethyl ester, dAp(CNEt,Cl_3Et) = deoxyadenosine 3′-phosphate β-cyanoethyl β′,β′,β′-trichloroethyl ester (triester).

(2) K. L. Agarwal, H. Büchi, M. H. Caruthers, N. Gupta, H. G. Khorana, K. Kleppe, A. Kumar, E. Ohtsuka, U. L. RajBhandary, J. H. Van de Sande, V. Sgaramella, H. Weber, and T. Yamada, *Nature (London)*, **227**, 27 (1970).

(3) F. Eckstein and I. Rizk, *Chem. Ber.*, **102**, 2362 (1969).

(4) T. Neilson, *Chem. Commun.*, 1139 (1969); T. Neilson and E. S. Werstiuk, *Can. J. Chem.*, **49**, 3004 (1971).

(5) C. B. Reese and R. Saffhill, *Chem. Commun.*, 767 (1968).

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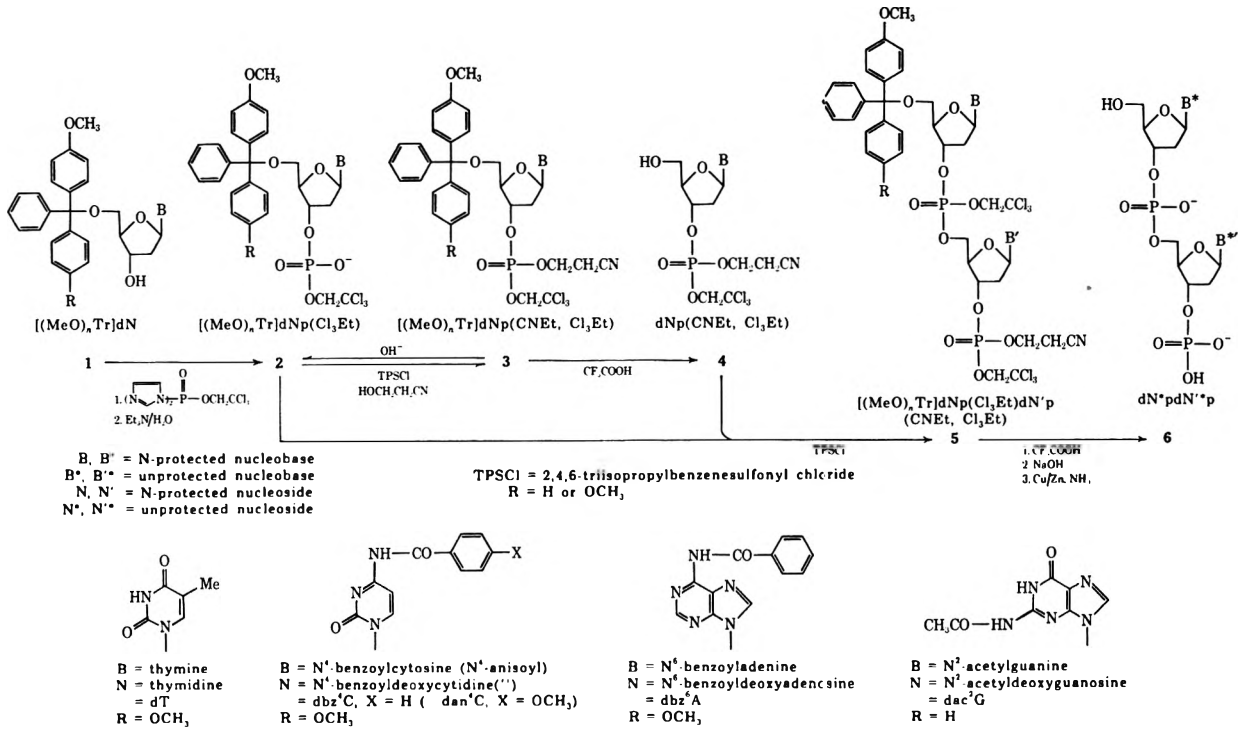
(7) R. L. Letsinger and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **91**, 3350(1969).



the β,β,β-trichloroethyl triester method, it was found that acetyl and other acyl protecting groups for the 3′-hydroxyl group in certain di- and trinucleotides were unexpectedly stable, perhaps owing to the steric hindrance, and could not be removed without loss of portions of the amino protecting groups.[8] Thus it was necessary to find an alternative protecting group for the 3′-hydroxyl group for use in oligonucleotide synthesis *via* the β,β,β-trichloroethyl triester method. A masked phosphate as protecting group for the 3′-hydroxyl group would have the advantage of permitting the introduction of the phosphate at the mononucleotide stage, rather than before each subsequent condensation.

In our synthetic approach, a nucleoside 3′-phosphate β,β,β-trichloroethyl ester, which carries an acid-labile blocking function on the 5′-hydroxyl, is condensed with the free 5′-hydroxyl group (primary hydroxyl) of a second nucleoside 3′-phosphate β,β,β-trichloroethyl ester in which the phosphate carries an additional base-labile group. The resulting fully protected dinucleotide can then be selectively deblocked at either the 5′ or the 3′ terminal by use of acid or base. The resulting partially protected dinucleotide can be used in a further condensation reaction. In the triester method it is necessary to allow a 3′-phosphate to react with a 5′-hydroxyl group; the reaction of a 3′-hydroxyl (secondary hydroxyl) with a 5′-phosphate ester goes in very low yield owing to the low reactivity of the secondary hydroxyl group.[3]

Results

An extensive series of di-, tri, and tetranucleotides was synthesized (formulae **1–6**, Tables II and III) using the above described concept. The dimethoxytrityl group was used as the acid-labile function to block the 5′-hydroxyl. The 3′ terminal was blocked by conversion of the nucleoside 3′-phosphate β,β,β-trichoroethyl ester to a triester by reaction with β-cyanoethanol. The β-cyanoethyl function is readily cleaved with dilute base. The combination of the dimethoxytrityl and β-cyanoethyl functions gave protected nucleotides and oligonucleotides, which could be deblocked at either the 5′ or the 3′ terminal.

Preparation of Protected Mononucleotides.—5′-O- and N-protected nucleosides **1** were prepared according to the procedures of Khorana, *et al.*,[9,10] and converted to the 3′-β,β,β-trichloroethyl phosphate esters (**2**) by reaction with β,β,β-trichloroethyl phosphodiimidazolidate.[8] Condensation of these protected diesters with β-cyanoethanol using triisopropylbenzenesulfonyl chloride gave the fully protected 3′-nucleotide triesters (**3**). Treatment of these protected nucleotides with dilute trifluoroacetic acid gave the desired protected 3′ nucleotides with a free 5′-hydroxyl (**4**), which were to be used at the 3′ terminal in our oligonucleotide synthesis. The 3′ protecting group could also be removed independently (**3** → **2**). The fully protected mononucleotides synthesized and the yields obtained in their preparation and in the selective cleavage of the dimethoxytrityl and β-cyanoethyl function are summarized in Table I.

Preparation of Oligonucleotides.—In order to synthesize the dinucleotides (**5, 6**) summarized in Table II a 5′-N-protected 3′-nucleotide β,β,β-trichloroethyl ester (**2**) was condensed with a N-protected 3′-nucleotide β-cyanoethyl β′,β′,β′-trichloroethyl ester (**4**); triisopropylbenzenesulfonyl chloride was used as the condensing agent. In synthesizing a trinucleotide a further condensation step, preceded by a cleavage of the β-cyanoethyl group, was applied. In the case of the tetranucleotides the same procedure as with the dinucleotides was followed, but dinucleotides were used as starting material (summarized in Table III).

(8) W. Frölke and W. Siehr, unpublished work.

(9) H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *J. Amer. Chem. Soc.*, **85**, 3821 (1963).

(10) S. A. Narang, T. M. Jacob, and H. G. Khorana, *ibid.*, **87**, 2988 (1965).

TABLE I
MONONUCLEOTIDE DERIVATIVES SYNTHESIZED AND CHARACTERIZED

5′ Protected 3′ nucleotides with two phosphate protecting groups	Registry no.	R_f Value[a] (solvent)	Yield, %	3′ Nucleotides with two phosphate protecting groups	Registry no.	R_f Value[a] (solvent)	Yield, %	5′ Protected 3′ nucleotides with one phosphate protecting group	Registry no.	R_f Value[a] (solvent)	Yield, %
$(MeO)_2Tr$]dTp(CNEt,Ch_2Et)[b,c]	36872-19-2	0.7 (D, 5%) 0.6 (D, 1:1)	84	dTp (CNEt,Ch_2Et)[b-d]	36872-23-8	0.2 (D, 1:1) 0.5 (D, 1:2)	79	[$(MeO)_2Tr$]dTp(Ch_2Et)[e,f]	37042-47-0	0.4 (Pr, 20%)	77
$(MeO)_2Tr$]dbz^{4}Cp(CNEt,Ch_2Et)[b,c]	36872-20-5	0.7 (D, 1:1)	84	dbz^{4}Cp (CNEt,Ch_2Et)[b-d]	36872-24-9	0.5 (D, 1:1)	81	[$(MeO)_2Tr$]dbz^{4}Cp(Ch_2Et)[e,f]	36872-28-3	0.4 (Pr, 20%)	82
[$(MeO)_2Tr$]dan^{4}Cp(CNEt,Ch_2Et)	36872-21-6	0.5 (Pr, 1:1)	5	dan^{4}Cp (CNEt,Ch_2Et)[d]	36872-25-0	0.3 (Pr, 1:1)	66				
[$(MeO)_2Tr$]dbz^{6}Ap(CNEt,Ch_2Et)[b,c,g]	36872-22-7	0.3 (D, 1:1)	68	dbz^{6}Ap (CNEt,Ch_2Et)[b-d]	36872-26-1	0.5 (D, 60%)	51	[$(MeO)_2Tr$]dbz^{6}Ap(Ch_2Et)[f]	36872-29-4	0.3 (D, 20%)	84
[$(MeO)Tr$]dac^{4}Gp(CNEt,Ch_2Et)[c]	36900-98-8	0.3 (Pr, 7%)	63	dac^{4}Gp (CNEt,Ch_2Et)[d]	36872-27-2	0.3 (Pr, 10%)	71	[$(MeO)Tr$]dac^{4}Gp(Ch_2Et)[f]	36872-30-7	0.4 (D, 30%)	59

[a] Chromatography on silica gel plates: D = thin layer plates (Merck, Darmstadt, Germany), Pr = preparative layer plates (Merck, Darmstadt, Germany); 5, 7, 10, and 20% methanol in chloroform, 1:1 and 1:2 benzene:acetone, 60% dioxane in chloroform. [b] Satisfactory analytical data (±0.3% for C, H, N, P, Cl) obtained. [c] Nmr spectrum consistent with the assigned structure. [d] Structure supported by incorporation into a dinucleotide and subsequent degradation into the expected 3′-mononucleotide. [e] Satisfactory analytical data (±0.3% for P, Cl) obtained. [f] Compared *via* thin layer chromatography with an authentic sample. [g] Analytical value for Cl, −0.5%.

In most cases the benzoyl function was found to be a satisfactory N-protecting group for deoxycytidine, as can be seen by the incorporation of N^4-benzoyldeoxycytidine into several di-, tri-, and tetranucleotides. The characteristic uv spectrum of N^4-benzoyldeoxycytidine was of considerable help in the characterization of the oligonucleotides prepared. Unfortunately, the benzoyl group was partially lost in the preparation of dinucleotides which contained N^6-benzoyldeoxyadenosine. Thus it was necessary to use N^4-anisoyldeoxycytidine.

The dimethoxytrityl and β-cyanoethyl functions were each removed independently from the fully protected compounds prepared, with either dilute trifluoroacetic acid or dilute sodium hydroxide solution. The conditions of deblocking were not closely studied, but during this work they were continually varied. The preferred cleavage conditions are reported in the Experimental Section.

The purity of the mononucleotides used in the preparation of di- and higher nucleotides seemed to be of minor importance, except in the case of deoxyguanosine, where the purity of each intermediate step in the preparation of 5′-dimethoxytrityl-N^2-acetyldeoxyguanosine 3′-phosphate β-cyanoethyl β′,β′,β′-trichloroethyl ester and the 5′-deblocked compound was of utmost importance.

On silica gel chromatography 0.5 g of protected mono- or oligonucleotide could readily be purified on one 100 × 20 cm plate which has a 2-mm layer of silica gel.

The yields obtained in the synthesis and stepwise degradation of the various oligonucleotides are reported in Tables II and III. The tetranucleotides prepared *via* block condensation of two dinucleotides were obtained in yields similar to those obtained for the di- and trinucleotides. The similarity of yields is of significance since equal molar proportions of the nucleotide and nucleoside components were used.

The characterization of the oligonucleotides and their derivatives by chromatography and, in part, by combustion analyses, spectroscopy, and enzymatic degradation is given in the tables. All compounds gave the expected uv spectra.

Discussion

The combination of the dimethoxytrityl group and the β-cyanoethyl β′,β′,β′-trichloroethyl phosphate diester has been shown to be of value as 5′ and 3′ terminal blocking groups in deoxy oligonucleotide synthesis *via* the triester method. They should be of equal utility in ribooligonucleotide synthesis. In addition, it should be possible to extend the use of the mixed phosphate diester blocking groups to other schemes of oligonucleotide synthesis where the phosphate protecting function is relatively stable to base, as is, *e.g.*, the phenyl group.

The value of the triester method of oligonucleotide synthesis with β,β,β-trichloroethyl as the phosphate blocking group has been extended by the synthesis of many di-, tri-, and tetranucleotides. However, it should be noted that at present the overall yields of unprotected oligonucleotides are quite low. The yields obtained for removal of the trichloroethyl groups are lower than reported in the literature.[3] This

TABLE II

DINUCLEOTIDES AND DERIVATIVES SYNTHESIZED AND CHARACTERIZED

5′-Protected dinucleotides with fully protected phosphate groups	Registry no.	R_f Value[a] (solvent)	Yield, %	5′-Protected dinucleotides with one protecting group per phosphate	Registry no.	R_f Value[a] (solvent)	Yield, %
[(MeO)$_2$Tr]dbz^{4}Cp(Cl$_3$Et)-dTp(CNEt,Cl$_3$Et)	36921-48-9	(0.6) (Pr, 1:1)	54	[(MeO)$_2$Tr]dbz^{4}Cp(Cl$_3$Et)-dTp(Cl$_3$Et)	36872-40-9	0.3 (0.4) (Pr, 20%)	70
[(MeO)$_2$Tr]dTp(Cl$_3$Et)-dbz^{4}Cp(CNEt,Cl$_3$Et)	36921-49-0	(0.3) (HM, 5%)	61	[(MeO)$_2$Tr]dTp(Cl$_3$Et)-dbz^{4}Cp(Cl$_3$Et)	36872-41-0	0.3 (0.5) (HM, 20%)	78
[(MeO)$_2$Tr]dbz^{4}Cp(Cl$_3$Et)-dbz^{4}Cp(CNEt,Cl$_3$Et)	36872-31-8	0.4 (0.5) (HM, 1:1)	55	[(MeO)$_2$Tr]dbz^{4}Cp(Cl$_3$Et)-dbz^{4}Cp(Cl$_3$Et)	36872-42-1	0.5 (0.7) (HM, 20%)	44
[(MeO)$_2$Tr]dbz^{6}Ap(Cl$_3$Et)-dCp(CNEt,Cl$_3$Et)[e,f]	36872-32-9	0.3 (0.5) (HM, 1:1)	49	[(MeO)$_2$Tr]dbz^{6}Ap(Cl$_3$Et)-dCp(Cl$_3$Et)	36872-43-2	(0.8) (HM, 20%)	50
[(MeO)$_2$Tr]dbz^{6}Ap(Cl$_3$Et)-dan^{4}Cp(CNEt,Cl$_3$Et)	36872-33-0	(0.5) (Pr, 7%)	70	[(MeO)$_2$Tr]dbz^{6}Ap(Cl$_3$Et)-dan^{4}Cp(Cl$_3$Et)	36872-44-3	0.4 (0.5) (Pr, 20%)	93
[(MeO)$_2$Tr]dbz^{6}Ap(Cl$_3$Et)-dTp(CNEt,Cl$_3$Et)	36872-34-1	(0.4) (Pr, 5%)	34	[(MeO)$_2$Tr]dbz^{6}Ap(Cl$_3$Et)-dTp(Cl$_3$Et)	36872-45-4	(0.4) (Pr, 30%)	66
[(MeO)$_2$Tr]dTp(Cl$_3$Et)-dbz^{6}Ap(CNEt,Cl$_3$Et)	36872-35-2	0.4 (0.6) (Pr, 7%)	27	[(MeO)$_2$Tr]dTp(Cl$_3$Et)-dbz^{6}Ap(Cl$_3$Et)	36872-46-5	0.5 (Pr, 30%)	59
[(MeO)Tr]dac^{2}Gp(Cl$_3$Et)-dTp(CNEt,Cl$_3$Et)	36872-36-3	0.4 (Pr, 1:1)	40	[(MeO)Tr]dac^{2}Gp(Cl$_3$Et)-dTp(Cl$_3$Et)	36872-47-6	0.1 (Pr, 20%)	40
[(MeO)Tr]dac^{2}Gp(Cl$_3$Et)-dac^{2}Gp(CNEt,Cl$_3$Et)	36872-37-4	0.2 (Pr, 1:1)	7	[(MeO)Tr]dac^{2}Gp(Cl$_3$Et)-dac^{2}Gp(Cl$_3$Et)	36872-48-7	0.6 (D, 30%)	59
[(MeO)$_2$Tr]dbz^{4}Cp(Cl$_3$Et)-dbz^{6}Ap(CNEt,Cl$_3$Et)[e,i]	36872-38-5	0.4 (0.7) (Pr, 5%)	13	dbz^{4}Cp(Cl$_3$Et)-dbz^{6}Ap(CNEt,Cl$_3$Et)[j]	36872-52-3	0.4 (Pr, 5%)	63
[(MeO)$_2$Tr]dan^{4}Cp(Cl$_3$Et)-dbz^{6}Ap(CNEt,Cl$_3$Et)	36872-39-6	0.4 (0.7) (Pr, 5%)	41	[(MeO)$_2$Tr]dan^{4}Cp(Cl$_3$Et)-dbz^{6}Ap(Cl$_3$Et)	36921-50-3	0.3 (Pr, 20%)	62

[a] Chromatography on silica gel plates: D = thin layer plates (Merck, Darmstadt, Germany), Pr = preparative layer plates (Merck, Darmstadt, Germany), HM = "home-made" preparative layer plates; PC = paper chromatography; 5, 7, 20, and 30% methanol in chloroform, 1:1 benzene:acetone, 7:3 ethanol:1 *N* ammonium acetate, 55:10:35 isopropyl alcohol:concentrated ammonia:water (occasionally before developing a plate with 7:3 or 55:10:35 it was first developed with 1:1 methanol:chloroform). R_f values are reported for after developing once and twice ( ). [b] β,β,β-Trichloroethyl groups cleaved with Zn. [c] Dinucleotide cleaved with spleen

suggests that further refinement of the deblocking reaction is needed. The question of how large an oligonucleotide can be prepared and purified by the triester method must still be explored.

Experimental Section

Pyridine was purified by distillation from P_2O_5 and then from CaH_2; it was stored over CaH_2 and redistilled immediately before use. Tetrahydrofuran was distilled twice from CaH_2, stored over CaH_2, and distilled immediately before use. Ethyl ether was distilled from $LiAlH_4$ immediately before use. Uv spectra were measured on a Cary 14 with methanol or water as solvent. Nmr spectra were measured in $CDCl_3$ on a Varian HA-100.

Preparation of 5′,N-Protected β,β,β-Trichloroethyl 3′ Nucleotides.—The appropriate protected nucleoside (2–30 g) was dried by distillation of pyridine *in vacuo*, followed by distillation of tetrahydrofuran. To an ice-cold solution of imidazole (13 equiv) in tetrahydrofuran was slowly added β,β,β-trichloroethyl phosphodichloridate[3] (3 equiv). The resulting mixture was stirred for 1 hr at 0° and filtered (to remove imidazole–HCl) and the filtrate was added to the predried nucleoside. The reaction solution was left overnight at room temperature. It was chilled in ice, water was added, and the pH was adjusted to 7.5–8 by the addition of triethylamine. The reaction mixture was stirred for 2 hr at room temperature, evaporated *in vacuo*, and dried by distillation of benzene. The protected nucleotide could be purified by chromatography on silica gel (plates developed with 20% MeOH/$CHCl_3$ or column eluted with a gradient of $CHCl_3$–15% MeOH/$CHCl_3$ containing 1% triethylamine). Yields of the protected nucleotides after purification were 40–80%.

Preparation of 5′,N-Protected β-Cyanoethyl β′,β′,β′-Trichloroethyl 3′ Nucleotides.—The 5′,N-protected β,β,β-trichloroethyl 3′ nucleotide (0.1–15 g) and 3–5 equiv of β-cyanoethanol were dried by distillation of pyridine *in vacuo*. A pyridine solution of 2,4,6-triisopropylbenzenesulfonyl chloride, an amount equal to, or in slight excess of, the β-cyanoethanol, was added to the dry mixture. After standing overnight at room temperature the reaction mixture was poured into water and the product was extracted into $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was purified by chromatography (Table I).

Cleavage of the β-Cyanoethyl Moiety.—The fully protected 3′ nucleotide or oligonucleotide (4–550 mg), or the derived material without 5′ protection, was dissolved in pyridine (100 mg/10 ml) and chilled in ice; ice-cold 0.1 *N* NaOH (1 ml/4 ml of pyridine) was added. After 5 min in ice the reaction was neutralized by the addition of a slight excess of 0.1 *N* HCl in aqueous pyridine or with Dowex 50 (pyridinium form). The reaction mixture was evaporated *in vacuo* and the product was purified on silica gel plates (Tables I, II, III).

Cleavage of the Mono- and Dimethoxytrityl Group.—An ice-cold solution of 1% trifluoroacetic acid in methylene chloride was added to the fully protected 3′ nucleotide (60–5000 mg) or oligonucleotide (10–550 mg), or to the analogous material after cleavage of the β-cyanoethyl moiety (60 ml/g). After 20 min in ice, the reaction was neutralized by addition of pyridine and evaporated *in vacuo*. The product was purified by chromatography on silica gel plates (Tables I, II, III).

Preparation of Protected Oligonucleotides.—Equal molar proportions of protected nucleotide component (80–2800 mg) and nucleoside component were dried by distillation of three portions of pyridine at 20–40°. To the dried mixture was added a two- to tenfold excess of triisopropylbenzenesulfonyl chloride in pyridine. After about 40 hr at room temperature the reaction mixture was evaporated *in vacuo*. Alternatively, the reaction mixture was poured into water and the product was extracted into $CHCl_3$, and the $CHCl_3$ solution, after being washed with H_2O and dried over Na_2SO_4, was evaporated *in vacuo*. The product was isolated following chromatography on silica gel (Tables II, III). A typical reaction was run on a 0.1-m*M* scale, although some were done on a much larger scale, in 10 ml of pyridine. Less than 40 hr was required if the reaction mixture was concentrated to an oil.

Cleavage of the β,β,β-Trichloroethyl, *N*-Benzoyl, and *N*-Acetyl Groups.—A sample of 3′ nucleotide or oligonucleotide (100–300 OD units), after cleavage of the mono- or dimethoxytrityl and β-cyanoethyl groups, was dissolved in 2 ml of absolute dimethyl formamide (in one case 5% acetic acid in pyridine). To this solution was added about 0.2 g of Zn/Cu couple.[11] The reaction mixture was shaken for 10 min, the solution was decanted, and the residue was washed with 25% aqueous NH_3. The combined solutions were evaporated *in vacuo* and the solid obtained was dissolved in 25% aqueous NH_3. The zinc ions were precipitated by bubbling H_2S through the solution. The resulting mixture

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Dinucleotides with one protecting group per phosphate	Registry no.	R_f Value[a] (solvent)	Yield, %	Dinucleotide	Registry no.	R_f Value[a] (solvent)	Yield, %	Relation of nucleotides	R_f Value[a] (solvent)
dbz⁴Cp(Cl₃Et)-dTp(Cl₃Et)	36900-99-9	0.5 (HM, 20%)	70	dCpdTp[b]	3922-65-4	0.5 (PC, 55:10:35)	3	dCp:dTp[c] 1:1	(PC, 7:3)[d]
dTp(Cl₃Et)-dbz⁴Cp(Cl₃Et)	36872-49-8	0.4 (0.6) (HM, 20%)	70	dTpdCp[b]	4105-16-2	0.1 (0.3) (D, 7:3)	23	dTp:dCp[c] 0.9:1	0.3/0.2 (PC, 7:3)
dbz⁴Cp(Cl₃Et)-dbz⁴Cp(Cl₃Et)	36872-50-1	0.4 (0.7) (HM, 20%)	56	dCpdCp[b]	3930-16-3	0.1 (D, 7:3)	18		
dbz⁶Ap(Cl₃Et)-dCp(Cl₃Et)	36872-51-2	(0.7) (HM, 20%)	50	dApdCp[b]	3930-15-2	0.5 (D, 7:3)	17	dAp:dCp[c] 1:0.9	0.6/0.5 (D, 7:3)
dbz⁶Ap(Cl₃Et)-dan⁴Cp(Cl₃Et)[g]	36872-53-4	0.5 (0.9) (Pr, 30%)	13	dApdCp[h]		0.5 (PC, 55:10:35)	37	dAp:dCp[c] 1:1	0.8/0.3 (PC, 7:3)
dbz⁶Ap(Cl₃Et)-dTp(Cl₃Et)	36872-54-5	0.5 (Pr, 30%)	57	dApdTp[h]	6818-27-5	0.5 (D, 7:3)	55	dAp:dTp[c] 1:1	0.5/0.6 (D, 7:3)
dTp(Cl₃Et)-dbz⁶Ap(Cl₃Et)	36872-55-6	0.5 (Pr, 30%)	100	dTpdAp[b]	3922-64-3	0.4 (D, 7:3)	25	dTp:dAp[c] 1:1	0.6/0.3 (PC, 7:3)
dac²Gp(Cl₃Et)-dTp(Cl₃Et)	36872-56-7	(Pr, 30%)[d]	71	dGpdTp[h]	36872-65-8	0.2 (PC, 55:10:35)	65	dGp:dTp[c] 0.95:1	0.1/0.4 (PC, 7:3)
dac²Gp(Cl₃Et)-dac²Gp(Cl₃Et)	36872-57-8	0.2 (D, 30%)	32	dGpdGp[h]	4417-99-6	0.2 (PC, 55:10:35)	30		
dbz⁴Cp(Cl₃Et)-dbz⁶Ap(Cl₃Et)[k]	36872-58-9	0.8 (D, 20%)	59						
dan⁴Cp(Cl₃Et)-dbz⁶Ap(Cl₃Et)[k]	36872-59-0	(0.8) (Pr, 30%)	62						

phosphodiesterase and components separated chromatographically according to ref 3. [d] R_f value not recorded. [e] Dinucleotides containing both dA and dC usually lost the *N*-benzoyl from dC. [f] [(MeO)₂Tr]dbz⁶Ap(Cl₃Et)dbz⁴Cp(CNEt,Cl₃Et) isolated from this reaction in 5% yield. [g] Run at room temperature and not the usual 0°. [h] β,β,β-Trichloroethyl groups cleaved with Zn/Cu. [i] [(MeO)₂Tr]dCp(Cl₃Et)dbz⁶Ap(CNEt,Cl₃Et) isolated from a similar reaction in 41% yield. [j] Order of cleavage of protecting groups reversed. [k] Not further degraded.

TABLE III

TRI- AND TETRANUCLEOTIDES SYNTHESIZED AND CHARACTERIZED

	Registry no.	R_f Value[a] (solvent)	Yield, %
5′-Protected tri- and tetranucleotides with fully protected phosphate groups			
[(MeO)₂Tr]dbz⁴Cp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(CNEt,Cl₃Et)	36901-00-5	0.5 (Pr, 7%)	57
[(MeO)₂Tr]dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(CNEt,Cl₃Et)	36901-01-6	0.4 (0.5) (D, 7%)	48
[(MeO)₂Tr]dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(CNEt,Cl₃Et)	36872-67-0	0.3 (Pr, 1:1)	54
[(MeO)₂Tr]dbz⁶Ap(Cl₃Et)dTp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(CNEt,Cl₃Et)	36901-02-7	0.2 (0.3) (D, 1:1)	39, 21[g]
Tri- and tetranucleotides with fully protected phosphate groups			
dbz⁴Cp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(CNEt,Cl₃Et)	36872-68-1	0.9 (D, 10%)	40
dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(CNEt,Cl₃Et)	36872-69-2	0.4 (Pr, 10%)	73
dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(CNEt,Cl₃Et)	36900-88-6	0.5 (Pr, 10%)	24
dbz⁶Ap(Cl₃Et)dTp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(CNEt,Cl₃Et)	36900-89-7	0.7 (Pr, 10%)	61
5′-Protected tri- and tetranucleotides with one protecting group per phosphate			
[(MeO)₂Tr]dbz⁴Cp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)	36900-90-0	0.3 (Pr, 20%)	46
[(MeO)₂Tr]dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)	36900-91-1	0.2 (D, 20%)	47
[(MeO)₂Tr]dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)	36900-92-2	0.3 (Pr, 20%)	24
[(MeO)₂Tr]dbz⁶Ap(Cl₃Et)dTp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)	36872-70-5	0.3 (Pr, 20%)	11[h]
Tri and tetranucleotides with one protecting group per phosphate			
dbz⁴Cp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)	36872-71-6	0.2 (D, 20%)	100, 39[b]
dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)	36900-93-3	0.4 (D, 30%)	68, 47[b]
dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)	36872-75-0	0.6 (D, 30%)	74
dbz⁶Ap(Cl₃Et)dTp(Cl₃Et)dTp(Cl₃Et)dbz⁴Cp(Cl₃Et)	36921-51-4	0.5 (D, 30%)	81, 45[b]

Tri-, tetranucleotide	Registry no.	R_f Value[a] (solvent)	Yield, %	Relation of nucleotides	R_f Value[a] (solvent)
dCpdCpdTp[c]	36872-72-7	0.3 (D, 55:10:35)	9	dCp:dTp (2:1.2)[d]	0.5/0.6 (D, 7:3)
dTpdCpdTp[c]	36872-73-8	0.5 (D, 55:10:35)	11	dTp:dCp (2:1.3)[d]	0.5/0.3 (D, 7:3)
dTpdCpdTpdCp[e,f]	36900-94-4	0.3 (PC, 55:10:35)	31	dTp:dCp (1:1.2)[d]	0.3/0.2 (PC, 7:3)
dApdTpdTpdCp[e]	36872-74-9	0.3 (PC, 55:10:35)	52	dAp:dTp:dCp (1:2.1:1.2)[d]	0.8/0.5/0.4 (PC, 7:3)

[a] Chromatography on silica gel plates: D = thin layer plates (Merck, Darmstadt, Germany), Pr = preparative layer plates (Merck, Darmstadt, Germany), HM = "homemade" preparative layer plates; PC = paper chromatography; 7, 10, 20, and 30% methanol in chloroform, 1:1 benzene acetone, 7:3 ethanol:1 *N* ammonium acetate, 55:10:35 isopropyl alcohol:concentrated ammonia:water (occasionally before developing a plate with 7:3 or 55:10:35 it was first developed with 1:1 methanol:chloroform). R_f values are reported for after developing once and twice ( ). [b] First yield for cleavage of [(MeO)₂Tr] from 5′-protected tri- and tetranucleotides with one protecting group per phosphate; second yield for cleavage of (CNEt) from tri- and tetranucleotides with fully protected phosphate groups. [c] β,β,β-Trichloroethyl groups cleaved with Zn. [d] Oligonucleotides cleaved with spleen phosphodiesterase and components separated chromatographically according to ref 3. [e] β,β,β-Trichloroethyl groups cleaved with Zn/Cu. [f] Chromatography on Whatman DE 81 paper, developing with 0.75 *M* $(NH_4)HCO_3$: dTpdCpdTpdCp, R_f 0.45, dTpdCp, R_f 0.62. [g] Two overlapping spots in thin layer chromatography, the lower spot being $HClO_4$ negative. [h] Product used in this reaction only ~50% pure; compare footnote *g*.

was centrifuged and the solution was decanted. The residue was washed with 25% aqueous NH_3 and the combined solutions were evaporated *in vacuo*. The residue was then allowed to stand overnight in 3 ml of pyridine:25% aqueous NH_3 (1:2, v/v). The solution was then evaporated *in vacuo* and the free nucleotide or oligonucleotide was isolated *via* chromatography (Tables II, III). In all cases where a lower yield than 30% was obtained, zinc in 5% acetic acid in pyridine or in 80% aqueous acetic acid was used instead of the above procedure to cleave the β,β,β-trichloroethyl function.

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Activated Phosphate Triesters. The Synthesis and Reactivity of *N*-Hydroxysuccinimide and *N*-Mercaptosuccinimide Esters

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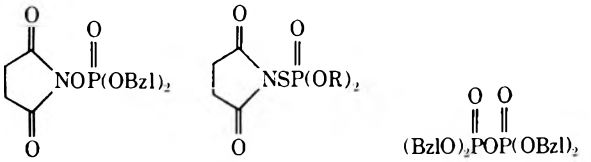
Phosphate esters based upon *N*-hydroxysuccinimide and *N*-mercaptosuccinimide have been prepared. It is shown that the reaction of *N*-hydroxysuccinimide with dibenzyl phosphate through the agency of diisopropylcarbodiimide can give a variety of products. Low temperatures in nonpolar solvents give the desired esters exclusively. Higher temperatures and polar solvents give mainly tetrabenzyl pyrophosphate. *O,O*-Dibenzyl *O*-(*N*-succinimidyl) phosphate phosphorylates benzyl alcohol in high yield: it does not react, however, with 3′-acetylthymidine. The thio esters phosphorylate benzyl alcohol in low yield, giving a large number of side products.

Although there have been remarkable achievements in the field of nucleotide synthesis,[1] it is clear that current methods for the synthesis of the internucleotide phosphate linkage are not satisfactory. The most successful procedures involve the use of condensing agents that remove a molecule of water between a nucleotide and a nucleoside. The most popular of these agents, dicyclohexylcarbodiimide[2] and triisopropylbenzenesulfonyl chloride,[3] are known to produce undesirable side reactions which become more serious when oligonucleotides are condensed; the starting materials are degraded[4-6] and larger and larger excesses of the phosphate-containing unit are required as the oligonucleotides grow in size. Just as the use of active esters[7,8] in peptide synthesis constituted an important advantage, the isolation of an activated phosphate species followed by coupling with a nucleoside hydroxyl group would be expected to result in much cleaner reactions. The possible utility of this scheme in phosphorylation reactions has been demonstrated with various reactive phosphates, *e.g.*, phosphorochloridates,[9] the adduct of phosphorochloridates with dimethylformamide,[10] phosphoromorpholidates,[11] imidazoyl phosphates,[12] oxidized or alkylated thio esters,[13] and activated phosphate esters with 2,4-dinitrophenol,[14] *p*-nitrophenol,[15] 2-hydroxypyridine,[16] and 2-mercaptopyridine.[17]

As a model for possible nucleotide synthesis we have prepared and studied phosphate *N*-hydroxysuccinimide and *N*-mercaptosuccinimide esters. These are *O,O*-dibenzyl *O*-(*N*-succinimidyl) phosphate (**1**), *O,O*-diethyl *S*-(*N*-succinimidyl) phosphorothioate (**2**), and *O,O*-di-*tert*-butyl *S*-(*N*-succinimidyl) phosphorothioate (**3**).



1 **2**, R = Et **3**, R = *t*-Bu **4**

It was our purpose to study phospho triesters because of advantages in maintaining phospho triester linkages during oligonucleotide synthesis[18] and their high susceptibility to attack by hydroxide ion.[19] *N*-Hydroxysuccinimide active esters have proven their value in peptide synthesis.[20]

The synthesis of **1** was accomplished by the reaction of dibenzyl phosphate (DBP) and *N*-hydroxysuccinimide (NHS) with diisopropylcarbodiimide in acetonitrile or anisole at low temperature. It was seen that solvent polarity or basicity[21,22] and temperature play an important role in determining the course of the reaction which can proceed to give **1**, tetrabenzyl

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pyrophosphate (**4**),[23] or a mixture of the two (Table I). The reaction could be readily followed, since the chemical shifts and coupling constants of the benzyl protons differ. At all temperatures studied DMF gives a 95% yield of pyrophosphate; similar results are obtained in acetonitrile and anisole at ambient temperature, but at −18° *no pyrophosphate forms.* These results may be generally applicable to reactions of phosphates with acidic alcohols. All attempts to treat dibenzyl phosphate with copoly(ethylene-*N*-hydroxymaleimide)[24] yielded only **4**, probably owing to the insolubility of the polymer in any but dipolar solvents.

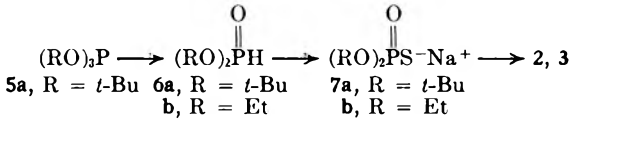
TABLE I

THE INFLUENCE OF SOLVENT AND TEMPERATURE ON THE FORMATION OF PHOSPHATE ACTIVE ESTER 1

Solvent	[NHS]: [DBP]	Temp, °C	% Yield of ester 1	% Yield of pyrophosphate 4
Acetonitrile	3:1	−18 to −15	45[a]	0
	4:1	0–4°	70	30
	7:1	Ambient	10	90
Anisole	3:1	−18 to −15	45	0
	3:1	Ambient	18	82
Dimethylformamide	3:1	−78	5	95
	7:1	−18 to −15	5	95
	3:1	Ambient	5	95
Dioxane	3.5:1	0–4	45	55
	3.5:1	10	30	70
	3:1	Ambient	5	95
	4:1	50–60	0	100
Hexamethylphosphoramide	5:1	0–4	0	90
Tetrahydrofuran	1:1	−18 to −15	40	9
	1:1	0–4	24	28
	1:1	Ambient	5	95

[a] The reaction stops after 50 hr; addition of more NHS or carbodiimide effects no further change. Reaction proceeds, however, upon warming.

Compounds **2** and **3** were prepared by the reaction of the corresponding sodium dialkyl phosphorothioates[25] (**7a,b**) with *N*-chlorosuccinimide.[26] Di-*tert*-butyl phosphonate (**6a**)[27] was obtained by heating tri-*tert*-butyl phosphite (**5a**)[28] with a trace of sulfuric acid. The dialkyl phosphorothioates **7a,b** were prepared by refluxing phosphonates **6a,b** with sodium and sulfur in dioxane. Compound **3** was a crystalline product but decomposed with the release of isobutylene, even at −18°. Tri-*tert*-butyl phosphate *has* been reported to undergo autocatalytic decomposition.[29]



Phosphorylation reactions were attempted by mixing the esters **1**, **2**, and **3** with alcohols in an excess of tertiary amine. The *N*-hydroxysuccinimide ester **1** reacts with simple alcohols to give phosphoryl product. The reaction with a twofold excess of benzyl alcohol in 2,6-lutidine proceeded to give a solution which showed a single product by nmr. Tribenzyl phosphate (**8**) was isolated in 80% yield; *N*-hydroxysuccinimide was recovered quantitatively. Other bases tried did not give substantial yields of phosphorylated products, these bases being triethylamine, pyridine, *N*-methylmorpholine, quinuclidine, and 1,8-bis(dimethylamine)naphthalene. A twofold excess of benzyl alcohol with **2** in 2,6-lutidine gave complete reaction; however, only a 13% yield of *O,O*-diethyl *O*-benzyl phosphate (**9**) could be isolated along with considerable amounts of *O,O*-diethyl phosphorothioate and *O,O,O,O*-tetraethyl thiopyrophosphate (**10**). Under similar conditions **3** phosphorylated benzyl alcohol to an extent of only 2%.

$$1 + PhCH_2OH \xrightarrow[2,6\text{-lutidine}]{} (PhCH_2O)_3P{=}O + NHS$$
8

$(EtO)_2P(O)OBzl$ **9**

$(EtO)_2P(O)SP(O)(OEt)_2$ **10**

An attempt was made to phosphorylate a deoxy ribonucleoside by treating **1** in lutidine with 3′-acetylthymidine. After 20 days there was no phosphorylation. The apparent lack of reactivity of nucleoside-hydroxyl groups compared to simple alcohols has been observed by others.[16,17,30]

Experimental Section

General.—All solvents were distilled from appropriate drying agents and stored over molecular sieves. Dibenzyl phosphate, *N*-chlorosuccinimide, and diisopropylcarbodiimide were purchased from Aldrich Chemical Co. and used without further purification; *N*-hydroxysuccinimide, also purchased from Aldrich, was recrystallized from ethyl acetate. *O,O*-Diethylphosphonic acid was distilled before using. Known compounds prepared in this work gave the expected nmr and ir spectra.

Nuclear magnetic resonance spectra were recorded using a Varian T-60 and a Varian A-60D spectrometer and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were obtained from an LKB 9000 mass spectrograph and ir spectra from a Beckman IR4 and Perkin-Elmer 247 ir spectrophotometer. Analyses were obtained by Galbraith Laboratories, Knoxville, Tenn., and Scandinavian Microanalytical Laboratories, Herlev, Denmark. Melting points are uncorrected.

***O,O*-Dibenzyl *O*-(*N*-Succinimidyl) Phosphate (1).**—*O,O*-Dibenzyl phosphate, 1.36 g (4.9 mmol), was dissolved in dry acetonitrile, 30 ml, with *N*-hydroxysuccinimide, 0.615 g (5.3 mmol). After the mixture was cooled to −15°, 0.6 ml (5 mmol) diisopropylcarbodiimide was added over a 30-min period. The reaction vessel was kept at −15° over a 5-day period with periodic monitoring for product formation using the nmr. The reaction mixture was then poured into cold (3°) 5% sodium bicarbonate and extracted twice with chloroform. The chloroform was dried over anhydrous sodium sulfate, evaporated to 5 ml, and filtered through a Millipore filter to remove diisopropylurea. Evaporation of the chloroform left an oil which crystallized upon addition of a seed crystal. Recrystallization from chloroform–petroleum ether (bp 30–60°) gave 0.69 g (51%). It was possible to recover 0.47 g of DBP from the basic aqueous solution. The yield of ester is 78% based upon unrecovered starting materials: mp 77–78°; mass spectrum parent *m/e* 284 (loss of benzyl); ir (KBr) 2900, 1782 (shoulder), 1730, 1210, 1010–1040, 850, 730, 690 cm^{-1}; nmr ($CDCl_3$) δ 7.4 (d, 10, PhH), 5.3 (d, 4, J_{PH} = 8 Hz, $POCH_2$), 2.7 (d, 4, J_{HP} = 1 Hz, O=CCH_2).

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Anal. Calcd for $C_{18}H_{18}O_6NO$: C, 57.5; H, 4.8; N, 3.7; P, 8.4. Found: C, 57.8; H, 5.03, N, 4.01; P, 8.09.

Sodium *O,O*-Diethyl Phosphorothioate (7b).—Sodium wire (1.9 g, 0.082 g-atom) and *O,O*-diethylphosphonic acid (**6b**) (12.0 g, 0.085 mol) were refluxed in 100 ml of anhydrous ether until all the sodium had reacted. Sulfur flowers (2.87 g, 0.089 mol) suspended in benzene were added over a 15-min period. This was refluxed for 35 min and then allowed to stand overnight. Evaporation gave a white precipitate which was recrystallized from benzene–ether, giving 11 g (80%) of product, mp 205–206° (lit.[25,31] mp 196°).

O,O-Diethyl *S*-(*N*-Succinimidyl) Phosphorothioate (2).—*N*-Chlorosuccinimide (1.2 g, 10 mmol) and sodium *O,O*-diethyl phosphorothioate (1.6 g, 9 mmol) were stirred in 20 ml of dry benzene for 10 min, then left to stand for 2 hr. Filtration and evaporation gave a crude oil, 2.14 g (97%). Alternatively, a sample was dissolved in chloroform and extracted with dilute citric acid, and the chloroform was dried over anhydrous sodium sulfate and evaporated to an oil which crystallized on standing: yield 72%; mp 61–63°; mass spectrum parent *m/e* 267 (corresponds to molecular ion); ir (KBr) 2950, 1780 (shoulder), 1720, 1300, 1250, 1140, 990–1000, 780 cm^{-1}; nmr ($CDCl_3$) δ 4.35 (dq, 4, J_{HH} = 7 Hz, J_{HP} = 8 Hz, $POCH_2$), 2.85 (d, 4, J_{HP} = 1 Hz, $CH_2C{=}O$), 1.3 (dt, 6, J_{HH} = 7 Hz, J_{HP} = 1 Hz, $POCH_2CH_3$).

Anal. Calcd for $C_8H_{14}NO_5PS$: C, 35.93; H, 5.24; N, 5.24; S, 12.00. Found: C, 35.28; H, 5.29; N, 4.73; S, 14.30.

Di-*tert*-butylphosphonic Acid (6a).—Tri-*tert*-butyl phosphite (**5a**) was prepared by the method of Mark and Van Wazer.[32] Conversion to **6a** required heating **5a** (13.07 g) with a catalytic amount of concentrated H_2SO_4 to 80° at aspirator pressure for 30 min. Vigorous bubbling occurred. The product (8 g, 80%) was obtained by distillation, bp 64° (5 mm), $n^{25}D$ 1.4186 (lit.[27,32] $n^{25}D$ 1.4168).

Sodium *O,O*-Di-*tert*-butyl Phosphorothioate (7a).—Sulfur flowers (1.32 g, 0.04 mol) and sodium wire (0.82 g, 0.04 mol) were stirred into a dioxane solution (80 ml) of di-*tert*-butylphosphonic acid (**6a**) (8.24 g, 0.04 mol). An exothermic reaction took place. After refluxing for 1 hr and stirring overnight at 60–70°, the solution was flash evaporated to 50 ml. The product was precipitated by addition of petroleum ether, collected by centrifugation, twice washed with petroleum ether, and crystallized from 2-propanol–petroleum ether, giving 7.72 g (77% yield): mp 156° dec; nmr (D_2O) δ 1.35 (s), 4.57 (s, HOD); ir (KBr) 3000, 1400, 1370, 1250, 1170, 1110, 970, 920, 820, 720 cm^{-1}. Comparison by ir of the free acid prepared by treatment of the sodium salt with Dowex 50WX8 ion exchange resin (H^+ form) with the same acid prepared in an alternative procedure[32] showed the identity of the two.

O,O-Di-*tert*-butyl *S*-(*N*-Succinimidyl) Phosphorothioate (3).—Sodium *O,O*-di-*tert*-butyl phosphorothioate (1.32 g, 0.530 mol) was suspended in 30 ml of dimethoxyethane. To this *N*-chlorosuccinimide (0.715 g, 0.530 mol) was added with stirring. A mildly exothermic reaction took place dissolving the sodium salt as well as the *N*-chlorosuccinimide. Finely divided sodium chloride formed after 10 min. The reaction was conveniently monitored by nmr as the succinimide protons are split by phosphorous–hydrogen coupling (1 Hz). This resonance is partially obscured by the solvent protons until a few drops of benzene are added to the nmr tube. This caused the succinimide protons to shift (δ 2.85 in dimethoxyethane, δ 1.85 in pure benzene.) After 2 hr the solution was centrifuged and the supernatant was evaporated to an oil. The oil was taken up in chloroform, extracted twice with dilute citric acid and twice with water, and then dried over anhydrous sodium sulfate. The solvent was evaporated, giving an oil which crystallized on standing (1.45 g, 85% yield): nmr ($CDCl_3$) δ 2.85 (d, 4, J_{HP} = 1 Hz, $CH_2C{=}O$), 1.57 (s, 18).

Tribenzyl Phosphate[33] (8).—Benzyl alcohol (0.097 g, 0.9 mmol) and *O,O*-dibenzyl *O*-(*N*-succinimidyl) phosphate (0.152 g, 0.4 mmol) were dissolved in 0.38 g of 2,6-lutidine. This was allowed to stand at room temperature in a desiccator for 8 days. The reaction was monitored by nmr. The benzyl protons of the product are separated from those of the starting material by 0.3 ppm. The nmr showed quantitative transesterification to the tribenzyl ester. The reaction mixture was evaporated to an oil and then evacuated at 0.1 mm for 4 hr to remove the 2,6-lutidine and most of the excess benzyl alcohol. The oil was then placed on a 10-g silica gel column and eluted with hexane (200 ml), carbon tetrachloride (100 ml), chloroform (100 ml), ethyl acetate (100 ml), and finally methanol (100 ml). From the chloroform eluate 0.115 g of pure tribenzyl phosphate was obtained, 80% yield, nmr ($CDCl_3$) δ 7.3 (s, 15 H), 5.0 (d, 6, J_{HP} = 8.5 Hz). Comparison of the ir spectrum obtained for the above with that of tribenzyl phosphate, Stadler index 9209, showed them to be identical. *N*-Hydroxysuccinimide was quantitatively recovered from the methanol fraction.

O,O-Diethyl O-Benzyl Phosphate (9).—*O,O*-Diethyl *S*-(*N*-succinimidyl) phosphorothioate (0.177 g, 0.45 mmol), **2**, benzyl alcohol (0.193 g, 1.8 mmol), and 2,6-lutidine (1.65 g) were allowed to stand for 12 hr at room temperature in a desiccator. Nmr showed succinimidyl protons, split 1 Hz by the phosphorus, to gradually give way to succinimide protons (singlet). The reaction mixture became dark brown and some succinimide (mp 126–127°) crystallized. The solution was evaporated to an oil (1 mm room temperature) to remove the 2,6-lutidine and most of the benzyl alcohol. The oil was then placed on a 10-g silica gel column, and eluted with methylene chloride (100 ml), chloroform (100 ml), ethyl acetate–chloroform (1:3, 100 ml), ethyl acetate–chloroform (1:1, 100 ml), and ethyl acetate–chloroform (3:1, 100 ml). From the chloroform–ethyl acetate fractions was isolated *O,O,O,O*-tetraethyl pyrophosphorothioate (**10**) (0.0105 g), 7% yield (calcd for $C_8H_{20}O_6P_2S$: 306 g/mol; parent *m/e* 306); nmr ($CDCl_3$) δ 4.6 (dq, 8, J_{HH} = 8, J_{HP} = 9 Hz, $POCH_2$), 1.3 (dt, 12, J_{HH} = 8, J_{HP} = 1 Hz, $POCH_3,CH_3$). This was followed by the desired product **9** (0.032 g, 13% yield).

O,O-Di-*tert*-butyl O-Benzyl Phosphate.—*O,O*-Di-*tert*-butyl *S* (*N*-succinimidyl) phosphorothioate (**3**) (0.122 g) was dissolved in pyridine (5 ml). The pyridine slows the decomposition observed for the compound as a solid. To this an excess of benzyl alcohol (0.5 ml) was added. The reaction mixture was allowed to stand at room temperature with periodic monitoring by nmr. The succinimidyl protons of the triester **3** were no longer visible after 12 hr. The dark brown solution was decanted from precipitated succinimide and sulfur. The nmr spectrum of the benzyl protons of the solution gave the yield of product to be approximately 2%. No further characterization was possible; nmr ($CDCl_3$) δ 7.3 (s, 5), 5.0 (d, 2, J_{HP} = 8 Hz, PhC_2H-), 1.55 (s, 18, *tert*-butyl).

Attempted Preparation of 5′-Dibenzylphosphoryl-3′-acetylthymidine.[34]—*O,O*-Dibenzyl *O*-(*N*-succinimidyl) phosphate (**1**) (0.120 g, 0.32 mmol) and 3′-acetylthymidine (0.089 g, 0.31 mmol) were dissolved in 1.67 g of 2,6-lutidine, then allowed to stand at room temperature in a desiccator for 20 days. Column chromatography of the products gave none of the desired material; however, recovery was made of 3′-acetylthymidine (0.073, g, 82%), *N*-hydroxysuccinimide (100%), and a mixture of dibenzyl phosphate and tetrabenzyl pyrophosphate. These compounds were identified by nmr, mass spectra, and/or melting point. No compound having the paper chromatographic properties reported for the desired product were found. Thioester **2** also failed to give phosphorylated nucleoside.

Registry No.—**1**, 37173-10-7; **2**, 37173-11-8; **3**, 37173-12-9; **4**, 990-91-0; **6a**, 13086-84-5; **7a**, 37173-14-1; **8**, 1707-92-2; **9**, 884-90-2; **10**, 7342-94-1; di-*tert*-butyl benzyl phosphate, 37173-17-4.

Acknowledgment.—We wish to thank the Health Research and Services Foundation, Pittsburgh, Pa., for their financial support of this work. We are grateful to Mr. Richard Montgomery for obtaining the mass spectra cited.

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Molecular Structure of 1-Ethoxy-1,2-diphenyl-3,3,5-tricarbethoxy-1,2-diphosphocyclopenten-5-one, a Heterocycle with Two Directly Linked Phosphorus Atoms of Different Valence States

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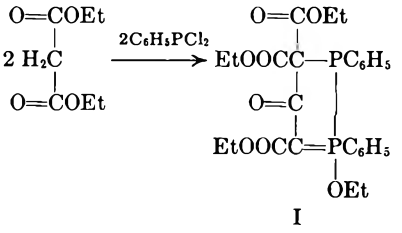
The title compound I forms when phenylphosphorus dichloride is treated with malonic acid diethyl ester in the presence of an amine. The structure of I was confirmed by X-ray diffraction analysis based on 2824 intensity data and refined to a discrepancy index of 9.7%. From this study it is concluded that two phosphorus atoms, of valence state 5 and 3, are linked together covalently and are part of a new, unusual five-membered heterocycle. A structure is proposed for the addition product of I with nickel tetracarbonyl, $Ni(CO)_3$–$C_{25}H_{30}O_8P_2$.

When phenylphosphorus dichloride is treated with malonic acid diethyl ester in the presence of triethylamine a colorless solid is obtained which can be recrystallized from methanol (mp 114° dec).[1] The formation of this product, 1-ethoxy-1,2-diphenyl-3,3,5-tricarbethoxy-1,2-diphosphocyclopenten-5-one (I), can



I

be described as the result of a 2:2 addition combined with the rearrangement of one ethoxy group.

The structure of I, as derived by spectroscopic and chemical methods,[1] is interesting not only from a mechanistic but also from a structural chemical point of view. Thus it seemed worthwhile to undertake, in continuation of our studies on addition products of reactive organic compounds,[2] a detailed structural analysis of I.

The crystallographic data of the lath-shaped colorless crystals are presented in Table I. The intensities of

TABLE I

CRYSTALLOGRAPHIC DATA

Crystal dimensions	0.15 × 0.4 × 0.3 mm
Space group, monoclinic, $P2_1/c$	
(extinctions $h0l$, $l = 2n + 1$, and $0k0$, $k = 2n + 1$)	
Cell dimensions	$a = 16.774 \pm 0.003$ Å
	$b = 8.078 \pm 0.002$ Å
	$c = 21.122 \pm 0.005$ Å
	$\beta = 108.66 \pm 0.05°$
Wavelength, Cu Kα, 1.54182 Å	
Density observed (CCl_4/cyclohexane)	1.305 g/cm³
calculated ($Z = 4$)	1.303 g/cm³

3248 reflections were measured with a four-circle diffractometer using Ni-filtered Cu Kα radiation. Since, when subjected to X-ray radiation, the crystals were stable only for about 4 days, a new crystal was mounted after the intensity of a reference reflection had dropped to 70% of its initial value and the data collection was then completed.

After the data were corrected for this intensity change, they were converted to normalized structure factors, E_h, neglecting absorption effects. Of the 3248 measured intensities, 2824 were "observed," with F_{obsd} values above twice the background counts. The structure was solved by direct methods applying Sayre's equation[3] to the 397 E_h's of magnitude greater than 1.5. The starting phase set consisted of seven E_h's. The phase angles of three of these seven E_h's served to determine the origin, and the phase angles of the other four E_h's were permuted in turn by 180°, yielding 16 phase angle sets.[4] One of these sets, according to consistency criteria, was most promising and an E map computed from its phase angle information revealed the positions of all the 36 nonhydrogen atoms of the structure.

The initial crystallographic discrepancy index $R = \Sigma||F_{obsd}| - |F_{calcd}||/\Sigma|F_{obsd}|$ was 23.4% for the 2871 "observed" reflection data. The structure was refined in five cycles of full matrix least squares refinement minimizing $\Sigma W(F_{obsd} - F_{calcd})^2$ where W is the weighting factor computed according to Hughes' method[5] and assigning first isotropic, then anisotropic temperature, parameters to the atoms. The scattering factors used were those given in the "International Tables of X-Ray Crystallography".[6] The final R factor is 9.7% for the 2871 "observed" data; the average parameter shifts in the last cycle of refinement were less than $^1/_3$ the average standard deviations estimated from the variance–covariance matrix. Since the temperature factors of the benzene ring and ethyl carbon atoms, 3.5–9 Å², indicated rather intense thermal motion and/or some measure of structural disorder, perhaps radiation induced, the protons could not be located from difference Fourier syntheses.

The X-ray results confirm the previously described structure elucidation of I.[7]

A list of the observed and calculated structure factors and of the atomic parameters can be obtained on request.[7] A projection of the structure down the b axis is illustrated in Figure 1; Figure 2 and Tables II and III contain data describing details of the molecular structure of I.

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(7) Listing of structure factors and atomic parameters will appear following these pages in the microfilm edition of this volume of this journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-253. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

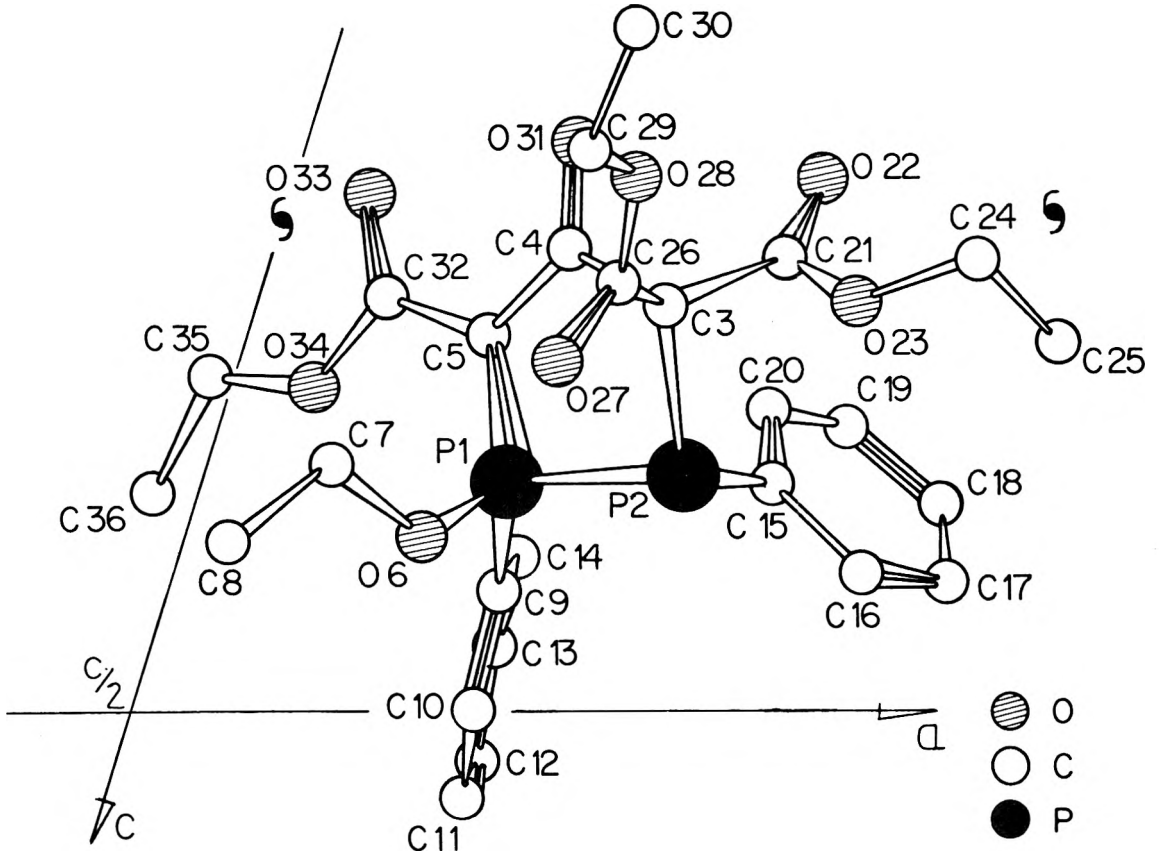

Figure 1.—The solid state structure of I as viewed down the crystallographic *b* axis, and numbering scheme used in the text.

TABLE II

DEVIATIONS OF SOME ATOMS FROM THE PLANE THROUGH ATOMS P(1), C(5), C(4)[a]

Atom	Deviation from plane, Å
C(3)	−0.149
P(2)	0.392
O(31)	−0.012
C(32)	0.013
O(33)	0.163
O(34)	−0.188
C(35)	−0.041
C(36)	−0.168
O(6)	−1.340
C(9)	1.177
C(15)	2.211
C(21)	−1.643
C(26)	0.626

[a] The equation of this plane is $0.551X - 0.821Y + 0.149Z - 2.553 = 0$, where X is along the crystallographic a axis, Y along b, and Z along c^+.

TABLE III

SELECTED TORSION ANGLES IN I

A. Five-Membered Ring and Substituents	
P(1)–P(2)–C(3)–C(4)	−24.0
P(2)–C(3)–C(4)–C(5)	23.1
C(3)–C(4)–C(5)–P(1)	−6.0
C(4)–C(5)–P(1)–P(2)	−10.5
C(5)–P(1)–P(2)–C(3)	18.4
C(4)–C(5)–C(32)–O(34)	171.1
C(4)–C(3)–C(21)–O(23)	−173.3
C(4)–C(3)–C(26)–O(28)	−79.8
C(5)–P(1)–O(6)–C(7)	0.3
C(5)–P(1)–C(9)–C(14)	21.7
P(2)–P(1)–C(9)–C(14)	−86.4
P(1)–P(2)–C(15)–C(16)	−129.5
C(3)–P(2)–C(15)–C(16)	139.7
B. Ethoxy Groups	
P(1)–O(6)–C(7)–C(8)	−136.4°
C(21)–O(23)–C(24)–C(25)	−104.0°
C(26)–O(28)–C(29)–C(30)	173.7°
C(32)–O(34)–C(35)–C(36)	−174.2°

The core of the molecule is formed by the five-membered heterocycle which is not planar but approximates to a half-chair conformation. Atoms P(2) and C(3) are at 0.392 and −0.149 Å distance from the plane through the atoms P(1), C(5), C(4), *i.e.*, on opposite sides (Table II); this unsymmetric puckering mode can also be visualized by the endocyclic dihedral angles which are given in Table III. Essentially coplanar with the three atom plane are the carbonyl oxygen atom O(31) and the atoms of the carbethoxy group bound to atom C(5), *i.e.*, the atoms C(32), O(33), O(34), C(35), and C(36) (Table II). The phenyl ring attached to atom P(1) is almost parallel to the bond P(1)–C(5) with an angle C(5)–P(1)–C(9)–C(14) of 21.5° and the plane through the phenyl ring bound to atom P(2) bisects the bond angle P(1)–P(2)–C(3) (Table III). The bond O(6)–C(7) of the ethoxy group linked to P(1) is cis planar with bond P(1)–C(5). The orientations of the carbethoxy groups bound to C(3) are such that the bonds C(4)–C(3) and C(21)–O(23) are trans planar but the bonds C(4)–C(3) and C(26)–O(28) are essentially gauche (Table III). Two of the four ethoxy groups are trans planar, C(26)–O(28)–C(29)–C(30), 173.7°, and C(32)–O(34)–C(35)–C(36), 174.2°, and two are gauche, P(1)–O(6)–C(7)–C(8), 136.4°, and C(21)–O(23)–C(24)–C(25), 104.0°. According to model studies, these different conforma-

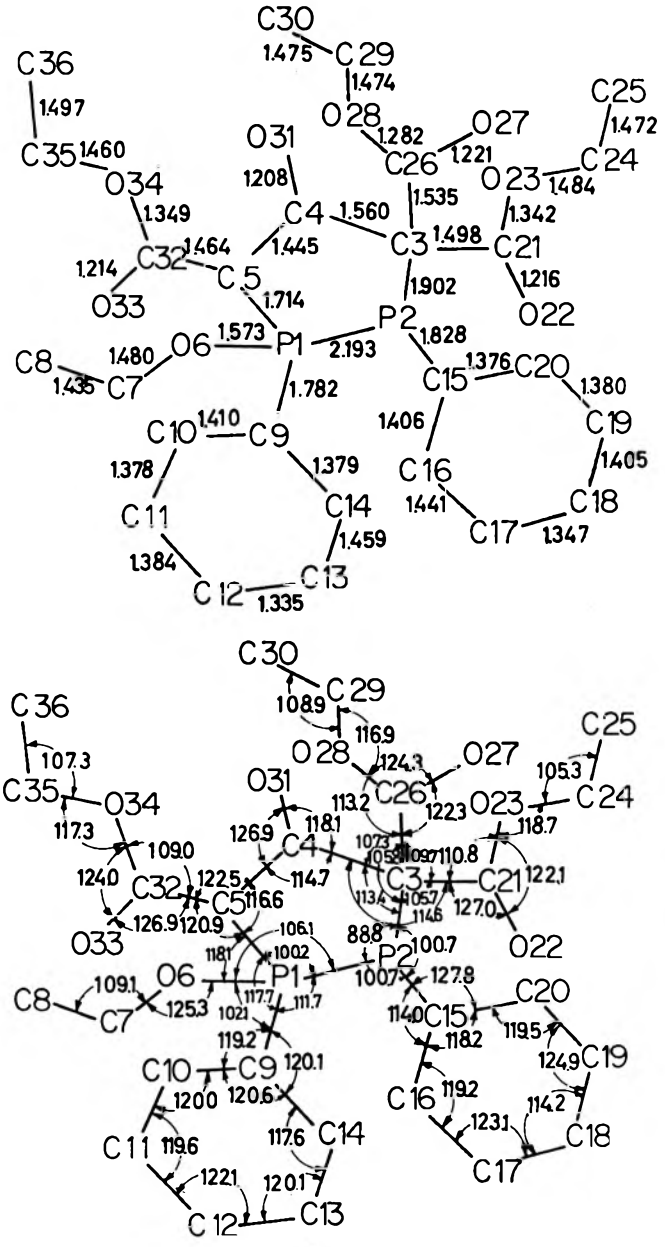

Figure 2.— Bond distances (Å) and angles in I. The standard deviations involving phosphorus atoms are 0.006 Å and 0.4°, respectively; those not involving phosphorus atoms are 0.01 Å and 0.7°, respectively.

tions of the ethoxy groups seem to be due mainly to crystal packing requirements rather than intramolecular overcrowding.

The valence states of the two phosphorus atoms are directly evident from the bond distances and angles involving these atoms. The distance P(1)–P(2), 2.193 Å, is only very slightly shorter than the P–P single distance in black phosphorus, 2.224–2.244 Å, and in other organic molecules containing P–P groups.[8,9] The P(1)–O(6) bond distance, 1.573 A, is similar to data obtained for a P–O–CH_3 group, 1.59 ± 0.01 A,[10] and the P(1)–C(5) bond has double bond character since the distance of 1.714 Å is shorter than the P–C single bond distance in $P(CH_3)_3$, 1.841 ± 0.005 Å, but similar to

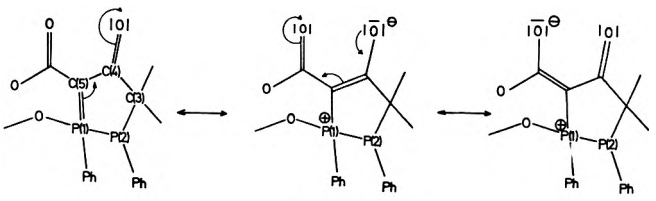

Figure 3.

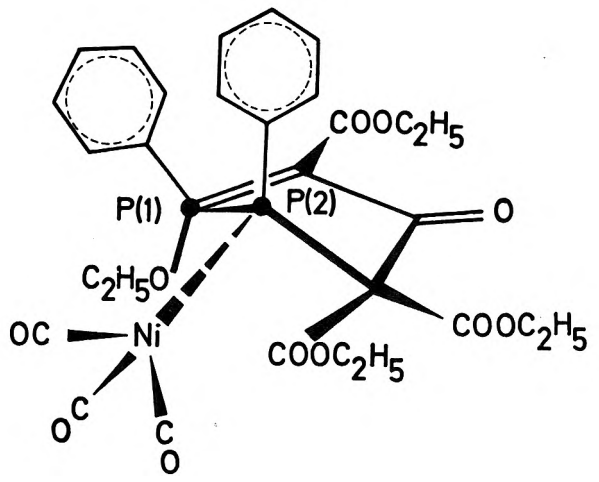

Figure 4.—Schematic drawing of the structure proposed for the complex formed between I and $Ni(CO)_4$.

the P=C double bond distance in $(C_6H_5)_3P=C$, 1.71 Å.[8] An isolated, "pure" P=C double bond is normally expected to be shorter than the observed P(1)–C(5) bond; conjugation, Figure 3, is indicated first by the bond distance C(4)–C(5), 1.445 Å, which is shorter than the C–C bond in the system CC=O, 1.506 ± 0.005 Å, but similar to the average C–C bond length in C=CC=O, 1.44 ± 0.01 Å,[11] and second by the short C(5)–C(32) distance, 1.464 Å, and the coplanarity of the C(32)-carbethoxy group with the five-membered heterocycle. From these considerations it follows that the valence state of the P(1) atom is 5.

On the other hand, the P(2)–C(3) and P(2)–C(15) distances, 1.902 and 1.828 Å, are in the range expected for $P–C_{aliphatic}$ and $P–C_{aromatic}$ single bonds, 1.874[12] and 1.82 Å.[13] Furthermore, the C–P(2)–C bond angles are all close to 98.9°, the C–P–C angle observed in $P(CH_3)_3$. P(2) is located on the vertex of a trigonal pyramid with the base formed by atoms P(1), C(3), C(15) and one should infer that the valence state of atom P(2) is 3.

It was observed that I forms a complex with nickel tetracarbonyl, $Ni(CO)_3–C_{26}H_{30}O_8P_2$[1]. From the present structural study of I it is clear that only the trivalent phosphorus atom P(2) is able to share its lone electron pair with the Ni atom. One can assume therefore that in the complex between I and $Ni(CO)_4$ one of the tetrahedrally arranged carbon monoxide groups has been replaced by the P(2) atom of I, similar to the dimeric complex between diphenylphosphine and

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(10) U. Thewalt, *Angew. Chem.*, **81**, 783 (1969).
(11) L. E. Sutton, "Tables of Interatomic Distances and Configuration in Molecules and Ions," The Chemical Society, London, Burlington House, W. 1, 1958.
(12) J. C. J. Bart, *Acta Crystallogr., Sect. B*, **25**, 762 (1969).
(13) D. L. Ward, C. N. Caughlan, G. E. Voecks, and P. W. Jennings, *ibid.*, **28**, 1949 (1972).

$Ni(CO)_4$;[14] the structure of the proposed complex is sketched in Figure 4.[15]

Registry No.—I, 25127-62-2.

(14) R. H. B. Mais, P. G. Owston, D. T. Thompson, and A. M. Wood, *J. Chem. Soc. A*, 1744 (1967).

(15) NOTE ADDED IN PROOF.—The proposed structure of the Ni complex has been confirmed by an independent X-ray study (G. Bergerhoff, private communication).

Acknowledgment.—The author is pleased to thank Professor F. Cramer for his interest in and support of this work and Dr. P. C. Manor for critically reading the manuscript. The computations were carried out with IBM 7040 and UNIVAC 1108 computers at the Aerodynamische Versuchsanstalt and Gesellschaft für wissenschaftliche Datenverarbeitung, Göttingen, respectively.

Nucleophilic Substitution at Phosphorus[1]

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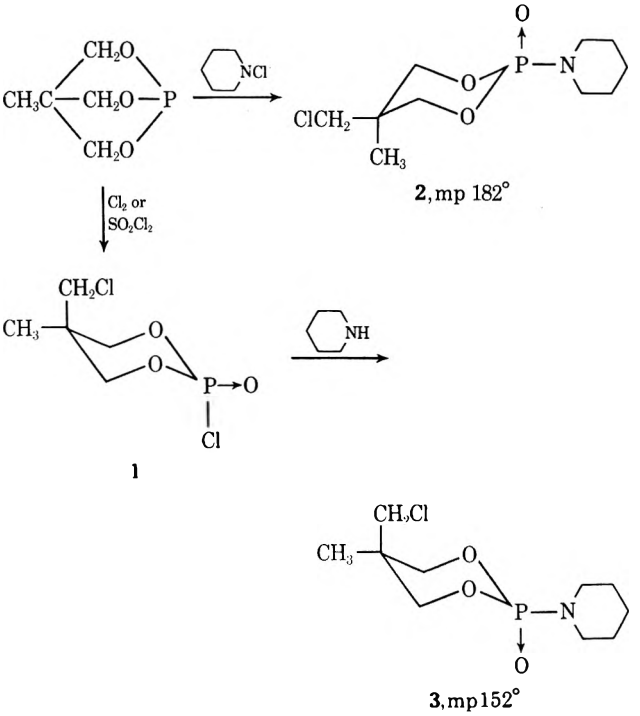
cis-5-Chloromethyl-5-methyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane was treated with a number of nucleophiles and the course of substitution at phosphorus was determined by analysis of the nmr spectra of the products. The geometry of the products with the aid of single-crystal X-ray analysis could be determined from the conformation of groups at the fifth position. In this manner the stereochemical outcome was found to be influenced by the basicity of the attacking nucleophile.

The mechanism of substitution reactions at phosphorus has been a subject of intensive study from which conflicting results have emerged. Mechanisms have been postulated on the basis of both kinetic and stereochemical results and both bimolecular, SN2(P), with and without inversion, and in a few cases monomolecular, SN1(P), pathways have been advanced.[2] In this paper we report results which we have obtained by means of a unique diagnostic tool which allows us to distinguish between possible stereochemical pathways.

In prior publications[3,4] we described the preparation of 2-substituted 5-halomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes which entailed the treatment of a bicyclic phosphite with halogen or alkyl halide in the normal Arbuzov manner. Thus, *cis*-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxophosphorinane (**1**), which is the starting point of our study, is prepared by treating methyl bicyclic phosphite with either chlorine or sulfuryl chloride.[5] The product, a phosphorochloridate, mp 69–70°, is easily recrystallized from carbon tetrachloride. Its configuration is based upon the known configuration of 2-bromo-5-bromomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane,[6] and is a consequence of its mode of formation.

Two isomeric phosphoramidates were obtained by treating the bicyclic phosphate with *N*-chloropiperidine and the phosphorochloridate with piperidine.[7]



Single-crystal X-ray analysis[8] of the low-melting trans isomer, **3**, has shown it to have the piperidinyl group equatorial and the chloromethyl group axial. The different chemical shifts of the methyl and chloromethyl hydrogens (Figure 1) indicate that the groups at the 5 position in the higher melting cis isomer, **2**, have a different environment. Consequently, as a result of the mechanism of the Arbuzov reaction and the caged structure of the starting phosphite it is most likely that the piperidinyl group in **2** is also equatorial and that the

(1) Taken in part from the Ph.D. Thesis of H. L. Horten, 1970, and M.S. Thesis of S. Larsen, 1971. Portions of this work were presented at the 5th Midwest Regional Meeting of the American Chemical Society, Kansas City, Mo., 1969, and the 4th Great Lakes Regional Meeting of the American Chemical Society, Fargo, N. D., 1970.

(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, Chapter 5; A. I. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, Chapter 10; W. E. McEwen, "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Wiley, New York, N. Y., 1965; R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapter 8; M. J. Gallagher and I. D. Jenkins in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1968, Chapter 1; P. Haake and P. S. Ossip, *Tetrahedron Lett.*, 4841 (1970).

(3) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **84**, 610 (1962).

(4) W. S. Wadsworth, Jr., *J. Org. Chem.*, **32**, 1603 (1967).

(5) In an earlier communication, W. S. Wadsworth, Jr., and H. L. Horten, *J. Amer. Chem. Soc.*, **92**, 3785 (1970), we stated that two different isomers of the phosphorochloridate were obtained under these conditions. We have since found the material reported to have mp 59–60° to be a mixture of isomeric phosphorochloridates produced upon distillation of the pure cis isomer.

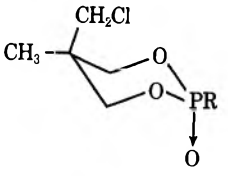
(6) T. A. Beineke, *Chem. Commun.*, 860 (1966).

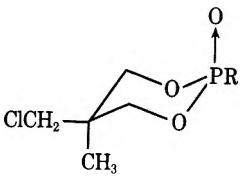
(7) A third phosphoramidate, mp 136–138°, reported in our previous paper[5] has subsequently been found to be a mixture of **2** and **3**.

(8) The X-ray analyses were carried out in this laboratory under the supervision of W. Jensen. Presented at the 163rd National Meeting of the American Chemical Society, Boston, Mass., 1972.

TABLE I

CHEMICAL SHIFTS OF 5,5-DISUBSTITUTED 2-AMINO-1,3,2-DIOXAPHOSPHORINANES[a]



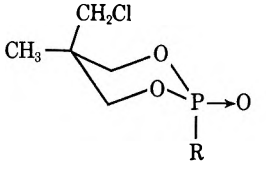


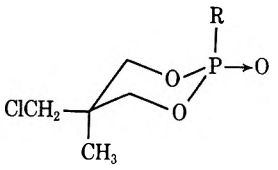
R	Registry no.	CH_3	CH_2Cl	Registry no.	CH_3	CH_2Cl
NC_5H_{11}	21071-82-9	0.98	3.83	21071-83-0	1.28	3.60
$NHC(CH_3)_3$	36912-22-8	0.95	3.70			
NHC_6H_5	36912-23-9	0.99	3.51			
p-$NHC_6H_4OCH_3$	36912-24-0	0.90	3.68			
$NHCH_2C_6H_5$	36912-25-1	0.90	3.62			

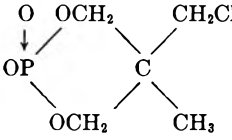
[a] Measured with a Varian A-60A instrument. In parts per million downfield from external TMS in $CDCl_3$.

TABLE II

CHEMICAL SHIFTS OF 2-SUBSTITUTED 5-CHLOROMETHYL-5-METHYL-2-OXO-1,3,2-DIOXAPHOSPHORINANES[a]





R	Registry no.	CH_3	CH_2Cl	Registry no.	CH_3	CH_2Cl
OCH_3	28097-12-3	1.01	3.89	36912-27-3	1.32	3.61
$OCH(CH_3)_2$				36912-28-4	1.36	3.60
OH	36912-29-5	1.03	3.80			
OC_6H_5	36912-30-8	0.98	3.77	36895-18-8	1.29	3.32
$OC_6H_4OCH_3$	36912-31-9	0.90	3.70	36912-32-0	1.25	3.32
$OC_6H_4CH_3$	36912-33-1	0.93	3.71	36912-34-2	1.28	3.29
OC_6H_5Br	36912-35-3	0.94	3.74	36912-36-4	1.30	3.32
$OC_6H_4NO_2$	36912-37-5	1.01	3.78	36912-38-6	1.38	3.40
$OC_6H_3(NO_2)_2$	36912-39-7	1.03	3.78	36912-40-0	1.43	3.40
OCC_6H_5[b]	36912-41-1	0.97	3.75	36912-42-2	1.36	3.45
 [b]	36914-95-1	1.03	3.77		1.41	3.42
SC_6H_5	36912-43-3	0.96	3.72	36912-44-4	1.19	3.11

[a] All samples run in $CDCl_3$ as solvent. In parts per million downfield from external TMS in $CDCl_3$. [b] In these cases the configuration at phosphorus is unknown.

structure drawn for 2 is correct. Interconversion between the isomers is not observed at temperatures over 200° or in solution, which is strong evidence that the two are indeed geometrical isomers.

We have used the variation in chemical shifts of hydrogens on groups at the 5 position to distinguish between isomers and in turn as a diagnostic tool in our study of substitution. The hydrogens of an axial chloromethyl group are shifted downfield from those of an equatorial chloromethyl group. Likewise the methyl hydrogens when axial are shifted downfield relative to those of an equatorial methyl group (Tables I and II).

The question of ring mobility in solution has yet to be fully clarified, although much work has been reported on analogous systems.[9] The phosphoramidates

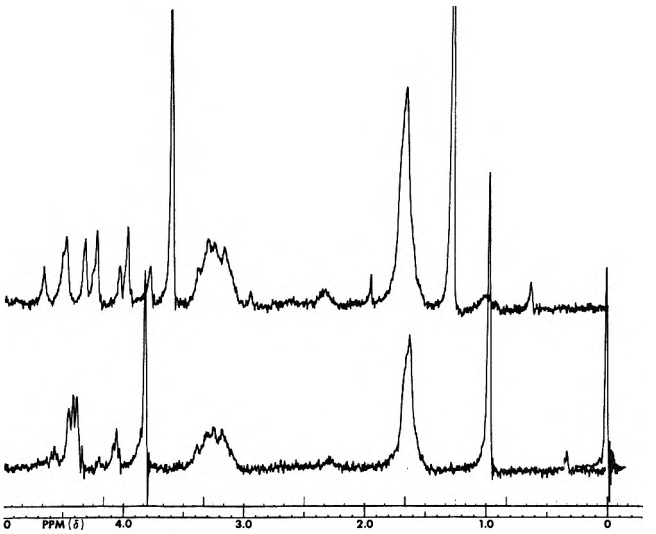


Figure 1.—Nmr spectra of phosphoromidates in $CDCl_3$: top, prepared from chloroamine and phosphite; bottom, prepared from amine and phosphorochloridate.

(9) R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc. C*, 3033 (1968); R. S. Edmundson and E. W. Mitchell, *ibid.*, 752 (1970); A. R. Katritsky, M. R. Nesbit, J. Michalski, Z. Tulimowski, and A. Zwierzak, *J. Chem. Soc. B*, 140 (1970); D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *ibid.*, 1454 (1971).

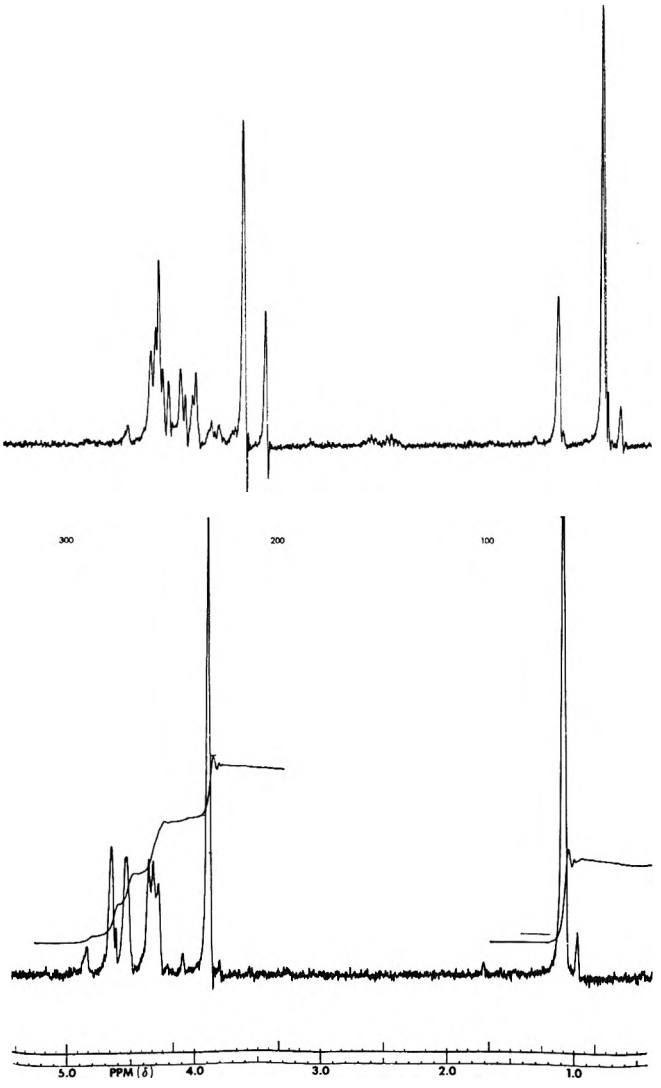


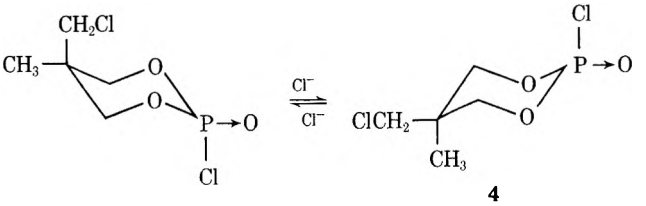
Figure 2.—Nmr spectra of phosphorochloridate (1): top, in DMF-d_7; bottom, in $CDCl_3$.

and other isomers described herein may indeed undergo conformational mobility; however, mobility in those cases where it does exist does not hinder us from distinguishing between two geometrical isomers.[10] Peaks never tend to coalesce even at elevated temperatures.

Treatment of the phosphorochloridate **1** with a number of amines, including *tert*-butylamine and aniline, gave, regardless of the solvent employed, a single isomer. Based on the similarity of the chemical shifts of groups at the fifth position (Table I) with those of the phosphoramidate **3**, the isomers are trans. It is apparent that amines attack solely by inversion of configuration at phosphorus. *p*-Nitroaniline did not react even upon refluxing the reagents in acetonitrile.

A sample of the phosphorochloridate which had been highly purified by means of repeated recrystallizations from carbon tetrachloride showed no evidence of isomerization when it was dissolved in polar solvents, *i.e.*, acetonitrile, nitrobenzene, trifluoroacetic acid, and the solutions were heated at 65° for 1 month.[10] Addition of LiCl to an acetonitrile-d_3 solution of pure phosphorochloridate did cause isomerization, as witnessed by the slow appearance of new peaks assigned to equatorial chloromethyl and axial methyl groups. Upon standing at room temperature for 1 month a final 2.5:1 ratio of isomers was observed with the original, cis, predominating. No isomerization was observed upon addition of $LiClO_4$ or $LiOSO_2C_6H_4CH_3$ to acetonitrile solutions of the pure phosphorochloridate. A 2.5:1 ratio of phosphorochloridate isomers was also obtained upon vacuum distillation of the pure starting material. The distillation is accompanied by partial decomposition. It is believed, upon the basis of these results and those reported by others with respect to reactions of phosphorochloridates,[11] that the phosphorochloridate reacts *via* an associative bimolecular mechanism and that the observed isomerization is initiated by added chloride ion or by chloride ion produced by decomposition during distillation.[12]

Addition of piperidine to an isomerized mixture of phosphorochloridate gave the two amides, **2** and **3**, in a 1:2.5 ratio and it is therefore assumed based on the preference for amines to react with inversion that the new isomer, **4**, also has the chlorine at phosphorus in an axial position.



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Upon dissolving the phosphorochloridate in dimethylformamide (DMF), isomerization to the equilibrium mixture was complete within 15 min (Figure 2). In this instance as with acyclic dialkyl phosphorochloridates[13] there is probably solvent participation with concurrent chloride ion formation. A similar phenomenon was observed when pyridine-d_5 was employed.

The preferred conformation of each isomer appears to be regulated by the preference of groups at phosphorus to be either axial or equatorial. Whereas single-crystal analysis has shown the amino group to prefer an equatorial position, we have by similar techniques shown that in the case of the phenyl esters the phenoxy group, like chloride, assumes in the solid state an axial position. It is obvious that in order to determine the stereochemical outcome of substitutions each class of compounds must be handled separately and the configuration about phosphorus must be known with certainty. The 2.5:1 equilibrium ratio of isomers obtained upon equilibration indicates that the chloromethyl group prefers an axial position, which may be the result of a dipole interaction between the chloromethyl group and ring oxygens. The ratio appears to be independent of the solvent employed.[14]

(10) In a subsequent paper we will describe in detail solvent and temperature studies with these and other isomer pairs. The isomers with chloromethyl group axial exist within experimental error in a single conformation. Nmr analysis indicates the isomers with chloromethyl group equatorial to exist as a mixture of the two possible conformers with the conformer having the chloromethyl group equatorial predominating by approximately a 3:1 ratio. There is very little, if any, effect of solvent on conformer ratios.

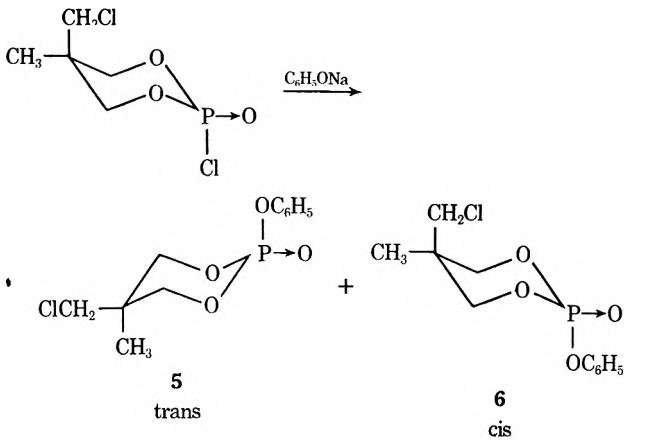
(11) P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, **93**, 6924 (1971).

(12) Only the most favorable conformations of the isomers are shown.

(13) F. Cramer and M. Winter, *Ber.*, **94**, 989 (1961).

(14) The preference of the chloromethyl to be axial has been noted in the case of 5-chloromethyl-5-methyl-2-methoxy-1,3,2-dioxaphosphorinans: D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970).

Treatment of an acetonitrile solution of phosphorochloridate (1) with sodium phenoxide gave a mixture of isomers which could be separated by chromatography (Figure 3). Single-crystal X-ray analysis indicated that the isomers have the phenoxy groups in an axial position. Thus substitution proceeds by both inversion and retention. Each isomer showed no tendency



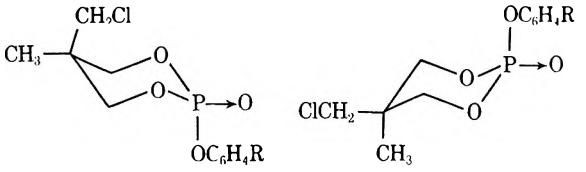
to isomerize on dissolving in polar solvents and heating the solutions. Also, an acetonitrile-d_3 solution of each to which sodium phenoxide had been added, when heated at 70° for 4 days, gave no indication of isomerization. The product ratio is therefore kinetically controlled. The same was true for the *p*-methoxyl, *p*-methyl, and *p*-bromophenyl esters.

As in the case of the phosphoramidates the isomers can easily be identified by chemical shift differences (Table II), once the configuration at phosphorus is known.

The ratio of geometrical isomers obtained varies with the basicity of the nucleophile (Table III). The

TABLE III

PHENYL ESTERS OBTAINED FROM PHOSPHOROCHLORIDATE 1 AND PHENOXIDE ION[a]



R	%	%
OCH_3	57	43
CH_3	50	50
H	48	52
Br	36	64
NO_2[b]	6	94

[a] Isomer ratios (%) were obtained by integration of spectra obtained in $CDCl_3$ as solvent. Reactions were carried out in dried acetonitrile. [b] Care had to be taken to avoid the use of excess sodium *p*-nitrophenoxide.

stronger the basicity of the nucleophile the greater the substitution by retention. In the case of the pure trans *p*-nitrophenoxy ester, as in the case of the other phenyl esters, there was no observed isomerization when an acetonitrile-d_3 or DMF-d_7 solution was heated at 70° for 1 month. Addition of a small amount of sodium *p*-nitrophenoxide in this case, however, did cause isomerization with the final 2.5:1 cis to trans ratio being obtained in acetonitrile after 3 days at room temperature and in DMF-d_7 after 2 hr (Figure 4). The results reflect the enhanced ability of *p*-nitrophenoxide ion to act as a leaving group. It is possible that the small amount of cis isomer obtained upon treatment of the phosphorochloridate with sodium *p*-nitrophenoxide might arise from subsequent isomerization of the product, and substitution in this case is entirely by inversion.

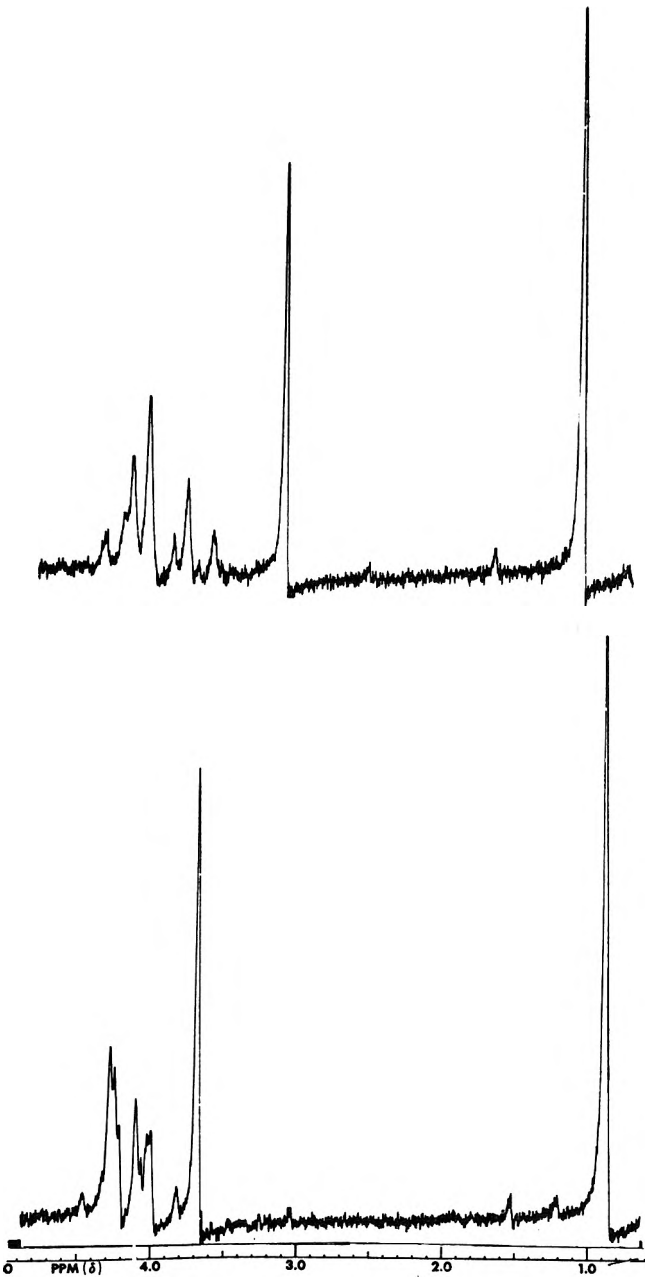


Figure 3.—Nmr spectra of phenyl esters in $CDCl_3$: top, trans; bottom, cis.

There was a noticable difference in the cis to trans ratio of isomers obtained when the substitutions were carried out in solvents in which the sodium salts were insoluble. Thus when sodium phenoxide was added to a benzene solution of the phosphorochloridate the amount of cis isomer rose to 85%. Under similar heterogeneous conditions the amount of *cis*-*p*-methoxyphenyl ester rose to 88% and the *p*-nitrophenyl ester to 40%. Under essentially homogeneous conditions, regardless of the solvent, results were similar to those obtained in acetonitrile, in which the salts were at least

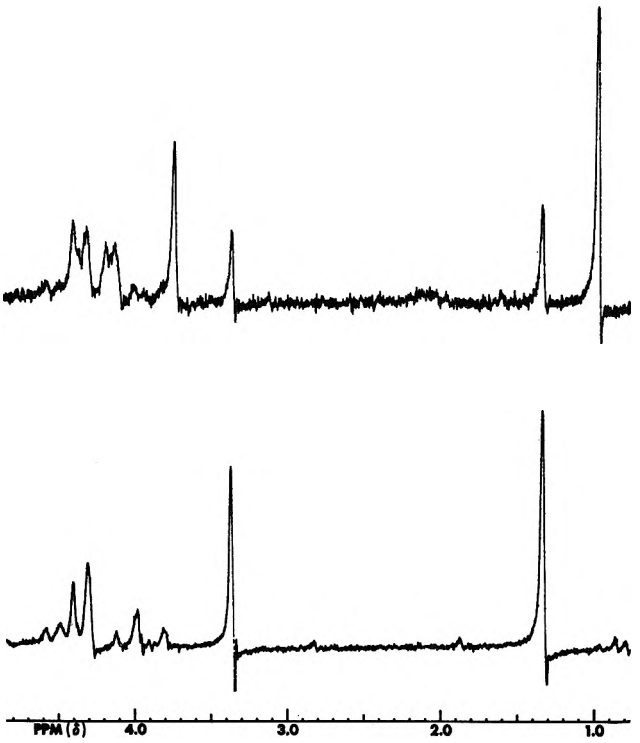
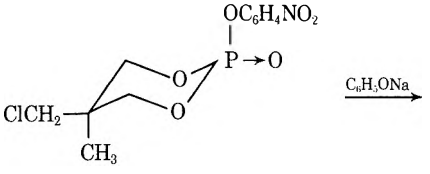


Figure 4.—Nmr spectra of *p*-nitrophenyl esters: bottom, ester **7** in DMF-d_7; top, after equilibration with sodium *p*-nitrophenoxide.

partially soluble. Thus retention is enhanced under heterogenous conditions.

Treatment of a benzene solution of the pure *trans*-*p*-nitrophenyl ester **7** with sodium phenoxide gave a mixture of phenyl esters. Again the cis isomer may arise



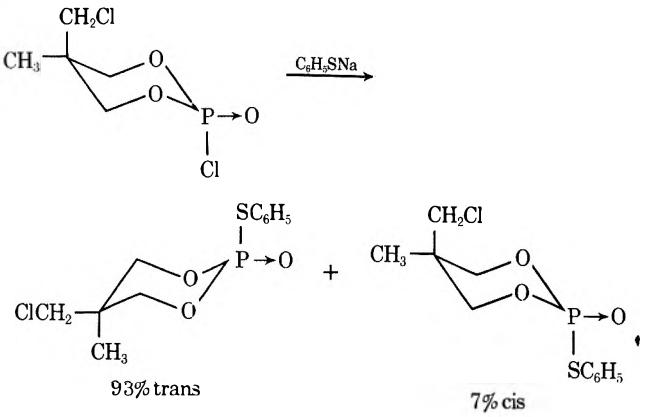
7

75% trans (**5**) + 25% cis (**6**)

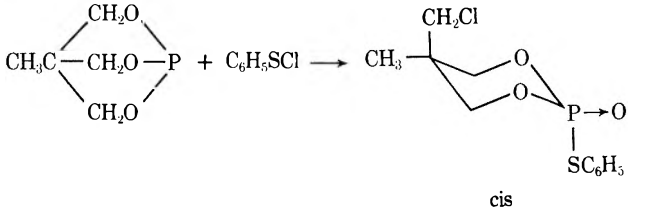
from partial equilibration of the starting material by *p*-nitrophenoxide ion formed as a by-product. Treatment of an equilibrated, 2.5:1 cis to trans mixture of *p*-nitrophenyl ester isomers with sodium phenoxide gave a mixture of phenyl ester isomers in a 2.5:1 cis to trans ratio. Thus substitution appeared to proceed predominantly by retention, which again reflects the ability of charged nucleophiles to substitute in this fashion. *p*-Nitrophenoxide ion is an excellent leaving group, which may also be a factor.

In contrast to results obtained at room temperature, under prolonged reflux in acetonitrile trans *p*-nitrophenyl ester **7** reacted with added sodium *p*-nitrophenoxide to give *p*-nitrophenyl ether. A similar C–O bond scission to give *N*-*p*-nitrophenylpiperidine took place when the ester was warmed with piperidine. In the latter case no products resulting from substitution at phosphorus could be detected.

Treatment of the phosphorochloridate dissolved in acetonitrile with sodium thiophenoxide gave a mixture of isomers with that having chloromethyl group equatorial predominating, 93%. When carried out in benzene the same isomer fell to 89% of the mixture, which would again indicate that heterogeneous conditions favor retention although substitution by inversion is the favored pathway. As in the case of the phenoxy analogs, the phosphoryl oxygen is assigned

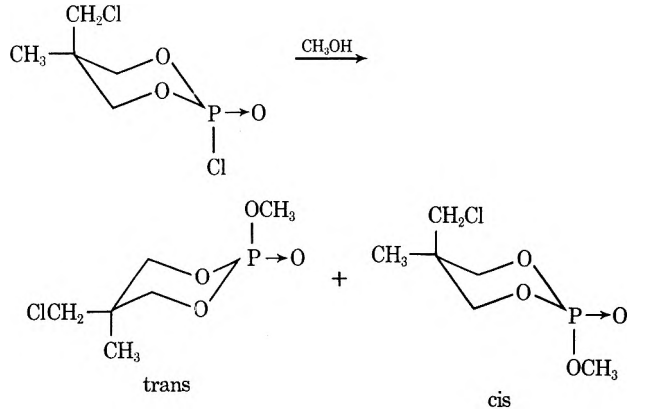


an equatorial position. Treatment of methyl bicyclic phosphate with benzene sulfenyl chloride gave a single isomer with the chloromethyl group axial. Based on the structure of the phosphite and the mechanisms



of the ring opening the product must be cis with the phosphoryl oxygen equatorial.

Upon distillation of a methanolic solution of the phosphorochloridate which had stood for 18 hr at room temperature, a mixture of isomers in which the trans predominated was obtained (Figure 5). We have



assumed based on an analogy with the phenyl esters that the methoxy groups at phosphorus which have the same magnetic environment in both isomers prefer an axial position.[15]

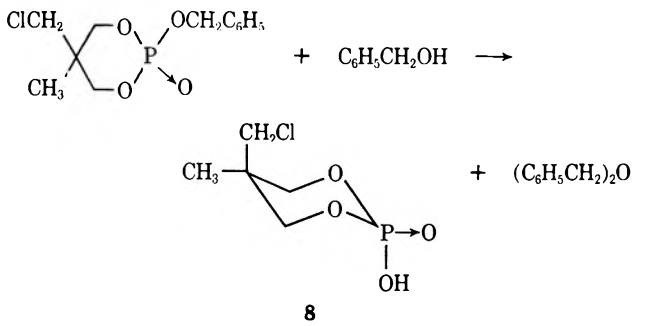
The solvolysis could be conveniently followed by employing methanol-d_4 and observing the appearance of new peaks due to the formation of equatorial chloro-

(15) There is precedent for assuming an equatorial phosphoryl oxygen in esters of this type: H. J. Geise, *Recl. Trav. Chim. Pays-Bas*, **86**, 362 (1967); D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971); J. R. Campbell and L. D. Hall, *Chem. Ind. (London)*, 1138 (1971).

methyl and axial methyl groups. Interestingly, upon continued standing, the peaks due to the cis isomer, chloromethyl group axial, slowly increased while those of the trans isomer decreased until after 1 month the equilibrium 2.5:1 ratio was obtained. Apparently the initially formed product is equilibrated by acid-catalyzed methanol exchange. A similar slow isomerization was observed by adding the trans methyl ester to methanol-d_4 containing *p*-toluenesulfonic acid.

Methanolysis in the presence of 1 equiv of sodium bicarbonate which removed HCl as it formed gave essentially pure trans isomer (Figure 5). In this case acid-catalyzed alcohol exchange was eliminated and no equilibrium of the initially formed product was observed. It is apparent that initially methanolysis proceeds by inversion of configuration, a not unexpected result considering the low basicity of the nucleophile. Solvolysis with isopropyl alcohol also gave, based on the chemical shifts of groups at the 5 position, pure trans isomer. In the latter case no equilibration due to alcohol exchange was observed even without removal of HCl. Alcohol exchange, if it does occur, must be extremely slow.

The solvolysis are complicated by concurrent formation of acid **8**. The acid arises from C–O bond scission, as indicated by the isolation of benzyl ether from a mixture of the phosphorochloridate and benzyl alcohol which had stood at room temperature for 6 months. The acid does not undergo esterification



8

when placed in methanol to which a small amount of *p*-toluenesulfonic acid had been added. Thus it is unlikely that results obtained upon methanolysis are complicated by esterification of the acid by-product. Unfortunately, treatment of a solution of the trans methyl ester with sodium methoxide gave an exothermic reaction from which the sodium salt of the acid **8** was the only isolable product.

The nmr spectrum of the acid (Table II) indicates that the chloromethyl group prefers an axial position. Treatment of an acetonitrile solution of the acid containing 1 equiv of triethylamine with benzoyl chloride gave a mixture of 2-benzoyloxy isomers in which, again assuming the phosphoryl oxygen to be equatorial, the cis predominated over the trans by a 3:1 ratio. Our results would indicate that the hydroxyl group is predominantly in the axial position.

The mechanism leading to inversion can be readily explained by assuming a trigonal bipyramid transition state in which the entering and leaving groups occupy axial positions. The transition state leading to retention is more difficult to define. There are a number of options, *i.e.*, a trigonal bipyramid with entering

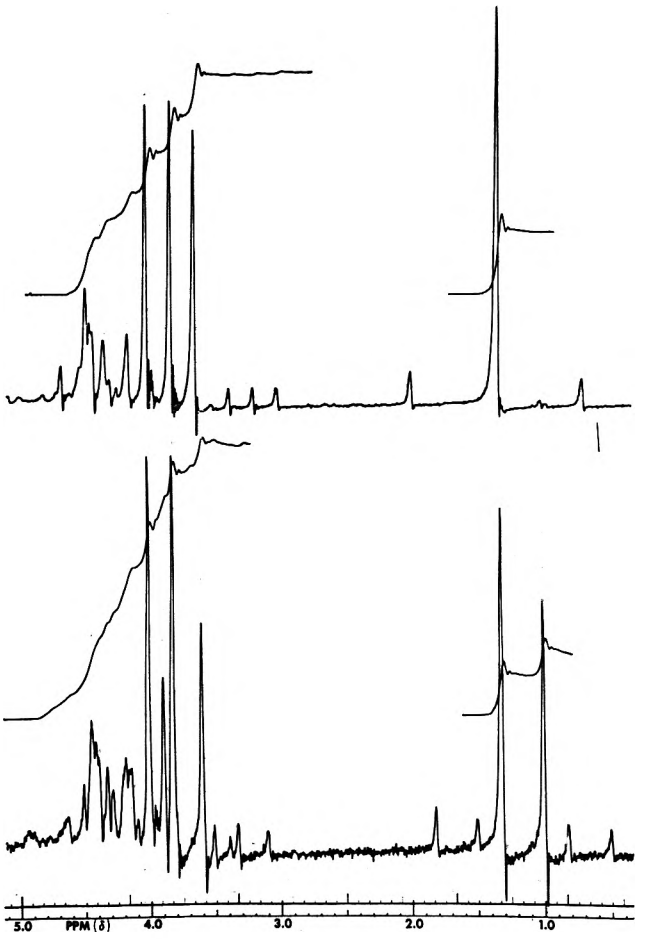
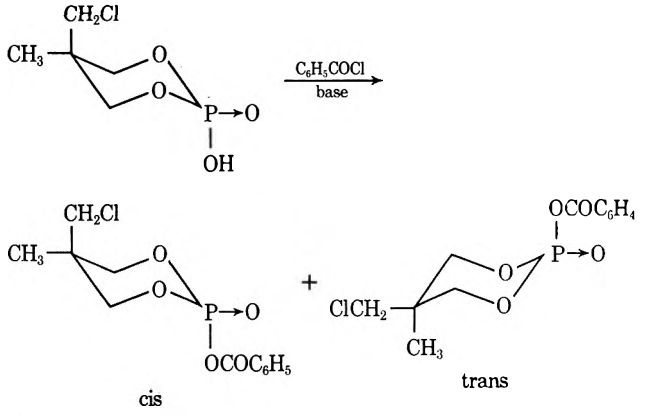


Figure 5.—Nmr spectra of methyl esters in $CDCl_3$: bottom, product resulting from methanolysis of phosphorochloridate (1); top, methanolysis in the presence of 1 equiv of solid sodium bicarbonate.



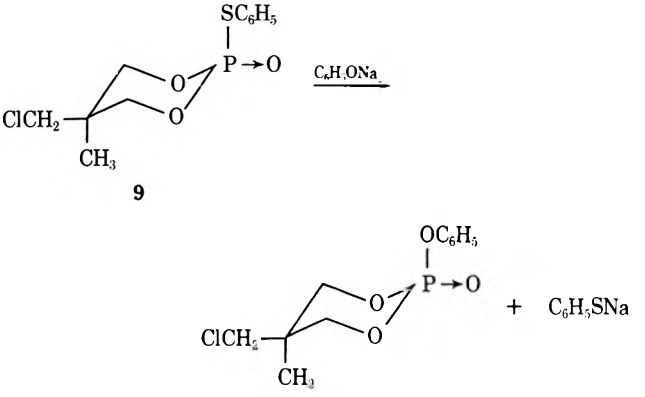
and leaving groups in different planes which may entail pseudorotation,[16] or a square pyramid with entering and leaving groups in radial positions. Pseudorotation appears to be unattractive, for the six-membered ring would be required to span both axial and equatorial positions, which might require considerable ring strain.

The stereochemical outcome appears to depend primarily upon the basicity of the attacking nucleophile, at least in those cases where a charged nucleophile is employed. Thus the thiophenoxide ion, which is a weaker base but stronger nucleophile than the phenoxide ion, displaces predominantly by inversion whereas the latter is more capable of substitution by

(16) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

retention. The P–O bond is nearly twice as strong as the P–S bond, which may be a factor.

The importance of the basicity of the nucleophile and its role in the stereochemistry of the displacement is perhaps best exemplified by the observation that phenoxide ion is capable of completely displacing thiophenoxide ion from phosphorus. Treatment of an acetonitrile solution of *trans*-2-thiophenoxyphosphorinane (**9**) with 1 equiv of sodium phenoxide gave



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at room temperature the trans phenyl ester. No starting material was recovered. As in the case of the treatment of the *p*-nitrophenyl esters with sodium phenoxide, the substitution proceeds entirely by retention. Again, the fact that treatment of the phosphorochloridate **1** with sodium phenoxide results in displacement with partial inversion would indicate that the leaving group has an influence on the stereochemical results.

The possibility of a dissociative mechanism is not supported by the evidence. Isomerization does not occur when the purified phosphorochloridate or esters are dissolved in polar solvents and the solutions heated. In contrast, when a better leaving group than chloride ion, *i.e.*, benzoyloxy, is at the 2 position, isomerization occurs readily merely upon melting or allowing solutions to stand.[17] In the latter case the rate of isomerization is dependent upon solvent polarity and is believed to involve prior ionization to a phosphoryl cation. A similar dissociative mechanism has been observed for pyrophosphate and 2,4-dinitrophenyl esters.[18]

Experimental Section

2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—A solution of methyl bicyclic phosphite, 37.0 g (0.25 mol), in 200 ml of carbon tetrachloride was added dropwise with ice-bath cooling and stirring to a solution of sulfuryl chloride, 33.75 g (0.25 mol), in 200 ml of carbon tetrachloride. After the exothermic addition, the solution was stirred for 1 hr and stripped under reduced pressure. The liquid residue which crystallized on standing was recrystallized twice from carbon tetrachloride to give 49 g (91% yield) of white crystalline product, mp 69–71°.

Anal. Calcd for $C_5H_9Cl_2O_3P$: C, 27.43; H, 4.15; P, 14.10. Found: C, 27.32; H, 4.25; P, 14.41.

The nmr spectrum of the product confirmed its structure. After heating a sample at 150° for 48 hr a dark liquid was obtained which upon distillation, bp 130–140° (0.2 mm), gave a distillate whose nmr spectrum indicated a mixture of isomers with that isomer having the chloromethyl group axial predominating in a 2.5:1 ratio, mp 59–60°. Near the end of the distillation violent decomposition took place.

(17) W. S. Wadsworth, Jr. *J. Chem. Soc., Perkin Trans. 2*, in press.
(18) To be published.

5-Chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinane (3).—A sample of the phosphorochloridate, mp 69–71°, was dissolved in benzene and a slight excess of piperidine was added. After the initial exotherm had subsided, the solution was stripped under reduced pressure and the residue after a water wash was recrystallized from hexane, mp 153–154°. The yield was nearly quantitative.

Anal. Calcd for $C_{10}H_{19}ClNO_3P$: C, 44.85; H, 7.14; N, 5.17; P, 11.61. Found: C, 44.53; H, 7.12; N, 5.29; P, 11.68.

Using an identical procedure the distilled phosphorochloridate gave a mixture of phosphoramidates, mp 137–138°.

2-Piperidino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (2).—A procedure identical with that reported earlier by the author[4] was followed.

Isomerization of Phosphorochloridate (1).—The phosphorochloridate, 1.0 g (0.0046 mol), was added to 5 ml of freshly distilled DMF. After standing for 2 hr, the solution was treated with an excess of piperidine, giving rise to an exotherm. The solution was stripped at reduced pressure and the crystalline residue was washed well with water. The insoluble material was dried to give 0.8 g (66% yield) of a mixture of the two phosphoramidates **2** and **3** in a 1:2.5 ratio as determined by nmr, mp 137–138°. The mixture could be separated into the pure phosphoramidates by fractional crystallization from hexane.

2-Hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate (1), 10.0 g (0.046 mol), was added to 25 ml of water and the mixture was heated with a low flame until it became homogeneous. The solution was chilled in an ice bath and suction filtered to give a white, crystalline product which after recrystallization from acetonitrile gave 8.5 g (92% yield), mp 144–146°.

Anal. Calcd for $C_5H_{10}O_4PCl$: C, 30.00; H, 5.00; Cl, 17.50. Found: C, 30.11; H, 5.14; Cl, 17.54.

Methanolysis of 2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxphosphorinane.—The phosphorochloridate, 10 g (0.046 mol), was dissolved in 50 ml of methanol. After standing for 18 hr excess methanol was removed under reduced pressure. The viscous residue was distilled to give 6.35 g (65% yield) of viscous distillate, bp 140–142° (0.6 mm), which crystallized on standing. The nmr spectrum confirmed the structure as 2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxophosphorinane. The methyl hydrogens are split into a doublet by the phosphorus atom.

Anal. Calcd for $C_6H_{12}ClO_4P$: C, 33.64; H, 5.60; Cl, 16.35. Found: C, 33.97; H, 5.95; Cl, 16.41.

The nonvolatile residue from the distillation was recrystallized from acetonitrile and proved to be identical with authentic acid **8**. A sample of the isomeric methyl esters when refluxed overnight in methanol and excess solvent removed under reduced pressure gave a nearly quantitative yield of the acid.

The methanolysis was repeated with the exception that the starting phosphorochloridate was added to methanol in which 1 equiv of sodium bicarbonate had been added. After standing for 18 hr the solution was filtered and the product was isolated as previously described, 60% yield. The nmr spectrum of the product in this case, however, showed the presence of only one isomer, that with the chloromethyl group equatorial.

The trans methyl ester was placed in methanol-d_4 and the solution was allowed to stand at room temperature for 2 weeks. No change in isomer ratio was noted. There was also no change upon warming a DMF-d_7 solution of the isomer. Addition of a small amount of *p*-toluenesulfonic acid to the methanol-d_4 solution gave slow equilibration to a 2.5:1 ratio of cis to trans isomers.

2-Isopropoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate (1), 10.0 g (0.045 mol), was dissolved in 100 ml of isopropyl alcohol and the solution was allowed to stand for 2 weeks. Solvent was removed under reduced pressure. The residue which solidified upon cooling was recrystallized twice from hexane, 7.2 g (65% yield), mp 74–75°.

Anal. Calcd for $C_8H_{16}ClO_4P$: C, 39.66; H, 6.61; P, 12.81. Found: C, 39.39; H, 6.86; P, 12.88.

The nmr spectrum of the product showed it to contain a single isomer having the chloromethyl group equatorial.

Benzyl Ether.—Phosphorochloridate (1), 5.0 g (0.023 mol), was dissolved in 75 ml of benzyl alcohol and the solution was allowed to stand for 6 months. Excess solvent was removed under reduced pressure and the semisolid residue was extracted with chloroform. The insoluble material was recrystallized from acetonitrile to give 3.4 g (74% yield) of acid **8**, identical with

authentic material. The chloroform filtrate was distilled, giving 2.10 g (46% yield) of product at 190° (60 mm) whose ir spectrum was identical with that of authentic dibenzyl ether.

2-Phenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate, 4.36 g (0.02 mol), and sodium phenoxide, 2.32 g (0.02 mol), were added to 20 ml of freshly distilled acetonitrile. The mixture was stirred at room temperature for 10 hr and stripped under reduced pressure. The residue was washed well with water and recrystallized from hexane to give 3.05 g (60.3% yield) of product which proved from its nmr spectrum to be a mixture of isomers, Table II. Recrystallization did not change the isomer ratio of the crude product.

Anal. Calcd for $C_{11}H_{14}ClO_4P$: C, 47.82; H, 5.07; P, 11.23. Found: C, 47.73; H, 5.12; P, 11.17.

A procedure similar to that described above was used to prepare other esters. The phenyl ester isomers were separated by silica gel column chromatography using chloroform elution; the isomer with the axial chloromethyl group has mp 105°; the isomer with the equatorial chloromethyl group has mp 131°. A DMF-d_7 solution of either isomer when warmed to 85° showed no sign of equilibration.

2-*p*-Nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—The phosphorochloridate (1), 8.72 g (0.04 mol), and sodium *p*-nitrophenoxide, 6.44 g (0.04 mol), were added to 50 ml of acetonitrile. The mixture was stirred overnight at room temperature and filtered. The filtrate was stripped of solvent under reduced pressure to give a viscous residue which crystallized on standing. The product was recrystallized from carbon tetrachloride to give 10.0 g (78% yield) of crystalline product, mp 106–107°. The nmr spectrum showed predominantly one isomer, that with the chloromethyl group equatorial.

Anal. Calcd for $C_{22}H_{23}ClNO_6P$: C, 41.12; H, 4.05; P, 9.65. Found: C, 40.96; H, 4.21; P, 9.47.

The nearly pure trans isomer was equilibrated by adding the product obtained above, 1.61 g (0.005 mol), and sodium *p*-nitrophenoxide, 0.81 g (0.005 mol), to 5 ml of DMF. The solution was stirred at room temperature for 2 hr and diluted with a large excess of water. The solution was filtered and the product was recrystallized to give 1.45 g (90% yield) of a mixture of isomers (Figure 4).

Transesterification with Sodium Phenoxide.—The trans *p*-nitrophenyl ester **7**, 1.6 g (0.005 mol), and sodium phenoxide, 0.56 g (0.005 mol), were added to 20 ml of acetonitrile. The solution after being stirred overnight at room temperature, was filtered and the filtrate was stripped at reduced pressure. The residue was washed well with water and recrystallized from hexane to give a mixture of phenyl isomers (60% yield). Recrystallization of the crude product mixtures from hexane had no noticable affect on isomer ratios.

***p*-Nitrophenyl Ether.**—The *p*-nitrophenyl ester **7**, 3.21 g (0.01 mol), and sodium *p*-nitrophenoxide, 1.61 g (0.01 mol), were added to 10 ml of acetonitrile. The solution was refluxed for 2 days, cooled, and filtered. The water-soluble precipitate, 1.2 g (55% yield), proved to be the sodium salt of the acid **8**, which was converted to the acid by treatment with HCl. The filtrate was stripped at reduced pressure to give 0.7 g (27% yield) of product, mp 141° (lit.[19] mp 142°), whose ir spectrum was identical with that of an authentic sample of *p*-nitrophenyl ether. The alcohol filtrate from the recrystallization was stripped to a viscous oil which was not characterized further.

(19) "Handbook of Chemistry and Physics," 49th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p C-318.

***N*-*p*-Nitrophenylpiperidine.**—*p*-Nitrophenyl ester **7**, 1.61 g (0.005 mol), was treated with 5 ml of piperidine and the solution was warmed at 40–45° for 5 hr. The solution was cooled and suction filtered to give 0.85 g (58% yield) of a water-soluble precipitate whose ir spectrum was identical after recrystallization from acetonitrile with that of the authentic piperidine salt of acid **8**. The filtrate was stripped of excess piperidine at reduced pressure and the residue was recrystallized from ethanol mp 105° (lit.[20] mp 105°), 0.55 g (55% yield).

2-Thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—Phosphorochloridate, 8.72 g (0.04 mol), and sodium thiophenoxide, 5.28 g (0.04 mol), were added to 40 ml of freshly distilled acetonitrile. The mixture was stirred at room temperature for 3 hr and stripped under reduced pressure. The residue was washed well with water and recrystallized from carbon tetrachloride to give 9.4 g (80.3% yield) of product, mp 88–89°, which proved from its nmr spectrum to be a mixture of isomers with the trans isomer, chloromethyl group equatorial, predominating by a 15:1 ratio. Recrystallization did not change the isomer ratio of the crude product.

Anal. Calcd for $C_{11}H_{14}ClO_3PS$: C, 45.24; H, 4.79; Cl, 11.98. Found: C, 45.31; H, 4.72; Cl, 12.07.

When repeated in benzene an 8:1 ratio of isomers was obtained with the trans predominating.

The pure cis isomer, chloromethyl group axial, was obtained by adding methyl bicyclic phosphite to a chloroform solution of benzenesulfenyl chloride. A procedure previously reported[21] for trialkyl phosphites was employed. The product (42% yield) was recrystallized from hexane, mp 124–125°.

Anal. Calcd for $C_{11}H_{14}ClO_3PS$: C, 45.24; H, 4.79; Cl, 11.98. Found: C, 45.18; H, 4.82; Cl, 12.10.

Treatment of 2-Thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-phosphosphorinane with Sodium Phenoxide.—To a solution of *trans*-2-thiophenoxyphosphorinane, 1.55 g (0.0053 mol), in 10 ml of dry acetonitrile was added sodium phenoxide, 0.62 g (0.0053 mol). The mixture was stirred at room temperature for 48 hr and solvent was removed under reduced pressure. The residue was washed well with water and recrystallized twice from hexane. The product, 1.029 (70% yield), had an nmr spectrum identical with that of the trans-2-phenoxy phosphorinane, mp 131°, chloromethyl group equatorial.

2-Benzoyloxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.—To the acid, 4.0 g (0.02 mol), and triethylamine, 2.02 g (0.02 mol), in 50 ml of acetonitrile was added dropwise with stirring and cooling benzoyl chloride, 2.80 g (0.02 mol). The mixture was stirred for 1 hr and suction filtered. Solvent was removed from the filtrate under reduced pressure, and the crystalline residue was washed well with water and dried, 5.4 g (90% yield). The nmr spectrum of the crude product showed a trans to cis ratio of 1:3. The pure cis form which equilibrated to a 2.5:1 cis to trans mixture of isomers on melting, 105–107°, could be obtained pure by fractional crystallization from benzene.

Anal. Calcd for $C_{12}H_{14}O_5PCl$: C, 47.36; H, 4.60; Cl, 11.51. Found: C, 47.40; H, 4.59; Cl, 11.66.

Registry No.—**1**, 28097-07-6.

Acknowledgment.—We are grateful to the National Science Foundation for support (Grant No. GP-10959).

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The Chemistry of Some 5-(2-Hydroxyalkyl)uracil Derivatives and a Synthesis of 5-Vinyluracil[1]

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From 5-(2-hydroxyethyl)uracil, its 2-*O*-methanesulfonate or 2′-*O*-*p*-toluenesulfonate, treated with acid or base, a variety of substitution or elimination products can be obtained, depending on the conditions used. Mechanisms for inter- and intramolecular nucleophilic substitutions, and their competition with elimination of the C-2′ groups, are discussed. The decarboxylation of *trans*-3-(5-uracilyl)propenoic acid to 5-vinyluracil is described, and the effects of association of the vinylic and propenoic acid side chains with the uracil ring on both the pK_a values and ultraviolet and infrared absorption spectra are interpreted. The chemical consequences of these finds in biologically active compounds are considered.

Pyrimidines with lipophilic substituents at position 5 display substantial biological activity.[2-4] In another line of investigation a number of *N*-vinyl derivatives of purines or pyrimidines,[5-10] and some *O*-acryloyl nucleosides[11-15] have been useful for studies of intramolecular forces in nucleic acid[16-19] and for chromatographic separation of nucleic acid components.[20-23]

We have now extended our synthetic approach to the 5-substituted pyrimidines[24] to 5-vinyluracil, which is of interest to both of the above areas of investigation. The van der Waals radius of the 5-vinyl substituent is expected to be nearer to that of the methyl of thymine than is that of the ethyl of 5-ethyluracil, which is a thymine analog.[25-27]

The presence of the 5-vinyl substituent should leave the hydrogen-bonding properties of the pyrimidine ring essentially unchanged, so that a polymer of this compound could be uniquely useful as a chromatographic medium selective for natural poly A sequences,[28,29] and a complex of poly A and poly (5-vinyl U) should also be of interest.[30]

Few 5- or 6-vinylpyrimidines[31] are known. In addition to 4-vinylpyrimidine and its 2-dimethylamino derivative,[32,33] it has been reported, although no experimental details were given, that 4-alkylamino-5-(2-chloroethyl)pyrimidines give 5-vinyl derivatives in ethanolic alkali.[34]

Dehydration of 5-(2-hydroxyethyl)uracil (**3**)[34,35] with potassium hydroxide,[32] which had proven satisfactory for dehydration of 4-(2-hydroxyethyl)pyrimidine, was tried unsuccessfully. The dehydration of **3** in concentrated H_2SO_4 at 90–100° proceeded to give 2*H*,3*H*,-5(7)*H*-furano[2,3]pyrimidin-6-one (**4**) (Scheme I). The structure of **4** was supported by nmr and ir data and its ultraviolet absorption properties (Table I).

TABLE I

Compd	pH	Charge	λ_{max}, nm ($\epsilon \times 10^{-3}$)		Apparent pK_a values (±)
4	7	0	280 (4.6)	206 (17.5)	
	13	−1	290 (6.6)	226 (8.1)	10.90 (0.03)
13	1	0	296 (18.5)	270 sh (13.6)	
	6	−1	293 (13.5)	260 (13.6)	4.33 (0.06)
	11.5	−2	319 (17.8)	278 (12.5)	9.01 (0.06)
14	7	0	286 (6.82)	238 (11.4)	
	11.5	−1	307 (8.06)	251 (12.2)	9.14 (0.05)
22	1	0	305 (19.4)	270 sh (12.9)	
	7.4	−1	301 (15.0)	261 (13.7)	4.32 (0.05)
	12.0	−2	301 (9.33)	265 (8.95)	9.76 (0.04)

Under the experimental conditions the H_0 value of the acid solution is ~−9.0.[36,37] The protonation pK_a of **3** should be similar to that of uracil (−3.38),[38,39] since the ionization pK_a's of **3** and uracil, 9.68[35] and

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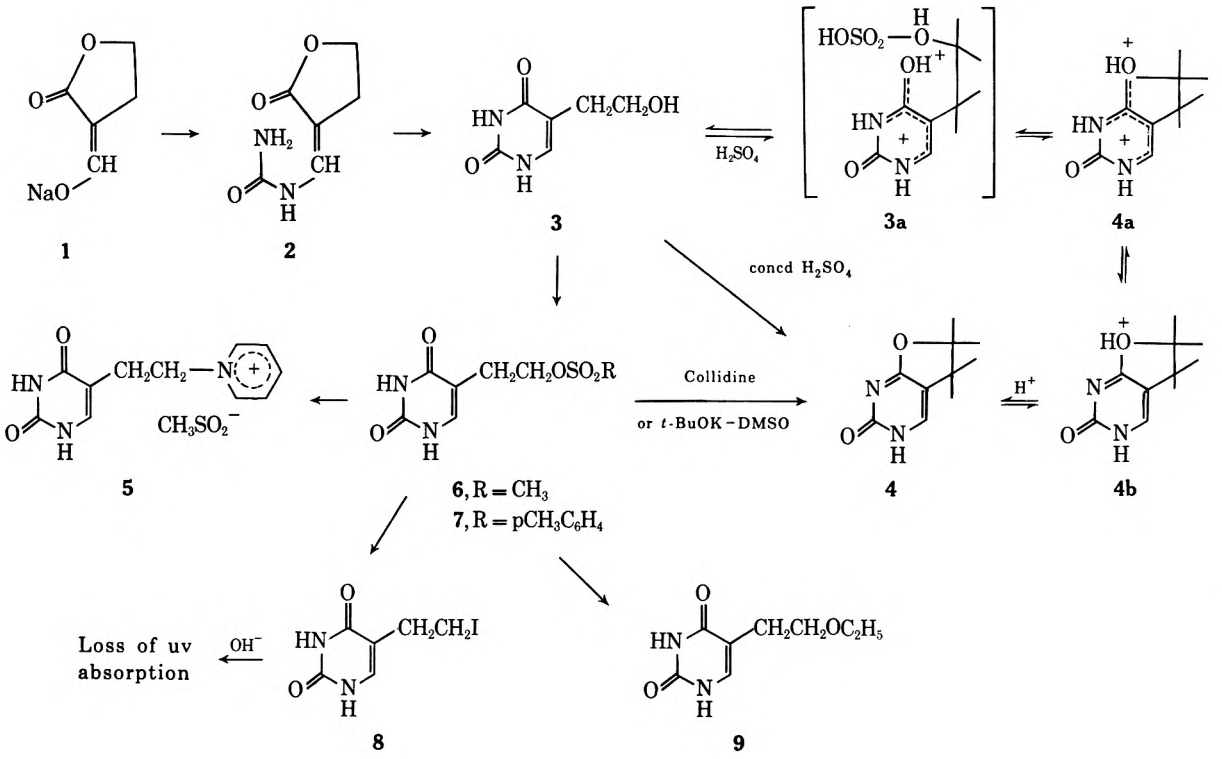
SCHEME I



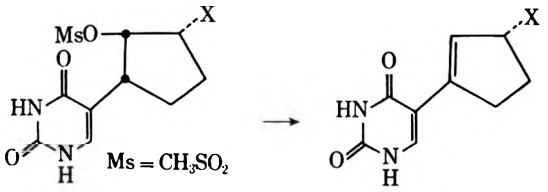
9.5,[40,41] differ but slightly. Therefore the pyrimidine moiety of **3** must exist as a monocation and in further analogy to uracil, protonation would occur at the C-4 carbonyl,[42] to form the resonance-stabilized cation **3a**. Nucleophilic intramolecular displacement of the 2′-*O*-sulfate followed by deprotonation would lead to **4**. Under conditions that promote sulfation of the side chain but preclude formation of the pyrimidine cation (*i.e.*, 30% H_2SO_4, 90–100°, $H_0 = -1.4$[37]) **4** could not be detected in the reaction mixture. In 70 or 80% H_2SO_4 ($H_0 = -4.8$ and -6.1, respectively[37]) the presence of **4** could again be demonstrated. These experiments suggest that protonation of the pyrimidine is a prerequisite for the cyclization (Scheme I). The conversion of **3** to **4** is reversible, as demonstrated by the quantitative conversion of **4** to **3** on a Dowex-50 (H^+) column eluted with H_2O. This acid lability is comparable to that of the analogous C-4, O-5′ "cyclonucleoside" derived from pseudouridine.[43]

When 5-(2-methanesulfonyloxyethyl)uracil (**6**) is treated with an organic base, it undergoes bimolecular nucleophilic substitution rather than elimination. Refluxing **6** in pyridine yields the crystalline methanesulfonate of the 5-(2-pyridiniumethyl)uracil (**5**) in quantitative yield. When steric effects prevent bimolecular substitution, as in the case with 2,4,6-collidine, **6** undergoes the alternative intramolecular reaction to give **4**. This base-catalyzed cyclization of **6** to **4** is analogous to the formation of the cyclopseudouridine derivative mentioned above.[43] Attempted conversion of **6** to the olefin **14** with excess potassium *tert*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO) also led to the cyclized oxetane derivative **4** in 70% yield. The latter reaction, used for the direct introduction of unsaturation into the carbohydrate moiety of nucleosides, proceeds through either an E2 mechanism[44] involving a cyclic intermediate analogous to **4**, or an E1cB mechanism.[45] A considerable degree of carbanion character would reside on the C-1′ atom of **6** or **4** if the base-promoted E2 elimination reaction mechanism as proposed for β-phenylethyl compounds[46] or the E1cB mechanism were to be operative. In either case the formation of a stable pyrimidine dianion would hinder the formation of the respective conjugate bases and inhibit the elimination reactions. The difficulty of establishing a negative charge on C-1′ of **4**, compounded with the relatively poor leaving group character of the uracilyl moiety, might account for the stability of **4** toward the *t*-BuOK–DMSO reagent.

The apparent difference between **6** and the related sulfonates **10a** and **10b**, which could be converted to the respective olefins 5-(1-cyclopentenyl)uracil (**11a**)[47] and 5-(3-methoxy-1-cyclopentenyl)uracil (**11b**) (Scheme II) by potassium *tert*-butoxide in dimethyl sulfoxide,[48] can be rationalized, since in the latter instances the respective sulfonlyl group is restricted to a position cis to the pyrimidine, rendering impossible the formation of an oxetane derivative by an SN2 nucleophilic attack by the C-4 carbonyl. Thus the elimination reaction to the olefin **11b** could take place. The observed differences in the products of the reaction (*i.e.*, 2′,1′ elimination *vs.* 2′,4 substitution) could also be the result of differences in the kinetic rate of the formation of the product **4** from the anion of **6** as

(40) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(41) N. Nakanishi, N. Suzuki, and F. Yamazaki, *Bull. Chem. Soc. Jap.*, **34**, 53 (1961).
(42) R. Wagner and W. von Philipsborn, *Helv. Chim. Acta*, **53**, 299 (1970).
(43) A. M. Michelson and W. E. Cohn, *Biochemistry*, **1**, 490 (1962).
(44) J. P. Horwitz, J. Chua, M. A. DaRooge, M. Noet, and I. L. Klundt, *ibid.*, **31**, 205 (1966), and references cited therein.
(45) J. Zemlicka, R. Gasser, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **92**, 4744 (1970).
(46) L. J. Steffa and E. R. Thornton, *ibid.*, **89**, 6149 (1967).
(47) J. D. Fissekis and B. A. Markert, *J. Org. Chem.*, **31**, 2945 (1966).
(48) J. D. Fissekis and B. Markert Creegan, *J. Org. Chem.*, **32**, 3595 (1967).

SCHEME II



10a, X = H
b, X = OCH_3

11a, X = H
b, X = OCH_3

opposed to the attraction (E2) or abstraction (ElcB) of C-1′ proton from the same anion.

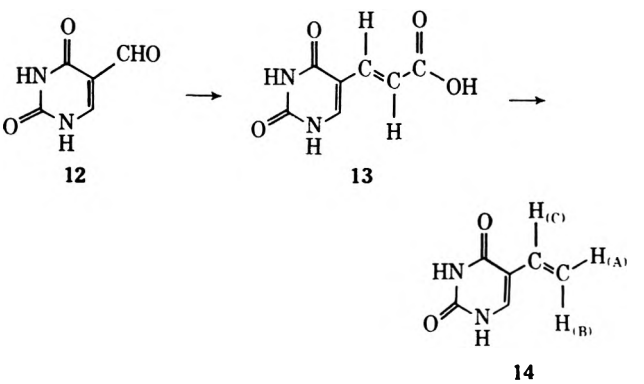
When the crude **7** is heated in ethanol, 5-(2-ethoxyethyl)uracil (**9**) is formed, possibly through an anhydro derivative such as **4**. This is consistent with a variety of analogous nucleophilic openings of the oxetane ring of "anhydronucleosides."[49] When **4** is heated under reflux in an ethanolic solution for several hours, no ring opening occurs, but in the presence of *p*-toluenesulfonic acid the conversion to **9** is quantitative. In the overall conversion of **7** to **9** 1 equiv of acid is liberated from **7** which is available for catalysis. Conceivably the bridged oxygen becomes protonated as in ethers, to give the pyrimidyl oxonium moiety **4b** which is a better leaving group.[50] Comparable examples in the "cyclonucleoside" series have been reported.[51,52] The overall reaction from **6** to **5** very likely also proceeds through the cyclic derivative **4**, which undergoes opening of the oxetane ring. This is supported by the fact that **4** is the main product of the reaction of **6** with collidine. Since **4** is a model of "cyclopseudonucleosides," the above reactions provide evidence that the vast experience with pyrimidine nucleoside transformations *via* anhydro nucleosides[49] is applicable to the "pseudonucleoside" series.

The sulfonate **6** can be converted to the corresponding 5-(2-iodoethyl)uracil (**8**) by the procedure of Pfitzner and Moffat.[53] In dilute aqueous sodium hydroxide at room temperature, the iodo compound undergoes a selective loss of ultraviolet absorption above 220 nm within 30 min. Under the same conditions the monoanion of **3** is stable.

Our failure to effect the direct dehydration of **3** to the vinyl derivative **14** led us to investigate 3-(5-uracilyl)propenoic acid (**13**, Scheme III) as an alternative intermediate for the synthesis of 5-vinyluracil. The preparation of the above acid has been mentioned in a footnote,[54] which described that **13** was obtained by base-catalyzed cyclization of the intermediate ureide **16** (Scheme IV) which had been obtained in crystalline form when a solution of 2 mol of urea and the sodium formylacetic ester from 10 g of sodium was treated with 150 cc of concentrated hydrochloric acid. We attempted to condense methyl β-methoxyacrylate (**17**)[55] with ureas in the respective stoichiometric ratio of 2:1. The only isolated products from these reactions under a variety of conditions were 1,2,3,4-tetrahydropyrimidin-2-ones **18** (R′ = CH_2COOH or CH_3). The mechanism and the scope of this reaction will be the subject of a future report. The propenoic acid derivative **13** was synthesized by the condensation of 5-formyluracil (**12**)[56] with malonic acid, to give exclusively the trans isomer as evidenced by nmr data. The coupling constant of the vicinal vinyl protons on the side chain is $J_{\alpha\beta}$ = 16 Hz, similar to that found in trans cinnamates ($J_{\alpha\beta\,trans}$ = 16.2, $J_{\alpha\beta\,cis}$ = 13.2 Hz),[57] and the *trans*-3(6-uracilyl)propenoates ($J_{\alpha\beta\,trans}$ = 16.5, $J_{\alpha\beta\,cis}$ = 13 Hz).[31,58] The acid **13** was decarboxylated to 5-vinyluracil (**14**) by heating it in quinoline at 200–210° under nitrogen. The structure of **14** was established by ultraviolet and nmr spectroscopy and elemental analysis. There is a striking similarity between the ultraviolet spectral characteristics of **14** and those[47] of the 2,4-dihydroxy-5-(1-cyclopentenyl)pyrimidine (**11a**). Moreover, the nmr spectrum of **14** shows the typical first-order ABX pattern of the vinyl group, with coupling constants of $J_{AB} \cong 3$, $J_{AC} \cong 10.5$, and $J_{BC} \cong 17.5$ Hz, similar to corresponding values reported for styrene.[59]

Association of the 5-vinyl group with the pyrimidine ring of uracil is expected to result in overlap of the ring π orbitals with that of the 5 substituent. This is evidenced by a bathochromic shift of the B_{2u} (259 nm,

SCHEME III

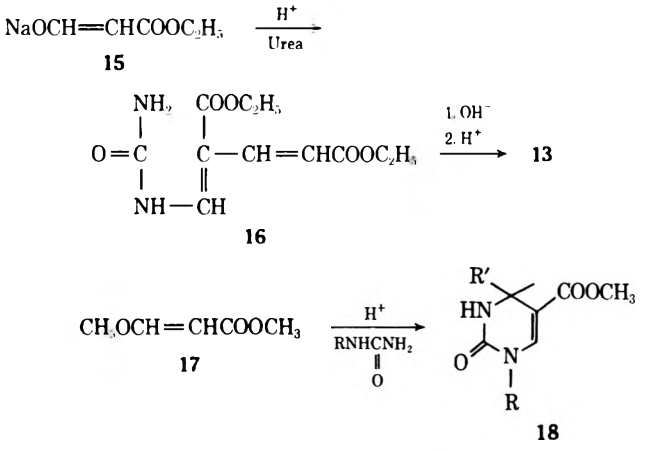


12

13

14

SCHEME IV



15

16

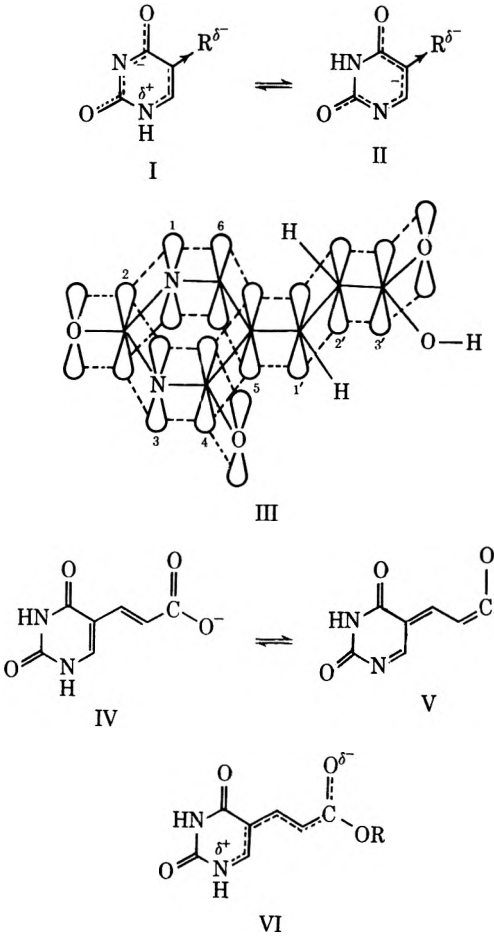
17

18

(49) For a review, see J. J. Fox, *Pure Appl. Chem.*, **18**, 223 (1969).
(50) J. March, "Advances in Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 290.
(51) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).
(52) N. Miller and J. J. Fox, *ibid.*, **29**, 1772 (1964).
(53) K. E. Pfitzner and J. G. Moffat, *ibid.*, **29**, 1508 (1964).
(54) D. Davidson and O. Baudisch, *J. Amer. Chem. Soc.*, **48**, 2379 (1926).
(55) The use of this ester was considered preferable to that of **15**, since the purity of preparations of the latter was highly questionable.
(56) R. Brossmer and D. Ziegler, *Tetrahedron Lett.*, 5253 (1966).
(57) M. C. Cagaleiro and M. D. Johnson, *J. Chem. Soc. B*, 565 (1967).
(58) It is also interesting that the only product of the condensation reaction of 3-formyl-2-pyridone with malonic acid is the trans isomer of (carboxy-2-vinyl)-3-hydroxy-2-pyridine: D. Bonnetand, G. Queguiner, and P. Pastour, *J. Heterocycl. Chem.*, **9**, 165 (1972).
(59) T. Yoshino, Y. Manabe, and Y. Kikuchi, *J. Amer. Chem. Soc.*, **86**, 4670 (1964).

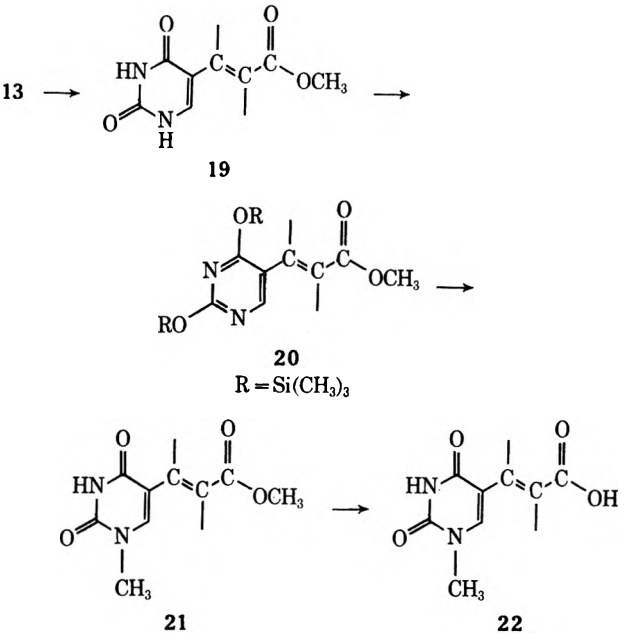
ϵ 8100) and E_{1u_a} (202 nm, ϵ 8800) bands of uracil[60] to 286 (ϵ 6820) and 238 nm (ϵ 11,400), respectively, at pH 7 (Table I). This shift is most likely due to a combination of effects[61] generated by the vinylic side chain in **14**. The significant increase in ϵ of the E_{1u_a} band parallels that of the respective band observed in benzene and styrene.[62] The vinyl substituent appears to exert a net electron-withdrawing effect upon the pyrimidine ring, since the acidity of **14** (pK_a = 9.14 ± 0.05) is increased relative to uracil (pK_a = 9.5).[40,41] The effect of the 5-propenoyl group in **13** upon the ionization and spectral properties of the uracil base is of interest.[63] As with **14**, an acid-strengthening effect is also observed in **13**, which exhibits pK_a's of 4.33 ± 0.06 and 9.01 ± 0.06, the first for the side chain carboxyl group. The ring anion probably contains a mixture of the two anionic species I and II (Scheme V) of the

SCHEME V



pyrimidine.[41,64] The diminished value for the second pK_a of **13**, along with the further bathochromic displacement of the B_{2u} band of uracil to 296 nm (for the neutral molecule) and the ultraviolet absorption change associated with the ionization of the side chain carboxyl group, indicate that the π-electron system of the pyrimidine ring is extended through the entire side chain (III, Scheme V). Intramolecular interaction between the side chain carboxyl group and the pyrimidine ring, such as an H bond, is precluded by the trans configuration. To study this phenomenon more fully the compounds **19** and **22** were synthesized as described in Scheme VI. The acid **13** was esterified

SCHEME VI



with methanol in the presence of sulfuric acid and the obtained ester was converted to the bis-*O*-trimethylsilyl derivative **20**. This derivative was selectively methylated with CH_3I[65] to give **21**, which was then saponified to the N-1 methyl derivative 22.

The ultraviolet spectrum of **19** displays no changes over the range of pH 2–6, and coincides with that of the *neutral* species of **13**, obtained at pH < 2. Therefore the spectral changes of **13** between pH 2–6 are not likely to reflect a shift in the tautomeric equilibrium toward the 4-enol form caused by the strong electron-withdrawing effect of the 5 substituent analogous to that suggested for 5-bromouracil.[66] Moreover, the similar ultraviolet spectral changes of the N-1 methyl derivative 22 in the range of pH 2–6 rules out the possibility of the tautomeric shift IV ⇄ V (Scheme V) in **13**. The first ionization pK_a (4.32 ± 0.05) due to the carboxyl group is identical with the corresponding one of **13**. The second pK_a (9.76 ± 0.04), corresponding to the monoanion I above, is comparable to that of 1-methyluracil (9.77,[41] 9.72[67]) but is higher than the second pK_a (9.06) of **13**. From these results it is clear that, in compounds **13** and **20**, the influence of the 5-propenoyl substituent is exerted exclusively upon the N-1 of the uracil as represented by the conjugated system VI (Scheme V). Such conjugation would be expected to increase the acidity of the N-1 proton, as is actually observed. It should render any nucleosidic bond at this position more labile to

(60) L. B. Clark and I. Tinoco, Jr., *J. Amer. Chem. Soc.*, **87**, 11 (1965).

(61) For a discussion of these effects, see A. R. Katritzky and R. D. Topsom, *Angew. Chem., Int. Ed. Engl.*, **9**, 87 (1970).

(62) For benzene E_{1u_a} 202 nm (ϵ 6900), B_{2u} 255 nm (ϵ 224); and for styrene E_{1u_a} 244 nm (ϵ 12,000), B_{2u} 282 nm (ϵ 450). E. A. Brande, in E. A. Brande and F. C. Nachod, Ed., "Determination of Organic Structures by Physical Methods," Vol. I, Academic Press, New York, N. Y., 1955, p 151.

(63) This uracil derivative is closely related to the 3-[5-(6-methyl)uracilyl]propenoic acid, isolated from the antibiotic sparsomycin: P. F. Wiley and F. A. Mackellar, *J. Amer. Chem. Soc.*, **92**, 417 (1970).

(64) K. L. Wierzchowski, E. Litonska, and D. Shugar, *ibid.*, **87**, 4621 (1965).

(65) E. Wittenburg, *Chem. Ber.*, **101**, 1095 (1968).

(66) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1521 (1962).

(67) J. Jonas and J. Gut, *Collect. Czech. Chem. Commun.*, **27**, 716 (1962).

acid hydrolysis, and it may not be coincidental that the antibiotic sparsomycin[63] has not been isolated in the nucleoside form.

Additional evidence supporting the existence of resonance interaction between the side chain and pyrimidine π-system in compounds **13** and **14** is obtained from their ir spectra. In the high-frequency region of multiple bonds uracil exhibits two intense bands which are split and centered at 1715 and 1750 cm^{-1} [41,68] due to the C=O and C=C functions. No bands are observed between 1500 and 1600 cm^{-1}.[69] In contrast, **14** shows, in addition to two similar uracil bands at 1740 and 1670 cm^{-1}, a third narrow, medium-intensity band at 1590 cm^{-1}, and **13** displays a broad band at 1680 cm^{-1} due to the carbonyl groups and another strong band at 1600 cm^{-1}. Probably the 1590-cm^{-1} band exists in the spectrum of uracil, but is too weak to be detected. However, the appearance of this band in the spectra of **13** and **14** is indicative of extended exocyclic conjugation.[70]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The nmr spectra were obtained using a Varian A-60 spectrometer with tetramethylsilane as an internal reference. Ultraviolet and infrared spectra were determined using a Unicam SP 800 and an Infracord spectrophotometer, respectively. All solvents were removed in a Büchler flash evaporator under reduced pressure, unless otherwise indicated. Drying of all solids was accomplished under reduced pressure over P_2O_5 at suitable temperatures. The pK_a's were determined by methods described[71] spectrophotometrically in 0.01 *M* buffers with a Beckman DU spectrophotometer or electrometrically with 0.001 *M* solutions. For tlc, Eastman chromagram silica gel sheet was used with the solvent systems indicated.

α-(1-Carbamyliminomethylene)-8-butyrolactone (2).—To a solution of 30 g (0.5 mol) of urea in ~200 ml of cold 3 *N* HCl was added 34 g (0.25 mol) of the sodium derivative of α-hydroxymethylene-γ-butyrolactone[35] in small portions. After stirring overnight in the cold, the precipitated product (23 g, 59%) was collected, washed with cold water, and dried. Recrystallization from H_2O–EtOH gave fine needles melting at 246–247°:[72] nmr τ 7.2 (pair of t, 2, $J_{3,4}$ = 7.5, $J_{1',3}$ = 2 Hz, $-CH{=}CCH_2-$), 5.65 (t, 2, $J_{4,3}$ = 7.5 Hz, $-CH_2CH_2O-$), 3.59 (s, 2, exch), 7.68 (pair of t, 1, $J_{1',3}$ = 2, $J_{1',2'}$ = 12 Hz, $-NHCH{=}CCH_2-$), 0.64 (d, 1, $J_{2',1'}$ = 12 Hz, exch).

5-(2-Hydroxyethyl)uracil (3).—To an alcoholic solution of C_2H_5ONa (2.18 g, 9.46 × 10^{-2} mol of Na in 250 ml of EtOH) was added 13.4 g (8.6 × 10^{-2} mol) of **2**. The mixture was heated under reflux for 6 hr, during which time a solid separated. The solvent was removed and the residue was dissolved in 400 ml of water. The resulting solution was passed through a heated (*ca.* 60°) Amberlite IRC-50 (H^+) column (2.5 × 14 cm) which was washed well until the eluent showed negligible uv absorption at 265 nm. The combined eluents were concentrated to ~500 ml, then treated with Norit and filtered, and the filtrate was further concentrated to ~250 ml and cooled. The product (12.4 g, 92%) was collected, washed with EtOH, and dried. It melted at 264–265°:[73] nmr τ 7.64 (t, 2, $J_{1',2'}$ = 7 Hz, $-CH_2CH_2OH$), 6.48 (t, 2, $J_{2',1'}$ = 7 Hz, $-CH_2CH_2OH$), 5.44 (broad s, 1, exch), 2.72 (d, 1, $J_{6,1}$ = 5.5 Hz), −0.66 (d, 1, $J_{1,6}$ = 5.5 Hz, exch), −1.0 (s, 1, exch).

5-(2-Methanesulfonyloxyethyl)uracil (6).—To a cold suspension of 1.56 g (10 mmol) of **3** in 20 ml of pyridine was added 1.54 ml (2.28 g, 20 mmol) of methanesulfonyl chloride.[74] After the solution was stirred in the cold overnight a few drops of water were added and the mixture was chilled for several hours. The solvent was removed and the residue was suspended in 25 ml of cold water. A tan precipitate was collected, washed well with cold water, and dried [2.0 g (87%)]. This material was recrystallized from MeOH. The product melted at 180–182°: nmr τ 6.8 (s, 3), 5.76 (t, 2, $J_{2',1'}$ = 7.5 Hz, $-CH_2CH_2O-$); ir λ_{max}^{KBr} 1315 (ν_{as} SO_2), 1168 cm^{-1} (ν_s SO_2).[70]

Anal. Calcd for $C_7H_{10}N_2O_5S$: N, 11.96; S, 13.69. Found: N, 11.90; S, 13.58.

2*H*,3*H*,5(7)*H*-Furano[2,3*d*]pyrimidin-6-one (4). Method A.—A solution of 0.5 g (3.2 mmol) of **3** in 5 ml of concentrated H_2SO_4 was heated at 100° for 1 hr. Then it was cooled and added, with stirring, to 1 l. of ether. After 1 hr at 4° the ether phase was decanted from the precipitate, which was washed with 250 ml of ether. The residue was dissolved in 300 ml of cold water and the solution was passed through a small Amberlite IR-45 (OH^-) column which then was washed well with water. The neutral eluent (1 l.) was concentrated to give a white, crystalline solid which was collected, washed with a small volume of methanol, and dried. The product [310 mg (70%)] decomposes gradually to a glass between 260 and 315°: nmr τ 6.92 (t, 2, $J_{1',2'}$ = 8 Hz, $-CH_2CH_2O-$), 5.30 (t, 2, $J_{2',1'}$ = 8 Hz, $-CH_2CH_2O-$), 2.41 (s, 1); ir λ_{max}^{KBr} 1015 cm^{-1} (ν_s COC), 1230 cm^{-1} (ν_{as} = COC).[75]

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.97; H, 4.35; N, 20.10.

Similar reaction mixtures in 80, 70, or 30% H_2SO_4 were diluted with cold water and neutralized with 60 ml of Dowex-1 (20 to 30 mesh, HCO_3^-) in the cold with stirring. Then the resin was washed in a column with 1.6 l. of water when the eluent no longer showed uv absorption. The solvents were removed *in vacuo* and the residues were chromatographed on tlc plates (chromagram, silica gel; C_6H_6–MeOH, 2:8). Individual bands were eluted with water and the uv spectral shifts of the solutions at several pH's were recorded and compared with those of the starting material **3** and anticipated product **4**. In 80 or 70% H_2SO_4 small amounts of **4** were detected, and none in 30% H_2SO_4.

Method B.—A solution of 468 mg (2 mmol) of the methanesulfonate **6** in 25 ml of freshly distilled 2,4,6-collidine was heated in a bath at 125–130° for 30 min and then was lyophylized. The residue was treated with EtOH and the mixture was again lyophylized. Finally the residue was dissolved in ~50 ml of MeOH, the solution was treated with Norit and filtered, and the filtrate was concentrated until a solid began to separate. After chilling the product was collected, washed twice with ether, and dried, yield 80 mg (29%).

Method C.—The methanesulfonate **6** (468 mg, 2 mmol) was dissolved in 10 ml of DMSO (freshly distilled from CaH) and 673 mg (6 mmol) of *t*-BuOK was added. After standing for 6 days at room temperature the mixture was added to a suspension of 10 ml of Amberlite IRC-50 (H^+) in cold water. The neutral mixture was transferred on a small column and the resin was eluted with water (~1.1 l.). The combined eluates were concentrated and the residual DMSO was removed in a lyophylizer. The residue was suspended in 200 ml of boiling EtOH, the mixture was filtered, and the filtrate was taken to dryness. The residue was recrystallized from MeOH as described in method B, yield 195 mg (70%).

5-(2-Pyridiniumethyl)uracil Methanesulfonate (5).—A solution of 234 mg (1 mmol) of **6** in 25 ml of dry pyridine was heated under reflux for 72 hr. After standing at room temperature for a few hours the crystals which separated were collected, washed twice with EtOH and then several times with ether, and dried: yield 280 mg (89%); mp 207–209°; nmr τ 7.10 (t, 2, $J_{1',2'}$ = 6.5 Hz, $-CH_2CH_2N{<}^+$), 5.24 (t, 2, $J_{2',1'}$ = 6.5 Hz, $-CH_2CH_2N{<}^+$).

Anal. Calcd for $C_{12}H_{15}N_3O_5S$: C, 46.00; H, 4.82; N, 13.41; S, 10.23. Found: C, 46.13; H, 4.77; N, 13.44; S, 10.18.

5-[2-(*p*-Toluenesulfonyloxy)ethyl]uracil (7).—To a solution of 312 mg (2 × 10^{-3} mol) of **3** in 10 ml of pyridine kept at −10° was added 419 mg (2.2 × 10^{-3} mol) of *p*-toluenesulfonyl chloride and the mixture was stirred (at −10°) for 3 days. After the solvent had been removed *in vacuo* at room temperature by means of a Dry Ice trap, 30 ml of crushed ice was added to the viscous residue, which immediately solidified. The solid was broken up

(68) B. I. Sukhorukor, V. Ts. Aikazyan, and Yu. A. Yershor, *Biophysics (USSR)*, **11**, 867 (1966).

(69) L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168 (1952).

(70) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1966, pp 41 and 72.

(71) A. Albert and E. P. Serjeant, "Ionization Constant of Acids and Bases," Wiley, New York, N. Y., 1962, p 69.

(72) K. A. Chkhikvadze and O. Yu. Magidson, *Zh. Obshch. Khim.*, **34**, 2577 (1964).

(73) Reported mp 273–274[35] and 259–261°.[72]

(74) Comparable results are obtained if methanesulfonyl anhydride is used nstead of the chloride.

(75) K. Nakanishi, "Infrared Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 36.

and the mixture was left in the cold overnight. Then the product was collected, dried, and washed twice on the filter with small volumes of dry ether. It was chromatographically pure [tlc, chromagram silica gel, C_6H_6–EtOH (8:2) or C_6H_6–EtOAc–MeOH (8:1:1)]: yield 496 mg (80%); mp 170–173°; nmr τ 5.83 (t, 2, $J_{2',1'}$ = 6.5 Hz); ir λ_{max}^{KBr} 1350 (ν_{as} SO_2), 1170, 1185 cm^{-1} (ν_s SO_2).[70]

Anal. Calcd for $C_{13}H_{14}N_2O_5S$: N, 9.03; S, 10.33. Found: N, 8.97; S, 10.19.

5-(2-Ethoxyethyl)uracil (9).—A sample of the *p*-toluenesulfonate **7** was dissolved in EtOH and the solution was refluxed for several hours until tlc [C_6H_6–EtOAc–MeOH (8:1:1)] indicated the absence of starting material. After the solvent was removed the residue was chromatographed on a Dowex 50 column (H^+, l 50 cm) which was eluted with water. The product-containing fractions were pooled and concentrated to dryness and the residue was recrystallized twice from EtOH to give a crystalline solid melting at 242–244°: nmr τ 8.92 (t, 3, J = 6.5 Hz, $-OCH_2CH_3$), 7.62 (t, 2, J = 6.5 Hz, $-CH_2CH_2O-$), 6.61 (9, 2, J = 6.5 Hz, $-OCH_2-CH_3$), 6.60 (t, 2, J = 6.5 Hz, $-CH_2CH_2O-$), 2.77 (s, 1); ir λ_{max}^{KBr} 1240 cm^{-1} (ν_{as} COC).[75]

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.56; N, 15.20. Found: C, 51.88; H, 6.57; N, 15.10.

5-(2-Iodoethyl)uracil (8).—A mixture of 937.0 mg (4 mmol) of the methanesulfonate **6**, 5.98 g (40 mmol) of NaI, and 180 ml of diglyme (freshly distilled from Na) was heated under reflux for 6 hr. After the solvent was removed the residue was triturated with cold water. The mixture was left in the cold for a few hours and then the solid product was collected, washed with water, and dried. It was recrystallized from ~200 ml of EtOH to yield 810 mg (76%) of crystals melting at 265°: nmr τ 7.29 (t, 2, $J_{1',2'}$ = 7 Hz, $-CH_2CH_2I$), 6.64 (t, 2, $J_{2',1'}$ = 7 Hz, $-CH_2CH_2I$), 2.65 (d, 1, $J_{6,1}$ = 5.5 Hz).

Anal. Calcd for $C_6H_7N_2IO_2$: N, 10.53; I, 47.70. Found: N, 10.53; I, 47.75.

In aqueous alkaline solutions, **8** seems to be unstable. Preliminary experiments have provided insight into several aspects of this reaction. When NaOD is added to a solution of **8** in DMSO-d_6, the vinylic signal (C_6H, τ 2.65) and those of the side-chain methylene protons ($C_{1'}$ H, τ 7.29; $C_{2'}$ H, τ 6.64) are almost completely quenched with simultaneous appearance of a broad signal centered at τ 8.8. No change other than a small downfield shift is noticed in the spectrum of **3** under the same conditions, even after several days. When an alkaline aqueous solution of **8** is allowed to stand for 1.5 hr at room temperature, until the absorption peak at 290 nm decreases by 95%, and then the solution is made strongly acid, the uv absorption is almost completely restored during a subsequent 24-hr period. A small amount of solid which separates during this period was found to be (melting point, nmr) starting material, **8**. Other products have not yet been identified.

3-(5-Uracilyl)propenoic Acid (13).—A mixture of 1.40 g (1×10^{-2} mol) of 5-formyluracil,[56] 2.08 g (1×10^{-2} mol) of malonic acid, and ~10 ml of dry pyridine was heated in a bath at 80–90° for 6 hr. The reaction mixture was evaporated to dryness, water was added to the residue, and again the mixture was taken to dryness, and the procedure was repeated twice more. The final residue was dissolved in 225 ml of boiling water, and the solution was acidified with 2 ml of glacial acetic acid and slowly cooled to room temperature. After further cooling at 4° the precipitated product was collected, washed with cold dilute acetic acid, and dried over P_2O_5 and KOH. The product (1.65 g, 90%) softens above 275° and melts with decomposition at 283–284°: nmr τ 3.19 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCOOH), 2.6 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CH-$), 1.96 (s, 1).

Anal. Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.05; H, 3.39; N, 15.36.

5-Vinyluracil (14).—A suspension of 364 mg (2 mmol) of **13** in 10 ml of dry quinoline was heated slowly to 220° (bath temperature) under nitrogen. The temperature of the reaction mixture was maintained between 175 and 200° for 20 min, and then the solvent was removed in a lyophylizer. Benzene was added to the residue and the solvent was removed as before. This treatment was repeated several times to remove as much of the quinoline as possible. The residue was chromatographed on either a silica gel column (30 g, 2.5 × 29 cm) which was eluted first with 200 ml of benzene and then with a mixture of benzene–ethanol (8:2) or a Dowex 50 (H^+) column (l 50 cm) which was eluted with water. In both cases, the combined fractions containing **14** were concentrated to dryness and the residue was recrystallized from ethanol (or methanol) to give 65 mg of product which decomposes between 230 and 270°: nmr τ 4.92 (pair of d, 1, J_{AC} = 10.5, J_{AB} = 3 Hz), 4.08 (pair of d, 1, J_{BC} = 17.5, J_{BA} = 3 Hz), 3.56 (pair of d, 1, J_{CB} = 17.5, J_{CA} = 10.5 Hz), 2.4 (s, 1).[76]

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.90; H, 4.32; N, 20.28.

Methyl 3-(5-Uracilyl)propenoate (19).—A mixture of 1.82 g (10^{-2} mol) of 3-(5-uracilyl)propenoic acid (**13**) and 30 ml of dry MeOH containing 2 drops of concentrated H_2SO_4 was heated under reflux for several days. Then about one half of the solvent was distilled, and the residual mixture was chilled. The product which separated was collected, washed with cold MeOH, and dried. It was found to be analytically pure. The average yield was over 90%: mp 288–289° dec; nmr τ 6.33 (s, 3, OCH_3), 3.20 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCO), 2.61 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CHCO$), 2.00 (s, 1).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.81; H, 4.09; N, 14.29.

Methyl 3-[5-(2,4-Bis-*O*-trimethylsilyl)uracilyl]propenoate (20).—A mixture of the ester **19** (4.12 g, 2.05×10^{-2} mol), 30 ml of hexamethyldisilazane, and 0.4 ml of trimethylchlorosilane was heated in a bath at 155° for 16 hr. The solvents were removed *in vacuo* and the oily residue was fractionated. The product fraction was collected at 117–118° (34–35 × 10^{-3} mm) as a viscous oil, weighing 6.5 g (91%).

Methyl 3-[5-(1-Methyl)uracilyl]propenoate (21).—The above product **20** (6.5 g, 1.9×10^{-2} mol) was dissolved in 50 ml of CH_3I and the solution was gently heated under reflux for 6 hr. Then the solvent was boiled off and 50 ml of MeOH was added to the residue. The mixture was heated under reflux for 10 hr and then cooled at −20°. The product which precipitated was collected, washed with ether, dried, and then dissolved in 1 l. of boiling water. The solution was filtered and then sufficient solvent was removed by distillation to promote crystallization. After cooling, the product was collected, washed twice with cold water, and dried: yield 3.7 g (92%); mp 256–260°; nmr τ 6.72 (s, 3, NCH_3), 6.35 (s, 3, OCH_3), 3.27 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCO), 2.7 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CHCO$), 1.8 (s, 1).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.49; H, 4.80; N, 13.16.

3-[5-(1-Methyl)uracilyl]propenoic Acid (22).—Hydrolysis of **21** (424 mg, 2×10^{-3} mol) was conducted in aqueous solution containing a stoichiometric amount of NaOH for 3 days at room temperature. The solution was chromatographed on a Sephadex G-10 column (l 16 cm) eluted with 0.05 *M* NaH_2PO_4 buffer at pH 7. The eluate containing the product was concentrated to a small volume, acidified to pH 1 with concentrated hydrochloric acid, and cooled. The crude product (327 mg, 82.5%) was recrystallized from H_2O to give needles: mp 284–286° dec; nmr τ 6.7 (s, 3, NCH_3), 3.29 (d, 1, $J_{2',1'}$ = 16 Hz, =CHCO), 2.71 (d, 1, $J_{1',2'}$ = 16 Hz, $-CH=CHCO$), 1.91 (s, 1).

Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.13; H, 3.69; N, 14.31.

Registry No.—**4**, 37107-74-7; **5**, 37107-75-8; **6**, 37107-76-9; **7**, 37107-77-0; **8**, 37107-78-1; **9**, 37107-79-2; **13**, 37107-80-5; **14**, 37107-81-6; **19**, 37107-82-7; **20**, 37107-83-8; **21**, 37107-84-9; **22**, 37107-85-0.

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(76) NOTE ADDED IN PROOF.—Ions identical with **4b** and 5-vinyluracil (**14**) were observed in the mass spectrum of 5-(4′,5′-dihydroxypentyl)uracil, a new pyrimidine from *Bacillus subtilis* phage SP-15 nucleic acid.[77]

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S-Acylcysteine Peptides. Synthesis and Kinetics of Hydrolysis[1]

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A series of *S*-acylcysteines, seryl-*S*-acylcysteines, and *S*-acylcysteinylthreonines was synthesized and characterized. Both *N*,*S*-diacetylcysteinamide and *N*-acetyl-*S*-benzoylcysteinamide are more reactive toward hydroxide ion than expected on the basis of the reactivity of simpler thiol esters: second-order rate constants for alkaline hydrolysis in water at 39° are 390 M^{-1} min^{-1} and 154 M^{-1} min^{-1}, respectively. *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester was found to be 5–6 times more reactive than *N*,*S*-diacetylcysteinamide; k_2 for reaction with hydroxide ion at 39° is 2300 M^{-1} min^{-1}. No S → O acyl transfer reaction was detectable during the hydrolysis of this *S*-acetyldipeptide. The magnitude of the solvent deuterium isotope effect for hydrolysis of this substrate, $k_{H_2O}/k_{D_2O} = 2.7$, suggests that the enhanced reactivity may reflect general acid–base catalysis involving the threonyl hydroxyl function. Imidazole catalyzes the hydrolysis of both *N*,*S*-diacetylcysteinamide and *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester by a general base mechanism; these two substrates are about equally reactive toward imidazole. *N*-Cbz-L-serinyl-*S*-benzoyl-L-cysteine methyl ester has a second-order rate constant for alkaline hydrolysis in 40% dioxane at 39° of 480 M^{-1} min^{-1}, some 40 times greater than that for *N*-acetyl-*S*-benzoylcysteinamide under the same conditions. Implications of these results for understanding the reactivity of S-acylated glyceraldehyde 3-phosphate dehydrogenases are discussed.

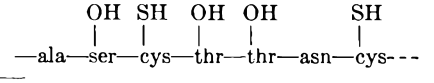
Glyceraldehyde-3-phosphate dehydrogenase [D-glyceraldehyde 3-phosphate: NAD oxidoreductase (phosphorylating)], abbreviated G3PD hereafter, is a well-charactreized polyfunctional enzyme which catalyzes a crucial step in the glycolytic pathway.[3] It has been clearly established that the catalytic pathway involves the transient formation of a covalent substrate–enzyme intermediate involving acylation of a particular cysteine residue.[3,4]

One of the simplest reactions catalyzed by this versatile enzyme is the hydrolysis of *p*-nitrophenyl acetate,[3]

$$E + S \rightleftharpoons ES \xrightarrow{-P_1} ES' \longrightarrow E + P_2$$

in which S is *p*-nitrophenyl acetate, P_1 is *p*-nitrophenol, P_2 is acetate, ES is the Michaelis–Menten complex, and ES′ is the acyl enzyme intermediate. It has proved possible to account for the rate of the acylation reaction in terms of the reactivity of the sulfhydryl anion at the active site of the enzyme and the local concentrations of ester and this anion in the Michaelis–Menten complex.[5] On the other hand, the rate of enzyme deacylation, hydrolysis of a thiol ester bond, is about one million times faster than the rate of hydrolysis of simple thiol esters under similar conditions, and this rate difference has not been satisfactorily explained.[5]

The complete sequence of G3PD has been established, and, specifically, the sequence of amino acids near the active site cysteine is known.[6] There are four nucleophilic amino acids in the sequence including this particular cysteine and a fifth is not far waay.



The occurrence of four consecutive nucleophilic groups at the enzyme active site suggests a variety of possible modes of catalysis for hydrolysis of a thiol ester involving the crucial cysteine residue. In an effort to judge the importance of the immediate neighbors of this cysteine as potentiators for the hydrolysis of such thiol esters, it was decided to synthesize some related *S*-acylcysteines and to determine their reactivity toward nucleophilic reagents. Results of these studies are detailed herein.

Experimental Section

Materials.—All inorganic chemicals and mineral acids were reagent grade. All water employed was distilled and that used in kinetic measurements was redistilled in a Corning AG-1a glass still and degassed before use. Silica gel used in column chromatography was 80–200 mesh from the Fisher Chemical Co. Silica gel G for thin layer chromatography was obtained from Merck and Sephadex LH-20 from Pharmacia, Inc. Organic materials employed were the highest grade commercially available. *N*-Acetylcysteinamide was the generous gift of Mead Johnson Co., Evansville, Ind. Hydroxylamine hydrochloride was recrystallized twice from ethanol–water; imidazole was recrystallized twice from ethanol–water; imidazole was recrystallized twice from benzene; triethylamine hydrochloride was recrystallized twice from ethanol. Triethylamine was redistilled prior to use. Dioxane was purified according to the method of Fieser[7] and was stored frozen, layered with argon. Analytical analyses were performed by Alfred Bernhardt, Mulheim, West Germany, and Midwest Microlabs, Indianapolis, Ind. Infrared spectra were taken in KBr pellets unless otherwise noted using Perkin-Elmer 137 and 137G infrared spectrophotometers. Ultraviolet and visible absorption spectra were recorded on a Cary-14 recording spectrophotometer. Proton magnetic resonance spectra were obtained with Varian A-60, HA-100, and HR-220 MHz nuclear magnetic resonance spectrophotometers. Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected.

Synthesis. ***N*,*N*′-Dicarbobenzoxy-L-cystine** was prepared according to the method of Bergmann and Zervas.[8]

***N*-Carbobenzoxy-*S*-acetyl-L-cysteine** (1) was prepared by a modification of the method of Zervas, *et al.*[9,10] *N*,*N*′-Dicarbobenzoxy-L-cystine (0.01 mol, 5.1 g) was dissolved in 30.0 ml of methanol and the solution was cooled to 0–5°. With continual stirring, 3.0 g of zinc dust was slowly added over a period of 20

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min at this temperature. The solution was filtered and the filtrate was reduced in volume by two-thirds under reduced pressure, maintaining the temperature of the solution below 40°. Several volumes of water were added to the concentrated methanolic solution, which was then extracted several times with benzene. The benzene solution was dried over $MgSO_4$, filtered, and taken to dryness under reduced pressure. The resulting viscous *N*-carbobenzoxy-L-cysteine was used directly in the next reaction without further purification.

N-Carbobenzoxy-L-cysteine (0.02 mol) was dissolved with vigorous stirring in 30.0 ml of 3.5 *N* NaOH and 200 ml of saturated $NaHCO_3$. To this was slowly added with stirring 24 ml of acetic anhydride and vigorous stirring was continued for 30 min, at which time the solution was acidified with 9 *N* H_2SO_4 until precipitation was completed. The resulting gummy residue crystallized upon cooling to yield **1**, 4.54 g (74%), mp 113°. Recrystallization from carbon tetrachloride raised the melting point to 116° (lit.[10] mp 116–117°).

***N*-Carbobenzoxy-*S*-acetyl-L-cysteinyl-L-threonine Ethyl Ester (2). Method 1.**—Threonine ethyl ester hydrochloride[11] (3.5×10^{-3} mol, 0.641 g) was dissolved in 10 ml of dimethylformamide and to this was added 30.0 ml of tetrahydrofuran and 5 ml of triethylamine. This mixture was stirred for 30 min at room temperature and filtered, and the filtrate was washed with tetrahydrofuran and taken to dryness under high vacuum. The oily residue was taken up in 40 ml of tetrahydrofuran, the solution was cooled to 0°, and 1.04 g of **1** was added. A cold solution of 0.72 g of dicyclohexycarbodiimide in 10 ml of tetrahydrofuran was then added and the resulting reaction mixture was stirred at 5° for 20 hr. Insoluble dicyclohexylurea was removed by filtration and the filtrate was taken to dryness under reduced pressure. Repeated recrystallization of the residue (0.64 g, 43%) yielded a product with a melting point of 140–141°. Chromatography of the recrystallized material on silica gel eluting with 1:1 chloroform–ethyl acetate and recrystallization of the chromatographed material from acetone–water yielded pure **2**, mp 141°. Infrared absorption spectra exhibited major peaks at 2.9, 3.05, 5.85 (sh), 5.91, 5.95 (sh), 6.06, 6.08 (sh), 6.54, 7.90, 9.20, 9.70, 13.3, and 14.4 μ. Ultraviolet absorption spectra had a λ_{max} 230 nm (ϵ 4630). Nmr (acetone-d_6) showed the following major absorption peaks: τ 8.80 (m, 6, $-CHOHCH_3$, $-CH_2CH_3$), 7.70 (s, 3, $-SCOCH_3$), 6.88 (s, unassigned), 5.85 (q, 2, $-CH_2CH_3$), 4.87 (s, 2, $-CH_2Ph$), and 2.61 (s, 5, $-CH_2Ph$). *Anal.* Calcd for $C_{19}H_{26}N_2O_7S$: C, 53.51; H, 6.15; N, 6.57; S, 7.50. Found: C, 53.44; H, 6.10; N, 6.47; S, 7.57.

Method 2.—**1** (0.01 mol, 2.97 g) was dissolved in 75 ml of chloroform and 50 ml of tetrahydrofuran and cooled to −5°. Isobutyl chloroformate (0.01 mol, 1.37 g) and 1.4 ml of triethylamine were added to this solution and stirred at −5° for 5 min. Threonine ethyl ester hydrochloride (0.01 mol, 1.84 g) in tetrahydrofuran was added and 1.4 ml of triethylamine was slowly dripped in over a 5-min period. The reaction mixture was then stirred at −5° for 30 min followed by stirring at room temperature for 3 hr. After it was allowed to sit overnight, the reaction mixture was filtered and the filtrate was taken to dryness under reduced pressure. Once recrystallized product from acetone–water gave 3.34 g (78%) yield. Purification, as in method 1, gave pure **2**, mp 141°.

***N*,*S*-Diacetylcysteinamide (3).**—*N*-Acetylcysteinamide (0.011 mol, 2.043 g) was dissolved in 50 ml of water containing 6 g of $KHCO_3$. Acetic anhydride (12 ml) was added dropwise with stirring; upon completion of the addition, the reaction mixture was stirred for an additional 30 min, acidified with 9 *N* H_2SO_4, and repeatedly extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered, and taken to dryness under reduced pressure, water was added to the resulting residue, and the solution was again taken to dryness. The resulting white residue was recrystallized from ethanol–ligroin (bp 60–90°) to yield 0.90 g (36%) of **3**, mp 146–147°. Infrared absorption spectra showed major absorption peaks at 2.98, 3.06, 3.15, 5.92, 6.18, 6.50, 7.10, 7.90, 8.90, 10.5, and 13.6 μ. An ultraviolet absorption spectrum revealed a λ_{max} at 226 nm (ϵ 5440) in water. The nmr spectrum (D_2O) exhibited the following major absorption peaks: τ 8.00 (s, 3, $-CONCH_3$), 7.63 (s, 3, $-SCOCH_3$), 6.73 (m, 1, 2, $-CH-$, CH_2-). *Anal.* Calcd for $C_7H_{12}N_2O_3S$: C, 41.16; H, 5.92; N, 13.72; S, 15.71. Found: C, 41.20; H, 6.09; N, 13.72; S, 15.71.

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***S*-Benzoyl-L-cysteine and *S*-benzoyl-L-cysteine methyl ester hydrochloride (4)** were synthesized according to the method of Zervas, *et al.*[10] ***N*-Carbobenzoxy-*S*-benzoyl-L-cysteine (5)** was made by the method of these authors[10] except that a purification step of chromatography on silica gel eluting with 5:1 chloroform–ethyl acetate was added prior to recrystallization.

***N*-Carbobenzoxy-L-seryl-*S*-benzoyl-L-cysteine Methyl Ester (6).**—Cbz-serine (1×10^{-3} mol, 0.239 g) was dissolved in a mixture of 80 ml of tetrahydrofuran and 20 ml of dimethylformamide at −5°. To this solution was added triethylamine (0.14 ml) and isobutyl chloroformate (0.14 ml) at −5° and the mixture was stirred for 15 min. At the end of this time, **4** (1.1×10^{-3} mol, 0.303 g) was added and triethylamine (0.14 ml) was dripped into the reaction mixture over a 5-min period. The reaction mixture was stirred at room temperature for 3 hr, kept at 0° overnight, and filtered. The filtrate was taken to dryness under reduced pressure, the oily residue was again taken up in tetrahydrofuran and filtered, and the filtrate was taken to dryness. The resulting yellow oil, when washed with ethyl acetate, gave a white precipitate, mp 173–175°. The white precipitate was washed with methanol, removing a trace of yellow color. Chromatography on silica gel eluting with 19:1 chloroform–methanol removed the remaining impurities. Recrystallization of the chromatographed material from chloroform gave 75 mg of product, mp 179.5–181.5°. An infrared absorption spectrum showed the following major absorption peaks: 2.9 (sh), 3.04, 5.80, 5.83 (sh), 5.95 (sh), 6.02 (sh), 6.10, 7.60, 8.00 (sh) 8.10, 8.30, 8.50, 9.90, 11.00, and 14.80 μ. Ultraviolet absorption spectrum showed major absorption peaks at λ_{max} 264 nm (ϵ 7.68×10^3) in ethanol containing 0.3% (v/v) dimethyl sulfoxide. Nmr spectrum ($CDCl_3$) showed the following assigned absorption peaks: τ 6.23 (s, 3, $-CO_2CH_3$), 4.95 (s, 2, 2H's of Cbz), 2.70 (s, 5, 5 H's of Cbz), 2.67 (m, 3, 3,4,5 H's of *S*-benzoyl), and 2.06 (d of d, 2, J = 6.2 Hz, 2,6 H's of *S*-benzoyl).

Anal. Calcd for $C_{22}H_{24}N_2SO_7$: C, 57.38; H, 5.25; N, 6.08; S, 6.96. Found: C, 56.93; H, 5.38; N, 6.07; S, 7.13.

***N*-Carbobenzoxy-*S*-benzoyl-L-cysteinyl-L-threonine Methyl Ester (7).**—L-Threonine methyl ester hydrochloride[12] (4.5×10^{-3} mol, 0.763 g) was dissolved in a mixture of 10 ml of dimethylformamide and 40 ml of tetrahydrofuran. To this was added with stirring triethylamine (0.7 ml) and, after 15 min, the solution was filtered and the filtrate was taken to dryness under vacuum. The resulting residue was taken up in 100 ml of tetrahydrofuran and to this was added **5** (1.6 g) and dicyclohexylcarbodiimide (0.928 g). The reaction mixture was stirred for 24 hr at 5° and filtered, and the filtrate was taken to dryness under reduced pressure. The residue was dissolved in ethyl acetate and washed with dilute hydrochloric acid and water. The ethyl acetate layer was dried over $MgSO_4$, filtered, and taken to dryness under reduced pressure. The residue was dissolved in acetone and cooled, and additional dicyclohexylurea was filtered off. The filtrate was again taken to dryness and the residue was chromatographed on silica gel eluting with 2:1 chloroform–ethyl acetate. The chromatographed sample was crystallized from ethyl acetate to yield 170 mg of **7**, mp 133–140°. The sample showed one spot on tlc (iodine vapor stain) in three solvent systems: 2:1 chloroform–ethyl acetate, 1:5 ethyl acetate–chloroform, and 10:1:3 1-butanol–acetic acid–water. The infrared absorption spectrum exhibited major absorption peaks at 2.88, 3.02, 5.81, 5.92, 5.95 (sh), 6.03 (sh), 6.08, 6.11 (sh), 6.56, 8.05, 8.30, 9.90, 11.05, 13.65, and 14.70 μ. Ultraviolet absorption spectra showed major absorption peaks at λ_{max} 238 nm (ϵ 1.07×10^4) and 264 (ϵ 8.55×10^3) in ethanol containing 3.3% (v/v) dimethyl sulfoxide. Nmr spectra ($CDCl_3$) exhibited assignable peaks at τ 8.83 (d, 3, J = 6 Hz, $-CHOHCH_3$), 6.31 (s, 3, $-CO_2CH_3$), 4.95 (s, 3, 2 H's of Cbz), 2.74 (s, 5, 5 H's of Cbz), 2.66 (m, 3, 3,4,5 H's of *S*-benzoyl), and 2.07 (d, 2, 2,6 H's of *S*-benzoyl). *Anal.* Calcd for $C_{23}H_{26}N_2SO_7$: C, 58.21; H, 5.52; N, 5.90; S, 6.76. Found: C, 58.54; H, 5.91; N, 6.23; S, 6.98.

***N*-Acetyl-*S*-benzoyl-L-cysteinamide (8).**—*N*-Acetylcysteinamide (0.111 mol, 2.04 g) was dissolved in 50 ml of water. To this was added 20 ml of ethyl ether and the solution was cooled to 5°. Benzoyl chloride (0.01 mol) was added followed by 6 g of $KHCO_3$ which was added slowly with stirring over a 15-min period. After an additional 20 min of stirring at room temperature, the reaction mixture was neutralized by the addition of 15 ml of 6 *N* hydrochloric acid to precipitate 2.1 g (75%) of a white

(12) T. Tanaka and N. Sugimoto, *Yakugaku Kenkyu*, **33**, 428 (1961).

solid which upon recrystallization from tetrahydrofuran yielded a product of melting point 195–198°. The infrared absorption spectrum exhibited major absorption peaks at 2.98, 3.05, 3.15, 5.92, 5.99, 6.12 (sh), 6.18, 6.50, 7.10, 7.70, 8.28, 10.95, 12.95, and 14.60 μ. Ultraviolet absorption spectra showed two major peaks at 266 nm (ϵ 1.15 × 10^4) and 241 (1.22 × 10^4) in water containing 3.3% (v/v) acetonitrile. *Anal.* Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.14; H, 5.46; N, 10.51; S, 11.96. Silica gel thin layer chromatography of the purified *S*-acylcysteines **2**, **6**, and **7** gave single spots with iodine vapor stain substantiating their homogeneity.

Kinetics.—A Zeiss PMQII spectrophotometer with thermostated cell holder through which water from a constant-temperature bath was circulated was used throughout this work. Values of pH were either taken at the beginning and end of a kinetic run or the pH of the blank was taken and compared to that of the reaction mixture at infinite time. All values of pH were taken on a Radiometer PHM4c pH meter employing a glass electrode or a combination glass–KCl electrode, and were taken at the temperature at which the kinetics were run. Kinetic runs in which the pH of the buffered solution fluctuated more than 0.10 pH unit between the infinite time pH and the initial pH value were discarded.

Hydrolysis of the thiol esters described in this study was performed at 39.0 ±0.1° by incubating the buffered reaction solutions, which had been layered with argon prior to introduction of the substrate, in a constant-temperature bath; the reactions were initiated by the addition of the substrate. The rate of hydrolysis was followed by monitoring the disappearance of the thiol ester as measured by the hydroxylamine–ferric chloride method;[13] the reactions were followed through a minimum of 2 half-lives.

The kinetics of the hydrolysis of the thiol acetates **2** and **3** were followed by the neutral hydroxylamine–ferric chloride method of Jencks, *et al.*[14] The hydrolysis of dipeptide **2** was also monitored in a separate series of kinetic runs by the alkaline hydroxylamine method of these workers.[14] For those kinetic runs monitored by the neutral hydroxylamine method, 0.05 *M* borate, tricine, and triethylamine buffers were used, each containing 10^{-4} *M* EDTA and maintained at ionic strength 0.25 by the addition of lithium chloride; the concentration of the tricine buffer was varied in the case of the hydrolysis of **2**. For those kinetic runs monitored by the alkaline hydroxylamine assay, a 0.05 *M* borate buffer containing 10^{-4} *M* EDTA at ionic strength 0.25 was used exclusively. For all the kinetic runs with the acetyl thiol esters, the final concentration (v/v) of organic solvent (acetonitrile) was 3.3%.

The hydrolysis of the thiol ester **3** was also studied titrimetrically, using a Radiometer pH-Stat apparatus equipped with a G-202B glass electrode and a calomel electrode. The hydrolytic reactions were run at 39° in a chamber which was continually flushed with nitrogen and stirred with a magnetic stirrer. Into a solution which was 0.25 *M* in lithium chloride was injected the thiol ester (final concentration 10^{-3} *M*) and pH-Stat recording was initiated at the desired pH. Several values of pH were studied.

Because the aromatic thiol esters **6**, **7**, and **8** were in general less soluble in water than the corresponding acetates and because they were much less reactive, higher concentrations of organic solvent and more alkaline buffer solutions were employed in the kinetic studies. For study of the kinetics of the hydrolysis of the dipeptide **6**, 0.15 *M* triethylamine buffer containing 10^{-4} *M* EDTA and a final concentration of organic solvent (dioxane) of 40% were found to be appropriate; for the dipeptide **7**, 10% (v/v) dimethyl sulfoxide in 0.05 *M* borate buffer containing 10^{-4} *M* EDTA sufficed. *N*-Acetyl-*S*-carbobenzoxycysteinamide (**8**) was hydrolyzed in both these solvent–buffer systems. For the hydrolysis of all the aromatic thiol esters, the ionic strength of the buffer system was maintained at 0.30 with lithium chloride. As was the case with the thiol acetates, hydrolysis of the aromatic thiol esters was performed at 39 ±0.1 and all buffer solutions were layered with argon prior to addition of substrate. The rate of hydrolysis of the aromatic thiol esters **6**, **7**, and **8** was followed by monitoring the loss of ester as measured by the hydroxylamine–ferric chloride method. A reproducible neutral hydroxylamine assay was not obtained and consequently a modification of the previous[14] alkaline hydroxylamine–ferric chloride method was used. Aliquots (2.0 ml) of the buffered reaction solution were withdrawn at given time intervals and pipetted into 0.5 ml of the alkaline hydroxylamine solution prepared as described previously. The resulting mixture was incubated for 2 min at room temperature and then 1.0 ml of the ferric chloride solution was added, shaken vigorously, and read at 540 nm against a blank prepared as previously described.

Calculation of the pseudo-first-order rate constants for the hydrolysis of thiol esters as monitored by the hydroxylamine–ferric chloride and pH-Stat methods was performed by determination of the half-life for each reaction from semilog plots of the differences in the optical density (or the equivalents of base consumed as in the titrimetric assay) at time t and at infinite time *vs.* time. Infinite time optical density readings were taken at approximately 10 half-lives and were taken repeatedly until the readings were constant. Infinite time values of equivalents of base consumed in the titrimetric assay were those values at which base consumption had ceased and agreed well with the theoretical amount calculated for the reaction.

Solvent Deuterium Isotope Effect.—The effect of D_2O upon the hydrolytic rate of the thiol ester **2** was studied. Separate kinetic runs, one in D_2O and the other in aqueous solution, were performed simultaneously at 39° using the neutral hydroxylamine–ferric chloride assay method. For the run in D_2O, tricine buffer (0.10 *M*) was used in which the tricine had been deuterated by equilibration in D_2O followed by lyophilization to dryness. The buffer was brought to the appropriate alkaline pH with 2 *M* NaOD such that the pD of this run was equal to the pH of the first kinetic run which was performed as previously described. The relationship pD = pH (reading of the pH meter) + 0.4 was used to calculate the pD of the second run.[15,16] Ionic strength was maintained at 0.25 with the use of 4 *M* LiCl in D_2O. The data were plotted in the fashion already described for the hydrolysis of dipeptide **2**.

Product Analysis.—For the thiol acetates **2** and **3**, the alkaline reaction solutions were assayed by the method of Ellman utilizing the reagent 5,5′-dithiobis(2-nitrobenzoic acid), DTNB.[17] At times approaching and/or identical with the infinite time of the hydrolytic reaction, 2.5 ml of a freshly prepared solution of 1.0 *M* tris, pH 8.0, containing 10^{-3} *M* DTNB was added to 0.5 ml of the reaction solution and this solution was read at 412 nm against a blank prepared by adding 2.5 ml of the buffered DTNB solution to 0.5 ml of the appropriate buffer. The production of the chromophoric 4-nitro-2-carboxyphenyl thiolate, λ_{max} 412 nm (ϵ 1.36 × 10^4)[17] was usually completed within 5 min after mixing the buffered DTNB reagent with the reaction solution. In addition, for the thiol acetates, the Cary 14 ultraviolet absorption spectrum of the reaction solutions at infinite time were recorded.

For the aromatic thiol esters **6**, **7**, and **8**, only the DTNB assays were performed on the infinite time hydrolysis solutions.

Kinetics of Aminolysis.—The reaction of imidazole with the thiol acetates **2** and **3** was studied as a function of imidazole concentration and pH. Solutions of imidazole containing 0.05, 0.10, 0.15, 0.20, and 0.25 *M* total imidazole at different values of pH, ionic strength maintained at 0.25 with lithium chloride, were treated with 1.33 × 10^{-4} *M* substrate. The rate of disappearance of thiol ester was followed spectrophotometrically at 232 nm in stoppered quartz cuvettes. The temperature was maintained at 25 ±0.1° by a circulating constant-temperature bath. Pseudo-first-order rate constants were obtained as described above.

Determination of pK_a Values.—The pK_a of *N*-acetylcysteinamide, mp 147–149°, was determined titrimetrically at ionic strength 0.25 (LiCl) and 25° and was found to be 8.50. To prevent air oxidation, the titrations were either performed under nitrogen or were done rapidly to minimize oxidation. Attempts to measure the value of the pK_a for *N*-Cbz-L-cysteine methyl ester by this same method failed owing to an intermolecular reaction of the thiol anion with the oxygen ester at basic values of pH resulting in a uv spectrum with a maximum at 230 nm.

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(14) W. P. Jencks, S. Cordes, and J. Carriuolo, *ibid.*, **235**, 3608 (1960), and references cited therein.

(15) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

(16) K. Mikkelsen and S. O. Nielsen, *ibid.*, **64**, 632 (1960).

(17) G. C. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

Table I

Reaction Conditions and the Second-Order Rate Constants for the Hydrolysis of a Series of Thiol Esters[a]

Thiol ester	Buffer	pH Range[b]	k_{OH}, M^{-1} min^{-1}	Assay
N,*S*-diacetylcysteinamide (3)	0.25 *M* LiCl 1.5% CH_3CN	9.5–10.0	4.6×10^2	T
	0.05 *M* Borate 3.3% CH_3CN	9.46–9.83	3.9×10^2	NN
N-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester (2)	0.05 *M* Borate 3.3% THF	8.21–9.07	3.2×10^3	NN
	0.05 *M* Borate 3.3% CH_3CN	8.37–9.12	2.0×10^3	NN
	0.05 *M* Et_3N 3.3% CH_3CN	9.50–10.13	1.7×10^3	NN
	0.05 *M* Tricine 3.3% CH_3CN	8.35–8.87	2.5×10^3	NN
	0.10 *M* Tricine 3.3% CH_3CN	8.32–8.82	2.3×10^3	NN
	0.05 *M* Borate 3.3% CH_3CN	8.44–9.00	2.5×10^3	AN
N-acetyl-*S*-benzoyl-L-cysteinamide (8)	0.05 *M* Borate 3.3% THF	9.62–10.09	1.54×10^2	AN
	0.05 *M* Borate 10% DMSO	9.64–9.98	1.22×10^2	AN
	0.15 *M* Et_2N 40% Dioxane	10.54–10.98	11.0	AN
N-Cbz-*S*-benzoyl-L-cysteinyl-L-threonine methyl ester (7)	0.05 *M* Borate	9.30–9.92	2.5×10^2	AN
N-Cbz-L-seryl-*S*-benzoyl-L-cysteine methyl ester (6)	0.15 *M* Et_3N 40% Dioxane	9.99–10.62	4.8×10^2	AN

[a] Abbreviations used: T, titrimetric assay; NN, neutral hydroxylamine–ferric chloride assay; AN, alkaline hydroxylamine–ferric chloride assay (see Experimental Section); THF, tetrahydrofuran. [b] Measured (glass electrode) pH.

Results

The hydroxylamine–ferric chloride methods described above sufficed to yield satisfactory kinetic data for the hydrolysis of the series of thiol esters studied. A typical plot of first-order rate data, that for hydrolysis of the dipeptide 2 at pH 8.37 in 0.05 *M* borate buffer, is shown in Figure 1. A titrimetric assay was also employed in one case and proved satisfactory. In contrast, efforts to follow the reactions employing ultraviolet spectrophotometry at the absorption maxima of the substrates failed, yielding first-order rate plots of continuously decreasing slope. This probably reflects the small changes in total optical density observed and, perhaps, the occurrence of side reactions.

In Table I, second-order rate constants for the alkaline hydrolysis of the series of thiol esters studied, together with the reaction conditions under which they were measured, are collected. In each case, the second-order rate constants were evaluated from slopes of plots of first-order rate constants against the activity of hydroxide ion; satisfactory plots were obtained in all cases. A typical example for the hydrolysis of 2 at six values of pH at 39° is provided in Figure 2. In the cases of all substrates studied, the intercept at zero hydroxide ion concentration was not detectably different from zero, indicating the unimportance of a neutral (water-catalyzed) reaction under the conditions employed.

A number of minor complications were observed in the study of the hydrolysis of these thiol esters. Values of pH above 10 could not be employed in studies of the hydrolysis of 3 and several of the other substrates, owing to the occurrence of β-elimination reactions under more alkaline conditions. Moreover, 6 was insufficiently soluble in water, necessitating the use of appreciable

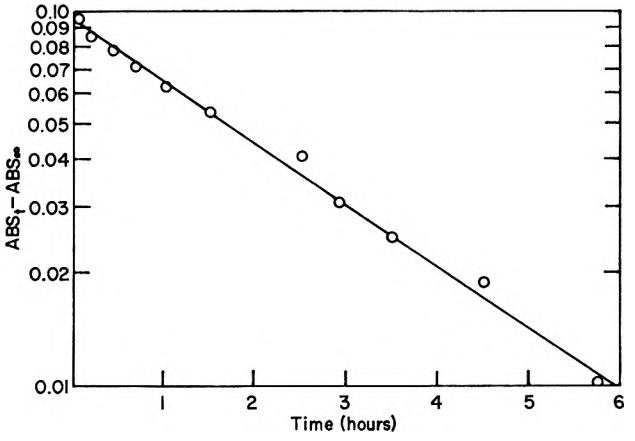


Figure 1.—Semilogarithmic plot of the difference of the optical density at time *t* and the optical density at infinite time as a function of time for the hydrolysis of *N*-Cbz-S-acetyl-L-cysteinyl-L-threonine ethyl ester at 39° (2) as followed by the neutral hydroxylamine–ferric chloride method. Initial substrate concentration was 2×10^{-4} *M* in 0.05 *M* borate buffer containing 10^{-4} *M* EDTA at pH 8.37 and maintained at ionic strength 0.25 with lithium chloride. Final concentration of organic solvent (acetonitrile) was 3.3%.

quantities of dioxane as solvent in this case. For comparative purposes, this solvent was also employed for the kinetics of hydrolysis of 8 (Table I). The rate of hydrolysis of 2 exhibited small variation as a function of the nature of the buffer or organic component of the solvent; buffer catalysis by tricine was not observed, however. Note that the measured second-order rate constant employing the neutral and alkaline hydroxylamine–ferric chloride assays yielded identical results, a matter to which we return later. The lower reactivity of the *S*-benzoyl substrates, 6, 7, and 8, compared to the *S*-acetyl substrates necessitated the use of the alkaline

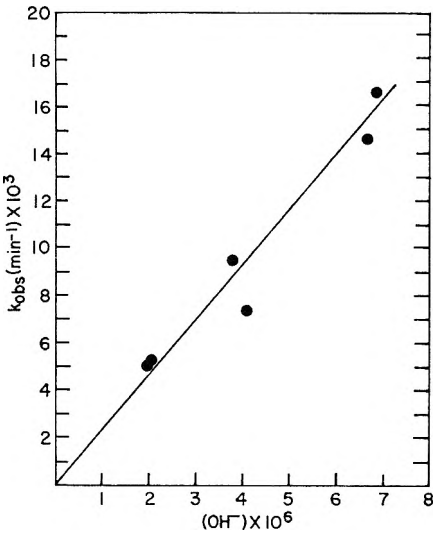


Figure 2.—Second-order rate constants for the alkaline hydrolysis of *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester (2) at 39° plotted against the activity of hydroxide ion. Initial concentration of substrate was 2×10^{-4} *M* in 0.10 *M* tricine buffers at ionic strength 0.25. Final concentration of organic solvent (acetonitrile) was 3.3%.

hydroxylamine–ferric chloride assay for the former group of compounds.

The alkaline hydrolysis of *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester (2) was found to be subject to a solvent deuterium effect, the value of k_{H_2O}/k_{D_2O} being 2.68 ± 0.40 under conditions in which pH equaled pD at 39°.

Analysis of the Products of Thiol Ester Hydrolysis.—Two methods were used to analyze the products of the hydrolysis of the thiol esters: assay for free thiol using the Ellman reagent DTNB,[17] and analysis of the uv spectrum with emphasis on the absorbance value at 241 nm. The last assay is a sensitive one for dehydroalanine type compounds which result upon β elimination of an amino acid. Consequently, if β elimination were to occur, either prior to or following thiol ester hydrolysis, it could be easily detected; Riley, *et al.*, have reported a λ_{max} of 241 nm (ε 5300) for α-*N*-Cbz-aminoacrylic acid.[18]

Upon hydrolysis of the thiol ester *N*,*S*-diacetylcysteinamide (3), at the conclusion of reactions monitored titrimetrically or by neutral hydroxylamine, the absorbance at 241 nm using the molar extinction coefficient for α-*N*-Cbz-aminoacrylic acid indicated that less than 3% β elimination had occurred, while analysis of free thiol by the DTNB method accounted for 93% of that expected theoretically for complete hydrolysis of the thiol ester. It would appear, therefore, that for this thiol ester, conditions of pH 10 and below resulted only in hydrolysis of the thiol ester.

On the other hand, analysis of the products of hydrolysis of the dipeptide *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester (2) by the DTNB method accounted at most for only 44% of the theoretical amount of thiol (0.10 *M* tricine buffer) and the average value was 20–30% of the theoretical quantity in the pH range 8.2–9.1 (0.05 *M* borate buffer). However, uv analysis at times considerably greater than 10 half-lives of the hydrolysis reaction revealed that less than 9% dehydroalanine had been formed. The possibility that thiol had been oxidized to sulfenic acid, or higher oxidation states, was explored by attempting to reduce with arsenate any oxidation product which may have been formed; several reports in the literature[19,20] indicate that large molar excesses of arsenate are necessary. Consequently, aliquots of the hydrolysis reaction mixture at infinite time were analyzed for thiol content by the DTNB method; one sample was treated, prior to reaction with DTNB, with a 2000:1 molar excess of sodium arsenate at room temperature for 30 min while a second sample was analyzed directly with DTNB. The amount of thiol accounted for in the arsenate-treated sample was 24% of the theoretical, while that for the untreated sample was 20%, ruling out oxidation of the thiol to the sulfenic acid as responsible for the loss of thiol at infinite time of the hydrolysis of **2**.

Analysis of the hydrolysis products of the aromatic thiol esters **6**, **7**, and **8** could only be performed for free thiol, since benzoic acid, which is liberated in the hydrolysis reaction, absorbs in the region of the uv at which α-*N*-Cbz-aminoacrylic acid absorbs.

DTNB assay for free thiol after hydrolysis of *N*-acetyl-*S*-benzoylcysteinamide (8) had been completed accounted for 75% of the theoretical amount of thiol released upon hydrolysis under conditions of hydrolysis identical with those used for the dipeptides **6** and **7**. However, analysis of the amount of thiol present at the conclusion of the hydrolysis of **6** and **7** accounted for only 17 and 27%, respectively, of the theoretical amounts. A study of the production of thiol with respect to time for the dipeptide **6** revealed that at a calculated 5 half-lives of the hydrolysis reaction, 75% of the theoretical thiol released at that point in the reaction was present; this value slowly decreased to that found (17%) for the hydrolysis solution at infinite time (10 half-lives).

Kinetics of Aminolysis.—The susceptibility to attack by imidazole was examined for the thiol acetates **2** and **3**, these thiol esters being more soluble in aqueous solutions than any of the others studied. In Figure 3 is illustrated the second-order rate plots for the attack of imidazole (free base) upon the thiol ester **3** at three different values of pH; Figure 4 shows similar data for the dipeptide **2**. As can be seen from these figures, the slopes of second-order rate plots are identical within the error of the experiments, indicating that imidazole free base is the reactive species. In Table II are collected the individual second-order rate constants for the attack of imidazole on the substrates **2** and **3** at various values of pH.

TABLE II

SECOND-ORDER RATE CONSTANTS FOR IMIDAZOLE-CATALYZED DISAPPEARANCE OF THIOL ESTERS **2** AND **3** AT 25°

Thiol ester	pH	k_{Im}, M^{-1} min^{-1} × 10^2
N-Cbz-S-acetyl-L-cysteinyl-L-threonine ethyl ester (2)	8.23	6.20
	7.70	5.10
	7.53	5.10
N,*S*-diacetylcysteinamide (3)	8.02	4.56
	7.77	4.31
	7.50	3.95

(18) G. Riley, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 1373 (1957).

(19) J. Parker and W. S. Allison, *J. Biol. Chem.*, **244**, 180 (1967).

(20) A. Gutmann, *Ber.*, **41**, 1650 (1908).

Table III

Values of pK_a of the Conjugate Acid of the Leaving Group and the Second-Order Rate Constants for the Alkaline Hydrolysis and the Attack of Imidazole upon a Series of Thiol Esters

Registry no.	R	pK_a[a]	Temp, °C	k_{OH}, M^{-1} min^{-1}	k_{Im}, M^{-1} min^{-1}	Ref
		CH_3COSR				
928-47-2	*n*-Bu	11.05	20	0.22	0.04	*b*
926-73-8	*i*-Pr	10.86	20	0.82		*b*
625-60-5	C_2H_5	10.50	20	1.54	0.996	*c*
32362-99-5	$CH_2C_6H_5$	9.43	0	3.80		*d*
36914-44-0	$CH_2CH(CONH_2)$-N-$COCH_3$	8.50	39	390–460	0.046	
14897-48-4	CH_2CF_3	7.30	30	64.5	6.85	*e*
		C_6H_5COSR				
7269-35-4	*n*-Bu	11.05	0	0.07		*d*
13402-51-2	$CH_2C_6H_5$	9.43	0	0.22		*d*
36914-48-4	$CH_2CH(CONH_2)$-N-$COCH_3$	8.50	39	154		

[a] pK_a data for the conjugate acids was taken either from the indicated reference or from W. P. Jencks, in H. A. Sober, Ed., "Handbook of Biochemistry," Chemical Rubber Publishing Co., Cleveland, Ohio, 1968, p J-186. [b] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966, pp 259–298. [c] M. L. Bender and B. W. Turnquist, *J. Amer. Chem. Soc.*, 79, 1656 (1957). [d] G. Losse, R. Mayer, and K. Kuntze, *Z. Chem.*, 7, 104 (1967). [e] M. L. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, 89, 2121 (1967).

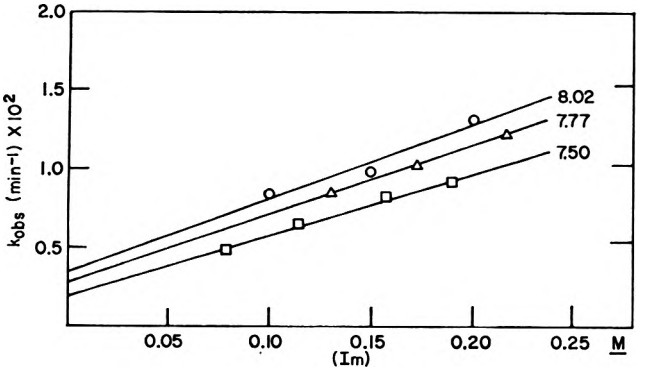


Figure 3.—Second-order rate constants for the attack of imidazole on *N*,*S*-diacetylcysteinamide (3) plotted against the concentration of imidazole over the pH range 7.50–8.02 at 25°. Initial concentration of substrate was 1.3×10^{-4} *M*. Ionic strength was maintained at 0.25 with LiCl and the final concentration of organic solvent (acetonitrile) was 3.3%.

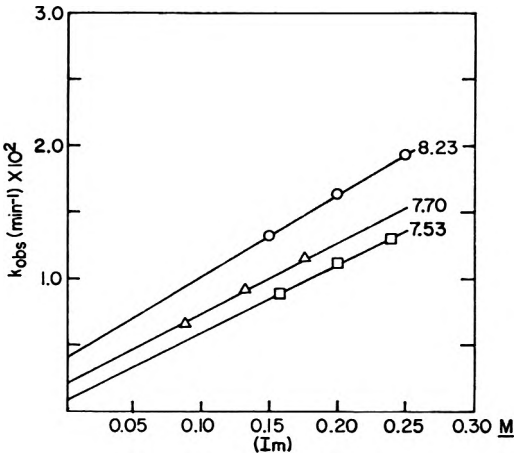


Figure 4.—Second-order rate constants for the attack of imidazole on the dipeptide *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester (2) plotted against the concentration of imidazole over the pH range 7.53–8.23 at 25°. Initial concentration of substrate was 1.3×10^{-4} *M*. Ionic strength was maintained at 0.25 with LiCl and the final concentration of organic solvent (acetonitrile) was 3.3%.

Discussion

The main thrust of the experimental work described above deals with reactivity and catalysis for the hydrolysis of thiol esters, a topic which has been extensively studied and thoroughly reviewed.[21–23] Special emphasis has been placed on possible roles of the nucleophilic groups which flank the crucial cysteine in the active site of G3PD in the process of thiol ester cleavage. Synthetic difficulties which precluded the synthesis of several desirable substrates (S → N acyl transfer reactions, the existence of which is most interesting for understanding the chemistry at the enzyme active site, were a particularly annoying plague in this respect) have left us with a less complete picture than might have been desired. Nevertheless, a number of new findings have come out of these studies. To begin with, let us consider the reactivity of the simplest substrates studied, the blocked *S*-acetyl- and *S*-benzoylcysteinamides, 3 and 8, in comparison to that of ordinary thiol esters. In Table III, second-order rate constants for alkaline hydrolysis and for reaction with imidazole of several thiol esters are collected as a function of the pK_a of the conjugate acid of the leaving thiolate anion. Qualitatively, the expected trend of greater reactivity toward hydroxide ion with increasing acidity of the conjugate acid of the leaving group is observed for both *S*-acetyl and *S*-benzoyl thiol esters. Evident from this table is the abnormal reactivity of the *S*-acylcysteines. Thus, making reasonable estimates of rate differences reflecting differences in the temperatures at which the reactions were run, it is found that the acylcysteines are about 20-fold more reactive than expected on the basis of the pK_a of the leaving group and the reactivity of simple thiol esters. This finding contrasts with that for hydrolysis of acylserines, which, though more reactive than simple oxygen esters, are not particularly more reactive than expected on the basis of the relatively high

(21) L. Zervas, I. Photaki, A. Cosmatos, and D. Borovas, *J. Amer. Chem. Soc.*, 87, 4922 (1965).
(22) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966.
(23) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

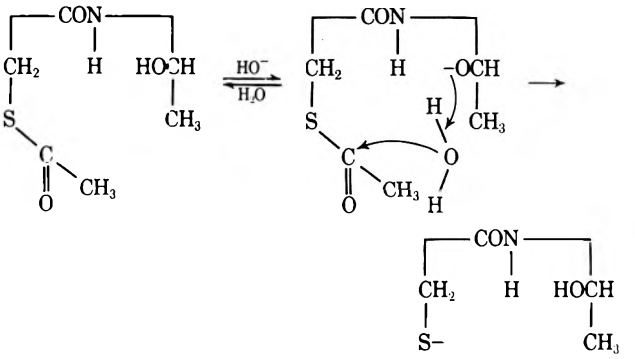
acidity of the leaving group.[24,25] Clearly, this is not the case for hydrolysis of the corresponding thiol esters. One may consider the possibility that the electron-withdrawing inductive effects of the substituted cysteine moiety are more important for the hydrolysis of derived thiol esters, perhaps reflecting the degree of polarization of the thiol ester bond, than for the ionization of the thiol itself. It is also possible that the amide substituents may facilitate the reaction through intramolecular general acid–base catalysis.

The observed greater reactivity of acetyl compared to benzoyl esters, Tables I and III, is expected; similar results have been previously obtained with oxygen esters as well.[26]

In contrast to the results obtained with hydroxide ion, acylcysteines are not abnormally reactive toward imidazole (Table III). If any trend can be discerned, just the opposite is true. This distinct behavior probably reflects the fact that imidazole facilitates the hydrolysis of thiol esters by general base catalysis of the attack of a water molecule rather than by direct nucleophilic attack.[22]

The reactivity of *S*-acylcysteines is appreciably enhanced by the presence of neighboring hydroxylic amino acids. For example, *N*-Cbz-*S*-acetyl-L-cysteinyl-L-threonine ethyl ester (2) is about five times as reactive toward hydroxide ion as *N*,*S*-diacetylcysteinamide (3), a suitable model compound (Table I). The presence of the neighboring threonine residue suggests the possibility of an S → O acyl transfer reaction, leading to an increased rate of loss of thiol ester. Assuming that the oxygen ester formed from such an acyl transfer reaction would be more stable than the initial thiol ester,[14,24] it is possible to examine this possibility by comparing the kinetic behavior using the neutral hydroxylamine test, which detects only the thiol ester, and the alkaline hydroxylamine test, which detects both thiol and oxygen esters. If the acyl transfer reaction was one of importance, one would expect to observe a lag phase in the alkaline hydroxylamine assay; moreover, the rate constant measured by this assay should be smaller than that measured using the neutral hydroxylamine assay. In fact, the two assay methods yield identical rate constants (Table I), ruling out an appreciable contribution to the rate of thiol ester disappearance from an S → O acyl transfer reaction. This is not surprising. Such reactions have been observed for those cases involving formation of tetrahedral intermediates having not more than six atoms.[27,28] In the case of the dipeptide, 2, formation of a nine-membered-ring intermediate would be required.

A possible mode of facilitation of thiol ester hydrolysis by the neighboring threonine residue is suggested by a study of the kinetics of hydrolysis of a series of diol monoacetates.[29] It was observed that a vicinal hydroxyl function has a small catalytic effect on the alkaline hydrolysis of the neighboring acetate moiety. In part because of a solvent deuterium isotope effect, k_{H_2O}/k_{D_2O} near 0.5, it was suggested that the rate increase reflected "internal solvation of the transition state for the attack of hydroxide at the ester carbonyl."[29] However, the solvent deuterium isotope effect for hydrolysis of the dipeptide 2 is 2.7, suggesting that this explanation will not suffice for the present case. On the whole, it seems most reasonable to assign the facilitation of the cleavage of the thiol ester bond by the neighboring threonine hydroxyl group to one of several possible mechanisms of the general acid–base type, such as the one shown below.



It is not clear why an adjacent threonine does not enhance the reactivity of an *S*-benzoylcysteine as it does for the corresponding *S*-acetyl compound (Table I).

Returning to the data in Table I, it is clear that introduction of a serine residue adjacent to the *S*-acylcysteine moiety also increases the reactivity of the thiol ester toward hydroxide ion. In fact, the rate increase elicited by serine is substantially greater than that observed for threonine. By analogy with the above discussion, one may tentatively conclude that a similar catalytic mechanism is involved in the two cases. The hydroxyl group of serine is, of course, less sterically hindered than that of threonine, which may increase its effectiveness as a general base catalyst.

An alternate mechanism for the acceleration of thiol ester hydrolysis by neighboring alcoholic functions is that proposed by Bernhard and coworkers[30] for the hydrolysis of some aspartyl serine derivatives. This mechanism postulates that the amide nitrogen of the peptide bond is ionized by abstraction of the amino proton by the anion of the alcoholic amino acid. Subsequent to this, the anion of the amide nitrogen attacks an adjacent ester carbonyl carbon, forming an imide. Several observations argue against such catalysis in the present case. First, increasing reactivity for the hydrolysis of neighboring thiol esters by serine and threonine derivatives exhibited small rate increases over that for the *N*-acetyl-*S*-acylcysteinamides, while hydrolysis of the β-benzylaspartylserines of Bernhard exhibited rate increases of 10^7. Secondly, the relatively small rate increases exhibited by the threonine and serine thiol esters are inconsistent with participation of the amide nitrogen in view of the well-known high susceptibility of thiol esters to attack by nitrogen nucleophiles.[22,23]

Isolation of the products of the reaction of imidazole or of hydroxide ion with the dipeptides 2, 6, or 7 was not attempted owing to the small concentrations of sub-

(24) B. M. Anderson, E. H. Cordes, and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961).

(25) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. G. Brandon, *Biochemistry*, **1**, 7 (1962).

(26) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, p 212.

(27) J. S. Harding and L. N. Owen, *J. Chem. Soc.*, 1528 (1954).

(28) J. S. Harding and L. N. Owen, *ibid.*, 1536 (1954).

(29) T. C. Bruice and T. H. Fife, *J. Amer. Chem. Soc.*, **84**, 1973 (1962).

(30) S. A. Bernhard, A. Berger, J. C. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Amer. Chem. Soc.*, **84**, 2421 (1962).

strate used. However, analyses for the products of alkaline hydrolysis were performed and several conclusions were drawn. First, it appears that little or no β elimination occurs in alkaline solution up to approximately pH 10.0. Secondly, the release of thiol as the ester hydrolyzes can, in the case of simple *N*-acetyl-*S*-acylcysteinamides, be quantitatively accounted for by the DTNB method. The picture which emerges for the dipeptides, however, is different; only modest fractions of total thiol released at infinite time can be accounted for by this method. However, the time course for production of thiol, as measured during the hydrolysis of dipeptide **6**, reveals that nearly quantitative amounts of thiol are released during the first 5 half-lives of the reaction, following which the amount of thiol diminishes. It would appear that thiol liberated is converted to some secondary product the nature of which, with the exception that oxidation to sulfenic acid is ruled out (see Experimental Section), is not known.

What are the implications of the modest rate facilitations observed in this study for the understanding of the reactivity of S-acyl-G3PD? First, the reactivity of simple *S*-acylcysteines toward hydroxide ion is about 20-fold greater than would have been expected on the basis of the valus of pK_a for the conjugate acid of the leaving group (Table III). Second, both the flanking serine and threonine residues do lead to appreciable increases in the reactivity of the adjacent thiol ester. Having both serine and threonine present in the same molecule might lead to either addition or multiplication of the catalytic effects, depending on whether the catalytic mechanisms are different or the same. At best, one might anticipate a total increase in reactivity toward hydroxide ion of some 200-fold in the presence of both serine and threonine functions. Combining this rate increase with that observed for the simple *S*-acylcysteines leads to a maximal total factor of perhaps 4000. While such a reactivity increase certainly partially bridges the gap between the reactivity of the acyl enzyme and that of simple thiol esters, it would still fall at least three orders of magnitude short of accounting for all of the difference. Hence the reactivity of the acyl enzyme must depend to a major extent on catalytic mechanisms involving residues not in the primary sequence of amino acids at the active site.

Registry No.—**2**, 36914-96-2; **3**, 16820-83-0; **6**, 36912-46-6; **7**, 36914-97-3; **8**, 36912-47-7.

Acknowledgment.—The expert technical assistance of Mr. Alan Stafford is gratefully acknowledged.

Studies on 3,3-Diaryltricyclo[3.2.1.0^{2,4}]octanes. I. Synthesis and Reactions of *exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-6-ene and Its Derivatives[1]

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Received August 18, 1972

The thermal reaction of diphenyldiazomethane and norbornadiene affords mono and bis adducts. These pyrazolines can be thermally transformed to polycyclic hydrocarbons with stereospecific loss of nitrogen. Comparison is made to similar reactions reported in the literature. The title hydrocarbon so obtained has been characterized by its nmr spectrum, most notably by the singlet resonance of its endo H-2,4 protons. Reactions in this system that have been studied include the reaction of the hydrocarbon with bromine and the solvolysis of the exo- and endo-6 tosylates. Both processes proceed *via* the same rearrangement solely to nortricyclyl derivatives, presumably because the phenyl groups present stabilize overwhelmingly the cation precursor to these derivatives. An exo/endo rate difference of over 4000 in aqueous dioxane implies that anchimeric assistance is well developed in the exo isomer. Possible mechanistic pathways are discussed. Other transformations of the title hydrocarbon to unrearranged dibromides and to its exo epoxide are also mentioned.

Although the unsubstituted tricyclo[3.2.1.0^{2,4}]-ocyl system has had its chemistry explored in a variety of processes,[3] much less is known about the 3,3-disubstituted cases. Two of the interesting results from our early studies on the exo-3,3-diphenyl-substituted system were the solvolytic rearrangements undergone by the *syn*- and *anti*-8-tosylates.[4] To understand more of the chemistry associated with the tricycle, the investigation of the title compound itself, as well as its 6 derivatives, was undertaken.

Discussion

Synthesis and Characterization of *exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-6-ene.—Addition of diphenyldiazomethane to norbornadiene afforded pyrazoline **1** which in turn was converted thermally into the title

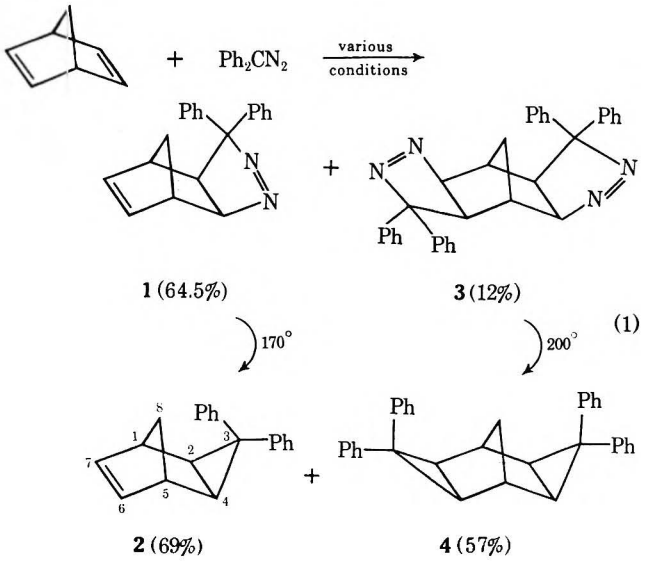
(1) Taken from portions of the dissertation of T. P. M., Loyola University of Chicago, 1970; Abstracts, 5th Great Lakes Regional Meeting of the American Chemical Society, Bradley University, Peoria, Ill., June 1971, Paper 55.

(2) National Science Foundation Trainee, 1969–1970.

(3) Of the many studies extant, the following are of special interest to the present article. (a) Synthesis of exo tricyclic 6-ene: H. E. Simmons, E. P. Blanchard, and R. D. Smith, *J. Amer. Chem. Soc.*, **86**, 1347 (1964). This preparation leads to 18% bicyclo[3.2.1]octadiene as well: T. J. Katz and S. A. Cerefice, *ibid.*, **93**, 1049 (1971). This fact must be considered when one peruses earlier studies in this area. (b) Synthesis of endo tricyclic 6-ene: K. B. Wiberg and W. Bartley, *ibid.*, **82**, 6375 (1960). (c) Solvolysis of arenesulfonates of exo and endo tricyclic 8-alcohols: H. Tanida, T. Tsuji, and T. Irie, *ibid.*, **89**, 1953 (1967); M. A. Battiste, C. L. Deyrup, R. E. Pincock, and J. Haywood-Farmer, *ibid.*, **89**, 1954 (1967); J. S. Haywood-Farmer and R. E. Pincock, *ibid.*, **91**, 3020 (1969). (d) Solvolysis of arenesulfonates of endo and exo tricyclic 6-alcohols: K. B. Wiberg and G. R. Wenzinger, *J. Org. Chem.*, **30**, 2278 (1965). (e) Hydrogenation of endo and exo tricyclic 6-enes: P. K. Freeman and K. B. Desai, *ibid.*, **36**, 1554 (1971). (f) Photochemical isomerization of endo and exo tricyclic 6-enes: H. Prinzbach and W. Eberbach, *Chem. Ber.*, **101**, 4083 (1968). (g) Reduction of endo and exo 6-oxides: B. C. Henshaw, D. W. Rome, and B. L. Johnson, *Tetrahedron*, **27**, 2255 (1971); D. W. Rome and B. L. Johnson, *ibid.*, **27**, 2271 (1971).

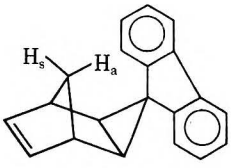
(4) J. W. Wilt and T. P. Malloy, *J. Amer. Chem. Soc.*, **92**, 4747 (1970).

compound 2. Minor amounts of the bis adduct 3[5] and its thermal product 4 were also obtainable in this reaction sequence (eq 1).



(1)

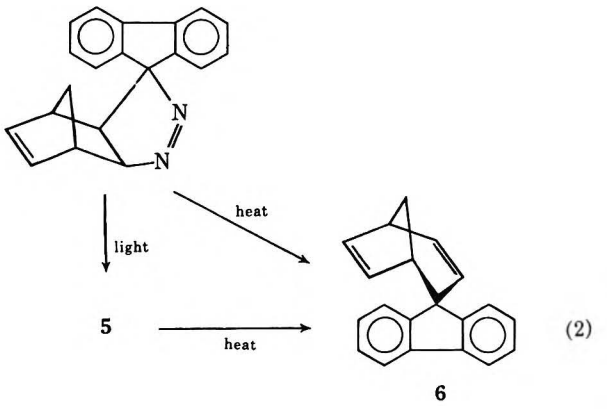
Similar reactions have been reported.[5,6] Most importantly, Filipescu and DeMember[6a] have prepared the fluorenylidene analogs of 1 and 2 and have characterized these compounds spectrally. The nmr spectra of 1 and 2 correspond to those reported for their products with the important exception in 2 that the anti 8-hydrogen (syn to the diphenylcyclopropyl moiety) is shielded (δ 0.63, doublet) relative to its syn 8-hydrogen neighbor (δ 0.93, doublet). In 5, one of Filipescu and DeMember's compounds, this situation is reversed. In 5, the anti 8-H (syn to the



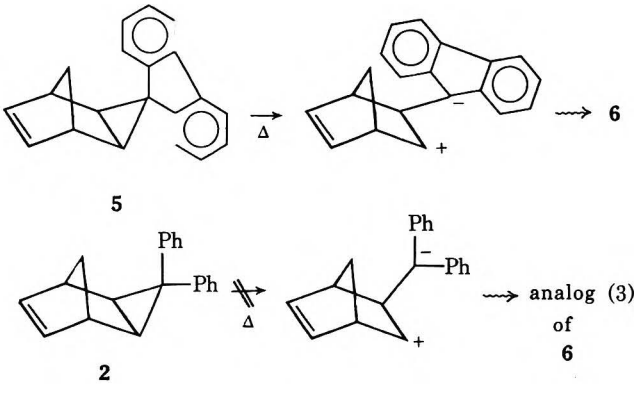
5

fluorenylidene) is reported[6a] at δ 2.58 (doublet) while its syn neighbor is at δ 1.39 (doublet). Clearly this difference results from the different environment of the anti 8-H's in 2 and 5. In the latter, as mentioned by Filipescu and DeMember,[6a] this hydrogen butts the 1′-fluorenylidene hydrogen and lies in the aromatic σ plane, resulting in deshielding In 2, however, framework molecular models indicate that the anti 8-H lies in the π-electron region of the proximate phenyl group, resulting in shielding. The exo nature of the cyclopropyl ring in 2 was apparent from the sharp singlet resonance at δ 1.72 arising from the H-2,H-4 pair of endo hydrogens. An unfavorable geometry precludes coupling of these hydrogens with the bridgeheads 1 and 5. Apparently the long-range "W coupling" anticipated with the syn 8-H is so small that its existence is implicated only by the nonringing nature of this singlet. Exactly the same thing was noted for 5.[6a] The bis,exo nature of 4 was likewise shown by the singlet nature of the resonance due to the endo cyclopropyl hydrogens at δ 1.78.

One of the more interesting differences between the earlier[6a] and present work is the mode of formation of 2 compared to 5. When the pyrazoline precursor to 5 was *photolyzed*, 5 was produced. Upon *thermolysis*, however, the pyrazoline yielded 6, not 5. Indeed, thermolysis of 5 also gave 6 (eq 2), and it seems possible that 5, not 6, forms first under both sets of conditions from the pyrazoline. The spectral data given above show that no such thermal rearrangement of 2 (or its pyrazoline precursor 1) to an analogously rearranged bicyclo[3.2.1]octadiene occurred in this work. We prefer not to comment extensively on this striking difference, largely because we feel the mechanism proposed[6a] for the formation of 6 is untested. If, however, the transformation of 5 is begun as Filipescu and DeMember suggested (eq 3), then



(2)



the difference with 2 may lie in the decreased stability of benzhydryl *vs.* 9-fluorenyl anion. The pK_A of fluorene is 22.8 whereas that of diphenylmethane is 33.1.[7] While the quantitative significance of these acidity values should maybe not be overemphasized,[8] nonetheless, a difference of 11 pK_A units is not minor. Obviously the difference indicates that the purported conversion of 5 *via* heterolysis into a zwitterion could be easier with it than with 2. The isolation of only exo products (2 and 4) from the pyrazoline adducts indicates that these adducts were also exo in configuration. To our knowledge, nitrogen loss from

(5) The bis adduct was reported earlier by R. Fleischmann, Dissertation, University of Munich, 1957. *Cf.* R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963). The stereochemistry of the bis adduct was illustrated as shown above in the text but no proof was offered. On the basis of the nmr evidence we concur in this assignment of a racemic structure rather than the alternative meso structure (see Experimental Section).

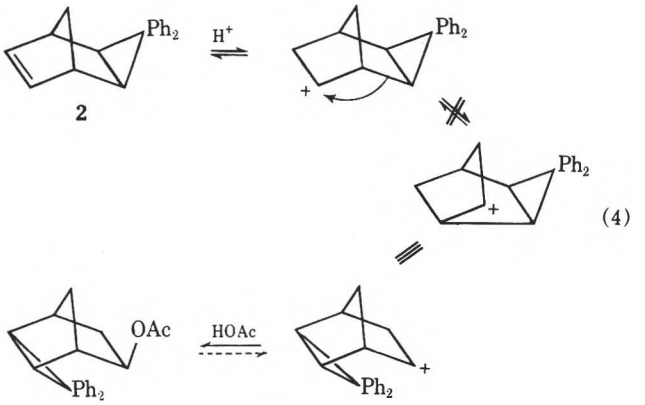
(6) (a) N. Filipescu and J. R. DeMember, *Tetrahedron*, **24**, 5181 (1969); (b) J. R. DeMember and N. Filipescu, *J. Amer. Chem. Soc.*, **90**, 6425 (1968); (c) A. A. Lamola, *ibid.*, **91**, 4786 (1969).

(7) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 27.

(8) Different pK_A values result in different solvent media; see ref 7.

thermolysis of pyrazolines *in such systems* is always stereospecific. Endo pyrazolines[9] yield endo cyclopropanes; exo pyrazolines yield exo cyclopropanes,[6a] though rearrangement may occur here subsequent to cyclopropane formation. On occasion, however, nitrogen loss does not even occur.[10]

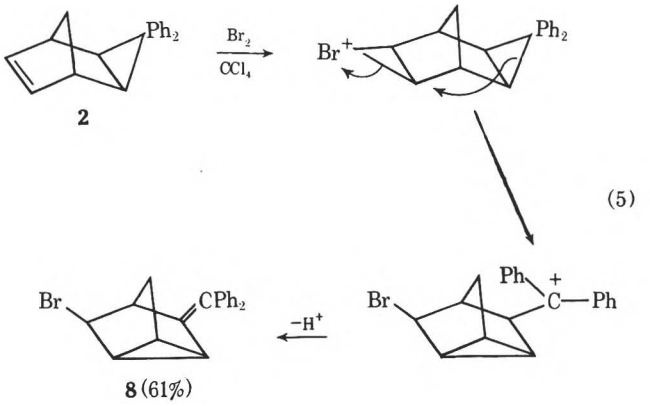
Functionalizations of 2.—Attempts to reverse the orientation of the cyclopropyl moiety in 2 from exo to endo as shown (eq 4) were unrewarding.[13] A complex



(4)

mix of apparently polymeric hydrocarbons was obtained. A possible reason for this disappointing result is that the ions shown in eq 4 (depicted as classical species for convenience) do not interrelate as shown. Rather, conversion into *benzhydryl* cationic species may occur, followed by polymerization. Such a view is supported by solvolysis studies (*vide infra*). The endo series, represented by 7 and other derivatives, is available by another route, however.[9,14]

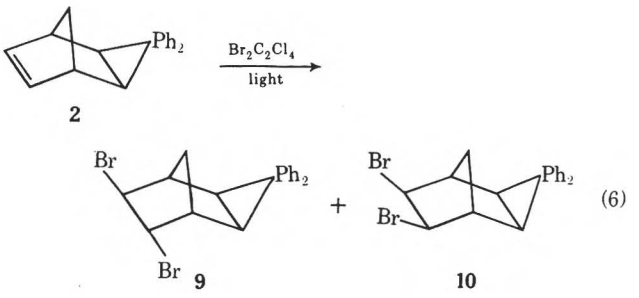
Nonetheless, a clean rearrangement could be manifested with 2. Reaction with bromine led to monobromide 8 as the only isolated product in 61% yield (eq 5). The pathway and structure assigned to 8



(5)

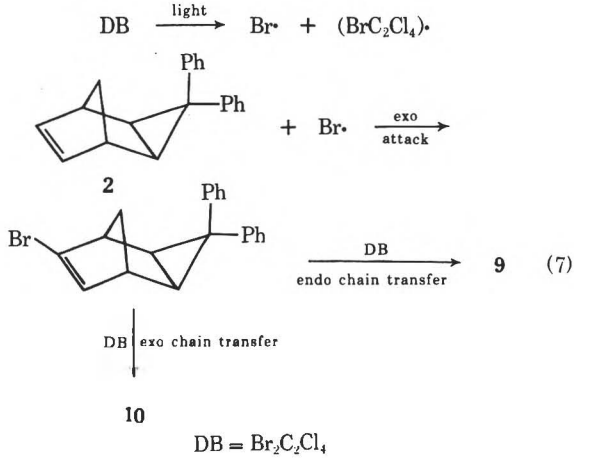
seemed reasonable on several grounds. First, the gross skeletal change shown in eq 5 is the same as that obtained in solvolysis studies (*vide infra*). Second, the loss of the exo cyclopropyl moiety of 2 was clear from the absence of the endo H-2,H-4 singlet resonance in the nmr spectrum of the bromide. And lastly, the presence of a single bromine (from combustion analysis) with its attendant -CHBr- resonance at δ 4.33 and the close similarity of the upfield portion of the nmr spectrum of the product to that of olefin **16** (*vide infra*) also suggested structure **8**. Nonetheless, it should be pointed out that the configuration of the bromine is supposed on the basis of the pathway only. We have no definitive evidence otherwise against the epimeric configuration.

An ionic pathway rather than a radical one in eq 5 was seemingly demanded by the fact that radical addition of bromine to 2 using dibromotetrachloroethane[15] led to *di*bromo adducts with *retained* structure (eq 6). The trans isomer (81%, **9**) possesses



(6)

triplet -CHBr resonances at δ 4.37 and 3.95, ($J \simeq$ 3 Hz) that indicated an endo and exo bromine, respectively. The cis isomer (19%, **10**) possessed a doublet ($J \simeq 2$ Hz) integrating to two hydrogens (both-CHBr's) at δ 4.10. The identity of the two hydrogens and the evidence of "W coupling" to the 8 position clearly showed the two bromines to be exo. Mechanistically, the addition probably followed the path shown (eq 7),



(7)

a path analogous to that reported earlier[15b] for another case.

Solvolysis of the 6-Alcohols.—A major goal in the study of 2 and its derivatives was the solvolysis of the tosylates of the 6-alcohols **11** and **12**. These alcohols

(9) J. W. Wilt and D. R. Sullivan, Abstracts, 6th Great Lakes Regional Meeting of the American Chemical Society, Michigan Technological University, Houghton, Mich., June 1972, p 64. The endo cyclopropanes so produced are easily differentiated from their exo isomers by nmr analysis. The H-2,H-4 pair of exo hydrogens in the endo analogs show triplet resonances downfield from the singlet observed with the exo compounds.

(10) The pyrazoline adducts of norbornene[11] and 5-norbornenone[12] fail to endergo the process.

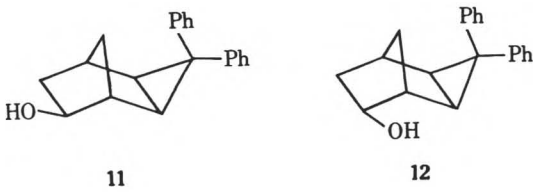
(11) N. S. Zefirov, P. Kadziauskas, and Yu. K. Yuriev, *Zh. Obshch. Khim.*, 6, 23 (1966).

(12) R. S. Bly, F. B. Culp, Jr., and R. K. Bly, *J. Org. Chem.*, **35**, 2235 (1970).

(13) For a discussion of the interrelationship between cations from *exo*-add *endo*-tricyclo[3.2.1.0^{2,4}]octyl systems, see J. A. Berson, R. G. Bergman, L. M. Clarke, and D. Wege, *J. Amer. Chem. Soc.*, **91**, 5601 (1969).

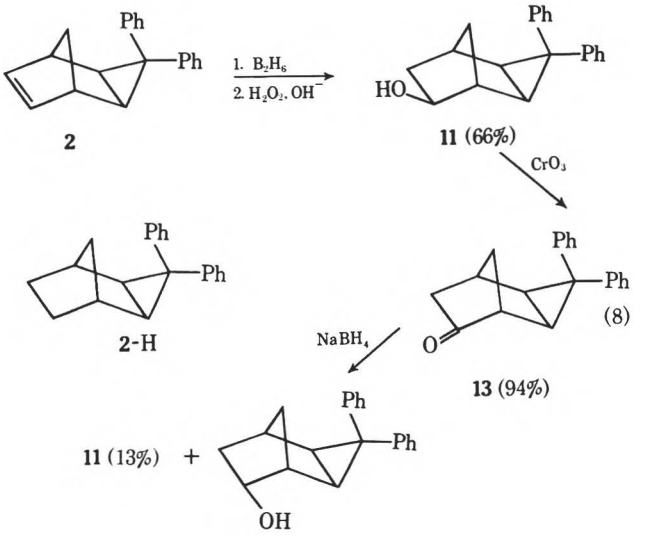
(14) J. W. Wilt and D. R. Sullivan, to be published. The route involved addition of diphenyldiazomethane to 7-*tert*-butoxynorbornadiene, separacon of the endo adducts, conversion into the endo cyclopropanes, and lastly modification or replacement of the functional groups.

(15) (a) E. S. Huyser and D. N. DeMott, *Chem. Ind.* (*London*), 1954 (1963); (b) J. W. Wilt and P. J. Chenier, *J. Org. Chem.*, **35**, 1562 (1970).



11 12

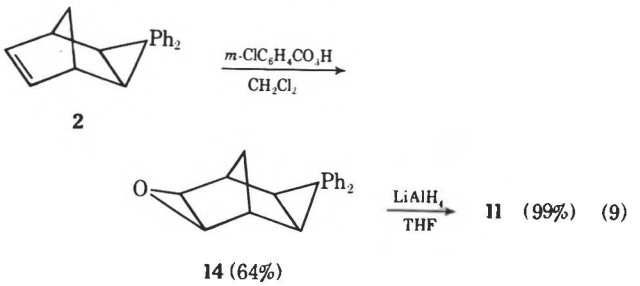
were readily prepared by the sequence outlined (eq 8),



2 11 (66%) 13 (94%) 2-H 11 (13%) + 12 (78%) (8)

a sequence modeled after that used by Wiberg and Wenzinger[3d] for the nonphenyl analogs. The oxidative hydroboration of **2** produced essentially pure exo 6-alcohol **11** (-CHOH δ 3.88), as would be expected. However, some protolysis product **2-H** was also detected in small amount (4%). The absence of vinyl absorption and the sharp singlet at δ 1.52 (endo H-2,-H-4) support the structure assigned, as does its formation under these conditions.[16]

Oxidation of **11** to ketone **13** was accomplished by Sarett's method. Reduction of **13** with sodium borohydride led to a 86:14 mixture of 6-alcohols with **12** predominating (-CHOH- δ 4.25). Exo alcohol **11** also was obtained from epoxidation of **2** to the exo oxirane **14** followed by treatment with lithium aluminum hydride (eq 9). The exo nature of **14** was indicated by the



2 14 (64%) 11 (99%) (9)

sharp singlet resonance of the oxiranyl endo hydrogen pair. No reductive rearrangement of epoxide **14** to isomers of **11**, as has been reported for several other norbornene oxides, was observed.[3g,17] Tosylates of **11** and **12** were then readily prepared in the usual manner.[19]

Solvolysis of the tosylates **11**-OTs and **12**-OTs in 80% aqueous dioxane proceeded *via* first-order kinetics. Theoretical infinity titers were obtained after 10 half-lives. The kinetic and activation parameter data are gathered in Table I.

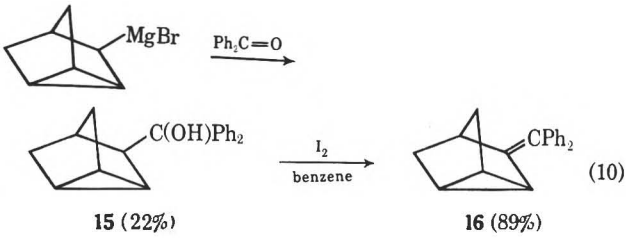
TABLE I

SOLVOLYSIS[a] OF 3,3-DIPHENYLTRICYCLO[3.2.1.0^{2,4}]OCT-6-YL TOSYLATES, 11-OTs AND 12-OTs

Tosylate	Temp,[b] °C	10^5k, sec^{-1} [c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
11-OTs	55.5	3.11 ± 0.05		
	64.0	7.82 ± 0.13		
	76.2	29.2 ± 0.10		
	25.0[d]	6.02 ± 0.90 × 10^{-7} [e]	23.7 ± 1.2	−7.44 ± 2.9
12-OTs	111.0	1.65 ± 0.01		
	121.0	4.41 ± 0.03		
	131.0	12.4 ± 0.20		
	25.0[d]	1.44 ± 0.50 × 10^{-10} [e]	30.2 ± 3.2	−2.47 ± 3.2

[a] In dioxane–H_2O, (80:20 v/v) containing 2,6-lutidine (0.044 *M*). [b] Below 100° the temperatures are ±0.2°; above 100°, ±0.3°. [c] Computer calculated. The error limits are standard deviations. [d] All data at 25° are extrapolated from data at higher temperatures. [e] This value is k, not 10^5k.

Both **11**-OTs and **12**-OTs underwent identical solvolytic rearrangements in quantitative yield to nortricyclyl derivatives, *viz.*, alcohol **15** from **11**-OTs and hydrocarbon **16** from **12**-OTs. The formation of but one product in these cases contrasts markedly with earlier studies on simple cases.[2d,13] The spectra of these products were in accord with the structures assigned. Confirmatory evidence was obtained, nevertheless, by treatment of benzophenone with nortricyclylmagnesium bromide (eq 10). Alcohol **15** so



15 (22%) 16 (89%) (10)

formed was then conveniently dehydrated with iodine in hot benzene to **16**. The samples of **15** and **16** prepared in this way were identified with the solvolysis products. The formation of **15** from **11**-OTs and **1** from **12**-OTs is presumably a consequence of the different temperatures[20] used for the preparative solvolyse (65 *vs.* 134°). Alcohol **15** does *not* dehydrate to **1** under solvolysis conditions; so the precursor to **16** i

(16) In the analog of **2-H** where the phenyl groups are replaced by a fluorenylidene group, the endo hydrogen pair resonate at δ 1.83 and again are a singlet.[6a]

(17) The lack of rearrangement with **14** (99% yield of **11**) is curious Both the endo and exo 6-oxides in the parent (nonphenyl) system rearrange upon reduction with lithium aluminum hydride, as do norbornene *exo*-oxide and benzonorbornadiene *exo*-oxide.[3g] The mechanisms suggested for the rearrangements[3g,18] would seemingly apply to **14** also and its structure fidelity in this reduction appears anomalous.

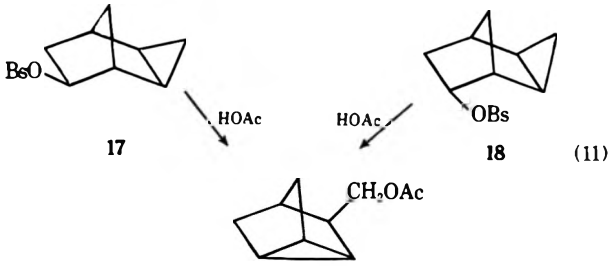
(18) G. D. Sargent M. J. Harrison, and G. Khoury, *J. Amer. Chem. So* **91**, 4937 (1969).

(19) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(20) Higher temperatures are known to maximize elimination/substiute tion ratios. *Cf.* E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 489.

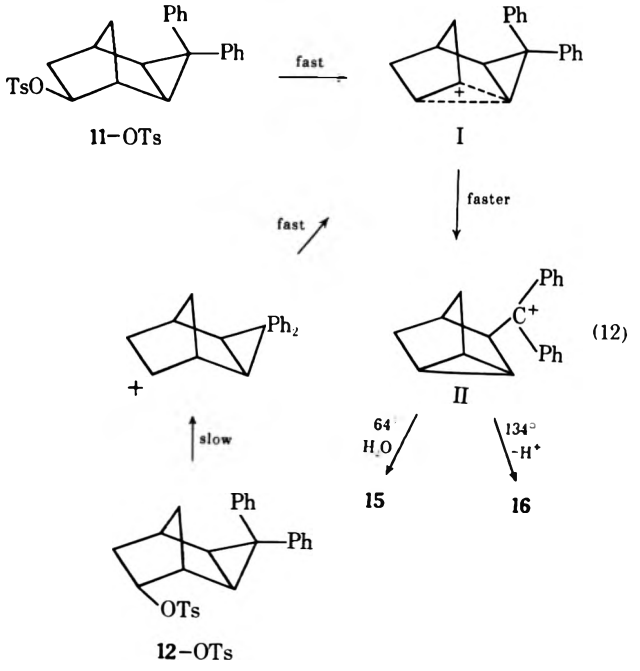
not **15**. Rather, some ion (*vide infra*) is precursor to both of them or the different products result from different mechanisms.

The obvious precedents to the present solvolysis are the earlier studies of principally Wiberg and Wenzinger[3d] and partly Berson, *et al.*,[13] on the parent tricyclo[3.2.1.0^{2,4}]octyl analogs of **11**-OTs and **12**-OTs. These earlier (and complicated) acetolytic studies uncovered much information on this type of system. The interested reader is directed to them. The present study in aqueous dioxane was, however, simpler than these in several respects. Ion-pair return was apparently obviated by the more polar medium, so rather free (essentially dissociated) ions may be invoked, and the complex kinetic schemes needed to rationalize the earlier studies do not seem necessary here. Among the products Wiberg and Wenzinger observed from both **17** and **18** was the nortricyclene **19** (eq 11). Whereas **19** was a minor product in the



(11)

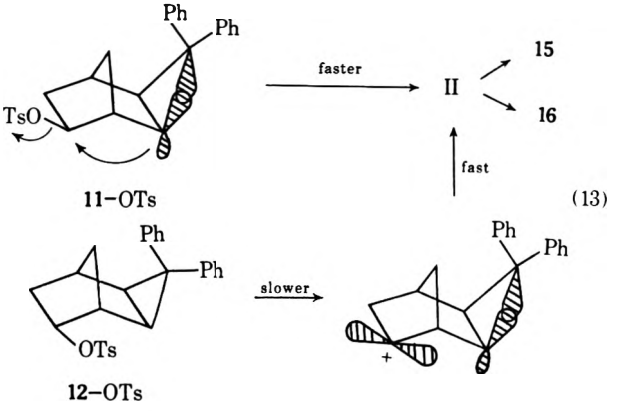
earlier studies (8.6%), in the present case the analogous product (**15** or **16**) was the sole product. If ion I be formed from both **11**-OTs and **12**-OTs (though undoubtedly with different rates), its isomerization to II would be rapid and probably irreversible because II is a benzhydryl cation (eq 12). Such an ionic



(12)

intermediate as well stabilized as is II would then swamp out any other potential product-forming ions. The net result would be to simplify both the kinetics (no internal return to kinetically slower isomers) and the products (one product instead of many).

That **11**-OTs and **12**-OTs do indeed differ in the rate-determining step is apparent from their rate ratio of 4180 at 25° (k_{17}/k_{18} = 1250 at 25° in HOAc[3d]). It is in fact conceivable that ion I is completely bypassed as no products from it were observed. Rather, II might form directly utilizing cyclopropyl participation from **11**-OTs and indirectly from **12**-OTs as shown (eq 13).[21] No clear-cut choice between the schemes given in eq 12 and 13 is made from the present



(13)

work. Other studies in progress in the system will, however, produce further data[22] and, hopefully, allow such a decision.

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block. Boiling points are uncorrected. Infrared spectra (λ) were determined on 1% KBr disks using a Beckman IR-5A instrument. Only prominent or structurally significant absorptions are usually given (in microns).[23] Nuclear magnetic resonance spectra (nmr) were taken in deuteriochloroform on a Varian A-60A spectrometer. Values are given in parts per million (δ) downfield from internal TMS. The usual splitting abbreviations are used. Integration of signals agreed with the structural assignments. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Addition of Diphenyldiazomethane to Norbornadiene.—Diphenyldiazomethane[24] (6.67 g, 34.3 mmol), norbornadiene (freshly distilled material from Frinton Laboratories, S. Vineland, N. J., 9.09 g, 98.6 mmol), and dimethylformamide (5 ml) containing a few milligrams of anhydrous copper sulfate were slowly warmed to 60° until the reaction became self-sustaining. Heating was discontinued as the solution was stirred at 60° for 2 hr (the red solution became light orange). The cooled solution was reduced in volume by rotary evaporation. Acetone (15 ml) was then added and the material was thoroughly chilled. The pale yellow precipitate so formed was collected and recrystallized several times from methanol to give the white monoadduct **1**: yield 6.34 g (64.5%); mp 147.5–149.5 dec; λ 6.47 μ (N=N); nmr δ 7.25–7.67 (m, Ar-H), 6.30 (t, vinyl H's), 5.30 (d, -CHN=N-), 3.61 and 2.23 (broad singlets, bridgehead H's), 2.87 (broad doublet, -CHCPh$_2$-), 1.10 and 0.75 (d, CH$_2$[25]).

Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34. Found: C, 84.15; H, 6.33.

The mother liquor from the acetone solution was concentrated to produce a sticky solid which was recrystallized several times from 95% ethanol. The bis adduct **3** so obtained was a white crystalline solid: yield 1.01 g (12%); mp 227–230° dec; λ 6.42 μ (N=N); nmr δ 7.25–7.52 (m, Ar-H, 5.10 (d, -CHN=N-), 2.92

(21) A similar path has been suggested in the tetracyclo[4.3.0.0^{2,4}.0^{3,7}]-nonane ("deltacyclane") system by P. K. Freeman, D. M. Balls, and J. N. Blazevich, *J. Amer. Chem. Soc.*, **92**, 2051 (1970).

(22) In particular, eq 12 and 13 may be differentiable by a $\rho\sigma^+$ study in that benzhydryl cationic stability should *directly* influence the latter but not the former.

(23) Complete details are available in the dissertation of T. P. M.

(24) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(25) No assignment is made as to which resonance is due to the anti and which to the syn protons.

(broad doublet, -CHCPh$_2$-), 2.47 (broad singlet, bridgehead H's), 0.10 (broad s, CH_2). The doublet J value was *ca.* 7 Hz.

Anal. Calcd for $C_{33}H_{28}N_4$: C, 82.47; H, 5.87. Found: C, 82.69; H, 5.92.

The structure assigned to **3** is supported by the identity of the bridgehead H's. Had the additions of diphenyldiazomethane been identical in orientation, a meso product with a difference in the bridgehead H's should have resulted. The strong upfield shift of the bridge methylene H's is surprisingly dramatic, being even farther upfield than the bridge H's in **4** (*vide infra*). Presumably the shift resulted from powerful shielding caused by the proximate aromatic *and* azo functions.

The addition above was carried out under other conditions as well. Reactions with neat norbornadiene, or in dioxane solvent, some with no copper salt, some at 25° and others at intermediate temperatures all gave **1** and **3**, though monoaddition was clearly favored by use of neat norbornadiene. Dioxane, curiously, has been found to be deleterious in other reactions of this type.[26] Higher temperatures disfavored a clean reaction. The described procedure was the most economical in time and chemicals, however.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-6-ene (2).**—Adduct **1** (2.28 g, 7.95 mmol) was heated as a neat melt in a wax bath at 170° for 30 min. Nitrogen (92%) was evolved. The cooled product was chromatographed on alumina (70 g). Elution with hexane gave white crystalline **2** which was then recrystallized several times from methanol: yield 1.42 g (68.6%); mp 82–83.5°; λ 3.33–3.36, 6.25, 6.66, 6.90, 7.92, 9.34, 9.96, 10.99, 11.44, 12.00, 13.01, 13.36, 13.96–14.36, 14.86, 15.82 μ; nmr δ 7.03–7.50 (m, Ar–H), 6.57 (t, vinyl H's $J \simeq 2$ Hz), 3.07 (m, bridgehead H's), 1.72 (sharp s, endo H-2,4), 0.93 (d, syn 8-H), 0.63 (d, anti 8-H, $J_{syn,anti} \sim 10$ Hz); λ_{max}^{EtOH} 227 nm (ε 18,000), 262, 267, 273.

Anal. Calcd for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 92.97; H, 7.05.

***exo,exo*-3,3,7,7-Tetraphenyltetracyclo[3.3.1.0^{2,4}.0^{6,8}]nonane (4).**—As described for **1**, adduct **3** (1.50 g, 3.54 mmol) was heated at 200° for 30 min. Isolation was *via* chromatography on alumina (25 g) by elution with carbon tetrachloride. White crystalline **4** was then purified by several recrystallizations from methanol: yield 1.02 g (57%); mp 205–207°; λ (quite featureless) 3.32, 3.42, 6.27, 6.71, 6.92, 13.10, 13.41, 14.25–14.41, 15.52 μ; nmr δ 6.70–7.28 (m, Ar–H), 2.85 (m, bridgehead H's), 1.78 (sharp s, endo H-2,4,6,8), 0.18 (m, CH_2).

Anal. Calcd for $C_{33}H_{28}$: C, 93.35; H, 6.65. Found: C, 93.09; H, 6.77.

Attempted Exo to Endo Isomerization of 2.—Reaction of **2** (2.94 g, 11.4 mmol) with glacial acetic acid (7.3 g) and sulfuric acid (50%, 0.4 g) on a steam bath for 4 hr resulted in a black solution. The cooled solution was neutralized with potassium hydroxide and extracted with ether. The ether extracts yielded a black tar. Saponification of the tar afforded a red sludge which was chromatographed on alumina (150 g). Various products eluted. The first fraction, eluted with carbon tetrachloride, was colorless, weighed 0.2 g and melted at 100–110°. Various characterizations indicated it to be a hydrocarbon, but no definite structure seemed assignable to it. Further elution with a variety of solvents gave colored materials of higher and higher mp, up to 210°. Presumably these substances were polymeric in nature, but no further studies were performed.

***exo*-5-Bromo-3-benzhydrylidenenortricyclene (8).**[27]—To hydrocarbon **2** (2.58 g, 10 mmol) in carbon tetrachloride (10 ml) at 0° was added bromine (1.76 g, 11 mmol) in carbon tetrachloride (15 ml) dropwise over a 1-hr period. The solution was then stirred at 25° for 1 hr as hydrogen bromide evolved. The material was then evaporated to yield a yellow oil. Trituration of this oil with 95% ethanol afforded a flocculent white solid which was purified by several recrystallizations from methanol: yield 2.05 g (61%); mp 107.5–108.5°; λ (strong absorptions only) 6.92, 8.30, 12.06, 12.34, 12.96, 13.20, 13.46, 14.18 μ; nmr δ 7.20–7.67 (m Ar–H), 4.33 (broad s, -CHBr), 2.88 (broad s, H-4 bridgehead), 2.53–1.70 (complex m, H-1,2,6 and CH_2).

Anal. Calcd for $C_{20}H_{17}Br$: C, 71.23; H, 5.08. Found: C, 71.22; H, 5.14.

The appearance of the complex multiplet mentioned (δ 2.53–1.70) resembled that observed in olefin **16** (*vide infra*).

***trans*- and *exo,cis*-6,7-Dibromo-*exo*-3,3-diphenyltricyclo[3.2.1.0^{2,4}]octanes (9 and 10, Respectively).**—A solution of hydrocarbon **2** (1.30 g, 5 mmol) and 1,2-dibromotetrachloroethane[28] (1.63 g, 5 mmol) in carbon tetrachloride (20 ml) was irradiated with a 275-W sun lamp under a reflux condenser. The deep yellow solution turned red. After 1 hr the solvent and tetrachloroethylene produced in the reaction were evaporated. The red oily residue, which later solidified, amounted to 1.5 g (71% yield). No combustion analysis was attempted. Analysis by nmr spectroscopy indicated the trans dibromide **9** comprised 81% of the crude product: nmr 7.00–7.50 (m, Ar–H), 4.37 (t, exo H-6), 3.95 (t, endo H-7), 2.77 (m, bridgehead H's), 1.77–0.62 (complex m, endo H-2,4 and CH_2). Also present (19%) was the exo,cis-dibromide **10**: nmr δ 7.00–7.50 (m, Ar–H), 4.10 (d, endo H-6,7), 3.05 (broad s, bridgehead H's), 1.77–0.62 (complex m, endo H-2,4 and CH_2). The coupling constants observed for **9** follow (J in Hz): exo-6,endo-7 = endo-7,anti-8 ("W" coupling) = exo-6,bridgehead = 3 Hz. That for **10** was endo-6,7,anti-8 ("W" coupling) = 2 Hz.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]octan-*exo*-6-ol (11).**—Reaction of diborane with hydrocarbon **2** (25.8 g, 0.10 mol) was achieved as described for the parent case.[3d] The product obtained upon removal of the solvent was chromatographed on silica gel (400 g). Elution with 1:4 hexane–benzene yielded *exo*-3,3-diphenyltricyclo[3.2.1.0^{2,4}]octane (**2**-H): wt 1.10 g (4.2%); mp 79.5–81.5° (after recrystallization from methanol); λ (strong absorptions only) 3.41, 6.71, 6.91, 11.06, 11.36, 12.86, 13.14, 13.31, 14.16, 14.36 μ; nmr δ 7.56–7.20 (m, Ar–H), 2.57 (broad s, bridgehead H's), 1.52 (s, endo H-2,4), 1.42 (broad s, 6,7-CH_2's), 0.62 (distorted d, 8-H anti to phenyls), 0.52 (distorted d, 8-H syn to phenyls).

Anal. Calcd for $C_{20}H_{20}$: C, 92.26; H, 7.74. Found: C, 91.99; H, 7.74.

Further elution using 1:1 ether–chloroform produced alcohol **11** as a sticky solid that afforded white crystals upon recrystallization from hexane: yield 18.3 g (66.3%); mp 133.5–135°; λ 3.05, 9.50 μ (C–OH); nmr δ 7.58–7.00 (m, Ar–H), 3.88 (broad d, endo H-6), 2.50 (m, bridgehead H's), 2.27 (s, OH), 2.13–1.00 (complex m, 7-CH_2, endo H-2,4), 0.87 (d, 8-H anti to phenyls), 0.47 (d, 8-H syn to phenyls, $J_{syn,anti} \simeq 11.5$ Hz). No evidence for the endo isomer **12** was found.

Anal. Calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 87.32; H, 7.41.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-*exo*-6-yl Tosylate (11-OTs).**—Alcohol **11** was treated with *p*-toluenesulfonyl chloride in pyridine in the customary fashion[19] to produce **11**-OTs: 99% yield; mp 120–123° dec upon several recrystallizations from benzene and petroleum ether (bp 30–60°).

Anal. Calcd for $C_{27}H_{26}O_3S$: C, 75.32; H, 6.09. Found: C, 75.14; H, 6.25.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]octan-6-one (13).**—Oxidation of alcohol **11** (10.0 g, 36.2 mmol) with chromium trioxide in pyridine[29] was performed as described for the parent case.[3d] Ketone **13** was recrystallized from hexane. The white crystalline solid weighed 9.32 g (94%); mp 117.5–119.5°; λ 5.74 μ (C=O); nmr δ 7.62–7.17 (m, Ar–H), 2.88 (m, bridgehead H's), 2.12 (m, 7-CH_2), 1.78 (q, $J \simeq 7$ Hz, AX pattern of endo H-2,4), 0.85 (broad s, 8-CH_2).

Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.37; H, 6.67.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]octan-*endo*-6-ol (12).**—To ketone **13** (4.0 g, 14.6 mmol) dissolved in absolute ethanol (50 ml) was added at 25° sodium borohydride (1.1 g, 29 mmol) in small quantities over a 15-min period. The reaction was completed on a hot plate for 2 hr. The mixture was then cooled and diluted with water. The flocculent precipitate was collected and dried, wt 3.67 g (91%). Analysis by nmr spectroscopy indicated the presence of 14% alcohol **11** and 86% alcohol **12**. The latter was obtained pure upon four recrystallizations from hexane as a white solid: mp 152.5–153.5°; λ 3.07, 9.50 μ (C–OH); nmr δ 7.57–6.95 (m, Ar–H), 4.25 (doublet of triplets, exo H-6, $J_{exo\text{-}6,exo\text{-}7} = 9.5$ Hz, $J_{exo\text{-}6,\ H\text{-}5} = J_{exo\text{-}6,endo\text{-}7} = 3.5$ Hz), 2.53 (m, bridgehead H's), 2.28 (s, OH), 2.13–1.53 (complex array, endo H-2,4,

(26) J. W. Wilt and P. K. Mookerjee, to be published.

(27) The prefix exo is arbitrary here. Structure **8** has the bromine exo in the sense that it is on the same side as the original methano bridge of **2**. The bromine is actually endo to the newly created methano bridge bearing the benzhydrylidene moiety.

(28) The material results from reaction of tetrachloroethylene and bromine (275-W sun lamp, white solid, dec. ~100°).

(29) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1963).

exo H-7), 0.93 (broad doublet with further splitting, endo H-7), 0.45 (narrow m, 8-CH_2). The AB H-7 pair possessed a $J \simeq 12$ Hz.

Anal. Calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 87.20; H, 7.42.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-*endo*-6-yl Tosylate (12-OTs).**—Alcohol 12 yielded tosylate 12-OTs upon treatment with *p*-toluenesulfonyl chloride in the usual way.[19] Upon recrystallization from absolute ethanol the product was a white solid, 68% yield, mp 155–157°.

Anal. Calcd for $C_{27}H_{26}O_3S$: C, 75.32; H, 6.09. Found: C, 75.54; H, 6.18.

***exo*-3,3-Diphenyltricyclo[3.2.1.0^{2,4}]oct-6-ene *exo*-Oxide (14).**—*m*-Chloroperbenzoic acid (85% material, 2.23 g, 11 mmol of peracid) in methylene chloride (21 ml) was added dropwise over a 15-min period to a solution of hydrocarbon 2 (2.58 g, 10 mmol) in methylene chloride (10 ml). The temperature was maintained below 25° during the addition and at 25° for 1.5 hr afterward. The excess peracid was destroyed with 10% sodium bisulfite solution (10 ml). The solution was then extracted with aqueous potassium bicarbonate, aqueous sodium hydroxide, and then water alone. The methylene chloride solution was dried ($MgSO_4$) and evaporated. The residual oxide 14 so obtained was recrystallized from methanol: yield 1.76 g (64%); mp 150–152°; λ (prominent absorptions only) 3.35, 6.70, 9.96, 11.80, 12.05, 13.30, 14.20–14.35 μ; nmr δ 7.55–7.07 (m, Ar–H), 3.35 (s, endo H-6,7), 2.76 (broad s, bridgehead H's), 1.67 (s, endo H-2,4), 0.77 (d, 8-H anti to phenyls), 0.33 (d, 8-H syn to phenyls, $J_{anti,syn}$ = 12 Hz).

Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.82; H, 6.72.

Reduction of Oxide 14 with Lithium Aluminum Hydride.—Oxide 14 (1.62 g, 5.9 mmol) was reduced with lithium aluminum hydride (0.24 g, 5.9 mmol) in tetrahydrofuran solvent (25 ml) at 25° for 3 days. After processing, the reaction yielded only alcohol 11, wt 1.62 g (99%), mp, mmp, and spectra identical with those given above (*vide supra*). The tosylates were also identical.

(3-Nortricyclyl)diphenylcarbinol (15).—3-Nortricyclylmagnesium bromide was prepared under nitrogen from the bromide (Frinton Laboratories, S. Vineland, N. J., 5.0 g, 28.9 mmol) and magnesium (0.72 g, 30 g-atoms) in anhydrous ether (15 ml). The reaction was initiated with some methyl iodide. Benzophenone (4.55 g, 50 mmol) in ether (15 ml) was then added, and the deep red solution was stirred for 30 min. Saturated ammonium chloride solution (10 ml) was added next, and the yellow organic layer that resulted was separated, washed, and dried ($MgSO_4$). Upon removal of the ether a yellow oil was obtained. Chromatography on alumina (500 g) separated this oil into benzophenone (with hexane elution), 1.24 g (24% recovery); alcohol 15 (with 1:4 benzene–CCl_4), crude weight 1.50 g (22%), mp 50–60°; unidentified oils (with chloroform), 1.3 g; and benzopinacol (with chloroform), 2.55 g (28%). The last product presumably resulted from bimolecular reduction of benzophenone with unreacted magnesium in the Grignard solution. Alcohol 15 was purified by recrystallization from pentane at −78° and from aqueous methanol: mp 75–77°; λ 2.86, 8.42–8.45 μ (*t*-C–OH); nmr δ 8.03–7.35 (m, Ar–H), 2.73 (s, OH), 2.40 (s, bridgehead H-4), 2.22 (d, exo H-5 $J_{exo\text{-}5,endo\text{-}5}$ = 12 Hz), 1.53 (broad s, bridgehead H-1), 1.35–0.87 (complex m, all remaining H's).

Anal. Calcd for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.62; H, 7.26.

3-Benzhydrylidenenortricyclene (16).—A mixture of alcohol 15 (0.60 g, 2.19 mmol), one small crystal of iodine, and benzene (50 ml) were refluxed under a water separator overnight. The solution was then washed with 10% aqueous sodium thiosulfate and water. The benzene solution was dried ($MgSO_4$) and evaporated. The brown viscous residue was then chromatographed on alumina (50 g). Elution with hexane produced olefin 16 as a white solid: yield 0.52 g (89%); mp 66.5–68° (after recrystallization from methanol containing a little water); λ (prominent absorptions only) 6.02, 6.92, 11.20, 12.07, 12.42, 12.67, 12.97, 13.97, 14.32 μ; nmr δ 7.12 (narrow m, Ar–H), 2.53 (broad s, bridgehead H-4), 1.82–1.30 (complex m, all remaining H's).

Anal. Calcd for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 93.01; H, 7.06.

The olefin could also be prepared by dehydration of alcohol 15 with 20% sulfuric acid–80% acetic acid,[30] but the yield was only 28%.

Solvolysis of Tosylates.—Dioxane was purified by a published procedure.[31] A solvent mixture of purified dioxane and water (80:20 v/v) containing freshly distilled 2,6-lutidine (0.044 *M*) was used in the solvolyses. Freshly recrystallized tosylates 11-OTs and 12-OTs were weighed into the solvent separately, each concentration being 0.03 *M*. Ampoules containing this solution were sealed under nitrogen, thermostated at given temperatures (see Table I) and periodically removed. The rate of the solvolysis was followed by titration of the unchanged lutidine with standardized hydrochloric acid to a bromphenol blue end point. The rate constants were obtained from the first-order rate expression with the aid of a least-squares computer program written in WAT IV language.[32] Activation parameters were calculated from the Eyring equation.

Preparative solvolyses were carried out analogously. Tosylate 11-OTs (0.65 g, 1.51 mmol) in the solvent (50 ml) was heated at 65° for 24 hr in a pressure bottle under nitrogen. Evaporation of the solvent left an oil which was washed with water and taken up in hexane. The hexane solution was extracted thoroughly with 10% hydrochloric acid and water, dried ($MgSO_4$), and evaporated. The residual oil solidified slowly (2 months) to a solid, wt 0.41 g (99%), with spectra identical with those of alcohol 15. One recrystallization from aqueous methanol gave white crystalline material, mp and mmp with authentic 15 74.5–77°. Tosylate 12-OTs (0.45 g, 1.04 mmol) in the solvent (45 ml) was heated at 134° for 17.5 hr in a pressure bottle under nitrogen. The processing described above gave a sticky solid, wt 0.29 g (100%), with spectra identical with those of 16. Chromatographic purification on alumina with hexane eluent gave the product as a white solid, mp and mmp with authentic 16 66–68°.

Registry No.—1, 35497-23-5; 2, 35495-68-2; 3, 35497-25-7; 4, 35497-27-9; 8, 36976-50-8; 9, 36976-51-9; 10, 36976-52-0; 11, 36994-54-4; 11-OTs, 36976-53-1; 12, 36976-54-2; 12-OTs, 36976-55-3; 13, 36994-55-5; 14, 36976-56-4; 15, 36976-57-5; 16, 36976-58-6.

(30) E. W. Garbisch, *J. Org. Chem.*, **26**, 4165 (1961).

(31) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 285.

(32) We thank Professors A. K. Jameson and J. F. Reed of this department for their assistance in this regard.

1,3-Dipolar Cycloaddition Reactions of the Azomethine Ylide Derived from the 1,3-Diazabicyclo[3.1.0]hex-3-ene System[1]

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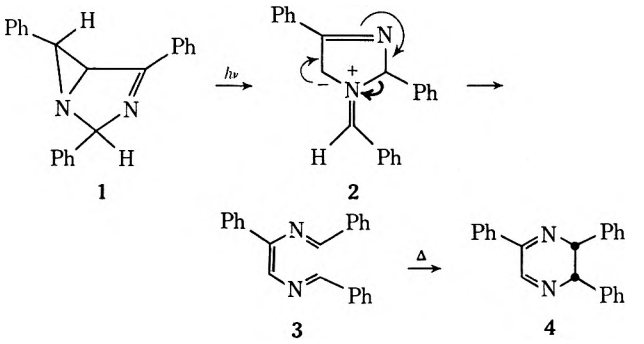
endo-2,4,6-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene reacts stereospecifically with dimethyl maleate and dimethyl fumarate in refluxing xylene or on irradiation to give Δ^2-pyrrolines as cycloadducts. The base-catalyzed epimerization of the various adducts supports the stereochemical structure assignments. A likely mechanism for these additions is the conversion of the diazabicyclo system into an azomethine ylide, which subsequently reacts with the unsaturated substrate. The photochemical results imply that the opening of the aziridine ring proceeds by a conrotatory motion in contrast to the disrotatory motion predicted from orbital symmetry considerations. Three possible explanations to account for these results are presented.

Cyclopropyl anions are predicted by Woodward and Hoffmann to open thermally to allyl anions by a conrotatory course.[3] To date, no clear-cut example of this electrocyclic process is known.[4] However, Huisgen and coworkers have recently established that the thermal ring cleavage of the isoelectronic aziridine system proceeds by conrotatory motion.[5] The azomethine ylide formed can undergo subsequent 1,3-dipolar cycloaddition with homo and hetero multiple bonds to give a variety of heterocyclic rings.[6-10] It has also been found that irradiation of aziridines[11-14] and oxiranes[15-17] frequently yields products derived from related 1,3-dipole intermediates. These reactions may be envisioned as electrocyclic processes proceeding by disrotatory ring opening.

As part of a broad program on the photochemical transformation of small ring heterocycles,[18] we recently described some characteristics of the 1,3-diazabicyclo-[3.1.0]hex-3-ene system.[19] The photoconversion of 2,4,6-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (**1**) into *cis*-2,3-dihydro-2,3,5-triphenylpyrazine (**4**) was formulated as proceeding *via* enediimine **3**, which thermally cyclized to *cis*-dihydropyrazine **4**.



1 2 3 4

The ring opening was suggested to proceed *via* the azomethine ylide **2**, formed by cleavage of the aziridine C–C bond.[20] One of the interesting features observed with this system is that azomethine ylide **2** could be trapped by 1,3-dipolar cycloaddition with an added dipolarophile prior to the formation of enediimine **3**.[14,21] Irradiation of a sample of **1** in an ethanol glass at liquid nitrogen temperature produced a bright red color which could be attributed to azomethine ylide **2**. Photolysis of **1** and dimethyl acetylenedicarboxylate at 77°K still gave the red color, but on warming it was rapidly discharged to give a single cycloadduct.[21] The structure of the adduct was assigned as (3*R**,7*R**,7a*S**)-dimethyl-7,7a-dihydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**6**). The stereochemical assignment rests on the magnitude of the coupling constants and their relationship to appropriate model systems[6,7,10,14] and was further supported by the facile oxidation of **6** with palladium on charcoal to **7**. The related *trans*-Δ^2-pyrroline system is known to be markedly resistant to further oxidation.[7]

The formation of cycloadduct **6** presumably proceeds by way of a transient Δ^3-pyrroline intermediate **5**, which undergoes a subsequent 1,3-suprafacial hydrogen shift.[22] It is particularly interesting to note that cycloadduct **6** is not the product expected on the basis of orbital symmetry considerations. Thermolysis of a solution of **1** and dimethyl acetylenedicarboxylate also resulted

(1) Photochemical Transformations of Small Ring Heterocyclic Compounds. XLV. For part XLIV, see A. Padwa, D. Dean, and J. Smolanoff, *Tetrahedron Lett.*, 4087 (1972).

(2) Alfred P. Sloan Foundation Fellow, 1968–1972; National Institute of Health Special Postdoctoral Fellow, 1972–1973.

(3) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(4) For some attempts see R. Huisgen and P. Eberhard, *J. Amer. Chem. Soc.*, **94**, 1348 (1972).

(5) R. Huisgen, W. Scheer, and H. Huber, *ibid.*, **89**, 1753 (1967).

(6) H. W. Heine and R. Peavy, *Tetrahedron Lett.*, 3123 (1965); *J. Org. Chem.*, **31**, 3924 (1966); W. H. Heine and R. Henzel, *ibid.*, **34**, 171 (1969).

(7) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); *J. Heterocycl. Chem.*, **4**, 118 (1967); A. Padwa and W. Eisenhardt, *Chem. Commun.*, 380 (1968).

(8) R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966); R. Huisgen W. Scheer, and H. Mader, *Angew. Chem., Int. Ed. Engl.*, **8**, 602 (1969); **2**, 633, 644 (1963); R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, **100**, 1802 (1967); J. H. Hall and R. Huisgen, *Chem. Commun.*, 1187, 1188 (1971).

(9) J. W. Lown, G. Dallas, and T. W. Maloney, *Can. J. Chem.*, **47**, 3557, 4335 (1969); *Chem. Commun.*, 1543 (1968); 247 (1971); J. W. Lown, *Rec. Chem. Progr.*, **32**, 51 (1971).

(10) P. B. Woller and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 579 (1968); *J. Org. Chem.*, **35**, 888 (1970).

(11) J. W. Lown and K. Matsumoto, *ibid.*, **36**, 1405 (1971).

(12) R. Huisgen and H. Mader, *Angew. Chem., Int. Ed. Engl.*, **8**, 604 (1969).

(13) S. Oida and E. Ohki, *Chem. Pharm. Bull.*, **16**, 764 (1968).

(14) T. DoMinh and A. M. Trozzolo, *J. Amer. Chem. Soc.*, **92**, 6997 (1970); **94**, 4046 (1972).

(15) T. DoMinh, A. M. Trozzolo, and G. W. Griffin, *ibid.*, **92**, 1402 (1970).

(16) D. Arnold and L. A. Karnischky, *ibid.*, **92**, 1404 (1970).

(17) H. Hamberger and R. Huisgen, *Chem. Commun.*, 1190 (1971); A. Dahmen, H. Hamberger, R. Huisgen, and V. Markowski, *ibid.*, 1192 (1971).

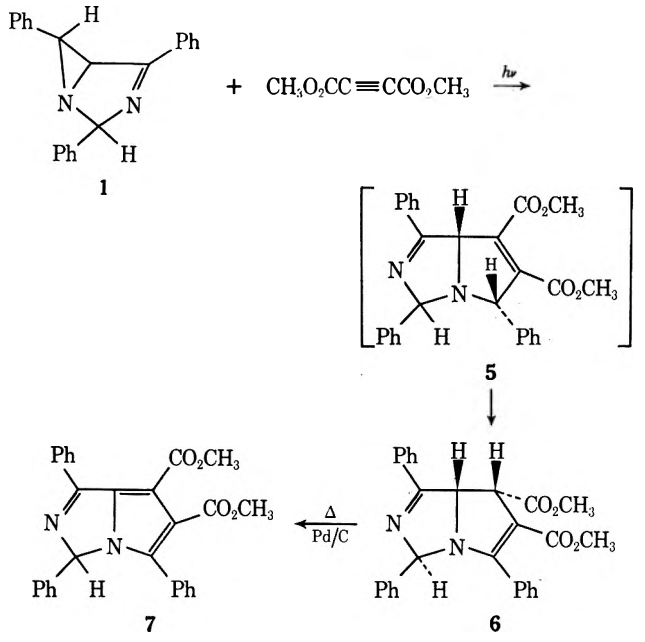
(18) For a review see A. Padwa, *Accounts Chem. Res.* **4**, 48 (1971).

(19) A. Padwa, S. Clough, and E. Glazer, *J. Amer. Chem. Soc.*, **92**, 1778 (1970); A. Padwa and E. Glazer, *Chem. Commun.*, 838 (1971).

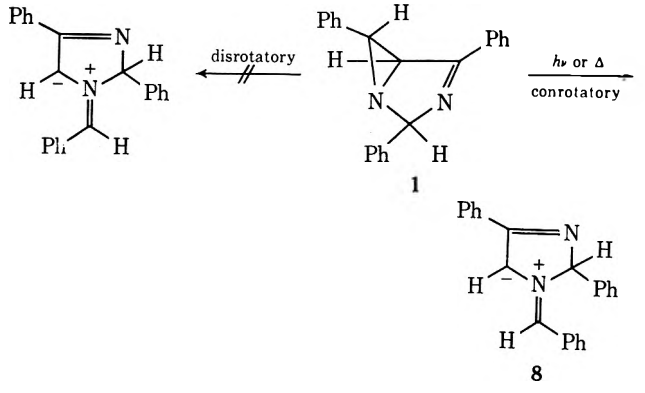
(20) For a review on C–C bond cleavage of the aziridine ring, see H. Heine in "Mechanism of Molecular Migrations," Vol. III, B. S. Thyagarajan, Ed., Interscience New York N. Y., 1971, p 145.

(21) A. Padwa and E. Glazer, *J. Amer. Chem. Soc.*, **94**, 7788 (1972).

(22) Similar results have been reported by Trozzolo and DoMinh with the related 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]-hex-3-ene system.[14] As was pointed out by these authors, the conversion of **5** to **6** may be a photoinduced process.



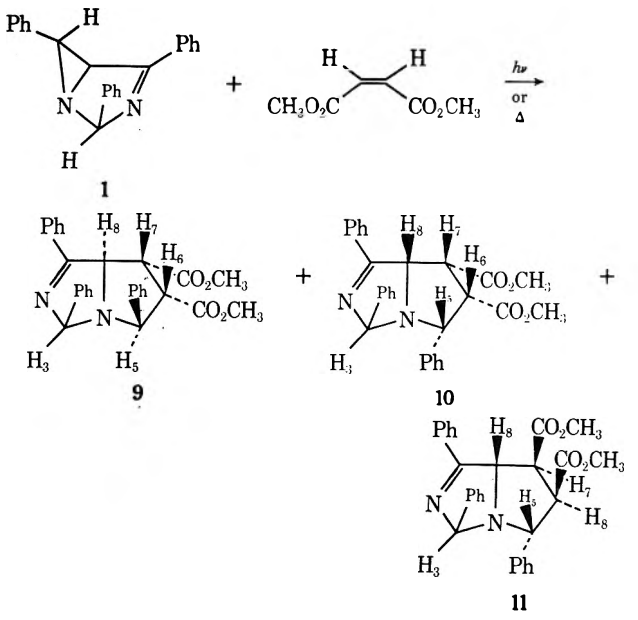
in the formation of the same product. From the structure of the cycloadduct **6**, it seems reasonable to assign the cis structure **8** to the azomethine ylide obtained



from both the thermolysis and photolysis of **1**.[23] Consequently, the photoinduced ring opening of **1** appears to proceed *via* a conrotatory opening, which is in direct contrast with the results described by Huisgen and coworkers.[5] In this paper we describe some additional experiments which confirm the photochemically disallowed valence tautomerization of **1** to **8** and offer a possible rationalization for its behavior.

Irradiation of a nitrogen-purged solution of *endo*-2,4,6-triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene and dimethyl maleate in benzene for 3.5 hr afforded a mixture of three cycloadducts, **9** (mp 221–222°, 9%), **10** (mp 172–173°, 9%), and **11** (mp 158–159°, 51%). Dimethyl maleate was also found to react with diazabicyclohexene **1** in refluxing xylene to produce the same three cycloadducts in the same relative yields.

The thermally induced ring opening of **1** to *cis*-azomethine ylide **8** can be assumed to occur according to the selection rules.[5] Huisgen and coworkers have convincingly demonstrated that the stereochemistry about the olefinic dipolarophile is always retained in

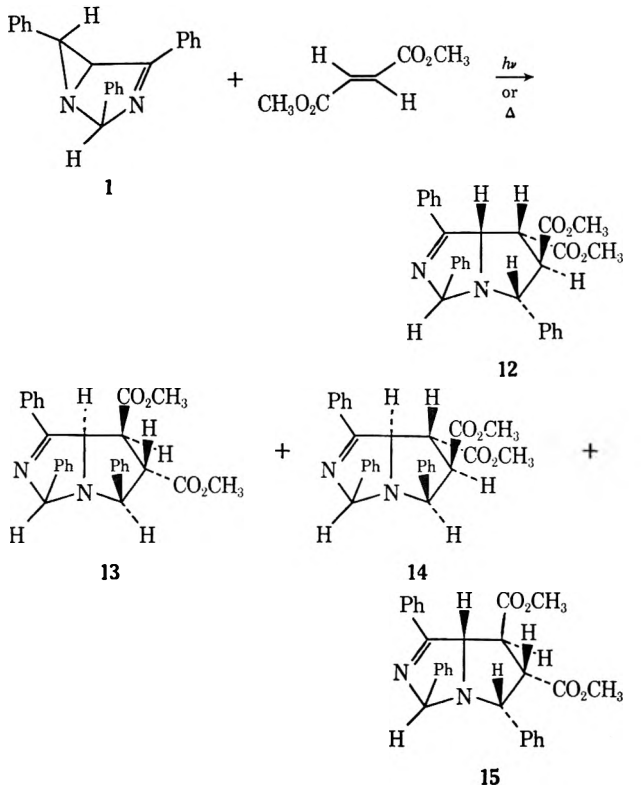


1,3-dipolar cycloadditions.[24] The three cycloadducts obtained can be attributed to the two possible orientation complexes for concerted cycloaddition of the azomethine ylide **8** to the dipolarophile. The assignment of configuration for adducts **9**–**11** rests on their characteristic nmr spectra (see Experimental Section). The most useful criterion for assigning configurations is that the ester methyl signal moves to higher fields when it is adjacent to a *cis*-phenyl ring. The appearance of a carbomethoxy signal at τ 6.82 in adduct **10** is consistent with this principle. Protons H_5 and H_8 in the various maleate adducts are cis to each other by virtue of the concerted cycloaddition. Assuming retention of dipolarophile stereochemistry, it follows that protons H_6 and H_7 must also be in a cis configuration. This reasoning suggests that all the protons are cis to one another in adduct **10**. The location of a carbomethoxy group at τ 6.76 in adduct **11** is also consistent with the stereochemical assignment. The configuration at C_5 in adducts **10** and **11** was shown to be the same but opposite to that of adduct **9**. This was demonstrated by some base-catalyzed epimerization experiments which will be discussed at a later point. The remaining adduct is assigned as pyrrolidine **9**. The splitting patterns observed with adducts **9**–**11** are in accord with first-order coupling patterns. The conformational mobility of the pyrrolidine ring however, deprives the coupling constants of their diagnostic value; trans couplings can reach larger values than are found for cis vicinal ring protons. For example, the trans coupling constant in adducts **9** and **11** for protons H_7 and H_8 has a value of 3.0 and 6.5 Hz, while the trans coupling constant for protons H_5 and H_6 is 10.0 Hz. The cis coupling constants ($J_{5,6}$ and $J_{7,8}$) for adduct **10** were found to be 6.0 Hz. A similar lack of consistency in the magnitude of the couplings was also found with the corresponding fumarate adducts (see below). These contradictions were not totally unexpected. The difficulties encountered in making assignments in the pyrrolidine ring based on the magnitude of the coupling constants was pointed out earlier by Huisgen and coworkers.[8]

(23) We have examined the photocycloaddition of dimethyl acetylenedicarboxylate with both *exo*- and *endo*-2,4,6-triphenyl-1,3-diazabicyclo-[3.1.0]hex-3-ene. Both photocycloadditions were found to produce the same cycloadduct (*i.e.*, **6**). This observation is consistent with the intermediacy of cis ylide **8**, which is subsequently trapped by attack of the dipolarophile from the less hindered side.

(24) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633, 637 (1963).

When the irradiation of diazabicyclohexene **1** was carried out with dimethyl fumarate, a mixture of four isomeric cycloadducts **12** (mp 147–149°, 27%), **13** (oil, 13%), **14** (mp 196–197°, 27%), and **15** (mp 137–139°, 13%) was obtained. The thermal reaction of **1** with dimethyl fumarate also gave the same four isomeric adducts.



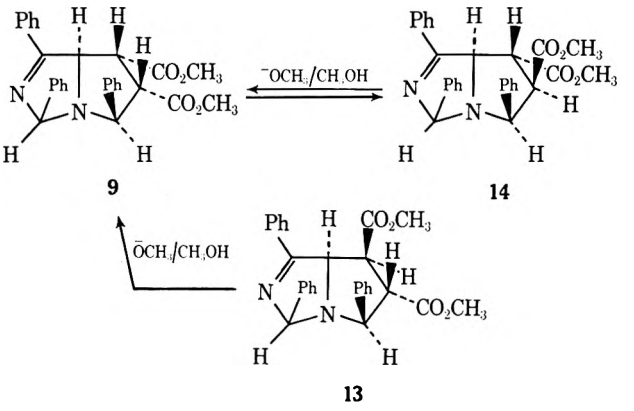
The stereochemical assignments for adducts **12–15** were based on the same considerations used in the dimethyl maleate system. In line with the previous discussion, thermal cycloaddition of dimethyl fumarate with *cis*-azomethine ylide **8** should result in protons H_5 and H_8 being cis to one another in each of the four adducts. The appearance of a carbomethoxy signal at relatively high field in adducts **14** and **15** is consistent with the vicinal shielding effect of the neighboring *cis*-phenyl ring. Protons H_6 and H_7 can be fixed as being trans in adducts **12–15** if one assumes retention of stereochemistry about the dipolarophile. As was noted previously, the vast spread of the vicinal coupling constants deprives them of their diagnostic value.

Additional information which supports the stereochemical assignments was obtained from some base-catalyzed epimerization experiments. Schemes I and II summarize the results obtained.

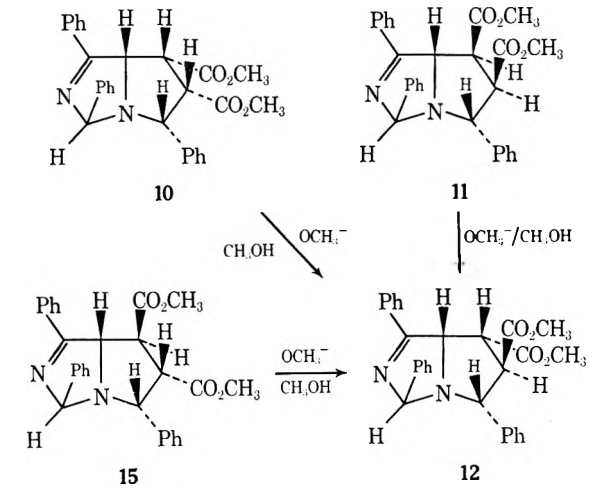
Fumarate adduct **13** was found to isomerize to maleate adduct **9** which, in turn, is in equilibrium with fumarate adduct **14**. Treatment of adducts **10**, **11**, or **15** with base results in the exclusive formation of adduct **12**.[25] These experiments clearly establish that compounds **9**, **13**, and **14** have configurations at C_5 and C_8 which are different from those of **10**, **11**, **12**, and **15**.

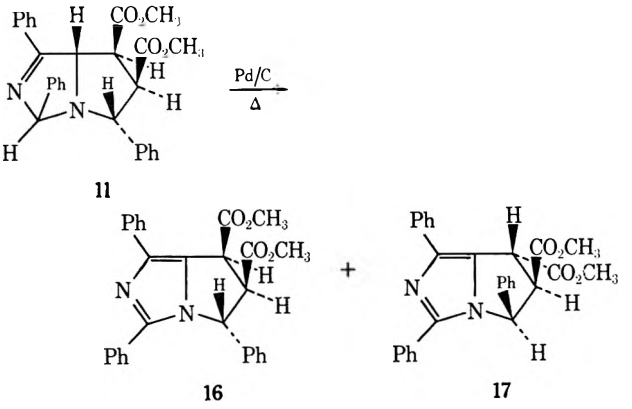
In an attempt to further interrelate the fumarate and maleate adducts, these compounds were heated in the presence of an oxidizing agent. Thus oxidation of maleate adduct **11** with palladium on charcoal in boiling benzene produced a mixture of (5*R**,6*R**,7*S**)- (**16**, 78%) and (5*R**,6*S**,7*S**)-dimethyl-5,6,7-trihydro-1,3,5-triphenylpyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**17**, 16%). The structure and stereochemistry of compounds **16** and **17** were assigned on the basis of nmr spectroscopy. The appearance of a carbomethoxy absorption in **17** at high field relative to **16** is compatible with the vicinal shielding effect of the neighboring *cis*-phenyl ring. The failure of both **16** and **17** to undergo further oxidation, even under more forcing conditions, is indicative of the extremely stable nature of the imidazole ring present in these systems. The fact that compound **17** is also formed in the oxidation of **11** suggests that epimerization occurs during the course of the reaction. This suggestion is supported by the

SCHEME I



SCHEME II





(25) The fact that adduct **12** is stable to further epimerization provides additional support for its stereochemical assignment.

observation that **16** is stable under the reaction conditions. Furthermore, oxidation of adduct **14** also results in a mixture of **16** and **17** (1:5). As a result of the oxidative epimerization, we are not able to use this procedure for elucidating the stereochemistry of the various cycloadducts.

All of the aforementioned reactions of diazabicyclohexene **1** with the activated dipolarophiles conform to the concept of 1,3-dipolar cycloaddition as proposed by Huisgen and coworkers.[26] The thermal ring cleavage of **1** involves stereospecific, conrotatory ring opening.[27] Our results, as well as those of DoMinh and Trozzolo,[14] on the photochemically induced 1,3-dipolar cycloaddition of **1** imply a conrotatory motion in contrast to the disrotatory motion described by Huisgen and coworkers for the simpler aziridine–azomethine ylide system.[5] The mechanism for formation of *cis*-azomethine ylide **8** from the irradiation of **1** remains an intriguing puzzle. One possibility to account for these results is that electron demotion in **1** occurs prior to molecular change and leads to an electronically unexcited but vibrationally excited molecule which ring opens by the equivalent of a pyrolytic process. This would be analogous to the "hot" ground-state reaction suggested by Ullman and Henderson for the indenone–pyrylium oxide system.[28] An alternate explanation involves the excited state of **1** undergoing a disrotatory ring opening to give a *trans*-azomethine ylide in its excited state. The electronically excited trans ylide may isomerize to ground-state cis ylide **8**, or react with the dipolarophile by a photochemically allowed $_4\pi_a + _2\pi_s$ process. This type of cycloaddition will give cycloadducts whose stereochemistry are equivalent to those produced from the thermal cycloaddition of yilde **8**. Reaction from an electronically excited state manifold of product has been suggested to occur in the photodeprotonation of phenols[29] and in the photoenolization of *o*-methylbenzophenone[30] and provides reasonable chemical precedent for the above suggestion. Still another possibility is that the photoinduced ring opening of **1** is not controlled by orbital symmetry factors but rather involves reaction of the thermodynamically more stable azomethine ylide.[31] This is not unreasonable, since, in this system, the three-membered ring is incorporated in a fused ring system where strain is relieved on bond heterolysis. The resulting 1,3 dipole will be more stable, relative to starting material, than the analogous acyclic system. Consequently, the passage of **1** to **8** will be significantly assisted by relief of ring strain and may proceed by a nonconcerted path. This possibility may be considered to be analogous to the thermally disallowed valence tautomerism of 6-cyclohexylimino-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirene to an isoquinolinium imine[32] and also to the tautomerization of 2,3-diphenylindenone oxide into the corresponding benzopyrylium 4-oxide.[33] The available data do not decisively distinguish among the three possibilities.

Experimental Section[34]

Irradiation of *endo*- and *exo*-2,4,6-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene with Dimethyl Acetylenedicarboxylate.—A solution containing 300 mg of diazabicyclohexene **1** and 140 mg of dimethyl acetylenedicarboxylate in 60 ml of benzene was irradiated with a 450-W Hanovia mercury lamp for 2.5 hr. Removal of the solvent at 50° under reduced pressure gave a dark oil whose nmr spectrum indicated the complete absence of 2,3-dihydro-2,3,5-triphenylpyrazine (**4**). Recrystallization of the oil from 95% ethanol gave (3*R**,7*R**,7a*S**)-dimethyl-7,7a-dihydro-1,3,5-triphenyl-3-*H*-pyrrolo[1,2-c]imidazole-6,7-dicarboxylate (**6**) as a white, crystalline solid (72%): mp 123–124°; ir (KBr) 5.80, 6.15, 6.95, 7.95, 10.60, 12.30, 13.40, 14.10, 14.40 μ; uv (95% ethanol) 240 nm (ϵ 19,000); nmr (100 MHz, pyridine-d_5) τ 6.62 (3 H, s), 6.58 (3 H, s), 4.54 (d, 1 H, J = 4.0 Hz), 3.80 (d, 1 H, J = 4.0 Hz), 3.62 (t, 1 H, J = 4.0 Hz), 1.96–3.02 (m, 15 H); mass spectrum *m/e* 452 (M^+), 450, 391, 285, 105, and 104 (base).

Anal. Calcd for $C_{28}H_{24}O_4N_2$: C, 74.32; H, 5.35; N, 6.19. Found: C, 73.94; H, 5.12; N, 6.15.

Dimethyl-1,3,5-triphenyl-3*H*-pyrrolo[1,2-c]imidazole-6,7-dicarboxylate (7).—A solution of 100 mg of photoadduct **6** in 50 ml of benzene was refluxed over palladium on charcoal for 1 hr. The catalyst was removed by filtration and the solution was concentrated under reduced pressure to give 65 mg (68%) of dimethyl-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**7**) as a yellow solid: mp 151–152°; ir (KBr) 5.90, 6.35, 6.50, 6.98, 7.20, 7.88, 8.35, 8.90, 9.12, 12.00 and 13.24 μ; uv (95% ethanol) 265, 290, and 378 nm (ϵ 17,350, 14,000, 15,300); nmr ($CDCl_3$, 100 MHz) singlets at τ 6.32 (3 H), 6.16 (3 H), and 3.80 (1 H), and a multiplet at 2.92–2.16 (15 H); mass spectrum *m/e* 450 (M^+), 391 (base), 105, and 77.

Anal. Calcd for $C_{28}H_{22}O_5N_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.47; H, 5.12; N, 6.26.

Thermal and Photochemical Cycloaddition of *endo*-2,4,6-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene with Dimethyl Maleate.—A solution containing 620 mg of endo aziridine **1** and 288 mg of dimethyl maleate in 50 ml of xylene was heated at reflux for 3 days. Removal of the solvent *in vacuo* gave a crude solid which showed a complex mixture of carbomethoxy adducts in the nmr. The mixture was separated by scanning liquid–liquid partition chromatography.[35] The optical density trace showed three peaks. The first peak contained 20 mg (2%) of 2,3,5-triphenylpyrazine, mp 152–153°. The second peak contained 170 mg (19%) of a crude solid that proved to be a two-component mixture (ratio 1:1). The mixture could be separated by fractional crystallization from ethanol and the more insoluble component was a white, crystalline solid whose structure is assigned as (3*R**,5*S**,6*S**,7*R**,7a*R**)-dimethyl-5,6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**9**): mp 221–222°; ir (KBr) 5.82, 6.15, 6.95, 7.25, 7.92, 8.22, 8.90, 9.46, 9.65, 11.32, 12.96, and 14.40 μ; uv (95% ethanol) 247 nm (ϵ 17,300); nmr ($CDCl_3$, 100 MHz) τ 6.44 (5 H), 6.24 (s, 3 H), 5.00 (d, 1 H, J = 10.0 Hz), 4.68 (dd, 1 H, J = 5.0 and 3.0 Hz), 4.36 (d, 1 H, J = 5.0 Hz), 3.36–2.16 (m, 15 H); mass spectrum *m/e* 454 (M^+), 351, 292, 260, 193, and 174 (base).

Anal. Calcd for $C_{28}H_{26}O_4N_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.83; H, 5.69; N, 6.12.

The second and less soluble component of the mixture was a white solid, mp 172–173°, whose structure is assigned as (3*R**,5*R**,6*S**,7*R**,7a*S**)-dimethyl-5,6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-c]imidazole-6,7-dicarboxylate (**10**): ir (KBr) 5.75, 6.90–7.00, 8.29, 8.50, 9.08, 10.28, 10.82, 13.30, and 14.38 μ; uv (95% ethanol) 245 nm (ϵ 15,100); nmr ($CDCl_3$, 100 MHz) τ 6.82 (4 H), 6.38 (4 H), 5.72 (d, 1 H, J = 6.0 Hz),

(26) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968), and leading references.

(27) The thermal cycloaddition of 1,3-diazabicyclo[3.1.0]hex-3-enes to activated dipolarophiles was first reported by Heine and coworkers: H. Heine, A. B. Smith, and J. D. Bowers, *ibid.*, **33**, 1097 (1968). These authors did not report on the direction of ring opening.

(28) E. F. Ullman and W. A. Henderson, *J. Amer. Chem. Soc.*, **86**, 5050 (1964).

(29) A. Weller, *Progr. React. Kinet.*, **1**, 199 (1961).

(30) E. F. Ullman, *Accounts Chem. Res.*, **1**, 353 (1968).

(31) See W. T. A. M. van der Lugt and L. J. Oosterhoff, *J. Amer. Chem. Soc.*, **91**, 6042 (1969), for criticism of the applicability of the Woodward–Hoffmann rules in photochemical reactions.

(32) J. W. Lown and K. Matsumoto, *Chem. Commun.*, 692 (1970).

(33) E. F. Ullman and J. E. Milks, *J. Amer. Chem. Soc.*, **86**, 3814 (1964).

(34) All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavia Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 60 MHz with a Varian Associates high-resolution spectrometer and at 100 MHz using a Jeolco-MH-100 spectrometer.

(35) A. Padwa and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 102 (1967).

4.44 (dd, 1 H, J = 6.0 and 3.0 Hz), 4.26 (d, 1 H, J = 3.0 Hz), 3.34–1.96 (m, 15 H); mass spectrum m/e 454 (M^+), 351, 292, 193, 189, and 174 (base).

Anal. Calcd for $C_{28}H_{26}O_4N_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.65; H, 5.89; N, 6.06.

The third and largest peak present in the liquid–liquid partition chromatogram amounted to 462 mg (51%) of a white solid, mp 158–159°, whose structure is assigned as (3*R**,5*R**,6*R**,7*S**,7a*S**)-dimethyl-5,6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]-imidazole-6,7-dicarboxylate (**11**): ir (KBr) 5.80, 6.98, 8.30, 9.48, 9.90, 13.35, and 14.40 μ; uv (95% ethanol) 247 nm (ϵ 16,700); nmr ($CDCl_3$, 100 MHz) τ 6.76 (s, 3 H), 6.46 (4 H), 6.20 (t, 1 H, J = 6.5 Hz), 5.16 (d, 1 H, J = 10.0 Hz), 4.60 (dd, 1 H, J = 6.5 and 5.0 Hz), 3.94 (d, 1 H, J = 5.0 Hz), and 2.04–2.96 (m, 15 H); mass spectrum m/e 454 (M^+), 452, 393, 311, 310 (base), 309, 193, and 174.

Anal. Calcd for $C_{28}H_{26}O_4N_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.27; H, 5.65; N, 6.23.

When the irradiation of *endo*-aziridine **1** (972 mg) and dimethyl maleate (120 mg) was carried out in 180 ml of benzene for 3.5 hr the same three adducts were isolated from the liquid–liquid partition chromatogram. There were no detectable signs of any other isomers.

Thermal and Photochemical Cycloaddition of *endo*-2,4,6-Triphenyl-1,3-diazabicyclo[3.1.0]hex-3-ene with Dimethyl Fumarate.—A solution containing 620 mg of the *endo*-diazabicycloaziridine **1** and 288 mg of dimethyl fumarate in 50 ml of xylene was heated at reflux for 3 days. Removal of the solvent *in vacuo* left a crude oil whose nmr spectrum indicated the existence of a complex mixture of carbomethoxy adducts. The mixture was subjected to scanning liquid–liquid partition chromatography and the optical density trace consisted of three peaks. The first peak contained 350 mg (39%) of a white solid whose nmr spectrum indicated it to be a mixture of two carbomethoxy adducts (ratio 2:1). The major component of the mixture was obtained by fractional crystallization from 95% ethanol. This material was assigned as (3*R**,5*R**,6*R**,7*R**,7a*S**)-dimethyl-5,-6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,-7-dicarboxylate (**12**): mp 147–149°; ir (KBr) 5.80, 6.18, 6.95, 7.30, 7.88, 8.30, 9.12, 9.78, 10.89, 13.08, 13.42, and 14.50 μ; uv (95% ethanol) 244 nm (ϵ 15,600); nmr ($CDCl_3$, 100 MHz) τ 6.50 (5 H), 6.34 (s, 3 H), 5.84 (d, 1 H, J = 10.0 Hz), 4.74 (dd, 1 H, J = 6.0 and 3.0 Hz), 4.10 (d, 1 H, J = 3.0 Hz), and 2.04–2.96 (m, 15 H); mass spectrum m/e 454 (M^+), 452, 393, 351, 310, 292, 193, and 174 (base).

Anal. Calcd for $C_{28}H_{26}O_4N_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.91; H, 5.71; N, 6.10.

The minor component of the mixture could not be cleanly separated from **12** but was characterized as (3*R**,5*S**,-6*S**,7*S**,7a*R**)-dimethyl-5,6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**13**) by its nmr spectrum ($CDCl_3$), which showed peaks at τ 6.28 (4 H), 6.32 (4 H), 5.08 (d, 1 H, J = 8.0 Hz), 4.74 (m, 1 H), 4.18 (d, 1 H, J = 4.0 Hz), and 2.2–3.1 (m, 15 H).

The second peak in the liquid–liquid partition chromatogram amounted to 360 mg (40%) of a solid whose nmr revealed it to be a two-component mixture of carbomethoxy adducts (ratio 2:1). The mixture was separated by fractional crystallization from 95% ethanol and the major component, mp 196–197°, was assigned as (3*R**,5*S**,6*R**,7*R**,7a*R**)-dimethyl-5,6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**14**): ir (KBr) 5.80, 6.90, 7.00, 7.25, 8.52, 8.98, 9.70, 10.68, 10.93, 12.97, 13.00, 14.35, and 14.50 μ; uv (95% ethanol) 247 nm (ϵ 16,100); nmr ($CDCl_3$, 100 MHz) τ 7.04 (3 H, s), 6.40 (3 H, s), 6.20 (m, 2 H), 5.24 (d, 1 H, J = 10.0 Hz), 4.60 (dd, 1 H, J = 9.0 and 5.0 Hz), 4.34 (d, 1 H, J = 5.0 Hz), 2.1–3.4 (m, 15 H); mass spectrum m/e 454 (M^+), 452, 351, 310, 309, 292, 233, 230, 206, and 193 (base).

Anal. Calcd for $C_{28}H_{26}O_4N_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.97; H, 5.90; N, 6.16.

The minor component from the second peak in the chromatogram was recrystallized from cyclohexane, mp 137–139°, and was assigned as (3*R**,5*R**,6*S**,7*S**,7a*S**)-dimethyl-5,6,7,7a-tetrahydro-1,3,5-triphenyl-3*H*-pyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**15**): ir (KBr) 5.80, 6.17, 6.90, 7.92, 8.15, 8.38, 8.52, 9.72, 13.12, and 14.36 μ; uv (95% ethanol) 247 nm (ϵ 15,800); nmr ($CDCl_3$, 100 MHz) τ 7.00 (s, 3 H), 6.86 (s, 3 H), 6.30 (m, 2 H), 5.14 (d, 1 H, J = 7.0 Hz), 4.42 (dd, 1 H, J = 8.0 and 4.0 Hz), 4.10 (d, 1 H, J = 4.0 Hz), 2.0–3.1 (m, 15 H): mass spectrum m/e 454 (M^+), 452, 393, 311, 310 (base), 309, 293, 233, 206, 193, and 174.

The third and smallest peak isolated from the liquid–liquid chromatogram contained 20 mg (2%) of a solid whose nmr spectrum showed it to be a mixture of oxidation products. These products were identical with those obtained from the palladium/charcoal oxidation of the dimethyl fumarate adducts (see below).

When the irradiation of *endo*-diazabicyclic aziridine **1** (1.89 g) and 140 mg of dimethyl fumarate was carried out in 300 ml of benzene for 3.5 hr, the same four adducts were isolated from the liquid–liquid partition chromatogram. There were no detectable quantities (*i.e.*, less than 3%) of any other isomers present in the chromatogram.

Base-Catalyzed Epimerization of the Dimethyl Maleate and Dimethyl Fumarate Adducts.—A representative example consists of stirring a solution containing 60 mg of the adducts with 25 mg of sodium methoxide in 25 ml of methanol at 55° for 4.5 hr. The mixture was diluted with 1.0 ml of water and the solvent was removed under reduced pressure. The residue was taken up in chloroform, washed with water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left a residue which was examined by nmr spectroscopy. In this way the following results were obtained.

Starting isomer	Epimerized product	Starting isomer	Epimerized product
9	**14**	**10**	**12**
13	**9** and **14**	**11**	**12**
14	**9**	**15**	**12**

Oxidation of the Dimethyl Maleate and Fumarate Adducts.—A solution containing 150 mg of the dimethyl maleate adduct **11** and excess palladium on charcoal was refluxed in 25 ml of benzene for 24 hr. Filtration of the catalyst followed by removal of the solvent under reduced pressure gave 142 mg (95%) of a white solid whose nmr spectrum indicated it to be a two-component mixture (ratio 4:1). The major product was purified by fractional crystallization from 95% ethanol, mp 193–195°, and was assigned as (5*R**,6*R**,7*S**)-dimethyl-5,6,7-trihydro-1,3,5-triphenylpyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**16**): ir (KBr) 5.85, 7.00, 7.56, 8.02, 8.25, 8.38, 9.58, 9.75, 13.05, 13.90, 14.25, and 14.60 μ; uv (95% ethanol) 274 nm (ϵ 21,700); nmr ($CDCl_3$, 100 MHz) τ 6.30 (6 H, s), 6.00 (t, 1 H, J = 8.0 Hz), 5.28 (d, 1 H, J = 8.0 Hz), 3.88 (d, 1 H, J = 8.0 Hz), 2.0–3.2 (m, 15 H); mass spectrum m/e 452 (M^+), 394, 393 (base), and 230.

Anal. Calcd for $C_{28}H_{24}O_4N_2$: C, 74.32; H, 5.35; N, 6.19. Found: C, 74.23; H, 5.34; N, 6.17.

The minor isomer obtained from the mixture was recrystallized from 95% ethanol, mp 181–183°, and was assigned as (5*R**,6*S**,-7*S**)-dimethyl-5,6,7-trihydro-1,3,5-triphenylpyrrolo[1,2-*c*]imidazole-6,7-dicarboxylate (**17**): ir (KBr) 5.85, 6.90, 7.00, 7.88, 8.05, 8.27, 9.28, 9.85, 12.85, 14.10, and 14.45 μ; uv (95% ethanol) 274 nm (ϵ 21,500); nmr ($CDCl_3$, 100 MHz) τ 6.54 (s, 3 H), 6.26 (s, 3 H), 5.88 (t, 1 H, J = 3.0 Hz), 5.36 (d, 1 H, J = 3.0 Hz), 4.00 (d, 1 H, J = 3.0 Hz), 1.9–3.0 (m, 15 H); mass spectrum m/e 452 (M^+ and base), 393, 333, 231, 230, and 77.

Anal. Calcd for $C_{28}H_{24}O_4N_2$: C, 74.32; H, 5.35; N, 6.19. Found: C, 73.92; H, 5.43; N, 6.18.

The dimethyl fumarate adduct **14** was also oxidized by a similar procedure. A solution containing 150 mg of the dimethyl fumarate adduct **14** and excess palladium on charcoal in 25 ml of benzene was heated at reflux for 60 hr. Filtration of the catalyst and removal of the solvent under reduced pressure gave 132 mg (89%) of a white solid whose nmr spectrum revealed it to be a mixture of two oxidation products (ratio 5:1). The major component was shown to be isomer **17** while the minor component was identified as **16**.

Registry No.—**6**, 36476-66-1; **7**, 36476-67-2; **9**, 36476-68-3; **10**, 36476-69-4; **11**, 36476-70-7; **12**, 36476-71-8; **13**, 36476-72-9; **14**, 36476-73-0; **15**, 36476-74-1; **16**, 36476-75-2; **17**, 36476-76-3; 2,3,5-triphenylpyrazine, 36476-77-4.

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The Addition of Dihalocarbenes to 3β-Acetoxy-*B*-norandrost-5-en-17-one

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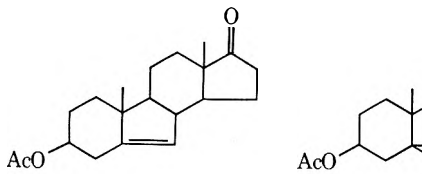
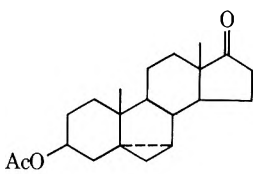
Depending on the nature of the dihalocarbene used and the stereochemistry of its addition to the title olefin, either a stable bicyclo[3.1.0]hexane ring system is formed or rearrangement occurs readily to give a 6,7-dihalo-Δ^5 steroid. Cyclopropane derivatives **8** and **9** are formed, respectively, from difluorocarbene and from chlorofluorocarbene when the latter adds to give an α-endo-F product. Both dichlorocarbene addition and the α-endo-Cl derivative arising from the reaction with chlorofluorocarbene give rise to 6,7-dihalo-Δ^5 steroids **6** and **12** *via* spontaneous ring opening of the initially formed cyclopropyl intermediates. Unlike the β addition of difluorocarbene to "normal" $\Delta^{5(6)}$ steroid olefins, the reaction with Δ^5 *B*-norsteroids occurs from the α face.

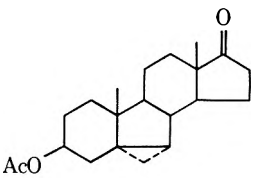
Recently[1] the Simmons–Smith reaction has been applied to the unsaturated *B*-norsteroid **1** to form the 5,7α and 5,7β cyclosteroids **2** and **3**, respectively, the latter compound being formed almost exclusively.



1



2

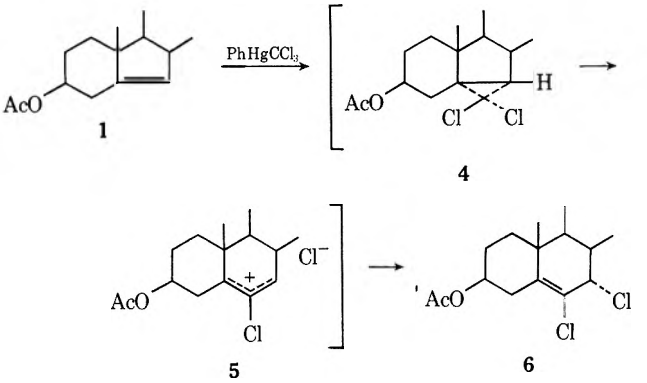


3

When a dihalogenocarbene is used in place of methylene for the formation of the bicyclo[3.1.0]hexane system, the reaction displays several interesting aspects which are not present in the unsubstituted case. Firstly, depending on ring strain and the halide used, the products formed are found to be either the 5,7 cyclosteroids or compounds derived from a thermal rearrangement of the initially formed adduct. Secondly, the thermal rearrangement observed suggests a concerted heterolytic process,[2] subject to the same stereochemical consequences predicted for the concerted rearrangement of a cyclopropyl cation ion *via* a solvolysis.[3]

Previous studies have indicated that both dichloro- and dibromocarbenes generated either from haloform and *tert*-alkoxide or the thermal decomposition of sodium trihaloacetates fail to add to $\Delta^{5(6)}$ steroids possessing a 10β-methyl group. In contrast, difluorocarbene has been shown to add β to the $\Delta^{5(6)}$ position.[4] Attempts to isolate any addition product from the reaction of **1** and dichlorocarbene generated from the thermal decomposition of the sodium salt of trichloroacetic acid in diglyme[5] proved fruitless. Apparently the steric requirements for addition are such as to allow the side reaction between the carbene and the trichloroacetate anion to predominate.[6,7]

The use of phenyl(trichloromethyl)mercury,[8] which has been shown to react with olefins by a free carbene mechanism,[9] results in the effective addition of dichlorocarbene to the *B*-norsteroid **1**.[10] In contrast to 6,6-dichlorobicyclo[3.1.0]hexane, which is thermally stable to heating at 75° for 2 hr in tetrahydrofuran,[11] the strained 6,6-dichlorobicyclo[3.1.0]hexane system present in compound **4** undergoes a spontaneous rearrangement at 80° *via* the ion pair **5** to form the allylic product **6**.



1 **4** **5** **6**

The axial configuration of the C-7 chlorine of compound **6** was determined by nmr spectroscopy: d of d at δ 4.4 (J_{7-8} = 3.4, J_{7-4} = 1.5 Hz). Because of the stereospecificity shown for the recapture step, *i.e.*,

(1) J. Joska, J. Fajkos, and F. Sorm, *Collect. Czech. Chem. Commun.*, **33**, 2049, 3342 (1968).

(2) M. S. Baird and C. B. Reese, *Tetrahedron Lett.*, 1379 (1967); 2117 (1969); D. C. F. Law and S. T. Tobey, *J. Amer. Chem. Soc.*, **90**, 2376 (1968); M. S. Baird, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc. C*, 1173 (1969); C. W. Jefford and W. Wojnarowski, *Tetrahedron*, **25**, 2089 (1969).

(3) P. v. R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust, *J. Amer. Chem. Soc.*, **88**, 2868 (1966); C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(4) L. H. Knox, E. Verlarde, S. Berger, D. Cuadriello, P. W. Landis, and A. Cross, *ibid.*, **85**, 1851 (1959).

(5) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959).

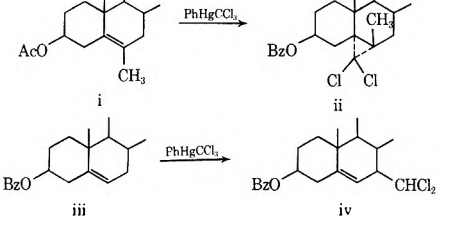
(6) W. M. Wagner, H. Kloosterziel, and S. van der Ven, *Recl. Trav. Chim. Pays-Bas*, **80**, 740 (1961).

(7) W. M. Wagner, H. Kloosterziel, and A. F. Bickel, *ibid.*, **81**, 925, 933 (1962).

(8) D. Seyferth, J. M. Berlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(9) D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *ibid.*, **89**, 4953 (1967).

(10) The phenyl(trichloromethyl) mercury reagent has recently been used as starting material for the addition of dichlorocarbene to the hindered Δ^5 position of 6-methylcholesteryl acetate (i) to give ii. Cholesteryl benzoate (iii) failed to give addition and afforded the allylic insertion product iv [F. T. Bond and R. H. Cornelia, *Chem. Commun.*, 1189 (1968)].

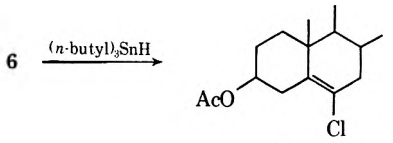


i ii iii iv

(11) E. Bergman, *J. Org. Chem.*, **28**, 2210 (1963).

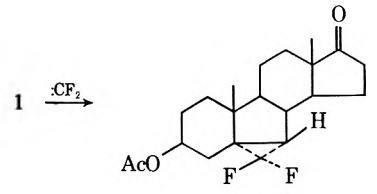
5 → **6**, in similar dichlorpropane rearrangements,[12] the axial (α) configuration of the C-7 chlorine in compound **6** clearly leads to the 5,7β assignment of configuration for the initially formed cyclopropyl derivative **4**.

The allylic nature of the 7-chloro substituent in compound **6** was demonstrated by its hydrogenolysis with tributyltin hydride[13] to the known monochloro derivative **7**.[14]



7

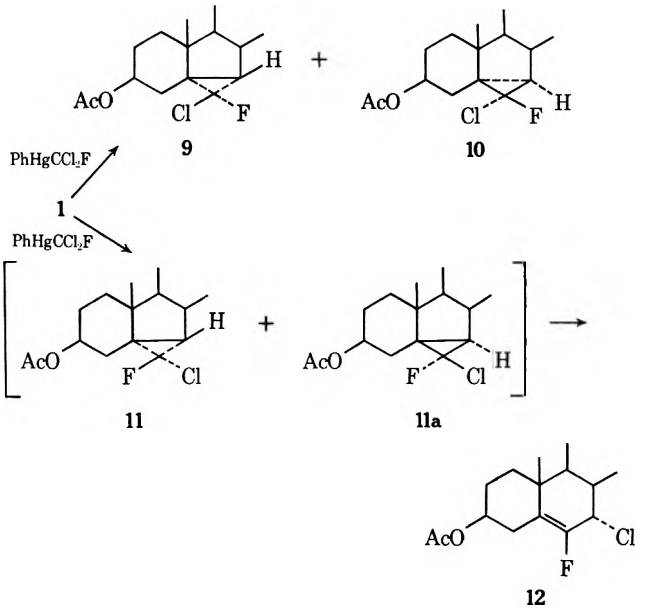
It was anticipated that the difluorocarbene generated by thermal decomposition of sodium difluorochloroacetate would successfully add to the *B*-norsteroid **1**, since $:CF_2$ produced in a like manner has previously been shown to add readily to the double bond of steroidal 5-ene systems.[4] Ring opening of such an adduct, *i.e.*, **4** → **6**, would require ionization of a fluorine atom. Since the rate of thermal rearrangement will depend on the ionizing ability of the leaving groups, *i.e.*, $Br^- > Cl^- > F^-$,[15] it was anticipated that the difluorocarbene adduct would be considerably more stable than the corresponding dichloro derivative; therefore, isolation of the cyclopropyl addition product should be possible. When compound **1** was treated with difluorocarbene generated by the dropwise addition of a solution of the sodium salt of difluorochloroacetate in diglyme[16] to a refluxing solution of **1** in the same solvent, the adduct **8** was formed in 65% yield.



8

Inspection of a Dreiding model of the 5,7α adduct indicates that a splitting of the C-19 H signal by long-range coupling with the β-endo-F atom would be expected since the geometrical requirements of the converging vector rule are fulfilled.[17] The nmr spectra of **8** reveals a sharp singlet, δ 1.07, for the C-19 angular Me proton resonance, suggestive therefore of the 5,7β stereochemistry.

The thermal stability of the difluorocarbene adduct as compared to the spontaneous rearrangement of the dichlorocarbene adduct demonstrates the dependence on the ionizing ability of the leaving group. As a means of clarifying the stereochemical factors involved in the ease of rearrangement, **1** was treated with fluorochlorocarbene generated by the thermolysis of phenyl(fluorodichloromethyl)mercury.[18] As expected, the reaction led to a mixture of products containing the cyclopropyl adducts **9** or **10** as well as the rearranged product **12**.



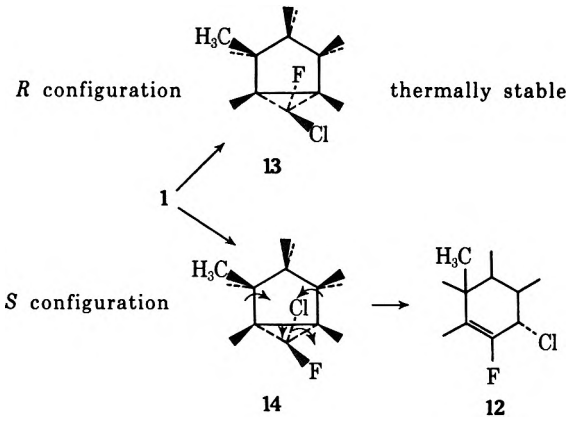
There has recently been much work regarding the ring opening of halocyclopropanes and it is well established that a stereospecific opening of the ring is concerted with the departure of the leaving group.[3,19] The concerted rearrangement of a cyclopropyl to an allylic cation should proceed by a stereospecific disrotatory process such that the groups trans to the leaving group rotate outward and those cis to it rotate inward.[20] In a bicyclo[3.1.0]hexane system such as **11**, however, the outward rotatory process is strongly hindered, since a six-membered ring cannot accommodate the trans,trans allyl cation which would be formed. On the other hand, an inward rotatory process is possible, since the cis,cis allyl cation is permissible in a six-membered ring system.

Application of these concepts to the present case predicts that compound **12** is the result of ring opening of a cyclopropyl derivative **11** or **11a** having the halides disposed in the *S* configuration, *i.e.*, **14**.

The nmr spectrum of compound **12**, d of d at δ 4.44 (J_{7-8} = 3.5, J_{7-4} = 1.5 Hz), is almost identical with that found for compound **6** and strongly suggests that the chlorine at C-7 is axial (α). The necessity for sterospecific[12] recapture of the halide in the ion pair produced by ring opening leads to the conclusion that **11** and not **11a** represents the initially formed cyclopropyl precursor of **12**.

The thermally stable chlorofluoro adduct, on the other hand, must possess the *R* configuration, *i.e.*, **13**, since in this form only ionization of the fluorine atom is permissible for ring opening. As discussed previously for the difluoro adduct **8**, compound **10** would be expected to show splitting of the C-19 H signal by long-range coupling with the fluorine atom.[17] This was not found to be the case, implying again an α addition leading to compound **9**.

(12) I. Fleming and E. J. Thomas, *Tetrahedron Lett.*, 2485 (1971).
(13) G. I. M. Van Der Kerk, J. G. Naltes, and J. G. H. Suijten, *J. Appl. Chem.*, **7**, 366 (1937).
(14) J. S. Mihina, *J. Org. Chem.*, **27**, 2807 (1962).
(15) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962,p184.
(16) J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *Proc. Chem. Soc.*, **81** (1960).
(17) A. Cross and P. W. Landis, *J. Amer. Chem. Soc.*, **86**, 4005 (1964).
(18) D. Seyferth and K. V. Darragh, *J. Organometal Chem.*, **11**, 9 (1968).
(19) C. S. Foote, *J. Amer. Chem. Soc.*, **86**, 1853 (1964); P. v. R. Schleyer, *ibid.*, **86**, 1854 (1966).
(20) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965).



Molecular rotation differences calculated for 3β-acetoxy-*B*-norandrost-5-en-17-one (1) and appropriate derivatives (Table I) further support the 5,7β configura-

TABLE I
MOLECULAR ROTATION DATA FOR 3β-ACETOXY-*B*-NORANDROST-5-EN-17-ONE AND SOME DERIVATIVES

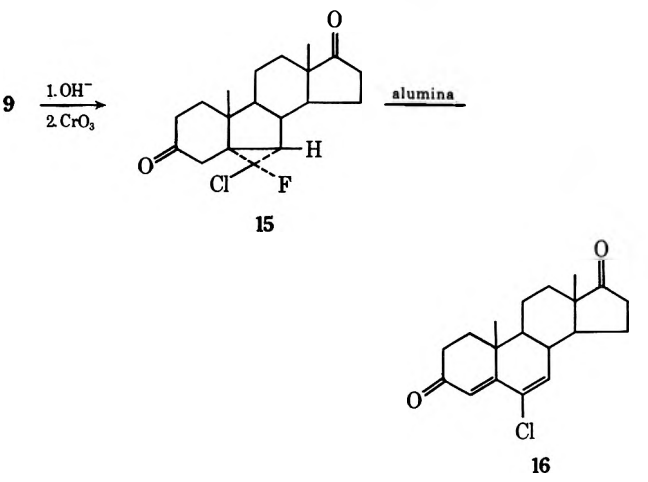
	[M]D	Δ[M]D
3β-Acetoxy-*B*-norandrost-5-en-17-one (1)[a]	−165°	
3β-Acetoxy-5β,6β-oxido-*B*-norandrostan-17-one (A)[b]	+200.8°	A–1 +365°
3β-Acetoxy-5α,6α-oxido-*B*-norandrostan-17-one (B)[c]	+63°	B–1 +228°
6,6-Difluoro-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (8)	+109°	8–1 +274°
6-Chloro-6-fluoro-(*R*)-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (9)	+88°	9–1 +253°

[a] See J. Joska and F. Sorm, *Collect. Czech. Chem. Commun.*, **23**, 1377 (1958). [b] J. Joska and J. Fajkos, *ibid.*, **28**, 621 (1963). [c] J. Joska, J. Fajkos, and F. Sorm, *ibid.*, **28**, 82 (1963).

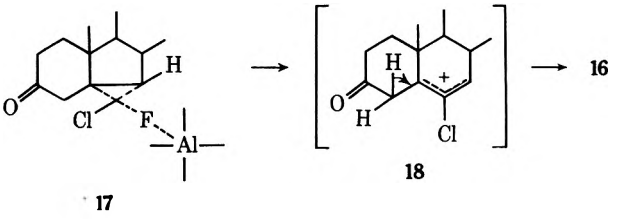
tion of the difluoro adduct **8** as well as the chlorofluoro derivative **9**. The molecular rotation changes observed on passing from 3β-acetoxy-*B*-norandrost-5-en-17-one (1) to the difluoro adduct **8** and the chlorofluoro compound **9** are positive. These changes parallel more closely the molecular rotation change observed on passing from **1** to the α-epoxide B as compared to the β-epoxide A.

The thermally stable α-F endo derivative **15** derived from the acetate **9** would be expected to ring open as predicted by the Woodward–Hoffmann–DePuy rule if ionization of the fluorine atom could be realized. However, the lack of reactivity of alkyl fluorides toward normal solvolysis reactions would tend to preclude such a reaction leading to rearranged product. On the other hand, the greater reactivity shown by alkyl fluorides as compared to other alkyl halides in the Friedel–Crafts reaction[21] suggested the use of a Lewis acid as a catalyst for the ring-opening reaction. The cyclopropyl derivative **9** was hydrolyzed and then oxidized with Jones reagent to the dione **15** which, when treated with neutral alumina (grade I), quantitatively rearranged to the diene **16**.

(21) G. A. Olah, "Friedel–Crafts and Related Reactions," Interscience, New York, N. Y., 1964, p 428. For the acid-catalyzed solvolysis of alkyl fluorides, see A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 50.



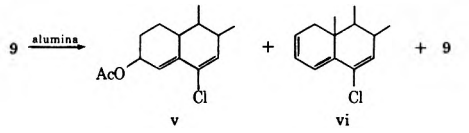
The alumina in the role of a Lewis acid can be pictured to bring about the loss of fluoride ion with simultaneous ring opening leading to the ion pair **18**. Loss of a proton at C-4 then affords the observed product **16**.[22]



Evidence for structure **16** was provided by the observed *m/e* 318 molecular ion peak and by comparison with the known absorption maxima and melting point.[23]

The necessary condition of maximum overlap which is postulated for the transition state of the addition of a dihalocarbene to a $\Delta^{5(6)}$ steroid olefin requires a β-axial attack of the carbene at the C-6 position with the development of a partial positive charge at tertiary C-5.[4,10] The inability of dichlorocarbene to give any β-addition product[10] is rationalized as being due to the steric hindrance of the 10β-methyl group. The fact that no α-addition product is observed may be rationalized as being due to a transition state which would require an axial attack at C-5 with the development of a partial positive charge at the secondary C-6. In the case of 6-methyl cholesteryl acetate, however, where axial attack at C-5 would lead to a positive charge at tertiary C-6, an α-addition product has been realized under forcing conditions.[10] With the smaller difluorocarbene the electronic requirement of maximum overlap outweighs the steric hindrance to the β-face ap-

(22) When compound **9** was treated with alumina, ring opening also occurred. In this case, however the major product v was contaminated with starting material **9** as well as triene vi.



(23) K. Brückner, B. Hampel, and V. Johnsen, *Chem. Ber.*, **94**, 1225 (1961).

proach.[24] In the case of the *B*-norandrost-5-ene steroid, inspection of a Dreiding model leads to the conclusion that a carbene addition to the double bond from the β face will encounter a greater steric repulsion from the 10β-methyl group than is found in the normal $\Delta^{5(6)}$ steroid. Since the necessity for maximum overlap in the transition state at the C-6 position in the *B*-norsteroid may be accommodated at the α face, the α-side addition of a dihalocarbene to a *B*-norsteroid can be considered to be the most favored process in light of the steric and electronic considerations.

Experimental Section

General.—All melting points were taken in glass capillaries and are corrected. The nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer with tetramethylsilane as the internal standard. A Cary 14 spectrophotometer was used to obtain the ultraviolet spectra. The high-resolution mass spectra were obtained with a Consolidated Electrodynamics Corp. 21-110 mass spectrometer.

3β-Acetoxy-*B*-norandrost-5-en-17-one (1).—A solution of 50 g (0.15 mol) of 3β-acetoxyandrost-5-en-17-one in 500 ml of methylene chloride was ozonized at −70° with an ozone flow of approximately 0.04 mol/hr. At the end of 3 hr the solution turned blue, the ozone was stopped, and the solution was flushed with a stream of nitrogen. The colorless solution was then added dropwise at 0° to a mixture of 100 g of zinc powder in 500 ml of acetic acid and stirred at that temperature for 6 hr. At the end of this time the methylene chloride was removed under reduced pressure and the residue was dissolved in 1.2 l. of 90% acetic acid. To the solution at 0° was added dropwise a solution of 20 g of chromium trioxide dissolved in 400 ml of 90% acetic acid. The mixture was stirred at room temperature for 5 hr, after which time 100 ml of ethanol was added and the mixture was stirred for an additional 15 min. The solvent was then removed at 35° under high vacuum and the residue was treated with 2 l. of water. The mixture was then extracted with ether and the ether solution was repeatedly washed with water. The ether solution was then dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude keto acid was dissolved in 100 ml of pyridine followed by the addition at 0° of 50 ml of benzoyl chloride. The mixture was then stirred at room temperature for 48 hr, cooled to 0°, and 50 ml of methanol was added. After the solution was stirred for 30 min, 2.5 l. of water was added and the mixture was extracted with ether–methylene chloride (9:1). The organic layer was washed with water and dilute hydrochloric acid (until pyridine is completely removed) and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was triturated with ether to give 18 g of yellow, crystalline β-lactone, mp 168–172°. The solvent was removed from the mother liquor under reduced pressure and the residue was pyrolyzed at 200° (0.1 mm) for 10 min. The crude product was dissolved in a small amount of benzene and washed through 200 g of neutral alumina (grade I) with 1 l. of benzene to give 11 g of **1**, mp 129–133°. Pyrolysis of the crystalline β-lactone (18 g) afforded an additional 15 g of **1**, mp 133–135°, total yield 26 g (55%) (lit.[25] mp 135–136°).

6,7α-Dichloro-3β-acetoxyandrost-5-en-17-one (6).—A solution of 0.5 g (1.5 mmol) of **1** and 1.18 g (3.0 mmol) of phenyltrichloromethylmercury in 5 ml of dry benzene was refluxed under nitrogen for 48 hr. The mixture was filtered and the solvent was removed under reduced pressure. The residue was chromatographed on 15 g of silica gel. From a 3% ethyl acetate–benzene eluent was obtained 0.35 g of crude product. Crystallization from ether gave 0.2 g of **6**, mp 180° dec, $[\alpha]^{25}D$ −79.9° (*c* 0.99, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}Cl_2O_3$: C, 63.16; H, 7.07; Cl, 17.76. Found: C, 62.86; H, 7.11; Cl, 17.92.

6,6-Difluoro-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (8).—To a refluxing solution of 1 g (3.0 mmol) of **1** in 10 ml of dry diglyme was added over a 45-min period a solution of 7.1 g of the sodium salt of chlorodifluoroacetic acid dissolved in 50 ml of diglyme. After the addition was completed the mixture was refluxed for another 15 min and the solvent was removed under high vacuum. The residue was suspended in a small amount of benzene and washed through 15 g of neutral alumina (grade I) to give 0.71 g of crude product. Crystallization from methylene chloride–ether afforded 0.5 g of **8**, mp 187.5–189.5°, $[\alpha]^{25}D$ +29.76° (*c* 1.58, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}F_2O_3$: C, 68.83; H, 7.70. Found: C, 69.03; H, 7.84.

6-Chloro-6-fluoro-(*R*)-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (9) **and 6-Fluoro-7α-chloro-3β-acetoxyandrost-5-en-17-one** (12).—A solution of 3 g (9.0 mmol) of **1** and 6 g (15.8 mmol) of phenyl(fluorodichloromethyl)mercury in 50 ml of dry benzene was refluxed for 48 hr. The precipitated phenylmercuric chloride was filtered and the filtrate was concentrated under reduced pressure. The resultant semisolid was chromatographed on 75 g of silica gel. Elution with 1% ethyl acetate–benzene gave several fractions consisting mostly of **9** (by tlc analysis). These fractions were combined and crystallized from methylene chloride–ether to give 0.45 g of **9**, mp 194–196° dec, $[\alpha]^{25}D$ +23.1° (*c* 0.69, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}ClFO_3$: C, 65.87; H, 7.37; F, 4.96. Found: C, 65.92; H, 7.38; F, 5.08.

Continuation of the chromatography with 1% ethyl acetate–benzene afforded 0.65 g of crude **12**. Crystallization from ether gave 0.5 g of **12**: mp 178° dec; $[\alpha]^{25}D$ −133.1° (*c* 0.42, $CHCl_3$); nmr ($CDCl_3$) δ 4.44 (d of d, $J_{7-8} = 3.5$, $J_{7-4} = 1.5$ Hz).

Anal. Calcd for $C_{21}H_{28}ClFO_3$: C, 65.87; H, 7.37; Cl, 9.26; F, 4.96. Found: C, 65.50; H, 7.43; Cl, 9.24; F, 4.62.

6-Chloro-6-fluoro-(*R*)-5,7-cyclo-5β-androstane-3,17-dione (15).—To a solution of 0.325 g (0.85 mmol) of **9** dissolved in 10 ml of glyme was added 3.5 ml of a 0.244 *M* solution of sodium hydroxide in ethanol. After the solution was stirred for 20 min at room temperature the solvent was removed under reduced pressure and water was added to the residue. The mixture was extracted with ether and the ether solution was dried ($MgSO_4$). The solvent was removed to give 0.298 g of crude 3β-alcohol. The alcohol (0.29 g) was dissolved in acetone (10 ml) and 0.23 ml of Jones reagent was added at 0°. The mixture was stirred at this temperature for 25 min, after which time 1 ml of isopropyl alcohol was added. The solvent was removed under reduced pressure and the residue was extracted with ether. The ether solution was dried ($MgSO_4$) and the solvent was removed. Crystallization of the residue from ether–methylene chloride gave 0.205 g of **15**, mp 182° dec, $[\alpha]^{25}D$ +118.2° (*c* 0.80, $CHCl_3$).

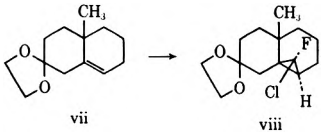
Anal. Calcd for $C_{19}H_{24}ClFO_2$: C, 67.35; H, 7.14; Cl, 10.46; F, 5.60. Found: C, 67.55; H, 7.37; Cl, 10,67; F, 5.71.

6-Chloro-4,6-androstadiene-3,17-dione (16).—A mixture of 2 g of neutral alumina (grade I) and a solution of 53.1 mg of **15** dissolved in 15 ml of dry benzene was stirred overnight. The mixture was filtered and the alumina was extracted with ethyl acetate. The benzene and ethyl acetate solutions were combined and the solvents were removed under reduced pressure to give 48.6 mg of crude **16**. Trituration with ether afforded 40 mg of **16**, mp 194–197° (lit.[24] mp 193–194°), λ_{max}^{EtOH} 284 mμ (ε 20,200).

Registry No.—**1**, 5323-23-9; **6**, 37108-24-0; **8**, 37108-25-1; **9**, 37108-26-2; **12**, 37108-27-3; **15**, 37108-28-4.

Acknowledgment.—The authors wish to thank Professor P. v. R. Schleyer for his interest and stimulating discussions of this work. We also wish to thank Dr. W. Benz, Dr. V. Toome, and Dr. T. Williams for the mass, ultraviolet, and nmr spectra, respectively, as well as Dr. F. Scheidl for the microanalyses.

(24) In support of these arguments, the addition of chlorofluorocarbene to 10-methyl-Δ^8-2-octalone 2-ethylene acetal (vii) has recently been shown to take place with almost exclusive β-endo-F stereoselectivity leading to compound viii [R. A. Moss, R. W. Kleinman, and K. L. Williamson, *Chem. Commun.*, 927 (1970)].



vii viii

(25) J. Joska and F. Sorm, *Collect. Czech. Chem. Commun.*, **23**, 1377 (1958).

Meerwein–Ponndorf–Verley Reduction of Mono- and Bicyclic Ketones. Rate of Reaction[1a,b]

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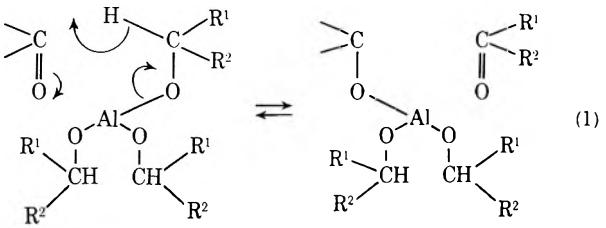
The Meerwein–Ponndorf–Verley (MPV) reduction rates of eight representative mono- and bicyclic ketones **1–8** were established at 82.3 ± 0.4° under nonequilibrating conditions resembling preparative utilization of this reaction. Results obtained enabled, for the first time, a systematic comparison of substituent effects and stereochemistry in the vicinity of the CO group. The following reaction half-lives ($t_{1/2}$, min) for the pseudo-first-order disappearance of 0.213 *M* ketone in *i*-PrOH containing 0.252 *M* Al(O-*i*-Pr)$_3$ were observed: 3-isothujone (**7**), 20.7; isomenthone (**5**), 21.9; menthone (**4**), 24.4; 3-thujone (**8**), 47.7; and camphor (**6**), 145.8. Reduction of cyclohexanone (**2**) and 2-methylcyclohexanone (**3**) was immeasurably rapid. Thus, in contrast to commonly held views, the MPV reduction of these ketones proceeds at a relatively high rate. The reduction of cyclopentanone (**1**) led to extensive by-product formation. Reduction of ketones **7** and **8** was studied in more detail at various ketone (0.483 and 0.0971 *M*) and Al(O-*i*-Pr)$_3$ (0.407, 0.147, and 0.0818 *M*) concentrations. It was found that the ratio of epimeric alcohols formed in the MPV reduction of ketones **7** and **8** was dependent on the concentration of ketone and Al(O-*i*-Pr)$_3$, their ratio being constant. In dilute solution the preponderance of cis alcohol was more pronounced than at higher concentration. The reduction rate of thujone **8** was also measured at 100 ± 0.5° in *sec*-BuOH with Al(O-*sec*-Bu)$_3$ as catalyst. The reduction was more stereospecific than with Al(O-*i*-Pr)$_3$ under comparable conditions. Various aspects of these findings are briefly discussed.

The Meerwein–Ponndorf–Verley (MPV) reduction[2] of ketones and aldehydes, formally described[3] by eq 1,

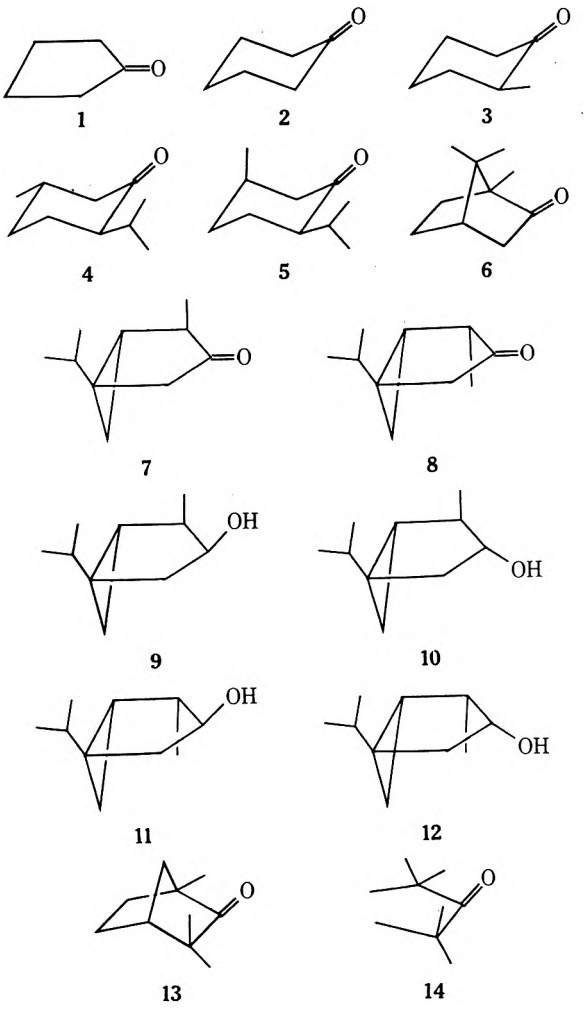


(1)

was introduced almost 50 years ago. Although in recent years its importance has declined due to the introduction of complex hydrides, there appear to be several instances where its application is preferable. Generally, *i*-PrOH and Al(O-*i*-Pr)$_3$ ($R^1 = R^2 = CH_3$) serve as reducing agent and catalyst, respectively. Other secondary alcohols (R^1, R^2 = alkyl) may be applied as well.

Two important aspects of this reaction remain obscure: first, its detailed mechanism including the rate-determining step and overall reaction order and, second, the relationship between the steric environment of the CO group and rate of reduction. Considerable efforts have been expended to elucidate the reaction mechanism.[4] In contrast, very little work has been done in regard to the second point.[4g]

In this study we addressed ourselves to the latter problem. We measured MPV reduction rates of eight mono- and bicyclic ketones **1–8**, which represent examples of stereochemical conditions in the vicinity of the CO group with regard to steric hindrance and strain. Bearing in mind the synthetic potential of the MPV reduction we aimed at developing experimental conditions resembling its preparative utilization characterized by continuous removal of acetone formed according to eq 1, a prerequisite for reaction completion. In previous kinetic work[4a,c–e,g] acetone or any other ketone



(1) (a) Acknowledgment is made to the National Research Council of Canada and to MacMillan Bloedel Research Ltd. for their support of this work. A part of it was carried out at the latter institution. (b) The encouragement, hospitality, and valuable comments of Professor J. P. Kutney are gratefully appreciated.

(2) (a) H. Meerwein and R. Schmidt, *Justus Liebigs Ann. Chem.*, **444**, 221 (1925); (b) W. Ponndorf, *Angew. Chem.*, **39**, 138 (1926); (c) M. Verley, *Bull. Soc. Chim. Fr.*, **37**, 537, 871 (1925); (d) A. L. Wilds, *Org. React.*, **2**, 178 (1944).

(3) (a) E. D. Williams, K. A. Krieger, and A. R. Day, *J. Amer. Chem. Soc.*, **75**, 2404 (1953), and references therein; (b) W. von E. Doering and T. C. Aschner, *ibid.*, **75**, 393 (1953).

(4) (a) L. M. Jackman and A. K. Macbeth, *J. Chem. Soc.*, 3252 (1952); (b) D. E. Pickart and C. K. Hancock, *J. Amer. Chem. Soc.*, **77**, 4642 (1955); (c) W. N. Moulton, R. E. VanAtta, and R. R. Ruch, *J. Org. Chem.*, **26**, 290 (1961); (d) M. S. Bains and D. C. Bradley, *Chem. Ind. (London)*, 1032 (1961); (e) V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **85**, 2337 (1963); (f) V. J. Shiner, Jr., D. Whittaker, and V. P. Fernandez, *ibid.*, **85**, 2318 (1963); (g) B. J. Yager and C. K. Hancock, *J. Org. Chem.*, **30**, 1174 (1965); (h) V. J. Shiner, Jr., and D. Whittaker, *J. Amer. Chem. Soc.*, **91**, 394 (1969); (i) L. Otvos, L. Gruber, and J. Meisel-Agoston, *Acta Chim. (Budapest)*, **43**, 149 (1965); *Chem. Abstr.*, **63**, 6803 (1965).

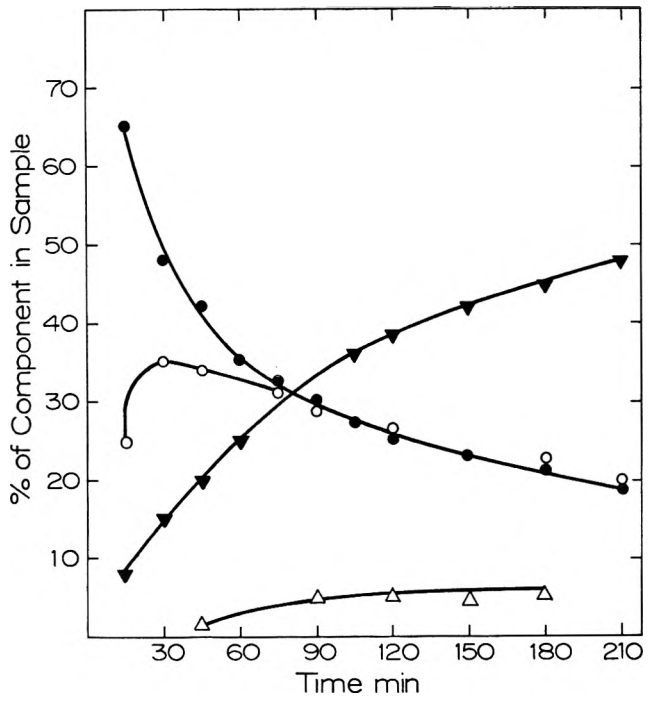


Figure 1.—MPV reduction of (+)-3-thujone (0.483 *M*) by Al(O-*i*-Pr)$_3$ (0.407 *M*) in *i*-PrOH under equilibrating conditions without acetone removal. Relationship between percentages of epimeric alcohols formed and reaction time: ●, (+)-3-thujone (**8**); ○, (+)-3-neothujanol (**12**); ▲, (+)-3-thujanol (**11**); △, (−)-3-neoisothujanol (**9**).

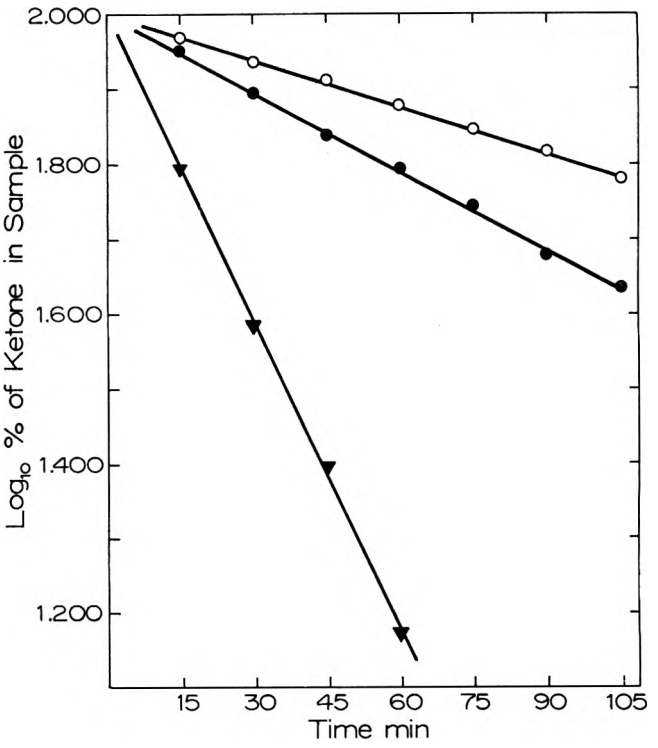


Figure 2.—MPV reduction of isomenthone, camphor, and (+)-3-thujone at 82.3 ± 0.4° with Al(O-*i*-Pr)$_3$ in *i*-PrOH. Representative pseudo-first-order plots of ketone disappearance: ○, camphor 0.252 *M*, Al(O-*i*-Pr)$_3$ 0.213 *M*; ▲, isomenthone 0.252 *M*, Al(O-*i*-Pr)$_3$ 0.213 *M*; ●, (−)-3-thujone 0.0971 *M*, Al(O-*i*-Pr)$_3$ 0.0818 *M*.

formed from the corresponding alcohol–alkoxide reducing system was not removed from the reaction mixture. Such measurements established only the difference between the forward and reverse reactions. We thought that separation of the equilibrating influence of the reverse reaction was an important condition for drawing relevant conclusions about structure–reactivity relationships. In addition, determination of the ratio of epimeric alcohols formed in the reduction was expected to yield information about stereochemistry of product formation and kinetic product control. Consequently, the choice of methods available for kinetic measurement and of applicable analytical methods became rather limited.[5] We chose to work up samples withdrawn from kinetic runs resembling preparative reaction conditions and analyze them by glpc. The percentages of starting ketone, epimerized ketone where applicable, both epimeric alcohols and by-products formed in the reaction mixture were easily determined. This would hardly be possible by polarographic, spectroscopic, and polarimetric methods applied previously.[4a,c,e,g,h]

Results and Discussion

Rate of Reduction.—In preliminary experiments with the two isomeric thujones **7** and **8** carried out under reflux without removal of acetone considerable equilibration of the epimeric alcohols formed took place. The kinetically controlled formation of the less stable cis alcohols **9** and **12**, respectively, prevailed only in the earlier phase of the reaction as exemplified by Figure 1 for the reduction of 3-thujone (**8**). Pseudo-first-order plots of ketone disappearance obtained from these runs showed nonlinear inconsistencies extending over the first 15–20% of reaction, similar to those that had been noted by Jackman, *et al.*[4b] This confirmed our suspicion that equilibrating conditions were not suitable for rate measurements.

Results (all with continuous acetone removal) obtained with ketones **1**–**8** are summarized in Table I. A representative run, the reduction of thujone **8**, is presented in Table II. A sample of pseudo-first-order plots of ketone disappearance obtained from the reduction of isomenthone (**5**), camphor (**6**), and 3-thujone (**8**) is portrayed in Figure 2.

Two principal observations emerge from these data. First, very good pseudo-first-order linear plots of ketone disappearance are obtainable using the distillation technique combined with glpc analysis of withdrawn samples. Second, in contrast to common opinion—Wilds[2d] indicates a standard reaction time of 12 to 24 hr for the reduction of ketones—purported by long reaction times given in the literature[6] the MPV reduction of simple mono- and bicyclic ketones is a relatively rapid reaction.[9] Only in sterically hindered *and* rigid systems like cam-

(5) Problems involved in the determination of MPV reduction rates were succinctly summarized by Jackman, *et al.*,[4a] and others.[4h]

(6) Where shorter reaction times were noted a 15-fold excess of Al(O-*i*-Pr)$_3$ was applied,[7] shifting the equilibrium in favor of alcohol formation. Also, some ketone–alcohol pairs are characterized by an equilibrium favoring the alcohol even in the absence of larger amounts of alkoxide. The dependency of this equilibrium on the structural setting of the CO group was explored by Yager, *et al.*,[4g] and Adkins, *et al.*[8] Little useful generalization regarding steric effects came up from this work. All this only adds to the uncertainty about structure–reactivity relationships and impedes reasonable predictions of reduction rates.

(7) W. L. Truett and W. N. Moulton, *J. Amer. Chem. Soc.*, **73**, 5913 (1951).

(8) H. Adkins, R. M. Elofson, A. G. Rossow, and C. C. Robinson, *ibid.*, **71**, 3622 (1949).

(9) In fact, the reduction of ketones **2** and **3** may be viewed as instantaneous.

TABLE I
MEERWEIN–PONNDORF–VERLEY REDUCTION OF MONO- AND BICYCLIC KETONES 1-8[a]

Entry no.	Reactants: Ketone	Alkoxide + alcohol[b]	[Ketone], M	[Alkoxide], M	Rate of pseudo-first-order disappearance of ketone: k, min⁻¹	t½, min
1	Cyclopentanone (1)	A	0.253	0.215		...[c]
2	Cyclohexanone (2)	A	0.253	0.215		3[d]
3	2-Methylcyclohexanone (3)	A	0.253	0.215		3[d]
4	(±)-Menthone (4)	A	0.252	0.213	2.8×10^{-2}	24.4
5	(±)-Isomenthone (5)	A	0.252	0.213	3.1×10^{-2}	21.9
6	(−)-Camphor (6)	A	0.252	0.213	4.7×10^{-3}	145.8
7	(−)-3-Isothujone (7)	A	0.483	0.407	4.4×10^{-2}	15.5
8		A	0.252	0.213	3.3×10^{-2}	20.7
9		A	0.0971	0.0818	2.5×10^{-2}	27.0
10	(+)-3-Thujone (8)		0.483	0.407	2.0×10^{-2}	34.2
11		A	0.252	0.213	1.4×10^{-2}	47.7
12		A	0.0971	0.0818	8.4×10^{-3}	81.8
13		A	0.252	0.147	1.2×10^{-2}	53.6
14		A	0.252	0.0837	6.6×10^{-3}	107.4
15		B	0.252	0.213	1.5×10^{-2}	43.5
16		B	0.0971	0.0818	1.1×10^{-2}	62.3

[a] Reaction rates at 82.3 ± 0.4° in isopropyl alcohol and at 100.0 ± 0.5° in *sec*-butyl alcohol with the corresponding aluminium alkoxides as catalysts. [b] A = Al(O-*i*-Pr)$_3$ + *i*-PrOH; B = Al(O-*sec*-Bu)$_3$ + *sec*-BuOH. [c] For detailed description of products see Results and Discussion. [d] Estimated from yield of corresponding alcohol after a reaction time of 15 min.

TABLE II
MEERWEIN–PONNDORF–VERLEY REDUCTION OF (+)-3-THUJONE 8 (0.0971 M) WITH Al(O-*i*-Pr)$_3$ (0.0818 M) IN *i*-PrOH AT 82.3 ± 0.4°. COMPLETE KINETIC RUN

Reaction time, min	Component % in isolated sample[a]: (+)-3-Thujone[b] (8)	(+)-3-Neothujanol[c] (12)	(+)-3-Thujanol[c] (11)	(−)-3-Isothujone (7)	(−)-3-Neoisothujanol (9)	Unknown[d]
15	89.0	8.1	1.9	0.2	0.2	0.4
30	78.4	16.5	3.9	0.4	0.2	0.8
45	68.6	23.2	5.8	0.3	0.5	1.1
60	62.0	29.2	7.0	0.2	0.6	1.5
75	55.1	34.3	8.3	0.3	0.8	1.4
90	47.5	40.2	10.1	0.4	1.3	1.5
105	43.0	43.1	10.8	0.3	1.5	1.8

[a] Determined by glpc; see Experimental Section. [b] See also Figure 2. [c] Ratio of alcohols; see Table IV. [d] Total of several unidentified reduction by-products.

phor the rate decreases considerably. Some values characteristic for this comparison[10-12] are summarized in Table III.[13-20] In this we projected from our results a time of 5 reaction half-lives corresponding to a yield of 96.8%. This is mostly above the yields indicated by the various authors. Also, alkoxide and ketone concentrations used by them were generally higher than in our measurements. Under comparable conditions our projected reaction times would be lower and the contrast more pronounced.

The discrepancy between high reaction rates observed here and long reaction times recorded in the literature is explicable when we consider the nature and application of the "acetone test" used in monitoring the progress of MPV reaductions.[2c,21,22] Let us consider a reaction carried out with 0.1 mol of ketone (mol wt 200) in a 0.5 *M* solution, *i.e.*, 20 g of ketone in 200 ml of *i*-PrOH. After 8 reaction half-lives 0.4% (0.08 g) of ketone will still be present and will produce in the next reaction half-life *ca.* 0.02 ml of acetone. When this amount is distilled over with 20 ml of *i*-PrOH, the concentration of acetone in the tested distillate will be 1 ppt. This is within or above the sensitivity limit of the 2,4-dinitrophenylhydrazine reagent used in this test.[2d,21,23] For preparative purposes a 98.6% conversion of the starting ketone corresponding to a mere 6 reaction half-lives would appear sufficient. Beyond this more harm is perhaps done by side reactions, and the production of acetone is in itself no proof that the starting ketone is still present.[24] We conclude without doubt that the traditional "acetone test" is not well suited for monitoring the progress of MPV reductions because of, paradoxically, its high sensitivity. Fortunately, more sophisticated methods are presently available for this purpose.

Discussion of relationships between structure and MPV reduction rate will be based on entries 2–6, 8 and 11 of Table I. Cyclopentanone 1 was the only ketone

(10) Reduction of 3-isopropylcyclohexanone and 3-bicyclo[3.1.0]hexanone required 8 and 17 hr, respectively.[11,12] Both ketones are structurally related to ketones of this study.

(11) W. Hückel and K. Thiele, *Chem. Ber.*, **94**, 96 (1961).

(12) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235 (1961).

(13) L. M. Jackman, A. K. Macbeth, and J. A. Mills, *J. Chem. Soc.*, 2641, 2646 (1949).

(14) W. Hückel and A. Hubele, *Justus Liebigs Ann. Chem.*, **613**, 27 (1958).

(15) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

(16) P. Anziani and R. Cornubert, *Bull. Soc. Chim. Fr.*, **12**, 359 (1945).

(17) W. Hückel and Ch. Z. Khan, *Chem. Ber.*, **91**, 311 (1958).

(18) O. Zeitschel and H. Schmidt, *ibid.*, **59**, 2303 (1926).

(19) D. V. Banthorpe and H. ff. S. Davies, *J. Chem. Soc. B*, 1356 (1968).

(20) (a) W. Hückel and S. Geiger, *Justus Liebigs Ann. Chem.*, **624**, 142 (1959); (b) W. Hückel, H. Feltkamp, and S. Geiger, *ibid.*, **637**, 1 (1960).

(21) H. Lund, *Chem. Ber.*, **70**, 1520 (1937).

(22) Reaction times given in the literature and quoted here are mostly based on this "acetone test." The reaction is considered complete when no acetone is detected in the distillate.

(23) We found that the limit of detectability of acetone is about 1 part in 2000. Wilds[2d] states that "1 part in 1000 is easily detected."

(24) Shiner and Whittaker[4h] pointed out that Al isopropoxide trimer **15** is a catalyst for ketone condensations.

TABLE III

COMPARISON OF REACTION TIMES RECORDED IN THE LITERATURE AND REACTION TIMES BASED ON THE PRESENT STUDY

Ketone	[Ketone],[a] M	[Al(O-i-Pr)3],[a] M	Reaction time, min × 10³	Yield, %	Ratio cis alcohol/ trans alcohol	Author
2-Methylcyclohexanone	1.35	0.45	1.8	95.0	1.0	Jackman, *et al.*[13]
	0.82	0.28	1.5	93.0	2.1	Hückel, *et al.*[14]
	0.82	0.28	1.5	85.0	1.3	Noyce, *et al.*[15]
	0.77	0.88	3.6	...[b]	0.16[c]	Anziani, *et al.*[16]
	0.253	0.215	0.15	96.8	1.3	This work
Menthone	1.35	0.45	2.1	92.0		Jackman, *et al.*[13]
	0.14	0.95	86.4	80.0		Hückel, *et al.*[17]
	2.17	0.32	7.2	96.0		Zeitschel, *et al.*[18]
	0.252	0.213	1.2	96.8		This work
Isomenthone	0.54	0.16	18.0	92.0		Hückel, *et al.*[20]
	0.252	0.213	1.0	96.8		This work
Camphor	1.35	0.83	...[d]	100.0[e]		Lund[21]
	1.35	0.45	5.4	...[f]	2.3	Jackman, *et al.*[13]
	0.252	0.213	7.2	96.8	3.0	This work
(+)-3-Thujone	0.0026	0.0078	2.4[g]	...[h]	2.7	Banthorpe, *et al.*[19]
	0.0971	0.0818	4.0	96.8	4.0	This work
(−)-3-Isothujone	0.0026	0.0078	2.4	...[h]	6.7	Banthorpe, *et al.*[19]
	0.0971	0.0818	1.3	96.8	8.1	This work

[a] Molar concentrations were calculated from amounts and/or concentrations of reagents given by the authors and relate to conditions at the beginning of reaction. Any change in concentration due to distillation was not taken into account. [b] Yield not given. [c] Extensive equilibration apparently took place. Noyce, *et al.*,[15] found a value of 0.30 for an Al(O-*i*-Pr)3 and acetone equilibrated mixture. [d] Rate quoted as "exceedingly slow." [e] Purity of product not documented. [f] Yield quoted as "nearly quantitative but a clean distillation could not be achieved." [g] Note excess of alkoxide used in reaction. [h] Yield of glpc isolated product not given. Reduction was carried out with 10–20 mg of ketone and was qualified as "completed."

that showed anomalous behavior. After a 15-min reaction time two unidentified by-products comprised 75 and 15%, respectively, of the reaction mixture, and only a trace of cyclopentanol was observed.[25,26] After 75 min 57% of cyclopentanol was formed,[27] the two original by-products decreased to 6 and 3%, respectively, and a third by-product emerged (26%). Upon further reaction these percentages remained unchanged. Reduction of ketones **2**–**8** was clean and the expected alcohols predominated as reaction products.

Reduction of cyclohexanone **2** and 2-methyl-cyclohexanone (**3**) was immeasurably rapid under our conditions. This indicates a negligible steric effect of the 2-Me group in **3** and is in sharp contrast with reaction times of 2.5–6 hr given in the literature for ketone **3** (see Table III). An isopropyl group adjacent to CO lowers the reaction rate sufficiently so as to enable its measurement under the present conditions. This is illustrated by results obtained with menthone (**4**) and isomenthone (**5**). We believe that in relation to 2-methyl-cyclohexanone the additional effect of the Me groups in ketones **4** and **5** is negligible. The rate difference between menthone (**4**) and isomenthone (**5**) can be explained by taking into account the two possible conformers of each of the two ketones. In **4** the Me and *i*-Pr groups will be either both equatorial in the more stable conformer or both axial in the less stable one, thus, in the latter case, providing an effective shielding of both sides of the molecule. In isomenthone (**5**) only one alkyl group, preferably Me, will be in axial conformation at any given time and, consequently, the total shielding will be less effective.

Turning to the more rigid bicyclic system of 3-isothujone (**7**) and 3-thujone (**8**), **7** shows the higher rate of reduction. This is instructive with regard to the possible steric influence of the cyclopropane methylene C-6 and the *i*-Pr group at the C-1 bridgehead. In ketone **7** the reagent approaches trans to the Me group adjacent to CO and produces a preponderance of cis alcohol **9** in accordance with previous observations on the directive effect of CO neighboring alkyl groups in MPV reductions.[28] Together with higher rate of reduction, this stereospecificity is more pronounced (see Table IV) than in the isomeric 3-thujone **8**. Alcohols **9** and **10** are formed in a ratio of 7:1, respectively, whereas thujone **8** yields alcohols **12** and **11** in a ratio of 3.2:1, respectively. This indicates that in **7** there is very little steric hindrance caused by the α H of the C-6 methylene when the reagent approaches from the α face and that the *i*-Pr group at C-1 assists in the primary directing effect of the CO adjacent CH_3 group. In ketone **8** the primary directing effect of this Me group (reagent approaching from the β side) is less pronounced. A larger proportion of the alkoxide is forced to approach and/or transfer its hydride anion from the α side. This confirms the negligible steric influence of the α H at C-6 and indicates that the rigidly positioned *i*-Pr group at C-1 contributes through substantial shielding of the β face to a decrease in rate as well as in stereospecificity of reduction of ketone **8**.[29,30]

(25) Self-condensation of cyclopentanone in the presence of base is known[26] to be about 1.4×10^4 more rapid than that of 2-methylcyclohexanone.

(26) J. M. Conia, *Rec. Chem. Progr.*, **24**, 43 (1963).

(27) Yields of cyclopentanol from the MPV reduction of cyclopentanone given in the literature[2,9,13] are in the 30–60% range.

(28) W. Hückel, M. Maier, E. Jordan, and W. Seeger, *Justus Liebigs Ann. Chem.*, **616**, 46 (1958), presents a valuable discussion and many leading references.

(29) In this brief discussion we are aware of our disregard for the subtle conformational problems involved in the adequate description of thujones **7** and **8**. Their conformation may range from an overall boatlike through an L-shaped (essentially flat five-membered ring) to a chairlike molecule. Although nmr studies indicated a boatlike conformation, this has not been proved conclusively.[30] Banthorpe, *et al.*,[19] in their study on the reduction of **7** and **8** by various reagents, including the MPV reduction, concluded that **7** prevails in a chairlike whereas **8** in a boatlike conformation. Our present results appear to be consistent with an L-shaped conformation in both ketones. Results of our recently completed and detailed conformational study of these two ketones support this latter view.

(30) V. Hach, F. R. Raimondo, D. M. Cartlidge, and E. C. McDonald, *Tetrahedron Lett.*, 3175 (1970).

TABLE IV

RATIO OF EPIMERIC ALCOHOLS FORMED IN THE REDUCTION OF KETONES 6, 7, AND 8 AND ITS DEPENDENCY ON REACTANT CONCENTRATION

Ketone	Concn, *M*	Alkoxide	Concn, *M*	Ketone reacted, %	Ratio[a] of cis alcohol/ trans alcohol
Camphor (6)	0.252	Al(O-*i*-Pr)$_3$	0.213	25	2.9
				50	3.0
				75	...[b]
3-Isothujone (7)	0.0971	Al(O-*i*-Pr)$_3$	0.0818	25	7.9
				50	7.9
				75	8.1
3-Isothujone (7)	0.252	Al(O-*i*-Pr)$_3$	0.213	25	...[c]
				50	7.0
				75	6.8
3-Isothujone (7)	0.483	Al(O-*i*-Pr)$_3$	0.407	25	...[c]
				50	5.9
				75	5.8
3-Thujone (8)	0.0971	Al(O-*i*-Pr)$_3$	0.0818	25	4.1
				50	4.0
				75	...[b]
3-Thujone (8)	0.252	Al(O-*i*-Pr)$_3$	0.213	25	3.5
				50	3.2
				75	2.9
3-Thujone (8)	0.483	Al(O-*i*-Pr)$_3$	0.407	25	3.0
				50	2.7
				75	2.0
3-Thujone (8)	0.0971	Al(O-*sec*-Bu)$_3$	0.0818	25	5.0
				50	5.0
				75	4.4
3-Thujone (8)	0.252	Al(O-*sec*-Bu)$_3$	0.213	25	...[c]
				50	4.5
				75	3.8

[a] In the case of camphor ratio of exo/endo alcohol, *i.e.*, isoborneol/borneol. In the case of 3-isothujone and 3-thujone ratio of 9:10 and 12:11, respectively. [b] Only 60% of reaction was followed. [c] Due to relatively high reaction rate the ratio at 25% ketone reacted was not established.

Camphor shows by a considerable margin the lowest rate of reduction indicating the effect of rigidity and steric hindrance in the vicinity of the CO group and along the reaction path. However, in its ultimate effect rigidity of a cyclic system may be a key factor enabling reagent approach by locking CO neighboring groups in a fixed position. This is revealingly demonstrated by results obtained with fenchone (**13**) and di-*tert*-butyl ketone (**14**). Yager, *et al.*,[4g] were unable to reduce **14** or, for that matter, to oxidize di-*tert*-butylcarbinol despite a reaction time of "several days." Consequently, one could be tempted to predict that fenchone (**13**) would not be reduced as well. However, fenchone **13** was reduced by two groups.[31,32] Apparently, the free rotation of *t*-Bu groups around the C–CO axis in ketone **14** can block the reagent approach completely whereas the "locked positions" of CH_3 and CH_2 groups in fenchone (**13**) leave a marginal opportunity for reagent attack from the endo side of the molecule to yield 95% of exo alcohol as shown by Hückel and Meinhardt.[32]

Finally, we may take a brief note of entries 7–14 in Table I. These results are in agreement with observations made by previous workers[4a,c,g] who detected pseudo-first-order disappearance of ketone and dependency of reaction rate on concentration and ratio of reagents. As stated in the previous the overall reaction rate has not been established conclusively.

Ratio of Epimeric Alcohols.—Results obtained in studies on the ratio of epimeric alcohols formed in the MPV reduction of camphor (**6**), isothujone **7**, and thujone **8** are briefly summarized in Table IV. Some stereochemical implications of these results have already been mentioned in the preceding discussion. Two additional aspects will be considered here.

First is dependency of the epimeric alcohol ratio on reaction time. To our best knowledge this facet of the MPV reduction has not previously received any attention.[33,34] Constancy of this ratio throughout the reduction would be a strong proof of nonequilibrating conditions and, consequently, of kinetic product control. Indeed, it follows from results in Table IV that this condition was achieved. As had been expected reduction with the bulkier Al(O-*sec*-Bu)$_3$ in *sec*-BuOH was more stereospecific. A slight downward drift of the cis/trans ratio was occasionally observed. However, when contrasted with experiments carried out under truly equilibrating conditions (Figure 1) this appeared to be of little significance.

Second is influence of concentration of reactants on the epimeric alcohol ratio. This was studied in more detail using ketones **7** and **8**. Surprisingly, this ratio was dependent on the absolute concentration of reactants, the ratio of reactants being constant. In

(31) P. Hirsjärvi and N. J. Toivonen, *Suom. Kemistilehti B*, **23**, 14 (1950); *Chem. Abstr.*, **45**, 1545 (1951).

(32) W. Hückel and G. Meinhardt, *Chem. Ber.*, **90**, 2025 (1957).

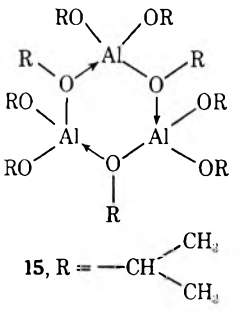
(33) Recently, Rickborn and Wuesthoff[34] studied the dependency between ratio of epimeric alcohols formed in $NaBH_4$ reductions of alkylcyclohexanones and reaction time. Surprisingly, a continuous change in the ratio of epimeric alcohols during the course of reduction was observed.

(34) B. Rickborn and M. T. Wuesthoff, *J. Amer. Chem. Soc.*, **92**, 6894 (1970).

dilute solutions the cis alcohol/trans alcohol ratio was higher, and thus the stereospecificity of reduction was more pronounced than in concentrated solutions. This observation may be of serious consequence in two respects: practical utilization of the MPV reduction and stereochemical interpretation of results published in previous literature. Regarding the first point it will be advisable to carry out MPV reductions at the highest dilution compatible with acceptable reaction rate when pursuing an increase in stereospecificity. Regarding the second point, it will be reasonable to reconsider ratios of epimers obtained from MPV reductions and recorded in the literature with respect to reactant concentration applied. Also, conclusions drawn from comparisons between ratios of epimers obtained by other reducing agents, particularly complex hydrides,[35-37] and by MPV reductions should perhaps be more cautious.[38]

Limited results of Jackman, Noyce, and Hückel and their collaborators with 2-methyl-cyclohexanone as well as our and Jackman's results on camphor (Table III) seem to support our observation that stereospecificity of MPV reduction is more pronounced in dilute solutions.[39]

We believe that the key factor governing the relation between product stereochemistry and reactant concentration will be the concentration-dependent association of Al(O-*i*-Pr)$_3$ with *i*-PrOH. Shiner and Whittaker[4e,h] have shown that at the boiling point of *i*-PrOH Al isopropoxide as a reactive species is trimeric **15**.



Apparently, this trimer will be subject to a high degree of solvation by solvent alcohol in addition to direct coordination through available d orbitals of aluminum. In support of this view Shiner, *et al.*, observed that the reaction between a ketone and trimer **15** had a higher rate in benzene than in a 1:1 mixture of benzene and *i*-PrOH, and they assumed that this rate acceleration was caused by greater accessibility of the trimer to coordination with ketone as *i*-PrOH was removed from its association with the trimer. A similar solvent association mechanism could possibly explain the results of Bains and Bradley[4d] who found that within a narrow range of 16–32° the reaction order of MPV reduction with respect to alkoxide changed by more than 50%. It is reasonable to assume that a higher degree of solvation of the bulky trimer **15** in dilute solution will require that its approach[40,41] by and coordination with a ketone[42] be more stereoselective. The same would apply to the subsequent hydride transfer step. This then could determine the higher degree of reaction stereospecificity[43] in dilute solution.

Experimental Section

Materials.—Ketones **1–6** were of commercial origin. Standard purification methods were applied when necessary so that materials used in rate measurements were at least 99% pure determined by glpc. Pure (+)-3-thujone (**8**) was obtained as described previously.[44] (−)-3-Isothujone (**7**) was obtained either by spinning band column distillation of Western red cedar (*Thuja plicata* Donn) leaf oil or by Brown oxidation[45] of crystalline (−)-3-neoisothujanol (**9**). Details of this work will be reported subsequently.

Aluminium isopropoxide and Al(O-*sec*-Bu)$_3$ were prepared *in situ* by dissolving Al cleaned by washing with CCl_4 in the corresponding alcohol. The solutions were used immediately. The main reason for this approach was the fact that crystalline Al(O-*i*-Pr)$_3$ is tetrameric whereas in solution at the boiling point of *i*-PrOH it is trimeric. In addition, the conversion of tetramer into trimer is slow, and its actual rate under our projected conditions is not known.[1f,h] However, according to previous results[4f,h] our procedure provided a solution of the trimer **15** only. To initiate the dissolution of Al a trace of $HgCl_2$ was used as catalyst. It is generally accepted that the MPV reduction is not influenced by its presence.[28] To support this point control experiments were carried out in which the dissolution of Al was initiated by I_2 or CCl_4. No difference in reaction rate was observed with any of these three catalysts.

Procedure.—A ground-glass joint apparatus consisting of a three-necked flask and a distilling condenser was used. The flask was equipped with a calibrated dropping funnel, thermometer reaching into the reaction mixture, and a magnetic stirring bar. The distilling condenser head was fitted with a thermometer, and the condenser receiving end was equipped with a calibrated receiver enabling distillate volume measurement. Reaction samples were withdrawn from the flask *via* a septum-like attachment. The whole apparatus was protected by a $CaCl_2$ tube. The flask was placed in an oil bath located on a thermostatically controlled stirrer–heater combination.

Aluminum alkoxide solutions were prepared by dissolving the necessary amount of Al in the appropriate amount of dry *i*-PrOH or *sec*-BuOH. In the calculation of molarity the volume of subsequently added ketone was accounted for. Change in alcohol volume caused by dissolution of Al was found to be negligible. The amount of $HgCl_2$ used as catalyst was 12.6 mg/0.1 mol of Al alkoxide. The time necessary to complete dissolution of Al was about 1 hr, and the practically clear alkoxide solution was then stirred for another hour at 45°. Throughout the dissolving process very little heat had to be supplied. The amount of alcohol that distilled off was exactly measured and

(35) Rickborn, *et al.*,[34] brought into serious doubt another common belief purported in the literature, that is, that the ratio of epimeric alcohols formed in hydride reductions is independent of the ratio hydride/ketone. Rickborn, *et al.*, have shown that this may be true in a few specific ketones but must not be accepted as a general rule; see ref 36 also. Snyder[37] has shown that the ratio of *cis*- and *trans*-cyclopentane- and -cyclohexane-1,2-diols formed by MPV reduction of the corresponding 1,2-diones was dependent on the ratio dione/alkoxide.

(36) (a) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2368 (1962); E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970), and references therein.

(37) (a) C. H. Snyder, *J. Org. Chem.*, **31**, 4220 (1966); (b) C. H. Snyder and M. H. Micklus, *ibid.*, **35**, 264 (1970).

(38) W. Hückel, *et al.*,[28] relates numerous examples and provides an extensive background on this topic.

(39) Banthorpe's and our results on thujones in Table III are not comparable. Banthorpe, *et al.*, carried out the reduction of both ketones under reflux and, apparently, brought about equilibration of the epimeric alcohols despite the fact that they worked in a more dilute solution than we did.

(40) Steric influence during such an approach are remotely illustrated by the findings of Bradley[41] who has shown that branched and sterically hindered alcohols interchange with Al alkoxides more slowly than straight-chain alcohols.

(41) D. C. Bradley, *Progr. Inorg. Chem.*, **2**, 303 (1960).

(42) Undoubtedly, solvation of the ketone itself will also be a contributing factor.

(43) There seems to be somewhat more evidence available in the area of complex hydride reductions in regard to solvation influencing the ratio of epimeric alcohols formed although, a coherent picture is still missing. These aspects were admirably discussed by Eliel, *et al.*,[35] and there is little doubt that the nature of solvent and its association with complex hydride indeed plays a role in determining the ratio of epimeric alcohols.

(44) V. Hach, R. W. Lockhart, E. C. McDonald, and D. M. Cartlidge, *Can. J. Chem.*, **49**, 1762 (1971). In the present paper as in our previous papers we adopted the thujone–thujanol nomenclature proposed by H. C. Brown; see also ref 30.

(45) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

was replaced by fresh dry alcohol after the completed dissolution. This amount was never more than a few milliliters.

Kinetic runs were carried out as follows. The solution was brought to gentle boiling and stirred magnetically to assure its smoothness. The rate of stirring was estimated at about 200 rpm and was kept constant throughout the experimental series. Immediately after the boiling point was reached the calculated amount of ketone was introduced and this moment was taken as time zero. The amount of ketone was mostly between 5 and 10 g depending on the desired molarity. Volume of the reaction mixture varied between 135 and 270 ml. Samples were withdrawn at 15-min intervals. In all cases eight samples were sufficient to establish very good kinetic plots. The mixture of acetone or 2-butanone formed in the reaction and the corresponding alcohol distilled off at an average rate of 8 ml per 15 min with limits of 5–11 ml. After each sampling in the standard 15-min interval a volume of dry alcohol was added to the reaction mixture equal to the volume of distillate collected in the preceding 15-min interval. This kept the volume of the reaction mixture essentially constant and guaranteed the continuous removal of acetone or butanone formed by the reaction. In control experiments total amounts of acetone in the distillate were found to be in rough agreement with the amounts expected. Obviously, losses of acetone in the reaction mixture may occur as a consequence of side reactions.[4h,46]

Each sample (about 5 ml) withdrawn from the reaction mixture was quenched in a 10% solution of tartaric acid containing 1.5 g of acid/0.1 g of Al in the sample. The products were extracted with ether; the extract was washed with a 3% $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated. Material balance experiments confirmed complete extraction. In the resulting sample starting ketone, epimerized ketone where applicable, alcohols produced and total percentage of by-products formed were determined by glpc analysis using procedures described by us previously.[30,44,47] No attempt was made to identify the individual by-products. All kinetic runs were duplicated. A precision of 4% or better was usually achieved in corresponding determinations at specific time intervals. When necessary the run was repeated for a third time or more in case of any doubt. Typical analytical results from the reduction of 3-thujone (**8**) are given in Table II. Reaction constants in Table I were established graphically from semilogarithmic plots of percentage of disappearing ketone *vs.* time as exemplified by Figure 2. Best fits were obtained according to Livingston.[48] Reaction half-lives were calculated using the standard equation $t_{1/2}(\text{min}) = 2.303 \log 2/k\,(\text{min})$.

In preliminary experiments without acetone removal the apparatus was similar except that a reflux condenser was used instead of a distilling condenser. Also, the procedure was similar and a typical result is exemplified by Figure 1.

Criticism of Method.—Three topics warrant a more detailed discussion: concentration of reagents, epimerization of starting ketones, and by-product formation.

The principle of our approach, *viz.*, the exclusion of equilibrating conditions, necessitated the continuous removal by distillation of acetone or 2-butanone formed in the reduction. A batch-type reaction rate measurement brings about the inherent problem of maintaining a constant reactant concentration. In extreme cases the change of volume during the 15-min interval in which the volume was being adjusted amounted to about 10% and thus to a corresponding 10% change towards higher molar concentration of reactants. From entries 7, 8, 10, and 11 of Table I it appears that a 100% rise in reactant concentration led to a 33% enhancement of rate constant. Consequently, 10% would cause approximately a 3% error in a rate constant. We reiterate that these conditions were applicable only in a few cases of lower reaction volumes and in the latter part of the reaction. Further, due to averaging of reaction times at lower and higher concentration the potential error will actually be lower. With reaction volumes of 250 ml a change of 8 ml would lead to a reaction rate constant uncertainty of about 1%. In regard to the starting concentration of Al alkoxide the assumption was made that all Al was converted into the alkoxide in accordance with established knowledge.[41] Unfortunately, there is no method available that would enable an accurate estimation of Al alkoxide in solution. In all previous kinetic work[4a,c,g] only the total content of Al in solution was estimated by absolutely irrelevant nonspecific procedures as Al_2O_3. The only loss in concentration of alkoxide could possibly occur by hydrolysis. However, traces of moisture would manifest themselves promptly by inhibiting the dissolution of Al and, subsequently, the reaction itself. Therefore, careful avoidance of moisture was one of the main prerequisites which was rigidly controlled.

Epimerization of ketones like **4**, **5**, **7**, and **8** by Al alkoxide would obviously distort the rate measurement. Fortunately enough its extent was in the 1.5–3% range, the higher value resulting from reductions with 0.407 *M* alkoxide beyond 60% ketone disappearance. This value is in accord with findings of Hückel[18] and Banthorpe[17] on the isomeric menthones and thujones respectively. As shown in Table II epimerization demonstrates itself predominantly by the presence of alcohols corresponding to the epimerized ketone.

As in the case of epimerization by-product formation was directly proportional to alkoxide concentration and stage of reduction. With alkoxide concentration of 0.407 *M* by-product formation reached about 3% after 75% reaction completion. Otherwise by-products were in the 1–2% range with the exception of cyclopentanone reduction discussed previously.

In conclusion, taking into account the outlined points and the accuracy of the glpc method used, which was established to be ±3%, we estimate an uncertainty limit of about ±10% for the rate constants at highest (0.407 *M*) alkoxide concentrations. The basis for our structure–reactivity discussion were rates obtained with 0.213 *M* alkoxide. These have a lower uncertainty limit and allow for a meaningful and conclusive discussion of the relationship between sterical environment of the CO group and its rate of reduction by the MPV method.

Registry No.—**1**, 120-92-3; **2**, 108-94-1; **3**, 583-60-8; **4**, 1074-95-9; **5**, 36977-92-1; **6**, 464-48-2; **7**, 546-80-5; **8**, 471-15-8; Al(O-*i*-Pr)$_3$, 13431-86-2; *i*-PrOH, 67-63-0; Al(O-*sec*-Bu)$_3$, 36977-99-8; *sec*-BuOH, 78-92-2.

Acknowledgments.—The skillful experimental assistance of Mrs. E. C. Fryberg is gratefully acknowledged. A substantial part of the glpc analyses was carried out by Dr. W. G. Howells and Mr. K. L. McDonald and their staff at MacMillan Bloedel Research Ltd. Their cooperation has been appreciated.

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The Bromination of Methoxyaromatic Ketones. An Interpretation of Substituent Interactions

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The rates of ring bromination of 11 variously substituted methoxyaromatic ketones are reported. The data are discussed with respect to the net substituent effect (represented by $\Sigma\sigma^+$) as modified by substituent interaction (represented by $\Sigma\sigma_i^+\sigma_j^+$) using the following equation, $\log (k/k_0) = p\Sigma\sigma^+ + q\Sigma\sigma_i^+\sigma_j^+$, where p and q describe the sensitivity of the reaction to the net substituent effect and substituent interaction, respectively. For compounds bearing the methoxy and propionyl groups ortho to each other the results are consistent with a steric inhibition to substituent interaction. This steric inhibition is evoked quantitatively in terms of the above equation. The treatment shows that electrophilic attack by bromine is itself insensitive to steric effects; these latter make their appearance *via* substituent interaction.

A recent publication[1] from these laboratories treated the bromination of polysubstituted benzenes in terms of both the inherent contribution of each substituent on reactivity (using $\Sigma\sigma^+$) and the influence of substituent interactions, as measured by the term $\Sigma\sigma_i^+\sigma_j^+$. The compounds used in this prior study were selected so as to avoid certain complications, such as the presence of very bulky groups, groups whose substituent action is orientation dependent, etc., which might conceivably be faced after the fundamental soundness of the approach was demonstrated. The provocative nature of the results obtained leads us at this time to a consideration of the bromination of aromatic ketones bearing a methoxy substituent in the aromatic ring. A study of the influence of the keto group on reactivity was our motivation for this work; the presence of the methoxy group was necessary to activate the ring towards electrophilic substitution, without which the keto–enol system might undergo bromination as well. As we shall see, this precaution ensures a sufficiently superior reactivity of the aromatic moiety over the keto moiety such that the latter may be disregarded as a reaction center and viewed as a substituent.

Results

For purposes of product analysis three compounds were chosen—*p*-methoxyacetophenone, *o*-methoxyacetophenone, and 4,5-dimethyl-2-methoxypropiophenone. Following a procedure given in the Experimental Section, each was brominated and gave rise to a single product along with a trace of starting material. An nmr analysis of these products revealed that only ring bromination had occurred. These data are given in Table I.

The rate data were obtained by the method of automated couloamperometry as previously described.[2,3] The kinetic characterization of the system was carried out in three series of rate studies allowing, in each instance, one factor among acidity, ketone concentration, and bromine concentration to vary. The ionic strength was controlled by the addition of NaBr. Table II shows these results, which demonstrate that the reaction rate is independent of acid concentration and first order in both bromine and ketone concentrations. The kinetic behavior is then adequately represented by eq 1. It is worth noting that an expression

$$\frac{-d[Br_2]}{dt} = k[Br_2][\text{ketone}] \qquad (1)$$

of the same form as eq 1 could be obtained for the bromination of the keto moiety if the bromination of its enol form were rate determining.[4,5] Thus the absence of a kinetic dependence on acidity does not constitute a criterion for deciding which part of the molecule reacts; product studies are necessary to clarify this point.

In all, the bromination rates of 11 variously substituted aromatic ketones were measured under identical conditions of temperature, solvent, and ionic strength. The rate constants are given in Table III, where the position of attack on the ring is noted as well.

Discussion

In Figure 1 the values of $\log k$ are plotted against the quantity $\Sigma\sigma^+$.[6] For ease of reference the points are numbered.[7] Two facts are immediately evident: that the points corresponding to bromination para to methoxy correlate well with $\Sigma\sigma^+$ and those (only three in number) corresponding to ortho bromination do not. Compounds **9** and **11**, which are brominated ortho to the methoxy group, represent one difficulty with a treatment of this kind—they are isomers which possess the same value of $\Sigma\sigma^+$ and lead one to expect equivalent rates. This is usually what is found, as demonstrated by the reaction rates of the following three pairs of compounds.

(1) J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doucet, F. Rothenberg, and R. Uzan, *J. Amer. Chem. Soc.*, **94**, 6823 (1972), and references cited therein.

(2) J. E. Dubois, P. Alcais, and G. Barbier, *J. Electroanal. Chem.*, **8**, 359 (1964).

(3) J. E. Dubois and J. J. Aaron, *J. Chim. Phys.*, **66**, 1109 (1969).

(4) R. P. Bell and G. C. Davies, *J. Chem. Soc.*, 902 (1964).

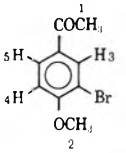
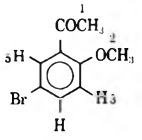
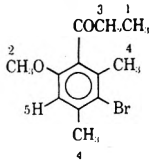
(5) J. E. Dubois and J. Toullec, *J. Chim. Phys.*, **65**, 2166 (1968); *Chem. Commun.*, 212 (1969).

(6) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

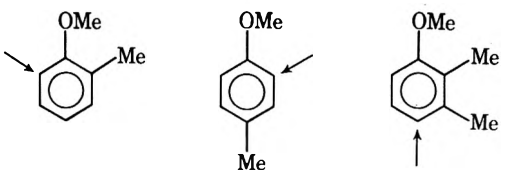
(7) (a) The value of σ_0^+ for the groups RCO– is unknown. We have used the σ_M value of CH_3CO– (0.376)[7b] for all groups RCO–. Because of the similarity of compounds **1**, **3**, and **5** and **2**, **4**, and **6** we consider only compounds **3** and **4** in the figures and tables presented. (b) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 173.

TABLE I

NMR SPECTRA OF SOME BROMINATED METHOXYAROMATIC KETONES

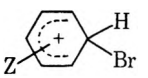
Registry no.	Brominated ketone	Chemical shift, δ, ppm[a] δ1	δ2	δ3	δ4	δ5
35310-75-9		2.53	4.04	8.02	7.20	8.22
16740-73-1		2.53	3.90	6.82	7.47	7.72
36871-61-1		1.10	3.75	2.61	2.19 2.38	6.61

[a] In CCl_4 solution, with tetramethylsilane as reference.



In the present instance this is not true, which causes one to seek some special effect which alters preferentially the reactivity of one of the isomers; this point will be considered later.

We would like to discuss these results in terms of a previous analysis from these laboratories[1] which concerned the correlation of bromination rates of a large population (44 polymethylated benzenes, substituted anisoles, and *N*,*N*-dimethylanilines) of mono- and polysubstituted benzenes. In this prior study the reaction mechanism for all compound was assumed to be identical (arguments were presented to show that this may be so), *i.e.*, all passing through a σ-complex transition state.



The reaction rates within each discrete family of compounds have long been known to correlate with $\Sigma\sigma^+$, yielding a different value of ρ^+ in each case.[8,9,10-12]

(8) J. J. Aaron and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 603 (1971).
(9) R. Uzan and J. E. Dubois, *ibid.*, 598 (1971).
(10) F. Rothenberg, P. Alcais, and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 592 (1971).
(11) J. E. Dubois, P. Alcais, and F. Rothenberg, *J. Org. Chem.*, **33**, 439 (1968).
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TABLE II

REACTION ORDER WITH RESPECT TO THE VARIOUS COMPONENTS

2,4-Dimethyl-6-methoxypropiophenone, $M^a \times 10^7$	Br_2, $M^b \times 10^7$	k_{obsd}, M^{-1} sec^{-1} [b] $\times 10^{-6}$
A. Variation of Bromine Concentration		
6.07	0.81	1.0
6.06	1.85	1.15
5.70	2.84	1.2
8.33	5.81	1.1
B. Variation of Ketone Concentration		
4.5	2.76	1.25
8.93	2.88	1.05
10.80	2.49	1.0
12.1	2.53	1.0

C. Variation of Acidity

Ketone	$HClO_4$, M	k_{obsd},[c] M^{-1} sec^{-1}
4-Methoxyacetophenone	0	0.85 ± 8%
	0.10	0.79 ± 3%
	0.20	0.80 ± 2.5%
4-Methoxypropiophenone	0	0.96 ± 8.5%
	0.10	1.06 ± 2%
2,4-Dimethyl-6-methoxypropiophenone	0	1.64 ± 4%
	0.20	1.62 ± 8%
		1.67 ± 7.5%

[a] Initial concentration, moles/liter. [b] Electrolyte concentration maintained at 0.10 M by addition of sodium bromide. [c] Total electrolyte concentration maintained at 0.30 M by addition of 0.10 M sodium bromide and sodium perchlorate as required.

A correlation of the entire population was considered by making use of both the term $\Sigma\sigma^+$ and a substituent interaction term of the form $\Sigma\sigma_i{}^+\sigma_j{}^+$, which was assumed to account for specific substituent interactions of an electronic nature. Equation 2 expresses this

$$\log k/k_0 = p\Sigma\sigma^+ + q\Sigma\sigma_i{}^+\sigma_j{}^+ = -11.3\,\sigma^+ - 6.3\,\sigma_i{}^+\sigma_j{}^+ \quad (2)$$
$$r = 0.988 \qquad \Psi = 0.15$$

correlation mathematically, where k_0 is the rate of bromination of benzene statistically corrected ($\log k_0 = -5.64$). The quantity p was associated with the ρ^+ for the bromination of monosubstituted benzenes

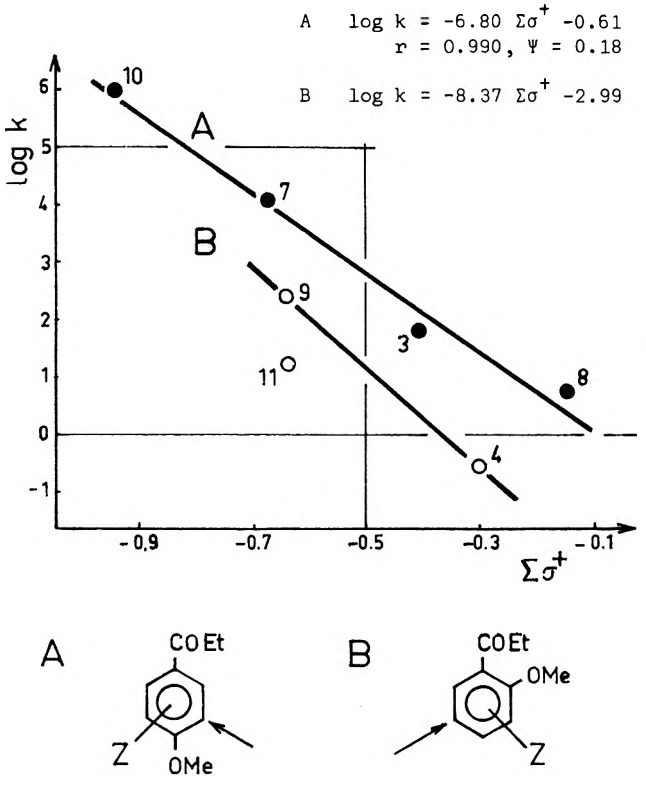


Figure 1.—Correlation of bromination rates with $\Sigma\sigma^+$.

TABLE III
BROMINATION RATES OF SOME METHOXYAROMATIC KETONES IN WATER AT 25.0°[a]

No.	Ketone	Reaction center[b]	k_{obsd},[c] M^{-1} sec^{-1} × 10^{-3}
1	2-Methoxyacetophenone	Para	0.0605
2	4-Methoxyacetophenone	Ortho	0.000282
3	2-Methoxypropiophenone	Para	0.088
4	4-Methoxypropiophenone	Ortho	0.000375
5	2-Methoxybutyrophenone	Para	0.089
6	4-Methoxybutyrophenone	Ortho	0.000362
7	4-Methyl-2-methoxypropiophenone	Para	12.9
8	4-Chloro-2-methoxypropiophenone	Para	0.00573
9	2,5-Dimethyl-4-methoxypropiophenone	Ortho	0.248
10	2,4-Dimethyl-6-methoxypropiophenone	Para	1.045
11	4,5-Dimethyl-2-methoxypropiophenone	Ortho	0.017

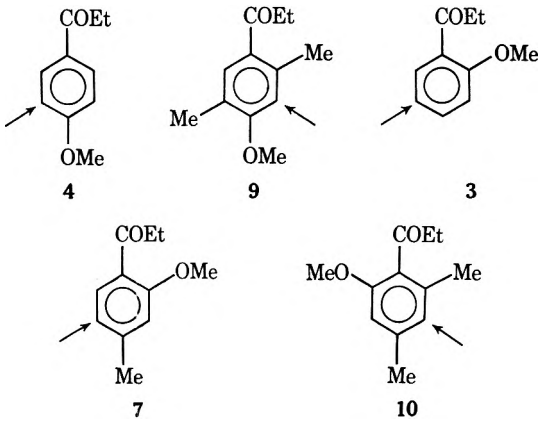
[a] NaBr = 0.10 *M*. [b] The reaction center is designated with respect to the methoxy group. In each case this was verified by vpc product analysis. [c] All rate constants statistically corrected for one reaction center.

(−11.6) and the term q with the sensitivity of the reaction to substituent interaction. The compounds employed in this previous correlation were selected with the hope that they would not exhibit any specific effects other than strictly electronic interactions. Such eventualities as noncoplanarity of rings or steric effects would be difficultly separable from other substituent interactions.

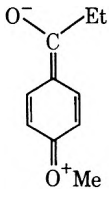
The manifest success of this correlation leads us to question the extent to which the rate constants given in Figure 1 can be estimated by the use of eq 2. The estimated values (log k_{calcd}) together with the differences between calculation and experiment (log k_{exp}) − log k_{calcd}) are given in Table IV. For compounds **4** and **9** the estimated values agree closely with experiment. The well-behaved nature of **9** indicates that the reactivity of its isomer **11** is controlled by features different from those taken into account by the terms $\Sigma\sigma^+$ and $\Sigma\sigma_i{}^+\sigma_j{}^+$.

We will come back to this point. This leaves compounds **3**, **7**, **8**, and **10** for consideration.

These four compounds are more reactive than anticipated by the summation of the interaction terms $\sigma_i{}^+\sigma_j{}^+$, compound **8** considerably so (2.32 log units) but the others by a quantity nearly equal for all three (≅1 log unit). An explanation of this behavior can be obtained by considering the structures and positions of attack of the predictably reacting compounds **4** and **9** compared with those of the three whose reactivity appears to be augmented over the anticipated value by a constant amount (**3**, **7**, and **10**).



For compounds **4** and **9** an interaction involving the following reasonance form must be important.



The predictability of the reactivity of **4** and **9** indicates strongly that such an interaction is incorporated into the interaction term $\Sigma\sigma_i{}^+\sigma_j{}^+$. However, for compounds **3**, **7**, and **10**, which have the keto group and the methoxy group in an ortho arrangement with respect to one another, such a resonance form would be less important for purely steric reasons. If an interaction of this kind is already included in the term $\Sigma\sigma_i{}^+\sigma_j{}^+$ the "estimated" reactivity will be necessarily smaller than that found from experiment. For these three compounds, then, what we could be observing is a *steric inhibition of substituent interaction*, pointed out by the application of eq 2. In the case of compound **10**, where the reaction center is flanked by two methyl groups, one is tempted to accord some steric contribution to these groups. This cannot be true, since such compounds fit acceptably into the general correlation (eq 2) along with other polymethyl benzenes which do not have this feature.[10,11]

The anomaly mentioned above concerning compounds **9** and **11** also bears on this interpretation. On the assumption that **9** reacts normally, we may inquire

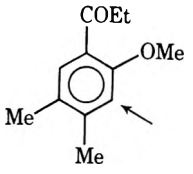
TABLE IV

ESTIMATION OF REACTION RATES USING EQUATION 2

Compd	Reaction center	$\Sigma\sigma^+$	$\Sigma\sigma_i^+\sigma_j^+$	log k_{exp}	log k_{calcd}	log k_{exp} − log k_{calcd}
3	Para	−0.402	−0.292	1.944	0.80	1.14
4	Ortho	−0.302	−0.254	−0.43	−0.62	0.19
7	Para	−0.678	−0.182	4.11	3.18	0.93
8	Para	−0.139	−0.398	0.758	−1.56	2.32
9	Ortho	−0.644	−0.134	2.394	2.45	−0.06
10	Para	−0.954	0.004	6.014	5.04	0.97
11	Ortho	−0.644	−0.134	1.230	2.48	−1.28
		(−0.415)[a]	(−0.125)[a]		(−0.16)[a]	(1.36)[a]

[a] Rate estimated using $\sigma^+_{o\text{-MeO}}$; solvolysis −0.445. All other estimates based on $\sigma^+_{o\text{-MeO}}$ −0.678.

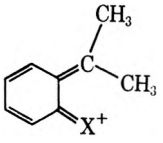
why **11** reacts more slowly than calculated by means of the interaction term $\Sigma\sigma_i^+\sigma_j^+$. Compound **11** is the



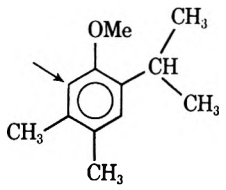
11

only one studied involving substitution ortho to methoxy with, at the same time, the keto and methoxy groups ortho to each other.

The large estimated rate may result from an injudicious choice of σ_0^+ for the methoxy group. The value used for compounds **4** and **9** is that obtained from electrophilic substitution reactions.[13] Another set of σ_0^+ values exists which have been determined from the solvolysis of ortho-substituted 2-phenyl-2-propyl chlorides.[6] These values are not so large as those determined from electrophilic substitution since resonance structures of the form



are to some extent sterically hindered. The very crowded environment of the methoxy group in compound **11** may inhibit such reasonance, which would make the σ_0^+ obtained from solvolysis a more valid choice. This value is used for the numbers given in parentheses in Table IV. The calculated rate is, in this case, smaller than the experimental value by 1.36 log units. This deviation is very similar to that found for compounds **3**, **7**, and **10**, where it was suggested that the substituent interaction suffered an attenuation for steric reasons. In compound **11** the keto and methoxy groups are ortho to one another, as they are in compounds **3**, **7**, and **10**. It is therefore suggested that in the case of **11** there are two interactions of steric origin, one of which can be accounted for by a suitable



choice of σ_0^+ and one of which is similar in nature to that suggested for **3**, **7**, and **10**. The reactivity of 2-isopropyl-4,5-dimethylanisole, considered in a related study,[14] also supports this point of view.

The estimated reactivity (log k_{calcd} = 5.23) is considerably superior to the experimental value (log k_{exp} = 3.516) when one uses the $\sigma^+_{o\text{-MeO}}$ obtained from electrophilic substitution; however, the agreement between calculation and experiment is excellent when the $\sigma_{O\text{-MeO}}$ solvolysis is employed (log k_{calcd} = 3.36). One might be inclined to believe that the low experimental rate is due to a steric effect on the bromination itself, since the reaction center is flanked by both a methyl group and a methoxy group. This interpretation seems unlikely if we consider the reactivity of compound **9** in the present work. In this compound the reaction center is also flanked by a methyl and a methoxy group but the reactivity is quite "normal." It appears that the extremely crowded environment influences the reactivity *via* the methoxy group and not by a direct effect on the reacting center. This line of thought provides a rationale for the anomalous behavior of **11**; to verify this fully more kinetic data for compounds of this kind are needed.

It would appear, then, that the ideas set out in ref 1 are of particular interest in assessing the importance of certain neighboring substituent interactions. The influence of electronic effects seems by and large to be accounted for by the interaction term $\Sigma\sigma_i^+\sigma_j^+$; steric effects appear as systematic deviations from this rule. The data used in ref 1 (except for four compounds possessing the group $-NMe_2$) do not incorporate groups whose electronic interactions would be sterically dependent. In the present case the group RCO– shows, according to its environment, instances of good behavior as well as ill behavior, demonstrated by the application of eq 2. This, we feel, indicates the utility of this approach in helping to disentangle the manifold complexities of substituent effects on the electrophilic substitution of polysubstituted benzenes.

Experimental Section

Materials.—All methoxyaromatic ketones were prepared by the reaction of the parent hydroxyaromatic ketones with dimethyl sulfate in methanolic sodium hydroxide.[15] The hydroxyaromatic ketones were synthesized by the Fries reaction, as previously described.[15,16] The data for three substituted methoxypropiophenones, not previously recorded, are now reported.

(13) C. W. MacGary, Y. Okamoto, and H. C. Brown, *J. Amer. Chem. Soc.*, **77**, 3037 (1955).

(14) J. E. Dubois and D. Balou, unpublished results.

(15) F. Krausz, R. Martin, and J. P. Gavard, *Bull. Soc. Chim. Fr.*, 640 (1966).

(16) F. Krausz and R. Martin, *ibid.*, 2192 (1965).

4-Methyl-2-methoxypropiophenone had ir (CH_2Cl_2, 5%) 1669 (C=O), 1610, 1570, 1495, 1460 (aryl C=C), and 1209 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.58; H, 7.80.

2,5-Dimethyl-4-methoxypropiophenone had ir (CH_2Cl_2, 5%) 1672 (C=O), 1610, 1560, 1508, 1462 (aryl C=C), and 1231 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.94; H, 8.39. Found: C, 74.34; H, 8.42.

4-Chloro-2-methoxypropiophenone had ir (CH_2Cl_2, 5%) 1673 (C=O), 1590, 1568, 1480, 1460 (aryl C=C), and 1241 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.11; H, 5.56; Cl, 17.74.

All inorganic compounds used (perchloric acid, sodium perchlorate, sodium bromide, bromine) were reagent grade. Water used as solvent was distilled twice over alkaline potassium permanganate.

Kinetic Measurements.—All kinetic measurements were performed by the automatic method of couloamperometry as previously described.[2,3]

Synthesis of Reaction Products.—The same method was used for the preparation of the three bromo ketones (3-bromo-4-methoxyacetophenone, 5-bromo-2-methoxyacetophenone, 3-bromo-2,4-dimethyl-6-methoxypropiophenone).

To a mechanically stirred solution of 4.5–4.9 g (0.025 mol) of methoxyaromatic ketone in 250 ml of acetic acid, a solution of 4.0 g (0.025 mol) of bromine in 50 ml of acetic acid was added in small portions. After complete addition of bromine (40 min), about 50 ml of water was added to accelerate the reaction; the mixture was stirred for 2 hr. It was extracted three times with carbon tetrachloride and dried over sodium carbonate. Most of the CCl_4 was evaporated. The CCl_4 concentrated layer was analyzed and its components were separated by preparative gas chromatography. The following columns were used: 20% XF-1150 and 10% UCON Polar on Chromosorb W (Aerograph Co.). Vpc analysis showed traces of the starting methoxy aromatic ketone and in each case only one brominated compound, identified by nmr as the nuclear bromo ketone (see Table I). The retention times of these synthesized bromo ketones were found to be identical with those of the bromo ketones obtained under kinetic conditions.

Registry No.—**1**, 579-74-8; **2**, 100-06-1; **3**, 5561-92-2; **4**, 121-97-1; **5**, 13404-83-6; **6**, 4160-51-4; **7**, 36871-54-2; **8**, 36871-55-3; **9**, 36871-56-4; **10**, 5384-14-5; **11**, 36871-58-6.

Cyclopropylamines as Intermediates in a New Method for Alkylation of Aldehydes and Ketones

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Received June 27, 1972

A series of 1-(N,N-disubstituted amino)bicyclo[*n*.1.0]alkanes was prepared from cyclic ketone enamine derivatives and methylene or ethylene iodide and diethylzinc or diazomethane or diazoethane and cuprous chloride. Thermal opening in aqueous methanol furnished the α-alkylated and ring-expanded ketones. Similarly, propionaldehyde was converted to isobutyraldehyde (49%), cholestenone to 4-methylcholestenone (76%), and 17-β-hydroxy-5-α-androstan-3-one to 2β-methyl-17β-hydroxy-5α-androstan-3-one (67%) through cyclopropylamine intermediates. The thermolysis is accelerated by surface-active agents, *i.e.*, 10% Pd/C. Opening of the cyclopropylamines in the presence of acrylonitrile gave products corresponding to those obtained with the alkylated enamines. Hydrogenolyses of some bicyclic cyclopropylamines furnished *N*-(2-methylcycloalkyl)amines.

In syntheses of aliphatic compounds, the α-alkylation of ketones and aldehydes is the most widely used reaction principle for carbon to carbon bond formation. Classically, such alkylations are accomplished by formation of enolate anions or enols and reactions of these with electrophilic alkylating agents. In order to overcome some of the difficulties inherent in enolate anion generation and alkylation and to achieve controlled monoalkylation, regiospecificity, and stereospecificity, considerable effort has been spent during the past decades on the development of new alkylation methods. The Stork enamine alkylation principle[1] was notably most stimulating[2] and useful[3] to synthetic chemists.

Our present report describes the formation and use of cyclopropylamines as intermediates in the α-alkylation of ketones and aldehydes. The advantages of this new synthetic principle are (a) selective formation and isolation of pure monoalkylation products; (b) regiospecificity in positioning of new substituents; (c) improved alkylation yields in some of the studied examples where reported yields obtained by other methods were found to be low.

This new alkylation route formally parallels the recently developed use of cyclopropyl ethers as alkylation intermediates.[4,5] However, in contrast to that reaction sequence it is now possible to avoid drastic acidic treatment and to achieve cleavage of the cyclopropane intermediates under neutral conditions.

Formation of Cyclopropylamines.—The most practical method for large-scale preparations of tertiary cyclopropylamines from carbonyl compound precursors was found to be the reaction of diethylzinc and diiodomethane[6,7] with enamines. For small-scale preparations the alternative method of diazomethane–cuprous chloride[8] induced addition of methylene to enamine double bonds was more satisfactory. Analo-

(1) G. Stork, R. Terrell, and J. Szmuszkovics, *J. Amer. Chem. Soc.*, **76**, 2029 (1954).

(2) For a summary of enamine chemistry with 731 references see M. E. Kuehne in "Enamines: Their Synthesis, Structure an Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969.

(3) A summary of enamine applications to syntheses of natural products is M. E. Kuehne, *Synthesis*, 510 (1970).

(4) E. Wenkert and D. A. Benges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).

(5) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970).

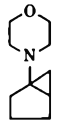
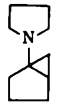
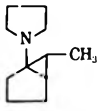
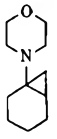
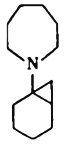
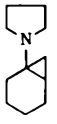
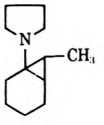
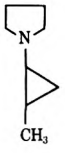
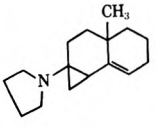
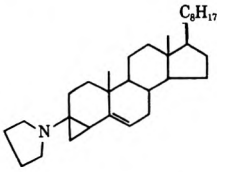
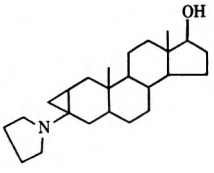
(6) J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).

(7) J. Nishimura, J. Furukawa, N. Kawabata, and M. Kitayama, *ibid.*, **27**, 1799 (1971).

(8) D. L. Muck and E. R. Wilson, *J. Org. Chem.*, **33**, 419 (1968).

TABLE I

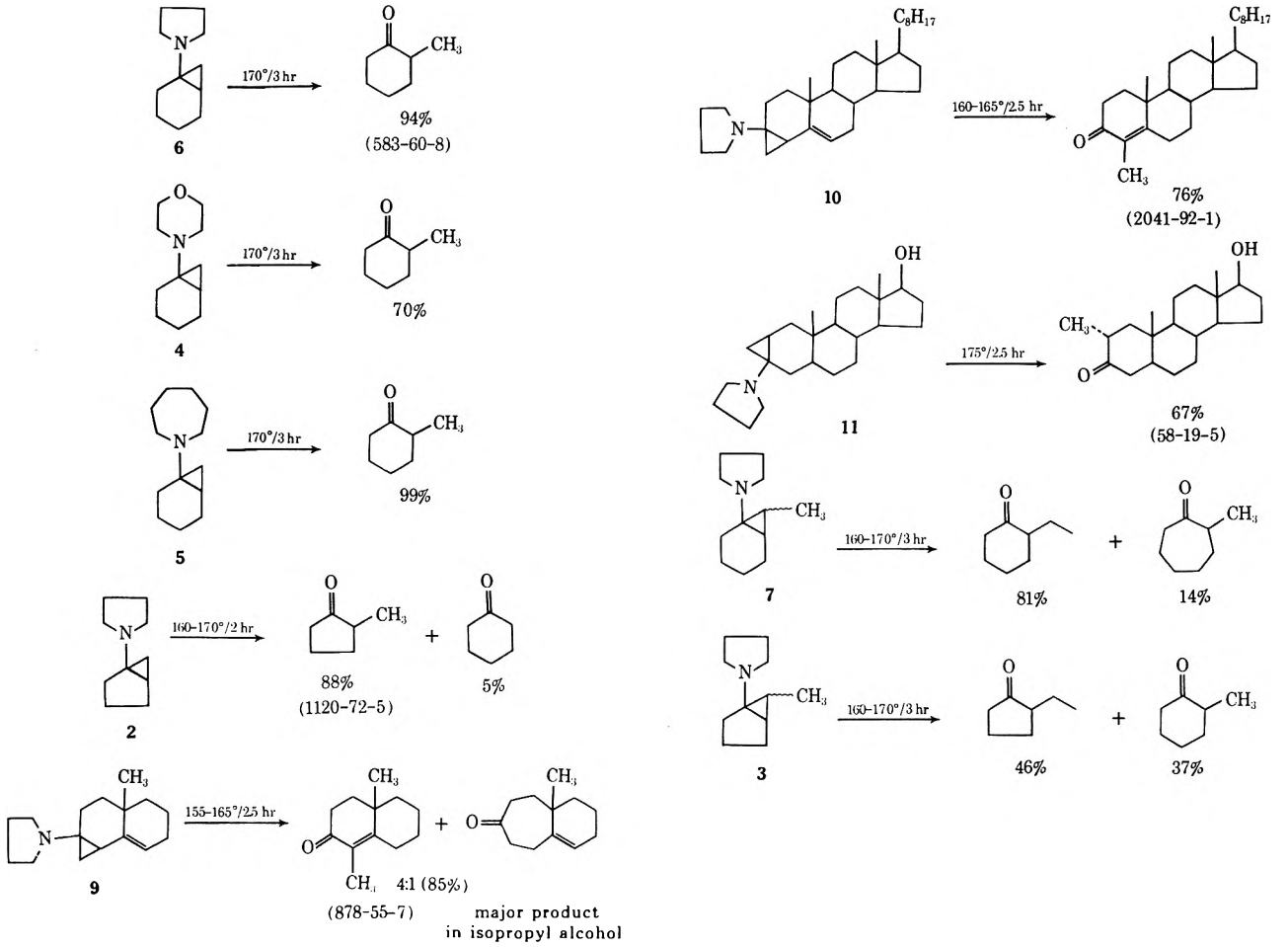
CONVERSION OF ENAMINES TO CYCLOPROPYLAMINES

	Cyclopropylamine	Yield, %	Method	Bp, °C (mm)	Salt, mp, °C	Anal., % Calcd for salt (top) Found (bottom) C	H	N[j]
1		68	*a*	72–75	HCl: 167–168	59.0	8.9	6.9
		86	*b*	(2.5)		59.1	8.8	6.9
2		71	*a*	114–117	HCl: 124–125	64.0	9.7	7.5
		(75)[g]	*b*	(53)		63.6	9.9	7.2
3		58	*c*	89–91 (10)	Methiodide: 228–230 dec	46.9	7.2	4.7
						46.8	7.4	4.6
4		32	*a*	144–146 (26)	HCl: 178–180	60.7	9.3	6.4
						60.5	9.6	6.7
		87	*b*					
5		67	*a*	156–158 (30)	HCl: 202–203	67.9	10.5	6.1
						67.9	10.6	5.9
6		48	*a*	128–132 (48)	HCl: 147–149	65.5	10.0	6.9
		61	*b*			65.2	10.1	6.7
		(72)[g]	*b*					
7		54	*d*	95–105 (7)	Picrate: 154–155	52.9	5.9	13.7
						52.9	5.9	13.8
8		57	*b*	68–69 (55)		76.7	12.1	11.2
						76.7	12.2 (for amine)	11.0
9		67	*b*	70–82 (0.06)	Methiodide: 196–197	54.6	7.6	3.8
						54.8	7.7	3.7
10		82	*b*	mp 132–142		Converted to methyl ketone		
11		>67	*b*	mp 82–87		Converted to methyl ketone		

[a] Diiodomethane–diethylzinc method. [b] Diazomethane–cuprous chloride method. [c] Diiodoethane–diethylzinc method. [d] Diazoethane–cuprous chloride method.

TABLE II

THERMOLYSIS–HYDROLYSIS REACTION IN 90% AQUEOUS METHANOL[a]



[a] Registry numbers are given in parentheses.

gous results were achieved with ethylene iodide or diazoethane.

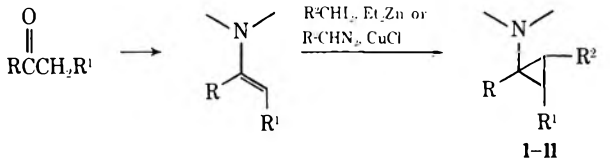


Table I indicates the cyclopropylamines obtained from corresponding cyclic ketone derived enamines and dienamines and from 1-pyrrolidinopropene. A stereoselective (α?) introduction of the cyclopropane methylene group in formation of compounds **9**, **10**, and **11** is suggested by the observation of one major rather than two C-10 or C-18 methyl signals in 100-MHz nmr spectra of crude product **9**.

Cyclopropylamine Ring-Opening Reactions.—The exploration of aminocyclopropanes as synthetic intermediates experienced setbacks with their failure to react as homologous enamines with electrophiles[9] and with the observation of their resistance to opening by acids.[4,10] Accordingly, we have found that the pyrrolidino[3.1.0]bicyclohexane **2** was largely recovered from a solution in acetic and sulfuric acids, at reflux for 3 days, while a similar alkyl-substituted bicyclic compound[11] and alkoxycyclopropanes[4] are readily cleaved under these strongly acidic conditions. Protonation of the nitrogen in acid thus prevents its assistance in ring opening and leads instead to inhibition of the cyclopropane fission.

Cyclopropylamines were also found to be resistant to treatment with base. They could be recovered from a methanol solution containing sodium methoxide after 2 days.

However, we have found that heating of bicyclic [n.1.0]aminocyclopropanes in aqueous alcohols gave ketones. Best yields from such thermolyses were obtained by heating the compounds at 150–170° in aqueous methanol in a sealed tube.[12] The results are shown in Table II.

In order to lower the activation temperature required for the cyclopropylamine ring cleavage, the effect of adsorbing surface agents was studied. Addition of 10% palladium on charcoal allowed good cyclopropane cleavage in refluxing aqueous methanol in 1–2 days (Table III). With various activated charcoal preparations the cleavage rate under these conditions was reduced to one half and without an additive to

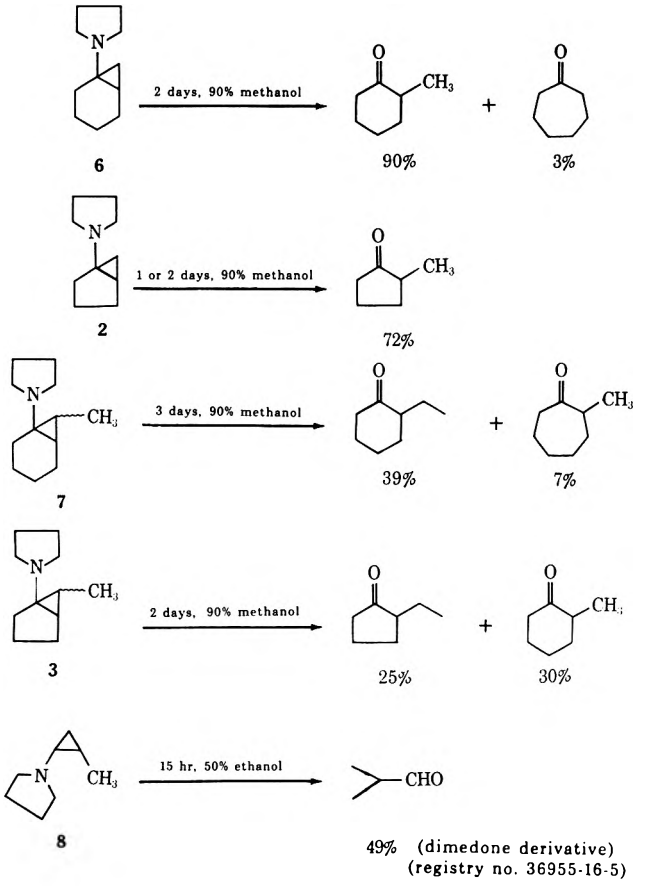
(9) R. A. Fouty, "Reactions of Cyclopropylamine and *N,N*-Dimethylcyclopropylamine," Ph.D. Dissertation, University of Pennsylvania, 1962.

(10) (a) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961); (b) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burger, C. S. Davis, T. J. Delia, and L. Zirngible, *J. Med. Chem.*, **5**, 1243 (1962); (c) J. E. Hodgkins and R. J. Flores, *J. Org. Chem.*, **28**, 3356 (1963).

(11) R. T. LaLonde and A. D. Debboli, Jr., *ibid.*, **35**, 2657 (1970).

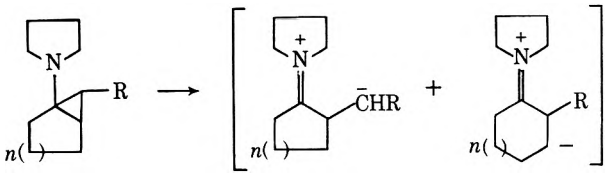
(12) I. G. Bolesov, S. A. Gladyr', A. S. Koz'min and R. Y. Levina, *J. Org Chem. USSR*, **6**, 2443 (1970). Concurrently it was found that heating o 1-morpholino-6,6-diphenylbicyclo[3.1.0]hexane and its next higher homolo at 185–195° in ethylene glycol gave 2-benzhydrylcyclopentanone and 2 benzhydrylcyclohexanone, respectively.

TABLE III
THERMOLYSIS–HYDROLYSIS REACTION
10% Pd/C IN REFLUXING AQUEOUS ALCOHOLS

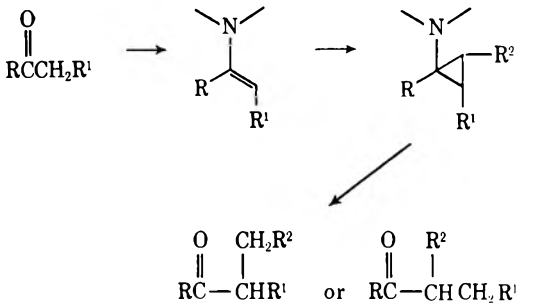


one quarter of the rate found with 10% palladium on charcoal.

The direction of cyclopropane ring cleavage was found to favor protonation at the carbon with the smallest number of alkyl substituents, thus resulting predominantly in methylation rather than ring expansion from the bicyclic [*n*.1.0] compounds and formation of isobutyraldehyde rather than *n*-butyraldehyde in the linear example. These observations are consistent with a transfer of negative charge from nitrogen to a β carbon atom in the transition state of the cyclopropane cleavage reaction. Accordingly, increased ring expansion was found for the two methyl-substituted cyclopropane examples **3** and **7** with the extent of this reaction pathway determined by the respective release of ring strain. Increased ring expansion was also found by allylic stabilization of negative charge in opening of the tricyclic skeleton **9**. When aqueous isopropyl alcohol rather than aqueous methanol was used as protonating solvent, ring expansion predominated with this last system.



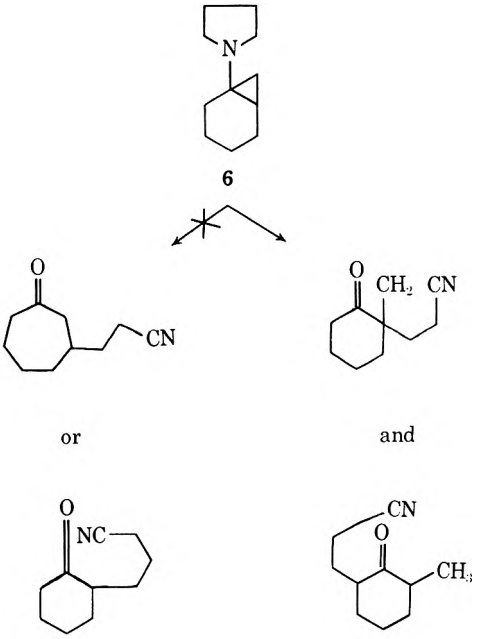
These results establish a new route for aldehyde and ketone alkylations.



Its usefulness is seen by contrasting the C-2 methylation of a 3-keto steroid in 69% yield by this new method with the corresponding enamine alkylation with methyl iodide, which gives a 14% yield.[13] The methylation of propionaldehyde to isobutyraldehyde serves as a model for aldehyde methylations which may otherwise be difficult because of aldehyde aldol condensation in base and alternatively because of extensive N-methylation of aldehyde enamine derivatives with methyl iodide.

Two other advantages of this alkylation sequence are apparent. (a) The aminocyclopropane intermediates can be easily separated from unreacted starting materials because of their basicity and acid stability. In the process of acid extraction unreacted starting aldehyde or ketone can be recovered through enamine hydrolysis. Since di- or polyalkylations are not possible, *pure monoalkylation products* are obtained. (b) Because of its resistance to acid and base treatment, the aminocyclopropane group can also be a *protective function for carbonyl groups*, allowing chemical transformations at other functional groups before liberation of the α-alkylated carbonyl function.

While thermal opening of aminocyclopropanes in the presence of water led to ketones and aldehydes, through formation and hydrolysis of imonium intermediates, their opening in the absence of water gave enamines. These could be demonstrated spectroscopically and by their reactions with acrylonitrile. Thus it was found that heating of the [4.1.0] aminocyclopropane compound **6** with acrylonitrile gave, after



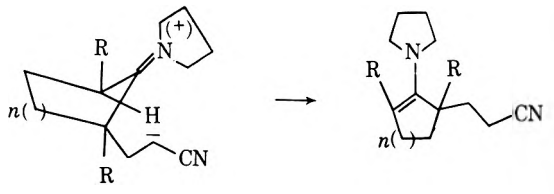
(13) U. S. Patent 3,098,850 (1957); J. C. Babcock, J. A. Campbell, and R. L. Pederson (Upjohn Co.), *Chem. Abstr.*, **59**, 14067 (1963).

hydrolysis, the same product ratio of 2-cyanoethyl-2-methylcyclohexanone and 2-cyanoethyl-6-methylcyclohexanone as the pyrrolidine enamine derivative of 2-methylcyclohexanone when it was heated with acrylonitrile in dioxane.[14,15] Interception of a zwitterionic intermediate or direct electrophilic attack by acrylonitrile on the aminocyclopropane, with formation of alternative ketone products, was not found.

When the [4.1.0]cyclopropylamine **6** was heated with acrylonitrile in methanol, only the 2,6-substituted cyclohexanone was obtained, again in agreement with the corresponding reaction of the enamine derivative of 2-methylcyclohexanone in ethanol.[16]

Heating of the [3.1.0]aminocyclopropane compound **2** with acrylonitrile led only to the 2,2-disubstituted cyclopentanone and some 2-cyanoethylcyclohexanone. Analogously, the methylcyclopentanone enamine derivative gave only the 2,2-disubstituted cyclopentanone when heated in dioxane with acrylonitrile.[17] When either the aminocyclopropane or the enamine was heated in methanol with acrylonitrile, the same mixture of 2,2- and 2,5-disubstituted cyclopentanone products was obtained (Table IV).

The opposite solvent effects found with the above five- and six-membered ring enamine derivatives are remarkable. They can be understood if one postulates a kinetically favored reaction of the predominant less substituted enamine double bond isomer to give a zwitterionic 2,6- (or 2,5-) substituted imonium intermediate which can undergo protonation by solvent or intramolecular proton transfer to yield the 2,6- (or 2,5-) substituted products. Alternatively, reversion of the 2,6- (or 2,5-) substituted zwitterionic intermediate to starting materials and slower formation of 2,2-substituted imonium intermediates provide a route to the less substituted enamine double bond isomers.[14] The latter pathway may be favored more in the five- relative to the six-membered ring enamine reaction by the smaller eclipsing interaction of the α,α substituents with the pyrrolidine ring system as well as by decreased intramolecular bridged proton transfer at the zwitterionic stage.



Hydrogenolyses of the pyrrolidino- and hexamethyleneimino[4.1.0]bicycloheptanes **6** and **5** and the pyrrolidino[3.1.0]bicyclohexane **2** gave *N*-(2-methylcycloalkyl)amines in 98, 96, and 84% yields, respectively. The *N*-(2-methylcyclohexyl)pyrrolidine obtained in this way appeared to be a mixture of cis and trans stereoisomers. Thus Cope pyrolysis of the *N*-oxide furnished 82% of 3-methylcyclohexene and 18% of 1-methylcyclohexene, indicating the presence of the trans isomer. The crude amine also furnished a crystalline methiodide which was matched with the methiodide of the cis isomer, obtained from pyrrolidine and *trans*-2-methylcyclohexanol tosylate.[18] The trans isomer, obtained from *cis*-2-methylcyclohexanol tosylate,[19] did not form a crystalline methiodide. A close similarity of nmr and ir spectra and vpc or tlc retention times of the amines obtained by these routes, or from the catalytic reduction of the pyrrolidine enamine derivative of 2-methylcyclohexanone, did not allow a quantitative stereochemical assignment to the aminocyclopropane hydrogenolysis product.

Experimental Section

Preparation of Cyclopropylamines Using Diethylzinc and Methylene Iodide.—The following procedure for the preparation of 1-(*N*-morpholino)bicyclo[3.1.0]hexane (**1**) is representative. To a three-neck flask equipped with a magnetic stirrer, thermometer, pressure-equalized addition funnel, and nitrogen inlet were added under a nitrogen atmosphere 50 ml of dry benzene, 7.0 g (0.045 mol) of 1-morpholinocyclopentene, and 5.2 ml (0.050 mol) of diethylzinc. The reaction vessel was cooled in an ice bath to 5° and stirred while 12.1 g (0.045 mol) of methylene iodide was added slowly *via* the addition funnel at such a rate that a temperature of less than 10° was maintained. The addition normally took about 1.5 hr. After addition the reaction mixture was allowed to warm to room temperature and stirred for an additional 0.5 hr. The mixture was then poured slowly onto 100 ml of 10% ammonium hydroxide–ice mixture. The mixture was stirred well, then shaken. The benzene was separated and the aqueous portion was extracted with a small amount of benzene. The benzene was combined, dried over magnesium sulfate, filtered, and distilled at approximately 110 mm, leaving a light brown oil which upon distillation through a 12-in. Vigreux column gave 5.1 g (68%) of clear, colorless liquid: bp 72–75° (2.5 mm); ir 3020 cm^{-1}; nmr δ 0.55 (m, 2 H), 1.5 (m, 7 H), 2.6 (t, 4 H), 3.6 (t, 4 H).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.8; H, 10.3; N, 8.4. Found: C, 72.0; H, 10.0; N, 8.6.

The methiodide derivative was formed by heating the amine in a sealed tube with excess methyl iodide at 85° for 3 hr. Recrystallization from ethanol gave white needles, mp 177–178°.

Anal. Calcd for $C_{11}H_{20}NOI$: C, 42.8; H, 6.5; N, 4.5. Found: C, 42.7; H, 6.3; N, 4.3.

Preparation of Cyclopropylamines Using Diazomethane and Cuprous Chloride.—The following preparation of 7-methyl-4-*N*-pyrrolidinotricyclo[5.4.0.$0^{2,4}$]undec-11-ene (**9**) is representative. To 0.952 g (4.37 mmol) of the pyrrolidine dienamine of 10-methyl-1(9)-octalone-2 in 20 ml of dry ether was added 0.7 g of finely powdered cuprous chloride. While the solution was stirred magnetically, approximately 0.5 g of ethereal diazomethane was slowly added, and 15 min after completion of the addition the solution was filtered and the ether was evaporated at reduced pressure leaving a light brown oil which was distilled at 70–82° (0.06 mm) to give 0.680 g (2.94 mmol) of product: yield 67.5%; ir 1650 cm^{-1} (very weak); nmr δ 0.3–0.8 (m, 2 H), 1.0 (s, 3H), 2.3 (m, 17 H), 2.7 (m, 4 H). The methiodide of the cyclopropylamine was formed in methanol and recrystallized from acetone–ether, mp 196–197° dec.

Anal. Calcd for $C_{17}H_{28}NI$: C, 54.6; H, 7.6; N, 3.8; I, 34.0. Found: C, 54.8; H, 7.7; N, 3.7; I, 34.2.

Thermolysis of 1-Pyrrolidinobicyclo[4.1.0]heptane.—The following procedure is representative of the thermolysis reaction of cyclopropylamines in aqueous methanol solution. 1-Pyrrolidinobicyclo[4.1.0]heptane (76 mg, 0.461 mmol) was sealed in a glass tube under a nitrogen atmosphere with 0.7 ml of methanol and 0.08 ml of water and heated for 3 hr at 170–175°. The tube was cooled and opened, and the contents were analyzed by glc (5 ft × 0.125 in. 10% FFAP column at 105°) using cycloheptanone as an

(14) N. F. Firrell and P. W. Hickmott, *Chem. Commun.*, 544 (1969).

(15) H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).

(16) G. Stork, A. Brizzolara, H. K. Landesman, J. Szmuszkovics, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

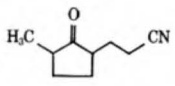
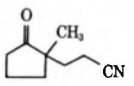
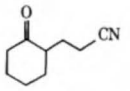
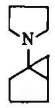
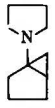
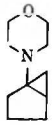
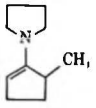
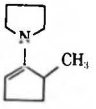
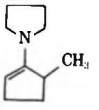
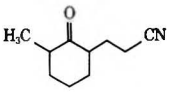
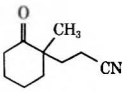
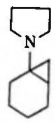
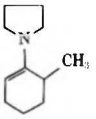
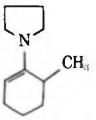
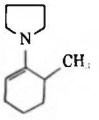
(17) In contrast to the 2,2 disubstitution obtained with the enamine of 2-methylcyclopentanone and acrylonitrile in dioxane, 2,5 disubstitution was found on reaction of the enamine of 2-ethylcyclopentanone with methyl vinyl ketone in dioxane: Ph.D. dissertation of Charles E. Bayha, University of Vermont, 1966. In this instance the kinetic alkylation product undergoes cyclization to a hydrindanone.

(18) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(19) W. Hückel and A. Hubele, *Justus Liebigs Ann. Chem.*, **613**, 27 (1958).

TABLE IV

THERMOLYSIS REACTIONS WITH ONE EQUIVALENT OF ACRYLONITRILE AND COMPARATIVE ENAMINE ALKYLATIONS

Amine	Temp, °C (time, hr)	Solvent	Yield, %	Products after hydrolysis, %[f]		
						
 2	165–175[a] (3)	None	67[d]	0 (36955-18-7)	80 (36955-19-8)	20 (4594-78-9)
 2	170–180[a] (4)	Methanol	40[d]	100[b]		0
 1	165–175[a] (6)	None	58[d]	85[b]		15
	Reflux (16)	Methanol	50[d]	100[b]		0
	Reflux (16)	Dioxane	52[d]		100	0
	150–155[a] (3)	None	62[d]		100	0
						
 6	170–180[a] (4)	None	56[c]	58 (16488-85-0)	42 (21197-29-5)	
 6	170–180[a] (4)	Methanol	41[c]	100	0	
	Reflux (16)	Dioxane	65[d]	57	43	
	150–155[a] (1.5)	None	90[c]	78	22	
	Reflux (4)	Ethanol	55[e]	100[e]	0	

[a] Sealed tube, nitrogen atmosphere. [b] Not separable. [c] Crude yield. [d] Distilled yield. [e] Reference 16. [f] Registry numbers are given in parentheses.

internal standard. The analysis indicated 48.3 mg (94%) of 2-methylcyclohexanone present. The identity of 2-methylcyclohexanone was established in another similar run by formation of a 2,4-dinitrophenylhydrazone derivative directly from the methanol solution. The derivative was recrystallized from ethanol, mp 128–129.5°. The melting point was not depressed when the derivative was mixed with the 2,4-dinitrophenylhydrazone derivative of authentic 2-methylcyclohexanone. In another similar run the glc analysis was performed without addition of cycloheptanone. The analysis indicated only a trace amount of cycloheptanone present (≪1%).

Thermolysis of 7-Methyl-4-pyrrolidinotricyclo[5.4.0.0^{2,4}]-undec-11-ene.—A solution of 0.538 g (2.33 mmol) of 7-methyl-4-pyrrolidinotricyclo[5.4.0.0^{2,4}]undec-11-ene in 2.0 ml of methanol

and 0.3 ml of water was heated in a sealed glass tube under a nitrogen atmosphere for 2.5 hr at 155–165°. The tube was opened and its contents were diluted with 3 ml of water and made acidic with 10% hydrochloric acid. The resulting mixture was shaken and then extracted with several portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated to yield 0.421 g of a yellow oil which was distilled up a glass tube (55–70°, 0.03 mm) to yield 0.352 g (1.98 mmol) of clear, colorless liquid: yield 85%; ir 1605, 1665, and 1700 cm^{-1}; nmr δ 1.1 (s, ~0.2 H), 1.2 (s, ~2.8 H), 1.4–2.6 (m, ~15 H), 5.5 (m, ~0.1 H). Tlc (silica gel, 5% methanol–methylene chloride, methylene chloride, ether, 4% methanol–ether, benzene, and ethyl acetate; alumina, ether, and ether–benzene) showed one spot. Glc (10% Carbowax, 150°, 10% Apiezon L, 130°, 10% SE-30, 115°) did not resolve the mixture consisting of a 4:1 ratio of α,β-unsaturated to saturated ketone component according to the ir spectrum. Column chromatography employing silver nitrate impregnated alumina (pentane–benzene and pentane–cyclohexene) also did not separate the mixture. A Girard Reagent T procedure also failed to separate the mixture. Refluxing the mixture in methanolic potassium hydroxide or sulfuric acid solutions did not alter the relative intensities of the carbonyl absorptions.

A brick red 2,4-dinitrophenylhydrazone derivative was formed from the mixture and recrystallized from ethanol, mp 195–197°. The mixture melting point of this derivative with the 2,4-dinitrophenylhydrazone derivative of 1,10-dimethyl-1(9)-octalone-2[20] was 195–196°.

Conversion of the Pyrrolidine Dienamine of Δ^4-Cholesten-3-one to 4-Methyl-Δ^4-cholesten-3-one.—To 380 mg (0.902 mmol) of the pyrrolidine dienamine of Δ^4-cholesten-3-one in 40 ml of dry ether was added 0.6 g of finely divided cuprous chloride. While the solution was stirred magnetically, approximately 0.2 g of ethereal diazomethane was added slowly at room temperature. The addition was completed and 15 min later the solution was filtered and the ether was evaporated, yielding a yellowish, solid residue. The residue was dissolved in boiling ethanol and crystallized, yielding 280 mg of solid material, mp 132–142°. Concentration of the mother liquor yielded an additional 35 mg, mp 131–142°. The nmr spectrum (100 MHz) of this material exhibited absorptions at δ 0.3 (cyclopropane), 0.68, 0.82, 0.88, and 0.95 (methyl singlets), 2.71 (NCH_2), and 5.40 (vinyl H). A solution of 75 mg of the cyclopropylamine, 1.5 ml of methanol, and 0.1 ml of water was sealed in a glass tube and heated at 160–165° for 2.5 hr. The tube was cooled and opened. The contents were diluted with water, acidified with hydrochloric acid, and extracted with ether. The ether was dried over magnesium sulfate, filtered, and evaporated, yielding a brownish solid residue. The residue was chromatographed on 6.0 g of neutral alumina with acetone–benzene, yielding 50 mg of white solid which was recrystallized from methanol: mp 101–102° (lit. mp 102–103°,[20] 101–103°[21]); 76% from the enamine; ir 1665, 1600 cm^{-1} (Nujol mull).

Conversion of the Pyrrolidine Enamine of Androstanolone to 2-Methylandrostanolone.—To 629 mg (1.83 mmol) of the pyrrolidine enamine of androstanolone in 30 ml of dry ether was added 431 mg of finely powdered cuprous chloride. While the solution was stirred magnetically, approximately 0.3 g of ethereal diazomethane was added slowly at room temperature. The addition was completed and 15 min later the solution was filtered and the ether was evaporated, yielding 679 mg of a white, fluffy solid, mp 82–87°. The nmr spectrum of this material showed characteristic cyclopropane absorptions at δ 0.1 and 0.5 and the ir spectrum (Nujol mull) showed the absence of the 1645-cm^{-1} enamine band. A solution of 88 mg (0.246 mmol) of the crude steroidal cyclopropylamine, 2.0 ml of methanol, and 0.1 ml of water sealed in a glass tube under a nitrogen atmosphere. The tube was heated at 175° for 2.5 hr, cooled, and opened, and the contents were diluted with water, acidified with hydrochloric acid, and extracted with ether. The ether was dried over magnesium sulfate, filtered, and evaporated to yield 73.9 mg of semisolid material which was chromatographed on 6.0 g of Florisil with petroleum ether (bp 60–75°)–acetone. The chromatography yielded 50.4 mg of white solid material: mp 151–152.5° (lit.[13] mp 174–176 or 151–153°); 67% from the enamine; ir (CCl_4) 1710 cm^{-1}.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane in the Presence of Palladium on Charcoal.—The following procedure is representative. A solution composed of 112 mg of 1-(*N*-pyrrolidino)bicyclo[3.1.0]hexane, 1.0 ml of 90% aqueous methanol, and 15 mg of 10% palladium on charcoal was refluxed for 24 hr. Glc analysis (6 ft × 0.125 in. 10% UC-W98 80–1005 operated at 140°) showed pyrrolidine and 2-methylcyclopentanone present. The yield, determined by the use of cycloheptanone as an internal standard, was 72%.

Reaction of 1-(*N*-Pyrrolidino)-2-methylcyclopropane in the Presence of Palladium on Charcoal and 5,5-Dimethyl-1,3-cyclohexanedione.—A solution composed of 128 mg (1.02 mmol) of 1-(*N*-pyrrolidino)-2-methylcyclopropane, 15 mg of 10% palladium on charcoal, and 429 mg (3.06 mmol) of 5,5-dimethyl-1,3-cyclohexanedione was refluxed for 19 hr in 3.0 ml of 50% aqueous ethanol. After cooling, sufficient hot ethanol was then added to dissolve in solid product. The solution was filtered and the volume was reduced to approximately 3 ml by evaporation at reduced pressure. The solution was cooled and the crystals were collected, 155 mg, mp 138–145°. Concentration of the mother liquor yielded additional crystalline material, 25 mg, mp 138–145°, which was combined with the first crop and recrystallized from aqueous ethanol to yield 168 mg of white solid, mp 151.5–152.0°. The mixture melting point determination of this material and the di 5,5-dimethyl-1,3-cyclohexanedione adduct of authentic isobutyraldehyde was 151.5–152.0° (lit.[22] mp 153–154.5°). The yield of adduct based on the cyclopropylamine was 49%.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[4.1.0]heptane in the Presence of Different Catalysts.—In all cases 40 mg of the cyclopropylamine, 1.50 ml of 90% aqueous methanol, and 20 mg of catalyst were refluxed for 2.5 hr and cooled, and the mixture was then analyzed by glc (6 ft × 0.125 in. 10% UC-W98 80–1005 operated at 140°) using 2-methylcyclopentanone as an internal standard. The corrected peak heights of 2-methylcyclohexanone and the catalyst employed are shown below.

Catalyst[23]	Peak height, mm
Nuchar B-100-N	34
Nuchar C-190-N	30
Nuchar C-N	39
Nuchar CEE-N	36
10% Pd/C	61
None	17

Hydrogenolysis of Cyclopropylamines.—A solution of 371 mg (2.25 mmol) of 1-(*N*-pyrrolidino)bicyclo[4.1.0]heptane in 2.5 ml of dry methanol was stirred with 60 mg of 10% palladium on charcoal for 3 days at room temperature under a hydrogen atmosphere. The solution was then filtered, yielding 367 mg (2.20 mmol) of clear, colorless liquid which was homogeneous on glc (5 ft × 0.125 in. 10% SE-30 operated at 105°): yield 98%; nmr δ 0.9 (d, 3 H), 1.7 (m, 14 H), 2.5 (m, 4 H). The methiodide of this amine was formed in methanol and recrystallized from methanol–ether, mp 210–212° dec.

Anal. Calcd for $C_{12}H_{24}NI$: C, 46.6; H, 7.8; N, 4.5. Found: C, 46.5; H, 8.1; N, 4.7.

1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane was treated as above and produced 84% of *N*-(2-methylcyclopentyl)pyrrolidine. The methiodide of this amine was formed in methanol and recrystallized from methanol–ether, mp 220–221° dec.

Anal. Calcd for $C_{11}H_{22}NI$: C, 44.8; H, 7.5; N, 4.8. Found: C, 44.5; H, 7.7; N, 4.7.

1-(*N*-Hexamethylenimino)bicyclo[4.1.0]heptane was treated as above and produced 96% of *N*-(2-methylcyclohexyl)hexamethylenimine. The methiodide of this amine was formed in methanol and recrystallized from methanol–ether, mp 237–238° dec.

Anal. Calcd for $C_{14}H_{28}NI$: C, 49.9; H, 8.4; N, 4.2. Found: C, 50.1; H, 8.6; N, 4.3.

Hydrogenation of the Pyrrolidine Enamine of 2-Methylcyclohexanone.—A solution composed of 861 mg of the pyrrolidine enamine of 2-methylcyclohexanone, 0.2 g of 10% palladium on charcoal, and 3.0 ml of dry methanol was stirred under a hydrogen atmosphere at room temperature. After 5 hr the solution was filtered and the methanol was evaporated, yielding 852 mg of a very slightly amber liquid. Glc analysis (5 ft × 0.125 in. 10% SE-30 operated at 105°) showed this material to be

(20) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.*, **31**, 1020 (1966).
(21) F. Sondheimer and Y. Mazur, *J. Amer. Chem. Soc.*, **79**, 2906 (1957).
(22) E. C. Horning and M. G. Horning, *J. Org. Chem.*, **11**, 95 (1946).
(23) Westvaco Chemical Division, Covington, Va.

95% pure, nmr δ 0.9 (d, 3 H), 1.7 (m, 14 H), 2.5 (m, 4 H). This spectrum was superimposable on that of the material obtained from the hyrogenolysis of 1-(*N*-pyrrolidino)bicyclo[4.1.0]-heptane. The methiodide derivative of this amine was formed in ethanol and recrystallized from ethanol–ether, mp 210–212°. The mixture melting point with the methiodide of the amine of cyclopropylamine origin was 209–211°.

Alternative Preparation of *N*-(2-Methylcyclohexyl)pyrrolidine.—An ethereal solution of 2.5 g of 2-methylcyclohexanone was reduced with 0.40 g of lithium aluminum hydride to yield 2.1 g of 1-hydroxy-2-methylcyclohexane. Dauben[18] has shown this reduction to produce 82% trans and 18% cis isomer. The tosylate of the alcohol mixture was formed by treatment in dry pyridine with *p*-toluenesulfonyl chloride at 0°. The crude tosylate mixture, which existed as a yellow oil, was then refluxed in dry pyrrolidine for 16 hr. The solution was cooled, diluted with water, and separated from 0.5 g of amber oil. This oil was shown by glc analysis to consist of olefin and amine in the ratio of 3:7, respectively. The nmr spectrum of this mixture exhibited a sharp methyl doublet at δ 0.9 which was superimposable on those obtained from the hydrogenolysis of 1-(*N*-pyrrolidino)-bicyclo[4.1.0]heptane and the hydrogenation of the pyrrolidine enamine of 2-methylcyclohexanone. The methiodide of the amine produced by this reduction had mp 210–212° and mixture melting point with the methiodide of the amine of cyclopropylamine origin 209–211°.

Preparation of *trans*-*N*-(2-Methylcyclohexyl)pyrrolidine.—The procedure of Hückel[19] was followed with the exception that extensive esterification of the *cis*-2-methylcyclohexanol had taken place. Therefore, the product after hydrogenation was refluxed for 10 hr in 20% aqueous sodium hydroxide to hydrolyze the acetate. The tosylate was obtained in 85% yield, mp 49–52° (lit.[19] mp 56–57°). The tosylate, 1.1 g (4.0 mmol), was refluxed for 16 hr in 5 ml of pyrrolidine. The solution was cooled and 20 ml of water was added. The mixture was extracted with several portions of ether. The ether was extracted twice with 5 ml of water, dried over magnesium sulfate, filtered, and evaporated, leaving a slightly yellow oil. The oil was distilled up a glass tube (86–89°, 15 mm) to yield 0.054 g of clear oil (8%). The presence of a large quantity of olefin in the crude oil was shown by the presence of an ir absorption at 1665 cm^{-1}. The distilled oil was homogeneous on tlc (silica gel, methylene chloride) and the nmr spectrum exhibited a methyl doublet at δ 0.9 which was superimposable on those of the amines prepared by other methods. This material would not form a crystalline methiodide derivative.

Preparation of the Amine Oxide of *N*-(2-Methylcyclohexyl)-pyrrolidine.—To 367 mg of *N*-(2-methylcyclohexyl)pyrrolidine was added 1 ml of 30% hydrogen peroxide and 1.3 ml of methanol. After standing at room temperature for 1.5 days, amine was still present (positive phenolphthalein test), and an additional 1 ml of hydrogen peroxide was added. After standing for one additional day no free amine was present. The excess hydrogen peroxide was destroyed with metallic platinum. The solution was filtered and the solvent was evaporated at reduced pressure. The residue was dried by evacuation to 0.03 mm overnight. After drying, the viscous yellow oil weighed 405 mg.

Pyrolysis of the Amine Oxide of *N*-(2-Methylcyclohexyl)-pyrrolidine.—The amine oxide from above was heated to 140°, and the pyrolysis products were distilled at 93–98°, yielding 101 mg: ir 1665 cm^{-1}; nmr δ 1.0 (d), 1.7 (m), 5.6 (m). Glc analysis (6 ft × 0.125 in. 10% UC-W98 80–1005 operated at 80°) showed two components present with retention times of 1.6 (82%) and 2.2 min (18%). The smaller component was shown to be 1-methylcyclohexene by peak enrichment techniques. The larger component was identified as 3-methylcyclohexene by the nmr spectra of the mixture.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[4.1.0]heptane with Acrylonitrile.—A mixture of 0.804 g (4.87 mmol) of 1-(*N*-pyrrolidino)-bicyclo[4.1.0]heptane and 0.258 g (4.87 mmol) of acrylonitrile was sealed in a glass tube under nitrogen and heated for 4 hr at 170–180°. The tube was opened and the contents were refluxed in 2.5 ml of water for 1 hr. The solution was cooled, acidified with hydrochloric acid, and extracted with several portions of ether. The ether was dried over magnesium sulfate, filtered, and evaporated, leaving 0.449 g (56%) of a clear liquid which was analyzed directly by glc (10 ft × 0.375 in. 10% Versamide column at 145°) to find two components present with retention times of 15 (58%) and 21.5 min (42%). The components were separated by preparative glc (same conditions as above). The component of shorter retention time had ir 2240, 1705 cm^{-1}; nmr δ 1.0 (d, 3 H), 2.0 (m, 12 H). This material was assigned the structure 2-β-cyanoethyl-6-methylcyclohexanone. The component with the longer retention time had ir 2240, 1710 cm^{-1}; nmr δ 1.2 (s, 3 H), 2.1 (m, 12 H); it was assigned the structure 2-β-cyanoethyl-2-methylcyclohexanone.

Reaction of 1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane with Acrylonitrile.—1-(*N*-Pyrrolidino)bicyclo[3.1.0]hexane (1.53 g, 10.1 mmol) and 0.53 g (10.1 mmol) of acrylonitrile were sealed in a glass tube under a nitrogen atmosphere and heated to 165–170° for 3 hr. After cooling, the contents of the tube were poured into 5 ml of water, made acidic with hydrochloric acid, and heated to 80° for 1 hr. The aqueous solution was extracted with several portions of ether. The ether was dried over magnesium sulfate, filtered, and evaporated at reduced pressure, yielding 1.13 g of slightly yellow oil, 74% crude yield. The oil was distilled at 70–75° (0.15 mm), yielding 1.01 g (67%) of clear, colorless liquid. The liquid was analyzed by glc (10 ft × 0.375 in. 10% Versamide column operated at 143°) and shown to consist of two components with retention times of 19.4 (80%) and 25.5 min (20%). The mixture was separated by preparative glc (same conditions as above). The larger component had ir 2245, 1735 cm^{-1}; nmr δ 1.1 (s, 3 H), 2.1 (m, 10 H).

Anal. Calcd for $C_9H_{13}NO$: C, 71.5; H, 8.7; N, 9.3. Found: C, 71.5; H, 8.9; N, 9.3.

This material was identified as 2-β-cyanoethyl-2-methylcyclopentanone by comparison with the authentic compound using glc peak enrichment techniques and by comparison of spectroscopic properties.

The smaller component had ir 2245, 1705 cm^{-1}; nmr center δ 2.2 (m). A 2,4-dinitrophenylhydrazone derivative was formed and recrystallized from ethanol yielding the analytical sample, mp 150–151°.

Anal. Calcd for $C_{15}H_{17}O_4N_5$: C, 54.4; H, 5.2; N, 21.1. Found: C, 54.1; H, 5.5; N, 21.4.

This derivative had mp 149.0–150.5° upon mixture with the 2,4-dinitrophenylhydrazone derivative of authentic 2-β-cyanoethylcyclohexanone.[16]

Preparation of 2-β-Cyanoethyl-2-methylcyclopentanone.—The procedure used was patterned after that of House.[15] To 2.00 g (18.5 mmol) of 2-methylcyclopentanone was added 89 mg of potassium in 20 ml of dry *tert*-butyl alcohol. The potassium was dissolved and 0.98 g (19.0 mmol) of acrylonitrile was added slowly at 25–30°. The mixture was stirred overnight and then poured onto 3% sulfuric acid and extracted with several portions of ether. The ether was rinsed with saturated sodium chloride, dried over magnesium sulfate, filtered, and evaporated, leaving a liquid which was distilled at 75–95° (0.15 mm), 0.53 g. A large amount of residue remained which was not distillable up to 115° (0.15 mm). The volatile material was analyzed by glc and found to consist of three components with retention times of 9.4 (20%), 12.3 (14%), and 19.4 min (66%). The 19.4-min component was separated by preparative glc and its nmr and ir spectra were identical with those of the larger component from the reaction of 1-(*N*-pyrrolidino)bicyclo[3.1.0]hexane with acrylonitrile. These compounds were also shown to be identical by peak enrichment glc techniques.

Registry No.—**1**, 36955-07-4; **1** (HCl), 36955-08-5; **1** (MeI), 36955-09-6; **2**, 15043-70-6; **2** (HCl), 36955-11-0; **3**, 36955-12-1; **3** (MeI), 36955-13-2; **4**, 36994-07-7; **4** (HCl), 36994-08-8; **5**, 36994-09-9; **5** (HCl), 36994-10-2; **6**, 4668-96-6; **6** (HCl), 36994-12-4; **7**, 36994-13-5; **7** (picrate), 36994-14-6; **8**, 36955-14-3; **9**, 36955-15-4; **9** (MeI), 36994-15-7; **10**, 36949-91-4; **11**, 36994-16-8; *cis*-*N*-(2-methylcyclohexyl)pyrrolidine, 36949-94-7; *trans*-*N*-(2-methylcyclohexyl)pyrrolidine, 36949-95-8; *cis*-*N*-(2-methylcyclohexyl)pyrrolidine (MeI), 36949-96-9; *N*-(2-methylcyclopentyl)pyrrolidine (MeI), 36994-17-9; *N*-(2-methylcyclohexyl)hexamethylenimine (MeI), 36994-18-0; amine oxide of *N*-(2-methylcyclohexyl)pyrrolidine, 36955-17-6; acrylonitrile, 107-13-1.

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The Alkylation of Aromatic Hydrocarbons with Saturated Hydrocarbons[1]

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Electron transfer resulting in alkylation of an aromatic hydrocarbon by a saturated hydrocarbon occurs when a mixture of the hydrocarbons is treated with cupric chloride and aluminum chloride at room temperature. The reaction of benzene and isopentane, for example, yields neopentylbenzene, *tert*-pentylbenzene, and *sec*-isopentylbenzene as well as some by-products. Aralkylation of benzene with ethylbenzene produces 1,1-diphenylethane. The cupric chloride may be replaced by ferric chloride or other higher valent halide of a metal which exists in more than one valence. The aluminum chloride may be replaced by another Friedel–Crafts catalyst, such as ferric chloride or zinc chloride. Isopentane serves as a promoter for the alkylation of benzene with other saturated hydrocarbons. During the reaction, cupric chloride is converted to cuprous chloride and hydrogen chloride: it may be regenerated, resulting in an increased yield of alkylbenzene, by carrying out the alkylation reaction in the presence of oxygen (air).

Aluminum chloride catalyzes the destructive alkylation of aromatic hydrocarbons with paraffins.[2] For example, *tert*-butylbenzene, *p*-di-*tert*-butylbenzene, and isobutane are the chief products of the reaction of benzene with 2,2,4-trimethylpentane at 20–50°.[2a] while toluene, ethylbenzene, *n*-propylbenzene, propane, and isobutane are obtained by the reaction of benzene with isopentane at 175°.[2b]

Alkylation of an aromatic hydrocarbon by a paraffin or a cycloparaffin without accompanying cracking occurs when the saturated hydrocarbon undergoes hydrogen transfer to form an intermediate carbonium ion which then condenses with the aromatic hydrocarbon. For example, the reaction of a dihaloalkane with benzene in the presence of aluminum chloride and an isoparaffin or a methylcycloalkane yields a monoalkylbenzene corresponding to the dihaloalkane and an alkyl- or cycloalkylbenzene corresponding to the saturated hydrocarbon.[3] The reaction of 1,1-dibromoethane with benzene in the presence of 2,3-dimethylbutane produces ethylbenzene and hexylbenzenes, chiefly 3-phenyl-2,2-dimethylbutane;[3c] the reaction of 1,1-dichloro-3,3-dimethylbutane, benzene, and methylcyclopentane yields 1-phenyl-3,3-dimethylbutane and (methylcyclopentyl)benzene.[3a]

Another method for converting a saturated hydrocarbon to a carbonium ion is described in this paper. It is shown that aromatic hydrocarbons may be directly alkylated with paraffins and cycloparaffins in the absence of other organic compounds by treating the reactants with a higher valent chloride of a metal which exists in at least two valences (*e.g.*, cupric chloride) and and a Friedel–Crafts catalyst.[4]

Experimental Section

Cupric Chloride–Aluminum Chloride.—The metal chloride mixture was preformed for some of the experiments by mixing equimolar quantities of commercial anhydrous cupric chloride (B & A Allied Chemicals) and aluminum chloride powders (Baker Analyzed). An induction period of about 30 sec permitted efficient mixing of the powders, for example by manual shaking. There was then a sudden evolution of heat accompanied by evolution of hydrogen chloride (probably due to the presence of $CuCl_2 \cdot 2H_2O$ in the commercial "anhydrous" cupric chloride). The product, a mustard-colored powder, showed a small loss in weight. For example, when 38 g (0.28 mol) of cupric chloride was mixed with 36 g (0.27 mol) of aluminum chloride, the product weighed 73 g. On the other hand, when 30 g (0.22 mol) of freshly dried cupric chloride was shaken with 28 g (0.21 mol) of aluminum chloride, there was little evolution of hydrogen chloride and no loss in weight.

In other experiments, the cupric chloride and the aluminum chloride were added separately to the mixture of hydrocarbons.

Most of the experiments were carried out in a fluted glass flask equipped with a mechanical stirrer, an efficient (usually Dry Ice cooled) condenser, and a thermometer well. A mixture of the hydrocarbon reactants (*e.g.*, 0.3 mol of benzene and 0.3–0.6 mol of isopentane) and 0.08–0.17 mol of the metal chloride complex was vigorously stirred at the desired temperature, usually for 2–4 hr. The product consisted of two layers: an upper layer, which was chiefly unreacted hydrocarbons and contained only a very small amount of reaction product; and a viscous lower layer, which was hydrolyzed with ice–water, yielding hydrocarbon [unreacted aromatic hydrocarbon, alkylated hydrocarbon, *p*-polyphenyl[5]—more properly named poly(*p*-phenylene)] and cuprous chloride. The *p*-polyphenyl and cuprous chloride were separated from the other products by filtration and the latter were then water and alkali washed, dried over potassium carbonate, and analyzed by gas–liquid chromatography (glc, F & M Model 720 instrument), the peaks being identified by comparison of their retention times with those of authentic samples and by preparative glc (Varian Aerograph Autoprep) combined with ir (Beckman IR-9), nmr (Varian A 60), and/or mass spectrum (CEC, Model 103C). In many cases pure samples for characterization were isolated by fractional distillation.

Some of the experiments were carried out in a 1-l. stainless steel turbomixer autoclave. The procedure and work-up were similar to those used with the glass alkylating flask except that usually no attempt was made to separate the reaction product layers. The entire product was treated with ice–water, suction filtered, washed, dried, and then distilled to remove unreacted hydrocarbons. The composition of the high-boiling residue was usually determined with the aid of chromatography and vacuum distillation.

Cupric Chloride–Zinc Chloride.—A mixture of the hydrocarbons (1.0 mol of isopentane and 0.8 mol of benzene), anhydrous cupric chloride powder (0.4 mol), and crushed zinc chloride (0.15 mol) in a glass liner was sealed into an Ipatieff-type rotating autoclave, nitrogen pressure (usually 30 atm) was added (chiefly for the purpose of keeping the reactants in the liner), and the rotating autoclave was heated (usually at 200°) for 4 hr. The hydrocarbon product was decanted or filtered from the metal chlorides, washed, dried, and characterized in the usual manner.

Results and Discussion

Cupric Chloride and Aluminum Chloride. A. Benzene and Isopentane.—Alkylation of aromatic hydro-

(1) Presented before the Division of Petroleum Chemistry, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28 to April 2, 1971.

(2) (a) A. V. Grosse and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **57**, 2415 (1935); (b) A. V. Grosse, J. M. Mavity, and V. N. Ipatieff, *J. Org. Chem.*, **3**, 137 (1938).

(3) (a) L. Schmerling J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.*, **77**, 1774 (1955); (b) L. Schmerling, R. W. Welch, and J. P. West, *ibid.*, **78**, 5406 (1956); (c) L. Schmerling, R. W. Welch, and J. P. Luvisi, *ibid.*, **79**, 2636 (1957).

(4) L. Schmerling, U. S. Patent, 3,420,908 (Jan 7, 1969).

(5) P. Kovacic and A. Kyriakis, *Tetrahedron Lett.*, 467 (1962); *J. Amer. Chem. Soc.*, **85**, 454 (1963).

carbons by saturated hydrocarbons occurs when the reactants are stirred at near room temperature with a mixture of aluminum chloride and cupric chloride. For example, treating a mixture of benzene and isopentane with cupric chloride and aluminum chloride at 17–21° resulted in the production of pentylbenzenes (about 40 mol % based on the formation of 0.5 mol per mol of cupric chloride) together with smaller amounts of ethylbenzene, isopropylbenzene, and 1,1-diphenylethane; polymerization of benzene to *p*-polyphenyl[5] occurred in about 12 mol % yield based on the cupric chloride. About one-third of the pentylbenzene was neopentylbenzene, the remainder being *tert*-pentylbenzene and *sec*-isopentylbenzene (3-phenyl-2-methylbutane).

The alkylation of benzene by isopentane proceeds by an oxidative (electron transfer) reaction involving the cupric chloride.

$$(CH_3)_2CHC_2H_5 + CuCl_2 \cdot AlCl_3 \longrightarrow (CH_3)_2\overset{+}{C}C_2H_5 + HCl + CuCl + AlCl_3$$

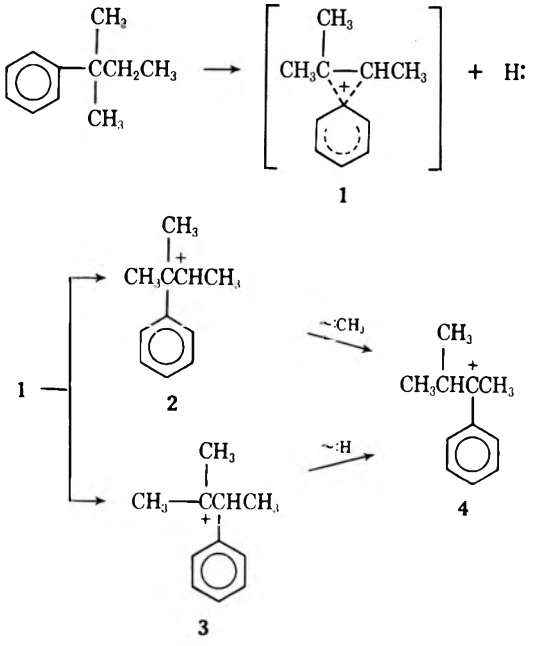
$$C_6H_6 + (CH_3)_2\overset{+}{C}C_2H_5 \longrightarrow C_6H_5C(CH_3)_2C_2H_5 + H^+$$

$$H^+ + CuCl_2 \longrightarrow HCl + CuCl$$

The overall reaction is

$$(CH_3)_2CHC_2H_5 + C_6H_6 + 2CuCl_2 \xrightarrow{AlCl_3} C_6H_5C(CH_3)_2C_2H_5 + 2CuCl + 2HCl$$

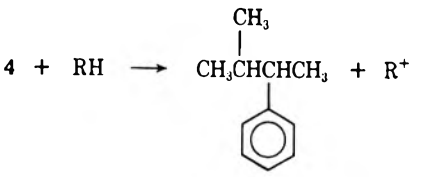
Most of the *tert*-pentylbenzene underwent isomerization to *sec*-isopentylbenzene[6] and neopentylbenzene.[7] The isomerization is believed to involve abstraction of hydrogen attached to a secondary carbon with neighboring phenyl group participation resulting in formation of a phenonium ion.[3c] (Conversion of **1** to **4** may



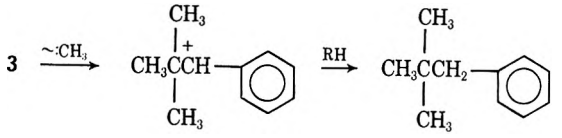
occur directly by migration of H: or CH_3: without formation of 2 and **3**; **4** is stabilized by resonance of the benzylic ion.)

(6) L. Schmerling and J. P. West, *J. Amer. Chem. Soc.*, **76**, 1917 (1954).

(7) (a) C. D. Nenitzescu, I. Necsoiu, A. Glatz, and M. Zalman, *Chem. Ber.*, **92**, 10 (1959); (b) R. M. Roberts and Y. W. Han, *J. Amer. Chem. Soc.*, **85**, 1168 (1963).

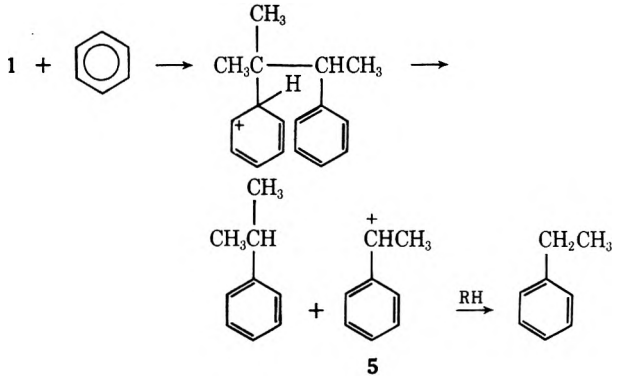


Migration of a methyl group in **3** yields neopentylbenzene.[7] (RH may be isopentane or *tert*-pentylbenzene.)



The fact that about one-third of the pentylbenzene formed by the alkylation of benzene with isopentane at 17–21° was neopentylbenzene suggests that isomerization of the primarily formed *tert*-pentylbenzene to neopentylbenzene occurs in the presence of the mixture of cupric chloride and aluminum chloride under milder conditions than those reported in the literature with aluminum chloride as catalyst. The ease of isomerization may be related to the fact that, at the end of the reaction, most of the alkylbenzene was in the viscous catalyst layer (presumably as a complex from which it was recovered by hydrolysis) rather than in the organic upper layer (excess benzene and isopentane).

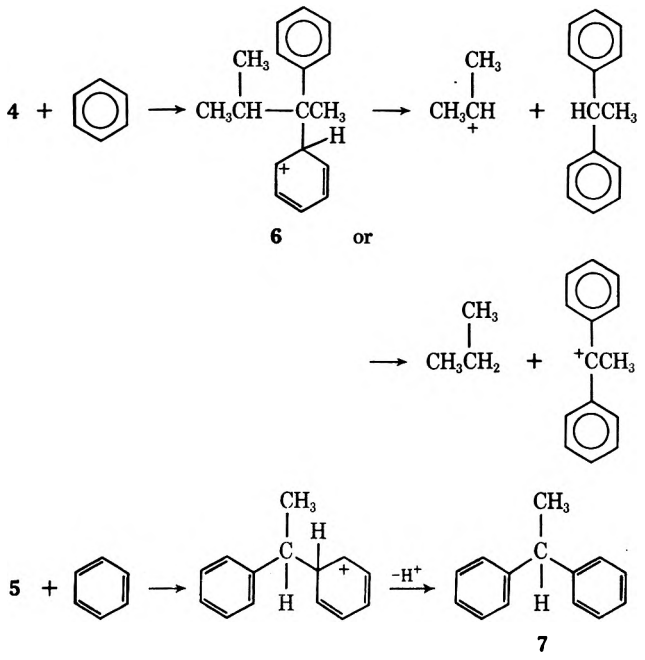
Formation of the small amounts of ethylbenzene and isopropylbenzene which were by-products of the isopentane reaction may be explained by a number of pathways. One involves destructive alkylation.[2] Another involves the phenonium ion (**1**) or another intermediate ion (**2** or **3**).



Alternatively, the phenylpentyl ion (**4**) may have added to benzene. The isopropyl cation may be converted to cumene, to propane or to polymeric product.[8]

Some other routes may be postulated to explain the formation of 1,1-diphenylethane. A phenylethyl ion (**5**) formed as indicated or by the action of cupric chloride and aluminum chloride on ethylbenzene may have added to benzene.

(8) A referee has pointed out that an objection to this pathway is that it favors the formation of 2,2-diphenyl-3-methylbutane (none of which was observed) by the simple (and energetically favorable) elimination of the ring proton of **6** (aromatization).



6 or

7

B. Benzene and Alkylbenzene.—The aralkylation of benzene by ethylbenzene in the presence of cupric chloride plus aluminum chloride is, of course, analogous to its alkylation by isopentane; a benzylic hydrogen is readily abstracted from ethylbenzene by electron transfer involving cupric chloride. When a solution of ethylbenzene in excess benzene was contacted with cupric chloride and aluminum chloride at 23–30°, 1,1-diphenylethane was produced in 40–45 mol % yield based on the cupric chloride present. Some other diarylalkanes also were formed, the major one being 1-phenyl-1-(ethylphenyl)ethane obtained in about 10% yield; its formation indicates addition of the intermediate benzylic cation to ethylbenzene, rather than to the more predominant benzene. It seems worth noting that again the ethylbenzene–benzene layer of the product contained only a small amount of the reaction products. Practically all of the diarylethane was recovered by hydrolyzing the catalyst layer (the so-called "lower layer").

Aralkylation also occurred when benzene was treated with cumene and a mixture of cupric chloride and aluminum chloride at 23–27°. An 8 mol % yield of 2,2-diphenylpropane based on the copper salt was obtained, together with a 15 mol % yield (based on the cumene) of diisopropylbenzene.

C. Benzene and 2,3-Dimethylbutane.—Alkylation of benzene with 2,3-dimethylbutane in the presence of an equimolar mixture of cupric chloride and aluminum chloride at 25–30° resulted in 9 mol % (based on the copper chloride) of hexylbenzenes and a small amount of ethylbenzene. The hexylbenzenes were the isomers obtained by the aluminum chloride catalyzed reaction of benzene with 1-chloro-3,3-dimethylbutane or with 2-chloro-2,3-dimethylbutane:[6] 2,2-dimethyl-3-phenylbutane (about 80% of the mixture) and 2,3-dimethyl-2-phenylbutane.

D. Benzene and Cycloparaffins.—The reaction of cyclohexane with benzene at 26–30° yielded only a trace of cyclohexylbenzene. The chief product was *p*-polyphenyl, which was obtained in 60 mol % yield based on the reaction of 1 mol of benzene per 2 mol of cupric chloride.

Under the same conditions, the reaction of benzene with methylcyclohexane resulted in a 52 mol % yield of (*x*-methylcyclohexyl)benzene.

Reaction of decahydronaphthalene with benzene gave a 48 mol % yield of decahydronaphthylbenzene (evidently a mixture chiefly of the cis and trans isomers of 2-phenyldecahydronaphthalene, apparently the same isomers as those obtained by the aluminum chloride catalyzed reaction of benzene with 1,1-dichloroethane and decahydronaphthalene[3c]). Only a very small amount of *p*-polyphenyl was produced.

E. Isopentane As a Promoter.—Isopentane serves as a promoter for the alkylation of aromatic hydrocarbons with other alkanes and cycloalkanes. For example, reaction at room temperature of 2.5 mol of benzene with 1 mol of 2,3-dimethylbutane mixed with 0.13 mol of isopentane produced 17 mol % of hexylbenzenes (about 80% 3-phenyl-2,2-dimethylbutane and 20% 2-phenyl-2,3-dimethylbutane) and 2 mol % pentylbenzenes, compared to 9 mol % of hexylbenzenes obtained in the absence of added isopentane. The yields of ethylbenzene (10 mol %) and isopropylbenzene (3%) by-products also were approximately double the yields (5 and 1%, respectively) obtained in the absence of isopentane.

Addition of a minor amount of isopentane (0.06–0.11 mol) to cyclohexane (1.0 mol) and benzene (2.5 mol) also increased the amount of cyclohexylbenzene formed, from merely a trace amount to 20 mol % (based on the cupric chloride in the 0.5 mol of complex used). Pentylbenzenes were obtained in 6–7 mol % yield based on the isopentane (about 3% based on the cupric chloride) while ethylbenzene and isopropylbenzene were formed in 16–23 and 13–21 mol % yields, respectively, based on 1 mol of either per mol of isopentane. *p*-Polyphenyl was formed in about 60% yield based on the cupric chloride.

The mechanism of the promoting effect of isopentane was not proved. However, it seems possible that isopentane is more readily converted to cation than the other hydrocarbons investigated (for example, 2,3-dimethylbutane and cyclohexane) and that the *tert*-pentyl cation abstracts hydride ion from the alkane or cycloalkane to regenerate the isopentane and form a new cation (2,3-dimethylbutyl or cyclohexyl) which yields alkylbenzene by condensing with benzene. The low yield of pentylbenzene which is produced is due to reaction of some of the *tert*-pentyl cation with benzene instead of alkane or cycloalkane.

F. Alkylation of Toluene.—At 25–28°, reaction of toluene with isopentane during 0.5 hr yielded 12 mol % of pentyltoluenes based on the cupric chloride. Alkylation with 2,3-dimethylbutane under the same conditions gave a 1 mol % yield of hexylbenzenes, chiefly a mixture of 2-tolyl-2,3-dimethylbutane and 2-tolyl-3,3-dimethylbutane, identified by comparison of the glc chromatogram with that of the product of the alkylation of toluene with neohexyl chloride. The only by-product seemed to be polytolylene, a granular, dark brown powder, obtained in about 30 mol % based on the formation of 0.5 mol of tolylene per mol of cupric chloride.

Cupric Chloride–Zinc Chloride.—It was of obvious interest to obtain information about the scope of the cupric chloride promoted alkylation. Zinc chloride was tested as an example of a Friedel–Crafts catalyst which

is markedly inferior to aluminum chloride in its activity and in its ability to catalyze reactions, such as isomerization and isoparaffin alkylation, which proceed *via* hydride ion abstration.

The reaction of benzene with isopentane at 200° in the presence of a mixture of cupric chloride and zinc chloride was very similar to that which occurred at 17–21° in the presence of cupric chloride and aluminum chloride. The liquid product (not the catalyst) contained ethylbenzene, isopropylbenzene, pentylbenzene, and 1,1-diphenylethane in about one-fourth the total yield obtained when aluminum chloride was used. Chlorobenzene was also formed.

The pentylbenzene consisted of a mixture of *tert*-pentylbenzene and *sec*-isopentylbenzene, no neopentylbenzene being observed. This is to be expected in view of the low reactivity of zinc chloride in isomerizations. The formation of *sec*-isopentylbenzene (and, indeed of any alkylation product) is apparently due to hydride ion abstraction (*via* electron transfer) involving the cupric chloride.

As suggested by the formation of 1,1-diphenylethane, the mixture of cupric chloride and zinc chloride caused the aralkylation of benzene by ethylbenzene. When a mixture of the hydrocarbons and the metal chlorides was heated at 200°, 1,1-diphenylethane was obtained in 12 mol % yield together with a 7 mol % yield of chlorobenzene and a 10 mol % yield of *o*- and *p*-chloroethylbenzene. Formation of the latter compounds suggests that ethylbenzene undergoes chlorination more readily than does benzene, which was present in the reaction mixture in four times the quantity of ethylbenzene.

tert-Butylbenzene (about 20 mol % yield) and small amounts of chlorobenzene, diphenylmethane, and triphenylmethane were obtained by the reaction of benzene and isobutane at 200° in the presence of cupric chloride and zinc chloride.

Ferric Chloride. Catalyst and Electron-Transfer Agent.—Ferric chloride is usually a more active condensation catalyst than zinc chloride but less active than aluminum chloride. At 50° a mixture of cupric chloride and ferric chloride catalyzed little reaction between benzene and isopentane; at 150°, it produced pentylbenzenes, consisting of a mixture of *tert*-pentylbenzene and *sec*-isopentylbenzene with little or no neopentylbenzene, in 40 ml % yield based on the cupric chloride.

Ferric chloride also serves as an electron-transfer agent, but is less effective than cupric chloride. The reaction of benzene and isopentane at 21–24° in the presence of an equimolar mixture of ferric chloride and aluminum chloride resulted in an 8 mol % yield of pentylbenzenes based on the ferric chloride. Ethylbenzene and cumene were also produced.

Effect of Oxygen.—As shown above, formation of pentylbenzene from benzene and isopentane involves conversion of cupric chloride to cuprous chloride, the theoretical yield being 0.5 mol of product per mol of cupric chloride. Experiments were performed to determine whether carrying out the reaction in the presence of oxygen pressure would increase the yield of alkylation products by regenerating the cupric chloride.

$$4CuCl + 4HCl + O_2 \longrightarrow 4CuCl_2 + 2H_2O$$

Stirring a solution of isopentane (1.0 mol) and benzene (2.5 mol) with a mixture of 0.5 mol each of cupric chloride and aluminum chloride at 21–26° in a stainless steel turbomixer resulted in 25 mol % yield of the three pentylbenzenes together with small amounts of the usual by-products; the metal reactor apparently had an adverse effect on the reaction compared to glass. Carrying out the reaction under 1200 psi air pressure almost doubled the yield of pentylbenzenes (46 mol %). Use of hydrogen chloride (0.6 mol) and air had little additional effect (the yield of pentylbenzenes was 48 mol %) other than to increase the yield of *p*-polyphenyl by about 50%. (The average yield of benzene polymer was 3–4 g, whereas the yield in the presence of added hydrogen chloride was about 6 g.)

Similarly, in the presence of cupric chloride and zinc chloride at 200°, the yield of pentylbenzenes (3%) and of 1,1-diphenylethane (4%) by the reaction of benzene with isopentane and ethylbenzene, respectively, were very markedly increased (to 14 and 22%, respectively) by carrying out the reaction under air pressure. Since zinc chloride, unlike aluminum chloride, is not inactivated by water, it is not affected by the water formed during the oxidation of the cuprous chloride/hydrogen chloride and the catalyst mixture may be used in continuous flow alkylation.

Conformational Analysis. LXXXIX. Stereochemical Studies of Some Dimethylated Six- and Seven-Membered-Ring Hydrocarbons[1,2]

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The *cis*- and *trans*-1,2-dimethylcycloheptanes were prepared and equilibrated over palladium in the liquid phase at elevated temperatures. The trans isomer was found to be more stable; $\Delta H^\circ = 0.54$, $\Delta G^\circ = 0.59$ kcal/mol, $\Delta S^\circ = 0.15$ eu (25°). The acid-catalyzed equilibria between the 1,2-dimethylcyclohexenes showed that the order of stability was 1,2-dimethylcyclohexene > 1,6-dimethylcyclohexene > 1-methyl-2-methylenecyclohexane. Similar experiments with the 1,2-dimethylcycloheptenes led exclusively to ring contraction.

While a great many conformational studies of all kinds have been reported on six-membered hydrocarbon rings,[4] very much less is known conformationally about the cycloheptane ring. This is in part because of the greater practical importance of six-membered *vs.* seven-membered rings, and also in part due to the fact that while the cyclohexane ring is very simple, containing only two nonequivalent positions, which can become equivalent by ring inversion, the cycloheptane ring contains no less than seven nonequivalent positions, which may become equivalent by ring inversion or by pseudorotation. While a six-membered ring consists of a unique chair form in all but very unusual cases, the seven-membered ring consists of a number of chair forms which are separated by small pseudorotational barriers, plus a boat form which itself consists of several forms separated by small pseudorotational barriers, and the boat form is only somewhat higher in energy than the chair, so that in substituted molecules one cannot assume automatically that the chair form will always predominate.

In an elegant theoretical study of the conformations of cycloheptane, using calculations of the Weissheimer type, Hendrickson[5] delineated the conformations available to cycloheptane and their relative energies. The data he obtained are still believed to be valid. The important point brought out by his calculations was that substitution of a reasonably small group, say a methyl group, into the cycloheptane ring could take place at any of several points, and lead to a structure that was at an energy minimum, corresponding to an equatorial methyl group in the cyclohexane ring. If two methyls were placed in the ring in positions located 1,3 or 1,4 to each other, and probably also if they were located 1,2 or 1,1, one could always have the methyls in an equatorial-like position, or in the 1,1 case, biaxial, which for purposes of energy calculations is substantially equatorial. Hendrickson therefore concluded that cycloheptane rings with two nonpolar substituents that were not too large would have very similar energies for both the cis and trans forms, in all cases. Insofar as evidence is available experimentally, this has been found to be the case. It was already known to Hendrickson that the cis and trans isomers of 3,5-dimethylcycloheptanone differed in energy by only 0.8 kcal/mol, with the cis isomer being the more stable.[6] Also, equilibration data on the perhydroazulene ring system showed that the trans isomer had an enthalpy of 0.3 kcal/mol less than did the cis isomer.[7] Further studies on more complex cycloheptane systems as found in the perhydroazuleneoid sesquiterpenes were carried out by Hendrickson[8] and similar considerations for A-homo steroids have been reported by Jones, Zander, and Price.[9]

It seemed to us that some more detailed studies on simple cycloheptanes would be desirable, whereupon we chose the dimethylcycloheptanes as suitable simple derivatives on which one could carry out conveniently both thermodynamic studies and force-field calculations. Studies on the 1,2-dimethylcycloheptanes were completed some years back. Subsequently, studies were published by Mann and coworkers[10] on the 1,2, the 1,3, and the 1,4 isomers, which included synthetic and equilibration experiments. Our studies on the 1,2 isomer are in reasonable agreement with those reported by Mann and will be outlined herein. In the course of this work, some studies were also carried out on intermediate olefinic compounds, which are also reported here.

Hendrickson's calculations[11] on the 1,2-dimethylcycloheptanes indicated that all dimethylcycloheptanes should have essentially the same energy, the energy difference between any pair of isomers being about 0 kcal/mol. While improvements have been made in force-field calculations since Hendrickson's work in this area, there is no reason to doubt that his conclusions are substantially correct for the case at hand. We therefore did not consider it worthwhile to repeat those calculations, but accept them as they stand.

As analogs we will have occasion to discuss the 1,2-dimethylcyclohexanes. Our synthetic scheme for obtaining both the dimethylcyclohexanes and dimethylcycloheptanes was such as to put a double bond into the ring system at one point. Since mixtures of olefins were obtained, it was of interest to inquire as to where the equilibria between these isomeric olefinic com-

(1) This work was supported in part by Grant No. 15263 from the National Science Foundation. Abstracted from the Ph.D. Dissertation of N. A. P., Wayne State University, March 1970.

(2) Paper LXXXVIII: C. J. Finder, D. Chung, and N. L. Allinger, *Tetrahedron Lett.*, 4677 (1972).

(3) Correspondence concerning this work should be directed to the University of Georgia.

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(5) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961).

(6) N. L. Allinger, *ibid.*, **81**, 232 (1959).

(7) N. L. Allinger and V. Zalkow, *ibid.*, **83**, 1144 (1961).

(8) J. B. Hendrickson, *Tetrahedron*, **19**, 1387 (1963).

(9) J. B. Jones, J. M. Zander, and P. Price, *J. Amer. Chem. Soc.*, **89**, 94 (1967).

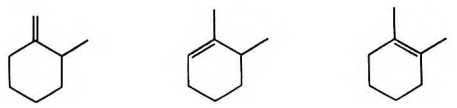
(10) G. Mann, M. Muhlstadt, R. Muler, E. Kern, and W. Hadeball, *Tetrahedron*, **24**, 6941 (1968).

(11) (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **84**, 3355 (1962); (b) *ibid.*, **89**, 7043 (1967).

pounds were to be found. We might consider the six-membered ring first.

The equilibrium between methylcyclohexene and methylenecyclohexane has been exhaustively studied, both experimentally and theoretically, and commented upon in the literature.[12-14] It is quite clear that the endocyclic isomer strongly predominates over the exocyclic isomer; the most important feature in the energy considerations is that the trisubstituted double bond is more stable than the disubstituted double bond. Also important is the fact that a double bond wants to be eclipsed by a substituent on the sp^3 carbon attached to it; any other alternative corresponds to an increase in torsional energy.

When the second methyl group is placed on the cyclohexane ring, the situation becomes more complicated, because there are now two endocyclic positions and one exocyclic position, which involve one or both of the tertiary centers (structures I–III).



I II III

A mixture of I, II, and III was prepared by adding methyl Grignard to 2-methylcyclohexanone to give 1,2-dimethylcyclohexanol. Dehydration of the alcohol with iodine resulted in a mixture of the olefins. Upon vpc analysis there were found three peaks; in order of increasing retention time they corresponded to 3.2, 30.9, and 65.9% of the total olefin. Fractions 2 and 3 were characterized as olefins II and III by isolation and examination of the nmr and ir spectra. Fraction 1 is assumed to be olefin I, but an insufficient amount was obtained for isolation and identification.

This mixture of olefins, which corresponds to a kinetic rather than a thermodynamic composition, was equilibrated in the presence of a trace of sulfuric acid in refluxing pentane. After the olefin composition ceased to change it was assumed that equilibrium was reached, and analysis showed that fraction 2 had decreased to 15.2% of the total, while fraction 3 had increased to 84.8% of the total, and fraction 1 had completely disappeared (less than 0.5%). In terms of free energy, these results indicate that isomer III is the most stable, isomer II having an energy some 1.0 kcal above that of isomer III, while the energy of I must be at least 3.3 kcal higher than that of III.

The synthesis of the seven-membered-ring compounds was carried out beginning with cycloheptanone, which was allowed to react with ethyl oxalate to give a diketo ester, which in turn was decarbonylated to give α-carboethoxycycloheptanone. Alkylation of the latter, followed by hydrolysis and decarboxylation, furnished 2-methylcycloheptanone. Addition of methyl Grignard to the latter gave the corresponding alcohol, which upon dehydration gave dimethylcycloheptane is a mixture of three isomers (by vpc). The three olefins were each isolated by preparative vpc, and identified as (a) the exo methylene compound; (b) the 1,7-dimethylcycloheptene; and (c) 1,2-dimethylcycloheptene, which could be identified by the absence of vinyl hydrogens. The infrared and nmr spectra of the compounds permitted unequivocal identification. Hydrogenation of the mixture of the olefins gave a mixture of the 1,2-dimethylcycloheptanes, cis and trans.

The equilibration of the seven-membered-ring olefins was carried out in a manner similar to that described for the six-membered-ring analogs. Thus the mixture of a, b, and c was treated with sulfuric acid in pentane at reflux, and the composition of the mixture was analyzed as a function of time. In Table I are summarized the results of the equilibration experiments.

TABLE I

ACID-CATALYZED EQUILIBRATION OF SEVEN-MEMBERED-RING OLEFINS a, b, AND c IN REFLUXING PENTANE (36°)

Fraction no.	Retention time,[a] min	Products, % Initial concn	9 days	28 days	30 days
1[b]	52.5	9.7	42.1	90.0	90.0
2[c]	60.0	28.6	4.9	2.3	2.5
3[d]	62.3	61.7	49.6		
4[b]	67.5		3.4	7.7	7.5

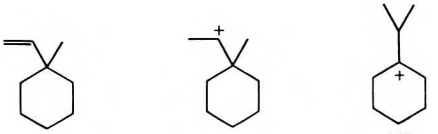
[a] Determined at a column temperature of 110°. [b] Structure determined at the end of the equilibration experiment. [c] Structure determined at the start, but not at the end, of the equilibration experiment. [d] Structure determined at the start of the equilibration experiment.

From the information in Table I, obviously events did not pursue the intended course. One certainly would not expect a, the exocyclic olefin, to be the stable one, and yet that is the peak that was the predominant one on vpc after a sufficient time had elapsed. On the other hand, peak 3, which corresponds to the isomer thought to be the most stable, disappeared after a sufficiently long time and, in addition, a new peak (4) appeared.

Peak 4 was separated by preparative vpc, and characterized as isopropylidenecyclohexane by infrared and nmr spectroscopy. Obviously, a skeletal rearrangement had taken place in addition to the hydride migrations which were sought. Peak 1 was therefore isolated and examined, and it proved to be isopropylcyclohexene. No direct evidence for any seven-membered-ring compounds was obtained, although the peak 2 may correspond in part to 1,7-dimethylcycloheptene, but this seems doubtful.

1-Isopropylcyclohexene was then prepared and equilibrated by treatment with sulfuric acid in refluxing pentane and also by sulfuric acid in acetic acid, and the same kind of equilibrium mixture was obtained. Several experiments were carried out, but in no case was it possible to obtain equilibration of the cycloheptene compounds without their conversion to cyclohexene derivatives.

We might note in passing that Mann[10] recently reported upon dehydration of 1,2-dimethylcycloheptanol with *p*-toluenesulfonic acid. It was claimed that 15% of the product consisted of the olefin IV,

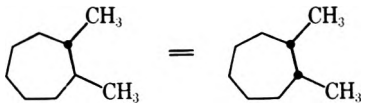


IV V VI

(12) E. Gil-Av and J. Shabtai, *Chem. Ind. (London)*, 1630 (1959).
(13) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954); (b) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).
(14) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **90**, 5773 (1968).

which is formed *via* cation V. This seems highly unlikely to us, and does not correspond to our observations. The rearrangement of the initially formed cation is more likely to go in stages, through V and on to VI by methyl migration, which then can lose a proton to form a mixture of isopropylidenecyclohexane and isopropylcyclohexene. The product which Mann assigned the structure vinylmethylcyclohexane is probably in fact isopropylidenecyclohexane, but his description of the preparation of the compound and its properties are too sketchy to tell.

The equilibration of the cis and trans isomers of 1,2-dimethylcycloheptane was carried out in a manner previously described for alkylcyclohexanes,[15] by heating the compounds in sealed tubes with small amounts of palladium at temperatures ranging from 200 to 324°. The tubes were filled sufficiently so that, when the equilibrium temperature was reached, the volume not occupied by the liquid was essentially zero. This avoided the problem of the presence of a gas phase in which the equilibrium constant differs from that in the liquid.[16] After the equilibrium constant (K = cis/trans) was calculated for each equilibration temperature, enthalpy and entropy values were obtained by a least squares fit of ln K *vs.* $1/T$. The thermodynamic quantities for the isomerization of *trans*- to *cis*-1,2-dimethylcyclohexane (VII and VIII) are $\Delta H°$



VII VIII

= 0.54 ± 0.02 kcal/mol; $\Delta S°$ = 0.15 ± 0.03 eu; $\Delta G°_{25°}$ = 0.59 kcal/mol.

The data show that the trans isomer of 1,2-dimethylcycloheptane is of lower enthalpy than the corresponding cis isomer by 0.54 ± 0.02 kcal/mol. This is in accordance to the prediction that the 1,2-trans isomer above should be more stable than the 1,2-cis isomer and that the difference in energy between the two should be small compared to what is found for similar six-membered-ring isomers.[4] The entropy difference between *cis*- and *trans*-1,2-dimethylcycloheptane is close to zero. This is reasonable considering that both of the isomers are about equally flexible. The amount of disorder is thus about the same for both isomers.

Experimental Section

1,2-Dimethylcyclohexenes (I, II, and III).—The olefinic mixture was prepared according to the procedure of Signaigo and Cramer.[17] The mixture was separated by preparative vpc (see below), and the compounds II and III were characterized by their nmr and ir spectra.

1,2-Dimethylcycloheptenes.—Methyl iodide, 24.0 g, was added dropwise to 4.1 g of magnesium turnings in 200 ml of anhydrous ether. The mixture was heated under reflux for an additional 1 hr, then 17.2 g of 2-methylcycloheptanone was added dropwise with cooling, and stirring was continued overnight. A saturated solution of ammonium hydroxide was slowly added to the reaction mixture, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were washed and dried over magnesium sulfate, the ether was evaporated, and the product was distilled, bp 69° (4 mm), wt 16.5 g (86.6%), ir broad hydroxyl band at 3420, CH_3 bending at 1370 cm^{-1}.

The 1,2-dimethylcycloheptanol obtained above, 16.5 g, was heated with a few iodine crystals and distilled to yield a fraction boiling at 90–155°. The water was separated from the distillate, and the hydrocarbon layer was dried with magnesium sulfate. Distillation gave the product, bp 150–152°, wt 11.2 g (77.9%).

Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.11; H, 12.96.

Vpc Separation of Isomeric Olefins.—The Varian Autoprep (Model 700) was used for separation purposes throughout this work. A 20 ft × 0.375 in. aluminum column containing 30% SE-30 on Chromosorb W (45/60 mesh) was used. The flow rate 200 ml/min, with helium carrier gas. Analyses were by the height × half band width technique.

The 1,2-dimethylcyclohexene isomers were separated at a temperature of 110°, as were the 1,2-dimethylcycloheptene isomers. The nmr and ir spectra of each fraction was consistent with the assignment made.

1-Isopropylcyclohexene and Isopropylidenecyclohexane.—Isopropyl bromide, 61.5 g, was added slowly to 15.2 g of magnesium turnings in 200 ml of dry ether. Cyclohexanone, 39.2 g, was then slowly added to the reaction flask, and the reaction mixture was stirred overnight. A saturated solution of ammonium chloride was added, and the ether layer was collected, washed with water, and dried over magnesium sulfate. The solution was filtered and the ether was evaporated. The ir of the residue showed a strong hydroxyl band.

A crystal of iodine was added to the above product and the mixture was refluxed in toluene overnight. A Dean-Stark trap was used to remove the water formed. The solvent was then removed and the product was distilled, bp 142°. The distillate was injected into the vpc at 110°. Two peaks were detected and were collected as fractions 1 and 2 with retention times of 52.5 and 67.5 min, respectively. Fraction 1 was the largest of the two by 9:1.

The data on the vpc fractions are as follows. Fraction 1 had nmr (neat with TMS) multiplet at δ 5.38 (1 H), multiplet between 1.40 and 2.32 (9 H), and a doublet at 0.95 (6 H) separated by 7.0 Hz.

Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.17; H, 12.86.

Fraction 2 had nmr (neat with TMS) broad singlet at δ 2.14 (4 H) and a broad region between 1.30 and 1.80 (12 H).

Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98. Found: C, 87.09; H, 12.99.

1,2-Dimethylcycloheptane.—A mixture of 1,2-dimethylcycloheptenes was hydrogenated using platinum oxide in acetic acid. The product was worked up as usual and it showed a negative tetranitromethane test. Vpc analysis at 110° showed two peaks with retention times of 47.5 (19% of total area) and 53.5 min (81% of total area). When the hydrogenation was carried out in ethanol with palladium catalyst, the composition of the mixture varied slightly, 31.7 and 68.3% of the two fractions being obtained. The cis structure is assigned to the predominant isomer (fraction 2).

The data on the two vpc fractions are as follows. Fraction 1 had nmr (neat with TMS) broad region between δ 1.12 and 1.80, converging to a singlet at 1.52 (10 H), sharp singlet at 0.96 (8 H). The latter is attributed to the sum of the methyl protons and the methine protons, and is similar to what is found with *trans*-1,2-dimethylcyclohexane.[18]

Anal. Calcd for C_9H_{18}: C, 85.63; H, 14.37. Found: C, 85.38; H, 14.16.

Fraction 2 had nmr (neat with TMS) broad region between δ 1.10 and 2.00, converging to a singlet at 1.52 (12 H), and a doublet at 0.85 (6 H), with a separation of 6.5 Hz.

Anal. Calcd for C_9H_{18}: C, 85.63; H, 14.37. Found: C, 85.41; H, 14.18.

Equilibration of 1,2-Dimethylcycloheptane Isomers.—In a capillary ampoule 1,2-dimethylcycloheptane (mixture of cis and trans) was inserted along with about 10% by weight of 10% palladium on carbon. The total amount of hydrocarbon was about 25 μl, which occupied approximately 70–80% of the capillary's volume. The ampoule was sealed and immersed in a furnace for the desired length of time at the proper temperature. Immediately upon removal from the furnace, the ampoule was

(15) (a) N. L. Allinger and S. Hu, *J. Org. Chem.*, **27**, 3417 (1962); (b) N. L. Allinger, W. Szkrybalo, and F. A. Van-Catledge, *ibid.*, **33**, 784 (1968).
(16) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **81**, 4080 (1959).
(17) F. K. Signaigo and P. L. Cramer, *ibid.*, **55**, 3326 (1933).
(18) N. L. Allinger and N. A. Pamphilis, *J. Org. Chem.*, **36**, 3437 (1971); J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960).

cooled in ice water. The contents of the ampoule were then analyzed by vpc. Each sample was analyzed at least twice and and average value was taken. The average deviation was about 0.1–0.2%. In Table II the results of the analysis are given.

TABLE II

EQUILIBRATION OF *cis*- AND *trans*-1,2-DIMETHYLCYCLOHEPTANE

Temp, °C	Length of run, hr	Fraction 1, % trans	Fraction 2, % cis
200	336	65.72	34.27
225	144	64.98	35.02
250	72	64.60	35.40
274	24	63.94	36.06
300	24	63.38	36.62
324	24	62.99	37.01

Acid-Catalyzed Equilibration Procedure.—1,2-Dimethylcycloheptene (mixture of isomers), 0.5 g, was heated under reflux in 25 ml of olefin-free pentane containing 2 drops of concentrated sulfuric acid. Samples were occasionally withdrawn and checked by vpc. At suitable intervals, larger samples were run through the preparative vpc and fractions were isolated. The fractions were identified by infrared and nmr spectra.

Other equilibration experiments starting with 1-isopropylcyclohexene and the 1,2-dimethylcyclohexenes were carried out in a similar manner. The results are summarized in Tables III and IV.

TABLE III

ACID-CATALYZED EQUILIBRATION OF 1-ISOPROPYLCYCLOHEXENE IN REFLUXING PENTANE (36°)

Fraction no.	Structure assigned	Retention time,[b] min	Products, % Initial concn	5 days	21 days	42 days	50 days
1		52.5	100.0	90.0	90.6	90.4	90.4
2	[a]	60.0				2.3	2.2
3		67.5		9.6	9.3	7.3	7.4

[a] Not isolated. [b] Determined at a column temperature of 110°.

TABLE IV

ACID-CATALYZED EQUILIBRATION OF SIX-MEMBERED OLEFINS I, II, AND III IN REFLUXING PENTANE (36°)

Fraction no.	Structure assigned	Retention time,[a] min	Products, % Initial concn	6 days	9 days
1		31.2	3.2		
2		35.2	30.9	15.2	15.1
3		42.5	65.9	84.8	84.9

[a] Determined at a column temperature of 110°.

Registry No.—1,2-Dimethylcycloheptanol, 37102-80-0; 1,2-dimethylcycloheptene, 20053-89-8; 1-isopropylcyclohexene, 4292-04-0; isopropylidenecyclohexane, 5749-72-4; *trans*-1,2-dimethylcyclohexane, 6876-23-9; *cis*-1,2-dimethylcyclohexane, 2207-01-4; 1-methyl-2-methylenecyclohexane, 2808-75-5; 1,6-dimethylcyclohexene, 1759-64-4; 1,2-dimethylcyclohexene, 1674-10-8.

Steric and Polar Effects in the Decarboxylation of Mercuric Salts of Unsymmetrical Aromatic 1,2-Dicarboxylic Acids (the Pesci Reaction). An Improved Procedure[1a]

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The conversion of mercury(II) salts of unsymmetrical aromatic 1,2-dicarboxylic acids to monocarboxylic acids through the intermediate anhydrohydroxymercuric acids (Pesci reaction) is discussed in terms of polar and steric effects. An improved procedure which involves heating of the mercury(II) salts in hexamethylphosphoramide containing powdered glass yields anhydrohydroxymercuric acids in higher yield and in shorter time than does the previously described procedure. The anhydrohydroxymercuric acids are rapidly and almost quantitatively converted into aromatic monocarboxylic acids by treatment with sodium borohydride.

The reaction of phthalic acid with mercury(II) acetate produces a salt (**1**) which on heating in boiling water yields anhydro-2-hydroxymercuribenzoic acid[2] (**2**) (eq 1). When the latter is refluxed for several days with aqueous hydrochloric acid benzoic acid is produced (eq 2).[2] If the mercury(II) salt of a 3-substituted phthalic acid is used, two anhydro-2-hydroxymercuric acids (**2**, **3**) and from them two substituted benzoic acids (**4**, **5**) may be formed. The object of the work herein reported was to study the effect of hydrocarbon moieties in the 3 position on the course of the Pesci reaction. During this work marked improvements in the method of decomposition of the mercury(II) phthalates, as well as replacement of mercury in the anhydro-2-hydroxymercuribenzoic acids, were made.

In earlier work, 3-chlorophthalic acid[3] (**6**), 3-bromophthalic acid[3] (**7**), 3-nitrophthalic acid[3] (**8**), and hemimellitic acid[4] (**9**) were subjected to the Pesci reaction. Each was reported to yield exclusively the corresponding meta-substituted benzoic acid (**4**). The conversion of 1,2-anthraquinonedicarboxylic acid to 2-carboxyanthraquinone was also noted.[5] Because all of

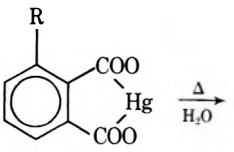
(1) (a) This work was supported by Grant 12445 of the National Science Foundation. (b) Predoctoral Research Associate.

(2) L. Pesci, *Atti Accad. Naz. Lincei*, [5] 10, I, 362 (1901); *Chem. Zentralbl.*, II, 108 (1901).

(3) F. C. Whitmore and P. J. Culhane, *J. Amer. Chem. Soc.*, **51**, 602 (1929).

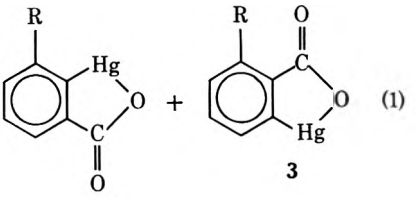
(4) F. C. Whitmore and R. P. Perkins, *ibid.*, **51**, 3352 (1929).

(5) F. C. Whitmore and F. L. Carnaham, *ibid.*, **51**, 856 (1929).



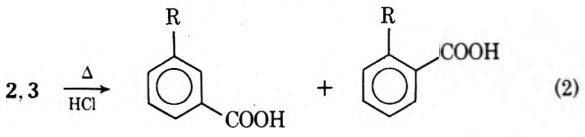
A

1, R = H 8, R = NO_2
6, R = Cl 9, R = COOH
7, R = Br 10, R = CH_3



B

2, R = H



the substituents adjacent to the carboxyl being replaced were electronegative, it was not clear whether steric or electronic factors were dominant. Work on 3- and 4-nitro-1,8-naphthalic acids[6] showed that a polar effect was operating in molecules in which no steric effect was possible (see eq 3 and 4) but no further work with other substituents has appeared. In the present study the mercury(II) salts of 3-methylphthalic acid (**10**), 1,2-naphthalic acid (**11**), and 3,4-phenanthrenedicarboxylic acid (**12**) were studied.

An alternate procedure for converting the mercury(II) salts (A) to anhydrohydroxymercuric acids (B) (eq 1) was sought because the conventional procedure calls for refluxing in water for 16 to 98 hours.

When suspensions of salts (A) in hexamethylphosphoramide (HMPA) containing powdered soft glass were heated, decarboxylation commenced at about 110° and was sufficiently rapid at about 165° that it was complete in 45 min. However, if powdered glass was not present, decarboxylation to only a minor extent occurred even on heating at 185° for 4 hr. Of other solvents tried [quinoline, ethylene glycol, tetramethylene sulfone (sulfolane), dimethylformamide, and *N*-methylpyrrolidone (NMP)] only the latter was effective, but NMP was not so good as HMPA, probably (see Experimental Section) because of the limited solubility of the mercury(II) salts in all solvents except HMPA and NMP.

The use of powdered glass was suggested by previous experience with the MacFayden–Stevens reaction.[7] Other examples of the use of powdered glass in decarbonylation[8] and decarboxylation[9] reactions are of interest.

The conversion of the anhydrohydroxymercury salts (B) to aromatic acids (**4**, **5**) was previously accomplished by long heating in aqueous hydrochloric acid[2] (eq 2). We have found that treatment of a suspension of the anhydrohydroxymercury salts (B) in ethanol with sodium borohydride[10] yields the demercurated acids in 10 min, even in the case of anhydro-4-hydroxymercuric-3-phenanthroic acid, which was not converted to 3-phenanthroic acid by the conventional procedure.[2]

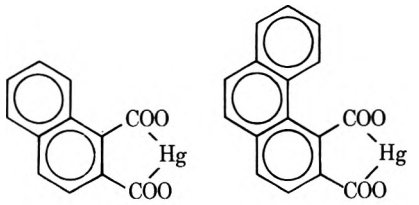
When **10**, **11**, and **12** were treated by our improved procedures, the results listed in Table I were obtained.

TABLE I
RESULTS FROM PESCI REACTIONS

Mercury(II) salt	Products[a]	Overall yield, %
6	Methyl 3-chlorobenzoate[b]	87
8	Methyl 3-nitrobenzoate–methyl 2-nitrobenzoate (3:1)[c]	94
10	Methyl 3-methylbenzoate–methyl 2-methylbenzoate (5:1)[d]	85
11	Methyl 2-naphthoate–methyl 1-naphthoate (9:1)[d]	82
12	Methyl 3-phenanthroate[b]	98

[a] All products identified by comparison with authentic samples. [b] Purity determined by nmr and glpc. [c] Ratio determined by nmr. [d] Ratio determined by glpc.

Thus, it appears that as the steric factor is increased from an ortho methyl group to an ortho fused ring to two continuously fused rings[11] the selectivity in favor of replacement of the sterically hindered carboxyl group increases. These facts suggest the operation of a pronounced steric effect in the Pesci reaction.

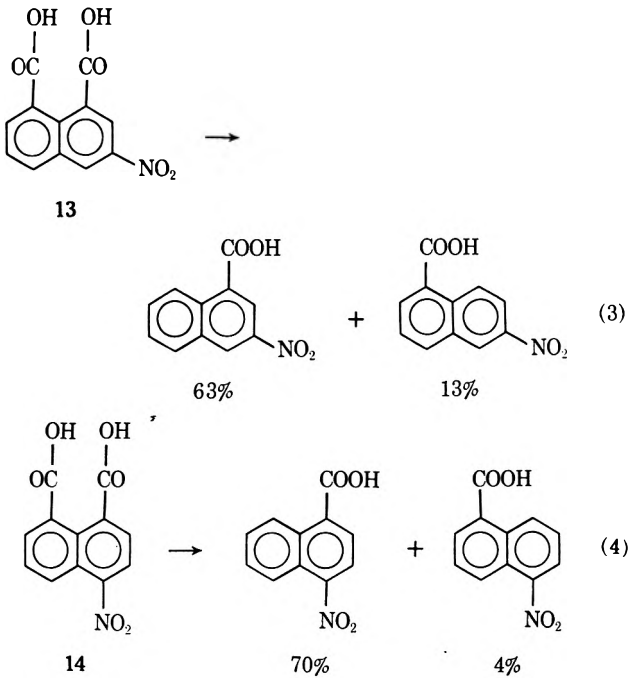


11 12

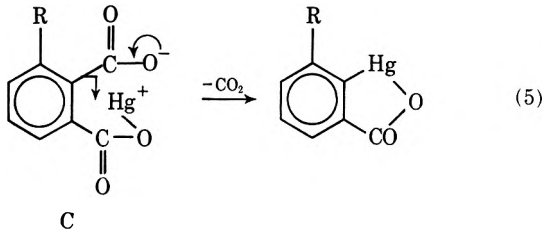
The only previous study of a polar effect in the Pesci reaction was that[6] on 3-nitro-1,8-naphthalic acid (**13**), which gave mainly (after replacement of the mercury by hydrogen) 3-nitro-1-naphthoic acid (eq 3), and 4-nitro-1,8-naphthalic acid (**14**), which gave mainly 4-nitro-1-naphthoic acid (eq 4). In each case the predominant product resulted from replacement of carboxyl from the ring *not containing the nitro group*.

These results suggest that the replacement of carboxyl by mercury involves initially an opening of the ring in the cyclic[12] salt A in either of two ways

(6) G. J. Leuck, R. P. Perkins, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **51**, 1831 (1929).
(7) M. S. Newman and E. G. Caflisch, Jr., *ibid.*, **80**, 862 (1958).
(8) W. E. Bachmann, W. Cole, and A. L. Wilds, *ibid.*, **62**, 824 (1940).
(9) D. V. Hertzler, J. M. Berdahl, and E. J. Eisenbraun, *J. Org. Chem.*, **33**, 2008 (1968).
(10) Compare H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959), for reduction of aliphatic mercurials and F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966), for conversion of phenylmercuric acetate to diphenylmercury with $NaBH_4$.
(11) For discussions of these steric effects see J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, **80**, 905 (1958); M. S. Newman and H. Boden, *ibid.*, **83**, 115 (1969); and M. S. Newman and W. H. Powell, *J. Org. Chem.*, **26**, 812 (1961).
(12) The mercury(II) salts are pictured as cyclic monomeric species. However, they might be polymeric (or multimembered cyclic polymeric) salts. In any case the mechanistic arguments would be similar.



(equilibria could be involved) in an unsymmetrical case. The open dipolar ion[13] (only one form C shown) can cyclize to the anhydrohydroxymercuric acid (B) as shown (eq 5).



C

The products obtained from **13** and **14** may be explained by polar factors, because the electron density at position 8 would be expected to be greater than that at position 1 in each case. However, with 3-nitrophthalic acid (**8**) a mixture of about 77% of 3-nitrobenzoic acid and 23% of 2-nitrobenzoic acid is formed.[14] This result is the opposite of that expected if the reaction pictured in eq 5 is governed by polar factors similar to those operating in compounds **13** and **14**. Hence we conclude that a steric effect is involved and may be rationalized by assuming that there is a greater release of strain in expelling carbon dioxide from the transition state involving the internal carboxylate anion than that involving the external carboxylate ion.

(13) Since addition of galvinoxyl had no effect on the rate of decarboxylation or on the products obtained in the case of **10**, we assume that a free-radical path is not operative. The lack of effect by galvinoxyl on rates or products does not rule out a free-radical cage process; see R. C. Lamb, *et al.*, *J. Amer. Chem. Soc.*, **85**, 3483 (1963), as pointed out by a referee.

(14) Whitmore and Culhane, ref 3, report only 3-nitrobenzoic acid. However, their crude acid was recrystallized three times.

Experimental Section

Formation of Anhydrohydroxymercuri Salts.—In a typical experiment, 1.62 g (0.01 mol) of 3-methylphthalic anhydride was added to 50 ml of 0.4 *N* sodium hydroxide. To the resulting solution was added a solution of 3.19 g (0.01 mol) of mercuric acetate in 50 ml of water and 0.5 ml of acetic acid. The colorless precipitate was collected, washed with 10 ml of alcohol, and air dried to yield 3.44 g (91%) of **10**. A suspension of this salt and 3 g of powdered soft glass[15] in 20 ml of HMPA in a 50-ml flask was placed in a silicone oil bath at 175°. The theoretical volume of carbon dioxide was collected in 60 min (for **6**, 60 min; for **8**, 25 min; for **11**, 1.5 hr; for **12**, 2 hr). The suspension was diluted with 200 ml of water and filtered. The moist solids were suspended in ethanol and stirred with 0.76 g (0.02 mol) of sodium borohydride for 15 min. After acidification with 15 ml of concentrated hydrochloric acid and dilution with 50 ml of acetone, the mixture was filtered through Celite. Removal of the solvents under reduced pressure afforded 1.22 g of a white solid which contained no neutral material. The solids were quantitatively esterified with diazomethane to yield 1.32 g (87% from 3-methylphthalic anhydride) of a clear liquid consisting of methyl 3-methylbenzoate (83%) and methy 2-methylbenzoate (17%).

Solvent Effect on Pesci Reaction.—On heating **6** and powdered glass in quinoline, ethylene glycol, sulfolane, dimethylformanide, NMP, and HMPA, at temperatures up to 200°, copious gas evolution was noted only in the case of HMPA. In order to see if solubility of the anhydrohydroxymercuri salt in the solvent concerned was the dominant factor, 5 mmol of **6**, **8**, **10**, and **12** (in separate tubes) in 10 ml of solvent was heated at 150–155° for 15 min. The solids were removed by filtration and hydrogen sulfide was passed through the filtrate. Only in the cases of NMP and HMPA did the formation of black mercury sulfide indicate appreciable solubility of the salts. In the other solvents only slight haziness was noted in a few cases. No appreciable amount of carbon dioxide was evolved in any experiment which did not include powdered glass. When powdered glass was added in similar experiments carbon dioxide evolution was appreciable *only in the HMPA case*. Thus, solubility of the salt is not alone responsible for the success of the new variation. Actually, the anhydromercuri salt from **10** is completely soluble in NMP; yet only a small amount of carbon dioxide was evolved after heating for a much longer time than that required for complete decarboxylation in HMPA.

Product Analysis.—Glpc analyses were performed on an F & M Model 500 gas chromatograph equipped with a thermal conductivity detector. A 7 ft × 0.25 in. column packed with 15% silicone gum rubber SE-30 on 60-80 mesh Chromosorb W was used. Nmr analyses were performed on a Varian A-60 spectrometer (all samples were dissolved in acetone-d_6 using TMS as internal standard).

Mercuric 3-chlorophthalate (**6**) afforded only methyl 3-chlorobenzoate, which was identified by glpc and the appearance of a single peak at δ 3.88 ppm whereas methyl 2-chlorobenzoate has a peak at 3.78.

Mercuric 3-nitrophthalate (**8**) yielded a mixture of about 77% methyl 3-nitrobenzoate (nmr methyl peak at δ 4.02) and 23% of methyl 2-nitrobenzoate (δ 3.92). Integration was effected by offsetting 200 Hz and using a 50-Hz sweep width.

The methyl ester obtained from **10**, **11**, and **12** were all separable by glpc. The product ratios given in Table I were determined from integrated peak heights. Nmr analysis of the ester from **12** confirmed that only one isomer was present (methyl 3-phenanthroate δ 4.08; only peak observed above 7.40).

Registry No.—**6**, 37102-75-3; **8**, 37102-76-4; **10**, 37102-77-5; **11**, 37102-78-6; **12**, 37102-79-7.

(15) Freshly ground or aged glass gave essentially the same result. Variation of the amount of glass from 0.5 to 5.0 g made no observable difference in the rate of decarboxylation. See also ref 9.

Tetrahydrofuran Decomposition. Condensation of Solvent Fragment with Benzophenone and Tritylllithium[1a,b]

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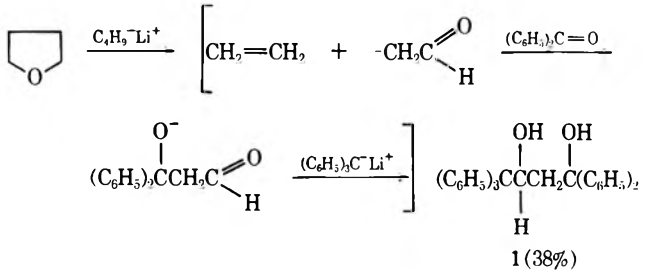
Decomposition of tetrahydrofuran by *n*-butyllithium producing ethylene and the enolate ion of acetaldehyde has been noted. Condensation of the latter with benzophenone and tritylllithium results in the formation of significant quantities of 1,1,4,4,4-pentaphenyl-1,3-butanediol (1). Conformational analysis of diol 1 by nmr is discussed. None of the para-condensation product[2] of tritylllithium with benzophenone is observed in this solvent.

This study of the decomposition of tetrahydrofuran (THF) resulted from an examination of the condensations of the bulky tritylllithium reagent with several large molecules in different solvents. In our earlier work,[2] reaction of tritylllithium with benzophenone in tetrahydropyran (THP) produced the para-condensation product *p*-(diphenylmethyl)diphenylhydroxymethylbenzene. The reduction of steric crowding achieved by para condensation of tritylllithium was intriguing, but when the reaction solvent is THF a more unusual result is observed. THF decomposes in the presence of *n*-butyllithium and tritylllithium, yielding ethylene and the enolate ion of acetaldehyde. The latter condenses with benzophenone and tritylllithium, furnishing 1,1,4,4,4-pentaphenyl-1,3-butanediol (1) in yields as high as 38% (Scheme I). *THF decomposition with*

SCHEME I



1 (38%)

subsequent two-carbon insertion has not been reported previously. Low yields of diol 1 were obtained when 2-methyltetrahydrofuran was employed as solvent.

Structure of Condensation Product.—Base-catalyzed thermal decomposition of diol 1 yielded triphenylmethane (86%), benzophenone (41%), and acetaldehyde (10%). 1,1,2,4,4-Pentaphenyl-1,3-butadiene (3) (Scheme II) resulted (74%) from treatment of diol 1 with iodine in acetic acid for 1 hr; dehydration of the secondary hydroxyl function is accompanied by rearrangement. 1,1,1,4,4-Pentaphenylbut-3-en-2-one (2) was isolated (63%) after refluxing diol 1 with acetic acid and sodium dichromate for 2.5 hr. Base-catalyzed thermal decomposition of ketone 2 furnished triphenylmethane and benzophenone. Acidification of the aqueous layer of the above decomposition produced 3,3-diphenylacrylic acid (5) in an 82% yield. Diol 1 dissolved in methylene chloride and refluxed for 2 hr with acetic acid and chromium trioxide yielded 1,1,1,4,4-pentaphenyl-4-hydroxy-2-butanone (4) (56%). Apparently, because of milder reaction conditions used in this oxidation, dehydration to the butenone 2 does not occur.

Keto alcohol 4 refluxed with iodine in acetic acid furnished ketone 2. Base-catalyzed thermal decomposition of keto alcohol 4 yielded triphenylmethane and benzophenone. The mass and spectroscopic data support the proposed structure of diol 1. The mass spectrum of diol 1 was analyzed by an element-mapping technique.[3] Dehydration of diol 1 to butadiene 3 in the mass spectrometer prevented observation of the parent peak of the diol, but fragments of both diol 1 and butadiene 3 were found to be present in the element map.

Using *p*-phenylbenzophenone instead of benzophenone, the corresponding analog of diol 1, 1-*p*-biphenyl-1,4,4,4-tetraphenyl-1,3-butanediol (6), was formed; its identity was established by comparison of its spectral characteristics with those of diol 1.

Decomposition of THF.—Ring opening[4-6] and decomposition[7-11] of THF with various organometallic reagents have been reported, but significant quantities of products from decomposition reactions have never been isolated. Bates has recently reported THF decomposition by *n*-butyllithium forming ethylene and the enolate ion of acetaldehyde.[11] The reactions were carried out in an nmr sample tube and the products were identified spectroscopically. THF has been found to decompose in the presence of Grignard reagents under some conditions. Nmr spectra of strongly heated Grignard reagents frequently have sharp resonances at τ 4.64, which is indicative of ethylene dis-

(1) (a) This research was supported in part by a Frederick Gardner Cottrell grant; (b) presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968; (c) to whom correspondence should be addressed; (d) National Science Foundation Undergraduate Research Participant.

(2) P. Tomboulian and K. Stehower (Dumke), *J. Org. Chem.*, **33**, 1509 (1968).

(3) Data obtained from high-resolution mass spectrometry were converted by computer to the elemental composition of the ion fragments *via* their accurate masses. Computer selection of empirical formulas was within ±3 mmu. See K. Biemann, P. Bommer, and D. M. Desiderio, *Tetrahedron Lett.*, **26**, 1725 (1964). We are indebted to Dr. Ronald Hites for these spectral determinations.

(4) F. R. Jensen and R. L. Bedard, *J. Org. Chem.*, **24**, 874 (1959).

(5) W. J. Bailey and F. Marktscheffel, *ibid.*, **25**, 1797 (1960).

(6) H. Gilman and E. J. Gaj, *ibid.*, **28**, 1725 (1963).

(7) R. L. Letsinger and D. F. Pollart, *J. Amer. Chem. Soc.*, **78**, 6079 (1956).

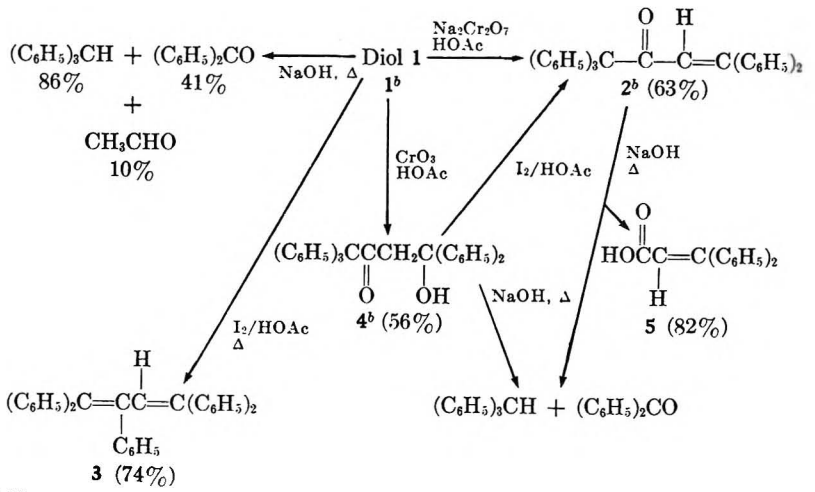
(8) A. Rembaum, S.-P. Siao, and N. Indictor, *J. Polym. Sci.*, **56**, No. 163, S17 (1962).

(9) E. A. Hill, *J. Org. Chem.*, **31**, 20 (1966).

(10) S. C. Honeycutt, *J. Organometal. Chem.*, **29**, 1 (1971).

(11) R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972).

SCHEME II[a]



[a] Reactions of diol 1. [b] New compounds.

solved in a Grignard solution;[9] the enolate ion could not be identified by nmr spectroscopy.

THF decomposition products have been isolated from reactions involving substituted THF's and organometallic reagents. The production of ethylene (95.5%) and acetophenone (56%) has been observed when 2-phenyltetrahydrofuran was treated with phenyllithium and the mixture was hydrolyzed.[7] This reaction clearly is more likely to occur than a decomposition involving an unsubstituted THF. Less than a 5% yield of ethylene was obtained when propylsodium and THF were allowed to react in hexane at 50°.[7] Decomposition of THF in the presence of ethyllithium has been reported[8] but the reaction products were not clearly identified. In the above THF reactions only small quantities of decomposition products, if any, were actually isolated.

In our system a significant quantity of the decomposition products have been obtained. To our knowledge, this is the first reported condensation of the acetaldehyde fragment of THF. This unusual combination of reactants traps the enolate ion of acetaldehyde and incorporates it in a stable adduct, diol 1. The stabilized enolate ion resulting from THF decomposition has no counterpart in the THP solvent system, in which no diol is formed. The other product of THF decomposition, ethylene, was isolated following triphenylmethane addition to the *n*-butyllithium solution while the mixture was permitted to warm to room temperature. Infrared analysis of the gases released at this point indicated the presence of butane and ethylene.

The quantity of diol 1 produced indicates that solvent decomposition can be of major significance in systems containing *n*-butyllithium and THF. The calculated yield of the diol (38% based on triphenylmethane) assumes that the trityl anion plays little or no role in solvent decomposition. The basis for this assumption is that *n*-butyllithium is a stronger base than tritylllithium and appears to be much less stable in THF.[10-14] The details of the solvent decomposition are as yet unclear, although mechanisms have been proposed.[7,8,11] Recent kinetic data suggest that the mechanism is complex; the rate of reaction of *n*-butyllithium was found to be first order in *n*-butyllithium but 2.5 order in THF.[10]

A possible reaction mechanism for the decomposition of THF is the nucleophilic abstraction of an α proton by *n*-butyllithium resulting in the cleavage of the solvent molecule to furnish ethylene and the enolate ion of acetaldehyde. Condensation of benzophenone, the enolate ion, and a trityl ion follows, as is evidenced by the formation of diol 1 (Scheme I). The order of condensation of these species has not been established. The inherent basicity of both the enolate and trityl ions would favor a condensation between benzophenone and the enolate followed by addition of the trityl anion to the new and less basic species.

Diol 1 results (9% yield) when commercial *n*-butyllithium in hydrocarbon solvent is added to a solution of triphenylmethane in THF, indicating that the THF decomposition reaction competes significantly with the metalation reaction. *Thus THF decomposition may be quite common in systems containing organolithium reagents*, and the involvement of THF in these systems probably has been underestimated.

This reaction scheme has been attempted in other solvents. When 2-methyltetrahydrofuran was employed, diol 1 was obtained in low yield (<1%), which can be attributed to the higher stability of this solvent. The half-life for α cleavage at 35° has been found to be 13 times longer for 2-methyltetrahydrofuran than for THF.[11] Attempted cleavage and condensation reactions in THF-d_4 and THF-d_8 failed; adequate yields of tritylllithium were not obtained presumably owing to solvent impurities.

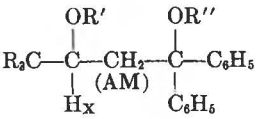
Conformational Studies by Nmr Spectroscopy.—The nonequivalency of the aliphatic protons of diol 1, as revealed by the nmr spectrum, suggested a further study of the conformation of this molecule.[15] 1,1-Diphenyl-4,4,4-trichloro-1,3-butanediol (7) was prepared and its nmr spectra were similar to those of diol 1. The mono- and dimethyl ethers of diol 7 also were synthe-

(12) H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957).
(13) R. Waack and P. West, *J. Amer. Chem. Soc.*, **86**, 4494 (1964).
(14) The deep red color of the trityl anion persists after stirring for 24 r at room temperature.

(15) We are indebted to Dr. Steven Beare for these syntheses and nmr determinations.

TABLE I

NMR DATA FOR DIOLS AND THE MONO- AND DIMETHYL ETHER OF DIOL 7

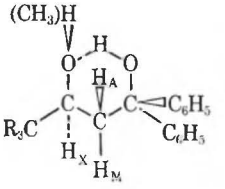


Solvent	R	R′	R″	Registry no.	J_{AX}, Hz	J_{MX}, Hz	J_{AM}, Hz	δ_{AM}, ppm	δ, ppm[a] H_A	H_M	H_X	OR′	OR″
Benzene	C_6H_5	H	H	36976-71-3	10.0		14.7		1.32	2.22	4.83	1.98[b]	3.67
$CDCl_3$[c]	C_6H_5	H	H		10.0	0.5	14.7	0.84	1.83	2.67	5.25		
CS_2[d]	C_6H_5[e]	H	H		10.0		14.7		1.7	2.7	5.3	2.3[f]	4.6
Acetone-d_6	Cl	H	H	36976-72-4	9.7	1.9	14.4	0.72	2.58	3.31	4.25	2.98	2.98
DMSO	Cl	H	H		8.1	≤1					1.55	4.33[g]	3.44
$CDCl_3$	Cl	H	H		10.1	1.8	14.7	0.57	2.69	3.26	4.22	3.90[h]	4.05
CCl_4	Cl	CH_3	H	36976-73-5	8.5	2.2	14.5	0.49	2.53	3.08	3.80	3.22	3.64
DMSO	Cl	CH_3	H		4.0[i]	4.0[i]					1.36	0.80	3.50
CCl_4	Cl	CH_3	CH_3	36976-74-6	5.1	3.4		0.007	2.90	2.90	3.58	3.17	3.41

[a] All spectra were obtained at 100 MHz and 27° unless otherwise stated, relative to TMS except for DMSO, where DMSO is used as an internal standard. [b] J_{CHXOH} = 4.5 Hz. [c] D_2O was added to the nmr tube. [d] Spectra obtained at 60 MHz. [e] Diol 6. [f] J_{CHXOH} = 5.0 Hz. [g] J_{CHXOH} = 5.2 Hz. [h] J_{CHXOH} = 3.0 Hz. [i] Measured from 1000-Hz sweep width.

sized in order to determine the extent of intramolecular hydrogen bonding[16] in this molecule.

The nmr spectral data indicate (Table I) that the conformation of these diols is indeed dependent on intramolecular hydrogen bonding, and the following model is suggested. This cyclic conformation would



place all of the aliphatic protons in dissimilar magnetic environments, and is also consistent with the observed coupling constants J_{AX}, J_{MX}, and J_{AM}.[17]

Evidence for intramolecular hydrogen bonding was obtained from the nmr spectra of diol 7 and its mono- and dimethyl ethers. The AMX pattern remained essentially unchanged in diol 7 and its monomethyl ether, indicating that significant intramolecular association exists in these compounds. The association is lost in the dimethyl ether, as evidenced by the chemical shift and coupling constant differences between the mono- and dimethyl ethers in the same solvent.[18] The intramolecular hydrogen bonding in the monomethyl ether, and presumably in diols 1 and 7, occurs through the tertiary hydroxyl hydrogen and the secondary hydroxyl oxygen.[19]

(16) Studies of intramolecular hydrogen bonding in 2,4-pentanediols have been reported previously. See (a) P. E. McMahon and W. C. Tincher, *J. Mol. Spectrosc.*, **15**, 180 (1965); (b) S. Fujiwara, Y. Fujiwara, K. Fujii, and T. Kukuroi, *ibid.*, **19**, 294 (1966).

(17) In substituted ethanes dihedral angles between vicinal protons of 180 and 70° correspond to coupling constants of 9 and 0.5 Hz, respectively. Geminal coupling constants of 14–15 Hz result if the H–C–H bond angle is 109°. See J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, pp 116–117.

(18) The most obvious differences were the J_{AX}–J_{MX} values of 6.3 and 1.7 Hz, respectively, and the chemical shift differences (δ_{AM}) of 0.49 and 0.00 ppm, respectively. Both of these observations are consonant with a favored conformation in the monomethyl ether.

(19) There is a substantial upfield shift of H_X (0.42 ppm) of the monomethyl ether relative to diol 7 which does not appear to be a solvent effect. When DMSO is used the nmr spectrum of the monomethyl ether exhibits a singlet hydroxyl proton, indicating the presence of a tertiary hydroxyl group. See O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964). Significantly, diol 7 gives rise to two different hydroxyl protons in DMSO, one showing doublet coupling to the carbinyl proton and the other showing no coupling.

Thus it appears that diols 1 and 7 and the monomethyl ether have similar conformations in nonpolar solvents. The same conformation is preserved for diol 7 in acetone-d_6 and DMSO; however, the monomethyl ether exhibits a loss of this conformation in DMSO. In the dimethyl ether there is no association, and the small difference in J_{AX} and J_{MX} is only a reflection of electronic interactions.

Experimental Section

General.—Melting points are corrected. Microanalyses were performed by Clark Microanalytical Laboratory, Urbana, Ill.; Galbraith Laboratories, Inc., Knoxville, Tenn.; and Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were measured with Beckman IR-5 and IR-12 spectrophotometers. Nmr spectra were recorded on Varian T-60, HA-100, and A-56/60 and Perkin-Elmer R-12 spectrometers. TMS was used as an internal standard except where noted otherwise.

Materials.—THF and 2-methyltetrahydrofuran were distilled from $LiAlH_4$ in an argon atmosphere. Argon was employed for all trityllithium reactions, and was purified by bubbling through a benzophenone–lithium ketyl mixture in THF.

1,1,4,4,4-Pentaphenyl-1,3-butanediol (1).—In a typical experiment trityllithium[2] was prepared by slowly adding 1.0 g (4.2 mmol) of triphenylmethane dissolved in 10 ml of THF to a 180% excess of freshly prepared *n*-butyllithium in THF and allowing the mixture to stir at room temperature for 3 hr. To the deep red mixture, 2.0 g (11 mmol) of benzophenone in 10 ml of THF was added. After 18 hr of stirring, the purple solution was treated with cold 9 *M* hydrochloric acid. Concentration of the organic layer furnished a solid, which when recrystallized yielded 0.76 g (38% based on triphenylmethane) of diol 1: mp 192–194°; ir (CS_2) 3467 (broad OH), 3079, 3050, 3022, 2964, 2929, 1069, 858, 770, 760, 743, and 591 cm^{-1}; nmr ($CDCl_3/D_2O$) δ 5.25 (m, 1, J = 10.0, 0.5 Hz, H_X), 2.67 (m, 1, J = 14.7, 0.5 Hz, H_M), 1.83 (m, 1, J = 14.7, 10.0 Hz, H_A); mass spectrum *m/e* (rel intensity) 434 (6), 357 (1), 356 (1), 279 (2), 267 (5), 244 (7), 243 (8), 183 (5), 180 (5); decomposition in spectrometer.

Anal. Calcd for $C_{34}H_{30}O_2$: C, 86.78; H, 6.43. Found: C, 87.17, 87.10; H, 6.19, 6.44.

Diol 1 from Preparation of Trityllithium Using Commercial *n*-Butyllithium.—Triphenylmethane (3.5 g, 14 mmol) was dissolved in 20 ml of THF. To this mixture 10 ml (16 mmol) of commercial *n*-butyllithium in hexane (Foote Mineral Co.) was added, causing the solution to warm and turn deep red. After the solution was stirred for 15 min, 2.6 g (14 mmol) of benzophenone was added over a period of 35 min. The mixture was stirred for 35 min and yielded 0.42 g (9% based on benzophenone) of white crystals, mp 195–196°. Infrared spectroscopic data indicate that this material is diol 1.

1-*p*-Biphenyl-1,4,4,4-tetraphenyl-1,3-butanediol (6).—A THF solution of 1.3 g (5.1 mmol) of *p*-phenylbenzophenone was added

to trityllithium (10.2 mmol) in 10 ml of THF and the mixture was allowed to stir overnight. Acidification, extraction of the organic layer followed by chromatographic separation on alumina, and subsequent recrystallization furnished a low yield (10.9 mg) of the analytical sample: mp 201–205°; ir (CS_2) 3481 (broad OH), 3095, 3068, 3040, 2978, 2936, 1070, 859, 769, 760, and 743 cm^{-1}; nmr (CS_2) δ 5.3 (m, 1, J = 10.0, 5.0 Hz, H_X), 2.7 (s, 1, J = 14.7 Hz, H_M), 1.7 (m, 1, J = 14.7, 10.0 Hz, H_A).

Anal. Calcd for $C_{40}H_{34}O_2$: C, 87.88; H, 6.27. Found: C, 88.48; H, 6.56.

Diol 1 from Decomposition of 2-Methyltetrahydrofuran.—Trityllithium was prepared from 3.5 g of triphenylmethane in freshly distilled 2-methyltetrahydrofuran and a stock solution of *n*-butyllithium (Foote Mineral Co.) at ice temperatures. A solution of 2.3 g of benzophenone in 10 ml of 2-methyltetrahydrofuran was slowly added after the reaction vessel had warmed to room temperature. The dark blue-green solution was stirred for 9 hr and was then hydrolyzed with 3 *M* hydrochloric acid. Extraction of the organic layer followed by crystallization furnished a solid sample; mixture melting point and infrared data indicated that this material was diol 1, 0.04 g (0.6%), mp 196–198°.

1,1-Diphenyl-4,4,4-trichloro-1,3-butanediol (7).—A mixture of 5.5 g (27 mmol) of racemic 4,4,4-trichloro-3-hydroxybutyric acid (mp 118–118.5°), 50 ml of methanol, and 0.5 ml of boron trifluoride etherate was refluxed for several hours. The solvent was distilled to furnish 5.7 g (97%) of off-white, glistening crystals. Recrystallization produced the colorless ester: mp 63–63.5° (lit.[20] mp 62–63°); the nmr spectrum showed the presence of CH_3, OH, CH_2, and CH absorptions with an AMX pattern for the methylene and carbinyl protons. A solution of 2.2 g (10 mmol) of the above ester in 10 ml of diethyl ether was added to phenylmagnesium bromide (41 mmol). The mixture was refluxed on a steam bath for 30 min. The organic layer yielded 1.2 g (35%) of diol 7, mp 174–175° (lit.[21] mp 178.5°).

Anal. Calcd for $C_{16}H_{15}Cl_3O_2$: C, 55.60; H, 4.37. Found: C, 55.41; H, 4.26.

The mono- and dimethyl ethers were prepared by refluxing diol 7 with a mixture of calcium sulfate, methyl iodide, and silver oxide in DMF for 2 days. The nmr spectrum indicated an equal mixture of the monomethyl and dimethyl ethers which was cleanly separated on a silica gel column with chloroform.

Stability of Diol 1 to Heat and Base.—Diol 1 was refluxed in 5 ml of benzene and 90 ml of 5% sodium ethoxide solution in ethanol for 22 hr. Column chromatography yielded 360 mg of triphenylmethane (86%) and 270 mg of benzophenone (41%).

Thermal decomposition was afforded by injecting 1.2 mg of diol 1 into a vapor phase chromatographic column (SE-30) maintained at 300°. Analysis of the chromatogram showed that triphenylmethane, benzophenone, and acetaldehyde account for 40, 32, and 10% of the recorded decomposition products, respectively. The presence of acetaldehyde was confirmed by heating 56 mg of diol 1 at 300° for 25 min in an argon atmosphere and treating the decomposition mixture with 2,4-dinitrophenylhydrazine. The orange derivative was recrystallized from ethanol, furnishing 3.4 mg (13%) of the analytical sample, mp 147–148°.

1,1,2,4,4-Pentaphenyl-1,3-butadiene (3) resulted after refluxing 0.35 g of diol 1 with 0.14 g of iodine for 1 hr in 19 ml of acetic acid. The organic layer yielded yellow prisms, 0.15 g (74%). (Lower yields of hydrocarbon 3 were obtained by dehydrating diol 1 with thionyl chloride or formic acid.) The hydrocarbon was identified by infrared, ultraviolet, and combustion data, which were consistent with literature values:[22] mp 169–170°; uv max (95% EtOH) 341 nm (ϵ 11,430), 244 (17,000).

Anal. Calcd for $C_{34}H_{26}$: C, 93.97; H, 6.03. Found: C, 93.78, 93.82; H 6.25, 6.13.

1,1,1,4,4-Pentaphenyl-4-hydroxy-2-butanone (4).—Diol 1 (172 mg) dissolved in methylene chloride was refluxed with 3 ml of chromium trioxide solution (1 g CrO_3 + 1 ml HOAc + 3 ml H_2O) for 2 hr. Crystallization of the organic layer provided 97 mg (56%) of white prisms: mp 144–145°; ir (CS_2) 3520 (broad OH), 1707 (C=O), 1070, 768, and 594 cm^{-1}; nmr ($CDCl_3$) δ 7.2, 7.1 (m, 25 H, aromatic), 5.3 (s, 1, OH), 3.5 (s, 2, CH_2).

Anal. Calcd for $C_{34}H_{28}O_2$: C, 87.15; H, 6.02. Found: C, 87.32; H, 6.14.

Stability of Keto Alcohol 4 to Heat and Base.—Keto alcohol 4 (11 mg) and 13 mg of sodium hydroxide were placed in a sealed tube in an argon atmosphere and heated to 157° for 1 hr. A carbon disulfide extract exhibited infrared absorption characteristic of a triphenylmethane and benzophenone mixture.

1,1,1,4,4-Pentaphenylbut-3-en-2-one (2).—Diol 1 (109 mg) was dissolved in 5 ml of acetic acid and a solution of 426 mg of sodium dichromate in 6 ml of acetic acid was added. The mixture was refluxed for 2.5 hr. Crystallization of the organic layer yielded a fine yellow powder (63% yield): mp 182–183.5°; ir (CS_2) 1705 (C=O), 1090, 675 cm^{-1}; uv max (95% EtOH) 308 nm (ϵ 8920), 272 (5960).

Anal. Calcd for $C_{34}H_{26}O$: C, 90.63; H, 5.82. Found: C, 91.00; H, 5.85.

Stability of Ketone 2 to Heat and Base.—Ketone 2 (31 mg) decomposed when heated at 200° for 1 hr with 38 mg of sodium hydroxide. The infrared spectrum indicated that the extracted organic layer contained triphenylmethane and benzophenone. Acidification of the basic solution produced 14 mg (82%) of 3,3-diphenylacrylic acid (5), mp 154–158°, compared to known sample.

Dehydration of Keto Alcohol 4.—Keto alcohol 4 (31 mg) was refluxed with 15 mg of iodine in 4 ml of acetic acid for 1 hr. Crystallization of the organic layer furnished 22 mg (75%) of ketone 2, mp 182–183°.

Detection of Ethylene and Butane.—After the addition of triphenylmethane in a typical trityllithium reaction, the gases were collected and qualitative infrared analysis indicated a mixture of butane and ethylene.

Registry No.—2, 36976-75-7; 3, 2639-26-1; 4, 36994-56-6; 6, 36976-77-9; tetrahydrofuran, 109-99-9; benzophenone, 119-61-9; trityllithium, 733-90-4.

(20) F. Arndt, L. Loewe, and L. Capuano, *Rev. Fac. Sci. Univ. Istanbul*, **8A**, 122 (1943).

(21) J. S. W. Boyle, A. McKenzie, and W. Mitchell, *Ber.*, **70B**, 2153 (1937).

(22) R. E. Lutz, R. G. Bass, and D. W. Boykin, Jr., *J. Org. Chem.*, **29**, 3660 (1964).

The Generation of Allyllithium Reagents by Lithium–Tetrahydrofuran Reduction of Allylic Mesitoates. A New Procedure for Selective Allylic Cross Coupling and Allylcarbinol Synthesis

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A variety of allylic mesitoates undergo alkyl–oxygen fission upon reduction by lithium metal in tetrahydrofuran at 0°. The allylic organolithium thus generated is sufficiently stable to undergo reactions with electrophilic species present *in situ*. *In situ* reaction with allylic bromides produces fair to excellent yields of 1,5-dienes in a cross-coupling reaction that is considerably more selective than Wurtz-type procedures, in regard to crossed nature and retention of double bond position and geometry. *In situ* reaction with aldehydes and ketones gives moderate to good yields of allylic carbinols, and has been used to synthesize a component of the *Ips confusus* pheromone. Both reactions are convenient and possess certain advantages over other currently available methods.

The allylic unit is a common structural feature of many compounds of natural origin and theoretical interest. One of the simplest synthons for such units is the allylic organometallic; however, the synthetic utility of allylic organometallics is seriously hampered by problems associated with their generation and ambiguities inherent in their pattern of reactivity. Coupling is often a major side reaction in the preparation of these reagents,[1] and reaction with electrophiles generally gives products consisting of mixtures of allylically transposed and geometrically isomerized materials.[2]

As part of a study of new approaches to the stereoselective synthesis of olefinic systems, we considered the possibility of generating an allylic organometallic reagent *in situ* in the presence of an electrophilic counterpart. Such an approach would minimize the lifetime of the allylic anion and might thus avoid some of the operational problems mentioned above. In particular, we sought to reduce the extent of cis–trans isomerization in some of the more highly substituted allylic anions and to avoid production of undesired self-coupling products.

The following three criteria must be met by the components of the *in situ* reaction scheme proposed above: (1) the precursor of the allylic organometallic must be inert toward attack by the allylic anion being generated (at least relative to the electrophile, with which reaction is desired); (2) the electrophile must survive, unaltered, the conditions necessary to generate the allylic anion from its precursor; and (3) the solvent must be compatible (at least for a short time period) with the allylic organometallic.

We have recently reported that a variety of allylic organometallic reagents can be generated, albeit transiently, by the action of lithium metal in tetrahydrofuran on allylic mesitoate esters,[3,4] and we have shown that this process can function in an *in situ* manner with allylic halides as the electrophilic species to produce 1,5-dienes (Scheme I).[3] This report provides a detailed description of the allyllithium generating system, and presents further results on the *in situ* 1,5-diene synthesis. In addition, it describes the extension of the lithium–allyl mesitoate method to the synthesis of allylic carbinols in a second *in situ* process, utilizing aldehydes and ketones as electrophiles (Scheme IV).

Results and Discussion

A. The Allylic Organolithium Generating System.—Allyllithium species are presumed to be the intermediates in a number of reductive alkyl–oxygen fission reactions of allylic and benzylic alcohol derivatives.[5,6] Most notable of these, the Henbest reduction of allylic benzoates with lithium in ethylamine,[7] has been of considerable synthetic utility as a deoxygenation procedure. There have been no reports, however, of the interception of the allylic anion by an electrophilic species; indeed, it is doubtful that the carbanion even has an appreciable lifetime before it undergoes protonation by the amine solvent. Nevertheless, it did seem likely that, with appropriate modification, the Henbest procedure might provide a method of generating allylic organometallics that would be suitable for use in a reaction with electrophiles present *in situ*.

Our selection of the mesitoate ester–lithium in tetrahydrofuran combination resulted from the following considerations. It is clear that the solvent must be aprotic for the organometallic to survive even briefly (criterion 3). As Eisch[8] and others[9] have reported the generation of allyllithium by reduction of allyl phenyl ether with lithium in tetrahydrofuran, these seemed to be resonable choices for reducing agent and solvent. The mesitoate ester was selected in preference to the benzoate for reasons related to the demands of criterion 1. The well-known reluctance of mesitoate esters to undergo nucleophilic addition at the acyl center[10] should make them considerably more inert than the benzoates toward attack by the allyllithium species

(1) H. Gilman and J. H. McGlumphy, *Bull. Soc. Chim. Fr.*, **43**, 1323 (1928).

(2) R. A. Benkeser, *Synthesis*, 347 (1971).

(3) J. A. Katzenellenbogen and R. S. Lenox, *Tetrahedron Lett.*, 1471 (1972).

(4) For a related study involving reductive cleavage of cyclopropylcarbinyl mesitoates, see J. A. Katzenellenbogen and T. Utawanit, *ibid.*, 1475 (1972).

(5) M. Smith in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, Chapter 2.

(6) Evidence for the intermediacy of the allylic anion comes from the fact that double bond isomerization often accompanies these reductions. Furthermore, the rate-retarding effect observed with increased alkyl substitution on the carbinol carbon is more consistent with anionic species than with radicals. See A. J. Birch, *J. Chem. Soc.*, 809 (1945); A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950).

(7) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(8) J. J. Eisch and A. M. Jacobs, *J. Org. Chem.*, **28**, 2145 (1963).

(9) P. Miginiac and C. Bouchoule, *Bull. Soc. Chim. Fr.*, 4156 (1968).

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 325.

being generated. The compatability of various electrophiles with lithium in tetrahydrofuran was the only aspect of the *in situ* process (criterion 2) that lacked adequate precedent.

Mesitoate esters of allylic alcohols can be prepared conveniently and in high yield by a slight modification of the procedure of Higgins,[11] utilizing mesitoyl chloride in pyridine–chloroform. They are easily purified and show no tendency to undergo cis–trans isomerization or allylic transposition either during their preparation or after prolonged storage at room temperature.

To investigate the efficiency of the allylic organolithium generating process and the stability of the mesitoate precursor toward the organometallic being generated, allyl mesitoate alone was treated with lithium in tetrahydrofuran. Within minutes at 0° the reaction turned deep red; the production of allyllithium was monitored periodically by gas evolution; and the titer as a function of time is illustrated in Figure 1.

Although the allyl mesitoate is completely consumed within 1.5 hr under these conditions, at no time does the allyllithium titer exceed 12% of the theoretical yield. Further investigation (*vide infra*) has established that, in the absence of added electrophiles, the allyllithium is consumed primarily by reaction with its precursor, allyl mesitoate.

This experiment indicates the extent to which the lithium–allyl mesitoate generating system satisfies criterion 1. However, as will be shown subsequently, when electrophiles are present (in the *in situ* reactions), they can compete quite efficiently for reaction with the allyllithium species, so that its reaction with starting material can become insignificant.

B. Allylic Coupling.—Despite its semblance of simplicity, the synthesis of 1,5-dienes by the direct coupling of allylic species is an approach that suffers from severe experimental limitations. Both the Grignard and Wurtz-type couplings result in complex mixtures of symmetrical and unsymmetrical products which show loss of double-bond geometry and position in at least one of the allylic units.[12]

Two more recent methods, one employing the coupling of π-allylnickel(I) halide complexes with allylic bromides[13] and the other a titanium-promoted deoxygenative coupling of allyl alcohols,[14] also suffer from a lack of efficient cross coupling, showing almost statistical mixtures of coupled products when two different allylic units are used. Two other methods, based on sulfur-[15] and phosphorus-stabilized[16] allylic anions, appear to give efficient cross coupling, but require a subsequent step to remove the stabilizing substituent. Allyl and methallyl Grignard have been efficiently cross coupled with allylic chlorides, but the stereochemical fate of the Grignard-derived portion of the molecule cannot be determined in these systems.[17]

(11) G. M. C. Higgins, B. Saville, and M. B. Evans, *J. Chem. Soc.*, 702 (1965).
(12) D. Barnard and L. Batemann, *ibid.*, 932 (1950).
(13) E. J. Corey, M. F. Semmelhack, and L. S. Hegedus, *J. Amer. Chem. Soc.*, **90**, 2416 (1968).
(14) E. E. van Tamelen, B. Akermark, and K. B. Sharpless, *ibid.*, **91**, 1552 (1969), and references cited therein.
(15) J. F. Bielmann and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969).
(16) E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **92**, 2139 (1970).
(17) (a) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969). (b) P. A. Grieco, *J. Amer. Chem. Soc.*, **91**, 5660 (1969).

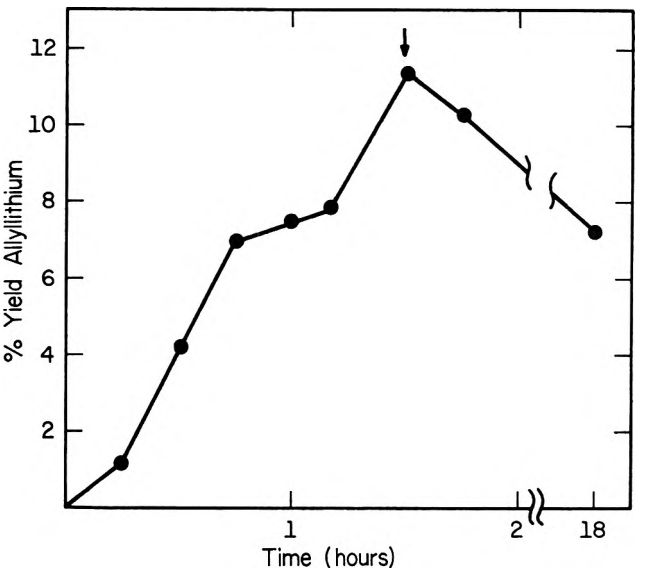
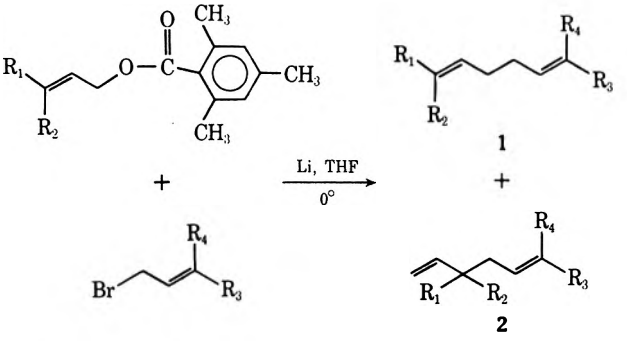


Figure 1.—Titer of allyllithium generated by reaction of allyl mesitoate with lithium in tetrahydrofuran. Arrow indicates the time at which allyl mesitoate consumption was complete.

1. Synthesis of 1,5-Dienes. Lithium Reduction of Allylic Mesitoates with Allylic Bromides *in Situ*.—As we have recently reported,[3] 1,5-dienes can be synthesized in a selective cross-coupling reaction by generating an allylic organolithium reagent according to the mesitoate–lithium procedure with an equimolar amount of allylic bromide present *in situ* as the electrophile (Scheme I). The reaction mixture in this case remains clear and colorless for *ca.* 0.5–1 hr at 0°, turning to a characteristic deep red within a matter of seconds as soon as the bromide has been consumed. Maximum yields are obtained if the reaction is quenched at this point. The results of our study of this reaction are summarized in Table I.

SCHEME I



1,2	R_1	R_2
a	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
b	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
c	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
d	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
e	CH_3	CH_3
f	CH_3	H
g	H	H

1,2	R_3	R_4
a	H	H
b	CH_2	CH_3
c	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
d	$(CH_3)_2C{=}CH(CH_2)_2(CH_3)C{=}CH(CH_2)_2$	CH_3
e	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
f	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3
g	$(CH_3)_2C{=}CH(CH_2)_2$	CH_3

TABLE I

PRODUCTS AND YIELDS OF CROSS COUPLING REACTIONS

	Mesitoate	Bromide	% yield[a] dienes	Isomer ratio	% Mesitoic acid recovered
1	Geranyl	Allyl	60 (35)	1a (80):2a (20)	66
2	Geranyl	3-Methyl-2-butenyl	(49)	1b (72):2b (18)	73
3	Geranyl	Geranyl	95 (93)	1c (60):2c (40)	61
4	Geranyl	Farnesyl	43	1d (77):2d (23)	
5	3-Methyl-2-butenyl	Geranyl	32	1e (65):2e (35)	43
6	*trans*-2-Butenyl	Geranyl	19	1f (55):2f (45)	11
7	Allyl	Geranyl	22	1g (100)	37

[a] Yields determined by glpc using internal standards. Yields given in parentheses are isolated yields.

The overall yield of coupling product by this process is quite variable, but appears to be highest when the allylic fragment derived from the mesitoate is more highly substituted (1–4 *vs.* 6 and 7). From the high yield in certain select cases (3) it is clear that all three criteria, as outlined in the first section, can be adequately met. However, it was of interest to determine whether the electrophilic component would be stable under the reaction conditions.

In separate experiments, geranyl, farnesyl, 3-methyl-2-butenyl, and allyl bromides were treated with lithium under conditions identical with those of the coupling reaction. The lower molecular weight bromides were found to undergo a rather rapid Wurtz coupling, thus giving high yields of self-coupled products in the time periods used for coupling by the mesitoate lithium procedure. Geranyl and farnesyl bromides showed some coupling, but the rate of this self-coupling process was much slower than the cross-coupling reaction.

The implication of these experiments is that certain allylic bromides, namely those of lower molecular weight, may be relatively unstable under the reaction conditions. In these cases reduced yields of cross-coupled products in the mesitoate–lithium procedure may be attributed in part to consumption of the electrophile, while reduced yields using higher molecular weight bromides may result from nonproductive consumption of both the electrophile and the allyllithium precursor (*vide infra*).

The products of the coupling reaction are mixtures of direct and transposed types with allylic transposition being limited to the allylic portion derived from the mesitoate. This can be seen by comparing the two allyl–geranyl couplings (1 and 7). The reaction of allyl mesitoate with geranyl bromide (entry 7) gives only one diene product, as allylic transposition in the nucleophile leads to the same product as direct coupling without rearrangement; however, the reaction of geranyl mesitoate with allyl bromide (1) gives two diene products, the minor one arising from allylic transposition of the geranyllithium species. These results are consistent with the known ambident behavior of allylic anions in coupling reactions.[2] No evidence of products arising from S$_N$2′ attack on the bromide has ever been found in the mesitoate–lithium coupling reaction, although this side reaction has been observed on many occasions in allylic coupling reactions.[11,17a,18]

The fact that only the mesitoate-derived portion of the 1,5-diene is subject to transposition in the unsymmetrical couplings (3–8) substantiates the fact that the nucleophilic fragment is derived from the mesitoate, and not the bromide. However, there are several reports in which allyl mesitoates and other hindered allyl esters have served as electrophiles in coupling reactions with alkyl and benzyl Grignard reagents.[11,19] Although reactions were run in the absence of free metal, using refluxing ethyl ether as a solvent (conditions under which our coupling reaction fails to work), we felt that it was important to establish unequivocally that the mesitoate is acting only as a source of nucleophile, and that no 1,5-diene is produced from the reaction of allyl bromide derived allyllithium with the mesitoate. Geranyllithium, generated from its phenyl ether,[8] was allowed to react with allyl mesitoate; no cross-coupling products could be detected. The small amount of geranyl dimer observed was produced during the geranyllithium preparation[9] and was present prior to the attempted couplings. In a separate experiment it was shown that no coupling product (digeranyl) was formed when geranyl mesitoate alone was treated with lithium in tetrahydrofuran.

A factor of prime importance in assessing the efficiency of an allylic coupling reaction is the degree of cross coupling that can be achieved. The advantage of the *in situ* mesitoate procedure over a Wurtz-type procedure in this regard is evident from the data presented in Table II. A geranyl–farnesyl coupling was performed by reaction of the respective bromides with magnesium in ether at reflux and by the *in situ* method using geranyl mesitoate and farnesyl bromide. The proportion of product that is cross coupled is twofold greater in the mesitoate procedure than in the magnesium one; the overall yield of the former process is greater as well.

TABLE II

COUPLING OF GERANYL AND FARNESYL UNITS

Reactants	Yield of C_{25} products, %[a]	Relative ratios, %[b] Ger–Ger[c] C_{20}	Ger–Far C_{25}	Far–Far C_{30}
trans-Geranyl bromide, *trans,trans*-farnesyl bromide, magnesium	32	13	30	57
trans-Geranyl mesitoate, *trans,trans*-farnesyl, bromide, lithium	43	14	62	24

[a] Determined by glpc using internal standards. [b] Glpc area ratio corrected for molecular weight differences. [c] Ger = geranyl; Far = farnesyl.

Since we have shown that Wurtz-type coupling of mesitoates alone does not take place under the conditions of the 1,5-diene synthesis, the C_{20} product (geranyl dimers, Ger–Ger) must result from a metal–halogen

(18) It has been reported (ref 11) that selective hydroboration using disiamylborane can reduce the fraction of transposed (vinyl-containing) product in a coupling mixture to less than 2%.

(19) R. T. Arnold and R. W. Liggett, *J. Amer. Chem. Soc.*, **64**, 2875 (1942); R. T. Arnold and R. W. Liggett, *ibid.*, **67**, 337 (1945); E. J. Corey, S. W. Chow, and R. A. Scherrer, *ibid.*, **79**, 5773 (1957).

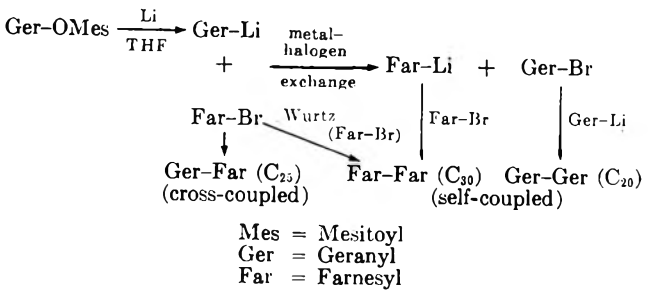
TABLE III
PRODUCT DISTRIBUTIONS FROM GERANYL–NERYL COUPLINGS

	Mesitoate	Bromide	Relative yield, %[a] 1c	2c	3	4	5	Total[b] yield, %	Yield of mesitoic acid, %
1	Geranyl	Geranyl	*77*[c]	*23*	0	Trace[d]	Trace	95	31
2	Neryl	Neryl	trace	9	*59*	13	*19*	95	10
3	Geranyl	Neryl	11	15	10	*54*	*10*	95	13
4	Neryl	Geranyl	16	*16*	13	*45*	10	95	6

[a] Determined by glpc; area ratios. [b] Determined by glpc using internal standards. [c] Expected coupling products are italicized. [d] Trace is <2%.

exchange reaction followed by a self-coupling (Scheme II). An equal amount of C_{30} product (farnesyl dimer,

SCHEME II

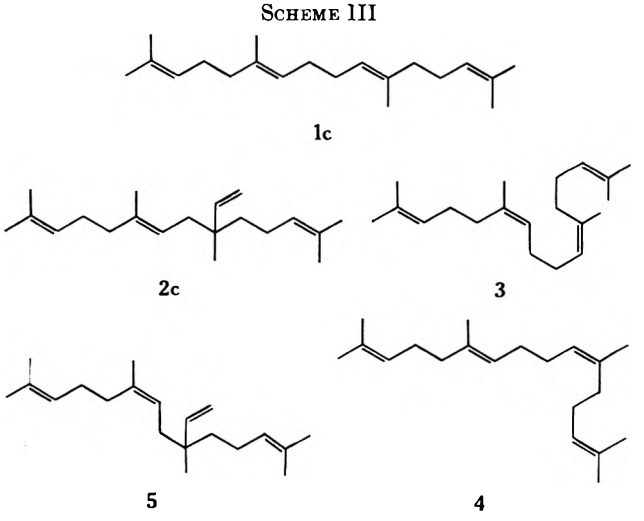


Far–Far) could also arise as a result of this exchange. A portion of the C_{30} product may also arise from a direct self-coupling (Wurtz) of the farnesyl bromide.

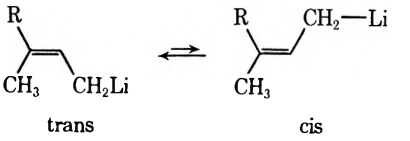
Further examination of the glpc traces of the products produced in the experiments described in Table II revealed two additional advantages of the mesitoate coupling procedure over the Wurtz-type method. The C_{25} product from the mesitoate procedure has suffered noticeably less allylic transposition (20%) than that from the Grignard procedure (30%), and the per cent cis double bond found in the nontransposed C_{25} product was also less in the mesitoate procedure (5%) than in the Grignard procedure (10%).

As one of the motivations for devising an *in situ* allylic cross-coupling procedure was our desire to reduce the extent of cis–trans isomerization that occurs in the allylic anion, this question was pursued in greater detail. Table III contains data describing the distribution of products (Scheme III) from four cross-

SCHEME III



coupling reactions utilizing all possible combinations of neryl and geranyl units. The overall yields of these couplings are high, consistent with the structure–yield correlations discussed in relation to Table I. It is evident, however, that cis–trans isomerization is taking place in some cases (entries 2–4). The geometric purity of the products from the geranyl–geranyl coupling (entry 1), however, indicates that at least in this instance geometric isomerization (trans to cis) can be kept to a minimum. The presence of geometrically isomerized products (2c and 4) in the neryl–neryl coupling (entry 2) establishes that some cis to trans isomerization is occurring; the difference between these two coupling experiments may represent the greater stability of the trans isomer of the allyllithium species of



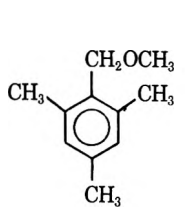
this particular substitution pattern. The other two entries in Table III represent cross coupling between neryl and geranyl units. Here a considerable proportion of the products appear to be geometrically isomerized. However, many of the isomers could only be produced subsequent to a metal–halogen exchange (*e.g.*, entry 4, product **3**: neryllithium + geranyl bromide → neryl bromide + geranyllithium; then neryl bromide + neryllithium → **3**) or by Wurtz coupling of the electrophile. It is difficult to factor out the per cent cis–trans isomerization that has taken place in these cases.

We have been unsuccessful in extending this coupling reaction to nonallylic systems. No coupling is observed when a primary alkyl group is substituted for allyl in either the mesitoate or the bromide. Furthermore, no coupling is detectable if an allylic benzoate is used in place of the corresponding mesitoate. Inclusion of biphenyl or dimethyl sulfoxide in the tetrahydrofuran solvent did not affect the yield or stereoselectivity of the coupling; with hexamethylphosphoramide as cosolvent, yields were decreased.

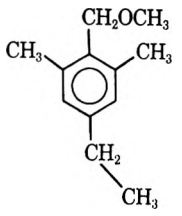
2. Side Reactions Accompanying the 1,5-Diene Synthesis.—Mesitoic acid can be recovered from these coupling reactions by sodium hydroxide extraction of the reaction mixture. The per cent recovery from a number of reactions are found in Tables I and III. It is evident that the yield of recovered acid varies widely, indicating that the mesitoate portion is being consumed through some secondary process. Indeed, treatment of mesitoic acid alone with lithium in tetrahydrofuran resulted in the generation of the deep red-brown color observed in the coupling reactions them-

selves. A methyl iodide quench of this reaction mixture allowed the isolation of a number of reduction products, two of which were tentatively identified by spectroscopic means as the benzyl methyl ethers **6** and **7**;[20] the structure of **6** was confirmed by an independent synthesis.

To investigate further the extent to which the mesitoate group is reduced, allyl mesitoate was similarly reduced and methylated. Glpc–mass spectroscopic analysis of the products obtained after quenching the dark red solution with methyl iodide showed at least 13 products ranging in molecular weight from 134 to 246. One of these products was shown by its mass spectrum to be 2,4,6-trimethylethylbenzene (**8**); no structures have been assigned to the remaining compounds.



6



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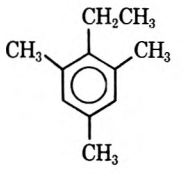

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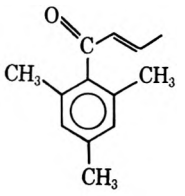


9

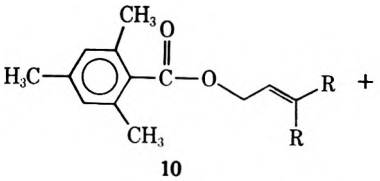
The unsaturated ketone **9** has been found as a by-product in a number of the coupling reactions utilizing allyl mesitoate. It results from allyllithium attack on allyl mesitoate, the double bond shifting into conjugation during the normal aqueous acid work-up. Indeed, **9** can be synthesized in 65% yield by the reaction of allyl mesitoate with allyllithium prepared from allyl phenyl ether.[8] Production of **9**, and presumably analogous ketones in other coupling reactions, reduces the yield of the desired product by consuming both the allyllithium and the allyllithium precursor.

C. Carbonyl Additions.—The synthesis of allylic carbinols from carbonyl compounds and allylic nucleophiles has been carried out in many different ways. The addition of a preformed allylic Grignard reagent to a carbonyl compound is often not a desirable method for two reasons. It requires the synthesis of the necessary allylic halide, and subsequently, generation of the allylic Grignard reagent, a step which can lead to extensive allylic coupling.[1] A recent communication has described the synthesis of carbinols by the reaction of a carbonyl compound and an organohalide together with lithium in tetrahydrofuran.[21] This *in situ*, Reformatsky-type procedure has been reported several times for the specific cases of allylic and propargylic halides using magnesium,[22] zinc,[23] or aluminum[24] as the reducing agent. The use of magnesium in this manner has been termed the Barbier–Grignard reaction, and, although known for many years, the reaction fell into disuse until 1963.[22]

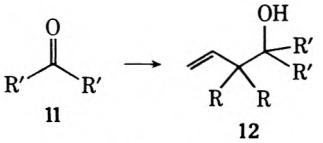
We have found that the *in situ* generation of allyl organolithium reagents can also be used to produce allylic carbinols, using aldehydes and ketones as electrophiles *in situ*. Although this method gives somewhat lower yields when compared to the zinc and magnesium methods mentioned above, it avoids the necessity of synthesizing an allylic halide. Also, side reactions such as α-alkylation of the carbonyl compound are minimized. Such side reactions often accompany the synthesis of carbinols by the Barbier–Grignard reaction and make the separation and purification of the carbinol extremely difficult in many instances. In cases where the carbonyl compound prossesses no α hydrogens, the use of allylic mesitoates appears to be the method of choice for carbinol formation.

1. Synthesis of Allyl Carbinols. Lithium Reduction of Allylic Mesitoates with Aldehydes and Ketones *in Situ*.—Treatment of an allylic mesitoate (**10**) and an aldehyde or ketone (**11**) in equimolar amounts with lithium under the same conditions used to produce 1,5-dienes results in rapid formation of the desired allylic carbinol (**12**) (Scheme IV) which may be readily isolated

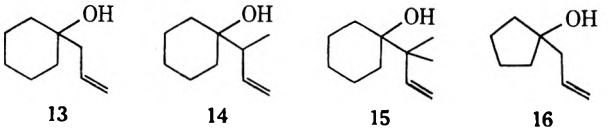
SCHEME IV



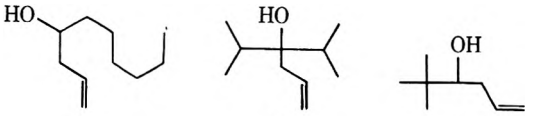
10



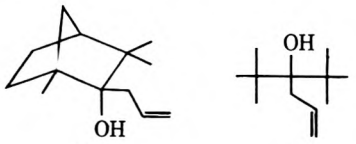
11 **12**



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



17 **18** **19**



20 **21**

by distillation or chomatography. As is the case with the magnesium and zinc procedures, the product has the allylic group attached at the more highly substituted terminus, regardless of the point of attachment of the mesitoate group in the starting ester. Table IV compares the results of the mesitoate method applied to several model systems with the magnesium and zinc procedures.

(20) Spectroscopic evidence does not allow distinction between structure **9** and the isomer with the ethyl ortho to the methoxymethyl substituent.

(21) P. J. Pearce, D. H. Richards, and N. F. Scilly, *Chem. Commun.*, 1160 (1970).

(22) M. P. Dreyfuss, *J. Org. Chem.*, **28**, 3269 (1963).

(23) M. Gaudemar, "Les Derives Organo-Metalliques," Colloques Internationaux du Centre National de la Recherche Scientifique, No. 120, Paris, 1963, p 133.

(24) M. Gaudemar, *Ann. Chim. (Paris)*, **1**, 161 (1956).

TABLE IV
SYNTHESIS OF ALLYLIC CARBINOLS

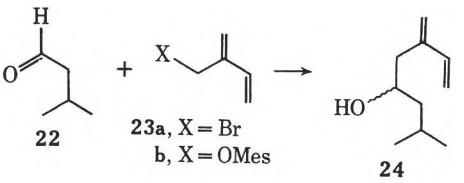
	Carbinol	Allyiic component	Carbonyl compound	Yield, %,[a] mesitoate procedure	Yield, %,[b] "Reformatsky" procedure	Metal used
1	13	Allyl	Cyclohexanone	42 56[c]	95	Mg
2	14	2-Butenyl	Cyclohexanone	39	72	Zn
3	14	1-Buten-3-yl	Cyclohexanone	35		
4	15	3-Methyl-2-butenyl	Cyclohexanone	22	64	Zn
5	15	3-Methyl-1-buten-3-yl	Cyclohexanone	25		
6	16	Allyl	Cyclopentanone	27	80	Mg
7	17	Allyl	Heptanal	14	69	Zn
8	18	Allyl	Diisopropyl ketone	60	75[d]	Mg
9	19	Allyl	Pivaldehyde	64 (49)	84	Zn
10	20	Allyl	Fenchone	67	50	Mg
11	21	Allyl	Di-*t*-butyl ketone	54, 52	75	Mg

[a] Determined by glpc using standards. Isolated yields in parentheses. [b] All yields from Reformatsky procedures are isolated yields. [c] Using 2 equiv of allyl mesitoate. [d] Allylmagnesium bromide used directly as Barbier–Grignard was unsatisfactory.

In most cases, the yield by the mesitoate lithium procedure is considerably lower than that of the Reformatsky-type procedures. However, it is notable that, in those cases in which the carbonyl component is severely hindered (entry 8) or has no α hydrogens (entries 9,10,11), the yield of alcohol by the mesitoate procedure is competitive or even superior to that of the Reformatsky procedure. Also, reaction conditions have not been optimized; the use of 2 equiv of allyl mesitoate improved the yield in the one case investigated (entry 1).

To demonstrate further the utility of the mesitoate reaction, we have synthesized one of the sex attractants (**24**) of *Ips confusus*, a bark beetle common to Ponderosa pine, by the mesitoate procedure and for comparison by the zinc method, using isovaleraldehyde (**22**) and 2-bromomethyl-1,3-butadiene (**23a**). Previously, it has been reported that the classical Grignard alcohol synthesis could not be utilized because the Grignard reagent of 2-bromomethyl-1,3-butadiene (**23a**) could not be prepared; in this case, the attractant was prepared by a several-step synthesis involving reaction between the anion of 2-isobutyl-1,3-dithiane and the bromide **23a**[25]

Our results with both the mesitoate–lithium and zinc procedures demonstrate that the direct alcohol synthesis is a possible route to this attractant. The reaction of 2-(mesitoyloxymethyl)-1,3-butadiene (**23b**) with lithium in tetrahydrofuran in the presence of isovaleraldehyde (**22**) gave a 10% isolated yield of the attractant **24**. The ester **23b** was prepared from the corresponding alcohol, which was made by a modification of a procedure given by Thomas.[26] Similarly, **23a**



22 **23a**, X = Br; **b**, X = OMes **24**

reacts readily with zinc in the presence of isovaleraldehyde in refluxing tetrahydrofuran to give the attractant in 52% yield after purification.

2. Side Reactions Accompanying Carbinol Formation.—Side reactions in the formation of allylic carbinols seem to be less complex and troublesome than those encountered in the allylic couplings. Examination of reaction mixtures by glpc frequently indicated that even when the mesitoate was consumed, considerable starting ketone or aldehyde could be detected. As the reactions were quenched by the addition of water, the presence of aldehyde or ketone suggested that α-hydrogen abstraction from the carbonyl compound by the generated allyllithium was a significant side reaction. Accordingly, allyl mesitoate was treated with cyclohexanone under the conditions used to give the yields shown in Table IV, and the reaction mixture was quenched with allyl bromide. 2-Allylcyclohexanone was found to be present along with the desired carbinol **13**. The high yields obtained by our method using carbonyl compounds containing no α hydrogens further substantiate the abstraction of hydrogen as an important side reaction. None of ketone **9** could be detected in reactions employing allyl mesitoate.

Experimental Section

Tetrahydrofuran (THF) was dried by distillation from sodium naphthalide and was used immediately. Ethanol-free chloroform was prepared by passing reagent chloroform (Fisher) through a column of alumina (Merck, neutral). Lithium wire (0.125 in., 0.1% Na) was purchased from Alfa Inorganics and was washed with hexane prior to use. Mesitoic acid[27] and mesitoyl chloride[28] were synthesized from 2-bromomesitylene; the acid chloride was purified by careful vacuum distillation. Commercially available allylic alcohols were obtained from the following sources: allyl alcohol and *trans*-2-buten-1-ol (crotyl alcohol), Aldrich Chemical Co.; 3-buten-2-ol, 3-methyl-3-buten-2-ol, *cis*- (95%) and *trans*- (95%) 3,7-dimethyl-2,6-octadien-1-ol (nerol and geraniol, respectively), Chemical Samples Co.; 3-methyl-2-buten-1-ol[29] and 2-hydroxymethyl-1,3-butadiene[26] were prepared according to published methods. Two allylic bromides were commercially available: 1-bromo-3-methyl-2-butene, Chemical Samples Co.; allyl bromide, Matheson Coleman and Bell. Allylmagnesium bromide (2 *M* in THF) was purchased from Alfa Inorganics. All ketones and aldehydes used in the formation of carbinols were purchased and used without further purification. Both magnesium turnings and zinc dust used in carbinol synthesis were obtained from Mallinkrodt. Magnesium sulfate ($MgSO_4$) was employed as a drying agent in all cases. All boiling points are uncorrected. Nmr spectra were run on a Varian A-60 spectrometer, and all chemical shifts are given in parts per million downfield from internal TMS (δ scale). Infrared spectra were taken as neat films using a Perkin-Elmer Model 521 spectrophotometer. Elemental analyses were performed by the analytical service of the University of Illinois.

All glassware used for the *in situ* generation of allyllithiums was dried for at least 3 hr at 125°. Glass-coated stirring magnets were used in all cases, and a dry nitrogen atmosphere was maintained throughout the course of the reaction. Analytical glpc

(25) C. A. Reece, J. O. Rodin, R. G. Brownlee, W. G. Duncan, and R. M. Silverstein, *Tetrahedron*, **24**, 4249 (1968).
(26) A. F. Thomas, *J. Amer. Chem. Soc.*, **91**, 3281 (1969).
(27) D. M. Bowen, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 553.
(28) R. P. Barnes, ref 27, p 556.
(29) R. H. Hall and M. H. Fleysher in "Synthetic Procedures in Nucleic Acid Chemistry," W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N. Y., 1968, p 517.

analyses were done on a Hewlett-Packard 5750 instrument fitted with flame ionization detectors using a carrier gas (N_2) flow of 30 ml/min. Product percentages were calculated from integrated peak area ratios, using *n*-alkanes with appropriate retention times as internal standards and correcting for differences in response factors. All analytical glpc columns have acid-washed, dimethyldichlorosilane-treated 80–100 mesh Chromosorb W as support and are referred to as follows: column A, 0.125 in. × 10 ft, 5% SE-30; column B, 0.125 in. × 6 ft, 10% UC-W98; column C, 0.125 in. × 3 ft, 5% SE-30; column D, 0.125 in. × 8 ft, 5% CW-4000; column E, 0.125 in. × 14 ft, 3% CW-4000; column F, 0.125 in. × 10 ft, 4.3% CW-4000.

All preparative glpc was done on a Varian Aerograph Model 90-P3 chromatograph with a thermal conductivity detector using a carrier gas (He) flow of 90 ml/min. The columns used are as follows: column G, 0.375 in. × 12 ft, 15% Carbowax 20M on 60–80 Chromosorb W; column H, 0.375 in. × 10 ft, 15% SE-30 on 60–80 Chromosorb W.

Synthesis of Mesitoates.—The mesitoates have been prepared by two general methods, denoted by A and B below, depending on the availability of the allylic alcohol. Specific cases are used to illustrate each method.

Method A. *trans*-3,7-Dimethyl-2,6-octadien-1-yl (Geranyl) Mesitoate.—Mesitoyl chloride (56.0 g, 0.307 mol) was dissolved in 80 ml of ethanol-free chloroform at 0°. Geraniol (55.6 g, 0.360 mol) and 43.6 g of dry pyridine were added over a 2-hr period. After stirring at room temperature for 72 hr, 300 ml of 10% hydrochloric acid was added, the organic layer was collected and washed with 10% NaOH and water, and solvent was removed under vacuum. Chromatography of the remaining oil on 400 g of neutral alumina using petroleum ether (bp 30–60°) gave 81.0 g (0.269 mol, 87.8% yield) of a clear oil: ir (neat) 1724 (s), 1078 cm^{-1} (s); nmr (CCl_4) δ 1.58–1.74 (m, 9 H), 2.08 (m, 4 H), 2.22 (s, 9 H), 4.69 (d, J = 8.0 Hz, 2 H), 5.01 (m, 1 H), 5.39 (t, J = 9.0 Hz, 1 H), 6.68 (s, 2 H).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 80.02; H, 9.39.

Method B. *trans*-2-Buten-1-yl (Crotyl) Mesitoate.—Mesitoyl chloride (56.0 g, 0.307 mol) was dissolved in 100 ml of ethanol-free chloroform. Crotyl alcohol (21.6 g, 0.300 mol) and 30.0 g of pyridine were dissolved in 50 ml of ethanol-free chloroform at 0° and added over a 1-hr period to the chloride. Stirring was continued at room temperature overnight, and 100 ml of water was added. The organic layer was washed twice with water, once with 10% HCl, and once with 5% $NaHCO_3$ (Caution: foaming) and dried. Solvent was removed under vacuum to leave a yellow oil which was vacuum distilled (103–104°, 0.2 Torr) to give 60.1 g (0.275 mol, 91.5% yield) of the desired ester: ir (neat) 1700 (s), 1242 (s), 1147 (s), 1055 cm^{-1} (s); nmr (CCl_4) δ 1.63 (m, 3 H), 2.19 (s, 9 H), 4.55 (m, 2 H), 5.69 (m, 2 H), 6.64 (s, 2 H).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.24. Found: C, 77.08; H, 8.24.

Allyl mesitoate (method A) (87.2% yield) had ir (neat) 1715 (s), 1257 (s), 1168 (s), 1078 cm^{-1} (s); nmr (CCl_4) δ 2.18–2.21 (m, 9 H), 4.67 (doublet of triplets, J_A = 5.5, J_B = 1.0 Hz, 2 H), 5.00–5.50 (m, 2 H), 5.90 (m, 1 H), 6.70 (s, 2 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.57; H, 7.79.

3-Methyl-2-buten-1-yl mesitoate (method A) (69.8% yield) had bp 138–139° (0.5 Torr); ir (neat) 1723 (s), 1265 (s), 1172 (s), 1083 cm^{-1} (s); nmr (CCl_4) δ 1.80 (m, 6 H), 2.22 (m, 9 H), 4.69 (d, J = 7.0 Hz, 2 H), 5.39 (t, J = 8.0 Hz, 1 H), 6.70 (s, 2 H).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.67. Found: C, 77.60; H, 8.66.

***cis*-3,7-Dimethyl-2,6-octadien-1-yl (neryl) mesitoate** (method A) (79.2% yield) had ir (neat) 1720 (s), 1611 (s), 1444 (s), 1379 (m), 1261 (s), 1169 (s), 1078 cm^{-1} (s); nmr (CCl_4) δ 1.60–1.76 (m, 9 H), 2.16 (m, 4 H), 2.28 (s, 9 H), 4.76 (d, J = 8.0 Hz, 2 H), 5.12 (m, 1 H), 5.48 (t, J = 7.0 Hz, 1 H), 6.68 (s, 2 H).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 80.20; H, 9.44.

3-Methyl-1-buten-3-yl mesitoate (method B) (69.2% yield) had bp 108–110° (0.8 Torr); ir (neat) 1736 (s), 1276 (s), 1086 cm^{-1} (s); nmr (CCl_4) δ 1.60 (s, 6 H), 2.17–2.30 (m, 9 H), 4.87–5.38 (m, 2 H), 6.24 (doublet of doublets, J_A = 18.0, J_B = 10.4 Hz, 1 H), 6.72 (s, 2 H).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.50; H, 8.70.

1-Buten-3-yl mesitoate (method B) (73.4% yield) had bp 94.5–95.0 (0.7 Torr); ir (neat) 1726 (s), 1265 (s), 1082 cm^{-1} (s); nmr (CCl_4) δ 1.40 (d, J = 6.6 Hz, 3 H), 2.28 (m, 9 H), 5.00–6.25 (m, 4 H), 6.74 (s, 2 H).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.80; H, 8.41.

Allylic Bromides.—Geranyl, neryl, farnesyl, and *trans*-2-butenyl bromides were prepared by the action of phosphorus tribromide (PBr_3) on the corresponding carbinols and gave a positive test with alcoholic silver nitrate. All bromides were stored at −20°, as decomposition was quite rapid at room temperature. The synthesis of geranyl bromide is typical of the method used.

***trans*-3,7-Dimethyl-2,6-octadienyl (Geranyl) Bromide.**—Geraniol (44.5 g, 0.288 mol) was dissolved in 250 ml of dry ether at 0°, and PBr_3 (32.4 g, 0.12 mol) was added dropwise. After 3 hr, ice water was added, the organic layer was collected and dried, and solvent was removed under vacuum to give 56.8 g (0.262 mol, 91% yield) of a pale yellow oil: nmr (CCl_4) δ 1.70 (m, 9 H), 2.08 (m, 4 H), 3.94 (d, J = 11.0 Hz, 2 H), 5.08 (m, 1 H), 5.5 (t, J = 9.0 Hz, 1 H).

Coupling Reactions (General Procedure).—The allylic bromide (0.01 mol) was added to the allylic mesitoate (0.01 mol) in 50 ml of dry THF. An excess of freshly cut lithium (*ca.* 0.1 g-atom, 0.1% Na) was added, and the reaction flask was evacuated and flushed several times with dry nitrogen. Stirring was done using a glass-coated stirring bar, and the reaction was kept at 0° until a deep red-brown color formed. The reaction was quenched by addition of 1 ml of water, and the mixture was immediately filtered through glass wool into 50 ml of 5% NaOH and 50 ml of ether. The aqueous layer was isolated and acidified (concentrated HCl) to give mesitoic acid, while the organic layer was collected and dried. Products were identified either by isolation or by comparison with a known sample.

***trans*-2,6-Dimethyl-2,6,10-undecatriene** (1a, 1g) was obtained from allyl mesitoate and geranyl bromide; yield 22% as determined by glpc using internal standard. Retention times (glpc) were identical with those of an authentic sample prepared from allylmagnesium bromide and geranyl bromide: column C (130°), 1.6 min; column B (105°), 4.9 min. From geranyl mesitoate and allyl bromide, the yield of coupled products was 60% from glpc. From a preparative scale reaction using the same components, the olefin fraction was isolated by chromatography over alumina using hexane. Glpc showed a 35% yield of cross-coupled products. An analytical sample was isolated by preparative glpc (column H) and gave glpc retention times and nmr spectra identical with those of the authentic sample: nmr (CCl_4) δ 1.52–1.78 (m, 9 H, $-CH_3$), 1.95–2.17 (m, 8 H, $-CH_2-$), 4.69–5.21 (m, 4 H), 5.30–6.10 (m, 1 H).

Anal. Calcd for $C_{11}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.62; H, 12.18.

***trans,trans*-2,6-Dimethyl-2,6,10-dodecatriene** (1f) was obtained from crotyl mesitoate and geranyl bromide; the yield of cross-coupled products was 19% as determined by glpc using internal standards. Retention times were found to be identical with those of an authentic sample prepared by coupling crotyl and geranyl bromides over magnesium: column C (130°), 2.8 min; column G (195°), 4.0 min. A sample isolated from mesitoate reaction by preparative glpc (column G) gave the following spectral data: nmr (CCl_4) δ 1.50–1.70 (m, 12 H, $-CH_3$), 1.85–2.14 (m, 8 H, $-CH_2-$), 4.85–5.50 (m, 4 H, olefinic H).

***trans*-2,6,11-Trimethyl-2,6,10-dodecatriene** (1b, 1e) was obtained from 3-methyl-2-butenyl bromide and geranyl mesitoate; preparative-scale reaction using 0.08 mol of each reactant gave a 49% yield of cross-coupled dienes. Preparative glpc (column H) was used to isolate the triene, which gave the following spectral and analytical data: nmr (CCl_4) δ 1.50–1.72 (m, 15 H, $-CH_3$), 1.95 (m, 8 H, $-CH_2-$), 5.03 (m, 3 H, olefinic H).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.15; H, 12.60.

From 3-methyl-2-butenyl mesitoate and geranyl bromide, the yield of cross-coupled products was 32%. The product was identified by comparison with a known sample on glpc: column B (170°), 3.5 min; column C (160°), 4.6 min.

***trans,trans,trans*-2,6,10,15,19-Pentamethyl-2,6,10,14,18-eicosapentaene** (1d) was obtained from geranyl mesitoate and fanesyl bromide; the yield of cross-coupled products was 43% as shown by glpc using an internal standard. Retention times were found to be identical with those of an authentic sample prepared by coupling geranyl and farnesyl bromides over magnesium column C (220°), 4.0 min.

Both C_{20} (Ger–Ger) and C_{30} (Far–Far) products formed in the mesitoate and magnesium (Wurtz) couplings of geranyl and farnesyl units were identified by glpc comparison to geranyl dimers[12] and a known sample of farnesyl dimer (squalene), respectively.

Coupling of Neryl–Geranyl, Neryl–Neryl, and Geranyl–Geranyl Units.—Digeranyl (1c) and isodigeranyl (2c) were prepared by the method of Barnard and Batemann[12] and were used as knowns for glpc identification. These compounds were obtained in 95% yield from reaction of 0.01 mol of geranyl mesitoate and 0.01 mol of geranyl bromide using glpc internal standards to determine the yield. A preparative-scale reaction using 0.10 mol of each component gave an isolated yield of 93% of the coupled products. These were identified by comparison to the known samples on glpc (Column A, 260°): digeranyl (1c), 4.8 min; isodigeranyl (2c), 2.1 min.

The dienes **3** and **5** were assigned the structures given, as they are the expected coupling products of two neryl units (based on analogy to what is known for the coupling of two geranyl units). Glpc retention times of these 1,5-dienes (column A, 260°) are as follows: dineryl (**3**), 4.2 min; isodineryl (**5**), 3.8 min.

The 1,5-diene **5** was assigned its structure, as it is the expected main coupling product to be formed in a coupling reaction between a neryl and a geranyl unit. Glpc retention time of this compound (column A, 260°) was 4.5 min. Yields of these compounds from the mesitoate coupling reactions were determined using internal standards.

Reaction of Mesitoic Acid with Lithium.—Mesitoic acid (3.4 g, 0.021 mol) was dissolved in 70 ml of dry THF. A large excess of freshly cut lithium chips (*ca.* 0.2 mol) was added, and the mixture was allowed to stir at 25° for 17 hr. The resulting deep red solution was transferred by means of a polyethylene tube to a flask containing 6.0 ml of methyl iodide, and after 10 min, the organic layer was diluted with 50 ml of ether and extracted twice with base (5 *M* NaOH) to remove any acidic material. The organic layer was dried and solvent was removed to give 1.7 g of a yellow oil shown by glpc to contain at least six components, three of which constituted about 85% of the total. Methyl (2,4,6-trimethylphenyl)methyl ether (**6**) and methyl (4-ethyl-2,6-dimethylphenyl) methyl ether (**7**), two of the three major products, were isolated together by column chromatography (alumina) using ligroin followed by ethyl ether. By glpc–mass spectral analysis (column A, 145°), compound **6** was shown to have a molecular weight of 164 and **7** a molecular weight of 178. Both compounds showed a large P − 32 peak. The structure of **6** was confirmed by an independent synthesis from 2,4,6-trimethylbenzyl alcohol and methyl iodide. The structure of **7** was inferred from the mass spectrum and the nmr spectrum.

Compound **6** had nmr (CCl_4) δ 2.11 (s, 3 H), 2.17 (s, 6 H), 3.12 (s, 3 H), 4.18 (s, 2 H), 6.71 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 164 (7), 149 (16), 133 (50), 132 (100), 117 (30), 105 (15), 91 (18).

Compound **7** had nmr (CCl_4) δ 1.08 (t, J = 4.0 Hz, 3 H), 2.11–2.17 (m, 6 H), 2.61 (q, J = 4.0 Hz, 2 H), 3.14 (s, 3 H), 4.18 (s, 2 H), 6.72 (s, 2 H); mass spectrum *m/e* (rel intensity) 178 (2), 163 (8), 157 (32), 146 (100), 132 (22), 131 (70), 105 (15), 91 (25).

Reduction of Allyl Mesitoate with Lithium.—Allyl mesitoate (2.94 g, 0.014 mol) was dissolved in 50 ml of THF, and an excess of lithium (*ca.* 0.15 g-atom) was added. After stirring for 24 hr at room temperature, the resulting dark red solution was transferred to a flask containing 15 ml of THF and 5 ml of methyl iodide. After reaction was complete, 50 ml of ether was added, and the mixture was extracted with 25 ml of 5 *M* NaOH solution. Acidification of the aqueous layer gave only a trace of mesitoic acid. Glpc–mass spectral analysis of the organic layer (column C) showed at least 13 compounds with a molecular weight range of 134–246. Only one of these, **8**, was identified by comparison to published mass spectral data.[30] No structures have been assigned to the remaining compounds.

In a separate experiment, 0.02 mol (2.08 g) of allyl mesitoate was mixed with 50 ml of dry THF, and an excess of lithium was added. Stirring was done under a dry nitrogen atmosphere at 0° with a glass-coated stirring bar. At the time intervals shown in Figure 1, 2.0-ml aliquots were withdrawn and injected into an inverted buret to measure the evolution of propene (and thus allyllithium). At no point did the volume of propene exceed 2.05 ml at STP (theoretical amount of gas formed if allyllithium was formed quantitatively was 17.9 ml). The reaction was monitored in such a fashion for 18 hr; glpc analysis indicated complete consumption of allyl mesitoate within 1.5 hr.

1-(2,4,6-Trimethylphenyl)-*trans*-2-buten-1-one (9).—Allyllithium, prepared from 10.0 g of allyl phenyl ether,[8] was added to allyl mesitoate (1.5 g, 0.0074 mol) in 5 ml of THF at room temperature. After stirring for 15 min, water was added; the organic layer was dried, and solvent was removed under vacuum. The ketone **9** was isolated by preparative tlc on silica gel using ether–hexane (1:9) to give 0.9 g (65% yield) of a clear oil: ir (neat) 2921 (w), 1659 (s), 1437 (w), 1282 cm^{-1} (m); nmr (CCl_4) δ 1.86 (d, J = 5.2 Hz, 3 H), 2.11 (s, 6 H), 2.26 (s, 3 H), 6.01–6.57 (m, 2 H), 6.75 (s, 2 H).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.68; H, 8.44.

Synthesis of Allylic Carbinols.—Each of the allylic carbinols was synthesized both by one of two Reformatsky-type procedures (method A, magnesium; method B, zinc) and by the mesitoate–lithium procedure (method C). The three methods are illustrated by the first three procedures given below.

In several cases with the Reformatsky method, no boiling points are reported for the distillation, as severe foaming occurred. In such cases, after crude distillation to give a fraction of about 95% purity, preparative glpc followed by molecular distillation was used to prepare a sample for spectroscopic analysis and microanalysis.

Method A (Magnesium). 1-Allylcyclohexanol (13).—Magnesium (14.4 g, 0.59 g-atom) was added to 500 ml of dry ether along with a few crystals of iodine. A small amount (<1 ml) of allyl bromide was added, and after Grignard formation had begun, the solution was cooled to 0°. A mixture of cyclohexanone (28.0 g, 0.255 mol) and allyl bromide (35.3 g, 0.28 mol) was then added dropwise over a 2-hr period. The reaction was allowed to stir overnight at 25°, and water was then added to quench the reaction. The aqueous layer was washed twice with ether and the combined organic layers were dried and placed under vacuum for solvent removal to give a clear liquid product. Distillation gave 33.8 g (0.242 mol, 95% yield) of the desired carbinol: bp 81–82° (9.0 mm) [lit.[22] bp 70–72° (8.0 mm)]; ir (neat) 3495 (m), 3080 (w), 2937 (s), 1638 (m), 1448 (m), 971 (m), 909 cm^{-1} (m); nmr (CCl_4) δ 1.47 (s, 10 H), 2.16 (doublet of triplets, J_A = 7.0, J_B = 1.0 Hz, 2 H), 2.25 (s, 1 H), 5.00 (m, 2 H), 5.83 (m, 1 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.10; H, 11.47.

Compound **13** was also prepared by method C from allyl mesitoate and cyclohexanone, 42% yield. A 56% yield was obtained by using 0.02 mol (2 equiv) of the mesitoate with 0.01 of the ketone. **13** was identified by comparison to a known sample on glpc: column A (145°), 2.3 min; column B (122°), 3.2 min.

Method B (Zinc). 1-Decen-4-ol (17).—To 200 ml of dry ether was added heptanal (51.5 g, 0.451 mol) and dry zinc dust (39.2 g, 0.60 g-atom). A small amount (5.0 g) of the total amount of allyl bromide (54.5 g, 0.451 mol) was added, and stirring was continued until vigorous reflux indicated the start of the reaction. The remaining bromide was added at such a rate so as to maintain vigorous reflux, and after the addition was complete, the reaction was allowed to stir for an additional 2 hr. The reaction mixture was quenched by slow addition to 500 ml of dilute hydrochloric acid, and the hydrolysate was stirred until most of the inorganic material had dissolved. The mixture was filtered, and the organic layer was collected, dried, concentrated, and vacuum distilled to give 48.6 g (0.312 mol, 69% yield) of the desired carbinol: bp 65.4–66.0° (0.16 mm); ir (neat) 3350 (m), 3080 (w), 2960 (m), 2930 (s), 2861 (s), 1639 (s), 1461 (m), 992 (w), 991 cm^{-1} (m); nmr (CCl_4) δ 0.90 (m, 3 H, $-CH_3$), 1.33 (s, 10 H), 2.18 (m, 2 H), 2.65 (s, 1 H, –OH), 3.57 (m, 1 H, –CHOH), 4.82–5.20 (m, 2 H), 5.50–6.20 (m, 1 H).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.92; H, 12.93.

Compound **17** was also prepared by method C from allyl mesitoate and heptanal, 14% yield. It was compared to a known sample on glpc: column C (110°), 2.6 min.

Method C (Lithium–Mesitoate). 1-[3-(1-Butenyl)]-cyclohexanol (14).—To a mixture of 2.18 g (0.01 mol) of 2-buten-1-yl mesitoate and 0.98 g (0.01 mol) of cyclohexanone in 25 ml of THF was added an excess of freshly cut lithium (*ca.* 0.1 mol). The reaction mixture was stirred under a dry nitrogen atmosphere at 0° for about 1 hr. The reaction mixture (dark green) was

(30) "Eight Peak Index of Mass Spectra," 1st ed, Vol. I, Mass Spectrometry Data Centre, Aldermaston, Reading, U. K., 1970, p 102.

filtered through glass wool into a mixture of 50 ml of dilute sodium hydroxide solution and 50 ml of ether. The organic layer was collected and dried, internal standard was added for glpc yields, and solvent was removed by vacuum to give a 39% yield of **14** by glpc analysis.

14 was also prepared from 3-(1-butenyl) mesitoate and cyclohexanone, 35% yield, and compared to a known sample (prepared by method B, below) on glpc: column E (170°), 5.2 min; column B (139°), 4.1 min. A sample was isolated by preparative glpc (column H) from the 2-buten-1-yl mesitoate reaction and gave an nmr identical with that of the known sample.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.87; H, 11.56.

Compound **14** was also prepared by method B from cyclohexanone and 1-bromo-2-butene in 72% yield: purified after distillation by preparative glpc, column H; ir (neat) 3450 (m), 3078 (w), 2939 (s), 2860 (m), 1449 (w), 949 (w), 908 cm^{-1} (w); nmr (CCl_4) δ 1.00 (d, J = 6.4 Hz, 3 H), 1.18–1.80 (m, 11 H, $-CH_2-$, -OH), 2.13 (m, 1 H), 4.80–5.17 (m, 2 H), 5.53–6.15 (m, 1 H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; 11.76. Found: C, 77.98; H, 11.59.

1-[3-(3-Methyl-1-butenyl)]cyclohexanol (15) (method A) was obtained from cyclohexanone and 3-methyl-2-butenyl bromide: 73% yield; bp 66.5–67.5° (1.5 mm); ir (neat) 3497 (m), 2941 (s), 2861 (m), 1632 (w), 1449 (w), 1130 (w), 961 (m), 911 cm^{-1} (m); nmr (CCl_4) δ 1.00 (s, 6 H), 1.27 (s, 1 H, -OH), 1.32–1.85 (m, 10 H), 4.71–5.13 (m, 2 H), 5.68–6.22 (doublet of doublets, 1 H).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.41; H, 11.80.

Compound **15** was also prepared by method C from 3-methyl-2-butenyl mesitoate and cyclohexanone, 22% yield, and from 3-(3-methyl-1-butenyl) mesitoate and cyclohexanone, 25% yield. It was compared to a known sample (prepared above by method A) on glpc: column A (145°), 4.6 min; column B (162°), 3.1 min.

1-Allylcyclopentanol (16) (method A) was obtained from cyclopentanone and allyl bromide: 80% yield; bp 66–67.5° (14 mm); ir (neat) 3389 (s), 3078 (m), 2950 (s); 2876 (s), 1638 (s), 1432 (m), 1182 (m), 989 (s), 909 cm^{-1} (s); nmr (CCl_4) δ 1.58 (s, 8 H), 2.25 (doublet of triplets, J_A = 7.0 Hz, J_B = 1.0 Hz, 2 H), 2.60 (s, 1 H, -OH), 4.75–5.20 (m, 2 H), 5.49–6.20 (m, 1 H).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.19; H, 11.12.

Compound **16** was also prepared by method C from allyl mesitoate and cyclopentanone, 27% yield. It was compared to a known sample (prepared above) on glpc: column F (95°), 3.1 min; column A (125°), 2.2 min.

2-Methyl-3-isopropyl-5-hexen-3-ol (18) was prepared by direct addition of 70 ml of 2 *M* allylmagnesium chloride (0.14 mol) in THF to 11.5 g (0.10 mol) of diisopropyl ketone in 150 ml of dry THF at 0°. After stirring for 12 hr at 25°, the reaction mixture was quenched by slowly adding to 100 ml of dilute hydrochloric acid. The organic layer was isolated and dried, and solvent was removed by vacuum. The remaining liquid was distilled under reduced pressure (91–95°, 30 mm) to give 11.8 g (0.0754 mol, 75.4% yield) of the desired carbinol. An analytical sample was prepared by preparative glpc (column H) followed by bulb-to-bulb distillation: ir (neat) 3500 (m), 3080 (w), 2968 (s), 1637 (w), 1468 (m), 1376 (m), 1096 (w), 991 (m), 977 (m), 910 cm^{-1} (m); nmr (CCl_4) 0.91 (doublet of doublets, J_A = 7.8, J_B = 1.7 Hz, 12 H), 1.25 (s, 1 H), 1.50–2.08 (m, 2 H), 2.12–2.31 (m, 2 H), 4.73–5.17 (m, 2 H), 5.46–6.14 (m, 1 H).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.88; H, 12.75.

18 was also prepared by method C using allyl mesitoate and diisopropyl ketone, 60% yield. It was compared to a known sample on glpc: column A (145°), 2.7 min; column B (170°), 1.5 min.

2,2-Dimethyl-3-hydroxy-5-hexene (19) (method B) was obtained from pivaldehyde and allyl bromide, 84% yield. A sample was prepared by preparative glpc, column G: ir (neat) 3439 (s), 3079 (m), 2951 (s), 2872 (s), 1638 (s), 1479 (s), 1363 (s), 1291 (m), 1071 (s), 1000 (s), 910 (s), 861 cm^{-1} (s); nmr (CCl_4) δ 0.88 (s, 9 H), 1.58–2.53 (m, 3 H, $-CH_2-$, -OH), 3.18 (doublet of doublets, J_A = 10.0, J_B = 2.8 Hz, 1 H), 4.77–5.20 (m, 2 H), 5.46–6.18 (m, 1 H).

Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.99; H, 12.34.

Compound **19** was also prepared by method C from pivaldehyde and allyl mesitoate, 64% yield. It was compared to an authentic sample (prepared above) on glpc: column A (120°), 2.0 min; column B (128°), 1.5 min. A preparative-scale reaction using 0.03 mol of each reagent gave an isolated yield of **19** of 49%. An nmr identical with that of the authentic alcohol was obtained from this sample.

***endo*-1,3,3-Trimethyl-2-allylbicyclo[2.2.1]heptan-2-ol (20)** (method A) was obtained from fenchone and allyl bromide, 50% yield. An analytical sample was prepared by preparative glpc (column H) as the reaction mixture could not be successfully fractionated: ir (neat) 3575 (m), 3080 (w), 2959 (s), 2881 (s), 1632 (m), 1467 (m), 1369 (m), 1063 (m), 994 (m), 923 cm^{-1} (m); nmr (CCl_4) δ 0.85 (s, 3 H), 0.97 (s, 3 H), 1.03 (s, 3 H), 1.12–2.60 (m, 10 H), 4.85–5.21 (m, 2 H), 5.60–6.29 (m, 1 H).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.35; H, 11.29.

Compound **20** was also prepared by method C from fenchone and allyl mesitoate, 67% yield, and compared to a known sample (prepared above) on glpc: column A (152°), 5.8 min; column B (163°), 4.7 min.

2,2-Dimethyl-3-hydroxy-3-*tert*-butyl-5-hexene (21) (method A) was obtained from di-*tert*-butyl ketone and allyl bromide: 75% yield; bp 130–135° (21 mm); ir (neat) 3585 (m), 3081 (m), 2962 (s), 1485 (s), 1396 (s), 1374 (s), 1210 (m), 1076 (m), 1004 (m), 922 cm^{-1} (m); nmr (CCl_4) δ 1.02 (s, 18 H), 1.36 (s, 1 H, -OH), 2.41 (m, 2 H), 4.73–5.14 (m, 2 H, $-C{=}CH_2$), 5.51–6.10 (m, 1 H).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.29; H, 13.03.

Compound **21** was also prepared by method C from allyl mesitoate and di-*tert*-butyl ketone, 54 and 52% yields in consecutive experiments. **21** was compared to a known sample (prepared above) on glpc: column F (136°), 2.0 min; column A (155°), 3.8 min.

2-Methyl-6-methylene-7-octen-4-ol (24) (method B).—To a mixture of 2-bromomethyl-1,3-butadiene[26] (5.0 g, 0.034 mol) and isovaleraldehyde (2.94 g, 0.034 mol) in 40 ml of dry THF was added 3.0 g (0.046 g-atom) of zinc. After refluxing for 4 hr, the entire reaction mixture was poured into a mixture of water and ether and filtered to remove inorganic salts, and the organic layer was dried and concentrated. The remaining oil was distilled (bulb to bulb, 1.5 mm, 150°) to give 2.7 g (0.0175 mol, 52% yield) of the alcohol **24**: ir (neat) 3480 (m), 3089 (w), 2960 (s), 1596 (m), 1468 (m), 1388 (w), 1368 (w), 1071 (w), 1023 (w), 993 (m), 898 cm^{-1} (s); nmr (CCl_4) δ 0.92 (doublet of doublets, J_A = 7.0, J_B = 2.1 Hz, 6 H), 1.28 (m, 2 H), 1.72 (m, 1 H), 2.12-2.38 (m, 3 H, $-CH_2-$, -OH), 3.74 (m, 1 H, -CHOH), 5.01–5.38 (m, 4 H), 6.31 (doublet of doublets, J_A = 17.0, J_B = 10.0 Hz, 1 H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.07; H, 11.67.

Compound **24** was also prepared by method C from 2-(mesitylmethyl)-1,3-butadiene (**23b**) and isovaleraldehyde (**22**); the attractant **24** was isolated by preparative tlc on silica gel using ether–hexane (1:10) to give a 10.0% yield. The material was identified by comparison to a known sample (prepared by method B) on glpc: column A (138°), 2.9 min; column B (150°), 2.1 min.

Registry No.—**1a**, 24120-53-4; **1b**, 36971-05-8; **1f**, 36971-06-9; **6**, 5336-55-0; **7**, 36971-08-1; **9**, 36971-09-2; **13**, 1123-34-8; **14**, 36971-11-6; **15**, 36971-12-7; **16**, 36399-21-0; **17**, 36971-14-9; **18**, 36971-15-0; **19**, 19550-89-1; **20**, 36971-17-2; **21**, 754-56-3; **24**, 14314-21-7; geranyl mesitoate, 1674-04-0; crotyl mesitoate, 1690-44-4; allyl mesitoate, 2000-88-6; 3-methyl-2-buten-1-yl mesitoate, 36971-23-0; neryl mesitoate, 1674-05-1; 3-methyl-1-buten-3-yl mesitoate, 36971-25-2; 1-buten-3-yl mesitoate, 36971-26-3; geranyl bromide, 6138-90-5.

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The Nickel(0)-Catalyzed Addition of Phenol to Butadiene

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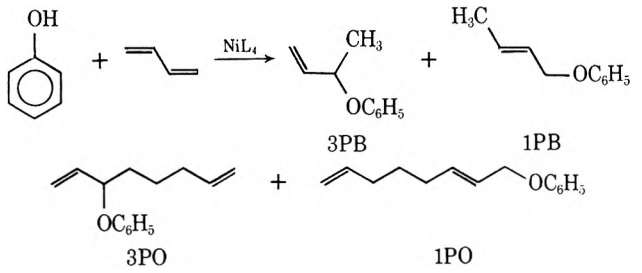
The (organophosphorus)nickel(0)-catalyzed reaction of phenol and butadiene gives mixtures of 3-phenoxy-1-butene, 1-phenoxy-2-butene, 3-phenoxy-1,7-octadiene, and 1-phenoxy-2,7-octadiene. The formation of phenoxybutenes is favored by electron-donor ligands, excess ligand, high phenol concentration, and low conversions. A mechanism based on dual reaction pathways for an (organophosphorus)nickel intermediate is presented to explain these results.

Mechanistic understanding of transition metal catalyzed reactions is far behind other fields of chemistry. Recently elegant studies have elucidated some details by isolation and identification of intermediates in catalytic cycles.[1-3] Hopefully the concepts developed in such pioneering work can be broadly applied to related reactions.

Phenol reacts with butadiene in the presence of tetrakis(organophosphorus)nickel(0) to give 3-phenoxy-1-butene, *trans*-1-phenoxy-2-butene, 3-phenoxy-1,7-octadiene, and *cis*- and *trans*-1-phenoxy-2,7-octadiene.[4]



The goal of this work was to optimize the formation of the phenoxybutenes, as palladium seems to be a superior catalyst for the synthesis of phenoxyoctadienes.[4,5]

Experimental Section

Analytical Runs.—A Pyrex tube was sealed with a serum stopper and evacuated. Butadiene was distilled into the tube at −78° from a calibrated reservoir. Solutions of phenol in ether, nickelocene in benzene, and ligand were injected *via* syringe and the tube was sealed. The order of addition was immaterial. After warming to room temperature the tubes were heated and agitated in a thermostatted oven. After the desired reaction time the tubes were cooled to −78° and opened, and the contents were examined by gas chromatography on a 6 ft × 0.25 in. column of 20% silicone 200 supported on Gas-Chrom RA (60–80) at 180° and 75 ml/min. The retention times (minutes) follow: phenol, 1.0; 3PB, 1.7; 1PB, 2.7; 3PO, 7.2; and 1PO, 11.7. Areas were calculated using triangular approximation of peak height times line width. Standards prepared using materials purified by preparative gas chromatography showed that area per cent calculated in this way corresponded closely to mole per cent. Precision is estimated at ±3% for duplicate runs; accuracy is undoubtedly lower.

Catalyst cycles are defined as moles of products per mole of nickel charged. The yield of the phenoxybutenes and phenoxyoctadienes is essentially quantitative based on phenol consumed.

Preparative Runs.—A Hastelloy C bomb was charged under nitrogen with solutions of ligand, nickelocene, and phenol in ether. The bomb was sealed, evacuated, and charged with butadiene. After the reaction was complete excess butadiene was vented and the remaining contents were discharged. The ether solution was extracted with sodium hydroxide until gc showed the absence of phenol. After removal of most of the solvent, the residue was distilled through a Nestor-Faust spinning-band column at reduced pressure. Four fractions were obtained: fraction 1, 3-phenoxy-1-butene, bp 37–40° (1 mm), n^{25}D 1.5072 [lit.[6] bp 43° (0.8 mm)]; fraction 2, 1-phenoxy-3-butene, bp 58–59° (1 mm), n^{25}D 1.5173 [lit.[6] bp 87° (8 mm); fraction 3, 3-phenoxy-1,7-octadiene, bp 87° (1 mm), n^{25}D 1.5077; fraction 4, 1-phenoxy-2,7-octadiene, bp 104° (1 mm), n^{25}D 1.5153. The proton nmr spectrum of fraction 4 suggested the presence of 15% cis and 85% trans isomers.[4] No attempt was made to separate these two compounds.

Phosphorus ligands and nickel(0) complexes were obtained from the same sources cited by Tolman.[7]

The results of the studies of several reaction variables are presented individually followed by discussion in terms of a single mechanistic proposal.

Temperature–Time.—Time studies at 100° with tetrakis(triphenylphosphite)nickel catalyst showed that the reaction was essentially complete after 2 hr, and the product composition was unchanged on extended heating. Higher temperatures gave lower conversions to the four addition products and new peaks began to appear in the gas chromatograms. Although these products have not been isolated and identified, they may result from phenol alkylation rather than addition.[4] Heating for 15 hr at 90° gave essentially identical yields and conversions as runs at 100°, but lower temperatures showed a sharp discontinuity. The product distribution at various temperatures for 15 hr is summarized in Table I while the product distribution as a function of time at 70° is given in Table II.

There is an induction period before the rapid formation of phenoxyoctadienes begins. The absolute amount of phenoxybutenes does not decline during this rapid formation of phenoxyoctadienes, but steadily increases. At low conversion the yield of 3PB is greater than that of 1PB, but later the relative amount of 1PB increases.

(1) (a) Hydroformylation: R. F. Heck, *Advan. Organometal. Chem.*, **4**, 243 (1966). (b) Palladium-catalyzed oxidations: A. Aguiló, *ibid.*, **5**, 321 (1967).

(2) (a) Rhodium-catalyzed ethylene dimerization: R. Cramer, *J. Amer. Chem. Soc.*, **87**, 4717 (1965). (b) Nickel-catalyzed addition of ethylene to butadiene: C. A. Tolman, *ibid.*, **92**, 6777 (1970).

(3) For a review of the chemistry of butadiene with nickel(0) see P. Heimbach, P. W. Jolly, and G. Wilke, "Advances in Organometallic Chemistry," Vol. 8, Academic Press, New York, N. Y., 1970, pp 29–86.

(4) E. J. Smutny, H. Chung, K. C. Dewhirst, W. Keim, T. M. Shryne, and H. E. Thyret, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr.*, 14 (2), B100–B111 (1969); H. Chung and W. Keim, U. S. Patent 3,636,162 (1969).

(5) Since the completion of this work, T. C. Shields and W. E. Walker, *Chem. Commun.*, 193 (1971), have described experiments in this area.

(6) H. L. Goering and R. R. Jacobson, *J. Amer. Chem. Soc.*, **80**, 3277 (1958).

(7) C. A. Tolman, *ibid.*, **92**, 2956 (1970).

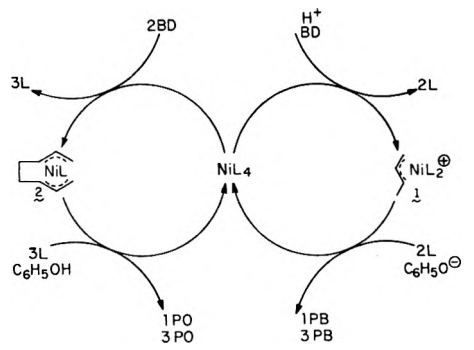


Figure 1.—Postulated mechanism for the nickel(0)-catalyzed synthesis of phenoxybutenes and phenoxyoctadienes.

TABLE I

TEMPERATURE EFFECTS[a]

Temp, °C	Catalyst cycles	Yield, % 3PB	1PB	3PO	1PO
64	7	58	25	1	16
80	8	55	28	0	19
90	71	14	10	9	68
100	79	11	13	16	60
113	55	13	12	10	65
125	40	12	12	8	68
151	20[b]	8	24	0	68

[a] 25 mmol of BD/10 mmol of phenol, 15 hr, 0.1 mmol of Ni[P(OC6H5)3]4, ether solvent. [b] Plus many side products.

TABLE II

EFFECT OF REACTION TIME ON PRODUCT DISTRIBUTION[a]

Time, hr	Catalyst cycles	Yield, % 3PB	1PB	3PO	1PO	Absolute yield of phenoxybutene
4	3	55	23	6	15	2
8	5	52	16	6	26	4
16	19	32	16	8	44	9
32	72	13	10	12	64	16

[a] 10 mmol of C6H5OH, 25 mmol of BD, 0.1 mmol of Ni(C5H5)2, 0.4 mmol of (C6H5O)3P, 70°, ether solvent.

Ligand to Metal Ratio.—Initially, preformed NiL_4 species served as catalysts and excess ligand was added to stabilize an intermediate if excessive ligand dissociation was the mechanism of catalyst deactivation. Starting with nickel–olefin complexes, ligand-to-metal ratios lower than 4:1 could be studied. The results of varying the ratio of triphenyl phosphite to nickelocene are shown in Table III. The adducts do not form in the absence

TABLE III

EFFECT OF LIGAND TO METAL RATIO[a]

Triphenyl phosphite, mmol	Catalyst cycles	Yield, % 3PB	1PB	3PO	1PO
0.1	6	13	5	7	75
0.2	44	11	6	11	72
0.3	38	13	7	9	71
0.4	54	10	16	23	51
0.8	59	10	16	21	53
1.2	35	28	26	9	37
2.0	15	47	40	3	10

[a] 0.1 mmol of nickelocene, 25 mmol of BD, 10 mmol of C6H5OH, 100°, 15 hr, ether solvent.

of a phosphorus ligand. As triphenyl phosphite is initially added, the major products are phenoxyoctadienes, and up to 8 equiv of ligand does not significantly change this product distribution, although the ratio of linear to branched products is affected. Excess ligand slows the reaction and increases the yield of phenoxybutenes. When runs with large excesses of ligand are cooled, tetrakis(triphenyl phosphite)nickel precipitates from solution.

TABLE IV

EFFECT OF REACTANT RATIOS ON PRODUCT DISTRIBUTION[a]

BD/C6H5OH	Catalyst cycles	Yield, % 3PB	1PB	3PO	1PO
Catalyst Ni[P(OEt3)]4					
1.25:1	46	32	54	2	10
2.5:1	84	22	36	10	32
5:1	96	21	31	8	40
Catalyst Ni[P(OC6H5)3]4					
0.67:1	14	39	33	6	23
1.25:1	49	20	21	8	52
2.5:1	79	11	13	11	60
10:1	77	13	10	12	65

[a] Solvent Et2O, 100°, 15 hr.

Reactant Ratios.—As the ratio of butadiene to phenol is increased, the phenoxyoctadienes comprise a larger proportion of the product; however, above 3 equiv of butadiene per phenol little change in the product distribution occurs. Table IV gives the results of varying the ratio of phenol to butadiene with tetrakis(triphenyl and triethyl phosphite)nickel catalysts.

Ligand Effects.—Table V gives the product distribution with different phosphorus ligands. For triphenyl phosphite the yields and conversion are identical whether the catalyst was preformed or prepared *in situ* from either nickelocene or bis(cyclooctadiene)-nickel and the ligand. Preformed complexes were required for triethyl phosphite and all phosphines. For the other ligands listed *in situ* preparation was apparently adequate. Phosphines and phosphonites give high yields of phenoxybutenes. Phosphines favor 3PO while phosphonites favor 1PO. Phosphinites and phosphites give high yields of phenoxyoctadienes. By varying *only* the ligand, any of three compounds can be the major product.

Mixtures of ligands give intermediate product distributions. Addition of triphenyl phosphite to tetrakis(triphenylphosphine)-nickel or triphenylphosphine to tetrakis(triphenyl phosphite)-nickel gave essentially the same product distribution.

Solvent.—Diethyl ether was generally used, but the reaction proceeded well in hydrocarbons or with no added solvent. Protonic solvents promote the formation of octatrienes. Halogenated solvents such as carbon tetrachloride or chloroform were unsatisfactory, possibly because of oxidation of the nickel(0) species. Traces of water inhibit this reaction and all reagents and reaction vessels must be dried.

Equilibration.—Heating solutions of either phenoxybutene in ether with catalytic amounts of tetrakis(triphenyl phosphite)-nickel establishes an equilibrium of 65% 1PB and 35% 3PB. Some leakage to the phenoxyoctadienes and butadiene dimers and phenol occurs, but the equilibrium could be established from both 1PB and 3PB. Equilibration was much slower than the addition reaction, requiring several days at 100° with 1 mol % catalyst. The phenoxybutenes are not equilibrated if butadiene is present, nor are phenoxyoctadienes formed. Attempts to equilibrate the phenoxyoctadienes gave only octatrienes and phenol.

Discussion

Figure 1 summarizes the mechanism postulated for the tetrakis(organophosphorus)nickel-catalyzed reaction of phenol with butadiene. The initial steps leading to complex **1** are probably identical with those postulated by Tolman in the nickel(0)-catalyzed addition of ethylene to butadiene.[2] The subsequent steps must differ because in Tolman's mechanism the nickel becomes bonded to the ethylene carbons carbons in the newly coupled product. The π-allyl complex **1** may react with phenoxide anion and lose phenoxybutene to reform the nickel(0) species. This intermediate can react in either of two ways to produce two interwoven catalytic cycles. Protonation continues the phenoxybutene reaction.

TABLE V
LIGAND EFFECTS ON PRODUCT DISTRIBUTION[a]

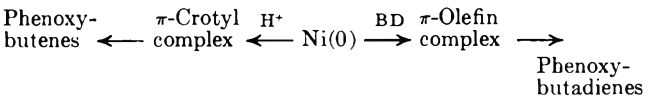
Phosphorus ligand $PR_1R_2R_3$			Catalyst	Yield, %			
R_1	R_2	R_3	cycles	3PB	1PB	3PO	1PO
OC_6H_5	OC_6H_5	OC_6H_5	74	10	12	18	60
C_6H_5	OC_6H_5	OC_6H_5	80	9	13	22	55
C_6H_5	C_6H_5	OC_6H_5	62	29	22	16	33
C_6H_5	C_6H_5	C_6H_5	36	71	9	7	12
C_6H_5	C_6H_5	OC_2H_5	45	27	46	8	19
C_6H_5	OC_2H_5	OC_2H_5	48	25	45	9	21
OC_2H_5	OC_2H_5	OC_2H_5	80	21	35	9	31
C_6H_5	C_6H_5	OCH_3	67	21	34	12	32
C_6H_5	OCH_3	OCH_3	51	47	28	8	18
C_6H_5	O-*n*-C_4H_9	O-*n*-C_4H_9	59	22	41	9	27
C_6H_5	O-*i*-C_3H_7	O-*i*-C_3H_7	54	23	41	10	26
$(O(4\text{-}OCH_3C_6H_4))_3$			66	9	17	21	52
CH_3	CH_3	CH_3	36	74	13	8	4
CH_3	OC_6H_5	OC_6H_5	34	44	39	4	13
C_2H_5	OC_6H_5	OC_6H_5	51	13	23	21	43

[a] 25 mmol of BD, 10 mmol of C_6H_5OH, 0.1 mmol of Ni, 0.4 mmol of ligand, ether solvent, 100°, 15 hr.

Alternatively, reaction with butadiene may begin a catalytic cycle leading to phenoxyoctadienes. The sequence of steps leading to Wilke intermediate 2 is straightforward.[3] At this point ring closure can give vinylcyclohexene or 1,5-cyclooctadiene. Protonation of the nickel followed by the transfer of the proton to the interior position of the allyl ligand leads to an intermediate analogous to 1. Elimination of a nickel hydride would form linear butadiene dimers.[3] The steps leading to the phenoxyoctadienes are now similar to those which convert 1 to phenoxybutenes.

Several observations suggest that the phenoxybutenes and phenoxyoctadienes are formed in separate, yet interrelated pathways. Both phenoxybutenes have methyl groups while neither of the phenoxyoctadienes has a methyl group, either terminal or internal. It is very difficult to conceive of a mechanism leading from π-allyl complex 1 to a product which does not contain a methyl group. The concentration of phenoxybutenes never declines during the reaction, though if the phenoxybutenes were intermediates in the formation of phenoxyoctadienes, their concentration would be expected to reach a maximum at some point. The phenoxybutenes do not react with butadiene under the reaction conditions to give phenoxyoctadienes.

Two competing reactions for a coordinatively unsaturated nickel(0) species are postulated to determine the course of the reaction.



The effects of the relative concentrations of phenol and butadiene are easily seen; the effects of reaction time and ligand are more subtle.

The equilibrium constant for the protonation of an organometallic complex depends on the protonating

$$H^+X^- + ML_n \rightleftharpoons H^+ML_nX^-$$

species, the metal, and its associated ligands. The equilibrium constant for the protonation of tetrakis(phosphorus)nickel(0) correlates with the CO stretching frequency of $Ni(CO)_3L$ and has the order $P(C_6H_5) > P(OC_2H_5)_3 > P(OC_6H_5)_3$.[8] Nickel is more basic than palladium,[9] which favors phenoxybutene formation. Initially a large proportion of the nickel may be protonated, thus forming phenoxybutenes. From the behavior of the product distributions with time the rate of the cycle producing phenoxyoctadienes appears to be faster than the cycle producing phenoxybutenes, though in the absence of data on the relative amounts of the various forms of nickel(0) actually present, absolute rate factors cannot be determined.

The π-allyl complex 1 has two ligands per nickel, while the Wilke intermediate 2 has only one. If the steps leading to 2 are reversible until the two butadienes are coupled, excess ligand would favor phenoxybutene formation.

Conclusion

Phenoxybutenes can be made the main product of the nickel(0)-catalyzed addition of phenol to butadiene by the use of excess phosphorus ligands, good electron-donor ligands, or a high ratio of phenol to butadiene. Phosphine ligands produce a high yield of 3-phenoxy-1-butene in a kinetically controlled process while phosphonites, phosphinites, and phosphites produce phenoxybutenes in proportions approaching thermodynamic equilibrium.

Registry No.—Nickel, 7440-02-0; phenol, 108-95-2; butadiene, 106-99-0; 3-phenoxy-1-butene, 22509-78-0; 1-phenoxy-3-butene, 2653-89-6; 3-phenoxy-1,7-octadiene, 15972-91-5; 1-phenoxy-2,7-octadiene, 13846-40-7.

Acknowledgments.—We wish to thank C. A. Tolman and G. W. Parshall for valuable discussions.

(8) C. A. Tolman, submitted for publication in *Inorg. Chem.*
(9) C. A. Tolman, W. C. Seidel, and D. H. Gerlach, *J. Amer. Chem. Soc.*, **94**, 2669 (1972).

Selenium Heterocycles. VI.[1] Mechanism of the Stereoselective Formation of 1,4-Diselenafulvenes from 1,2,3-Selenadiazoles and Base

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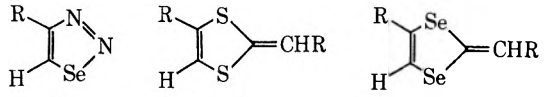
4-Substituted 1,2,3-selenadiazoles were found to react with base to form 2,ω-disubstituted 1,4-diselenafulvenes. The mechanism for the stereoselective formation of the product is discussed.

We have previously reported the synthesis of 1,2,3-selenadiazoles (I).[2] Light- and heat-induced decomposition of these new compounds produced substituted acetylenes[3] while the sulfur analog produced the dithiafulvene (II).[4] In an effort to obtain the selenium analog of II various basic reagents were examined. Good results were obtained with alcoholic solutions of potassium hydroxide or potassium ethoxide in ethanol or by the addition of potassium hydroxide pellets to ethanolic solutions of the selenadiazole. This resulted in an immediate effervesence of nitrogen gas and production of a new organoselenium compound (no reaction occurred when 5-substituted selenadiazoles were used). Elemental analysis and the mass spectra of these compounds were in agreement with a diselenafulvene structure (III). The nmr spectra of the more easily



I II III

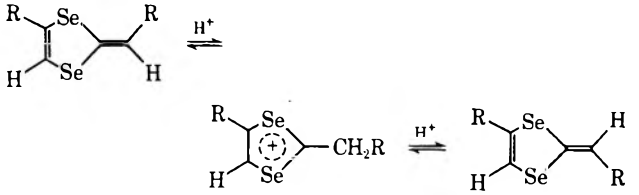
obtained fulvene from 4-aryl-1,2,3-selenadiazoles were unrevealing, since H_3 and H_ω of the ylidenes had signals in the aromatic region.

Useful spectra were obtained of the fulvenes formed from 4-alkyl derivatives such as 4-isopropylselenadiazole. Figure 1 shows the nmr spectrum of the diisopropyl-substituted derivative (III, R = isopropyl). The protons of the isopropyl groups are clearly resolved into two doublets at 1.10 ppm for the two different methyl groups and two septets for the two methine hydrogens at 2.00 and 2.66 ppm. In the low-field part of the spectrum two groups of hydrogens are observed, each integrating for one hydrogen. The signal at 6.46 ppm shows the characteristic ^{77}Se splitting pattern, with a coupling constant of 57 cps.[2] This is obviously due to the proton at position 3 in the ring, and appears to be a triplet (probably the result of the superposition of a double doublet). The signals at 5.60 ppm resolve into a doublet of doublets and a doublet. Integration shows the relative intensities of the doublet of doublets to the doublet signal to be 1:1. This spectrum can be rationalized by the presence of a mixture of two isomers. In one the two isopropyl groups are in the cis and in the other in the trans configuration. Possibly larger long-range coupling constants of the two olefinic protons in the trans configuration would result in the splitting of H_ω into a doublet and of H_3 into what appears to be a triplet.

Rapid and careful work-up of the reaction mixture resulted in a product which showed the nmr spectrum shown in Figure 2. The doublet of doublets at 5.60 ppm is reduced to a doublet and the triplet at 6.46 ppm appears now as a narrow doublet. Leaving the sample in the nmr tube for several hours resulted in the reappearance of the former spectrum (Figure 1). Clearly the product of rapid and careful work-up is a single isomer which on standing isomerizes into a mixture of the cis and the trans isomers. The rate of isomerization can be enhanced by the addition of a trace of an acid. It is noteworthy that the similar base-catalyzed dimerization of 4-phenyl-1,2,3-thiadiazole is reported to yield II (R = Ph).[5] In this series the initially obtained solid was converted to a higher melting material of the same composition on heating, a finding which was interpreted as the conversion of a cis–trans isomer mixture to the more stable isomer.[5] The possibility that the initially isolated substance was a pure isomer from a stereospecific reaction was not considered and no nmr evidence pertinent to this point was given.[6]

It appears that the isomerization happens as shown in Scheme I *via* the diselenolium ion IV. Evidence for

SCHEME I



IV

the existence of IV in solution was obtained from the nmr spectrum of the pure cis or the trans isomer of III (R = Ph) in trifluoroacetic acid. In this solvent a peak appears at 4.30 ppm for the methylene protons of IV integrating for two hydrogens relative to the aromatic region's 11 hydrogens at 7.10 ppm.

An equilibrium mixture of the *cis*- and *trans*-di-*tert*-butyl derivative of III (R = *tert*-butyl) could be

(1) Part V: A. Shafiee and I. Lalezari, *J. Heterocycl. Chem.*, **8**, 835 (1971).

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(3) I. Lalezari, A. Shafiee, and M. Yalpani, *Angew. Chem., Int. Ed. Engl.*, **9**, 464 (1970).

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(5) R. Raap and R. G. Micetich, *Can. J. Chem.*, **46**, 1057 (1968); R. Raap, *ibid.*, **46**, 2251 (1968).

(6) We have observed a definite stereoselectivity in the conversion of the thiadiazoles to the corresponding dithiafulvenes. These findings will be reported elsewhere.

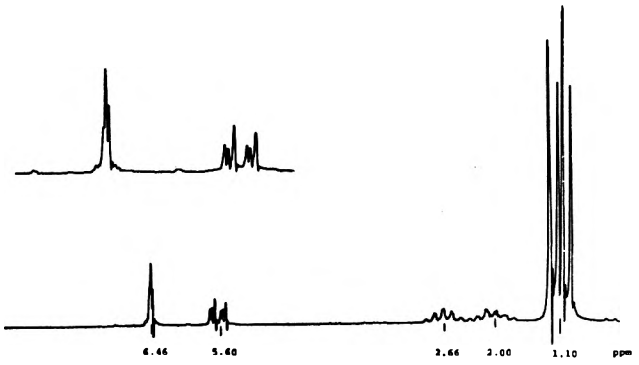


Figure 1.—Nmr spectrum of a mixture of *cis*- and *trans*-2,ω-diisopropyl-1,4-diselenafulvenes.

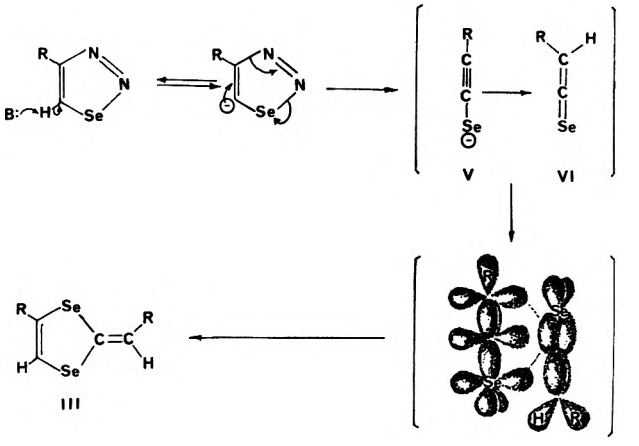
crystallized from acetone to yield one of the isomers in pure form leaving an equilibrium mixture in the mother liquor. Repeated crystallizations from the mother liquor nearly completely converted the material into the one isomer.

In analogy with the base-catalyzed decomposition of 1,2,3-thiadiazoles, the intermediate V could be obtained as an insoluble potassium salt when the reaction was carried out in dioxane using alcoholic potassium ethoxide as a base. This salt showed an acetylenic band at 2200 cm^{-1} in the ir and an ultraviolet band at 308 nm. Dissolving this salt in 95% alcohol converted it slowly but quantitatively into the same pure isomer of III that would be formed directly from the selenadiazole.

The factor that controls this stereoselectivity in an apparently symmetrical intermediate is probably the steric hindrance of a relatively bulky R group on the selenaketene. This could lead to a preferred approach of the selenaketene from the hydrogen side. Consistent with this mechanism, when a smaller R group, such as methyl, was used, no matter how carefully the work-up was carried out, the product was always a mixture of the two isomers.

Scheme II shows a mechanism which would account for the products obtained. Evidence for the first step

SCHEME II



in this mechanism has been obtained in the exchange of deuterium for protium in a sample of I (5-deuterio, R = Ph) in dilute alcoholic potassium hydroxide solution. The exchange was observed to take place faster than the ring cleavage.[7] The ring scission I to V

(7) M. H. Ghandehari, D. Davallian, S. G. Shirazi, H. Partovi, and M. Yalpani, unpublished results.

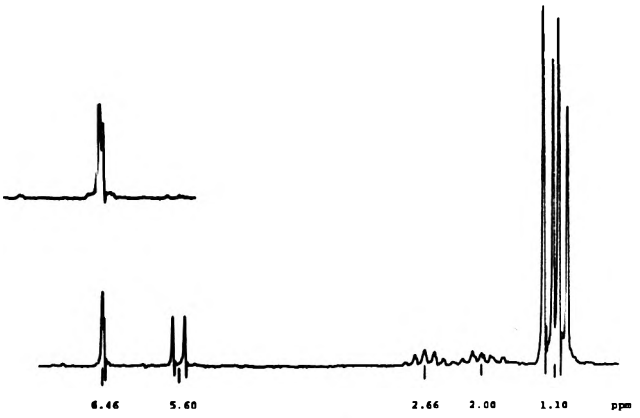


Figure 2.—Nmr spectrum of *cis*-2,ω-diisopropyl-1,4-diselenafulvene.

cannot therefore be a concerted reaction starting with the elimination of a proton by base and the C_5 carbanion species must be a discrete intermediate. The scheme also indicates that the isomer initially formed is in the cis configuration. The larger H_3–H_ω long-range coupling constants observed for the products after isomerization (see Figure 1) is in agreement with the trans configuration for the second isomer.

The initial formation of the cis isomer from the intermediate selenaketene VI is interesting because it indicates the presence of a pure C–Se double bond the π orbitals of which require a particular geometry of approach in a concerted 1,3-dipolar addition to the ethynylselenolate ion V. As indicated in Scheme II, in the transition state the approach of the selenolate ion to the selenaketene must be in the plane of the ketene substituents as well as that of the π orbitals of the C–Se double bond. This constitutes a sterically unfavorable approach relative to that of an approach 90° out of that same plane. The latter experiences the least effect of the substituents but would require orbital rearrangement subsequent to the initial Se–C bond formation, and would lead to the formation of a mixture of both geometric isomers, which was not observed. In Woodward–Hoffmann terminology the reaction is thus probably best interpreted as a symmetry-allowed one-step ($_\pi4_s + _\pi2_s$) cycloaddition of class C,[8] a category exemplified previously by most 1,3-dipolar cycloadditions. Examples of class C [4 + 2] cycloadditions of simple allyl anions have also been reported recently.[9]

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Nmr spectra were determined using Varian A-60A and T-60 spectrometers. Infrared spectra were obtained from a Leitz Model III. Mass spectra were run on a Varian Model MAT CH5 instrument.

General Procedure for the Preparation of 1,4-Diselenafulvenes. Method A.—The selenadiazole[2] (0.1 g) was dissolved in about 3 ml of 95% ethanol and a KOH pellet was added. In most cases the evolution of N_2 gas on the surface of KOH usually commenced immediately. Heating increased the rate of the reaction. The 4-aryl derivatives, which are solids, usually crystallized in pure form out of solution at the end of the reaction and could be recrystallized from alcohol. The aliphatic derivatives are liquids and were purified by preparative tlc on silica gel using

(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 87.

(9) T. Kauffmann and E. Koeppelmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 291 (1972).

chloroform or less polar solvents. Chromatographic purification always lead to the formation of the two geometrical isomers.

Method B.—The selenadiazole was dissolved in 10% KOH or potassium ethoxide in ethanol. The reaction product was purified as described in method A.

2,ω-Di-*tert*-butyl-1,4-diselenafulvene.—4-*tert*-Butyl-1,2,3-selenadiazole (0.5 g, 2.6 mmol) was dissolved in 10 ml of 95% ethanol and a pellet of KOH was added. After the gas evolution had ceased water was added and extracted with chloroform. The chloroform layer after drying was evaporated to yield 0.3 g (72%) of an oil: nmr (CCl_4) 6.45 (s, 1 H), 5.90 (s, 1 H), 1.20 (s, 9 H), 1.10 (s, 9 H); upon standing for some times 6.45 (s, 0.5 H), 6.44 (d, J = 1.5 Hz, 0.5 H), 5.97 (d, J = 1.5 Hz, 0.5 H) 5.90 (s, 0.5 H), 1.29 (two lines, 9 H), 1.10 (two lines, 9 H). Repeated recrystallization from acetone gave a product: mp 78–80° (*Anal.* Calcd for $C_{12}H_{20}Se_2$: C, 44.72; H, 6.21. Found: C, 44.81; H, 6.02.); nmr (CCl_4) 6.44 (d, J = 1.5 Hz, 1 H) 5.97 (d, J = 1.5 Hz, 1 H), 1.21 (s, 9 H) 1.10 (s, 9 H); mol wt (mass spectrum) m/e 324.

2,ω-Diphenyl-1,4-diselenafulvene.—4-Phenyl-1,2,3-selenadiazole (2.2 g, 0.01 mol) was dissolved in about 15 ml of ethanol, and a few pellets of KOH were added. Upon heating the solution slightly, gas evolution commenced. Yellowish crystals began to separate when gas evolution ceased. These crystals, ir (KBr) 912 (w), 900 (w), 890 (m), 821 (w), 846 (w), 840 (m), 835 (s), 692 (m), 512 cm^{-1} (m) (yield 1.5 g, 90%; another 0.1 g of material could be obtained from the mother liquor by trituration with water), had mp 139–140° and upon cooling and reheating melted at 219–220°: ir (KBr) 890 (m), 832 (m), 820 (m), 735 (s), 682 (s), 510 cm^{-1} (s); uv (EtOH) 340 nm (ϵ 1.8 × 10^4) (*Anal.* Calcd for $C_{16}H_{12}Se_2$: C, 53.04; H, 3.32. Found: C, 52.85; H, 3.06.); mol wt (mass spectrum) m/e 364.

2,ω-Diisopropyl-1,4-diselenafulvene.—4-Isopropyl-1,2,3-selenadiazole (1.0 g, 5.7 mmol) was dissolved in 10 ml of 95% ethanol, and a few pellets of KOH were added. After gas evolution had ceased, water was added and the solution was extracted with chloroform. From the chloroform extracts 0.6 g (79%) of an oil was isolated. The oil was purified on silica gel plates using petroleum ether as solvent, nmr shown in Figure 1, mol wt (mass spectrum) m/e 296. The nmr of the oil without purification on silica gel and obtained immediately after the reaction is shown in Figure 2.

Potassium 2-Phenylethyneselenolate.—4-Phenyl-1,2,3-selenadiazole (0.5 g, 2.4 mmol) was added to a solution of 50 mmol of potassium ethoxide in 50 ml of dioxane containing 2 ml of ethanol. After the gas evolution had ceased the precipitate was filtered under a dry atmosphere and washed with dry ether to give the white potassium salt, ir (KBr) 2200 cm^{-1}, uv (EtOH) 308 mm (ϵ 2.1 × 10^4). This salt, which was always formed contaminated with, apparently, some potassium ethoxide (the weight of material isolated was always more than the theoretically calculated amount and the percentage of potassium in the sample was variable, but always in excess of that calculated) rapidly turned yellow on standing in moist air. Dissolution of this salt in 10 ml of ethanol gave 0.42 g (99% based on 4-phenyl-1,2,3-selenadiazole) of III, mp 139–140°.

Registry No.—*cis*-III (R = Bu), 36912-13-7; *trans*-III (R = Bu), 36912-17-1; *cis*-III (R = Ph), 36912-14-8; *trans*-III (R = Ph), 36912-18-2; *cis*-III (R = *i*-Pr), 36912-15-9; *trans*-III (R = *i*-Pr), 36912-16-0; potassium 2-phenylethyneselenolate, 36928-61-7; 1,2,3-selenadiazole, 26223-16-5.

Sensitized Photolyses of DDT and Decyl Bromide

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The photolysis of alkyl halides can be sensitized by aromatic amines in oxygenated or degassed solutions. The photoproducts from irradiation of diethylaniline in the presence of decyl bromide in cyclohexane are decane (22.7%), *N*-ethylaniline (3.6%), *o*-decyl-*N*,*N*-diethylaniline (48.5%), *p*-decyl-*N*,*N*-diethylaniline (30.8%), and diethylaniline hydrobromide (88%). Similar yields are formed in solvents methanol, dimethylformamide, and benzene and the quantum yields for decyl bromide disappearance are similar to the value of 0.19 found for methanol solution. This photolysis is not quenched by oxygen or piperylene and decyl bromide photolysis is not sensitized by benzophenone. This implicates the excited singlet state of diethylaniline as the first reactive intermediate. A mechanism involving decyl radicals is proposed. Diethylaniline also sensitizes DDT degradation. In aerated methanol the following photoproducts are formed: DDD, DDE, DDCO, diethylaniline hydrochloride, methyl 1,1-bis(*p*-chlorophenyl)acetate, *cis*- and *trans*-1,1,4,4-tetrakis(*p*-chlorophenyl)-2,3-dichloro-2-butene, 1,1-bis(*p*-chlorophenyl)-2-(*p*-diethylaminophenyl)-2-methoxyethylene, and 1,1-bis(*p*-chlorophenyl)-2,2-bis(*p*-diethylaminophenyl)ethylene. Mechanistic hypotheses involving the 2,2-bis(*p*-chlorophenyl)-1,1-dichloromethyl radical are given. It is shown that in degassed solutions of DDT in ethanol or cyclohexane a radical chain reaction is initiated by 310-nm light which efficiently converts DDT to DDD. This reaction can be inhibited by dibutyl sulfide or hexyl mercaptan, and is quenched by oxygen. Oxygen quenching may explain the inefficiency of DDT degradation by sunlight.

It has been observed that aromatic amines can induce the photodecomposition of alkyl halides.[1-4] It seemed that this process might be applicable to halogenated pesticide degradation. We have, therefore, initiated a study of pesticide photolyses with particular attention to sensitization. It was hoped that new designs for degradable pesticides[5] and information about natural degradation pathways would result.

This paper reports results which enucleate this problem. Thus we have explored the feasibility of degrading the persistent pesticide DDT with several photosensitizers both under air and under nitrogen and we have studied the photolysis of a simple alkyl halide in order to gain more mechanistic insight into the processes available to halogenated pesticides.

The photosensitization of pesticide degradation has not escaped attention by other chemists. Casida and Ivie[6] placed mixtures of known photosensitizers and pesticides on silica gel and found that several pesticides, including halogenated compounds, were degraded in sunlight. They also investigated the solar decomposition of chlorinated pesticides on bean leaves as accelerated by rotenone, triphenylamine, and other insecticides.

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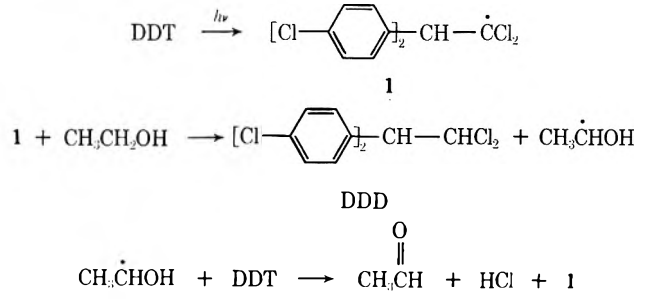
(5) H. J. Liu, P. J. Silk, and J. Unger, *Can. J. Chem.*, **50**, 55 (1972).
(6) G. W. Ivie and J. E. Casida, *Science*, **167**, 1620 (1970); G. W. Ivie and J. E. Casida, *J. Agr. Food Chem.*, **19**, 405 410 (1971).

The sensitized photodecomposition of chlorinated cyclodienes has received considerable attention.[7-10] The reaction can be sensitized by transfer of triplet energy and results primarily in photoisomerization. Other chlorinated pesticides which have been decomposed by photosensitization include 2,4-dichlorophenol.[11]

The direct photolysis of DDT at 254 nm has been studied by several groups.[12-14] An extensive elucidation of the products formed during irradiation in oxygenated methanol has been performed by Plimmer and coworkers.[14] Some 17 products were identified, most of which directly involved trapping of radical intermediates by oxygen. A mechanistic rationale for several of these products was advanced which involved initial cleavage of a carbon–chlorine bond. This scheme followed an earlier mechanism suggested[13] for the formation of DDD, DDE, and 4,4′-dichlorobenzophenone (DDCO) from DDT during photolysis at 254 nm. In that study radical scavenging results were obtained which indicated the unimportance of chain processes during photolysis in hexane and the precursorial role of radical 1 to DDD. These schemes are, however, largely speculative and the photophysical chemistry involved has not received attention.

Results and Discussion

DDT Photochemistry.—The photolysis of DDT at 310 nm in a nitrogen atmosphere affords only DDD and HCl. The reaction in either ethanol or cyclohexane seems to involve a radical chain mechanism. This



mechanism was suggested by Sherman[15] for γ radiations of DDT in alcohol and is similar to photoinitiated chain reactions between amines and carbon tetrachloride.[16] Addition of hexyl mercaptan (5×10^{-3} M) to an irradiation of 10^{-3} M DDT in ethanol slowed the rate by about a factor of 10. DDD was still the product. This behavior has been taken as evidence for inhibition of a DDT–alcohol chain reaction[15] *via* the following chain transfer and termination steps.

$$1 + RSH \longrightarrow DDD + RS\cdot$$

$$2RS\cdot \longrightarrow RSSR$$

It seems likely that this is also involved here, since the above chain reaction explains the stability of DDD. In contrast to DDT, reaction of ethanol radicals with DDD should not give chlorine atom transfer, but instead hydrogen atom transfer in analogy with chloroform, if it reacts at all. Thus, DDD is not dechlo-

$$DDD + CH_3\dot{C}HOH \longrightarrow 1 + CH_3CH_2OH$$

rinated. There is, however, an additional inhibition mechanism open to hexyl mercaptan, since sulfur compounds can quench excited states.[17] We found DDT photolysis to be slowed by a factor of about 3 by addition of 10^{-3} M dibutyl sulfide. This sulfide is not a good radical scavenger and demonstrates the duality of quenching mechanisms. This study has reconfirmed that such drastic mercaptan inhibitory effects are not noted if DDT is photolyzed in hexane[13] or in ethanol at 254 nm. There is apparently more direct photolysis occurring under these conditions and the products are more complex.[13,14]

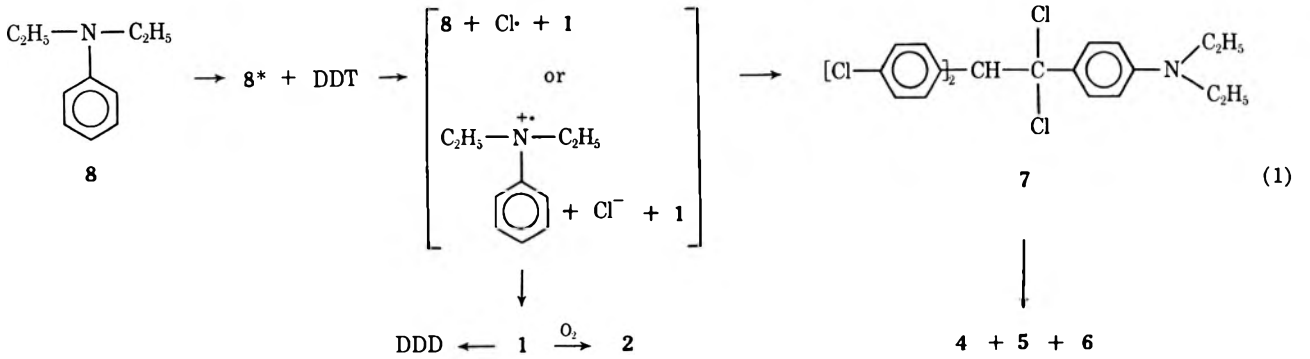
We find that, while photolysis at 310 nm is quenched by oxygen or by 5×10^{-2} M piperylene, photolysis at 254 nm is not quenched by oxygen.[14] This again indicates the wavelength dependence of DDT photochemistry. There are two bands in the absorption spectrum of DDT and it appears that photolysis at 254 nm involves a singlet after excitation in the band λ_{max} 256 nm while 310-nm photolysis yields a triplet after excitation in the band λ_{max} 270 nm.

Quenching of solar wavelength photochemistry by oxygen is an important discovery, since it may explain the long lifetime of DDT in the environment. DDT absorbs solar light and is photoreactive, but the reaction can be quenched by atmospheric oxygen.

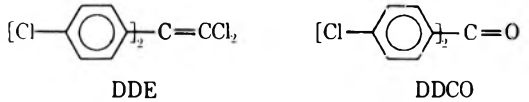
DDT–Diethylaniline Photochemistry.—An initial goal of this research was to sensitize DDT photolysis in air with light of solar wavelengths. Unfortunately, sensitization by triplet energy transfer is generally ineffective in the presence of oxygen and indeed benzophenone does not effect DDT decomposition in undegassed samples. It has been found, however, that a variety of aromatic amines are effective sensitizers in air for alkyl halides including DDT.[1] The reaction of DDT and diethylaniline at 310 nm in methanol was chosen for more careful investigation. This reaction in air has a quantum yield of 0.30 at conversions of 5–15%. Longer irradiation times will destroy more than 85% of the DDT but the rate slows down. This may be related to the fact that the absorptivity of the reaction mixture at 310 nm is essentially invariant during the reaction. Diethylaniline is being consumed, but the products absorb at this wavelength and may account for the apparent quantum yield decrease with time.

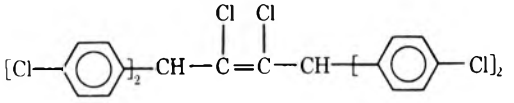
The following decomposition products from an 8-hr, 310-nm irradiation of DDT (12 g) and diethylaniline (12 g) in 500 ml of methanol were identified by glc retention times and mass spectra or by chromatographic separation and spectral characterization: DDD, DDE, DDCO, diethylaniline hydrochloride, methyl 1,1-

(7) W. R. Benson, *et al.*, *J. Agr. Food Chem.*, **19**, 857 (1971).
(8) L. Vollner, W. Klein, and F. Korte, *Tetrahedron*, **34**, 2967 (1969).
(9) R. C. Cookson and E. Crundwell, *Chem. Ind. (London)*, 1004 (1958).
(10) J. D. Rosen, D. J. Sutherland, and G. R. Lipton, *Bull. Environ. Contam. Toxicol.*, **1**, 133 (1966); J. D. Rosen, D. J. Sutherland, and M. A. Q. Khan, *J. Agr. Food Chem.*, **17**, 404 (1969); J. D. Rosen and D. J. Sutherland, *Bull. Environ. Contam. Toxicol.*, **2**, 1 (1967).
(11) D. G. Crosby and M.-Y. Li, "Degradation of Herbicides," P. C. Kearney and D. D. Kaufman, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 12; J. R. Plimmer, *Science*, **174**, 407 (1971).
(12) E. E. Fleck, *J. Amer. Chem. Soc.*, **71**, 1034 (1949).
(13) A. R. Mosier, W. D. Guenzi, and L. L. Miller, *Science*, **164**, 1083 (1969).
(14) J. R. Plimmer, U. I. Klingebiel, and B. E. Hummer, *ibid.*, **167**, 67 (1970).
(15) R. Evans, E. Nesyto, C. Radlowski, and W. V. Sherman, *J. Phys. Chem.*, **75**, 2762 (1971).
(16) W. J. Lautenberger, E. N. Jones, and J. G. Miller, *J. Amer. Chem. Soc.*, **90**, 1110 (1968).
(17) J. Guttenplan and S. G. Cohen, *Chem. Commun.*, 247 (1969).



bis(*p*-chlorophenyl)acetate (**2**), *cis*- and *trans*-1,1,4,4-tetrakis(*p*-chlorophenyl)-2,3-dichloro-2-butene (**3**), α,α-bis(*p*-chlorophenyl)-*p*-diethylaminoacetophenone (**4**), 1,1-bis(*p*-chlorophenyl)-2-(*p*-diethylaminophenyl)-2-methoxyethylene (**5**), and 1,1-bis(*p*-chlorophenyl)-2,2-bis(*p*-diethylaminophenyl)ethylene (**6**).





cis- and *trans*-**3**

DDE, DDD, and ester **2** are the products present in highest analyzable yield, since separation of the other components is extremely tedious. A combination of glc and nmr analysis of an unchromatographed product mixture indicated the yields in Table I based

TABLE I
PRODUCT YIELDS[a] FROM DIETHYLANILINE–DDT PHOTOLYSIS IN METHANOL

Time, hr	% DDT consumed	% DDD	% DDE	% **2**
0.5	22	5	2	3
1	37	6	5	6
2	54	6	9	9
7	72	6	8	23

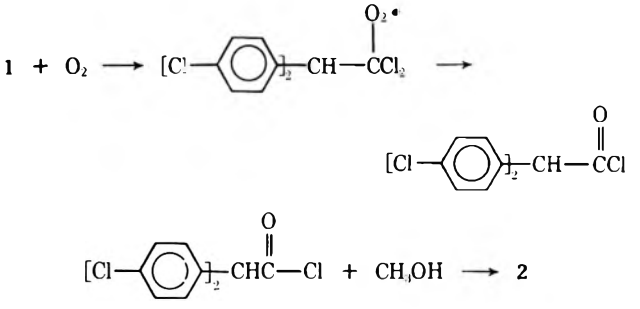
[a] Yields based on the initial amount of DDT; 0.32 mmol of DDT and 0.64 mmol of diethylaniline in 4 ml of methanol were irradiated in each of four tubes.

on the initial amount of DDT. Considering the other products recovered, about 70% of the reacted DDT is accounted for. DDD and DDE are not stable to the reaction conditions, as demonstrated by independent photolyses in the presence of diethylaniline. Therefore, they do not build up during the reaction.

Two dimeric compounds were isolated. One of these, mp 235°, had the same properties as a compound formed in the direct photolysis of DDT at 254 nm.[13] An isomeric compound, mp 278°, with an essentially similar mass spectrum was also isolated. These products are *cis*- and *trans*-**3**.

Only limited mechanistic conclusions can be drawn about this process because of the complexity of the reaction products and the unelucidated role of oxygen and chain reactions. It is suggested that since the reaction proceeds in air and is not quenched by piperylene (10^{-2} *M*), an excited singlet diethylaniline (**8***) is involved. **8*** can produce **1** by reaction with DDT and this radical can then lead to the observed products *via* hydrogen abstraction, disproportionation, reaction with oxygen, or coupling (eq 1).

Transformation of **1** into DDD, DDE, and DDCO may involve previously proposed pathways.[13] The formation of ester **2** seems to involve oxygen and methanol and may be related to the chemistry observed in the irradiation of aromatic amines and chloroform in air.[3,18] Electron transfer was invoked in this reaction followed by trapping of dichloromethyl radicals by oxygen to produce phosgene. The analog for DDT would be



If peroxy radicals are involved, the complexity of the reaction is necessarily increased, since these radicals can in turn produce alkyl and alkoxy radicals, initiate chain reactions, and dimerize.

Three products involve coupling between diethylaniline and DDT in analogy with results found for the simple alkyl halide, decyl bromide. These may arise *via* dihalide **7**, which will be extremely labile. Photochemically it could lead to substitution of a second diethylaniline moiety, thus compound **6**, or to **4** by reaction with oxygen. The diethylaniline function in **7** also activates the halides toward chemical reaction[19] and **5** could be formed by methanolysis.

It is important to iterate that the reaction of aromatic amines with DDT is not quenched by oxygen and could provide interesting environmental chemistry. This reaction is general for organic halides and should, therefore, be applicable to a variety of pesticides. It has been shown, for example, that triphenylamine sensitizes degradation of Dieldrin and Aldrin in air.[20]

Sensitized DDT Photolysis in Degassed Solution.—

(18) See K. Thomas, C. Huybrechts, and J. Olbregts, *Trans. Faraday Soc.*, **63**, 1647 (1967), and A. T. Chapman, *J. Amer. Chem. Soc*, **54**, 3852 (1932), for photolytic mechanisms of acyl chloride formation from oxygen and trichloromethyl groups.

(19) S. Patai, Ed., "The Chemistry of the Carbonyl Group," Wiley, New York, N. Y., 1966, p 182.

(20) Unpublished work in these laboratories by Mr. Thomas Rogers.

Sensitization of DDT photolysis is extremely interesting. We find that in degassed solution triplet sensitizers with $E_T \geq 59$ kcal/mol effectively sensitize the decomposition of DDT to DDD, while those with $E_T \leq 53$ kcal/mol do not. The sensitizers used were benzophenone, diethylaniline, phenanthrene, 2-acetonaphthone, pyrene, biphenyl, fluoren-9-one, and 7*H*-benz[*d*,*e*]anthracen-7-one. In each case the reaction was run with 10^{-3} *M* DDT in *degassed* ethanol at either 350 or 310 nm and the sensitizer absorbed >95% of the light. The same results were obtained in cyclohexane solvent. These data are characteristic of triplet energy transfer. It seems likely that sensitization initiates a chain reaction and that the initiation step could involve an acceptor with $E_T \cong 56$ kcal/mol. A problem with this interpretation is that DDT should not have a triplet with that low an energy and, if it did, it should not decompose to give radical **1**. The carbon–chlorine bond energy is about 70 kcal/mol and, if only 56 kcal/mol are available from the sensitizer, the reaction requires too much extra thermal energy to be effective from a short-lived excited state. More important is the fact that the phosphorescence spectrum of DDT[21] indicates a triplet with $E_T \cong 70$ kcal/mol. This is exactly what is expected from a *p*-chlorotoluene moiety and the carbon trichloride group is expected to be even higher in energy, since benzophenone triplets are not quenched by carbon tetrachloride. Involvement of a DDE impurity was suspected, but DDE photolysis is not sensitized by benzophenone and addition of a little DDE to DDT does not change the reaction rate. A direct generation of radicals from attack on solvent seems improbable, since phenanthrene is an effective sensitizer even in cyclohexane. Singlet energy transfer is also ruled out since it is endothermic for almost all the sensitizers used. Attempted purification of the DDT by recrystallization or zone refining did not change the behavior at all. The nature of initiation by triplet sensitizers, therefore, remains obscure.

Casida and Ivie[6] have previously evaluated the feasibility of sensitizing pesticide photolyses on silica gel tlc plates. It was found that DDT was effectively sensitized by triphenylamine and carbazole and less efficiently sensitized by dibenzothiophene, fluorene, anthraquinone, stilbene, and pyrene. Many other sensitizers, including benzophenone, were ineffective. Comparison of these results with those in solution or on bean leaves[6] indicates that the tlc plate technique is not very informative. It seems likely that the photochemistry of the *adsorbed* sensitizers is important in the latter.

Sensitized Decyl Bromide Photolysis.—In order to demonstrate the generality of the photoreaction between aromatic amines and organic halides, several simple halides were decomposed by diethylaniline and 310-nm light in undegassed solutions. Several examples were cited previously[1] and we have shown that *n*-butyl bromide, chloride, and iodide, as well as *tert*-butyl bromide, are destroyed under these conditions. The photoproducts from decyl bromide (**9**) and diethylaniline at 310 nm were investigated as a model system. Most runs were made in closed but not degassed tubes. Glc revealed that a very similar product mixture resulted in solvent methanol, dimethylformamide, benzene, or cyclohexane (Table II). The presence of air or triethylamine also had little effect. The samples were stable in the dark and the individual components did not photolyze alone. Decane (**10**), *N*-ethylaniline (**11**), *o*-decyl-*N*,*N*-diethylaniline (**12**), and *p*-decyl-*N*,*N*-diethylaniline (**13**) were measured by glc. Hydrogen bromide was measured as diethylaniline hydrobromide (**14**). Decane and *N*-ethylaniline were identified by glc retention times and mass spectra. *o*- and *p*-decyl-*N*,*N*-diethylaniline were collected by glc and identified spectrally. Also *p*-decyl-*N*,*N*-diethylaniline was independently synthesized for comparison. The differences in the nmr spectra of these isomers were considered as evidence for their structure. In the ortho isomer the diethylamine group is twisted out of the plane of the ring, causing the aromatic proton signal to collapse to a singlet[22] and the quartet due to the methylene protons to be deshielded.[23]

TABLE II

PRODUCTS OF PHOTOLYSIS OF DECYL BROMIDE AND DIETHYLANILINE

	Product yields,[a] %				
Solvent	**10**	**11**	**12**	**13**	**14**
Methanol[b]	8.7	1.8	51.0	33.4	63
Dimethylformamide	13.5	2.7	56.8	28.2	69
Benzene	15.0	2.5	49.2	30.6	83
Cyclohexane	21.7	3.6	48.5	30.8	88

[a] Yields based on decyl bromide consumed after 36 hr of photolysis. The original solution was 0.345 *M* in decyl bromide and 0.725 *M* in *N*,*N*-diethylaniline. This photolysis in DMF consumed 40% of the decyl bromide. [b] Triethylamine (0.65 *M*) or degassing by freeze–thaw did not significantly change these yields.

One mechanism which accommodates the above products is indicated in eq 2. The diethylaniline, **8**, absorbs all the light at 310 nm indicating an excited state of **8** is involved. Any ground state complexing between **8** and **9** should be weak and, indeed, uv spectrometry shows no evidence for a complex when decyl bromide is added to diethylaniline. The reactive excited state of **8** seems to be a singlet.[19,24] The obvious alternative pathway *via* the triplet is eliminated because the reaction of 10^{-3} *M* decyl bromide in degassed benzene is not quenched by 10^{-2} *M* piperylene nor by oxygen and is not sensitized by benzophenone. The latter is not surprising, since the alkyl bromide excited state energies should be high.

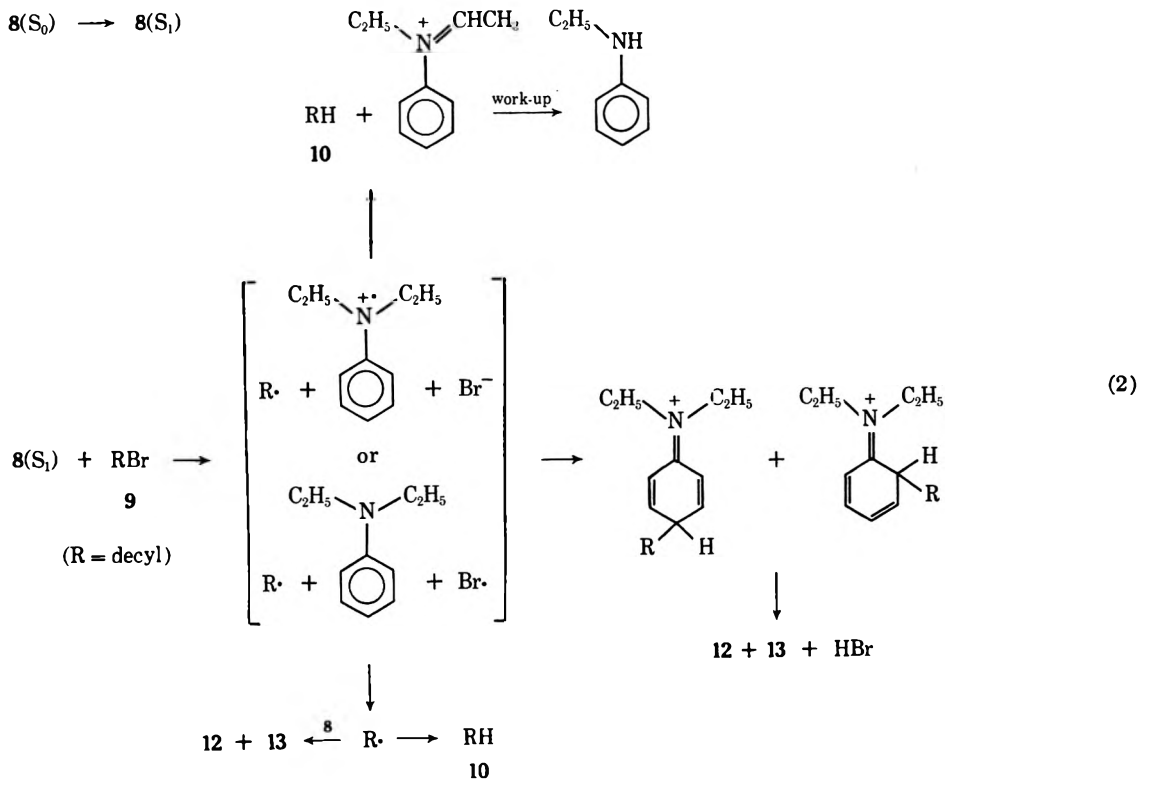
The products are easily rationalized in terms of this mechanism. Thus, decane seems diagnostic for decyl radicals. Coupling between decyl radicals and diethylaniline cation radicals explains the formation of products **12** and **13** and especially accounts for the preferred formation of the ortho, para isomers. Attack on neutral diethylaniline by decyl radicals should not be nearly so selective. It seems that an initial

(21) H. A. Moye and J. D. Winefordner, *J. Agr. Food Chem.*, **13**, 516 (1965); emission spectra were also recorded by Dr. C. M. O'Donnell with careful attention to the undetected possibility of a long-wavelength component. The band is, however, extremely broad in comparison to that of *p*-chlorotoluene or chlorobenzene and extends into the region where a 56 kcal/mol triplet would be observed.

(22) W. F. Reynolds and T. Schaefer, *Can. J. Chem.*, **41**, 2339 (1963).

(23) L. Yamaguchi and S. Brownstein, *J. Phys. Chem.*, **67**, 525 (1963).

(24) Other electron transfers *via* excited singlets have been demonstrated. See, for examples, W. Ware and H. P. Richter, *J. Chem. Phys.*, **48**, 1595 (1968); H. Leonhardt and A. Weller, *Ber. Bunsenges. Phys. Chem.*, **67**, 791 (1963); G. R. Seely, *J. Phys. Chem.*, **69**, 2779 (1965).



(2)

complex between $8(S_1)$ and **9** must primarily collapse to form **12** and **13** and perhaps **10** before dissociation in order to account for the high yields of coupled products. Free decyl radicals will be rapidly scavenged by oxygen or solvent in competition with coupling. The nature of the initial complex is not known, but is presumed to be similar to that described in similar reactions[25,26] which have been studied by emission spectroscopy and quantitative quenching experiments. The photolysis of mixtures of dimethylaniline and chlorobenzene,[25] for example, produces emission from a species containing both reactants, as well as photoproducts suggestive of charge transfer.

Solvent effects on photoreactions involving electron transfer are of considerable current interest.[27,28] In the present case, the quantum yield for decyl bromide disappearance is rather insensitive to solvent polarity. The relative rates are, cyclohexane, 1.0; benzene, 1.5; methanol, 1.5; dimethylformamide, 1.8. This is perhaps unexpected if the complex involves charge transfer, but, since the singlet may react at near diffusion controlled rates, and because we are measuring the overall quantum yield, the rate data may be irrelevant to mechanistic conclusions without further information.

Since a chain reaction was implicated in some of the DDT chemistry, we have checked this possibility for the reaction between **8** and **9** in methanol. Addition of butyl mercaptan to this photolysis mixture did not substantially change the quantum yield for decyl bromide disappearance of 0.19. It did, however, increase the yield of decane by several per cent. This rules out a chain mechanism, since the radical scavenger would have slowed the overall reaction rate. The difference between the decyl bromide and DDT reactions lies in two factors. One is the relative instability of decyl radicals compared to DDT radical, **1**. The latter is readily formed from DDT and can propagate chain reactions in suitable media. Other differences are due to the aromatic moiety of DDT, which provides a chromophore for direct photolysis and quenchable excited states.

(25) T. Tosa, C. Pac, and H. Sakurai, *Tetrahedron Lett.*, 3635 (1969).
(26) M. T. McCall, G. S. Hammond, O. Yonemitsu, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 6992 (1970).
(27) S. G. Cohen and A. D. Litt, *Tetrahedron Lett.*, 837 (1970).
(28) P. J. Wagner and A. E. Kemppainen, *J. Amer. Chem. Soc.*, **91**, 3086 (1969).

Experimental Section

Materials.—DDT was 99%+ 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane. Some of this material was also purified by recrystallization and some was zone refined without changing the observed chemistry. Methanol, ethanol, benzene, dimethylformamide, and cyclohexane were reagent grade materials used without purification. Diethylaniline was purified by distillation under nitrogen. Triplet sensitizers were from the J. T. Baker kit and were not purified.

Photolyses.—A Rayonet reactor equipped with a bank of 16 254-, 310-, or 350-nm lamps was employed. Except for one large-scale reaction run in a flask and 254-nm photolyses, the samples were held in Pyrex tubes in a merry-go-round apparatus. Degassing was accomplished by a 5 min nitrogen flush or by five freeze–thaw cycles at 0.005 mm.

Glc Analysis.—A F & M Hewlett-Packard Model 5750 gas chromatograph equipped with a flame ionization detector was used. Other samples in which DDD was the major (>90%) product were assayed on a Bendix Model 2110 chromatograph with an electron capture detector. The column employed there was Teflon-lined aluminum tubing, 6 ft × 0.25 in., packed with 5% OV-1 on Chromosorb W (60/80 mesh).

Photolysis of DDT.—DDT (70.9 mg, 0.005 mmol) in EtOH (200 ml) was irradiated in capped Pyrex tubes (5-ml aliquots). Degassing of samples consisted of a 5-min nitrogen flush or five freeze–thaw cycles at 0.005 mm. Oxygen gas was bubbled through the samples for 5 min before irradiation in the oxygen quenching experiments. In sensitizer experiments the sensitizer concentration was controlled so as to absorb >95% of the irradiation. Glc analysis at 175°, was accomplished by comparing retention times with those of authentic samples.

Photoproducts from DDT and Diethylaniline.—DDT (12 g, 33.9 mmol) and diethylaniline (12 g, 80.5 mmol) in methanol (500 ml) were irradiated in Pyrex tubes using a merry-go-round

for 8 hr. Concentration of the reaction mixture and chromatography on a silica gel column (400 g) was performed, and 1-l. to 1500-ml fractions were collected with the following solvents: fraction A and B with Skellysolve H (SSH), C with CCl_4–SSH (1:1), D with CCl_4, E with CCl_4–benzene (1:1), F with benzene, G with $CHCl_3$, and H with $CHCl_3$ and methanol (9:1). These fractions were concentrated on a rotary evaporator at 40–70°, transferred to 10-ml vials with acetone, and kept at 5° until further analysis.

Fraction A.—Glc analysis on column 1, a 6 ft × 0.25 in. glass column packed with 10% DC-200 and 15% QF-1 on Chromosorb W (60/80 mesh), at 228°, showed three major peaks with retention times identical with those of authentic samples of DDE, DDD, and DDT.

Fraction B.—When acetone was added to the concentrate of fraction B, a white solid separated and was filtered. Glc analysis of the filtrate showed the presence of DDT, DDD, and DDE, while the white solid would not elute from column 1. It was recrystallized from benzene and dried. Its nmr spectrum was identical with one reported by Mosier[13] for one isomer of **3** and showed a singlet at δ 6 (1 H) and an AA'BB' multiplet at 7.25 (8 H). The mass spectrum showed a molecular ion of *m/e* 564 (abundance 2.3%) with M, M + 2, M + 4, M + 6, and M + 8 peaks in the ratio 1.0:1.86:1.61:0.74:0.17, indicating the presence of six chlorine atoms. Other prominent ions were *m/e* 235 (100), with M, M + 2, M + 4, in the ratio 1.0:0.69:0.12, and *m/e* 165 (35.3). It melted at 235° (lit.[13] mp 232°).

Fraction C.—Glc analysis showed that this fraction contained small amounts of DDT, DDD, and DDE.

Fraction D.—It was rechromatographed on a silica gel column (60 g), using SSH, CCl_4, and benzene. Several compounds were isolated, one being a white solid, insoluble in acetone. It was crystallized from benzene and melted at 278°. Its nmr spectrum showed a broad singlet at δ 5.5 (1 H) and an AA'BB' quartet (8 H) with δ_a 7.2, δ_b 7.6, and J_{ab} = 10 Hz. Its mass spectrum gave a parent ion (2.1%) of *m/e* 564 with M, M + 2, M + 4, M + 6, and M + 8 ions in the ratio 1.0:1.95:1.62:0.67:0.19, which is indicative of six chlorines. Other prominent ions were *m/e* 235 (100), with M, M + 2, and M + 4 in the ratio 1.0:0.61:0.11, and *m/e* 165 (47.8). It is identified as an isomer of **3**.

A second compound gave an nmr spectrum with three singlets at δ 3.8 (3 H), 4.9 (1 H), and 7.3 (8 H). Its mass spectrum showed a molecular ion with *m/e* 294 with M, and M + 2 ions in the ratio 1.5:1. The prominent mass spectral peaks are *m/e* (rel intensity) 296 (13), 294 (20), 237 (66.5), and 235 (100). The ir spectrum showed a strong peak at 1735 cm^{-1}. This compound is identified as methyl 1,1-bis(*p*-chlorophenyl)acetate (**2**) by matching its spectra with literature reports.

A yellow solid was also obtained that had an nmr spectrum with a triplet at δ 1.1 (6 H), a singlet imposed on a quartet at 3.3 (7 H), and a multiplet at 6.8 (12 H). Mass spectrometry gave a molecular ion of *m/e* 425 with M, M + 2, and M + 4 peaks in the ratio 1.2:0.9:0.11, indicating the presence of two chlorine atoms. Other prominent peaks are *m/e* 412, 410, 384, 382, 340, 338, 275, 274, 272, 239, 199, 170, 164, 163, 162, 133, 105, 104, 91, 77, and 49. This compound was identified as **5**. A dirty white solid was isolated, which was recrystallized from EtOH and gave an nmr spectrum which had only an AA'BB' quartet centered at δ 7.6. Its mass spectrum gave a molecular ion of *m/e* 250 with M and M + 2 in the ratio of 1.5:1, indicating the presence of two chlorine atoms. The major mass spectral peaks at *m/e* (rel intensity) 252 (28.6), 250 (43.6), 139 (100). Its ir and nmr spectra and mp matched with an authentic sample of 4,4'-dichlorobenzophenone (DDCO).

Fraction E.—It was rechromatographed on a silica gel column (60 g), with SSH, CCl_4, and benzene. One major component was obtained and recrystallized from benzene. White crystals (mp 114°) were obtained and these gave nmr spectra with a triplet at δ 1.3 (6 H), a quartet at 3.16 (4 H), and AA'BB' quartet at 6.4 (2 H), 7.7 (2 H), and a singlet at 7.3 (8 H). Its mass spectrum gave a molecular ion of *m/e* 411 with M and M + 2 in the ratio 1.4:0.9. The ir spectrum showed a strong band at 1665 cm^{-1}. This compound is identified as α,α-bis(*p*-chlorophenyl)-*p*-diethylaminoacetophenone.

Anal. Calcd for $C_{24}H_{23}Cl_2NO$: C, 69.95; H, 5.58; Cl, 16.99. Found: C, 69.71; H, 5.75; Cl, 16.99.

Fraction F.—A yellow solid had separated on standing and it was filtered off and crystallized from a 1:1 mixture of benzene and methanol. Yellow crystals were obtained (mp 253°) which gave a nmr spectrum with a triplet at δ 1.2 (12 H), a quartet at 3.3 (8 H), and a multiplet centered at 6.8 (16 H). Its mass spectrum showed a molecular ion of *m/e* 542 with M and M + 2 peaks in the ratio 1.4:0.9, required for two chlorine atoms. It is identified as 1,1-bis(*p*-chlorophenyl)-2,2-bis(*p*-diethylaminophenyl)ethylene.

Anal. Calcd for $C_{34}H_{36}Cl_2N_2$: C, 75.4; H, 6.62. Found: C, 74.31; H, 6.69.

Fraction G.—The solution was evaporated to dryness. Ether was added to the dark brown mass and a brown solid separated out. After filtering and recrystallizing it from carbon tetrachloride, it was identified as diethylaniline hydrochloride by matching its nmr and ir spectra and melting point with those of an authentic sample.

Quantitative Analysis of DDT–Diethylaniline Products.—DDT (1.416 g, 3.99 mmol) and DEA (1.2 g, 8.05 mmol) were dissolved in methanol (total volume 50 ml). Seven 4-ml aliquots of this solution were placed in Pyrex tubes and irradiated for different lengths of time. The concentrations of DDT, DDD, DDE, DDCO, and **2** were followed by glc on column 1 at 228°. Only about 1% of DDCO was formed. It was not possible to separate DDE and methyl 1,1-bis(*p*-chlorophenyl)acetate so that the latter was measured by nmr in $CDCl_3$ with an internal standard.

Identification of Photoproducts of Decyl Bromide and Diethylaniline Reaction.—Decyl bromide (5.75 g, 27.2 mmol) and diethylaniline (10 g, 67 mmol) in DMF (160 ml) were irradiated in Pyrex tubes for 44 hr. Water was added to the reaction mixture which was then extracted with ether. The water-soluble portion contained diethylaniline hydrobromide as identified by nmr, ir, and melting point. The ether extract was washed with dilute HCl and again with water. The HCl extract was neutralized with dilute NaOH and extracted with ether. After washing with water it was dried over magnesium sulfate and analyzed by glc using a Teflon-lined aluminum column, 6 ft × 0.25 in., packed with 10% DC-200 on Chromosorb Q. It showed a peak with a retention time identical with that of *N*-ethylaniline on several columns. Glc of the neutral material used temperature programming. After injection, the temperature was held at 130° for 10 min and raised at the rate of 10°/min to 230°. Five major peaks with retention times of 3.16, 15.6, 21.8, 28, and 33.2 min appeared. The peak with a retention time of 15.6 min was due to decyl bromide.

The peak with a retention time of 3.6 min and a molecular ion at *m/e* 142 is due to *n*-decane, as shown by comparison of its nmr spectrum and glc retention time with those of authentic sample. The compound with a retention time of 33.2 min had a mass spectrum with a molecular ion of *m/e* 289 and major peaks of 289 (22), 274 (100), 134 (40), 105 (10), and 91 (14). The nmr spectrum showed a multiplet at δ 7.0–6.2 (4 H), a quadruplet at 3.2 (4 H), 2.3 (2 H), and 1.4–0.08 (25 H). This was identified by comparison of nmr and glc retention time with those of authentic *p*-decyl-*N*,*N*-diethylaniline. The compound with retention time 28.0 min had a mass spectrum with major peaks at *m/e* (rel intensity) 289 (1), 274 (2), 218 (50), 134 (17), 105 (22), 92 (95), 91 (100); nmr δ 9.70 (s, 4), 2.87 (q, 4), 2.6 (q, 2), and 1.4–0.8 (q, 25). This was identified as *o*-decyl-*N*,*N*-diethylaniline.

Solvent Effects on Decyl Bromide–Diethylaniline Photolysis.—Decyl bromide (7 g, 34.5 mmol), diethylaniline (10 g, 72.5 mmol), and a dodecanol standard (6 ml) were mixed. Four 5-ml aliquots of this solution were taken in Pyrex tubes, and to each of these was added 15 ml of one of the following solvents: DMF, methanol, benzene, and cyclohexane. These were irradiated for 36 hr, followed by glc analysis. After glc analysis, solutions were concentrated and extracted with dry ether. The solid left after ether extraction was diethylaniline hydrobromide, which was weighed to determine the amount of hydrogen bromide evolved.

***p*-Decyl-*N*,*N*-diethylaniline.**—1-Phenyldecane (6 ml) was added dropwise to a mixture of 5 ml of 70% HNO_3 and 6 ml of concentrated H_2SO_4 at 5°. This mixture was then neutralized with cold aqueous sodium hydroxide and extracted with ether. The ether soluble material had an nmr spectrum consistent with a mixture of nitrated decyl bromides. This material was reduced with tin (9 g) and concentrated hydrochloric acid (25 ml) on a steam bath for 45 min. Addition of aqueous sodium hydroxide and ether gave an ether soluble material with nmr δ 6.9–6.3 (m, 3.5), 3.4 (s, 2), 2.5–2.2 (m, 2), and 1.4–0.8 (m, 19). This material was not purified since the above nmr looked like primarily *p*-decylaniline (a poorly resolved AA'BB' quartet

in the aromatic region). This product (1 ml) was treated with 4 ml of ethyl bromide in a sealed tube at 130° for 19 hr. After cooling, the contents of the tube were neutralized with aqueous sodium hydroxide and extracted with ether. The ether extract was dried with magnesium sulfate. Glc showed three components, two with retention times identical with those obtained from the photolysis of decyl bromide and diethylaniline. The mixture was chromatographed on acid-washed alumina with Skellysolve H as the eluent. The major component had an nmr spectrum with an AA'BB' quartet centered at δ 6.65 (4, J = 9 Hz), 3.25 (q, 4, J = 8 Hz), 2.4 (m, 2), 1.2–0.9 (m, 25).

Anal. Calcd for $C_{20}H_{35}N$: C, 83.0; H, 12.1. Found: C, 83.4; H, 11.9.

Photolysis of *n*-BuI, *n*-BuBr and *n*-BuCl with Dimethylaniline.—Solutions of *n*-BuI, *n*-BuBr, and *n*-BuCl in benzene were prepared such that these contained 0.01 mol of halide, 0.03 mol of DMA, and 1.5 ml of toluene and the total volume was 10 ml. These solutions were irradiated for 96 hr. The progress of the reaction was followed by nmr, and it was shown that 27% of *n*-BuBr, 12% of *n*-BuCl, and 10% of *n*-BuI had reacted.

Quantum Yields.—The following solutions were prepared: benzophenone (0.91 g) and benzhydrol (0.92 g) in benzene (50 ml); DDT (1.41 g) and diethylaniline (1.2 g) in methanol (net volume 100 ml); and decyl bromide (1.105 g), diethylaniline (1.49 g) and dodecanol (1 ml) in methanol (total volume 25 ml). The uv spectrum of the benzophenone and benzhydrol solution was recorded by diluting 0.5 ml of this solution to 10 ml with benzene. Two 5-ml aliquots and two 7-ml aliquots of this solution were taken in identical Pyrex tubes with long stems. These tubes were degassed by three freeze–thaw cycles to 0.005 mm and sealed *in vacuo*. Three 5-ml aliquots of the DDT solution were taken in Pyrex tubes which were similar to the actinometer tubes. These were photolyzed with two actinometer tubes containing 5 ml of solution for 5 min. The amount of DDT reacted was determined by glc on column 1 at 240° using triphenylmethane as an internal standard which was added after irradiation. The per cent of DDT lost in three tubes was 12.24, 12.2, and 12.4. The per cent benzophenone reacted was determined by recording the uv spectrum of the irradiated solution after diluting 0.5 ml of this solution to 10 ml; the percentage lost was 7.5 and 7.5. The quantum yields were calculated for disappearance of DDT as 0.30, 0.30, and 0.31. Two 7-ml aliquots of the decyl bromide solution prepared above were placed in Pyrex tubes. These were irradiated along with two actinometer tubes (containing 7 ml of solution) for 30 min. The loss of benzophenone was determined as 23.5% in both tubes and of decyl bromide by glc, which was 6.3 and 6.5%. Quantum yields for the reaction were 0.19 and 0.20.

Registry No.—*cis*-**3**, 36954-66-2; *trans*-**3**, 36954-67-3; **5**, 36955-24-5; DDT, 50-29-3; diethylaniline, 91-66-7; decyl bromide, 112-29-8; α,α-bis(*p*-chlorophenyl)-*p*-diethylaminoacetophenone, 36955-25-6; 1,1-bis(*p*-chlorophenyl)-2,2-bis(*p*-diethylaminophenyl)ethylene, 36955-26-7; *p*-decyl-*N*,*N*-diethylaniline, 36955-27-8; *o*-decyl-*N*,*N*-diethylaniline, 36955-28-9.

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The Free-Radical Bromination of Bromobutane with Bromotrichloromethane

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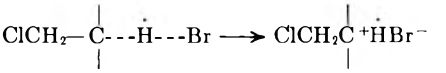
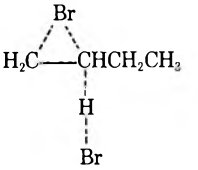
The photolytic bromination of 1-bromobutane with bromotrichloromethane was studied at three different temperatures. Product ratios were observed to be independent of per cent conversion with products resulting from β-hydrogen abstraction predominating. This result is discussed in terms of the stabilization of the β radical by a bromo substituent. A rearrangement product, 2-bromobutane, was also observed and a 1,2 bromine migration in the radical intermediate is proposed to account for its formation.

A large amount of work has dealt with the selectivities of hydrogen atom abstraction from hydrocarbons.[1] Some of the more interesting observations have resulted from studies in which alkyl halides serve as the hydrogen donor.[2-8] These systems are complicated by the effects of the halogen, which could potentially either stabilize or destabilize nearby radical centers. Studies of the photolytic bromination of alkyl chlorides with bromine have shown that a position β to the chlorine substituent is deactivated toward hydrogen abstraction.[3,4] This has been attributed to the polar effect of the electronegative substituent. The electronegative bromine atom is apparently repelled by the decreased electron density adjacent to the chlorine. This can be explained by including in the transition state for hydrogen abstraction an appropriate resonance structure showing some polar contribution to the radical reaction.



A more complicated situation obtains in alkyl bromides. If 1-bromobutane is photolytically brominated using Br_2 as the halogen source, 1,2-dibromobutane is the predominant product.[4] The polar effect has apparently been superseded by a stronger stabilizing influence of the bromo substitutent. Many authors have attributed this effect to a bridged radical species in which the neighboring bromine can anchimerically assist hydrogen abstraction from a β position.[3-9] This bridged radical intermediate postulation is supported by the observed retention of optical activity when optically active 1-bromo-2-methylbutane is halogenated under the same conditions.[9]



An alternative explanation has recently been pro-

(1) J. M. Tedder, *Quart. Rev., Chem. Soc.*, **14**, 338 (1960).
(2) M. S. Kharasch, W. S. Zimmt, and W. Nudenberg, *J. Org. Chem.*, **20**, 1430 (1955).
(3) (a) P. S. Fredericks and J. M. Tedder, *J. Chem. Soc.*, 144 (1960); (b) *ibid.*, 3520 (1961).
(4) W. Thaler, *J. Amer. Chem. Soc.*, **85**, 2607 (1963).
(5) P. S. Skell and P. D. Readio, *ibid.*, **86**, 3334 (1964).
(6) P. S. Juneja and E. M. Hodnett, *ibid.*, **89**, 5685 (1967).
(7) P. S. Skell, R. G. Allen, and N. D. Gilmour, *ibid.*, **83**, 504 (1961).
(8) J. G. Traynham and W. G. Hines, *ibid.*, **90**, 5208 (1968).
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posed by Tanner and coworkers.[10] These authors have reported that at low conversions, 1,3- rather than 1,2-dibromobutane predominates. This observation is interpreted on the basis of a reversible reaction in which the radical formed by abstraction of a β or γ hydrogen by a bromine atom may subsequently react with HBr to regenerate starting material. The observed product ratios thus are dependent not on the kinetics of hydrogen abstraction but rather on the relative stabilities of the radical intermediates. This interpretation is supported by the demonstration that the product ratio varies as a function of HBr concentration.

We have examined the bromination of 1-bromobutane using bromotrichloromethane with photolytic initiation. It was anticipated that under these conditions large concentrations of HBr would not be formed; thus the reaction could be examined in the absence of this complicating factor.

Results

Degassed solutions containing approximately 8.5:1 ratios of 1-bromobutane to bromotrichloromethane were sealed in Vycor tubes and irradiated for varying lengths of time with a sun lamp at three different temperatures. At completion of the photolyses the products were determined using gas chromatography. Product retention times were compared with those of authentic samples and the detector response was calibrated using known mixtures. The products observed are shown in eq 1 and tabulated in Table I.

$$Br(CH_2)_4H + BrCCl_3 \xrightarrow{h\nu} CHCl_3 + CH_3CHBr(CH_2)_2H + BrCH_2CHBr(CH_2)_2H + Br(CH_2)_2CHBrCH_3 \quad (1)$$

Small amounts of an approximately equimolar mixture of the diastereomeric 2,3-dibromobutanes (0.9, 1.4, and 4.3% of consumed $BrCCl_3$ at 0, 20 and 40°, respectively) were also formed. The absence of 1,1-dibromobutane was demonstrated by an independent synthesis[11] of this material and noting the lack of a corresponding signal in gas chromatograms of product mixtures.

To establish quantitatively the HBr formed in these reactions, 20° photolysis mixtures corresponding to 5.0 and 11.1% reaction were titrated with base. The titrations allow HBr concentrations of 3.8×10^{-3} and $5.5 \times 10^{-3} M$, respectively, to be calculated.

A control reaction showed that 1,2- and 1,3-dibromobutane as well as 1-bromobutane are photostable under our conditions. A 3:1 ratio of 1,2- to 1,3-dibromobutane dissolved in 1-bromobutane was unchanged after 24-hr photolysis at 20°.

An effort to detect 1-butene from the reaction mixture was made by photolyzing ~5 ml of solution at 35° with a medium-pressure Hg lamp while flushing with N_2 and trapping effluent in a liquid air cooled trap. No detectable butenes were formed when the reaction was allowed to proceed to *ca.* 20% completion. In addition no products corresponding to those from a photolytically initiated addition of $BrCCl_3$ to 1-butene at 20° could be detected in our reaction mixtures.

TABLE I
PRODUCTS[a] OF REACTION OF 1-BROMOBUTANE WITH BROMOTRICHLOROMETHANE

Temp, °C	% R[b]	$CHCl_3$	2BrBu	$BrCCl_3$	1,2-BrBu	1,3-Br_2Bu
40[c]	0	0.01	0.03	8.80		
	19.3	1.78	1.11	7.10	0.59	0.42
	23.4	2.39	1.36	6.74	0.73	0.52
	35.6	3.12	1.84	5.66	0.92	0.72
	36.7	3.53	1.73	5.58	0.99	0.73
	51.0	4.27	1.91	4.48	1.26	0.85
	87.0	6.40	2.34	2.02	1.82	1.13
20[c]	0	0.01	0.03	8.80		
	10.3	0.87	0.26	7.88	0.29	0.13
	22.6	1.87	0.52	6.80	0.65	0.32
	27.0	2.62	0.63	6.43	0.96	0.43
	40.5	3.69	0.64	5.24	1.48	0.70
	48.7	4.23	0.89	4.52	1.51	0.72
	63.2	5.30	0.99	3.23	2.12	0.94
0[d]	0	0.02	0.03	8.50		
	2.2	0.23	0.05	8.32	0.13	0.03
	6.4	0.73	0.08	7.96	0.41	0.08
	13.2	0.92	0.09	7.38	0.53	0.13
	54.2	4.55	0.42	3.90	2.53	0.71
0[e]	0	0.01	0.03	8.80		
	4.8	0.46	0.10	8.39	0.19	0.05
	7.0	0.71	0.09	8.17	0.34	0.06
	14.0	1.42	0.16	7.57	0.65	0.20
	26.0	2.58	0.21	6.51	1.34	0.38

[a] μmol of product in sample with PhCl standard normalized to 0.736 mol. [b] Based on consumption of $BrCCl_3$. [c] 70.66 μmol of 1-bromobutane originally. [d] 62.80 μmol of 1-bromobutane originally.

Discussion

The C–H bond of chloroform and the H–Br bond have similar dissociation energies (90 and 87 kcal/mol, respectively).[12] The ρ values observed in Br· and CCl_3· abstraction reactions from substituted toluenes (-1.36[13] and -1.46,[14] respectively) indicate that these radicals also have similar polar characteristics. These parallel properties allow an interesting comparison of the selectivities of hydrogen atom abstraction from 1-bromobutane to be made. The predominant bromination product in each case is 1,2-dibromobutane. There are, however, significant differences. In contrast to the observations of Tanner, *et al.*,[10a] on the Br_2 system, the 1,2- to 1,3-dibromobutane product ratios (1,2-Br_2Bu/1,3-Br_2Bu) remain essentially constant over a large range of conversions.[15] Figure 1 is a plot of 1,2-Br_2Bu/1,3-Br_2Bu *vs.* per cent conversion at three temperatures. The large scatter of points from the 0° experiments is probably due to an inability to precisely control the temperature in our crude reactor vessel at significantly subambient temperatures. For comparison Tanner's data of Br_2 bromination at 30° are included in Figure 1.

(10) (a) D. D. Tanner, D. Darwish, M. W. Mosher, and N. J. Bunce, *ibid.*, **91**, 7398 (1969); (b) D. D. Tanner, H. Yabuuchi, and E. V. Blackburn, *ibid.*, **93**, 4802 (1971); (c) D. D. Tanner, M. W. Mosher, N. C. Das, and E. V. Blackburn, *ibid.*, **93**, 5846 (1971).

(11) J. C. Conly, *ibid.*, **75**, 1148 (1953).

(12) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 48–50.

(13) R. E. Pearson and J. C. Martin, *J. Amer. Chem. Soc.* **85**, 3142 (1963).

(14) E. S. Huyser, *ibid.*, **82**, 394 (1960).

(15) Since completion of this work two groups of workers have reported being unable to duplicate the large variation of dibromobutane ratios with per cent conversion: P. S. Skell and K. J. Shea, *ibid.*, **94**, 6550 (1972), and J. G. Traynham, E. E. Green, Y. Lee, F. Schweinsberg, and C. Low, *ibid.*, **94**, 6552 (1972).

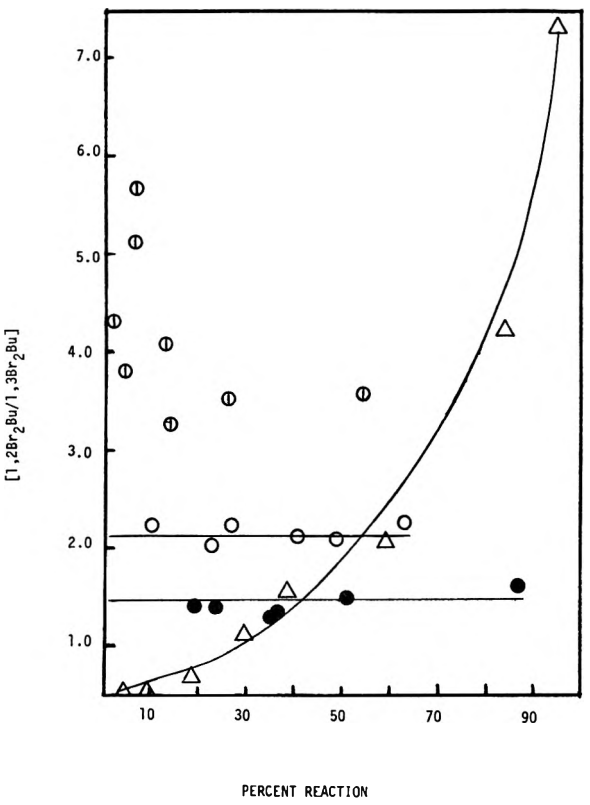


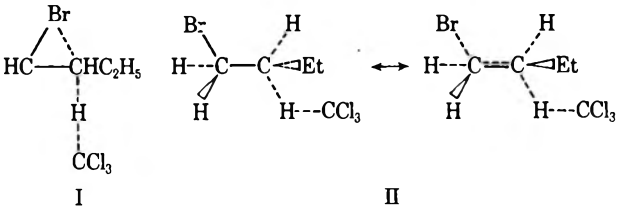
Figure 1.—Ratio of 1,2-dibromobutane to 1,3-dibromobutane as a function of per cent reaction: ⊕, 0°; ○, 20°; ●, 40°; △, Br_2 bromination at 30°.[10a]

We observe consistent predominance of the β abstraction product. We interpret this data to indicate that β-hydrogen abstraction is kinetically favored over γ abstraction. Although we do observe acid formation (6–9% of consumed $BrCCl_3$), the demonstration that the product ratio remains constant while the acid concentration increases argues against HBr allowing reversible formation of bromoalkyl radicals and a thermodynamically controlled product ratio. It is possible that extremely small concentrations of HBr could catalyze the thermodynamic equilibration of the β and γ radicals and thus increasing amounts of HBr would not further affect the observed product ratios. If this were the case, one would expect the ratio of products to be independent of the abstracting species and at least equal to or greater than those observed in the Br_2 system (7.3) as equilibrium is being approached at high HBr concentrations. Since our observed ratios fall far short of this value even when the amount of rearrangement product, which presumably results from β-hydrogen abstraction (*vide infra*), is included (3.46 at 20°), we conclude that the smaller amounts of HBr present in our system are not large enough to allow thermodynamic control to obtain.

We could be observing thermodynamically controlled products if the bromoalkyl radicals originally formed were being equilibrated *via* chain transfer with starting material before reaction with $BrCCl_3$. The argument above concerning the independence of abstracting species and equilibrium ratios must also be invoked here. On the basis of these arguments and the expected rapid rate of chain transfer with $BrCCl_3$[16] we regard this mechanism for equilibration as a remote possibility.

We must also consider the possibility that the presence of chloroform could result in equilibration. The large difference in reactivity of $CHCl_3$ relative to $BrCCl_3$[16] and the invariance of product ratios when the chloroform concentration has increased argue against this possibility.

The observation of preferential β-hydrogen abstraction by the electronegative trichloromethyl radical[14] necessitates the participation of the bromine substituent in an activating manner rather than the deactivation predicted on the basis of electronic arguments alone. Three possible explanations could be invoked: (1) anchimeric assistance of hydrogen atom abstraction



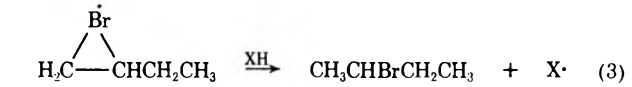
via formation of a bromine bridged radical, I; (2) a hyperconjugative delocalization of electron density to bromine *via* a preferred conformation, II; or (3) some type of elimination–addition mechanism proceeding through an intermediate alkene.

Since efforts to trap alkene or detect the addition products of $BrCCl_3$ to 1-butene proved futile, we regard the third possibility as unlikely. Although we cannot definitely distinguish between possibilities 1 and 2, our recent demonstration using CIDNP[17] that the ground-state configuration of the β-bromoethyl radical cannot be the symmetrical bridged structure as well as recent esr data[18] causes us to favor case 2. It is noteworthy that either case 1 or 2 by providing an energetically favored configuration for radical formation would favor the retained product configurations observed using optically active substrates in the Br_2 system.[9,10b]

We also observed formation of a rearrangement product, 2-bromobutane, which has not been reported in the Br_2 system. The most logical mode of formation of this product is *via* bromine atom migration in the β-radical intermediate followed by hydrogen abstraction (eq 2) or abstraction of hydrogen by a bridged radical species (eq 3). A possible alternative route would involve the mechanism proposed by Martin and Williams[19] to explain the γ-radiation induced isomerization of 1-bromobutane to 2-bromobutane. An originally formed β radical could lose Br· to form 1-butene, which can add HBr after the double-bond migration takes place through an allylic radical intermediate. Alternatively, the original alkene

$$BrCH_2CHCH_2CH_3 \rightleftharpoons$$

$$\cdot CH_2CHBrCH_2CH_3 \xrightarrow{XH} CH_3CHBrCH_2CH_3 + X\cdot \quad (2)$$



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could add HBr ionically to form product directly. The inability to gain evidence for alkenes again argues against this mechanism. In addition separate isotopic labeling studies by Tanner[10b] and Ronneau, *et al.*,[20] have failed to provide evidence for "free" alkene intermediates in brominations of 1-bromobutane. 1,2-Bromine atom migrations in free radicals have been previously reported[5-8] usually when a more stable radical is being produced. Traynham,[8] however, has reported products corresponding to a 1,2-bromine migration from a primary to a tertiary carbon.

The failure to note 2-bromobutane from the Br_2 bromination reactions may be due to the decreased rate of chain transfer of $BrCCl_3$ relative to Br_2, but the observation of 10% radiolabeled bromine in the 2 position of 1,2-dibromobutane produced when ^{82}Br 1-bromobutane is brominated with isotopically normal Br_2 suggests that a similar migration is operative in this system.

The observation of the 2-bromobutane product, which must result from β-hydrogen abstraction, is indicative that the ratio of β to γ hydrogen abstraction may be higher than the value obtained from the relative yields of the dibromination products.

The formation of small amounts of *meso*- and *dl*-2-3-dibromobutane is also explicable on the basis of the rearrangement product. A bromotrichloromethane bromination of 2-bromobutane produced these compounds in the same ratio observed in the 1-bromobutane system (~50:50).

Another major difference in the two modes of bromination is the absence of 1,1-dibromobutane formation in the $BrCCl_3$ system while it is a significant product from the Br_2 reaction. This may be due to an unfavorable dipole–dipole interaction between the chlorines of the near-planar CCl_3·[21] and the substrate bromine in the transition state for α-hydrogen abstraction.

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(21) C. Hesse and N. Leray, *Mol. Phys.*, **22**, 137 (1971).

Experimental Section

With the exception of 1,1-dibromobutane, all chemicals were commercial products. 1,1-Dibromobutane was synthesized by the method of Conly[11] and identified on the basis of its nmr spectrum (CCl_4), δ 0.98 (distorted t, 3), 1.51 (m, 2), 2.40 (m, 2), 5.75 (t, 1). Purification of 1-bromobutane was accomplished by the method of Tanner.[10] All other materials were used without further purification.

Photolyses.—Small portions of approximately 8.5:1 molar ratios of 1-bromobutane to bromotrichloromethane with chlorobenzene added as internal standard were placed in Vycor tubes, degassed by three freeze–thaw cycles, and sealed under vacuum. These tubes were placed in a larger Vycor tube and an ethylene glycol–water mixture from a thermostated bath was pumped through to regulate the reaction temperature.

Photolyses were conducted for various lengths of time with a 275-W G. E. sun lamp. Products were quantitatively determined with a 12 ft × 0.25 in. 20% SE-30 on Chromosorb W glpc column (80° column temperature with 30 ml/min carrier gas flow). The detector response was calibrated using known mixtures. Results are tabulated in Table I.

Titration Experiment.—Solutions containing 2.00 ml of reaction mixture were photolyzed at 20°. The tubes were opened and a 10.0-μl sample was analyzed by glpc. The remaining solution was immediately washed into a flask with a water–isopropyl alcohol mixture and titrated with 0.001 *M* NaOH to a phenolphthalein end point.

Registry No.—1-Bromobutane, 109-65-9; bromotrichloromethane, 75-62-7; 2-bromobutane, 78-76-2.

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Anomalous Hydrogen Exchange Reactions in HSO_3F–SbF_5

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Olefins, when added to SbF_5–HSO_3F solutions in the presence of alkylcycloalkanes or alkanes, are converted into the corresponding paraffin. However, labeling studies using tritiated acid and methylcyclohexane-d_{14} show that significant amounts of product do not arise *via* a normal carbonium ion path, which would have introduced one proton from the acid and one from the hydride donor into the products. Instead, much of the product appears to form by a process in which the alkylcycloalkane transfers two hydrogen atoms to the olefin. The possibility of a chain reaction at the acid–hydrocarbon interface or the intervention of radical cations leading to these results is considered.

Solutions of antimony pentafluoride in fluorosulfonic acid and other solvents are commonly used for the study of carbonium ions. Much of this work is due to enthusiasm with which Olah and coworkers have explored the field.[1] Recently, a study has been done of the behavior of alkyl cations in the SbF_5–tritiated HSO_3F system wherein the ions were formed by solvolysis of halides and trapped by hydride transfer to yield kinetically controlled products.[2] There it was shown that during many rearrangements a species which contained a very loosely bound and hence exchangeable proton formed. The species could be considered as a protonated alkylcyclopropane inter-

(1) (a) G. A. Olah, Abstracts of the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1962, p 45; (b) G. A. Olah, W. S. Tolgyesi, J. S. McIntyre, I. J. Bastion, M. W. Meyer and E. B. Baker, Abstract A, 19th International Congress of Pure and Applied Chemistry, London, June 1963, p 121; (c) G. A. Olah and J. A. Olah, "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 715.

(2) G. M. Kramer, *J. Amer. Chem. Soc.*, **92**, 4344 (1970).

mediate or transition state in the rearrangement process.

To provide another source of information concerning cation nature and behavior, olefin protonation has been investigated in the same media. Olah has indicated that alkyl cations can be formed from olefins in SbF_5–HSO_3F, but notes that the nmr resonance spectra are worse than obtained from solvolytic routes to the ion for obscure reasons.[1c] Thus it was expected that, although polymerization would be a competing reaction, simple olefins could be protonated once by the acid forming a cation which could be trapped by hydride transfer from a good donor like methylcyclopentane.

If the reaction was carried out in the same SbF_5–tritiated acid used in the alkyl halide solvolysis studies, one would expect the following normal sequence of reactions

$$C_nH_{2n} + L^+ \longrightarrow C_nH_{2n}L^+ \quad (1)$$

$$C_nH_{2n}L^+ + CH_3\text{-}c\text{-}C_5H_9 \longrightarrow C_nH_{2n+1}L + CH_3\text{-}c\text{-}C_5H_8^+ \quad (2)$$

In eq 1, L^+ is a proton with the average specific activity of the acid. These reactions lead to the formation of a paraffin, $C_nH_{2n+1}L$, which has acquired one hydrogen from the acid and one from methylcyclopentane. Accordingly, the specific activity of the paraffin produced is expected to reflect the introduction of one proton from the acid. However, when the experiments were performed, it was found that many olefins were converted into paraffins in reasonable yields but with substantially less than one proton having been derived from the acid. These anomalous results are reported in the paper, and speculation is presented regarding the mechanism and possible intervention of radical cations in the reactions.

Experimental Section

Tritium Exchange.—Olefins were mixed with a large excess of a hydride donor like methylcyclopentane (1:50), and the solution was then contacted with 2 *M* solutions of SbF_5 in HSO_3F. The acid had a specific activity of *ca.* 1 mCi/ml and had been diluted with about 5% H_2O to catalyze proton exchange between cations or intermediates present during rearrangements and the acid system.[2] A hydrocarbon–acid volume ratio of 0.5 was used in nearly all experiments.

Experiments were run at −50°, either in nmr tubes or in a modified Kjeldahl flask fitted with a mechanical stirrer and an injection port. The reagents were vigorously mixed for 10 sec and then allowed to settle. The hydrocarbons separated immediately from the acid and were quickly removed by vacuum distillation at −50° and condensed in a −80° trap. They were analyzed in a radioassaying gas chromatograph system. The extent of exchange in the products was determined by comparing the specific activity of each component with that of a standard solution of methylcyclopentane which had equilibrated 11 protons in the same acid system (2).

Deuterium Exchange.—Methylcyclohexane-d_{14} (Norell Chemical Co.) was employed instead of methylcyclopentane in a similar series of experiments to those described above. In this case however, the acid did not contain any tritium. After vacuum distillation the products were separated on a gas chromatograph from which the paraffin corresponding to the reacting olefin was trapped in a gas collection vessel. This gas was analyzed by mass spectrometry on a CEC-21-103C spectrometer to determine the extent of deuterium exchange (50-μA trap current and 70-eV electrons).

Results and Discussion

The SbF_5–HSO_3F system is known to provide one of the strongest acids available. As a consequence, alkyl cations formed *via* solvolysis appear to be relatively stable and hence can be observed by nmr spectroscopy. Thus, even the addition of 5% water does not provide enough nucleophiles to induce sufficient proton exchange to prohibit the apparent observation of a *tert*-butyl or *tert*-amyl cation at −50°.

Accordingly, it is reasonable to expect that the addition of isobutylene to such an acid should result in instant protonation of much of the olefin forming a *tert*-butyl ion which should either take up a quiescent residence in its nonnucleophilic surroundings or perhaps add to another incoming butylene and ultimately form a polymer of variable size. If the acid contained tracer concentrations of tritium, the *tert*-butyl ion would be expected to have acquired a proton with the same specific activity as in the acid unless protonation were slow and a kinetic isotope effect was important. In that case substantially less tritium would find its way into the butyl ion than was in the acid. After subsequently being trapped by hydride transfer from methycyclopentane, the isobutane formed would then appear to have less radioactivity than would be expected from the acquisition of a proton from the acid.

In Table I are shown the apparent number of exchanged protons present in paraffins obtained by reacting a series of olefins with methylcyclopentane or methylcyclohexane in 2 *M* SbF_5–$H(T)SO_3F$ at −50°. While there is some scatter in the data it is clear that propylene, isobutylene, 2-methyl-1-butene, and 2,3,3-trimethylbutene were converted into paraffins in fairly good yields with low tritium contents.

TABLE I
OLEFIN PROTONATION BY 2 *M* SbF_5–$H(T)SO_3F$ APPEARS LOW, −50° [a]

Olefin	Hydride donor[b]	Reactor[c]	RH, %[d]	No. of H_{ex}
	MCP	K	32	0.1
	MCH	K	27	0.5
	MCP	K	30	0.5
	MCH	K	100	0.5
	MCH	K	78	0.9
	MCH	K	40	1.8
	MCP	K	100	0.2
	MCP	K	100	2.7
	MCP	N	44	0.9
	MCP	N	40	0.6
	MCP	N	12	0.9
	MCP	N	31	0.9
	MCP	N	49	0.8
	MCP	N	30	0.4
	MCP	N	97	2.9

[a] Donor/olefin ratio 50:1. [b] MCP, methylcyclopentane; MCH, methylcyclohexane. [c] K, modified Kjeldahl flask; N, nmr tube. [d] The paraffin with the same C skeleton as the olefin.

To explain the unusually low tritium results the following possibilities have been considered. (1) There was a rate-limiting protonation with a strong isotope effect. (2) There was a rapid chain reaction at the acid–hydrocarbon interface after the acid had protonated an olefin resulting in first hydride transfer from the donor to the cation and then proton transfer from the new cation to another olefin. (3) Methylcyclopentane or methylcyclohexane extensively exchanged protons with the acid thus reducing the latter's specific activity before the acid protonated the olefin. (4) A new type of reaction involving the oxidation of either the olefin or the cycloalkane to a radical cation followed by an H_2 or an H_2^- transfer has occurred.

The low values are not likely to have been caused by an isotope effect in a slow protonation step for several reasons. First, if such an effect was really in operation at −50°, it should have been much more pronounced. Thus one can estimate that a normal effect at this temperature would have resulted in the acquisition of only 0.02 exchanged protons.[3] This is much less than was observed, and the isotope effect is inconsistent with the data in Table I.

A second and stronger reason for disregarding the isotope effect explanation is obtained however by considering the results of reacting isobutylene and other olefins with methylcyclohexane-d_{14} under similar conditions but with unlabeled acid (Table II). There it

TABLE II
DEUTERIUM TRANSFER FROM MCH-d_{14} TO OLEFINS IN 2 M SbF_5–HSO_3F[a]

Olefin	Reactor	T, °C	D distribution in paraffin d_0	d_1	d_2	d_3	d_4	d_5
	K	−50	+	89	11			
	K	−20	+	65	35	+	+	
	K	−50	−	70	20	10	+	
...[b]	N	−50	?	61	16	16	7	
	K	−50	0	77	23	+		
	K	−50	0	80	20	+	+	+
	K	−50	0	60	40			
...[b]	N	−50	0	50	50			
	K	−50	8	71	13	4.5	2.4	1.3

[a] MCH-d_{14}/olefin ratio 50:1. [b] These experiments used anhydrous HSO_3F. The other reactions were run with 5% H_2O present.

is seen that the paraffinic product has been produced after multiple exchange with methylcyclohexane. This result is clearly inconsistent with a rate-limiting protonation of the olefin which would be necessary for the isotope effect to be responsible for the data.

The possibility of a rapid chain reaction at the acid–hydrocarbon interface is difficult to assess. For it to be responsible for the observations would require that the adsorption of the olefins into SbF_5–HSO_3F was slow relative to the acquisition of a proton from a methylcyclopentyl cation, at the interface or in the hydrocarbon phase. If this condition actually obtains, the anomalous hydrogen exchange results are readily explained.

The existence of such an interfacial chain reaction, although not subject to quantitative evaluation at this time because of lack of information of both salient events (the rate of absorption and the rate of proton transfer from the methylcyclopentyl cation), is considered to be doubtful for several reasons.

One reason is that reactions were carried out in the two types of reactors: nmr tubes and a modified Kjeldahl flask. Both reactors were well mixed, the Kjeldahl reactor certainly more effectively and yet anomalous results were obtained in each. As efficient mixing should have led to more rapid adsorption of olefin in the acid, one might have expected a trend to less anomalous data in the Kjeldahl experiments, but it is not apparent.

Another reason for questioning a surface chain reaction is the high yield of propane when propylene reacted with either methylcyclopentane or methylcyclohexane-d_{14}. In these reactions the chain-carrying proton transfer

$$C_3H_6 + CH_3\text{-}c\text{-}C_6H_8^+ \longrightarrow i\text{-}C_3H_7^+ + CH_3\text{-}c\text{-}C_5H_7$$

from the cyclic cation to propylene is substantially endothermic (~10–15 kcal/mol) and hence unlikely to occur in the hydrocarbon phase. Nevertheless, such a possibility exists and is an alternate to the reaction to be proposed below.

The possibility of methylcyclopentane diluting the specific activity of the acid by rapid exchange prior to protonation of the olefin can be discounted for several reasons.

(a) The specific activity of recovered methylcyclopentane always showed that less than one proton had been exchanged with the acid and the exchange of one would only have diluted the activity by 12%. (b) Nmr investigations of 2 M SbF_5–HSO_3F solutions (with 5% H_2O) that were mixed with methylcyclopentane at and above the temperature of the tracer experiments showed neither methylcyclopentane nor the methylcyclopentyl ion in the acid. (c) Tertiary ions like t-$C_4H_9^+$ and t-$C_5H_{11}^+$ are trapped by hydride transfer much faster than they exchange protons *via* olefin formation in this acid.[2]

An oxidation reaction which would be compatible with our results has been observed in the mass spectrometer[4] and in vapor phase radiolysis studies by Ausloos and his coworkers.[5,6] They have formulated H_2 and H_2^- transfer reactions as illustrated in eq 3 and 4. The latter possibility provides a rational

$$C_nH_{2n} + c\text{-}C_6H_{12}^+ \longrightarrow C_nH_{2n+2} + C_6H_{10}^+ \quad (3)$$

$$C_nH_{2n}^+ + c\text{-}C_6H_{12} \longrightarrow C_nH_{2n+2} + C_6H_{10}^+ \quad (4)$$

explanation of the exchange data and is a major alternate to the proposal of an interfacial chain reaction.

In the remainder of this paper we will discuss the data in terms of the hypothetical existence of radical cations. Before doing so, however, we must report two pieces of negative information which indicate that *stable*, long-lived radicals or radical cations are not present. First, attempts have been made to detect stable radicals in the acid by esr at −50°, but they

(3) An estimation was made by extrapolating the hydrogen isotope effect data in L. Melander, "Isotope Effects on Reaction Rates," Ronald Preske, New York, N. Y., 1960, p 22. Use is made of eq 2-10 assuming a stretching frequency of *ca.* 3000 cm^{-1}.

(4) M. S. B. Munson, J. L. Franklin, and F. H. Field, *J. Phys. Chem.*, **68**, 3098 (1964).

(5) P. Ausloos and Sharon G. Lias, *J. Chem. Phys.*, **43**, 127 (1965).

(6) R. D. Doepker and P. Ausloos, *ibid.*, **44**, 1951 (1966).

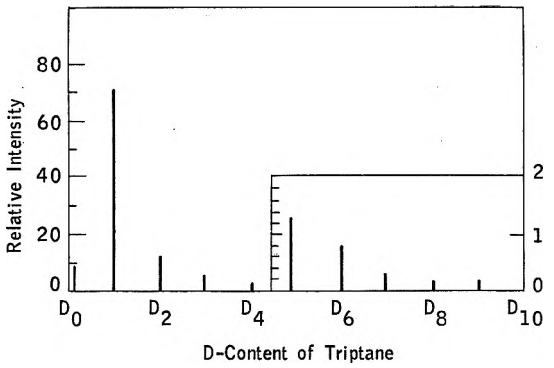

Figure 1.—MCH-d_{14} + trimethylbutene undergo extensive exchange.

have thus far been unsuccessful. Second, experiments have been run which were designed to detect these species by chemically induced dynamic nuclear polarization (CIDNP) by carrying out the reactions in an A-60 nmr spectrometer, but they have also been unsuccessful. Neither of these results however is considered to be conclusive evidence against the possible presence of short-lived radical cation intermediates. Since they do present a viable alternative to the proposal of the interfacial chain reaction and their formation would be consistent with the oxidizing ability of either SbF_5 or HSO_3F, the following analysis of the exchange data is appropriate.

The data in Table II indicate that the isobutane which formed contained significant amounts of $C_4H_8D_2$ and $C_4H_7D_3$ as well as more highly deuterated derivatives besides the normal expected product C_4H_9D. The multiple deuterium incorporation could not have arisen by transfer of deuterium from methylcyclohexane to the acid and then to the butyl fragment because this would be inconsistent with all the tritium results and the nmr spectral observations which show that the alkyl ion is not engaged in rapid exchange with acid protons.

The implication of the observation of multiple deuterium transfer is that a rather direct exchange process between methylcyclohexane and isobutylene occurred which did not involve the passage of protons from one reagent to the acid and then to the other. Clearly to the extent that the same reaction occurred in the tritium experiments, isobutylene would have been converted into isobutane without any tritium incorporation.

The results of the tritium and deuterium experiments taken together imply that isobutylene is converted into isobutane by more than one path. One is the normal carbonium ion route, A; the other or others

$$i\text{-}C_4H_8 \xrightarrow{SbF_5\text{-}HSO_3F} \begin{cases} \xrightarrow{A} t\text{-}C_4H_9^+ \xrightarrow{MCP} i\text{-}C_4H_{10} & (A) \\ \xrightarrow{-e} [i\text{-}C_4H_8^+] \xrightarrow{MCP} i\text{-}C_4H_{10} + R^+ & (B) \end{cases}$$

are open to conjecture. A strong possibility is a route involving the intermediacy of radical cations, B. The SbF_5–HSO_3F system provides an oxidizing atmosphere and might abstract an electron either from the cycloalkane or the olefin. If this happened, the H_2 or H_2^- transfer illustrated in eq 3 and 4 could naturally occur, just as in the gas phase.

Many questions about H_2 transfer reactions in the gas phase are unanswered at this time. Thus, whether the transfer represents a concerted or stepwise reaction or if electron transfer between the reactants leads to an immediate equilibrium between the olefin, cycloalkane, and radical cation of each, eq 5, is not

$$C_nH_{2n} + c\text{-}C_6H_{12}^+ \rightleftharpoons C_nH_{2n}^+ + c\text{-}C_6H_{12} \quad (5)$$

known. On the other hand, much is known about the reactions which appears related to those of this study. Thus Doepker and Ausloos[5] have shown that the H_2^- transfer is a general reaction observed with many paraffins and cycloparaffins in addition to methylcyclopentane and methylcyclohexane.

In Table III the results of trapping propylene with methylcyclopentane, isobutane, *n*-pentane, and cyclopentane in the tritiated acid system are shown. They are compared with the relative efficiency of the compounds to transfer H_2^- in the vapor phase to $C_3D_6^+$. The tracer results indicate that the H_2 transfer reaction is a general phenomenon in solution, but a quantitative relationship between the two sets of data is clearly lacking and a further kinetic analysis is not warranted at this time.

TABLE III

TRAPPING PROPYLENE IN SbF_5–$H(T)SO_3F$[a]

	Propane, %	No. of H_{ex}	k_{H_2}[b]
Methylcyclopentane	100	0.2	0.89
Isobutane	20	0.1	0.23
n-Pentane	17	0.2	1.12
Cyclopentane	2	0.4	0.95

[a] −50°; RH/C_3H_6 ratio 50:1. [b] C_5D_{10} was the reference compound, ref 5.

Returning to Table I it may be noted that the low-molecular-weight α olefins, propylene, 2-methyl-1-propene, 2-methyl-1-butene, 2-methyl-1-pentene, and 2,3-3-trimethylbutene, generally gave evidence of the radical cation route. On the other hand, all the linear butenes and some of the internal olefins acquired one or more protons from the acid and hence gave no indication of any unusual chemistry. The deuterium results of Table II, however, indicate that both the internal olefin, 2-methyl-2-butene, and its isomer, 2-methyl-1-butene, behave in a very similar manner. In both cases about 20% $C_5H_{10}D_2$ and 80% $C_5H_{11}D$ were formed with small amounts of more highly deuterated pentane. The extent of H_2^- transfer from methylcyclohexane is less than from methylcyclopentane in the radiolysis experiments, $k_{MCH} = 0.55$ *vs.* $k_{MCP} = 0.89$, so that the deuterium experiment is fairly consistent with the tritium exchange data.

Similarly, about 20% of the propane formed from propylene in the tritium experiments could be attributed to the carbonium ion route while 80% could be due to a radical cation path. This is consistent with the deuterium experiment where 40–50% of the propane was $C_3H_6D_2$.

2,3,3-Trimethylbutene was quantitatively converted into triptane when reacted with methylcyclohexane in the tritiated acid, about 45% being formed *via* the carbonium ion. In the deuterium experiment somewhat more of the normal product was obtained but of greater interest was the fact that significant quan-

tities of d_2, d_3, . . ., d_9 trimethylbutanes were found. Such extensive exchange was also obtained with isobutylene and the methylbutenes and suggests that after a D_2^- transfer occurs in solution the products are able to react several more times before separating. Thus the reactants and product participating in the radical cation exchange appear to undergo reaction while in a solvent cage.

In the trimethylbutene experiment some triptane-d_0 was also formed. This was probably formed by allylic hydride transfer from triptene to the triptyl ion. The relative intensity of the d_0 through d_9 isomers is shown in Figure 1.

Assuming that the reactions observed involve radical cations, it is likely that they are examples of eq 4 and hence an H_2 transfer. This may be inferred from the ionization potential or appearance potential of the respective radical cations. In Table IV it may be seen that saturated compounds generally are more difficult to oxidize than olefins although the difference between propylene and methylcyclopentane or methylcyclohexane is not large. This question ought to be the subject of future research.

In summary, a dual approach to the reaction of olefins in the SbF_5–HSO_3F system has shown that in addition to normal carbonium formation and reactivity much of the olefin reacts *via* an unexpected route.

TABLE IV
APPEARANCE POTENTIALS OF REPRESENTATIVE RADICAL CATIONS

Ion	AP or IP, eV[a]
$C_3H_6^+$	9.74
i-$C_4H_8^+$	9.23
$(CH_3)_2C{=}CHCH_3^+$	8.8
CH_3-c-$C_6H_{11}^+$	9.9
CH_3-c-$C_5H_9^+$	9.9
i-$C_4H_{10}^+$	10.57

[a] J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. T. Herron, K. Draxl, and F. H. Field, NSRDS-NBS (26), June 1969.

Several possible routes exist. One involves an interfacial chain reaction in which the olefin is protonated and extracts a hydride from the donor forming a cation which then protonates another olefin, etc. An alternative involves the formation of radical cationic intermediates. In any event, the addition of olefins like propylene or isobutylene to SbF_5–HSO_3F solutions in the presence of hydride donor does not proceed to paraffin products exclusively by a normal path where one proton is transferred by the acid and the other from the hydride donor.

Registry No.—Antimony pentafluoride, 7783-70-2; fluorosulfonic acid, 7789-21-1.

Stable Carbocations. CXXXIV.[1] Protonation of Mono- and Dihydroxybenzenes and Their Methyl Ethers in Superacids

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The protonation of mono- and dihydroxybenzenes and their methyl ethers was studied in four different superacid media, HF–SbF_5 (1:1 M:M)–SO_2ClF (I), HSO_3F–SbF_5 (1:1 M:M)–SO_2ClF (II), HSO_3F–SbF_5 (4:1 M:M)–SO_2ClF (III), and HSO_3F–SO_2ClF (IV) by low-temperature nmr spectroscopy. The sites of protonation (O- *vs.* C-) were dependent upon the acid media used. The structures of the formed ions were assigned based on their nmr (^1H and ^{13}C) spectra. Isomeric ions derived from the same precursor were also observed. Stability of hydroxy(alkoxy)benzenium ions, including isomeric ion forms derived from the same precursors and the relative ease of protonation is discussed in terms of steric, resonance, and inductive effects. Phenyloxonium ion (O-protonated phenol) formation was generally observed in HF containing small amounts of antimony pentafluoride at low temperature ($-105 \sim -80°$) while C-protonated phenols were found in acids of higher strength and at higher temperature.

Hydroxy- and alkoxy-substituted benzenium ions have been studied by a number of investigators.[2] The site of protonation seemed to depend on the acid–solvent system and temperature. However, no systematic study of protonation of hydroxy(alkoxy)-benzenes in different acid systems was so far attempted. Furthermore, the sites of protonation are not yet well understood. The effect of substitutents on benzenium ions were also not yet extensively studied. Isomeric ions derived from the same precursor are known (*e.g.*, C- and O-protonated anisole),[2b] but the factors (electronic and steric, as well as those of media) that control the relative amounts of isomeric ions formed were not known.

We now report a systematic study of these questions by pmr spectroscopy of ions obtained from mono- and dihydroxybenzenes and their methyl ethers. Four superacid systems were used: I, HF–SbF_5 (1:1 M:M)–SO_2ClF; II, HSO_3F–SbF_5 (1:1 M:M)–SO_2ClF, III, HSO_3F–SbF_5(4:1 M:M)–SO_2ClF; and IV, HSO_3F–SO_2ClF. In addition, protonation of phenol was carried out in weaker acids, like HF containing traces of SbF_5, in order to study both substituent and solvent effects. The nature of the extensive charge delocalization in the *p*-hydroxy- and methoxybenzenium ions was also studied by carbon-13 nmr spectroscopy.

Results and Discussion

The hydroxybenzene derivatives were protonated in the four different superacid systems (I–IV). Ions

(1) Part CXXXIII: G. A. Olah, G. Liang, J. R. Wiseman, and J. A. Chong, *J. Amer. Chem. Soc.*, **94**, 4729 (1972).

(2) (a) T. Birchall, A. N. Bourns, R. J. Gillespie, and P. J. Smith, *Can. J. Chem.*, **42**, 1433 (1964); (b) D. H. Brouwer, E. L. Mackor, and C. MacLean, *Recl. Trav. Chim. Pays-Bas*, **85**, 109, 114 (1966); (c) R. W. Alder and F. J. Tayler, *J. Chem. Soc. B*, 845 (1970); (d) M. P. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *ibid.*, 1624 (1971).

TABLE I

ION FORMATION UPON PROTONATION OF MONO- AND DIHYDROXYBENZENES AND THEIR SUBSTITUTED DERIVATIVES[a]

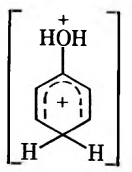
Aromatic precursor	Ions formed in superacid systems I	II	III	IV
1	2	2	2	2
5	6	6	6	6
9a	10a	10a	10a, 9a ⇌ 11	9a ⇌ 11
9b	10b (syn) ⇌ 10b (anti)	10b (syn) ⇌ 10b (anti) (35%) (35%) 9b ⇌ 12 (30%)	10b (syn) ⇌ 10b (anti) (12.5%) (12.5%) 9b ⇌ 12 (75%)	9b ⇌ 12
13	14a	14a	14a	14a
15	16a	16a	16a	16a
17	18a (80%) ⇌ 18b (20%)	18a (80%) ⇌ 18b (20%)	18a (8%) ⇌ 18b (20%)	18a (80%) ⇌ 18b (20%)
19	20	20	20	20 (75%), 19 ⇌ 20a (25%)
21	22	22	22	22
23	24 (40%) 26 (60%)	24 (87%) 25 (13%)	24 (80%) 25 (20%)	24 (65%) 25 (35%)
27	28	28	28	28
29	31	30	30	29 ⇌ 30
33	Polymerization	34	34	34
35	36 (98%) 37 (2%)	36 (98%) 37 (2%)	36 (98%) 37 (2%)	36 (98%) 37 (2%)
38	39 40	39	39	39
41	Polymerization	42	42	42 ⇌ 45
46	Polymerization	47	47	47
48	Polymerization	48 ⇌ 50	48 ⇌ 50	48 ⇌ 50
52	55	53	53	53, 52 ⇌ 54
56	57a	57	57	57
58	60	58 ⇌ 59 ⇌ 60	58 ⇌ 59 ⇌ 60	58 ⇌ 59 ⇌ 60

[a] For actual experimental conditions (*e.g.*, temperature), see text.

formed are summarized in Table I. The pmr data of the hydroxy- and methoxybenzenium ions as well the related oxonium ions obtained under varied conditions are tabulated in Tables II and III, respectively.

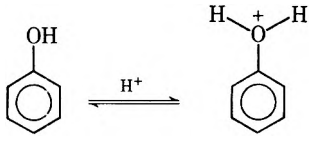
Phenol and Anisole. C-Protonation *vs.* O-Protonation. A. Phenol (1).—The chemical behavior of phenol in strong acid systems, like fluorosulfuric acid[2a] and $HF–BF_3$–sulfolane,[2c] has been studied by Gillespie and Adler, respectively. Our interests in the protonation of phenol are to investigate the behavior of phenol in various superacid media and hopefully to find the conditions for O-protonation as well as C-protonation. Furthermore, the extensive charge delocalization of ion 2 was studied by carbon-13 nmr spectroscopy (INDOR method).

In all superacid systems I–IV, 1 was completely C-protonated to give ion 2. The nmr spectra (Figure 1, bottom trace) of these solutions were identical except that the hydroxylic proton was not observable in superacid system IV. The hydroxylic proton absorption of 2 in superacids I–III is temperature dependent. At −30°, it becomes a broadened line at δ 11.3 indicating rapid proton exchange with the superacid. The exchange reaction may involve diprotonation on the oxygen atom and thus involvement of dipositive transition state **3**.



3

When 1 was dissolved in liquid HF containing 5% of SbF_5, the pmr spectrum (Figure 1) of the solution at −40° showed a multiplet centered at δ 6.8 and the acid peak at δ 8.8. When the solution was cooled to −90°, the multiplet became a broadened absorption line remaining at δ 6.8 but a new, very broad absorption appeared at δ 9.4. Upon further cooling down to −105°, the new very broad absorption line sharpened and remained at δ 9.4 (Figure 1). The intense acid peak forms a shoulder at ~δ 9.0. These results indicate the formation of O-protonated phenol, **4**. As expected, the aromatic protons of **4** show a multiplet



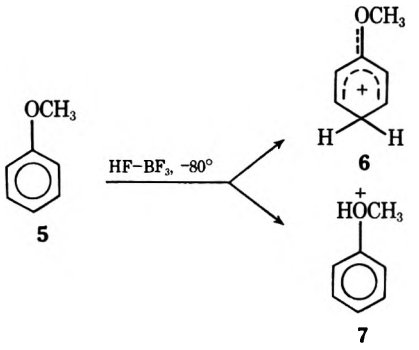
1 **4**

and the $-OH_2^+$ shift is similar to those of $-OH_2^+$ of protonated aliphatic alcohols, $^+ROH_2$.[3] In relatively weak acids it is always difficult to observe nonexchanging protonated heteroorganic compounds. In order to slow down the rate of proton exchange, O-protonated phenol must be observed at very low temperature.

The multiplet of the aromatic protons of ion **4** is shielded from the ring protons of ion 2, indicating that O-protonation of phenol leads to a charge-localized ion. On the other hand, C-protonation of phenol involves π electrons and leads to a charge-delocalized benzenium ion 2 (see subsequent discussion of carbon-13 nmr studies of ions 2 and 6).

(3) (a) G. A. Olah and E. Namanworth, *J. Amer. Chem. Soc.*, **88**, 5327 (1966); (b) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, **89**, 3576 (1967).

B. Anisole (5) has been protonated in various acid media by Gillespie,[2a,4] Brouwer,[2b] Olah,[5] and their coworkers. In fluorosulfuric acid with or without antimony pentafluoride, *p*-methoxybenzenium ion (6) is generated. In HF-BF_3 solution at −60°, **5** was both C- and O-protonated to ions **6** and **7**.[2b] As the



temperature was raised to −10°, only ion **6** was observed. In the four superacid systems I–IV, **5** was found to be C-protonated to give ion **6**. The pmr spectrum of ion **6** was temperature dependent because of the inhibition of rotation about the partial C=O double bond.

C. Carbon-13 Nmr Studies of Ions 2 and 6.—In order to study the trend of charge distribution of ions **2** and **6**, we undertook a carbon-13 nmr study, which is an excellent tool for the investigation of carbocations. The carbon-13 data provide important new information about the nature of ions **2** and **6**. Table IV summarizes the carbon-13 nmr data of protonated and parent phenol and anisole and, for comparison, we also list the carbon-13 shifts of protonated toluene.[6]

The sp^3 methylene carbon has almost identical carbon shifts in both ion **2** and **6**. These data further prove that protonation is indeed occurring at the aromatic ring. The sp^3 carbon of *p*-toluenium ion **8** has a carbon shift deshielded by 6 ppm from those of ions **2** and **6**, indicating partial charge delocalization to the oxygen atoms. The sp^2 carbon shifts of all the three ions **2**, **6**, and **8** clearly show that the deshielding effects follow the order para < ortho < meta. In other words, charge is mainly delocalized into the ortho,para carbons and the oxygen atom. These results are consistent with theoretical calculation.[7]

Owing to the anisotropy effect of the oxygen atom in ion **6**, carbons 5 and 6 are more deshielded than carbons 3 and 2, respectively. Long-range proton–proton coupling between *p*-CH_3 and CH_2 protons in *p*-toluenium ion[7] and proton–fluorine coupling between CH_2 and *p*-F in *p*-fluorobenzenium ion[8] are known. In ion **6**, we also observe long-range proton–carbon coupling (T_{CH} = 143.8 Hz) between CH_3O carbon and CH_2 protons through six bonds. The proton–carbon coupling was evidenced from the CH_2 proton main peak enhanced INDOR spectrum. The INDOR spectrum showed a quartet at δ 129.3 ppm (from CS_2) when the CH_2 protons were doubly irradiated.

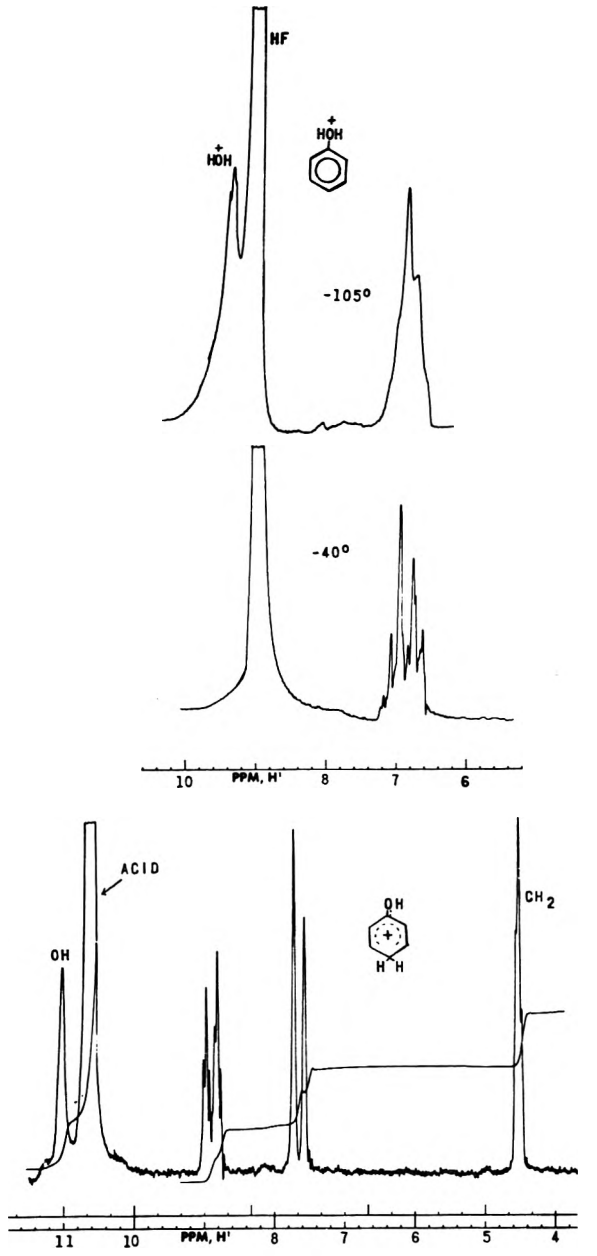
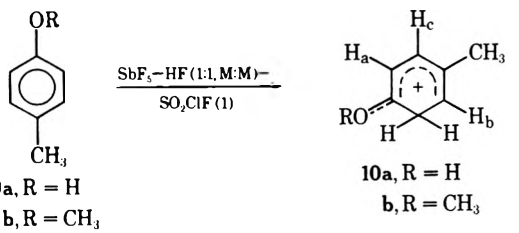


Figure 1.—Pmr spectra (60 MHz) of C-protonated phenol **2** (bottom trace) and O-protonated phenol at −40° and −105° (middle and upper traces).

Finally, it should be mentioned that the carbon-13 shifts of ions **2** and **6** show a close relationship to those of protonated α,β-unsaturated carbonyl compounds.[9]

Protonation of Isomeric Cresols and Their Methyl Ethers. A. *p*-Cresol and *p*-Methylanisole.—Protonation of *p*-methylanisole (**9b**) in HF-BF_3 at −85° has been reported by Brouwer and coworkers.[2b] They found that the site of protonation was at the ethereal oxygen atom and not at the aromatic ring. In super-



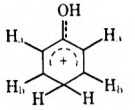
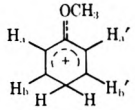
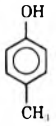
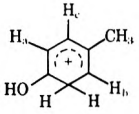
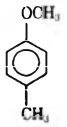
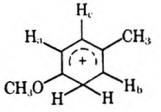
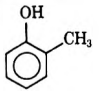
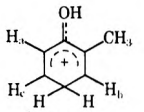
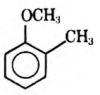
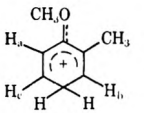
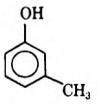
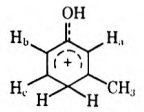
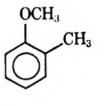
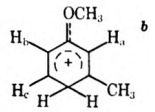
9a, R = H
b, R = CH_3

10a, R = H
b, R = CH_3

(4) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **42**, 502 (1964).
(5) G. A. Olah, M. B. Comisarow, E. Namanworth, and B. Ramsey, *J. Amer. Chem. Soc.*, **89**, 5259 (1967).
(6) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelley, and G. D. Mateescu, *ibid.*, **94**, 2034 (1972).
(7) D. M. Brouwer, E. L. Mackor, and C. MacLean in "Carbonium Ions," G. A. Olah and P. V. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 865.
(8) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **89**, 5692 (1967).
(9) G. A. Olah, Y. Halpern, Y. K. Mo, and G. Liang, *ibid.*, **94**, 3554 (1972).

TABLE II

^{1}H MAGNETIC RESONANCE DATA OF MONO- AND DIHYDROXY(METHOXY)BENZENIUM IONS[a]

Precursor	Benzenium ion	Superacid system, temp in °C	CH_3	OCH_3	CH_2	H_a	H_b	H_c	OH
 1	 2	II, −15			4.50 (t) J_{HH} = 2.5 Hz	7.68 (d) J_{HH} = 10 Hz	8.91 (d t) J_{HH} = 10 and 2.5 Hz		11.3 (br)
 5	 6	II, −50		4.80 (s)	4.50 (br s)	7.5 (br d) J_{HH} = 10 Hz 7.8 (br d) J_{HH} = 10 Hz	8.6 (br d) J_{HH} = 10 Hz 9.0 (br d) J_{HH} = 10 Hz		
 8	 10a	I, −60	2.60 (s)		4.6 (br s)	7.40 (d) J_{HH} = 10 Hz	7.6 (br s)	8.86 (d) J_{HH} = 10 Hz	*c*
 9b	 10b	I, −48	2.68 (s)	4.79 (s)	4.6 (br s)	7.57 (d) J_{HH} = 10 Hz	7.7 (br s)	8.88 (d) J_{HH} = 10 Hz	
 15	 16a	IV, −16	2.51 (s)		4.4 (m)	−7.54 (d) J_{HH} = 9 Hz	8.55 (q) J_{HH} = 1.8 Hz	8.73 (d q) J_{HH} = 2.5 and 9 Hz	−12.2 (br)
 13	 14a	IV, −16	2.40 (s)	4.68 (s)	4.3 (br s)	7.67 (d) J_{HH} = 10 Hz	8.3 (br s)	8.77 (d q) J_{HH} = 10 and 1.5 Hz	
 19	 20	I, −60	2.97 (s)		4.5 (br s)	7.50 (s)	7.57 (d) J_{HH} = 10 Hz	8.74 (d) J_{HH} = 10 Hz	*c*
 17	 18a ⇌ 18b	I, −16	2.83 (s)	4.69 (s)	4.3 (br s)	7.50 (s)	7.42 (d) J_{HH} = 10 Hz	8.5 (br d) J_{HH} = 10 Hz	

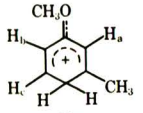
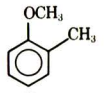
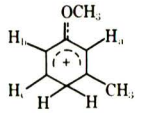
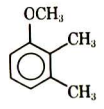
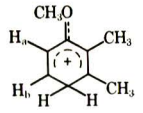
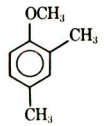
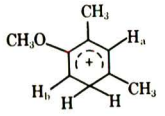
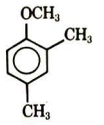
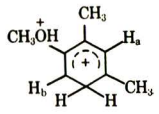
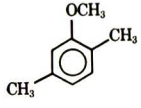
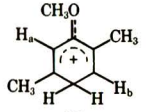
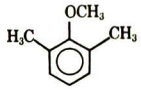
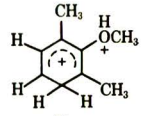
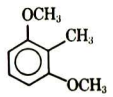
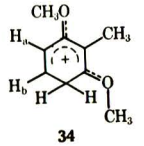
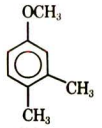
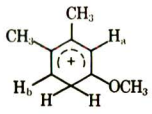
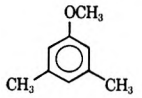
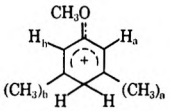
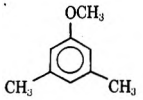
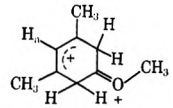
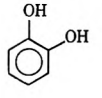
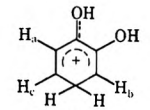
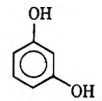
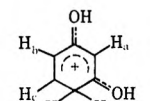
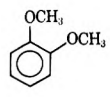
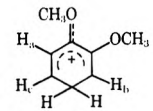
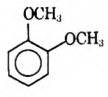
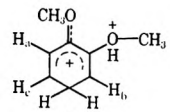
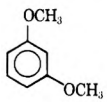
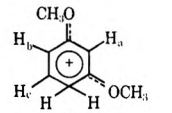
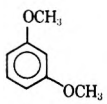
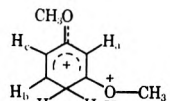
	 18a		2.91 (s)	4.72 (s)	4.3 (br s)	7.64 (s)	7.33 (d) J_{HH} = 9 Hz	8.4 (br d) J_{HH} = 9 Hz	
 17		IV, −64							
	 18b		2.78 (s)	4.72 (s)	4.3 (br s)	7.78 (s)	7.33 (d) J_{HH} = 9 Hz	8.7 (br d) J_{HH} = 9 Hz	
 21	 22	II, −60	2.52 (s) 2.86 (s)	4.87 (s)	4.5 (br s)	7.87 (d) J_{HH} = 10 Hz	8.80 (d t) J_{HH} = 10 and 2.2 Hz		
 23	 24	III, −60	2.50 (s), 6 H	4.70 (s)	4.43 (br s)	7.5 (s)	8.55 (s)		
 23	 26	I, −40	3.43 (s)	3.4 (s)	5.6 (br)	8.6 (br)	9.16 (br)		*c*
 27	 28	IV, −60	2.42 (s, meta) 2.85 (s, ortho)	4.73 (s)	4.2 (br s)	7.60 (s)	8.22 (t)		
 29	 31	I, −80	3.5 (br)	5.4 (br)	5.8 (br s)	8.5 (br s)	9.6 (br s)		13.8 (br)
 33	 34	III, −40	2.28 (s)	4.50 (s, ortho) 4.64 (s, para)	4.21 (d) J_{HH} = 3 Hz	7.60 (d) J_{HH} = 10 Hz	8.08 (d t) J_{HH} = 10 and 3 Hz		*c*
 35	 36	III, −60	2.51 (s) 2.92 (s)	4.52 (s)	4.31 (br s)	7.40 (s)	7.60 (t) J_{HH} = 3 Hz		

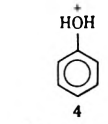
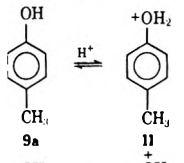
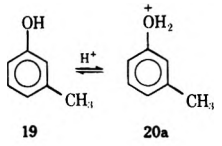
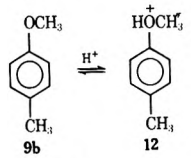
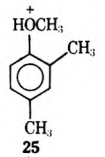
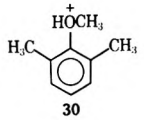
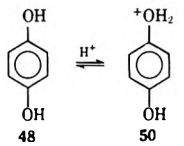
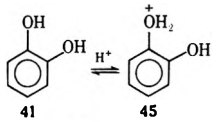
TABLE II (*Continued*)

Precursor	Benzenium ion	Superacid system, temp in °C	CH_3	OCH_3	CH_2	H_a	H_b	H_c	OH
 38	 39	III, −60	2.70 (s) (a) 2.83 (s) (b)	4.64 (s)	4.23 (s)	7.23 (s)	7.50 (s)		
 38	 40	I, −40	3.62 (s)	5.60 (s)	5.5 (br s)	8.66 (s)			
 41	 42	II, −40			4.6 (br s)	7.74 (d) J_{HH} = 9 Hz	8.03 (t) J_{HH} = 2 Hz	8.90 (d t) J_{HH} = 9 and 2 Hz	*c*
 46	 47	II, −40			4.73 (d) J_{HH} = 3.5 Hz	6.82 (s)	7.31 (d) J_{HH} = 10 Hz	8.10 (d t) J_{HH} = 10 and 3.5 Hz	*c*
 42	 43	III, −40		4.70 (s, meta) 4.93 (s, para)	4.8 (s, br)	7.90 (d) J_{HH} = 10 Hz	7.96 (s)	9.16 (d) J_{HH} = 10 Hz	
 42	 45	I, −60		3.34 (s, para) 5.6 (br s, meta)	5.3 (br s)	−8.32 (d) J_{HH} = 10 Hz	9.2 (br s)	9.6 (br d) J_{HH} = 10 Hz	*c*
 56	 57	II, −40		4.52 (s, ortho) 4.63 (s, para)	4.24 (d) J_{HH} = 3 Hz	6.8 (d) J_{HH} = 0.5 Hz	7.20 (d d) J_{HH} = 10 and 0.5 Hz	7.84 (d t) J_{HH} = 10 and 3 Hz	
 56	 57a	I, −60		5.5 (br s, para) 5.6 (br s, ortho)	5.2 (br s)	8.2 (d) J_{HH} = 10 Hz	8.3 (br s)	9.2 (br d) J_{HH} = 10 Hz	*c*

[a] Proton chemical shifts are referred to external capillary TMS in parts per million. [b] Rapid interconversion of two isomeric ions. [c] OH proton is not observable owing to rapid exchange.

TABLE III

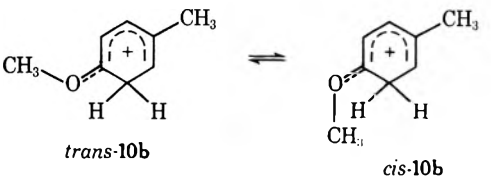
^{1}H MAGNETIC RESONANCE DATA OF ARYLOXONIUM IONS

Oxonium ion	Superacid system, temp in °C	Chemical shifts[a] CH$_3$	OCH$_3$	Ring	OH	Remarks
 4	See text			6.8 (m)	9.4 (br)	
 9a 11	IV, −40	2.43 (s)		7.33 (s)	*b*	100%
	III, −60	2.52 (s)		7.50 (s)	*b*	35% with 65% C-protonation
 19 20a	IV, −80	2.43 (s)		7.09 (s)	*b*	25% with 75% C-protonation
 9b 12	II, −40	2.66 (s)	5.04 (s)	7.68 (s)	*b*	30% with 70% C-protonation
	III, −40	2.50 (s)	4.98 (s)	7.65 (s)		75% with 25% C-protonation
	IV, −90	2.48 (s)	4.67 (s)	7.50 (s)		100%
 25	III, −60	2.63 (s)	5.01 (d) J_{HH} = 2.5 Hz	7.62 (s)	11.8 (br)[c]	
 30	II, −60	2.70 (s)	5.07 (d) J_{HH} = 2 Hz	7.4 (s)	11.6 (br)[c]	
 48 50	III, −40			7.93 (s)	*b*	
	IV, −40			7.50 (s)	*b*	
 41 45	IV, −40			7.44 (s)	*b*	
 60	I, −40		5.48 (d) J_{HH} = 3 Hz	8.24 (s)	11.92 (q) J_{HH} = 3 Hz	

[a] Chemical shifts are referred to external TMS: s = singlet; b = broad; d = doublet. [b] The OH peak is not observable since it exchanges with acid systems. [c] The broad peak should be a quartet.

acid I both **9a** and **9b** were C-protonated to give the stable benzenium ions, **10a** and **10b**, at −48 and −60°, respectively. The structure of ion **10a** is based on its pmr spectrum (Table II). The hydroxylic proton cannot be observed in the spectrum, presumably because it exchanges rapidly with the superacid.

The pmr spectrum of ion **10b** is similar to that of **10a**, except for an additional three-proton singlet is found at δ 4.79 (see Table II). The two isomeric ions (*cis*-**10b** and *trans*-**10b**) were not observed in superacid I, presumably because interconversion of

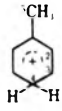


trans-**10b** *cis*-**10b**

the cis–trans isomers is rapid. We were so far unable to freeze out the relatively low energy process in this particular medium even at −80°. However, the cis–trans isomers of **10b** can be observed in superacid media II–IV.

TABLE IV

COMPARISON OF CARBON-13 NMR SHIFTS OF PROTONATED AND PARENT PHENOL, ANISOLE, AND TOLUENE[a]

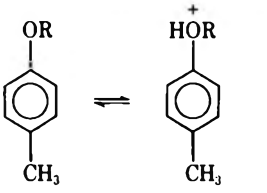
	C_1	C_2	C_3	C_4	C_5	C_6	C_7	Ref
	+37.4	+76.8	+62.4	+71.7				5b
	+12.1 (−25.3)	+66.9 (−9.9)	+17.3 (−45.1)	+151.6 (+80.5)				This work
	+32.7	+79.0	+63.0	+72.0	+63.0	+79.0	+138.4	5b
	+0.8 (−31.9)	+71.4 (−7.6)	+25.0 (−38.0)	+151.8 (+79.8)	+18.2 (−44.8)	+65.2 (−13.8)	+129.3 (−91.0)	This work
	+56.5	+65.3	+68.4	+171.8				2
	−7.3 (−49.2)	+55.2 (−10.1)	+13.4 (−41.9)	+145.1 (+76.7)				6a

[a] Carbon-13 shifts are referred to CS_2.

In superacid II at −10°, **9a** was found to be completely C-protonated, giving ion **10a**. In the same superacid (II) **9b** showed a more complicated pmr spectrum, indicating that two or three isomeric ions were formed. The pmr spectrum of this mixture is temperature dependent. At −80°, the two isomeric ions (*cis*-**10b** and *trans*-**10b**) are present in about equal portions (35% each) with 30% of O-protonated *p*-methylanisole (**11**) (based on comparison with pmr spectra of individual ions). As the temperature was raised to −40°, the intensities of the pmr resonances corresponding to ions *cis*-**10b** and *trans*-**10b** became identical with those observed when **9b** was protonated in superacid system I. The remaining portions of the spectrum are consistent with formation of ion **11**, since they are identical with the spectrum observed when **9b** was completely O-protonated in superacid IV. Thus, the complicated pmr spectrum of this reaction mixture (**9b** in superacid system II) indicates the equilibria **11** ⇌ **9b** ⇌ *cis*-**10b** ⇌ *trans*-**10b**.

It is of interest to note that **9a** is completely C-protonated in superacid II while **9b** is partially C-protonated under identical conditions. The only difference between ions **10a** and **10b** is the nature of the stabilizing groups, OH and OCH_3, respectively. That a hydroxy group is a better substituent in stabilizing arenium ions than an alkoxy group, as has been observed in other systems.[10]

In superacid III, **9a** is 25% C-protonated to give **10a** and 75% O-protonated to give ion **11**. The pmr spectrum of the solution also shows two additional singlets at δ 2.52 and 7.50, besides the resonance absorption of ions **10a**. These two singlets were also observed when **9a** was completely O-protonated in superacid IV, except that the proton shifts are slightly changed owing to different media (see Table III). Similarly, **9b** is also 35% C-protonated to give **10b** and 65% O-protonated to ion **12** in superacid III. The ratio of C-protonation to O-protonation decreased with the decreasing molar ratio of HSO_3F/SbF_5, *i.e.*, the acidity of the medium.



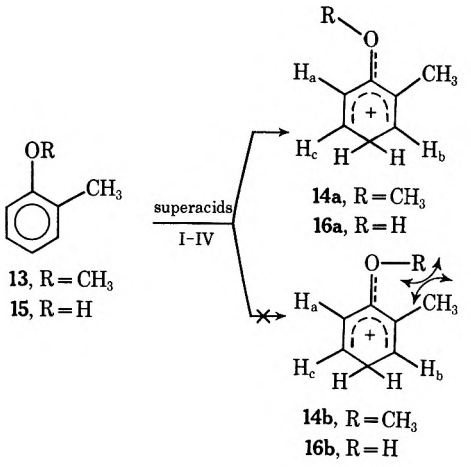
9a, R = H **11**, R = H
9b, R = CH_3 **12**, R = CH_3

The hydroxylic protons were not observable in both cases. However, the pmr spectrum of ion **12** was consistent with that reported by Brouwer[2b] except for the methoxy protons. The methoxy protons show a singlet at δ 4.67 instead of a doublet, indicating that rapid equilibration (*i.e.*, protonation–deprotonation) occurs. Table III also shows the influence of medium toward the proton shifts of both ions **11** and **12**. In stronger acid systems, more deshielding is observed and the individual aryloxocarbenium ions also have longer lifetimes.

B. *o*-Cresol and *o*-Methylanisole.—*o*-Methylanisole (**13**) is C-protonated in all the four superacid systems at low temperature to give the transoid benzenium ion (**14a**). The cisoid ion (**14b**) was not observed in the temperature range −80 to −28°, owing probably to the fact that ion **14b** is sterically less favorable than ion **14a**.

The methoxy protons show a sharp singlet at δ 4.68, indicating that only the more stable transolid ion **14a** is formed and no cisoid ion **14b** is present. The meta proton, H_a of ion **14a**, is a doublet at δ 7.67 (J_{HH} = 10 Hz) and is coupled to the ortho proton, H_c, which shows a doublet of quartets at δ 7.77 (J_{HH} = 10 and 1.5 Hz). The doublet of quartets of the

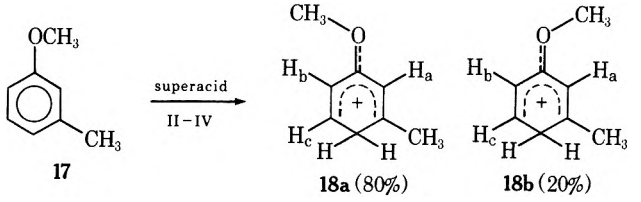
(10) (a) A. J. Kresge, Y. Chiang, and L. E. Hakka, *J. Amer. Chem. Soc.*, **93**, 6167 (1971); (b) G. A. Olah and Y. K. Mo, *ibid.*, **94**, 5341 (1972).



H_c proton arises from coupling between H_c and the CH_2 protons and also the long-range coupling to the H_b proton. Owing to the almost identical magnitude of coupling constant between H_c and CH_2, and H_c and H_b, a quartet is observed. Furthermore, the large coupling is due to coupling between H_a and H_c. All these couplings have been proven by double irradiation experiments.

Similarly, *o*-cresol (**15**) is also C-protonated in the four superacid systems at low temperature. In all cases, the site of protonation is on the ring carbon para to the hydroxy group and thus all give the same transoid benzenium ion (**16a**). The cisoid ion (**16b**) was again not observed and variable-temperature pmr studies indicated no interconversion of **16a** and **16b** between −80 and −20°. Rapid proton exchange between the hydroxylic proton and solvent system can be ruled out because of the observed pmr singlet for the OH proton absorption at δ 12.2. Thus, as in the previously discussed case, ion **16a** is sterically more favored than ion **16b**. The pmr spectrum of ion **16a** is similar to that of ion **14a**, except that a deshielded singlet at δ 12.2 (OH) is present instead of the methoxy absorption (Figure 2). The long-range coupling between the H_b and H_c protons is again observed.

C. *m*-Cresol and *m*-Methylanisole.—Protonation of *m*-methylanisole (**17**) in superacids II, III, and IV at −80° all give the isomeric benzenium ions **18a** and **18b**



in a ratio of 4:1. The clearest evidence for the formation of two isomeric ions **18a** and **18b** arises from the temperature-dependent pmr studies. The solution at −64° shows in its pmr spectrum two sharp singlets for the methyl protons in a ratio of 4:1, at δ 2.90 and 2.78. In addition, two sets of slightly broadened doublets (both have J_{HH} = 10 Hz) for the ortho proton are observed at δ 8.4 and 8.7 (also in a ratio of 4:1). When the temperature of the solution was raised to −16°, the two methyl singlets became a sharp singlet at δ 2.83 and the two sets of doublets (ortho proton) showed a doublet at δ 8.5 (J_{HH} = 10 Hz). These results indicate that interconversion of ions **18a** and **18b**

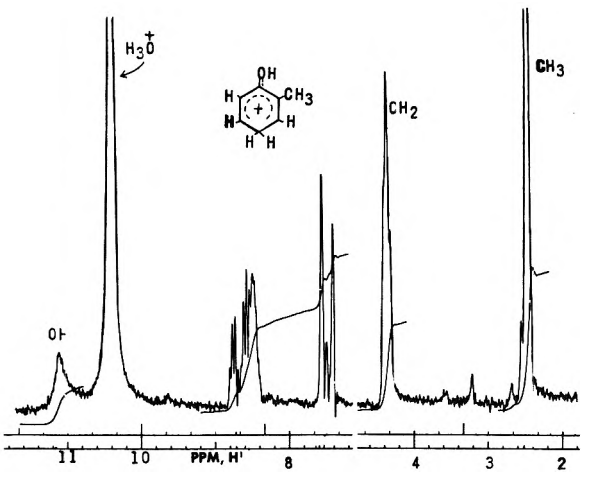
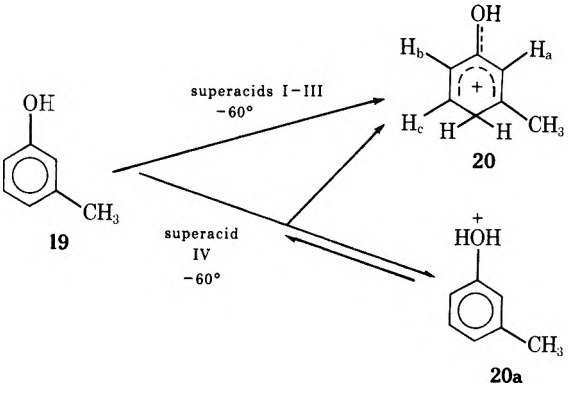


Figure 2.—Pmr spectrum of C-protonated *o*-cresol (3-methyl-4-hydroxybenzenium ion).

occurs at higher temperature. It should be noted that the methoxy protons and the two meta protons (H_a and H_b) have coincidental chemical shifts in ions **18a** and **18b**.

Protonation of **17** in superacid I gave the rapidly equilibrating ions **18a** ⇌ **18b** even at −80°. The pmr spectra of equilibrating ions **18a** ⇌ **18b** are almost identical in all four superacid systems at −10°.

m-Cresol (**19**) is completely C-protonated in the superacids I, II, and III, giving ion **20**. Since the

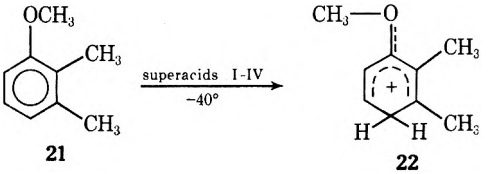


hydroxyl proton is not observable, isomeric ions cannot be observed even at −90°, indicating that rapid proton exchange occurs between ion **20** and the superacid system.

In superacid system IV, both C- and O-protonation of **19** was found. The pmr spectrum shows a singlet at δ 7.10 for the aromatic protons and the CH_3 singlet at δ 2.43 in addition to the pmr resonance lines of ion **20**.

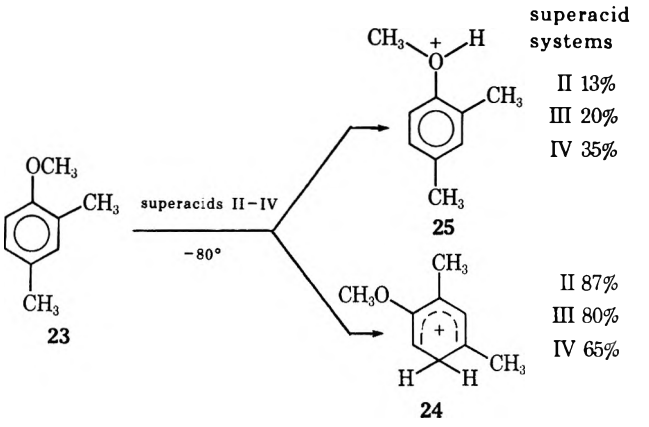
Protonation of Isomeric Dimethylanisoles.—Four isomeric dimethylanisoles (2,3-, 2,4-, 2,5-, and 2,6-) were protonated in all the four superacids.

A.—2,3-Dimethylanisole (**21**) is monoprotonated in all the four superacid systems to give the benzenium ion **22**. Owing to the steric effect of the *o*-CH_3 group, only



a single isomeric ion was observed. It is suggested that the methoxy group is preferentially trans to the methyl group.

B.—Two different monoprotonated ions (C-protonated ion **24** and O-protonated ion **25**) are formed in various ratios when 2,4-dimethylanisole (**23**) was



treated in the superacids II, III, and IV. The ratio of 24:25 increases as the acidity is increased (*i.e.*, the ratio of SbF_5–HSO_3F is increased). The relative amount of each ion was determined by the peak areas of a specific resonances in the pmr spectra.

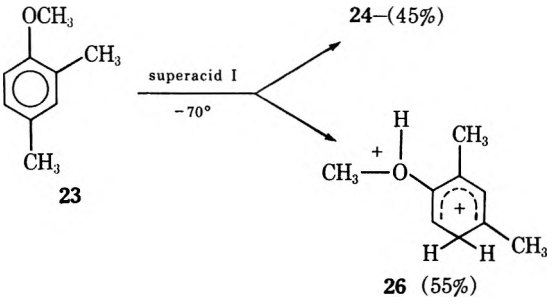
The site of protonation in **23** is of interest. Usually, a methoxy group is the most powerful orienting substituent. As the para position (with respect to OCH_3) of **23** is blocked, the proton attacks the C_5 carbon to give ion **24**. Inductively, ion **24** is stabilized by the two methyl groups (ortho and para) and the methoxy group is freely rotating (no partial double bond character) and has almost no influence on the stabilization of ion **24**. The ratio of 24:25 was found temperature independent, ranging from −80 to −30° in superacids II and III. It decreases, however, with increasing temperature in superacid IV. For example, the ratio is 3.5:6.5 at −80° and is decreased to 1.3:8.7 at −20°.

The pmr spectrum of ion **24** (mixed with ion **25**) shows a slightly broadened methylene singlet absorption at δ 4.43. The two methyl groups, coincide at δ 2.50 (sharp singlet), and the methoxy group show a singlet at δ 4.70. The ortho-vinyl proton shows a slightly broadened singlet absorption at δ 8.5, since it couples to the methylene protons. The meta-vinylic proton also is a singlet at δ 7.5.

The pmr spectrum of ion **25** shows the methoxy doublet at δ 5.01 (J_{HH} = 2.5 Hz) indicative of O-protonation. The hydroxylic proton is a rather broad quartet at δ 11.8 in the characteristic region of O-protonated ethers.[11] The two methyl groups show a coincidental singlet at δ 2.63 and the three aromatic protons as a singlet at δ 7.62.

In superacid I, **23** is both monoprotonated and diprotonated to give ions **24** and **26**, respectively. The evidence for the formation of dication **26** comes from the pmr spectrum of the reaction mixture. In the pmr spectrum, nothing corresponding to O-protonated ion **25** was observable. However, there are five absorption lines identical with those of ion **24** in every respect. The remaining five absorption lines show similar features to those of ion **24** but deshielded by

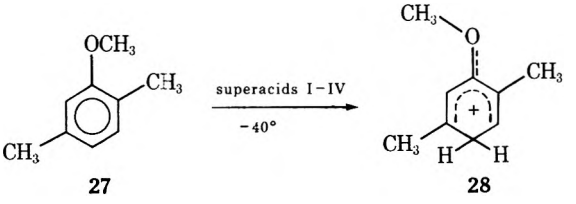
(11) G. A. Olah and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 1725 (1967).



about 0.8 ppm. This indicates that a diprotonated species with a structure resembling ion **24** is formed. Ion **26** seems best to fit spectral data (Table II). The unusual behavior of superacid system I toward **23** is rather surprising. However, as previously mentioned, the methoxy group in ion **24** has almost no conjugative effect and additional protonation in superacid I could take place on the oxygen lone pair to yield ion **26**.

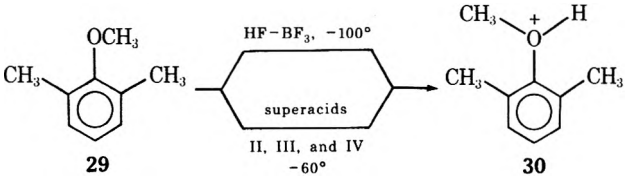
The pmr spectra of the mixture of ions **24** and **26** is slightly temperature dependent. The ratio of **26**:**24** decreased from 5:4 at −70° to 4:5 at −10° and the change was found to be reversible. Ion **26** is the first directly observed diprotonated long-lived benzenium type ion derived from a monoalkoxybenzene (diprotonation also was observed in the case of 2,6-dimethylanisole, *vide infra*).

C.—Protonation of 2,5-dimethylanisole (**27**) in all four superacids gave the identical benzenium ion **28**. The pmr spectrum of ion **28** is well resolved and can be



readily assigned. The meta- and ortho-methyl proton absorptions show two singlets at δ 2.42 and 2.85, respectively. Owing to the steric effect of the ortho CH_3 group, we only observed the isomeric trans ion. Thus, a sharp singlet at δ 4.73 was assigned to the methoxy protons. The methylene protons show a slightly broadened singlet at δ 4.2, since they are coupled to the ortho-vinyl proton. The ortho proton appears as a triplet at δ 8.22 (J = 1.5 Hz).

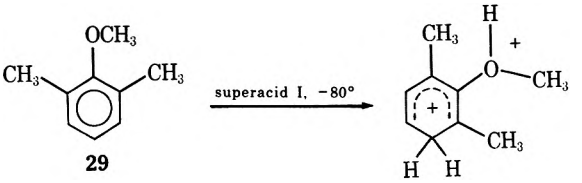
D.—Protonation of 2,6-dimethylanisole (**29**) in HF–BF_3 at −100° has been studied by Brouwer, Mackor, and MacLean.[2b] They found that only the O-protonated oxonium ion **30** was obtained under their



experimental conditions. We extended this study to the behavior of **29** in the four superacids. Indeed, **29** was O-protonated in superacids II, III, and IV at −60°. The best medium is superacid III, in which a well-resolved pmr spectrum is observed (Figure 3, upper trace). In superacid IV, no hydroxylic proton

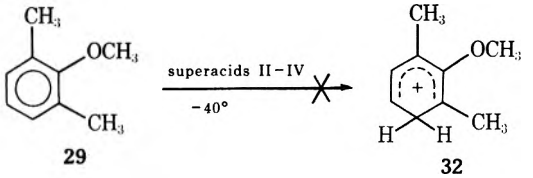
was observed, indicating rapid equilibration with the solvent acid. The pmr spectrum of ion **30** is similar (with slight differences) to the reported data (Table II).

It is, however, interesting to observe the different behavior of **29** in superacid I. The pmr spectrum (Figure 3, lower trace) shows no indication of ion **30**. The aromatic protons are split into two equal intensity broadened peaks at δ 8.5 and 9.6. In the $-OH_2^+$ region, a relatively broadened absorption is observed at δ 13.8. There are three slightly broadened singlets at δ 3.5 (6 H, CH_3), 5.4 (3 H, OCH_3), and 5.8 (2 H, CH_2). Based on these data, we conclude that **29** is diprotonated in superacid I to give ion **31**. In comparison,



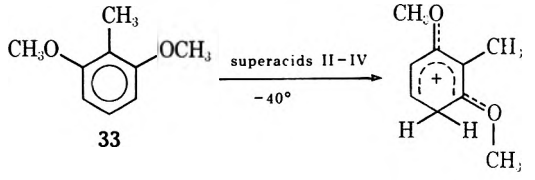
29 31

ion **31** is sterically less favored than ion **26**, even though they both formed in the same superacid medium. However, it is rather surprising that in superacids II–IV **29** does not undergo C-protonation to give the monoprotonated benzenium ion **32**, and only O-pro-



29 32

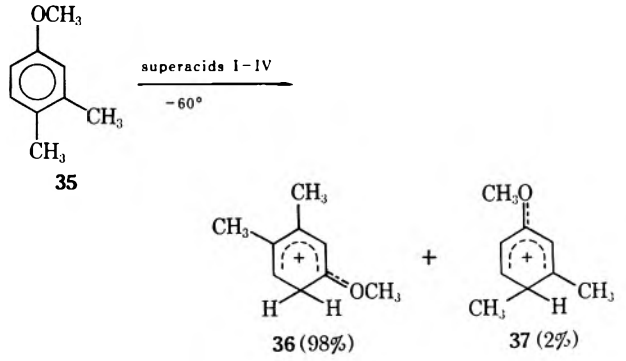
tonation is observed to give ion **30**. In contrast, 2,6-dimethoxytoluene (**33**) is C-protonated in superacids II–IV to give 2,4-dimethoxy-3-methylbenzenium ion (**34**). The structure of ion **34** was confirmed by its



33 34

pmr spectrum (see Table II). In superacid I, **33** was polymerized to unidentified products.

E.—Protonation of 3,4-Dimethylanisole (**35**) in HSO_3F solution has been studied by Vaughan and coworkers.[2d] They found two different C-protonated ions, **36** (98%) and **37** (2%). Similar results were



35 36 (98%) 37 (2%)

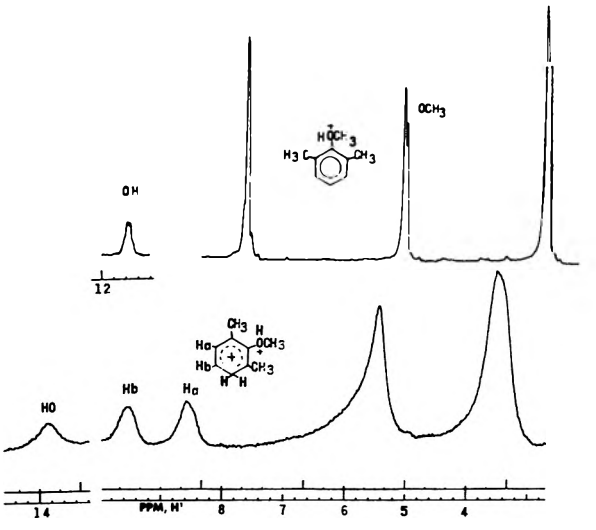
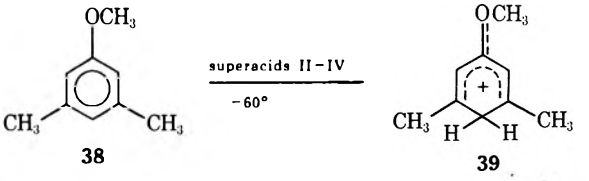


Figure 3.—Pmr spectra of O-protonated 2,6-dimethylanisole (upper trace) and diprotonated 2,6-dimethylanisole (bottom trace).

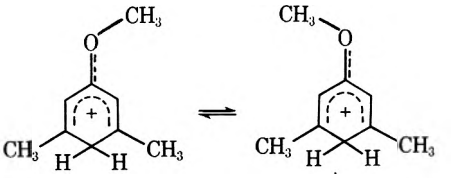
obtained in the protonation of **35** in the four superacids. The pmr spectrum of ion **36** is in accordance with its structure (Table II). Formation of ion **37** is based on the presence of a low-intensity (*ca.* 2%) shielded doublet at δ 1.8 ($J_{CH_3,H}$ = 7 Hz) corresponding to the methyl proton attached to the methylene carbon atom.

F.—Protonation of 3,5-dimethylanisole (**38**) in HF solution was examined by Brouwer and coworkers.[2b] They found only a single benzenium ion **39**. In super-



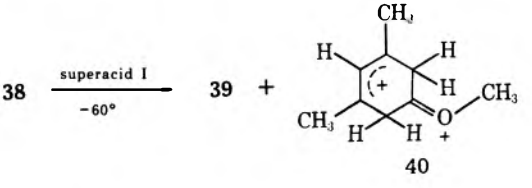
38 39

acids II–IV, ion **39** is obtained and the pmr spectrum is similar to that reported.[2b] The pmr spectrum of ion **39** is found, however, to be temperature dependent, owing in all probability to the hindered rotation of the methoxy group. At low temperature (−80°),



the rotation is slow or does not occur at all, as different methyl groups and vinylic methine protons are observed. (Table II). At higher temperatures (*e.g.*, −20°), each set of the two singlets collapsed and finally became a singlet. The rotation of the OCH_3 group at −20° is rapid, causing two methyl groups and also the two ring methine protons to become equivalent.

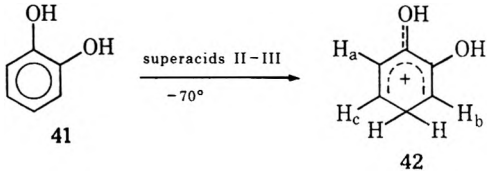
In superacid I, **38** is both mono- and diprotonated to give ions **39** and **40**, respectively. The ratio of ions



40

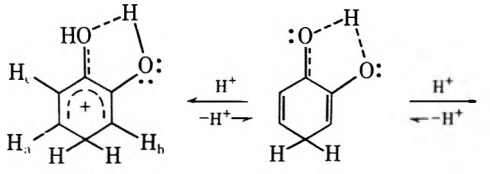
39:40 is dependent on the ratio of the molar concentration of HF–SbF_5 and 38. Dication 40 was formed predominantly at higher concentration of HF–SbF_5 in the solution. The formation of dication 40 is indicated by its substantially deshielded pmr absorbtions. The pmr spectrum shows (besides the absorption lines of ion 39) a singlet due to the two methyl groups at δ 3.62 (6 H), a methoxy singlet at 5.60 (3 H), a slightly broadened methylene singlet at 5.5 (4 H), and a vinyl singlet at 8.66 (1 H).

Protonation of Dihydroxybenzenes. A. Catechol (41) is C-protonated in superacids II and III to give the 3,4-dihydroxybenzenium ion 42. The pmr spectrum

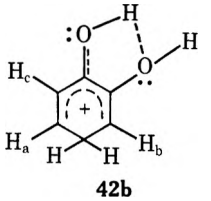


41 42

is temperature independent ranging from −90 to −20°, indicating the absence of isomeric cisoid and transoid ions of 42 and no 1,2-hydrogen shift of the methylene protons. Furthermore, the hydroxylic protons were not observable, presumably because of rapid protonation–deprotonation equilibrium (exchange), even though the hydroxylic proton of C-protonated phenol[2] was observed under identical conditions. Apparently, intra- and intermolecular hydrogen bonding seem to be responsible for such observation. A possible mechanism for the rapid proton exchange involves the *p*-quinoidal intermediate (43). On the other hand, di-

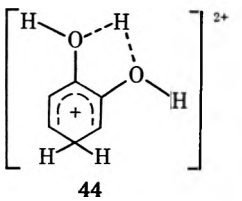


42a 43



42b

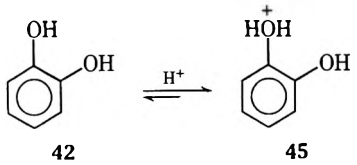
protonated catechol (44) as an intermediate could



44

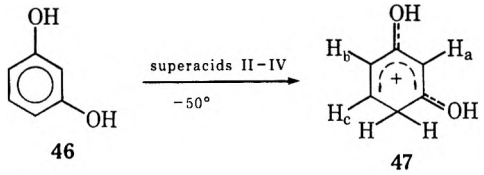
equally well explain the rapid proton exchange of 42 with the superacid systems. The pmr spectrum of ion 42 shows a slightly broadened singlet at δ 4.6 (2 H, CH_2), a doublet at 7.74 (1 H, H_a, J_{HH} = 9 Hz), a triplet at 8.03 (1 H, H_b, J_{HH} = 2 Hz), and a doublet of triplets at 8.90 (1 H, H_c, J_{HH} = 9 and 2 Hz). The shielding (0.9 ppm) of the ortho proton by the adjacent hydroxyl group should be noted.

When 41 was protonated in superacid IV, the pmr spectrum indicated the formation of ion 42 and an additional sharp singlet at δ 7.44. This sharp singlet can be tentatively assigned to the aromatic protons of O-protonated catechol (45) undergoing rapid hydrogen exchange with the solvent system.



42 45

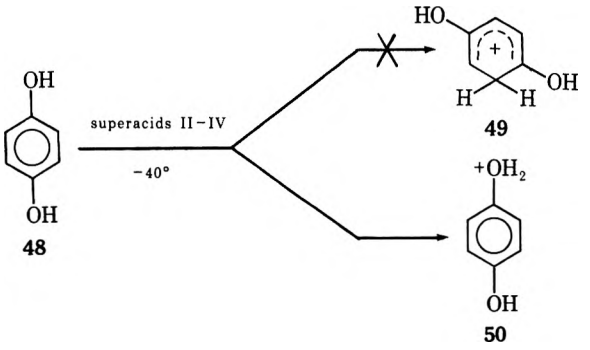
B. Resorcinol (46) is the strongest base among the three dihydroxybenzenes. It is completely C-protonated in superacids II–IV at −50° to give the 2,4-dihydroxybenzenium ion (47). Alder and Taylor[2c]



46 47

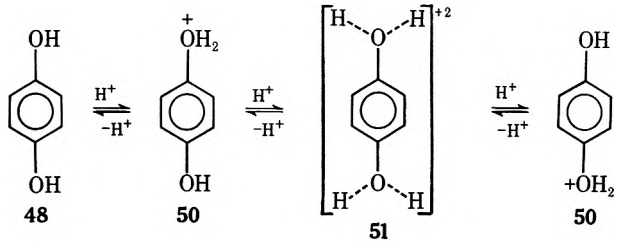
also found that 46 was C-protonated in BF_3–HF sulfolane solution, but gave no report on either peak multiplicities or coupling constants. The pmr spectrum of ion 47 as obtained in our work shows a doublet at δ 4.73 (CH_3, J_{HH} = 3.5 Hz), a singlet at 6.82 (H_a), a doublet at 7.31 (H_b, J_{HH} = 10 Hz), and a doublet of triplets at 8.10 (H_c, J_{HH} = 10 and 3.5 Hz). The shielding effect of the H_a proton in ion 47 by the two OH groups is noteworthy. The well-resolved doublet of triplets of the H_c proton clearly shows the rapid conformational interconversion about the benzenium ring. The hydroxylic protons are again not observed, implying rapid exchange (*via* intra- and intermolecular processes).

C. Hydroquinone (48) is not C-protonated in any of the superacids to give the 2,5-dihydroxybenzenium ion 49. The pmr spectra of 48 in superacids II, III,



48 49 50

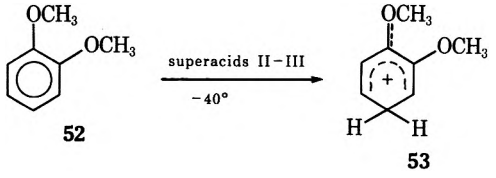
and IV (at −40°) show a sole singlet absorption at δ 8.52, 7.91, and 7.50, respectively. These results imply a rapid O-protonation–deprotonation process (48 ⇄ 50). In the strongest of the three superacid systems (*i.e.*, II), the equilibrium is shifted to the right and the singlet absorption is deshielded by about 1.5 ppm from that of the precursor 48. Furthermore, the hydroxylic protons cannot be observed even at −90°, indicating that 48 ⇄ 50 is an extremely rapid and low activation energy process. One possible mechanism for the proton exchange reaction may be involvment of the dipositive ion (or transition state) 51.



Protonation of **41**, **46**, and **48** in superacid I at −78° all gave only unidentified polymeric products. The reason for this difference in chemical behavior is not readily apparent, although superacid I is the strongest of the superacid systems used and may cause the most exothermic, difficult to control reactions, with possibility of local overheating causing polymerization.

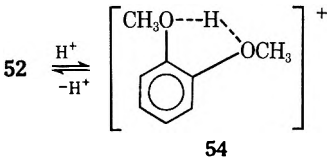
Protonation of Dimethoxybenzenes.—In many respects, protonation of dimethoxybenzene in the four superacid systems is similar to the protonation of dihydroxybenzenes. The only obvious difference is that no polymerization takes place when any of the dimethoxybenzenes is protonated in any of the four superacids.

A. *o*-Dimethoxybenzene (veratrole) (52) was found C-protonated in superacids II and III, giving the 3,4-dimethoxybenzenium ion **53**. The pmr spectrum of



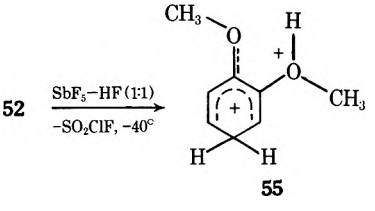
ion **53** shows the methylene proton absorption at δ 4.8 (slightly broadened). The assignment of the ring protons is similar to those of C-protonated catechol **52** (also see Table II).

In HSO_3F–SO_2ClF (IV), **52** undergoes both C- and O-protonation. However, the O-protonated ion **54**

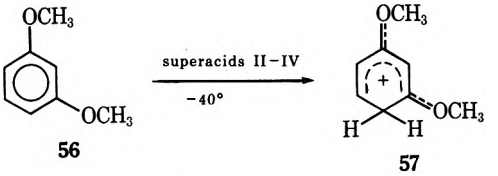


is in equilibrium with **52**. It is likely that the acidic proton is attached to both methoxy oxygens *via* hydrogen bonding.

In HF–SbF_5(1:1)–SOClF, (I) **52** was C-protonated. The pmr spectrum of the solution shows a similar pattern to that of ion **53**, but all the absorption lines are deshielded by 0.43–1.24 ppm (see Table II). The deshielding effect is probably coming from additional protonation of the oxygen atom (ortho OCH_3) of ion **57** to give the dication **55**, but rapidly exchanging with the acid solvent.

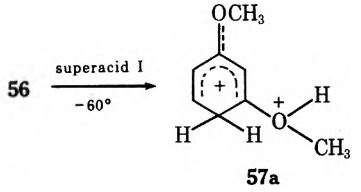


B. *m*-Dimethoxybenzene (56) was C-protonated in superacids II–IV to give 2,4-dimethoxybenzenium ion (**57**). Brouwer and coworkers[2b] also found ion **57** when

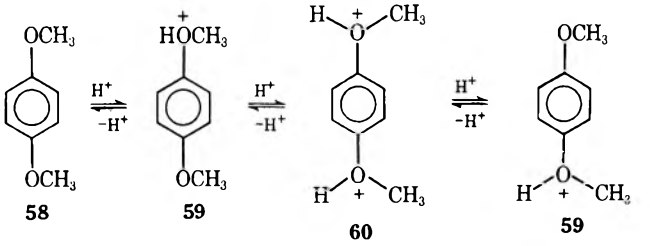


56 was treated with HF at −70°. The pmr spectrum of ion **57** is similar to that of ion **47** except that there are two additional sharp singlet absorptions at δ 4.52 and 4.63 for the ortho and para OCH_3, respectively.

56 in superacid I at −40° gave a pmr spectrum similar to that of ion **57** but all the resonance lines were deshielded by ~1 ppm (see Table II). In addition, a broadened, deshielded absorption was found at δ 12.2. These data suggest that a diprotonated species is formed. The second proton is likely attached to the ortho OCH_3 rather than the para OCH_3 group. These data indicate that **56** was diprotonated to give dication **57a**, which, however, exchanges with the solvent system.



C. *p*-Dimethoxybenzene (58) was O-protonated in all the four superacids. In the weakest acid (IV), the pmr spectrum shows two singlet absorptions at δ 4.46 and 7.58 for the methoxy and the aromatic protons, respectively. When the acidity is increased in III and II, the methoxy singlet absorptions were deshielded to δ 5.23 and 5.30, as were the aromatic singlet absorptions to δ 8.10 and 8.18, respectively. These results are similar to those derived for the protonation of hydroquinone **48**, which involves a O-protonation–deprotonation process. No polymerization took place when **58** was treated in superacid I, and indeed, the



dication **60** was observed. The pmr spectrum of dication **60** shows the methoxy doublets at δ 5.48 (J_{HH} = 3 Hz), an aromatic singlet absorption at δ 8.24, and the deshielded hydroxyl quartets at δ 11.92 (J_{HH} = 3 Hz).

Conclusion

The sites of protonation of mono- and dihydroxybenzenes as well as their substituted derivatives were found to be dependent on the acid media used. Generally, O-protonation is favored in weaker acid media, while C-protonation was usually achieved in stronger

superacid media (for example, in the case of protonation of phenol, anisole, *m*- and *p*-cresols, and 2,4,6-dimethylanisole). In some cases, a mixture of O- and C-protonated species were observed in the same solution and their relative ratio is related to the acid media used. The ratio of stereoisomer (cis and trans) formation is also dependent on the acid media used.

Based on their protonating ability the decreasing acidity of the four superacid systems used is I > II > III > IV.

Substituent effects play an important role in the course of protonation. In FSO_3H–SO_2ClF solution, *m*-methylanisole (**17**) was completely C-protonated (**18**) while *m*-cresol (**19**) was partially O-protonated (25%) to **20a** under identical experimental conditions. These results suggest that a methoxy group can stabilize a benzenium ion better than a hydroxy group. In contrast, we found in the protonation of 3,5-dimethoxyphenol that the site of protonation is four times more favorable at the carbon atom para to the hydroxyl than para to the methoxyl groups.[10] Similarly, *p*-cresol (**9a**) is completely C-protonated in superacid II to give ion **10a**, while **9b** is partially C-protonated under identical conditions. The reason for these differences is not yet completely understood. It is known that methoxyl groups activate the aromatic ring in electrophilic substitutions. However, we were not able to C-protonate *p*-dimethoxybenzene (**58**) even in the strongest superacid I medium, as it gave only the O-diprotonated dication **60**.

It is reasonable to assume that initial kinetic protonation is on oxygen, which, however, in many systems is a completely reversible process and O-protonated ions can be observed only in low-nucleophilicity media (*i.e.*, superacids), but even in these their exchange processes frequently remain rapid. In contrast C-protonated ions [hydroxy(alkoxy)benzenium ions] show considerably less tendency to exchange with solvent.

Finally, three different types of dications were observed in the protonation of studied hydroxy (alkoxy) aromatic compounds. These are (i) di-O-protonated *p*-dimethoxybenzene (**60**), (ii) di-C-protonated 3,5-dimethylanisole (**40**), and (iii) O- and C-diprotonated 2,4-dimethylanisole (**26**), *o*- and *m*-dimethoxybenzenes (**55** and **57a**). Diprotonation was only achieved in the strongest superacid I. The nature of these dications is further discussed in our subsequent paper.[10b]

Experimental Section

Materials.—All the mono- and dihydroxybenzenes and their methyl ethers were commercially available in high purity and were used without further purification. Antimony pentafluoride (Allied Chemical Co.) was refluxed for 12 hr while passing a stream of dry nitrogen throught it to remove HF. The material was then twice distilled (bp 150°). Fluorosulfuric acid (Allied Chemical Co.) was twice distilled (bp 160–164°) before use. Hydrogen fluoride was obtained from Baker Chemical Co., sulfuryl chloride fluoride from Allied Chemical Co.

Preparation of Ions.—Superacids were prepared by mixing antimony pentafluoride and HF or HSO_3F at −78° in Teflon bottles. The resulting solutions were then diluted with sulfuryl chloride fluoride. Ions for nmr studies were prepared by adding ~50 mg of the aromatic compound to be protonated in an nmr tube to 1 ml of the above superacid solutions (at −78°), with good stirring, which was continued until a clear solution was obtained. Following their nmr study the solutions were quenched (as previously described[3]) and starting hydroxy (methoxy) compounds were recovered (as indicated by nmr, ir, and glc studies) showing that no side reactions took place otherwise as described.

Nmr Spectra.—A Varian Associates Model A-56/60A nmr spectrometer equipped with a variable-temperature probe was used for ^1H nmr spectra. Carbon-13 INDOR spectra[12] were obtained on a Varian Associates Model HA100 nmr spectrometer as described.

Registry No.—**2**, 37145-55-4; **4**, 19527-06-1; **6**, 37396-37-5; **10a**, 37396-38-6; **10b**, 37396-39-7; **11**, 37145-49-6; **12**, 37145-50-9; **14a**, 37145-56-5; **16a**, 37145-57-6; **18**, 37145-58-7; **20**, 37145-59-8; **20a**, 37396-35-3; **22**, 37145-60-1; **24**, 37145-61-2; **25**, 37145-51-0; **26**, 37145-62-3; **28**, 37396-40-0; **30**, 37145-52-1; **31**, 37145-63-4; **34**, 37145-64-5; **36**, 33516-56-2; **39**, 37145-66-7; **40**, 37145-67-8; **42** (ion), 37145-68-9; **43**, 37145-69-0; **45**, 37145-70-3; **45a**, 37396-36-4; **47**, 37145-714; **50**, 37145-53-2; **57**, 37145-72-5; **57a**, 37396-41-1; **60**, 37145-54-3.

Acknowledgment.—Support of our work by the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health is gratefully acknowledged.

(12) A. M. White and G. A. Olah, *J. Amer. Chem. Soc.*, **91**, 2943 (1969).

Onium Ions. V.[1] Di- and Trihalonium Ions

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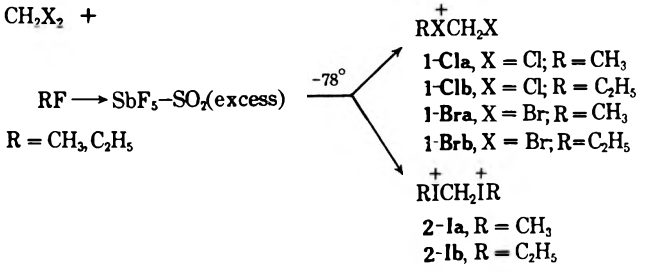
Alkylation of dihaloalkanes and dihalobenzenes with methyl and ethyl fluoroantimonate in SO_2 solution was carried out and products were studied by pmr spectroscopy. Monoalkylation giving alkyl- and haloalkyl(aryl)-halonium ions, as well as dialkylation leading to the formation of the corresponding dialkylalkylene(phenylene)-dihalonium ions, were observed. Alkylation of triiodobenzene and triiodomesitylene resulted in formation of the corresponding trialkylphenylene trihalonium ions.

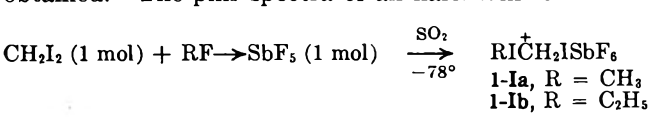
In our previous studies we have reported the preparation of a variety of dialkylhalonium ions by alkylating alkyl halides.[2] More recently, we have also prepared alkylarylhalonium ions and studied their behavior in Friedel–Crafts alkylation reactions.[1] In order to gain further insight into the nature of halonium ions and the donor ability of halogens toward electrophiles, we have now undertaken the preparation of dihalonium and trihalonium ions by alkylating dihaloalkanes, dihalobenzenes, and trihalobenzene with methyl and ethyl fluoroantimonate in SO_2 solution at low temperatures.

Results and Discussion

A. Dialkylalkylenedihalonium Ions. Alkylation of Dihalomethanes.—When excess methyl or ethyl fluoroantimonate in SO_2 solution[3] was treated with dichloro(bromo)methane (CH_2X_2, X = Cl and Br) at −78°, monoalkylated dihalomethanes **1-Cl** and **1-Br** were formed. In the case of diiodomethane, dimethyl- and diethylmethylenediiodonium ions **2-Ia,b** were



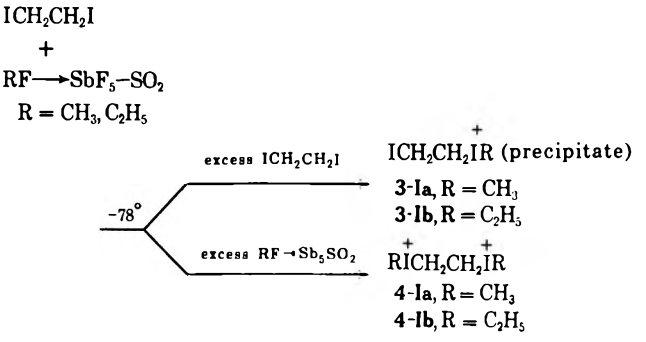
formed. However, when equal molar diiodomethane was used, monoalkylated iodonium ions **1-Ia,b** were obtained. The pmr spectra of all halonium ions **1-Xa**



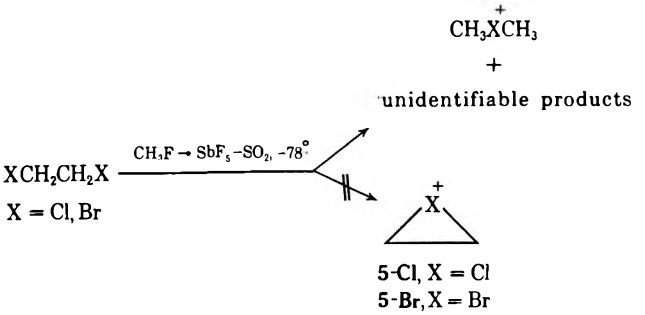
shows two sharp singlet absorptions in a ratio of 2:3 for the methylene and methyl protons, respectively (Table I). The pmr spectrum of dihalonium ion **2-Ia** shows two deshielded singlet absorptions at δ 4.10 (CH_3) and 5.80 (CH_2) in a ratio of 3:1. The pmr spectra of halonium ions **1-Xb** and **2-Ib** all show a set of triplet (CH_3), quartet (CH_2), and singlet absorptions. It is of interest to note that the CH_3 proton shifts of halonium ions **1-Xb** are deshielded in the order I > Br > Cl (δ 2.40 > 2.22 > 2.01) while the methylene proton shifts show an opposite trend, Br > Cl > I (See Table I).

Attempted preparation of dialkylmethylenedichloronium (bromonium) ions by treating even a large excess of methyl (ethyl) fluoroantimonate in SO_2 with CH_2Cl_2 or CH_2Br_2 at −78° was unsuccessful, and only the monoalkylated ions **1X-a,b** were observed to formed. At the same time the preparation of *gem*-dihalonium ions **2-Ia,b** shows that iodine has unusual ability to delocalize positive charge and thus allows formation of dialkylmethylenedihalonium ions **2-Ia,b**, the two positive iodonium cations separated by a single methylene group.

Alkylation of Dihaloethanes.—When 1,2-diiodoethane was treated with methyl and ethyl fluoroantimonate, respectively, in sulfur dioxide solution, dialkylethylenedihalonium ions **4-1a,b** were formed. When equal or excess 1,2-diiodoethane was used, an insoluble iodonium salt precipitated, which is assumed to be monoalkylated 1,2-diiodoethane, **3-I** (low solubility prevented so far its identification).



When 1,2-dihaloethanes, XCH_2CH_2X (X = Cl or Br), were treated with methyl fluoroantimonate in SO_2 at −78°, the only identifiable products were dimethylhalonium ions, $CH_3XCH_3^+$ (X = Cl or Br), indicating that ionization cleavage of XCH_2CH_2X occurred *via* the formation of $XCH_2CH_2X^+CH_3$. No ethylenehalonium ions **5-X** were formed under these reaction



(1) Part III: G. A. Olah and E. G. Melby, *J. Amer. Chem. Soc.*, **94**, 6220 (1972). Part IV: G. A. Olah and E. G. Melby, *ibid.*, submitted for publication.

(2) G. A. Olah and J. R. DeMember, *ibid.*, **91**, 2113 (1969); **92**, 718 (1970).

(3) G. A. Olah, J. R. DeMember, and R. H. Schlosberg, *ibid.*, **91**, 2112 (1969).

TABLE I

PMR PARAMETERS OF MONO- AND DIALKYLATED DIHALOALKANES[a]

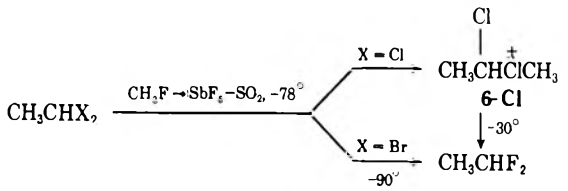
Registry no.	Ion	δ_{CH}	δ_{CH_2}	δ_{CH_2X}	$\delta_{CH_2X^+}$	$\delta_{X^+CH_2}$	δ_{CH_3}	$\delta_{X^+CH_3}$
37160-90-0	$ClCH_2\overset{+}{C}lCH_3$				5.56 (s)			4.51 (s)
37160-91-1	$ClCH_2\overset{+}{C}lCH_2CH_3$				5.50 (s)	5.52 (q) $J = 7$	2.01 (t) $J = 7$	
37160-92-2	$BrCH_2\overset{+}{B}rCH_3$				6.33 (s)			4.30 (s)
37160-93-3	$BrCH_2\overset{+}{B}rCH_2CH_3$				6.32 (s)	5.46 (q) $J = 7$	2.22 (t) $J = 7$	
37160-94-4	$ICH_2\overset{+}{I}CH_3$				5.17 (s)			3.58 (s)
37160-95-5	$ICH_2\overset{+}{I}CH_2CH_3$				5.40 (s)	4.90 (q) $J = 7$	2.40 (t) $J = 7$	
37160-96-6	$(CH_3\overset{+}{I})_2CH_2$				5.80 (s)			4.10 (s)
37160-97-7	$(CH_3CH_2\overset{+}{I})_2CH_2$				5.88 (s)	5.33 (q) $J = 7$	2.44 (t) $J = 7$	
37160-98-8	$(CH_3\overset{+}{I}CH_2)_2$				5.06 (s)			4.00 (s)
37160-99-9	$(CH_3CH_2\overset{+}{I}CH_2)_2$				4.90 (s)	4.93 (q) $J = 7.5$	2.20 (t) $J = 7.5$	
24400-25-7	$CH_3\overset{+}{C}HClCH_3$ (Cl)	6.23 (q) $J = 6$					2.17 (d) $J = 6$	4.50 (s)
37161-01-6	$Cl(CH_2)_3\overset{+}{C}lCH_3$		2.90 (qu) $J = 5$	4.00 (t) $J = 5$	5.47 (t) $J = 5$			4.52 (s)
37161-02-7	$Cl(CH_2)_3\overset{+}{C}lCH_2CH_3$		2.74 (m)	3.91 (t) $J = 6$	5.3 (m)[b]	5.3 (m)[b]	2.00 (t) $J = 7$	
37161-03-8	$Cl(CH_2)_3\overset{+}{B}rCH_3$		2.70 (qu) $J = 5$	3.84 (t) $J = 5$	5.10 (t) $J = 5.5$			4.08 (s)
37161-04-9	$Cl(CH_2)_3\overset{+}{B}rCH_2CH_3$		2.83 (m)	3.94 (t) $J = 6$	5.2 (m)[b]	5.2 (m)[b]	2.20 (t) $J = 6.5$	
37161-05-0	$Br(CH_2)_3\overset{+}{B}rCH_3$		2.82 (qu) $J = 7$	3.70 (t) $J = 7$	5.20 (t) $J = 6$			4.10 (s)
37161-06-1	$Br(CH_2)_3\overset{+}{B}rCH_2CH_3$		2.93 (m)	3.80 (t) $J = 7$	5.1 (m)[b]	5.1 (m)[b]	2.17 (t) $J = 7$	
37161-07-2	$I(CH_2)_3\overset{+}{I}CH_3$		2.70 (qu) $J = 7$	3.58 (t) $J = 7$	4.57 (t) $J = 7$			3.58 (s)
37161-08-3	$I(CH_2)_3\overset{+}{I}CH_2CH_3$		2.90 (m)	3.92 (t) $J = 7$	4.7 (m)[b]	4.7 (m)[b]	2.28 (t) $J = 7$	
37161-09-4	$CH_2(CH_2\overset{+}{B}rCH_3)_2$		3.24 (qu) $J = 7$		5.03 (t) $J = 7$	5.03 (t) $J = 7$		4.26 (s)
37161-10-7	$CH_2(CH_2\overset{+}{B}rCH_2CH_3)_2$		3.2 (m)		4.93 (t) $J = 7$	5.28 (q) $J = 7$	2.16 (t) $J = 7$	
37161-11-8	$CH_2(CH_2\overset{+}{I}CH_3)_2$		3.2 (m)		4.60 (t) $J = 8$			3.80 (s)
37161-12-9	$CH_2(CH_2\overset{+}{I}CH_2CH_3)_3$		3.2 (m)		4.60 (t) $J = 8$	4.83 (q) $J = 7$	2.30 (t) $J = 7$	

[a] Proton chemical shifts are referred to external capillary TMS. Abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; qu = quintet; m = multiplet. J values are in hertz. [b] Overlapping multiplet.

conditions, although the ethylenebromonium ion **5-Br** was known to form from 1,2-dibromoethane in SbF_5–SO_2 solution.

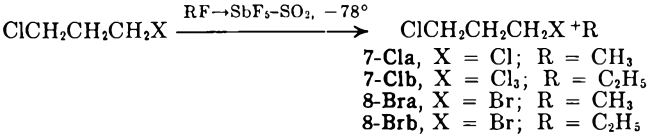
Methylation of 1,1-dichloroethane in CH_3F–SbF_5–SO_2 solution at −78° gave the methyl α-chloroethylchloronium ion **6-Cl**. Halonium **6-Cl** decomposed

and gave the halogen-exchanged cleavage product CH_3CHF_2 at higher temperature (*ca.* −30°). In the case of 1,1-dibromoethane, no methyl α-bromoethylbromonium ion **6-Br** could be observed even at −90°,



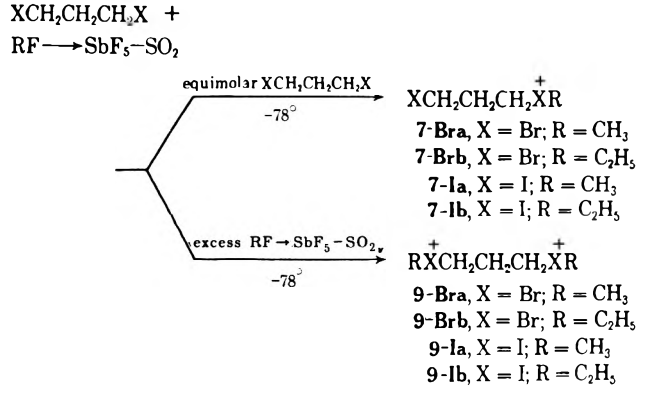
as halogen-exchanged decomposition product CH_3CHF_2 formed immediately.

Alkylation of Dihalopropanes.—1,3-Dichloro- and 1-bromo-3-chloropropanes were monoalkylated in excess RF–SbF_5–SO_2 (R = CH_3, C_2H_5) solutions at −78° to give halonium ions **7-Cl** and **8-Br**, respectively. The



pmr spectra of halonium ion **7Cla** and **8-Bra** are very similar. Monoalkylation was evidenced by the observed nonequivalent terminal methylene groups of **7-Cl**. Thus, the $-CH_2Cl^+$ protons show a more deshielded triplet (δ 5.47) than that of $-CH_2Cl$ (δ 4.00). Alkylation of 1-bromo-3-chloropropane occurs at the bromine atom rather than chlorine to give **8-Br**. This is based on the fact that bromine has better ability to delocalize charge, and also the methyl and methylene proton shift (of the ethyl group) in **8-Br** are too shielded for $BrCH_2CH_2CH_2Cl^+R$ (R = CH_3, C_2H_5). Ions **8-Cl** were not stable above −20° and decomposed to yet unidentified products. On the other hand, ions **8-Br** were stable to −10°.

Alkylation of 1,3-dibromo(iodo)propane in RF → SbF_5–SO_2 solution gave mono- or dihalonium ions **7-X** and **9-X** (X = Br, I), respectively, dependent on the reaction conditions. The pmr spectra of **9-Bra**



and **9-Brb** are shown in Figure 1. Similar pmr characteristics are observed for ions **7-X** (X = Cl, Br, I) and ions **9-X** (X = Br and I) (Table I). The formation of dihalonium ions **9-X** is evidenced from the observation of the two equivalent terminal methylene

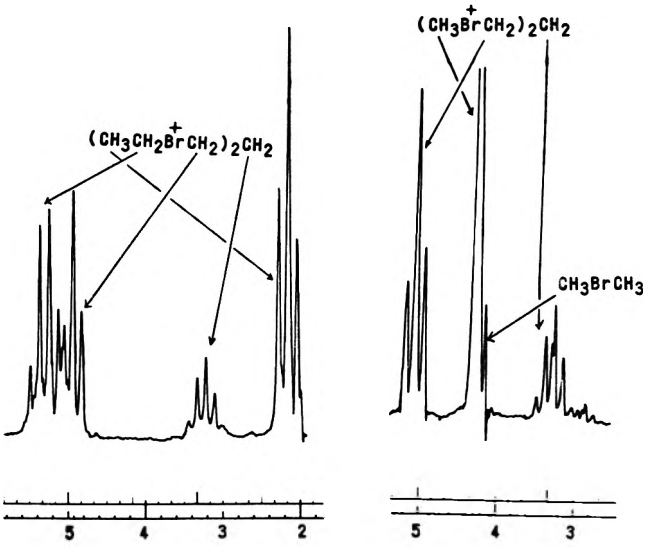
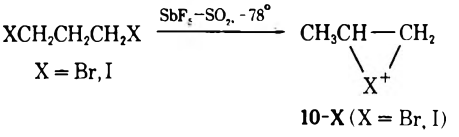


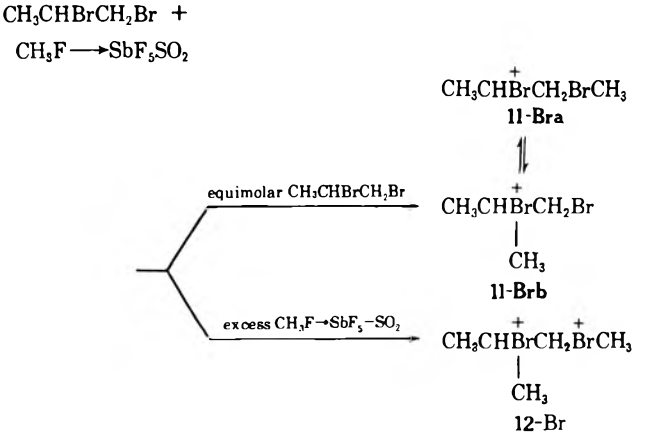
Figure 1.—Pmr spectra of dimethylated (right) and diethylated (left) 1,3-dibromopropane (**9-Bra** and **9-Brb**).

pmr absorptions (4 H) and a quintet absorption for the center methylene protons (2 H).

It should be noted that halonium ions **7-X** (except **7-Cl**) and dihalonium ions **9-X** are stable to −10° although 1,3-dihalopropanes are known to generate methylethylenehalonium ions **10-X** when treated with SbF_5–SO_2 solution.[4]



When 1,2-dibromopropane was added to excess methyl fluoroantimonate in SO_2 solution at −78°, dihalonium ion **12-Br** was formed. On the other hand, monomethylated 1,2-dibromopropane **11-Br** was obtained when equal molar methyl fluoroantimonate was used.



The site of monomethylation of 1,2-dibromopropane cannot be ascertained because both methine and methylene pmr absorptions are deshielded to a similar extent. Thus, it is assumed that the two possible monomethylated halonium ions **12-Bra** and **12-Brb** are in equilibrium. Consequently, monomethylated

(4) G. A. Olah, J. M. Bollinger, Y. K. Mo, and J. M. Brinich, *J. Amer. Chem. Soc.*, **94**, 1164 (1972).

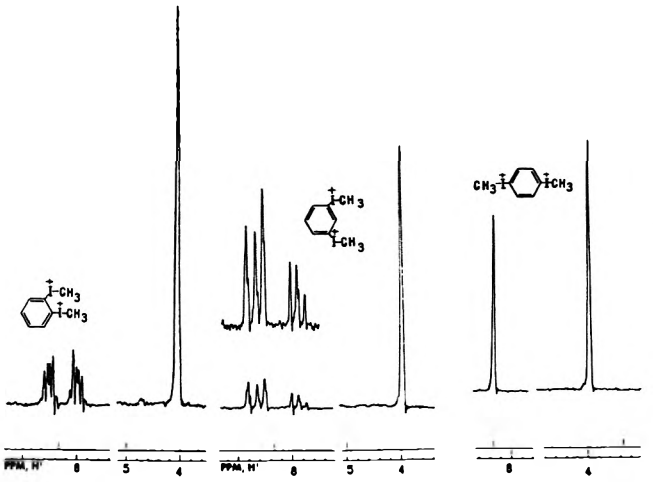
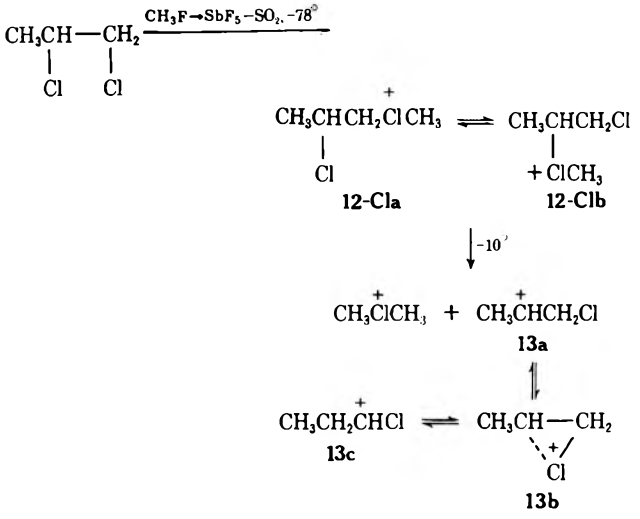


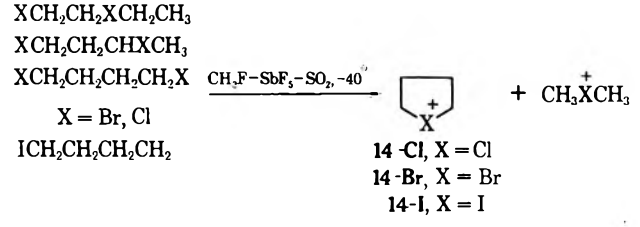
Figure 2.—Pmr spectra of dimethylated *o*-diiodobenzene, **16a** (left), *m*-diiodobenzene, **16b** (middle), and *p*-diiodobenzene, **16c** (right).

1,2-dichloropropane obtained under similar conditions may also exist in equilibrium (**12-Cla** ⇌ **12-Clb**). Di-



methylated 1,2-chloropropane was not formed even in the presence of a large excess of methyl fluoroantimonate. When the solution was warmed to −10°, dimethylchloronium ion and ions **13a** ⇌ **13b** ⇌ **13c**, together with some yet unidentified products, were formed.

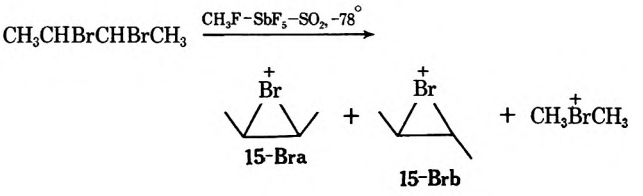
Dihalobutanes.—Methylation of 1,2-, 1,3-, and 1,4-dibromo(chloro)butanes and 1,4-diiodobutane with methyl fluoroantimonate in SO_2 solution at −40° results in cyclization to a mixture of dimethylhalonium ions $CH_3XCH_3^+$ and tetramethylenehalonium ions **14-X**.[5] The driving force for this cyclization is as-



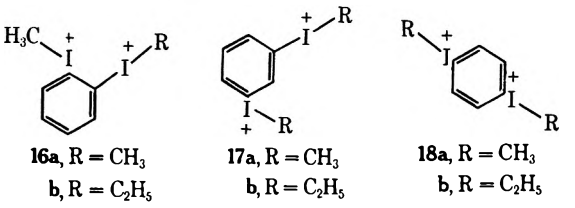
sumed to be the formation of the very stable five-membered ring ion.

(5) G. A. Olah and P. E. Peterson, *J. Amer. Chem. Soc.*, **90**, 4675 (1968).

In addition, treating *meso*- and *dl*-2,3-dibromobutane with CH_3F–SbF_5–SO_2 solution at −78° results in the formation of dimethylbromonium ion and *cis*- and *trans*-1,2-dimethylethylenebromonium ions **15-Br** (giving identical pmr spectra with those reported).[6]

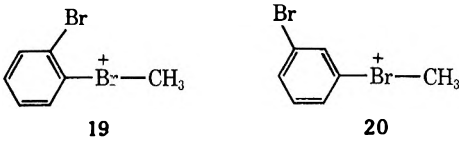


B. Dialkylphenylenedihalonium Ions.—Dialkylation of *o*-, *m*-, and *p*-diiodobenzene with excess methyl and ethyl fluoroantimonate at −78° in SO_2 solution results in the formation of the corresponding dialkylphenylenediiodonium ins, **16**, **17**, and **18**.

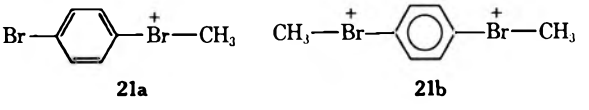


The pmr spectra of **16a**, **17a**, and **18a** are shown in Figure 2. The dialkylphenylenediiodonium ions are all stable to −10°. Attempts to prepare monomethylated diiodobenzenes by reaction of equimolar methyl fluoroantimonate with *o*-, *m*-, or *p*-diiodobenzene were unsuccessful because under these conditions, owing to low solubility of monomethylated products, formation of precipitates prevented identification.

Methylation of *o*- and *m*-dibromobenzene with excess methyl fluoroantimonate resulted in the formation of the monomethylated ions, **19** and **20**.



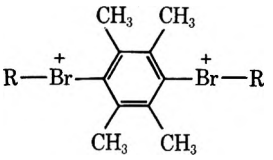
p-Dibromobenzene forms under similar conditions a mixture of monomethylated ion **21a** and dimethylated ion **21b** at −80° (as indicated by the pmr spectrum of the solution). Upon heating to −20°, dimethylated **21a** begins to disappear and an increasing amount of monomethylated **21b** is formed. Cooling the solution back to −80° reverses the process, giving the same ratio of ions **21a** and **21b**. Ethylation of *o*-, *m*-, and *p*-



dibromobenzene with ethyl fluoroantimonate resulted in a complex mixture, consisting of aromatic ring ethylated products. Alkylation of 2,3,5,6-tetramethyldibromobenzene with methyl and ethyl fluoroanti-

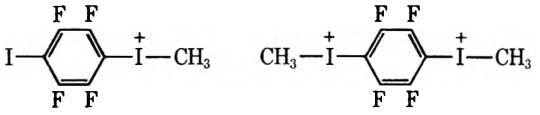
(6) G. A. Olah, J. M. Bollinger, and J. M. Brinich, *ibid.*, **90**, 2587 (1968).

monate resulted in complete formation of the corresponding dihalonium ions, **22a,b**.



22a, R = CH_3
b, R = C_2H_5

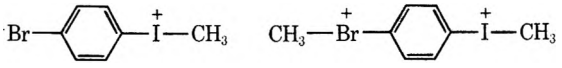
Methylation of 2,3,5,6-tetrafluorodiiodobenzene in CH_3F–SbF_5–SO_2 solution at −78° results in a mixture of monomethylated and dimethylated ions **23a,b**.



23a **23b**

The fluorine-19 spectrum of ion **23a** shows multiplets centered at ϕ 119.6 and 126.9 (relative to CCl_3F), while the ^{19}F nmr spectrum of **23b** is a singlet at ϕ 113.4. Attempts to form the corresponding ethylated ions failed owing to the insolubility of the starting material in the reagent. Likewise, 2,3,5,6-tetrafluorodibromobenzene was insoluble in both methyl and ethyl fluoroantimonate in SO_2 solution.

Methylation of *p*-bromoiodobenzene with CH_3F–SbF_5–SO_2 at −78° also resulted in a mixture of monomethylated and dimethylated ions **24a** and **24b**.



24a **24b**

The methyl group is attached to the iodine atom in ion **24a** instead of the bromine on the basis of the pmr chemical shift (δ 3.90) which agrees with all other methylphenyliodonium ions.[1] Ethylation of *p*-bromoiodobenzene with ethyl fluoroantimonate resulted in ring-ethylated products.

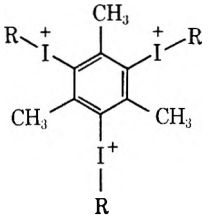
We have not yet succeeded in obtaining alkylarylchloronium ions under long-lived conditions, since reaction of chlorobenzenes with CH_3F–SbF_5 complex at −78° results in fast aromatic ring substitution. Likewise, alkylation of dibromo- and diiodobenzenes with methyl fluoroantimonate at temperatures higher than −78° results in irreversible ring substitution. As we observed previously,[1] all alkylarylhalonium ions are efficient alkylating agents. Therefore, solutions of alkylarylhalonium ions and dihalonium ions are unstable at higher temperatures since aromatic ring alkylation occurs *via* an intermolecular nucleophilic displacement mechanism. The pmr parameters of all dialkylphenylenedihalonium ions studied are summarized in Table II.

C. Trialkylphenylenetriiodonium Ions.—When 2,4,6-triiodomesitylene is mixed with CH_3F–SbF_5–SO_2 at −78°, no reaction occurs (the starting material is insoluble in the reagent, which may account for lack of reactivity). Addition of 2,4,6-triiodomesitylene to methyl fluoroantimonate in SO_2ClF results in the formation of a dark-colored precipitate. When SO_2 is added to this mixture, the precipitate dissolves. The pmr of this solution shows two singlets with a peak area ratio of 1:1 at δ 3.65 and 4.00. The pmr data are consistent with the formation of the trimethyl 2,4,6-trimethylphenylenetriiodonium ion (**25a**). Ethylation of 2,4,6-triiodomesitylene with ethyl fluoroantimonate in SO_2 resulted in the formation of the corresponding triethylated halonium ion, **25b**.

Table II
Pmr Parameters of Mono-, Di-, and Trialkylated Halobenzenes[a]

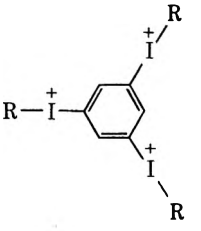
Ion	δ_{XCH_3}	δ_{CH_3}	δ_{CH_3CX}	δ_{CH_2X}	$\delta_{aromatic}$
16a	4.10 (s)				8.0–8.8 (m)
16b			2.23 (t) J = 7	5.23 (q) J = 7	8.1–8.7 (m)
17a	3.97 (s)				7.7–8.9 (m)
17b			2.15 (t) J = 7.5	5.06 (q) J = 7.5	7.8–8.7 (m)
18a	3.95 (s)				8.35 (s)
18b			2.14 (t) J = 7.5	5.02 (q) J = 7.5	8.35 (s)
19	4.55 (s)				7.6–8.3 (m)
20	4.48 (s)				7.5–8.2 (m)
21a	4.53 (s)				7.95 (s)
21b	4.56 (s)				8.38 (s)
22a	4.40 (s)	2.85 (s)			
22b		2.80 (s)	2.05 (t) J = 7	5.30 (q) J = 7	
23a	4.20 (s)				
23b	4.31 (s)				
24a	3.90 (s)				7.7–8.2 (m)
24b	4.05 (s)				7.7–8.2 (m)
	4.65 (s)				8.2–8.7 (m)
25a	4.00 (s)	3.65 (s)			
25b		3.60 (s)	2.18 (t) J = 7	5.20 (q) J = 7	
26a	4.00 (s)				8.38 (s)
26b			2.12 (t) J = 7	5.02 (t) J = 7	8.30 (s)

[a] From TMS in external capillary tube. Spectra were recorded at −70° in SO_2 solution at 60 MHz. Abbreviations: s = singlet, t = triplet, q = quartet, and m = multiplet. J values are in hertz.



25a, R = CH_3
b, R = C_2H_5

Alkylation of 1,3,5-triiodobenzene with methyl and ethyl fluoroantimonate in SO_2 solution resulted in the formation of the corresponding trialkylphenylenetriiodonium ions, **26a,b**. Attempts to prepare mono- or



26a, R = CH_3
b, R = C_2H_5

dialkylated triiodobenzenes failed, since the starting materials would dissolve only in excess CH_3F–SbF_5. The formation of these ions further illustrates the unusual donor ability of iodine toward electrophiles. Furthermore, based on nmr data, most of the positive charge must reside on iodine and not on the aromatic ring. Methylation of 1,3,5-tribromobenzene, 1,3,5-tribromomesitylene, and 1,3,5-tribromotrifluorobenzene was not achieved, since the starting materials were insoluble in the reagent CH_3F–SbF_5 complex under all conditions.

Conclusion

The unusual donor ability of iodine toward electrophiles is reflected in the formation of dihalonium ions even in the cases of diiodomethane and *o*-diiodobenzene. The formation of the trimethylphenylenetriiodonium ion further reveals the ability of iodine to accommodate a positive charge. Dialkylalkylenedibromonium ions were formed only when dibromopropanes were treated with methyl (ethyl) fluoroantimonate solution at low temperature. Methylation of dibromobenzenes results in the formation of either monomethylated species or a mixture of monomethylated and dimethylated species. It was not found possible to trimethylate tribromobenzenes. Dichloronium ions were never observed. These results reveal that the ease of halonium ion or dihalonium ion formation is the decreasing order I < Br < Cl.

Owing to the localization of charge on halogen, dihalonium ions need only one methylene group between the two electropositive iodines, *e.g.*, $^+RICH_2IR^+$ (R = CH_3, C_2H_5), in contrast to the formation of dicarbenium ions, which require at least two methylene groups to separate the two carbenium centers.

Experimental Section

Materials.—All of the dihaloalkanes used in this study were commercially available materials. All of the dihalo- and trihalobenzenes were commercially available except the following. Dibromodurene (mp 198.5–199.5°) was prepared by the method of Smith and Moyle.[7] 3,6-Dibromo-1,2,4,5-tetrafluorobenzene (mp 78.2–78.5°) and 2,4,6-tribromo-1,3,5-trifluorobenzene (mp 98.0–99.0°) were prepared by the method of Hellmann and Bilbo.[8] 3,6-Diiodo-1,2,4,5-tetrafluorobenzene (mp 89.5–90.5°) was prepared by the method of Nield, Stephens, and Tatlow,[9] modified by the use of excess iodine. 2,4,6-Triiodomesitylene (mp 208.0–209.0°) was prepared by the method of Varma and Sreenwasmurthyacher.[10] 2,4,6-Tribromomesitylene (mp 224.0–225.0°) was prepared by the method of Hennion and Anderson.[11] 1,3,5-Triiodobenzene was prepared by the method of Jackson and Behr.[12]

Preparation of Ions and Their Pmr Studies.—The preparation of methyl (ethyl) fluoroantimonate in SO_2 solution has been described previously.[3] (i) Monoalkylation of dihaloalkanes was achieved when equimolar dihaloalkanes in SO_2 solution (cooled at −78°) were mixed with methyl (ethyl) fluoroantimonate in SO_2 solution at −78°. The mixtures were stirred vigorously until clear solutions were formed. (ii) Dihalonium ions were prepared similarly to i except that excess methyl (ethyl) fluoroantimonate was used. (iii) Alkylation of 2,4,6-triidomesitylene was achieved by addition of CH_3F–SbF_5 complex in SO_2ClF to solid triiodomesitylene at −78°. The dark precipitate that formed was dissolved in SO_2.

Monohalonium ions referred to (pmr spectra in this paper were already reported and characterized in our previously reported studies. Nmr spectra were obtained on a Varian Associates Model A-56/60A nmr spectrometer equipped with a variable-temperature probe. Proton chemical shifts are referred to external TMS. Fluorine chemical shifts are referred to external $CFCl_3$.

Registry No.—**16a**, 37406-81-8; **16b**, 37161-13-0; **17a**, 37161-14-1; **17b**, 37161-15-2; **18a**, 37161-16-3; **18b**, 37161-17-4; **19**, 37161-18-5; **20**, 37161-19-6; **21a**, 37161-20-9; **21b**, 37161-21-0; **22a**, 37161-22-1; **22b**, 37161-23-2; **23a**, 37161-24-3; **23b**, 37161-25-4; **24a**, 37161-26-5; **24b**, 37161-27-6; **25a**, 37161-28-7; **25b**, 37161-29-8; **26a**, 37161-30-1; **26b**, 37161-31-2.

Acknowledgment.—Support of our work by grants from the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(7) L. I. Smith and C. L. Moyle, *J. Amer. Chem. Soc.*, **55**, 1676 (1933).

(8) M. Hellmann and A. J. Bilbo, *ibid.*, **75**, 4590 (1953).

(9) E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 166 (1959).

(10) P. S. Varma and C. Sreenwasmurthyacher, *J. Indian Chem. Soc.*, **13**, 187 (1936).

(11) G. F. Hennion and J. G. Anderson, *J. Amer. Chem. Soc.*, **68**, 424 (1946).

(12) C. L. Jackson and G. E. Behr, *Amer. Chem. J.*, **26**, 55 (1901).

An Extension of the Smiles Rearrangement. The Displacement of an Aromatic Amide Group by an Amine Nitrogen[1]

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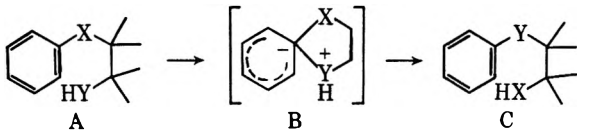
The reaction of a variety of 2-bromoacetanilides with amines has been shown to lead to an intramolecular nucleophilic aromatic rearrangement, analogous to the Smiles rearrangement. The reaction is facilitated by activation of the aromatic ring by electron-withdrawing groups in the ortho and para position. With sterically hindered amines no rearrangement is observed. The scope and mechanism of this rearrangement are discussed. The reaction is of synthetic utility for the formation of N^2-substituted phenylglycinamides.

Aromatic rearrangements which result in the migration of an aromatic system from one heteroatom to another belong to a class of reactions known as the Smiles rearrangement (A → B → C).[2]



A B C

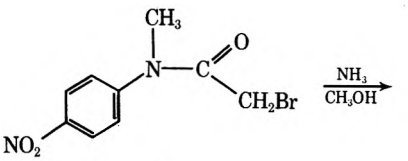
In most of the early work on the Smiles rearrangement, X was a sulfone group, Y was either an oxygen or nitrogen atom, and the two-carbon bridge was part of an aromatic ring. However, more recent investigations have shown that other heteroatom combinations are possible for X and Y. For example, (1) X can be oxygen, Y nitrogen, and the two-carbon bridge aromatic;[3] (2) X can be oxygen, Y nitrogen, and the bridge –NC=O;[4] (3) X can be oxygen, Y nitrogen, connected by a three-carbon bridge;[5] (4) X can be oxygen, and Y oxygen connected by either an aromatic[6] or an aliphatic bridge.[7]

However, no examples of a nitrogen–nitrogen Smiles rearrangement have been reported. The reaction of 2-bromoacetanilides with amines represents a novel extension of the Smiles rearrangement in which X and Y are nitrogen atoms connected by a two-carbon aliphatic bridge.

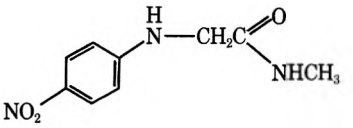
Results and Discussion

A typical example of this rearrangement is the reaction of 2-bromo-4′-nitro-*N*-methylacetanilide (**1**)[8] with methanolic ammonia, which leads to the rearranged glycinamide **2**.[9]

The rearrangement is not limited to the use of ammonia for the displacement of bromine, as almost any primary amine causes the formation of rearranged products. The results obtained from the reaction of **1** with amines are summarized in Table I. All reactions were carried out at room temperature in methanol or hexamethylphosphoric triamide (HMPA) with an excess of the appropriate amine. The rearrangements were followed by thin layer chromatography, and reaction times of 4–18 hr were needed in most cases to achieve complete rearrangement.

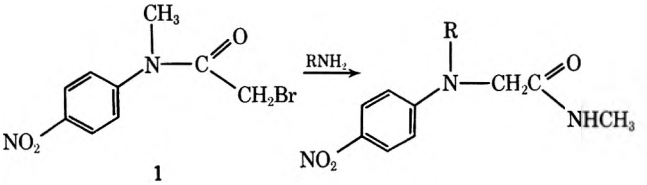


1

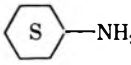
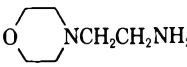
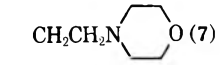


2

TABLE I



1

Amine	Product, R =	Yield, %
NH_3	H (**2**)	68
CH_3NH_2	CH_3 (**3**)	75
	 (**4**)	94
$CH_2{=}CHCH_2NH_2$	$CH_2CH{=}CH_2$ (**5**)	85
$(CH_3)_2NHCH_2CH_2NH_2$	$CH_2CH_2N(CH_3)_2$ (**6**)	59
	 (**7**)	69
CH_3ONH_2	OCH_3 (**8**)	38

The structures of the products were assigned on the basis of their chemical and physical properties (see Experimental Section). The mass spectra were especially significant since they showed, in most cases, the loss of *m/e* 58. This peak, which is the base peak, corresponds to the loss of ·CONHCH$_3$. The mass spectrum for compound **6** shows a base peak at *m/e* 58 which is assigned to the fragment $^+CH_2N(CH_3)_2$.

(1) A preliminary account of this work has been published: N. W. Gilman, P. Levitan, and L. H. Sternbach, *Tetrahedron Lett.*, 4121 (1970).

(2) For reviews of the Smiles rearrangement see (a) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 369 (1951); (b) R. M. Forbis, University of Illinois Organic Seminar Abstracts, 1st semester, 1968–1969, p 62.

(3) G. E. Bonvicino, L. G. Yogodzinski, and R. A. Hardy, Jr., *J. Org. Chem.*, **27**, 4272 (1962).

(4) P. Baudet, M. Calin, and E. Cherbuliez, *Helv. Chim. Acta*, **47**, 1047 (1964).

(5) W. T. Caldwell and G. C. Schweiker, *J. Amer. Chem. Soc.*, **74**, 5187 (1952).

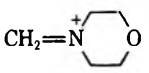
(6) J. D. Loudon, J. R. Robertson, J. N. Watson, and S. D. Alton, *J. Chem. Soc.*, 55 (1950).

(7) M. Harfenist and E. Thom, *J. Chem. Soc. D*, 730 (1969).

(8) T. Noguchi, Y. Hashimoto, T. Mori, and S. Kano, *J. Pharm. Soc. Jap.*, **88**, 1620 (1968).

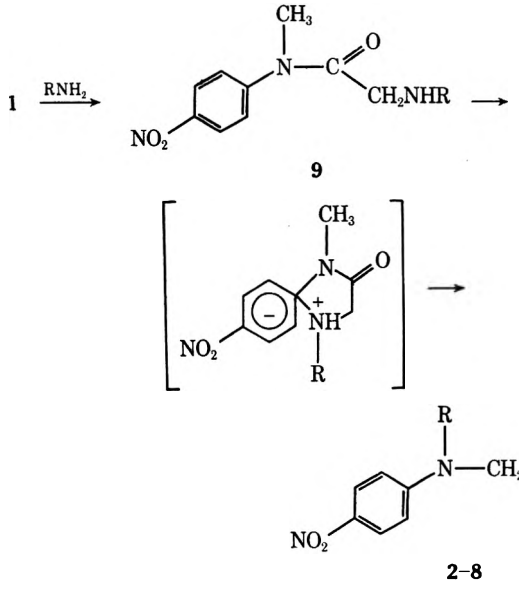
(9) The assignment of structure **2** was based on spectral data and on the acid hydrolysis of **2** which led to the known *N*-(4-nitrophenyl)glycine: L. Lantz and P. M. J. Obellianee, *Bull. Soc. Chim. Fr.*, 311 (1956).

In the case of compound **7**, the base peak appears at *m/e* 100 which corresponds to the fragment

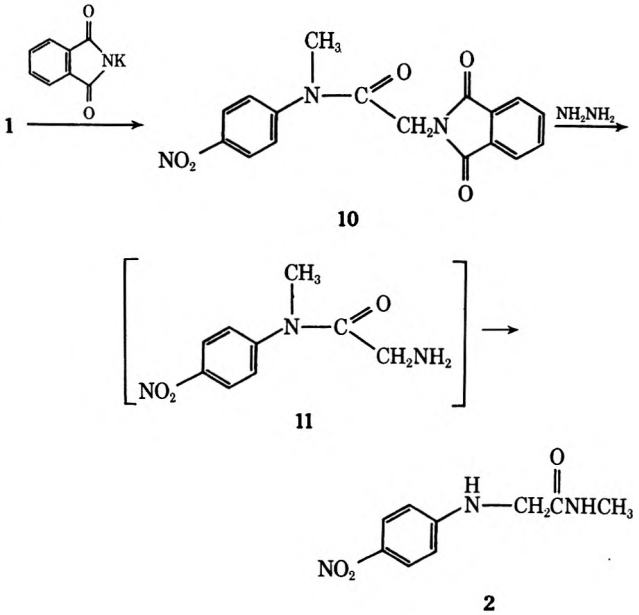


In all cases the products were yellow, whereas the starting material **1** was colorless. The color change is to be expected, since in the products the anilino nitrogen is in conjugation with the nitro group, whereas in **1** conjugation is interrupted since the anilino nitrogen is part of an amide function.

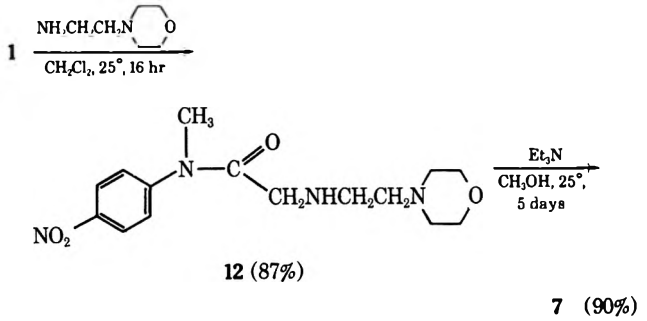
The most plausible mechanism for this reaction would appear to be, in analogy with other studies of the Smiles rearrangement,[10,11] the formation of the intermediate **9** followed by an aromatic displacement of an amide group.



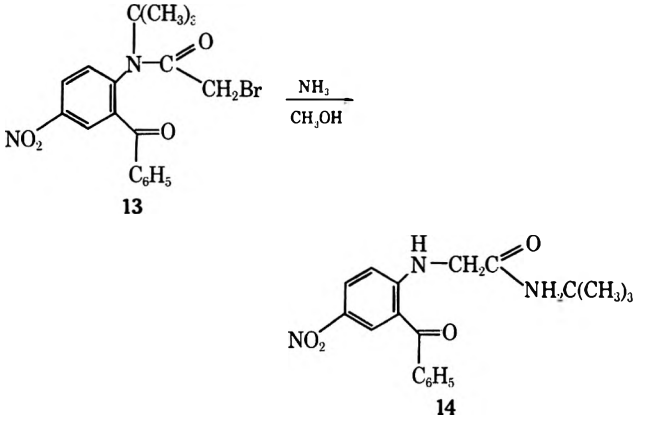
In support of this mechanism was the finding that the treatment of the phthalimido compound **10** with hydrazine led directly to the rearranged product **2**. The free amine **11**, which must be an intermediate in the reaction, could not be detected in the reaction mixture.



However, in one example, by substituting the nonpolar solvent methylene chloride for methanol, a normal SN2 substitution product was isolated, and in a separate experiment the product was found to undergo rearrangement. Thus, treatment of **1** with *N*-β-aminoethylmorpholine in CH_2Cl_2 gave **12**. The reaction of **12** with triethylamine in methanol (the rearrangement did not proceed to any extent in the absence of triethylamine) then led to the rearranged product **7**.



In an approach to the synthesis of 1-*tert*-butyl-1,3-dihydro-5-phenyl-1,4-(2*H*)-benzodiazepin-2-ones,[12] the reaction of compound **13** with ammonia was investigated.[13] However, the reaction of **13** with methanolic ammonia led only to the rearranged product **14**.

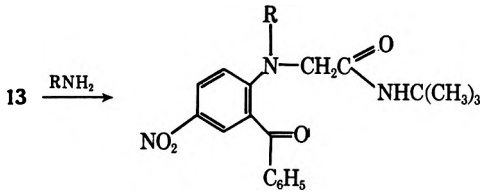


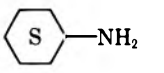
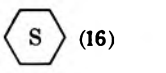
The substrate **13** was then found to undergo rearrangement with other primary amines in the same manner as compound **2**. The results are tabulated in Table II.

The experimental conditions were the same as those used for the reaction of **2** with amines (see preface to Table I). In all cases the products were yellow, whereas the starting bromoacetamido compound **13** is colorless. In all of the products except for compound **18**, the base peak in the mass spectrum was at *m/e* M − 100, where M is the molecular ion. The loss of 100 mass units corresponds to the fragment $(CH_3)_3CNHCO$. The side chain in **18** is also lost, so that in this case an ion appears at *m/e* 255 (M − 171). A

(10) J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).
(11) F. Pictra, *ibid.*, **23**, 504 (1969).
(12) For a review of the benzodiazepines see G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
(13) For a successful synthesis of the 1-*tert*-butylbenzodiazepine see N. W. Gilman and L. H. Sternbach, *J. Heterocycl. Chem.*, **8**, 297 (1971).

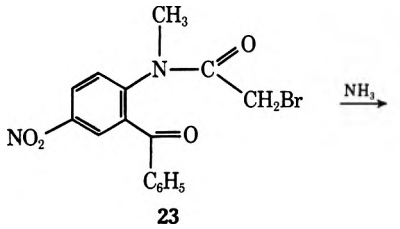
TABLE II



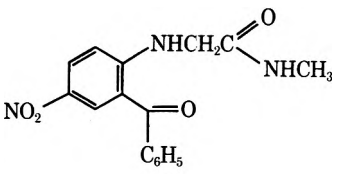
Amine	Product, R =	Yield, %
NH_3	H (**14**)	84
CH_3NH_2	CH_3 (**15**)	76
	 (**16**)	82
$CH_2{=}CHCH_2NH_2$	$CH_2CH{=}CH_2$ (**17**)	92
$(CH_3)_2NCH_2CH_2NH_2$	$CH_2CH_2N(CH_3)_2$ (**18**)	76
$(CH_3)_2NNH_2$	$N(CH_3)_2$ (**19**)	47

small peak at *m/e* 326 (M − 100) was also present (2% of base peak).[14]

The presence of the *tert*-butyl group in **13** was not a prerequisite for this rearrangement, since the *N*-methyl analog **23** also yielded **24** when treated with ammonia.



23

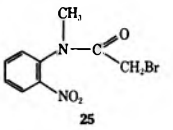
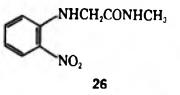
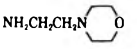
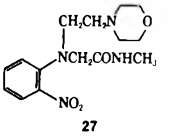
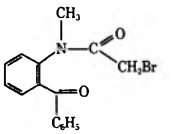
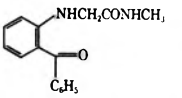
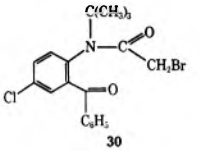
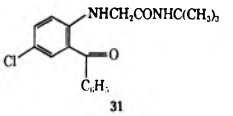


24

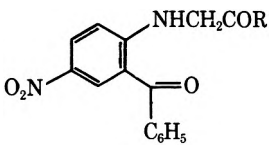
The structure of **24** was confirmed by the synthesis from **22**. The use of other substrates in the rearrangement was also investigated and the results are shown in Table III (experimental conditions as stated for Table I).

The use of **28** as a substrate shows that the ortho carbonyl group has a similar but less pronounced activating effect than the nitro group.[15,16]

TABLE III

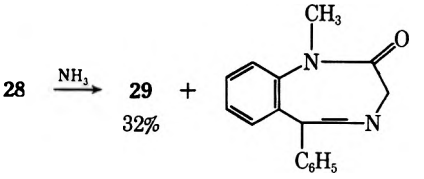
Substrate	Amine	Product	Yield %
 **25**	NH_3	 **26**	93
25		 **27**	66
 **28**	NH_3	 **29**	32
 **30**	NH_3	 **31**	77

(14) The structure of **14** was confirmed by an independent synthesis, starting from ethyl N^2-(2-benzoyl-4-nitrophenyl)glycinate (**20**) [G. A. Archer and L. H. Sternbach, U. S. Patent 3,317,518 (1966); *Chem. Abstr.*, **65**, 16988 (1966)]. The acid hydrolysis of **20** gave **21**, which with thionyl chloride yielded **22**, which upon treatment with *tert*-butylamine gave **14**.



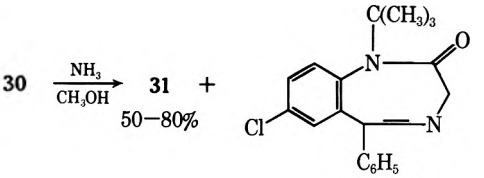
20, R = OEt
21, R = OH
22, R = Cl

(15) The low yield in this case (reaction in methanol) is due to competitive normal substitution and cyclization of the substitution product to the known benzodiazepine, **32**: L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).



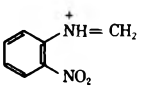
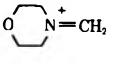
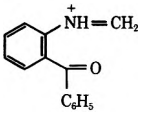
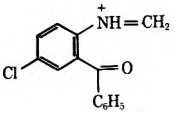
32 32%

In a similar manner the rearrangement of **30** proceeds in high yield in HMPA, but, if done in methanol, mixtures of **31** and the benzodiazepine **33** are formed.[13]



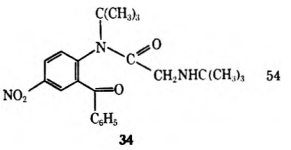
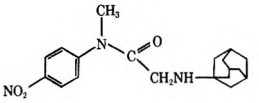
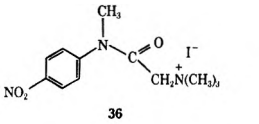
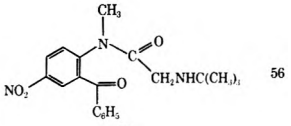
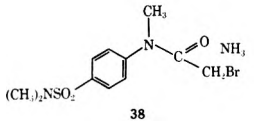
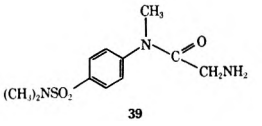
33 50–20%

(16) As in the previous examples, the fragmentation patterns in the mass spectra indicated that a rearrangement had occurred. In all cases, the base peak was due to the fragment $^+RNH{=}CH_2$, as shown below.

Product	Molecular ion, *m/e*	Base peak	Fragment
26	209	151	
27	322	100	
29	268	210	
31	344	244	

Although most of the previously discussed reactions lead to clean rearranged products, in some examples, no rearrangement took place. These cases are listed in Table IV.

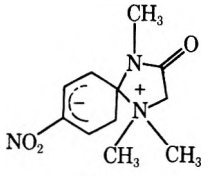
TABLE IV

Substrate	Amine	Product	Yield, %
13	$(CH_3)_3CNH_2$	 34	54
1		 35	51
1	$(CH_3)_2NH$	 36	87[a]
23	$(CH_3)_3CNH_2$	 37	56
		 38	
		 39	64

[a] The crude oily product was treated with methyl iodide to give the solid methiodide derivative.

The formation of the unrearranged products **34**, **35**, and **37** is undoubtedly due to the steric bulk of the nucleophilic amine, which prevents the formation of the five membered ring transition state required for a rearrangement.

If secondary amines, as in the preparation of **36**, are used in the reaction, no rearrangement would be expected, since this would necessitate the formation of the intermediate **40** which would simply revert back to the unrearranged compound.

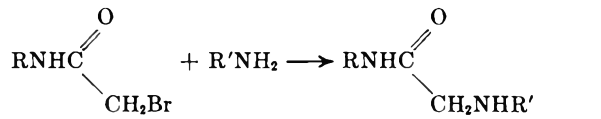


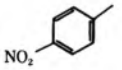
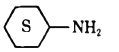
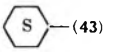
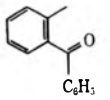
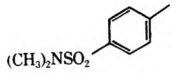
40

The reaction of **38** with ammonia to give only the unrearranged product **39** was unexpected. Absence of rearrangement may be due to the fact that the *N*,*N*-dimethylsulfamoyl group is not electron withdrawing enough to induce rearrangement. This, however, was not investigated in detail.[17]

In all of the previous examples, tertiary bromoacetanilides were used. The use of secondary bromoacetanilides was also investigated, but in no case were rearrangements noted. The results are summarized in Table V.

TABLE V



Substrate, R =	Amine	Product, R′ =	Yield, %
 41	CH_3NH_2	CH_3 (42)	74
41		 (43)	97
41	$CH_2{=}CHCH_2NH_2$	$CH_2{=}CHCH_2$ (44)	67
 45	CH_3NH_2	CH_3 (46)	72
 47	CH_3NH_2	CH_3 (48)	78

In the case of the secondary bromoacetanilides, there is increased electronegative charge on the anilino nitrogen, which would make the displacement reaction less likely to occur than in the case of the tertiary anilides.[18]

From a comparison of all the results obtained for the nitrogen–nitrogen Smiles rearrangement, a few generalities about the reaction can be formulated.

(1) The starting bromoacetanilide must be tertiary in order for rearrangement to occur.

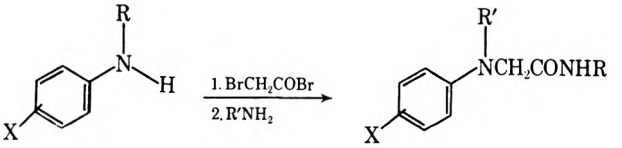
(2) Sterically hindered amines lead only to the simple substitution products without any rearrangement.

(3) The polarity of the solvent is important with the more polar solvents giving better yields of rearranged products.

(4) The activation of the aromatic ring by electron-withdrawing groups greatly facilitates the rearrangement.

Although many of the rearranged products can be synthesized by alternate routes, the simplicity of the rearrangement should find synthetic utility for the preparation of glycinamides according to the generalized Scheme I.

SCHEME I



X = ortho or para electron-withdrawing group

Table VI lists the analytical data for all new compounds described in this report.[18a]

(17) The structures of the unrearranged products were established by comparison of the nmr and mass spectra with spectra obtained on rearranged compounds with similar structures. In the products **34**, **35**, **37**, and **39**, the base peak in each case is due to the fragment $CH_2{=}NHR^+$, where R is *tert*-butyl, adamantyl, *tert*-butyl, and hydrogen, respectively. This pattern is in sharp contrast to products resulting from rearrangements, in which case none of the products show this type of ion.

(18) As in the examples given in Table IV, all of the above products have base peaks in the mass spectra resulting from the loss of the fragment $CH_2{=}NHR^+$.

(18a) NOTE ADDED IN PROOF.—After submission of this manuscript for publication, a further example of the nitrogen–nitrogen Smiles rearrangement appeared in print K. Ishizumi, S. Inaba, and H. Yamamoto, *Chem. Pharm. Bull.*, **20**, 592 (1972).

TABLE VI[a]

Compd	Crystd[b] from	Color, shape	Mp, °C	Formula
2	A + H	Yellow needles	176–177	$C_9H_{11}N_3O_4$
3	A + H	Yellow needles	184–186	$C_{10}H_{13}N_3O_4$
4	A + H	Yellow prisms	193–195	$C_{15}H_{21}N_3O_4$
5	B + H	Yellow prisms	150–151.5	$C_{12}H_{15}N_3O_4$
6	A + H	Yellow prisms	125–127.5	$C_{18}H_{20}N_4O_4$[c]
7	MC + H	Yellow prisms	153–155	$C_{15}H_{22}N_4O_4$
8	MC + H	Yellow prisms	131–132	$C_{10}H_{13}N_3O_4$
10	E	Colorless needles	203–205	$C_{17}H_{13}N_3O_5$
12	A + H	Yellow prisms	89–91	$C_{15}H_{22}N_4O_4$
13	E	Off-white needles	203–204	$C_{19}H_{15}BrN_2O_4$
14	B + P	Yellow crystals	175–176	$C_{19}H_{21}N_3O_4$
15	A + H	Yellow crystals	153–155	$C_{20}H_{23}N_3O_4$
16	d	Yellow foam		$C_{28}H_{31}N_3O_4$
17	d	Yellow foam		$C_{22}H_{25}N_3O_4$
18	e	Yellow foam		$C_{23}H_{30}N_4O_4$
19	MC + H	Yellow needles	176–177	$C_{21}H_{26}N_4O_4$
23	e	Pale yellow gum		$C_{16}H_{13}BrN_2O_4$
24	MC + H	Yellow needles	250.5–251.5	$C_{16}H_{15}N_3O_4$
25	Et + P	Colorless prisms	57–59	$C_9H_9BrN_2O_2$
26	M	Orange needles	163–165	$C_9H_{11}N_3O_4$
27	e	Brown oil		$C_{16}H_{22}N_4O_4$
28	E	Colorless prisms	89–90	$C_{16}H_{14}BrNO_2$
29	B + H	Yellow plates	150–152	$C_{16}H_{16}N_2O_2$
30	MC + P	Colorless prisms	161–162	$C_{19}H_{19}BrClNO_2$
31	Heptane	Yellow needles	147–149	$C_{19}H_{21}ClN_2O_2$
34	Et + P	Off-white prisms	108–109	$C_{28}H_{29}N_3O_4$
35	E + H_2O	Yellow prisms	171–172.5	$C_{19}H_{25}N_3O_4$
36	E	Yellow prisms	197–199	$C_{12}H_{16}IN_3O_4$
37	MC + P	Yellow crystals	119.5–120.5	$C_{20}H_{23}N_3O_4$
38	A + H	Colorless needles	111–113	$C_{11}H_{15}BrN_2O_2S$
39	B + H	Colorless needles	127–129	$C_{11}H_{17}N_3O_2S$
41	E + H_2O	Yellow needles	175–176.5	$C_8H_7BrN_2O_2$
42	MC + P	Pale yellow prisms	98–99	$C_9H_{11}N_3O_4$
43	E	Pale yellow plates	125–127	$C_{14}H_{19}N_3O_3$
44[f]	M + E	Colorless prisms	237–239	$C_{11}H_{13}N_3O_2 \cdot HCl$
46	d	Yellow oil		$C_{16}H_{16}N_2O_2$
48	MC + P	Colorless needles	115–117	$C_{11}H_{17}N_3O_2S$

[a] Elemental analyses for all new compounds were submitted to the reviewers and found to be within acceptable limits (except for 6). [b] A = acetone, B = benzene, E = ethyl alcohol, Et = ether, H = hexane, MC = methylene chloride, M = methyl alcohol, P = petroleum ether (bp 30–60°). [c] A satisfactory carbon analysis could not be obtained. All spectra were in agreement with proposed structure. [d] Purified by chromatography. [e] Purified by preparative tlc. [f] Converted to the hydrochloride salt for analysis.

Experimental Section

All melting points are corrected. The nmr spectra were determined on a Varian A-60 instrument, using tetramethylsilane as an internal standard, the ir spectra were determined on a Beckmann IR-9 instrument, and the mass spectra on a CEC-110B instrument.

Preparation of the 2-Bromoacetanilides.—The 2-bromoacetanilides were prepared by bromoacetylation of the corresponding anilines utilizing method D of Sternbach, *et al.*[15] The following compounds are known: **1**,[8] **13**,[13] **30**,[13] **41**,[19] **45**,[15] and **47**.[20] The other 2-bromoacetanilides were prepared as follows: (a) **23** from 2-*N*-methylamino-5-nitrobenzophenone;[21] (b) **25** from commercially available 2-nitro-*N*-methylaniline (Eastman Organic Chemicals); (c) **28** from 2-*N*-methylaminobenzophenone;[22] (d) **38** from 4-dimethylsulfamoyl-*N*-methylaniline (**49**).[23]

General Procedure for the Reaction of 2-Bromoacetanilides with Amines.—A solution of the 2-bromoacetanilide (0.05–0.1 *M*) and an excess of the appropriate amine in either methanol or HMPA was stirred at room temperature until the reaction was complete. The course of the reaction was followed by thin layer chromatography. The solution was concentrated, and the residue was dissolved in CH_2Cl_2. After the solution was washed with saturated $NaHCO_3$ and saturated NaCl, the organic phase was dried ($MgSO_4$) and concentrated, and the residue was recrystallized from the appropriate solvent.

***N*-Methyl-4′-nitro-2-phthalimidoacetanilide (10).**—A solution of 1.0 g (3.66 mmol) of **1** and 676 mg (3.66 mmol) of potassium phthalimide in 10 ml of hexamethylphosphoric triamide was heated at 90–95° for 2 hr, cooled, and poured into 125 ml of H_2O. The resulting solid was filtered, washed with H_2O, and recrystallized from EtOH to yield 960 mg (77%) of **10** as white needles, mp 203–205°.

Preparation of 2 from 10.—A mixture of 1.3 g (3.8 mmol) of **10** 5.7 ml (11.4 mmol) of hydrazine hydrate, 20 ml of EtOH, and 20 ml of $CHCl_3$ was stirred at room temperature for 4 hr. The solvents were removed *in vacuo* and the residue was treated with H_2O. Filtration gave 520 mg (65%) of **2** as a yellow solid, mp 175–176.5°. All spectral data were identical with those obtained on a sample of **2** prepared by treating **1** with ammonia.

Registry No.—**1**, 23543-31-9; **2**, 31108-40-4; **3**, 37102-88-8; **4**, 37102-89-9; **5**, 37102-90-2; **6**, 37102-91-3; **7**, 37102-92-4; **8**, 37103-93-5; **10**, 37103-94-6; **12**, 37103-95-7; **13**, 33186-46-8; **14**, 33186-47-9; **15**, 37102-98-0; **16**, 37102-99-1; **17**, 37156-96-0; **18**, 37156-97-1; **19**, 37103-00-7; **23**, 37103-01-8; **24**, 34466-64-3; **25**, 37103-03-0; **26**, 37103-04-1; **27**, 37156-98-2; **28**, 37103-05-2; **29**, 37103-06-3; **30**, 33191-28-5; **31**, 33186-45-7; **34**, 37103-09-6; **35**, 37103-10-9; **36**, 37103-11-0; **37**, 37103-12-1; **38**, 37103-13-2; **39**, 37103-14-3; **41**, 3598-91-2; **42**, 37103-16-5; **43**, 37103-17-6; **44** (HCl), 37103-18-7; **45**, 14439-71-5; **46**, 37103-20-1; **47**, 37103-21-2; **48**, 37103-22-3.

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(19) R. A. Nyquist, *Spectrochim. Acta*, **19**, 1595 (1963).

(20) Seishi Takagi, Japanese Patent 10,775 (1960); *Chem. Abstr.*, **55**, 587*a* (1961).

(21) L. H. Sternbach, R. Ian Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(22) L. H. Sternbach, R. Ian Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(23) Compound **49** was prepared by methylation of 4-dimethylsulfamoylaniline: J. Walker, *J. Chem. Soc.*, 686 (1940).

Nuclear Magnetic Resonance Spectra of Cyclopropyl Derivatives[1]

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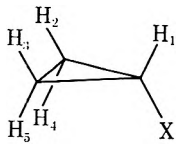
The analysis of the nmr spectra of 22 monosubstituted cyclopropanes is reported. An attempt has been made to estimate the anisotropy of the C–X bond in these compounds. The effect of chemical shift on coupling constants and the relationships between the several coupling constants are also considered. These data should be useful in estimating parameters for other systems.

Our interest in the nmr spectra of cyclopropane derivatives stems from their rigid, well-defined geometry which permits a detailed study of the effects of substituents. Earlier, we reported the analysis of the spectra of cyclopropyl bromide and cyclopropanecarboxylic acid,[2] and studies of other monosubstituted cyclopropanes have also been reported.[3]

The spectra were determined at 60 and 100 MHz with peak positions being measured to ±0.1 Hz. The analysis was initially carried out using the 60-MHz spectra and the NMRIT program.[4] Later, 100-MHz spectra were obtained and a complete reanalysis was performed using LAOCOON III.[5] The average deviation between calculated and observed spectra was 0.06 Hz and in no case were the deviations between observed and calculated line positions greater than 0.20 Hz.

To minimize concentration effects, all spectra were determined in 0.5 *M* (approximately 3–6%) carbon tetrachloride solutions, and tetramethylsilane (TMS) was used as the internal standard. The coupling constants and chemical shifts derived from the analysis of the spectra are summarized in Table I.[6]

The analysis of the spectra does not, of course, specify which protons are cis and trans to the functional group. However, the assignment is easily made since the cis-vicinal hydrogens (with a 0° dihedral angle) will give a large coupling constant whereas the trans-vicinal hydrogens (with a 145° dihedral angle) will give a relatively small coupling constant.[2,7] It can be seen from Table I that the coupling constants to the α-ring proton (indicated as no. 1) fall cleanly into two groups, one of which is 6–8 Hz whereas the other is 3–5 Hz. The former must then be the cis coupling constant whereas the latter must be the trans coupling constant. The sign of the geminate coupling constant is assigned as negative since this leads to a better fit between observed and calculated spectra. The numbering of the protons based on the above assignment is



In most of the cases in which one of these compounds had been analyzed previously,[3,8] our results are in satisfactory agreement with the reported values. However, in the case of *p*-fluorophenyl cyclopropyl ketone and *p*-methoxyphenyl cyclopropyl ketone,[9] the results are markedly different. The previous values appear out of line with those obtained for related compounds and almost certainly are incorrect.

The chemical shifts for cyclopropanol and dicyclopropyl ketone have been obtained in benzene solution by Scherr and Oliver.[3] It is interesting to note that they found differences in chemical shift between the cis and trans hydrogens of 0.246 and 0.466 ppm, respectively. The corresponding values in carbon tetrachloride are 0.079 and 0.170. It seems unlikely that carbon tetrachloride would be oriented in a specific fashion with respect to either compound. On the other hand, benzene has been observed to have such effects,[10] and it seems likely that the differences observed in benzene solution are enhanced by orientation of the solvent.

Let us examine the chemical shifts. The chemical shifts of the α protons with respect to that of cyclopropane is largely determined by the electronegativity of the substituent and the anisotropy of the C–X bond. Thus, attempts to correlate the chemical shifts with electronegativity[11] alone have not been too successful. We have found it of interest to compare the chemical shifts in the cyclopropane series with those for *n*-propyl and isopropyl derivatives (Figures 1a and 1b).[12] Considering the difference in substitution at the carbon in question in cyclopropane and propane, the correlation with *n*-propyl derivatives is fairly good. The slope of the line is 1.33. One might expect a better correlation with the isopropyl derivatives since the substitution pattern is now quite similar. Except for the halogens, a reasonable correlation is found with a slope of 1.34.

The deviation of the halogens with isopropyl probably results from the size of the substituent which will alter the geometry. Since the anisotropy of the carbon–halogen bonds is quite large (see below), a change in geometry will result in a significant change in chemical shift. Iodine would be expected to lead to the largest deviation, and this is the case.

The correlation with methyl chemical shifts (Figure

(1) This investigation was supported by the U. S. Army Research Office, Durham. The nmr spectrometer was obtained with the aid of a National Science Foundation departmental equipment grant.

(2) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963).

(3) P. A. Scherr and J. P. Oliver, *J. Mol. Spectrosc.*, **31**, 109 (1969), have summarized the previously available data.

(4) J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962).

(5) S. Castellano and A. A. Bothner-By, *ibid.*, **41**, 3863 (1964).

(6) Some small difference will be noted between these results and those reported previously.[2] This results from the use of the lower concentrations than was possible previously and from additional information available from the 100-MHz spectra.

(7) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **40**, 875 (1962).

(8) Reference 2 (cyclopropyl bromide and cyclopropanecarboxylic acid), H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 2774 (1963) (cyclopropylamine); and ref 3 (cyclopropanol and dicyclopropyl ketone).

(9) H. Weitkamp and F. Korte, *Tetrahedron*, **20**, 2125 (1964).

(10) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

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(12) The data for *n*-propyl and isopropyl were taken from ref 13, p 672, and are on the methane reference scale.

(13) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, Oxford, 1966.

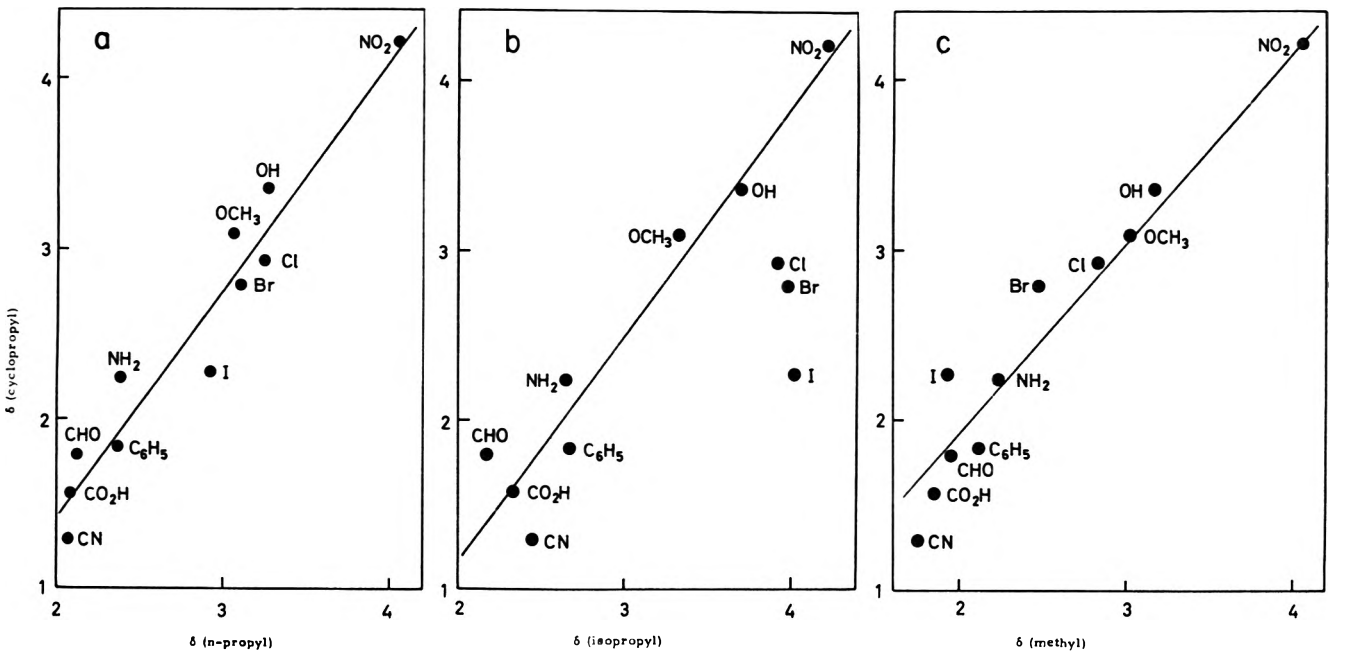

Figure 1.—Relationship between α-chemical shifts for cyclopropyl derivatives and (a) *n*-propyl, (b) isopropyl, and (c) methyl derivatives.

TABLE I
COUPLING CONSTANTS AND CHEMICAL SHIFTS FOR MONOSUBSTITUTED CYCLOPROPANES[a]

R	Registry no.	δ_1	$\delta_2 = \delta_3$	$\delta_4 = \delta_5$	$J_{12} = J_{13}$	$J_{14} = J_{15}$	J_{23}	$J_{24} = J_{25}$	$J_{25} = J_{34}$	J_{45}	δ_6	J_{16}	No. of lines assigned	Rms error of line positions
C_6H_5	873-49-4	1.8346	0.8913	0.6469	8.41	5.13	9.36	−4.56	6.22	9.33			53	0.086
CN	5500-21-0	1.2871	0.9627	1.0391	8.47	5.09	9.42	−4.93	7.02	9.88			49	0.066
CH_2OH[b]	2516-33-8	1.0145	0.4600	0.1747	8.04	4.89	8.93	−4.52	5.70	9.34	3.3430*	6.70*	58	0.060
CH_2OCOCH_3	36982-54-4	1.0779	0.5265	0.2599	8.06	4.83	8.99	−4.71	5.91	9.41	3.8080*	7.24	240	0.068
CH_2CH_2OH[c]	2566-44-1	0.7126	0.4203	0.0431	8.02	4.92	9.06	−4.40	5.59	9.25	1.4070*	6.94	151	0.098
CH_2CH_2Br[c]	36982-56-6	0.8387	0.4914	0.1039	8.06	4.87	9.25	−4.58	5.66	9.43	1.7520*	6.91	164	0.078
$C(CH_3)C_3H_5$[b,d]	822-93-5	1.2448	0.5736	0.4820	8.36	5.29	9.24	−4.26	6.00	9.36	4.4930*		53	0.070
CHO[b]	1489-69-6	1.7895	0.9872	1.0262	7.98	4.56	8.80	−4.46	6.99	9.60	8.9730*	5.00*	51	0.051
$COCH_3$[b]	765-43-5	1.8310	0.7665	0.9305	7.85	4.58	9.16	−3.53	6.98	9.54	2.1625*	0.30*	56	0.046
COC_2H_5	1121-37-5	1.9592	0.7925	0.9630	7.83	4.58	9.16	−3.51	6.96	9.45			54	0.072
COC_6H_5	3481-02-5	2.5759	0.9244	1.1625	7.84	4.58	9.05	−3.37	7.00	9.50			57	0.064
$COC_6H_4OCH_3$[e]	7152-03-6	2.5127	0.8725	1.1130	7.84	4.58	9.12	−3.33	6.91	9.48			56	0.065
COC_6H_4F[e]	772-31-6	2.5327	0.9406	1.1638	7.83	4.56	9.15	−3.41	7.03	9.54			58	0.057
CO_2H	1759-53-1	1.5654	0.8828	1.0453	8.04	4.61	9.17	−3.98	7.12	9.74			58	0.052
NH_2	765-30-0	2.2379	0.3276	0.2220	6.60	3.52	9.77	−4.40	6.15	10.02			53	0.055
NO_2	13021-02-8	4.2144	1.1291	1.6025	7.01	3.42	10.09	−5.52	8.26	11.27			57	0.068
OH	16545-68-9	3.3646	0.4026	0.4814	6.17	2.93	10.08	−5.45	6.78	10.82			47	0.060
OCH_3	540-47-6	3.0857	0.3591	0.4665	6.04	2.98	10.48	−5.52	6.78	11.31			56	0.062
$OCOCH_3$	4606-06-8	4.0500	0.6588	0.6175	6.60	3.07	10.85	−6.26	7.45	11.77			43	0.065
Cl	7393-45-5	2.9325	0.8653	0.7837	7.02	3.59	10.55	−6.08	7.09	10.83			54	0.052
Br	4333-56-6	2.7896	0.9623	0.8536	7.16	3.82	10.27	−6.14	6.98	10.49			54	0.060
I	19451-11-7	2.2690	1.0385	0.7817	7.55	4.37	9.83	−5.94	6.65	9.90			59	0.052

[a] Coupling constants are given in Hz. Chemical shifts are given in ppm downfield from TMS. Starred items are based on direct measurements of spectra and have not been fitted. [b] Protons in R group were irradiated while observing cyclopropyl protons. [c] Side-chain protons α and β to the cyclopropyl ring were irradiated while observing cyclopropyl methylene and methine protons, respectively. [d] 1,1-Dicyclopropylethylene. [e] Para isomer.

1c)[12] also is reasonable, but the slope (1.13) is significantly less than for the *n*-propyl and isopropyl cases. One factor which may affect the slope is the amount of s character in the bond. According to the CNDO molecular orbital calculations,[14] the fraction of s character in the C–H bond is 0.22 for isopropyl, 0.25 for methyl, and 0.29 for cyclopropyl.

In considering the chemical shifts of the β protons, it is convenient to divide the substituents into two groups, those which are saturated and those which are unsaturated. We shall first consider the former group. If the effect of the O–H and N–H bonds are neglected,[15] the substituent effects may be considered in a simple fashion. The chemical shift due to the difference in anisotropy between the C–X bond and a C–H bond is approximately given by[16]

$$\delta_{C-H} - \delta_{C-X} = \frac{\Delta\chi}{3R^3}(1 - 3\cos^2\theta)$$

where δ_{C-X} is the observed chemical shift, δ_{C-H} is the chemical shift which would be found if the X group was replaced by H with geometry unchanged, R is the distance between the proton in question and the electrical center of gravity of the C–X bond, and θ

(14) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968).

(15) To a certain extent, their effect will be minimized because of the essentially free rotation about the C–O and C–N bonds.

(16) H. M. McConnell, *J. Chem. Phys.*, **27**, 226 (1957).

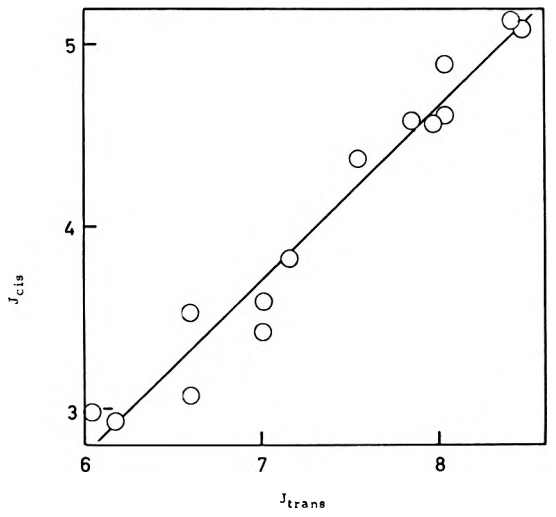

Figure 2.—Relation between J_{cis} and J_{trans} for the β-cyclopropyl protons.

is the angle between the line defining R and the axis of the C–X bond. The quantity $\Delta\chi$ is given by

$$\Delta\chi = (\chi_{||} - \chi_{\perp})_{C-X} - (\chi_{||} - \chi_{\perp})_{C-H}$$

where $\chi_{||}$ is the magnetic susceptibility along the z (bond) axis and $\chi_{\perp}$ is the magnetic susceptibility along the x or y axis of the given bond.

Separate expressions may be written for the cis and trans protons (with respect to X) giving two equations and two unknowns (δ_0 and $\Delta\chi$).[17] It is assumed that the chemical shifts of the two protons would be the same if there were no contribution from the anisotropy of the bond to the substituent. The geometry of the compounds was assumed to be the same as for cyclopropyl chloride,[18] except for the C–X bond length. The terms were evaluated for each of the compounds making the assumption that the electrical center of gravity is at the carbon covalent radius (0.772 Å) and are summarized in Table II. It must be emphasized that the anisotropies calculated in this manner are not pure quantities but probably contain a significant contribution from the difference in field effect at the two protons in question. However, the ordering of the values should be correct. The contribution of the field effect to the chemical shift will be considered in detail at a later time in connection with the nmr spectra of monosubstituted cyclobutanes.

Two trends may be seen. First, there is an increase in the anisotropy on going down the periodic table from fluorine to iodine and, second, there is a decrease in anisotropy in going across the periodic table from carbon to fluorine. The effect on the chemical shifts is quite marked. For the cases having a positive value of $\Delta\chi$, the trans protons are found at lower field than the cis protons. The chemical shifts are reversed when the sign of $\Delta\chi$ is negative.

(17) This method was used in considering the difference between axial and equatorial substituents on a cyclohexane ring (L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1959, p 117) and in other cases (*cf.* ref 9, Chapter 10). Problems associated with the calculation of magnetic spectroscopy by this method have been discussed by A. A. Bothner-By and J. A. Pople, *Ann. Rev. Phys. Chem.*, **16**, 43 (1965).

(18) R. H. Schwendeman, G. D. Jacobs, and T. M. Krigas, *J. Chem. Phys.*, **40**, 1022 (1964).

TABLE II

NEIGHBORING BOND ANISOTROPY FOR CYCLOPROPYL DERIVATIVES

Substituent	δ_{C-H}	$\Delta\chi$[a]
F	0.49	−13.33[b]
Cl	0.82	2.58
Br	0.91	3.44
I	0.90	8.13
C	0.31	9.03[c]
	0.22	11.94
	0.29	12.27
N	0.27	3.34[d]
O	0.44	−2.49[e]
	0.42	−3.40
F	0.49	−13.33[b]

[a] Anisotropy units are 10^{-30} cm^3 molecule^{-1}. [b] Based on the values for cyclopropyl fluoride of ref 3. These data were obtained in benzene solution rather than in carbon tetrachloride and may not be strictly comparable to the other values. [c] Based on the values for cyclopropylcarbinol, 2-cyclopropylethanol, and 2-cyclopropylethyl bromide, respectively. [d] Based on the values for cyclopropylamine. [e] Based on the values for cyclopropanol and cyclopropyl methyl ether, respectively.

The larger values of $\Delta\chi$ are associated with atoms having higher polarizability. Polarizability increases on going down the periodic table and decreases on going across the table from left to right. Since the magnetic susceptibility is associated with the circulation of electrons in the bonds, it is not surprising that a relation with polarizability is found.

The compounds which possess double bonds represent a quite different problem. The double bond generally assumes a preferred geometry with respect to the cyclopropane ring.[19] The chemical shifts should be temperature dependent since the proportions of the conformers change with changing temperature. Thus, it is not profitable to consider in detail the experimental chemical shifts at any one temperature. It is generally found that the cis-β protons are at lower field than the trans protons. The one exception is the phenyl ring.

We should now like to consider the coupling constants. An examination of Table I indicates that there is a relationship between the cis and trans coupling constants for the β protons. We have noted this previously and suggested a relationship with electron density.[2,20] This has indeed proved to be the case.[3]

The correlation may now be examined in more detail using only monosubstituted derivatives (Figure 2). A very good correlation is found. Since the origin of the change in coupling constants might be related at least in part to the origin of the chemical shifts, the correlation between these quantities was examined giving the data in Table III. Except for the geminate coupling constant ($J_{2,4}$), reasonable correlations were found. These proved useful in estimating coupling constants as starting points for the analysis of new cyclopropane derivatives.

The correlation of coupling constants with electronegativities was found to give essentially the same slope as found by Scherr and Oliver[3] using substituents having a wider range of electronegativity values.

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(20) *Cf.* R. E. Glick and A. A. Bothner-By, *J. Chem. Phys.*, **25**, 362 (1956).

TABLE III
CORRELATION OF COUPLING CONSTANTS WITH CHEMICAL SHIFTS[a]

$J = a\delta_1 + b\delta_2 + c\delta_4 + d$

J	a	b	c	d	R[b]	Error[c]
1,2	−0.700	1.221	0.289	7.990	0.937	0.271
1,4	−0.751	0.891	0.284	5.074	0.939	0.273
2,3	0.662	1.095	−1.321	8.251	0.887	0.299
2,4	−0.917	−4.363	3.746	−2.185	0.824	0.582
2,5	0.304	−0.186	1.128	5.353	0.963	0.190
4,5	0.786	0.135	−0.676	8.653	0.895	0.366

[a] δ_1 is the chemical shift for the α proton, δ_2 is the shift for the β proton trans to the substituent, and δ_4 is the shift for the β proton cis to the substituent. [b] Correlation coefficient. [c] Standard error.

Experimental Section

Materials.—Cyclopropylamine, cyclopropyl bromide, cyclopropylcarbinol, cyclopropanecarboxylic acid, cyclopropyl cyanide, cyclopropyl methyl ketone, cyclopropyl phenyl ketone, cyclopropyl 4-fluorophenyl ketone, cyclopropyl 4-methoxyphenyl ketone, 1,1-dicyclopropylethylene, and dicyclopropyl ketone were commercial samples (Aldrich). Cyclopropyl acetate,[21] cyclopropanol,[22] cyclopropyl methyl ether,[23] 2-cyclopropylethanol,[24] cyclopropyl chloride,[25] cyclopropyl iodide,[26] cyclopropanecarboxaldehyde,[27] nitrocyclopropane,[28] and phenylcyclopropane[29] were prepared using previously reported methods. All samples were purified by preparative scale vpc using a 20-ft 20% Carbowax 20M column.

Samples of 2-cyclopropylethanol and 2-cyclopropylethyl bromide were supplied by Dr. Elliot Barber. A sample of nitrocyclopropane was provided by Dr. Gary Lampman, and a sample of cyclopropylcarbinyl acetate was provided by Dr. Gunther Szeimies.

Spectra.—All spectra were taken using a Varian HA-100 nmr spectrometer in the frequency sweep mode. The peak positions were determined by stopping the frequency sweep at the peak maximum and counting the difference in frequency between the observing and locking oscillators. The compounds were examined as 0.5 *M* solutions in carbon tetrachloride and were degassed using three freeze–thaw cycles. Tetramethylsilane was generally used as the internal standard. In those cases for which this overlapped the cyclopropyl protons, the reference and locking signals were obtained using concentric capillaries containing either benzene or methylene chloride.

The analysis of the spectra were performed using LAOCN3.[30] The coupling constants which are obtained are not unique since the calculated spectra are not affected by interchanging the cis-β-β' coupling constants. All of the calculated and observed spectra are reproduced in the Ph.D. thesis of D.E. Barth.

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(22) C. H. DePuy, L. R. Mahoney, and K. L. Eilers, *J. Org. Chem.*, **26**, 3616 (1961).
(23) W. T. Olson, *et al.*, *J. Amer. Chem. Soc.*, **69**, 2451 (1947).
(24) H. Hart and D. P. Wyman, *ibid.*, **81**, 4891 (1959).
(25) J. D. Roberts and P. H. Dirstine, *ibid.*, **67**, 1281 (1945).
(26) M. Hanack and H. Eggensperger, *Tetrahedron Lett.*, 1975 (1963).
(27) D. I. Schuster and J. D. Roberts, *J. Org. Chem.*, **27**, 51 (1962).
(28) G. L. Lampman, D. A. Horne, and G. D. Hager, *J. Chem. Eng. Data*, **14**, 396 (1969).
(29) D. Davidson and J. Feldman, *J. Amer. Chem. Soc.*, **66**, 488 (1944).
(30) A. A. Bothner-By and S. M. Castellano in "Computer Programs for Chemistry," Vol. I, D. F. DeTar, Ed., W. A. Benjamin Inc., New York, N. Y., 1968, Chapter 3.

Dipolar Nature of Lanthanide-Induced Shifts. Detection of the Angular Dependency Factor

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The contribution of the angular dependency factor can be clearly seen in the improvement of the pseudocontact shift correlations with the Eu(dpm)$_3$, Eu(fod)$_3$, and Pr(fod)$_3$ induced shifts in the symmetrical and rigid ethers, 1,4-dihydronaphthalene 1,4-oxide (**1**), 1,2,3,4-tetrahydronaphthalene 1,4-oxide (**2**), and benzonorbornadiene *exo*-oxide (**3**). The lanthanide positions in the complexes were determined through a least-squares fit. These improvements upon inclusion of this geometric factor support the contention that the lanthanide-induced shifts are largely dipolar in origin.

The pseudocontact nature of the lanthanide-induced paramagnetic shifts in the pmr spectra of a large number of organic compounds is generally accepted although it has not been rigorously established. The observed shift is a weighted average reflecting the rapid equilibration of a lanthanide shift reagent, Ln(Y)$_3$, and the organic substrate, RX:. The size of the induced

$$\mathrm{Ln(Y)_3} + \mathrm{RX:} \rightleftarrows \mathrm{RX:Ln(Y)_3}$$

shift obviously depends on these relative concentrations as well as the value of the equilibrium or binding constant, which in turn is related to the basicity of the coordination site in the organic molecule.

The magnitude of a lanthanide-induced pseudocontact shift within a given molecule can be expressed as[1]

$$\Delta\delta_i = \delta_i[\mathrm{Ln}\neq 0] - \delta_i[\mathrm{Ln}=0] = k(3\cos^2\theta_i - 1)(1/R_i^3)$$

where δ_i is the chemical shift of the ith proton, k represents[2] a collection of constants, R_i is the proton–lanthanide distance, and θ is the angle between the crystal field axis of the complex and the radius vector from the lanthanide ion to the ith proton. A vast amount of evidence already suggests a reasonable correlation of the paramagnetic shift with $1/R_i^3$, a correlation that tends to substantiate the importance of the pseudocontact contribution to these induced shifts.[3] Small discrepancies from the $1/R_i^3$ dependency possibly reflect contact contributions[4] or the failure to consider

(1) B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan, and L. F. Johnson, *J. Amer. Chem. Soc.*, **93**, 3281 (1971).

(2) (a) H. J. Keller and K. E. Schwartzhaus, *Angew. Chem., Int. Ed. Engl.*, **9**, 196 (1970); (b) G. N. La Mar, *J. Chem. Phys.*, **43**, 1085 (1965); (c) H. M. McConnell and R. E. Robertson, *ibid.*, **29**, 1361 (1958).

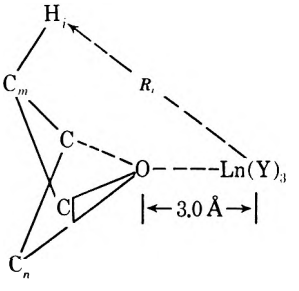
(3) For example see (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) J. K. M. Sanders and D. H. Williams, *ibid.*, **93**, 641 (1971); (c) K. J. Liska, A. F. Fentiman, and R. L. Foltz, *Tetrahedron Lett.*, 4657 (1970); (d) O. Achmatowicz, A. Ejchart, J. Jurczak, L. Kozerski, and J. St. Pyrek, *Chem. Commun.*, 98 (1971); (e) F. I. Carroll and J. T. Blackwell, *Tetrahedron Lett.*, 4173 (1970).

(4) For example see (a) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734, 5737 (1970); (b) A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149, 5153 (1970); (c) A. J. Rafalski, J. Barciszewski, and M. Weiwiorowski, *ibid.*, 2829 (1971).

the angular dependency portion of the pseudocontact relationship. This geometric factor, which often does not vary greatly from proton to proton, has been more difficult to evaluate, owing largely to uncertainties in vector distances and angles in nonrigid molecules with flexible coordination sites. Nevertheless, certain results have clearly shown that this dependency can be detected and it has been used to account for anomalous shifts.[1,5] An improvement in the correlation of the tris(dipivalomethanato)prasoedymium(III), $Pr(dpm)_3$, induced shifts in borneol by inclusion of the angular dependency factor has been reported.[6,7]

We hoped to circumvent some of the uncertainties associated with a flexible coordination site by examining the rigid bicyclic ethers **1**, **2**, and **3**. In all these ethers the coordination site is locked in the skeletal system. These ethers seem to be ideally suited for an investigation of this type for several other reasons. First of all, the ether coordination site should lead to adequate isotropic shifts. Secondly, the ethers **1**, **2**, and **3** have a variety of spectrally distinct hydrogens at varying distances from the coordination site. Furthermore, the ethers, possessing a plane of symmetry, provide relatively simple spectra with minimal coupling and the shifted spectra are amenable to a first-order analysis with no ambiguity in the assignment of chemical shifts and hence $\Delta\delta_i$ values.

One must still place the lanthanide ion at some given position around the oxygen atom. For our initial work we placed the lanthanide ion in a plane defined by the oxygen and the two adjacent carbons. We made the oxygen–lanthanide distance 3.0 Å, and, although this value cannot be determined exactly, this appears to be a reasonable selection.[8] Furthermore, small changes in this distance are relatively unimportant in comparison to the larger R_i distances. The distance and angle parameters are then defined as indicated. We desired to see, then, if inclusion of the $3\cos^2\theta_i - 1$ factor,



as defined in this model, would improve the induced chemical shift correlations. It must be assumed in this model that at least the average structure simulates axial symmetry along the O–Ln bond.[9]

Our preliminary results have shown in fact that one can detect an improvement by inclusion of the angular term with the tris(dipivalomethanato)europium(III), $Eu(dpm)_3$, induced shifts in the rigid bicyclic ethers **1**, **2**, and **3**.[10] It seemed reasonable to test the validity of this correlation by comparing the induced shifts with the more soluble, and hence often more useful, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium(III), $Eu(fod)_3$, shift reagent and especially with the praseodymium(III) analog, $Pr(fod)_3$, which typically induces larger shifts in the upfield direction. Successful correlations of this type, in the process of showing the significance of the geometric factor, certainly aid in confirming the pseudocontact (dipole) nature of these induced shifts, justify the assumption of axial symmetry in solution, and will hopefully permit a better estimate of the oxygen–lanthanide distance in the complex.

Although the 60-MHz nmr spectra for the ethers **1**, **2**, and **3** are straightforward, a striking improvement can be made with the addition of shift reagents. For example, upon addition of 0.2 equiv of $Eu(fod)_3$ to **2**, magnetically equivalent aromatic hydrogens, δ 431 Hz, are resolvable as an A_2B_2 pattern where $\Delta\delta_A$ = 206 Hz and $\Delta\delta_B$ = 160 Hz and a first-order analysis yields J_{ortho} and J_{meta}. The A protons are, of course, closer to the coordination site and hence shifted further downfield. With 0.2 equiv of $Pr(fod)_3$, complementary upfield shifts are observed for the aromatic hydrogens with $\Delta\delta_A$ = 231 Hz and $\Delta\delta_B$ = 144 Hz. The value of using these complementary reagents is often in making unequivocal spectral assignments. Thus in the A_2B_2 pattern of the aromatic portion of ether **1**, δ_A = 434 Hz and δ_B = 416 Hz. This small separation increases upon incremental addition[11] of $Eu(fod)_3$. This A_2B_2 assignment is further confirmed by the incremental addition of $Pr(fod)_3$, whereby the A_2 portion, which must still be affected more strongly, moves through the B_2 portion leading to an inverted B_2A_2 pattern. Similar considerations can be made for the other protons in **1**, **2**, and **3**.

It has been suggested that the shifts will be pseudocontact in nature except for protons extremely close to the coordination site where a contact contribution might be anticipated.[3a,b] In fact we have observed, with the ethers **1**, **2**, and **3** with the shift reagents $Eu(dpm)_3$, $Eu(fod)_3$, and $Pr(fod)_3$, that the hydrogens on the carbons bearing oxygen (H_1 and H_4 in **1** and **2**, and H_2 and H_3 in **3**) sometimes exhibited a deviation that probably could be attributed to a contact contribution. To remove this doubt, these hydrogens were deleted from the correlation plots.[11] The results are shown in Tables I–III. A comparison of the standard deviations of the plots of the induced shifts, $\Delta\delta_i$, *vs.* R_i^{-3} shows a significant improvement in every instance upon inclusion of the geometric, $3\cos^2\theta_i - 1$, factor. The results are most striking for the ethers **1** and **2** and this suggests that steric considerations can probably influence the lanthanide position in **3**.

A statistical refinement of data of this type can be used to test the initial assumption regarding the lanthanide–substrate geometry.[6,7,12] This has been accomplished more recently by Willcott and Davis[13] by utilizing the statistical agreement factor R.

(5) (a) M. R. Willcott, J. F. M. Oth, J. Thio, G. Plincke, and G. Schroder, *Tetrahedron Lett.*, 1579 (1971); (b) P. H. Mazzocchi, H. J. Tamburin, and G. R. Miller, *ibid.*, 1819 (1971); (c) S. Farid, A. Atega, and M. Maggio, *Chem. Commun.*, 1285 (1971); (d) C. Beaute, Z. W. Wolkowski, J. P. Merda, and M. D. Lelandais, *Tetrahedron Lett.*, 2473 (1971); (e) S. B. Tjan and F. R. Visser, *ibid.*, 2833 (1971).

(6) J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Commun.*, 1506 (1970).

(7) J. Briggs, F. A. Hart, and E. W. Randall, *ibid.*, 364 (1971).

(8) R. R. Fraser and Y. Y. Wigfield, *ibid.*, 1471 (1970).

(9) W. DeW. Horrocks, Jr., and J. P. Sipe, III, *J. Amer. Chem. Soc.*, **93**, 6800 (1971), and references cited therein.

(10) R. Caple and S. C. Kuo, *Tetrahedron Lett.*, 4416 (1971).

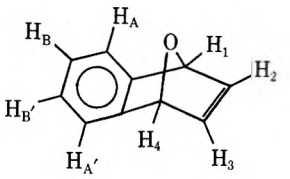
(11) In every instance the shift reagents were added in increments to yield unambiguous chemical shift assignments.

(12) S. Farid, A. Ateya, and M. Maggio, *Chem. Commun.*, 1285 (1971).

(13) M. R. Willcott, R. E. Lenkinski, and R. E. Davis, *J. Amer. Chem. Soc.*, **94**, 1742, 1744 (1972).

TABLE I

SHIFT CORRELATIONS FOR 1,4-DIHYDRONAPHTHALENE 1,4-OXIDE (1)[a]

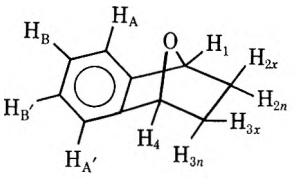


Shift reagent[b]	$1/R_i^3$ Std dev	$1/R_i^3$ Slope	$\frac{3\cos^2\theta_i - 1}{R_i^3}$ Std dev	$\frac{3\cos^2\theta_i - 1}{R_i^3}$ Slope
Eu(dpm)$_3$[c]	0.36	12.89	0.03	7.29
Eu(fod)$_3$	0.27	9.36	0.03	5.31
Pr(fod)$_3$	0.48	15.82	0.06	8.99

[a] Spectra obtained with $CDCl_3$ solutions on a Varian A-60D. [b] Ln(Y)$_3$ about 0.2 equiv. [c] Refinement of Eu(dpm)$_3$ shifts in ref 10.

TABLE II

SHIFT CORRELATIONS FOR 1,2,3,4-TETRAHYDRONAPHTHALENE 1,4-OXIDE (2)[a]

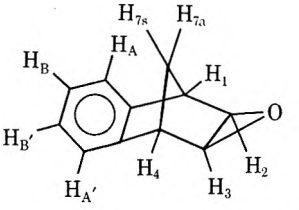


Shift reagent[b]	$1/R_i^3$ Std dev	$1/R_i^3$ Slope	$\frac{3\cos^2\theta_i - 1}{R_i^3}$ Std dev	$\frac{3\cos^2\theta_i - 1}{R_i^3}$ Slope
Eu(dpm)$_3$[c]	0.52	8.15	0.07	6.40
Eu(fod)$_3$	0.39	8.60	0.14	6.51
Pr(fod)$_3$	0.81	13.13	0.17	10.25

[a] Spectra obtained with $CDCl_3$ solutions on a Varian A-60D. [b] Ln(Y)$_3$ about 0.2 equiv. [c] Refinement of Eu(dpm)$_3$ shifts in ref 10.

TABLE III

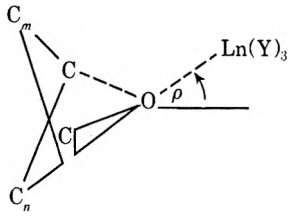
SHIFT CORRELATIONS FOR BENZONORBORNADIENE *exo*-OXIDE (3)[a]



Shift reagent[b]	$1/R_i^3$ Std dev	$1/R_i^3$ Slope	$\frac{3\cos^2\theta_i - 1}{R_i^3}$ Std dev	$\frac{3\cos^2\theta_i - 1}{R_i^3}$ Slope
Eu(dpm)$_3$[c]	0.30	7.46	0.11	7.63
Eu(fod)$_3$	0.22	7.24	0.07	7.40
Pr(fod)$_3$	0.23	8.90	0.16	9.07

[a] Spectra obtained with $CDCl_3$ solutions on a Varian A-60D. [b] Ln(Y)$_3$ about 0.2 equiv. [c] Refinement of Eu(dpm)$_3$ shifts in ref 10.

This type of least-squares fit to a model is easy to apply to ethers **1**, **2**, and **3** owing to the plane of symmetry. Thus the lanthanide, Ln, need only be moved in a plane rather than over the surface of a sphere. For a lanthanide–oxygen distance of 3.0 Å, one therefore needs only to find the angle ρ that provides the best fit to the observed shifts. The angle $\rho = 0°$ corresponds to the positioning of Ln in the plane defined by the oxygen and the two adjacent carbons as was done in the initial assumption.



These results are listed in Table IV. The ρ values listed are all positive, which corresponds to an angle

TABLE IV

STATISTICAL EVALUATION OF ANGLE ρ

Compd	Shift reagent	ρ, deg	Minimum agreement factor R
1	Eu(dpm)$_3$	9	0.005
	Eu(fod)$_3$	13	0.014
	Pr(fod)$_3$	7	0.008
2	Eu(dpm)$_3$	27	0.011
	Eu(fod)$_3$	6	0.048
	Pr(fod)$_3$	16	0.008
3	Eu(dpm)$_3$	42	0.018
	Eu(fod)$_3$	42	0.034
	Pr(fod)$_3$	42	0.014

to the right of 0° as the structures are written for the ethers **1**, **2**, and **3**. The small deviation from 0° for the ethers **1** and **2** is consistent with the similarity in steric requirements on either side of oxygen. It is difficult to say whether the small observed differences for the three shift reagents is real, but the general agreement is very satisfactory.

With benzonorbornadiene *exo*-oxide (**3**) a definite tipping away from the methylene bridge is noted. The agreement with the three reagents is unexpectedly good and the results suggest that considerable steric interaction must arise as ρ approaches 0° in the oxide. This is again stereochemically agreeable.

The agreement observed with these ideal systems certainly supports the contention that the induced shifts are very likely dipolar in nature. The results again illustrate the improvement in shift correlations that can be observed by inclusion of the angular dependency factor and also the type of refinement that can be obtained by a statistical fit such as with the agreement factor R.

Experimental Section

Analytical.—Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were obtained on a Varian A-60D spectrometer with tetramethylsilane as an internal standard.

Reagents.—1,2,3,4-tetrahydronaphthalene (2) and 1,4-dihydronaphthalene 1,4-oxide (1) were made according to reported procedures.[14,15] Nmr for 1: H_1 and H_4, s,[16] 340 Hz, H_2 and H_3, s,[16] 420 Hz, and A_2B_2 pattern centered at 425 Hz. Nmr for **2**: H_1 and H_4, q,[17] 323 Hz, H_{2x} and H_{3x}, m, 123 Hz, H_{2n}, and H_{3n} m, 81.5 Hz, aromatic s, δ 431 Hz.

Benzonorbornadiene *exo*-oxide (**3**) was made by the epoxidation of benzonorbornadiene with *m*-chloroperbenzoic acid in the usual

(14) G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956).
(15) L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 1599 (1965).
(16) J values less than 0.5 Hz.
(17) Small, *ca.* 1.5 Hz virtual coupling observed in addition to bridgehead exo coupling of 3.0 Hz.

manner.[18] Only **3** could be detected in the nmr spectrum of crude product, which was obtained in a near quantitative yield.

Recrystallization from cyclohexane–benzene gave an analytical sample, mp 93°.

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.05; H, 5.05.

Analytical Procedure.—The nmr samples were made by dissolving *ca.* 70 mg of the ether in 1.0 ml of $CDCl_3$ and adding the shift reagent (Norell Chemical Co., stored over P_2O_5) in quantities up to 0.2 equiv. Dreiding models were used to estimate distances and angles. Angles were both measured directly and checked by appropriate geometric relationships.

Statistical Correlations.—A calculation of an agreement factor R was accomplished in a manner similar to the procedure employed by Willcott and Davis.[13] As mentioned in the Discussion, the lanthanide was moved in a plane bisecting the ethers **1**, **2**, and **3** at a distance of 3.0 Å from the coordination site. At each position of Ln, the variable term $\Delta H_i = \alpha(3\cos^2\theta_i - 1)/R_i^3$ was evaluated for all the ith protons to yield a set of calculated $(\Delta H/H)_{ci}$ values (α is a constant). A minimum value of R was then obtained by the best least-squares fit for

$$R = \left\{ \frac{\sum_i \left[\left(\frac{\Delta H}{H}\right)_{oi} - \left(\frac{\Delta H}{H}\right)_{ci} \right]^2}{\sum_i \left(\frac{\Delta H}{H}\right)_{oi}^2} \right\}^{1/2}$$

where $(\Delta H/H)_{oi}$ are observed shifts.

(18) L. F. Fieser and M. Fieser, "Organic Reagents," Vol. 1, Wiley, New York, N. Y., 1967, p 135.

Registry No.—**1**, 573-57-9; **2**, 35185-96-7; **3**, 13137-34-3; Eu(dpm)$_3$, 15522-71-1; Eu(fod)$_3$, 17631-68-4; Pr(fod)$_3$, 17978-77-7.

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Hydrogenolysis of Acetals and Ketals by Alkoxyalanes and Alkoxychloroalanes[1]

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The hydrogenolysis of acetals, ketals, and 1,3-dioxolanes was examined using alkoxy-substituted alanes. Alkoxychloroalanes are moderately reactive and show potential as stereoselective reducing reagents. Alkoxyalanes were less reactive and dialkoxyalanes too unreactive for hydrogenolysis.

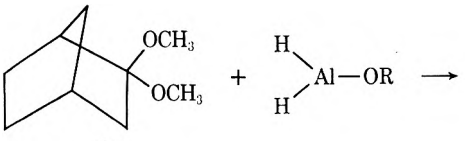
Cyclic and acyclic acetals and ketals can be hydrogenolyzed to the corresponding ethers by alane, chloroalane, and dichloroalane.[2] Having previously examined what structural features in the ketals affect the hydrogenolysis reaction,[3,4] we turned our attention to what structural modifications in the hydrogenolyzing reagent might affect the course of the reaction. Chloro groups are known to increase the reactivity of alanes.[5] Since oxygen and chlorine have similar electronegativities, we have investigated the use of alkoxyalanes, dialkoxyalanes, and alkoxychloroalanes for hydrogenolyzing acetals and ketals.

Isopropoxyalane and diisopropoxyalane have been prepared from the proper ratios of alane and triisopropoxyalane.[6] Ethoxyalane and diethoxyalane were prepared in a similar manner.[7] Many of the simpler alkoxyalanes and dialkoxyalanes have been prepared by the addition of 1 or 2 molar equiv of the corresponding alcohols to alane in THF.[8] The alkoxyalanes and dialkoxyalanes have been characterized by elemental analyses, molecular weight determinations, nmr and ir spectra,[6,8] and X-ray diffraction patterns.[7]

Early work showed dialkoxyalanes to be selective reagents which will reduce aldehydes, ketones, and acid chlorides, but not esters, nitriles, amides, nitrates, or aryl halides.[9] The use of alkoxyalanes has been extended to the reduction of epoxides.[10] The lone acetal reaction reported is the hydrogenolysis of 2-methyl-1,3-dioxolane by chloroethoxyalane.[11]

Results and Discussion

The hydrogenolysis of norcamphor dimethyl ketal (**1**) to 2-*endo*-norbornyl methyl ether (**2**) was examined



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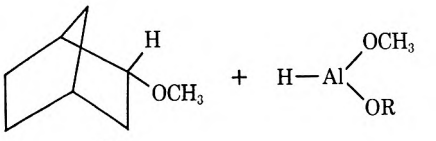

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using various alkoxyalanes and solvents to find the best conditions for the hydrogenolysis of acetals and ketals. These exploratory results are listed in Table I. First it can be seen that the dialkoxyalanes are less reactive than the alkoxyalanes. Secondly, Table I shows that none of the alkoxyalanes are as reactive as the parent compound, alane. Thirdly, the results show that both ether and benzene are better solvents than is THF.

(1) Taken from the Ph.D. Thesis of K. J. B., Villanova University, 1972.

(2) M. N. Rerick, "Reduction," R. L. Agustine, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, pp 46–50.

(3) W. W. Zajac, Jr., and K. J. Byrne, *J. Org. Chem.*, **37**, 521 (1972).

(4) W. W. Zajac, Jr., and K. J. Byrne, *ibid.*, **35**, 3375 (1970).

(5) (a) U. E. Diner, H. A. Davis, and R. K. Brown, *Can. J. Chem.*, **45**, 207 (1967); (b) H. O. Honse, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 48.

(6) E. E. Flagg and D. L. Schmidt, *J. Inorg. Nucl. Chem.*, **31**, 2329 (1969).

(7) N. E. Matzek and W. H. Crawford, U. S. Patent 3,524,870 (1970); *Chem. Abstr.*, **73**, 98379k (1970).

(8) H. Noth and H. Suchy, *Z. Anorg. Allg. Chem.*, **358**, 44 (1968).

(9) M. W. Hunt, U. S. Patent 3,281,443 (1966); presented at Midwest Regional Meeting of the American Chemical Society, Lincoln, Nebr., Oct 1970.

(10) B. Cooke, E. C. Ashby, and J. Lott, *J. Org. Chem.*, **33**, 1132 (1968).

(11) H. A. Davis and R. K. Brown, *Can. J. Chem.*, **49**, 2166 (1971).

TABLE I
HYDROGENOLYSIS OF NORCAMPHOR DIMETHYL KETAL

Alane	Solvent[a]	% Hydrogenolysis
H_2AlOMe	THF	<1[b]
H_2AlOEt	THF	<1
H_2AlO-*t*-Bu	THF	<1
$HAl(O$-*t*-$Bu)_2$	THF	<1
H_3Al	Ether	100
H_2AlOMe[c]	Ether	39
H_2AlOEt	Ether	10
H_2AlO-*i*-Pr	Ether	21
H_2AlO-*t*-Bu	Ether	2.4
$H_2AlOCH_2CH_2OCH_3$	Ether	9
$HAl(OEt)_2$	Ether	1
H_2AlOMe	Benzene	8.5
H_2AlO-*i*-Pr	Benzene	58
$HAl(O$-*i*-$Pr)_2$	Benzene	<1

[a] Room temperature for 22 hr. [b] 100 hr at reflux temperatures gave 76% hydrogenolysis. [c] Methoxyalane gave 46% hydrogenolysis of norcamphor diethyl ketal to 2-*endo*-norbornyl ethyl ether at room temperature for 22 hr in ether. Dimethoxyalane gave only 1% hydrogenolysis after 48 hr in refluxing ether.

The alkoxyalanes and dialkoxyalanes have been studied in THF and benzene and found to exist as dimers, trimers, and insoluble polymers depending on the alkoxy groups.[6,8] They are associated into these aggregates by bridge bonding of the alkoxy oxygens. Chloroalane and dichloroalane exist in diethyl ether as monomeric etherates.[12] In the first step of hydrogenolysis an alane must complex with an acetal. The complex opens to give an oxocarbonium ion intermediate which reacts with a hydride to give an ether product. An alane must be available to form the initial acetal complex. The alkoxyalanes satisfy their Lewis acid nature by bridge bonding into aggregates even in a strong Lewis base such as THF. Clearly the equilibrium between such a stable aggregate and an acetal complex will be less favorable than the equilibrium between an etherate complex and acetal complex. Therefore, the low reactivity of the alkoxyalanes is explainable by the strength of the aggregates and corresponding small shift in the equilibrium to acetal–alane complexes. Because the strength of the different aggregates are unknown at this point, the hydrogenolyzing strengths of different alkoxyalanes are not easily predictable. Also the question of whether except for bridging an oxygen atom on alane has the same properties as a chlorine atom cannot be answered. Ashby found the alkoxyalanes to be less reactive than alane or chloroalane for the reduction of β-diisobutylene oxide and styrene oxide in THF.[10] In these reactions the dialkoxyalanes are even less effective.

Methoxyalane was the most reactive alkoxyalane for the hydrogenolysis of norcamphor dimethyl ketal in ether and it was used to study the reactivity of various acetals and ketals. The results of this study appear in Table II. The ortho ester is the most reactive. It is completely hydrogenolyzed in the presence of its product, benzaldehyde dimethyl acetal, which in itself is 61% hydrogenolyzed to benzyl methyl ether (there was an 80% excess of methoxyalane in all reactions). The reactivity of the acetals is what would be predicted for methoxyalane if it is analogous

(12) (a) E. Wiberg, K. Modritzer, and R. Uson Lacel, *Rev. Acad. Cienc. Exactas, Fis-Quim. Natur. Zaragoza*, **9**, 91 (1954); (b) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966).

TABLE II
HYDROGENOLYSIS OF ACETALS AND KETALS BY METHOXYALANE

Acetal	Time,[a] hr	% Hydrogenolysis
Trimethylorthobenzoate	48	100[b]
Benzaldehyde dimethyl acetal	48	100
Norcamphor dimethyl ketal	48	96
Cyclododecanone dimethyl ketal	48	72[c]
Norcamphor ethylene ketal	48	55
Norcamphor ethylene ketal	168	73
Heptanal dimethyl acetal	48	24
Heptanal dimethyl acetal	168	53

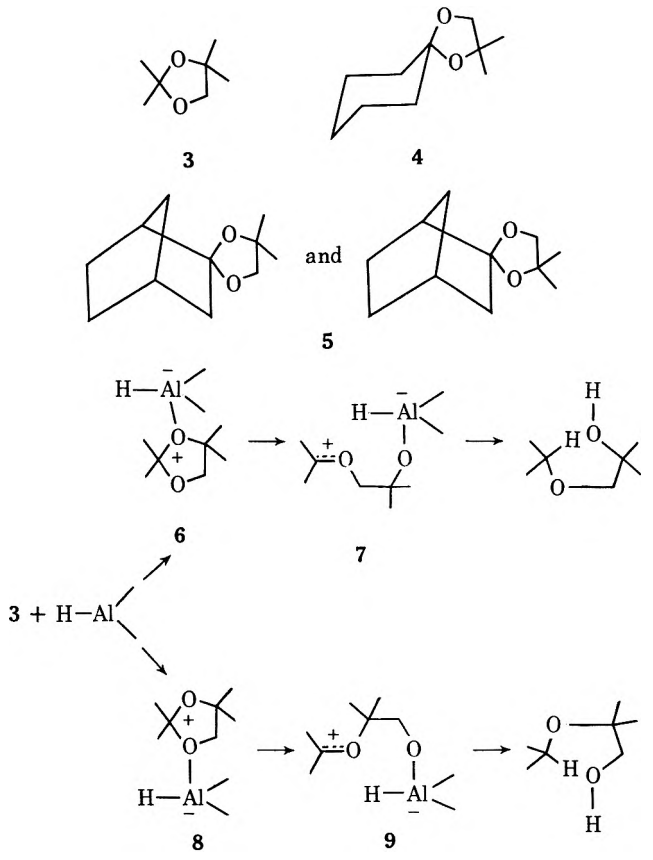
[a] Refluxing ether. [b] The product was 61% benzyl methyl ether and 39% benzaldehyde dimethyl acetal. [c] The unhydrogenolyzed part was 3% ketal, 13% *trans*-1-cyclododecenyl methyl ether, and 12% *cis*-1-cyclododecenyl methyl ether.

to chloroalane. The acetal or ketal that yields the more stabilized oxocarbonium ion intermediate is more reactive.[3,13] Thus, benzaldehyde dimethyl acetal is more reactive than aliphatic ketals, which in turn are more reactive than an aliphatic acetal. The open norcamphor dimethyl ketal is more reactive than the cyclic norcamphor ethylene ketal. Cyclododecanone dimethyl ketal gave 25% elimination of methanol to give a vinyl ether. Strained ring systems are prone to such elimination because it reduces the crowding of ring substituents and therefore strain. Cycloheptanone dimethyl ketal is a compound with considerable eclipsing strain.[4] This ketal was allowed to react for 22 hr at room temperature with methoxyalane in THF as well as in ether. In THF this very reactive ketal hydrogenolyzed 30% to cycloheptyl methyl ether. The elimination product, 1-cycloheptenyl methyl ether, amounted to 6%, while 64% of the ketal survived. In the more favorable solvent, diethyl ether, no ketal survived. There was 4.5% hydrogenolysis and 95.5% elimination to the vinyl ether. Since the Lewis acidity of the alane is involved in both the hydrogenolysis and elimination, methoxyalane appears to be a more effective Lewis acid in ether. The methoxyalane seems to be a good hydride donor in THF, but the predominance of the elimination product in ether suggests that the monomeric methoxyalane has lost much of its hydride donating ability in ether or that some other aluminum species is catalyzing the elimination in ether. Ashby has noted the strong hydride donor properties of alkoxyalanes in THF.[10]

2,2,4,4-Tetrasubstituted 1,3-dioxolanes such as **3**, **4**, and **5** give predominantly tertiary alcohol when they are hydrogenolyzed and not primary alcohol. For 2,2,4,4-tetramethyl-1,3-dioxolane (**3**), chloroalane complexes mainly with the more crowded oxygen (**6**) and opens to give the less inductively stabilized oxocarbonium ion intermediate (**7**).[14] This unusual route is believed to be due to the steric strain in **9** (resulting from the alternate complex **8**) which is not present in the intermediate **7**.

The hydrogenolysis of **3** by chloroalane is reported to give 6% primary alcohol,[14] and **4** to give exclusively tertiary alcohol.[15] When **3** was treated for 1 week

(13) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964).
(14) B. E. Leggether and R. K. Brown, *ibid.*, **42**, 1005 (1964).
(15) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).



with methoxyalane in refluxing ether, there was 64% hydrogenolysis with 10% of the product being primary alcohol. Under the same conditions **4** was 23% hydrogenolyzed with 12% of the product being primary alcohol. This could indicate that methoxyalane has greater steric requirements than chloroalane or dichloroalane and complexes like **6** are less favorable. This is unlikely because chloromethoxyalane gives only 3.5% primary alcohol with **3** (Table III).

TABLE III
HYDROGENOLYSIS OF 2,2,4,4-TETRAMETHYL-1,3-DIOXOLANE BY SOME ALKOXYCHLOROALANES

Alane[a]	% Hydrogenolysis	% Primary alcohol
HAlClOMe	80	3.5
HAlClOEt	70	4.7
HAlClO-*i*-Pr	30	9.8
HAlClO-*t*-Bu[b]	11	24.4
HAlClO$(CH_2)_2OCH_3$[c]	<1	

[a] Refluxing ether for 2 hr. [b] When refluxed for 1 week norcamphor isobutylene ketal gave 10% hydrogenolysis with methoxyalane with 22% being exo primary alcohol and 78% endo tertiary alcohol. Chloroisobutoxyalane gave 59% hydrogenolysis with 42 and 58% of the two alcohols, respectively. Chloroalane is reported to give 32 and 68%, respectively: P. C. Loewen, W. W. Zajac, Jr., and R. K. Brown, *Can. J. Chem.*, **47**, 4059 (1969). [c] 2-methoxyethoxyalane gave 4% hydrogenolysis under the same conditions with 10% being primary.

Since dialkoxyalanes are relatively quite unreactive as hydrogenolyzing agents (Table I), several alkoxychloroalanes were examined to detemine if they would exhibit more selectivity. The results for the hydrogenolysis of 2,2,4,4-tetramethyl-1,3-dioxolane are listed in Table III. As the alkoxy group changes from Me to Et to *i*-Pr to *t*-Bu, the extent of hydrogenolysis decreases and the percentage of primary alcohols in the product increases. The increase of primary alcohol suggests that complex **6** is becoming more hindered as the alkoxy group becomes larger. It is not known whether alkoxychloroalanes are monomeric in ether or associated. The reactivity of a particular alkoxychloroalane would depend on the reactivity of the monomer and the association energy of larger aggregates if any. Since the reactivity falls off with larger alkoxy groups in a way which would be expected for the monomeric alanes, it appears that the aggregates, if they exist, dissociate to monomers about equally readily. The steady change in reactivity for alkoxychloroalanes and steady change in primary alcohol product rule out any possibility that the alkoxychloroalanes disproportionate and react through a common chloroalane or dichloroalane. No measurable hydrogenolysis was obtained with 2-methoxyethoxychloroalane (Table III). When this alane was prepared it formed a tacky precipitate, as has been reported.[11] In contrast 2-methoxyethoxyalane had about the same reactivity as ethoxyalane (Table I).

The alkoxychloroalanes are reactive hydrogenolysis reagents suitable for the hydrogenolysis of acetals and ketals. By using more substituted alkoxy groups in the alkoxychloroalane it has been possible to moderately alter the products of the hydrogenolysis of **3**. This family of reagents offers promise in the reduction of acetals, ketals, and other functional groups in which the reaction is subject to steric factors. Alkoxyalanes and dialkoxyalanes do not appear to have the general usefulness of chloroalane and dichloroalane, although the former will satisfactorily hydrogenolyze reactive acetals and ketals.

Experimental Section

Hydrogenolyses with Alkoxyalanes and Dialkoxyalanes.—Clear, standardized (~1.2 *M*) solutions of $LiAlH_4$ in THF and Et_2O were prepared as described by Brown and Weissman.[16] When standardizing the Et_2O solution the described ethylene glycol was replaced by 30 ml of bis(2-methoxyethyl) ether and 5 ml of 1-butanol stirring at 0°. A quantity of a standardized solution (~30 ml) containing 36 mmol was syringed into a 100-ml flask having a magnetic stirring bar, septum fitted neck, N_2 atmosphere, and adequate vent for N_2 and H_2.[17] THF or Et_2O were added to bring the volume to 60 ml. AlH_3 was prepared by syringing 0.96 ml (18 mmol) of 100% H_2SO_4 slowly to the flask in an ice bath. The Li_2SO_4 was not filtered out. After 0.5 hr without the ice bath it was returned and 36 mmol of an alcohol was syringed into the flask slowly to yield an alkoxyalane. This corresponds to 1.50 ml of MeOH, 2.20 ml of EtOH, 2.85 ml of *i*-PrOH, 3.50 ml of *t*-BuOH, or 2.95 ml of methoxyethyl alcohol. For dialkoxyalane 72 mmol of alcohol was used. For reactions in PhH, 60 ml of PhH was added in 10-ml portions to an alkoxyalane in Et_2O. The Et_2O was distilled out; when 60 ml of distillate was removed the thermometer temperature was 72°. The acetal or ketal (0.20 mmol) was syringed into the reagent when it was at the desired temperature. At work-up the reaction was poured into a separatory funnel containing 150 ml of ice water, 75 ml of Et_2O, and a small amount of K_2CO_3. The aqueous layer was extracted a second time with 75 ml of Et_2O. When dioxolanes were hydrogenolyzed, concentrated HCl was now added to the aqueous layer until the aluminum salts dissolved and 100 ml of Et_2O was used to extract the aqueous layer again, which was back extracted with 10 ml of 5% NaOH. The combined Et_2O extracts were washed with 50 ml of saturated NaCl and dried over K_2CO_3. After evaporation of solvent the products were identified

(16) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965).
(17) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966).

by glpc comparison with known compounds or by collecting the glpc peaks for spectra. The percentage yields reported correspond to the peak area.

Hydrogenolyses with Alkoxychloroalanes.—Into the flask described above was weighed 2.40 g (18 mmol) of $AlCl_3$. In an ice bath 45 ml of Et_2O was syringed into the flask to dissolve the $AlCl_3$; 18 mmol of the standardized $LiAlH_4$ solution (~15 ml) was added by syringe. After 15 min without the ice bath it was returned, the alcohol was added, and the hydrogenolysis was run as above. For work-up the reaction mixture was poured into a separatory funnel containing 4 g of NaOH, 50 ml of H_2O, 50 g of ice, and 75 ml of Et_2O. The rest of the work-up was as above.

Materials.—THF and Et_2O were dried by distillation from $LiAlH_4$. Alcohols were distilled from CaH_2. The preparations of norcamphor dimethyl ketal, cycloheptanone dimethyl ketal, and cyclodecanone dimethyl ketal have been described.[4] The published preparation for 2,2,4,4-tetramethyl-1,3-dioxolane also yielded cyclohexanone isobutylene ketal and norcamphor isobutylene ketal.[13] The preparations of norcamphor diethyl ketal,[3] norcamphor ethylene ketal,[18] and trimethyl orthobenzoate[19] are reported. Benzaldehyde dimethyl acetal and heptanal dimethyl acetal were prepared from the aldehydes and trimethyl orthoformate.

Registry No.—**1**, 10395-51-4; **3**, 13372-34-4; methoxyalane, 36803-31-3.

(18) E. J. Salmi, *Ber.*, **71**, 1803 (1938).
(19) S. M. McElvain and J. T. Venerable, *J. Amer. Chem. Soc.*, **72**, 1661 (1950).

The Vapor Phase Pyrogenesis of Phenol

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Phthalic acid and 3- and 4-methylphthalic acids (precursors of benzyne, methylbenzyne, water) were pyrolyzed at 700° and their interaction products were determined. From phthalic acid, the major products, in addition to benzyne interaction products, were benzoic acid, phenol, and phenyl benzoate. It is proposed that decarboxylation of phthalic acid competes with benzyne formation *via* the anhydride and that phenol and phenyl benzoate arise through a competitive addition of water and benzoic acid, respectively, to the benzyne intermediate. The vapor phase addition of water to methylbenzynes produces the expected isomeric cresols.

The high-temperature pyrolysis (*ca.* 800°) of a number of natural products such as tobacco,[1] lignin,[2] and carbohydrates[3] has been reported to produce significant amounts of phenol and substituted phenols. Because of the reported activity of phenols as tumor-promoting agents,[4] the origin of these substances in the pyrolytic process is of considerable interest. It was recently found that the pyrosynthesis of phenols occurs when both aromatic and nonaromatic substances, such as amino acids[5a] and maleic hydrazide,[5b] are pyrolyzed at high temperatures. The presence of hydrocarbons in the pyrolysate, which have been shown to arise from benzyne, suggested that benzyne might be a precursor to the phenols observed in the high-temperature pyrolyses. While the addition of water to benzyne in the liquid phase has been adequately demonstrated,[6] no evidence was available to indicate that the addition would occur in the vapor phase at high temperatures (700°) or in what way. Because of the recent reports that the addition of carbon disulfide to benzyne gives different products in the vapor phase[7] as compared to the liquid phase,[8] the possible vapor phase addition of water to benzyne was investigated.

Results and Discussion

The ease with which phthalic acid undergoes dehydration to phthalic anhydride and water and the fact that the thermal decomposition of phthalic anhydride at 700° produces benzyne[9] suggests that the pyrolysis of phthalic acid and methyl-substituted phthalic acids at 700° would provide convenient systems for observing the interaction of benzyne with water in the vapor phase.

When phthalic acid was pyrolyzed at 700°, phenol, phenyl benzoate, and benzoic acid were produced in addition to the usual benzyne products of biphenyl and naphthalene. Substituted phenols were likewise obtained from the thermolysis of 3- and 4-methylphthalic acids at 700°. The yields of these products as well as the relative concentrations of other pyrolysate constituents are summarized in Tables I and II.

TABLE I

YIELDS[a] OF SELECTED COMPONENTS OBTAINED FROM THE PYROLYSIS OF PHTHALIC ACID, BENZOIC ACID, AND METHYL-SUBSTITUTED DERIVATIVES AT 700°

Component	Phthalic acid	Benzoic acid	Toluic acids			Methylphthalic acids	
			o-	*m*-	*p*-	3-	4-
Naphthalene	1.2						
Biphenyl	1.8						
Phenol	3.9	0.4				0.09	0.14
o-Cresol			0.01	*b*	*b*	0.10	*b*
m-Cresol			*b*	0.02	*b*	0.11	
p-Cresol			*b*	*b*	0.01	*b*	1.25[c]
Phenyl benzoate	2.2						

[a] Yields are reported as moles of compound per mole of substance pyrolyzed × 100 and were determined by glpc using internal standards. [b] Not found. [c] Mixture of *m*- and *p*-cresol incompletely resolved by glpc. Ratio of para to meta isomer as determined by infrared spectroscopy was 0.83:1.

It is proposed that the major reaction products arise through a competitive decarboxylation and de-

(1) R. L. Stedman, *Chem. Rev.*, **68**, 153 (1968).
(2) W. S. Schlotzhauer, I. Schmeltz, and L. C. Hickey, *Tobacco Sci.*, **11**, 31 (1967).
(3) E. B. Higman, I. Schmeltz, and W. S. Schlotzhauer, *J. Agr. Food Chem.*, **18**, 639 (1970).
(4) C. E. Searle, *Chem. Brit.*, **6**, 5 (1970).
(5) (a) J. M. Patterson, M. L. Baedecker, R. Musick, and W. T. Smith, Jr., *Tabacco Sci.*, **13**, 26 (1969); (b) J. M. Patterson, C. H. Issidorides, V. C. Groutas, and W. T. Smith, Jr., *Chem. Ind. (London)*, 337 (1972).
(6) R. Howe, *J. Chem. Soc.*, 478 (1966); G. Wittig and R. W. Hoffman, *Chem. Ber.*, **95**, 2718 (1962).
(7) E. K. Fields and S. Meyerson, *Tetrahedron Lett.*, 629 (1970).
(8) I. Tabushi, K. Okazaki and R. Oda, *ibid.*, 3287 (1967).
(9) E. K. Fields and S. Meyerson in "Advances in Physical Organic Chemistry," Vol. 6, V. Gold, Ed., Academic Press, New York, N. Y., 1968, p 1.

SCHEME I

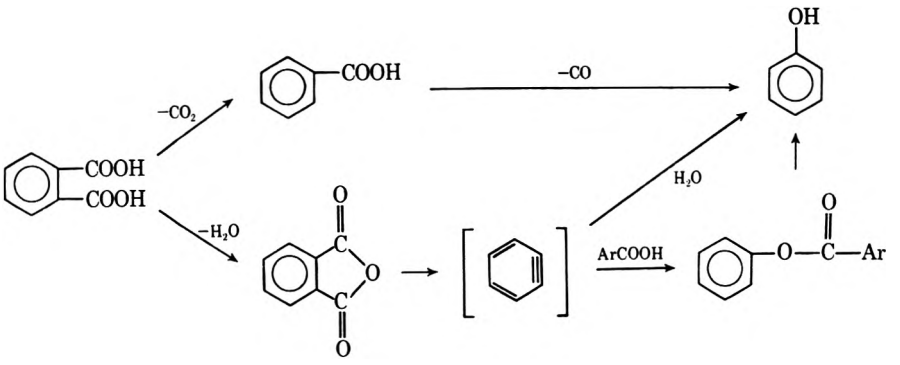

TABLE II

RELATIVE CONCENTRATIONS[a] OF SELECTED PYROLYSATE CONSTITUENTS OBTAINED FROM PHTHALIC, BENZOIC, TOLUIC, AND SOME METHYL-SUBSTITUTED PHTHALIC ACIDS

Component	Phthalic acid[e]	Benzoic acid[f]	Toluic acids[g] o-	Toluic acids[g] m-	Toluic acids[g] p-	Methylphthalic acids[h] 3-	Methylphthalic acids[h] 4-
			A. Neutral Fraction				
Benzene	3.4	61.0	0.2	0.3	0.1		0.8
Toluene	0.3	0.3	95.1	72.1	96.0	23.1	51.6
Styrene	1.2	0.5	0.1	0.2	0.2	1.7	0.5
o-Methylstyrene	0.5		0.1	0.2	0.2		0.1
β-Methylstyrene	0.8					4.0	0.4
Naphthalene	9.5	1.4	0.05		0.01	0.2	0.4
2-Methylnaphthalene					0.2	1.3	3.6
1-Methylnaphthalene						7.3	
Biphenyl	15.0	28.1		0.2	0.06		
3-Methylbiphenyl							0.9
4-Methylbiphenyl					0.6		0.8
Ditolyl				2.1			4.5
Fluorene			0.2			1.7	2.3
Anthracene						1.1	0.3
Phenylacetylene	0.7						
Dibenzofuran	3.5						
Phenyl benzoate	42.2	0.5					
Fluorenone	0.8						
Biphenylene	0.5						
Phenanthrene	7.5						
Wt neutral fraction	5.02	0.5	1.7	1.9	5.2	0.8	4.4
			B. Acidic Fraction				
Phenol	13.2	1.1				0.3	0.4
o-Cresol			0.4			2.7	
m-Cresol				0.5		2.4	26.2
p-Cresol					5.0		
o-Toluic Acid			99.1			0.7	
m-Toluic Acid				97.8		0.3	22.6
p-Toluic Acid					95.0		3.9
Benzoic Acid	53.5	98.9					
Phthalic acid[b]	21.2						
3-Methylphthalic acid[b]						92.8	
4-Methylphthalic acid[b]							35.2
Wt of acid fraction	3.65	9.94	1.30	15.8[c]	0.85[d]	1.60	2.15
Wt of substance pyrolyzed	43.65	16.00	7.90	21.70	11.80	9.60	18.40

[a] Relative concentrations are area per cent as determined by glpc analysis. [b] Compounds dehydrated to the anhydride during glpc analysis and percentages reported are for the anhydride. [c] Of the 15.8 g only 4.7 g was ether soluble. Concentrations reported are for the ether-soluble material. [d] Of the 0.85 g only 0.25 g was ether-soluble. Concentrations reported are for the ether-soluble material. [e] Registry no.: 88-99-3. [f] Registry no.: 65-85-0. [g] Registry no.: o-, 118-90-1; m-, 99-04-7; p-, 99-94-5. [h] Registry no.: 3-, 37102-74-2; 4-, 4316-23-8.

hydration of the phthalic acid followed by the addition of water or benzoic acid to the benzyne generated from the phthalic anhydride intermediate (see Scheme I).

Experiments carried out under the conditions used in the pyrolysis of phthalic acid demonstrated that the phenyl benzoate observed was produced primarily by the addition of benzoic acid to benzyne rather than by a thermal esterification of phenol by benzoic acid.[10] Benzoic acid, on pyrolysis with phthalic anhydride (benzyne precursor), gave 2.5% phenyl benzoate while

(10) Benzoic acid has been reported to add to benzyne in the liquid phase. See M. Stiles, R. G. Miller, and U. Burckhardt, *J. Amer. Chem. Soc.*, **85**, 1792 (1963).

pyrolysis with phenol (equimolar mixture) gave only 0.3% phenyl benzoate.[11]

The facts that the pyrolysis of a mixture of benzoic acid and phthalic anhydride produced phenol (yield nearly equivalent to that of phenyl benzoate) and that neither the thermal decomposition of phthalic anhydride alone nor the previously reported[12] decarbonylation of benzoic acid produced significant quantities of phenol (0.05 and 0.3%, respectively)[11] suggest that phenyl benzoate decomposes at 700° to give mainly phenol along with naphthalene, biphenyl, benzene, dibenzofuran, and trace amounts of benzaldehyde. While the formation of naphthalene suggests that the addition of benzoic acid to benzyne is reversible, it is likely that the major decomposition pathway involves a homolytic acyl–oxygen cleavage as outlined in Scheme II (compare products from phthalic anhydride and phenyl benzoate in Table III).

SCHEME II

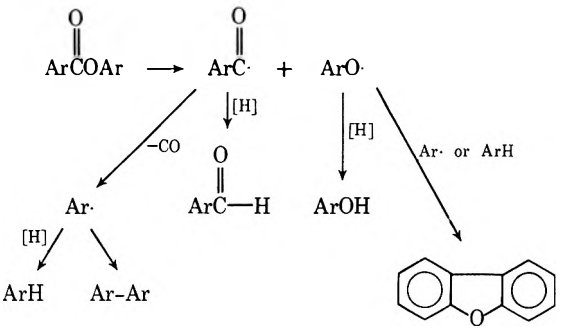

TABLE III

YIELDS[a] OF SELECTED COMPONENTS PRODUCED ON THE PYROLYSIS OF PHTHALIC ANHYDRIDE, PHENYL BENZOATE, PHTHALIC ANHYDRIDE–BENZOIC ACID MIXTURE, AND PHENOL–BENZOIC ACID MIXTURE AT 700°

Component	Phthalic anhydride[b]	Phenyl benzoate[c]	Phthalic anhydride–benzoic acid	Phenol–benzoic acid[d]
Naphthalene	0.7	0.6	0.7	0.3
Biphenyl	0.6	8.7	2.8	0.3
Dibenzofuran		6.5	0.5	0.4
Phenyl Benzoate		10.4	2.5	0.3
Phenol	0.05	18.0	2.2	62.8

[a] Yields are reported as moles of compound produced/mole of substance (or equimolar mixture) pyrolyzed × 100 and were determined by glpc using internal standards. [b] Registry no.: 85-44-9. [c] Registry no.: 93-99-2. [d] Registry no.: 108-95-2.

A measure of the extent of the competition between water and benzoic acid for benzyne can be obtained by a comparison of the yields of phenol and phenyl benzoate produced in the phthalic acid pyrolysis. The yields reported in Table I, however, must be corrected for the thermal conversion of phenyl benzoate into phenol. A rough estimate of the extent of this conversion in the phthalic acid reaction can be made by assuming in the reaction of phthalic anhydride with benzoic acid that the major portion of the phenol formed arises from the decomposition of the phenyl benzoate (see Tables I and III). Using the phenyl benzoate–phenol ratio (from the phthalic anhydride–benzoic acid reaction) and the phenyl benzoate concentration (phthalic acid reaction), the contribution of phenyl benzoate to the phenol yield in the phthalic acid reaction is obtained. A comparison of the corrected yields indicates that benzyne exhibits the same slight preference for the stronger acid in the vapor phase that was observed in the liquid phase.[10]

Further support for the participation of benzyne in the vapor phase pyrogenesis of phenol is obtained from experiments involving substituted benzyne precursors. The pyrolysis of 3-methylphthalic acid at 700° gave *o*- and *m*-cresol (but no *p*-cresol) in a ratio of 1.1:1. A similar ratio (1.07:1) was reported by Roberts[13] in the production of cresols in the liquid phase hydrolysis of *o*-chlorotoluene. Likewise, 4-methylphthalic acid at 700° produced *p*- and *m*-cresol (but no *o*-cresol) in the ratio of 0.8:1. 4-Methylbenzyne has been reported[14] to produce *p*- and *m*-cresyl phenyl ether in a similar ratio of 0.7:1.

As was true with phenol, cresol formation may occur by decarbonylation of the corresponding toluic acid. However, this path was found to be of minor importance when compared with the addition of water to methylbenzyne. *o*-, *m*-, and *p*-toluic acid gave 0.01, 0.02, and 0.01% of *o*, *m*, and *p*-cresol, respectively.

Experimental Section

Ultraviolet spectra were measured in cyclohexane using a Perkin-Elmer Model 202 spectrophotometer, and infrared spectra were measured in chloroform or carbon tetrachloride using a Beckman IR-8 spectrophotometer equipped with a mirror beam condenser. Mass spectra were determined on a Hitachi RMU-6E double-focusing mass spectrometer using 70 eV ionizing energy with the inlet system at 200°. Glpc analyses and preparative separations of the pyrolysate constituents were carried out on an F & M Model 810 gas chromatograph using a thermal conductivity detector.

Materials.—Benzoic and the toluic acids were commercially available samples and were used as received. Phthalic acid, mp 208–210°, and 4-methylphthalic acid, mp 150–151°, were produced by the alkaline hydrolysis of the available anhydrides. 4-Methylphthalic acid, mp 153–155°, was synthesized by the procedure of Smith and Kan[15] using *m*-toluyl chloride and lead isothiocyanate.

Pyrolyses.—The pyrolyses were carried out in the apparatus previously described[16] using 14 ml of Berl saddles or Vycor beads, a nitrogen flow of 100 ml/min, and a rotating screw device (driven by a Troemner monodrum unit) for the introduction of the solid samples into the pyrolysis tube. The liquid products were collected in two traps, each of which was cooled in a Dry Ice–chloroform–carbon tetrachloride mixture, dissolved in ether, and separated into a neutral and acidic fraction by extraction with 5% NaOH. See Table II.

Separation and Identification of Components.—Components of the neutral and acidic fractions were separated by glpc using a 25 ft × 0.375 in. 20% Apiezon L (Anakrom 50/60 U) column heated at 90° for 8 min and then programmed at 2°/min to 280°.

Identifications of components are based on comparisons of glpc retention times, ultraviolet spectra, and infrared spectra with those obtained from authentic samples. Estimation of relative abundances of constituents are based on area per cent values obtained from glpc using a 12 ft × 0.125 in. Hewlett-Packard Hi-pak Apiezon L column for the neutral fraction and a 12 ft × 0.125 in. 2% polyphenyl ether (six-ring) column for the acidic fraction.

(11) The yields of compounds indicated represent the upper limits possible, since the reactants are present in considerably lesser amounts in the phthalic acid or phthalic anhydride pyrolyses.

(12) W. Moser, *Helv. Chim. Acta*, **14**, 971 (1931).

(13) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **79**, 1458 (1957).

(14) R. W. Hoffmann, *Chem. Ber.*, **97**, 2772 (1964).

(15) P. A. S. Smith and R. O. Kan, *J. Amer. Chem. Soc.*, **82**, 4753 (1960).

(16) J. M. Patterson, A. Tsamasfyros, and W. T. Smith, Jr., *J. Heterocycl. Chem.*, **5**, 727 (1968).

The results are reported in Table II. Yields of selected components were determined in the acidic and neutral fractions using the internal standard method. Naphthalene and/or biphenyl were used as internal standards in the acidic fraction analysis and 2-methylnaphthalene was used in the neutral fraction analysis. The results are reported in Tables I and III.

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The Synthesis of a Large-Ring Ketone Containing a Lactone Function. The Dieckmann Condensation *vs.* the Thorpe–Ziegler Condensation[1]

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A method has been found for the synthesis in good yield of a large-ring ketone from an α,ω diester (**2a**) whose structure contains a third functional group that is susceptible to basic cleavage. This cyclization, an adaptation of the Dieckmann reaction, has been applied to the preparation of the 2,4-dibenzyl ethers of racemic 5′- and 7′-carbomethoxyzearalanone (**4** and **5**) which are necessary intermediates in the total synthesis of *R,S*-zearalanone (**1a**). This cyclization was compared to the Thorpe–Ziegler cyclization of the parallel α,ω-dinitrile (**2b**). In this case, the enamino nitriles first formed (**9** and **10**) were found to rearrange under the influence of base by nucleophilic attack of the enamino anion on the carbonyl carbon to give amides **11** and **12**. The physical and chemical properties of **11** and **12**, as well as those of the dimer (**19**) produced in this cyclization, are discussed.

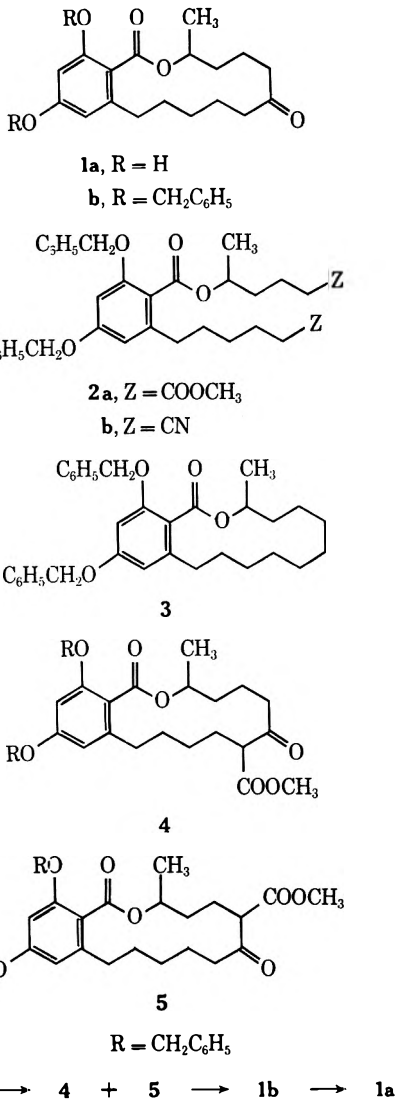
The Thorpe–Ziegler condensation has been known for many years as a principal method for syntheses of large-ring ketones. In contrast, the Dieckmann condensation appears to be little known as a source of large-ring ketones[3] even though its application in useful yields has been demonstrated with a series of α,ω diesters.[4] Many modern texts and references[5-7] still continue to state that the scope of the Dieckmann cyclization is restricted to formation of five- or six-membered rings.

To our knowledge there is no reference in the literature to the synthesis of a large-ring ketone from an α,ω-difunctional compound by either the Thorpe–Ziegler or the Dieckmann reactions, where the starting dinitrile or diester, respectively, has a structure in which there is a third functional group that is susceptible to basic cleavage.

The problem of cyclizing such a structure became real to us in completing a total synthesis of zearalanone[8] (**1a**), where it became necessary to cyclize either triester **2a** or ester dinitrile **2b** to a 14-membered lactone intermediate that could be converted readily to **1a** (Scheme I).

The Dieckmann Cyclization of 4-Carbomethoxy-1-methylbutyl 2,4-Bis(benzyloxy)-6-(5-carbomethoxypentyl)benzoate (2a).—The reaction conditions successfully used by Leonard and Schimelpfenig[4] for the cyclization of alkanedioic esters, namely, potassium *tert*-butoxide in refluxing xylene, did not appear promising for the cyclization of **2a**. The dibenzyl ether of zearalane (**3**) was completely destroyed in less than a day by this treatment, indicating that substantial

SCHEME I



(1) Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minnesota, April, 1969, MEDI 28.

(2) G. D. Searle International Co., P.O. Box 5486, Chicago, Ill. 60680.

(3) K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94 (1933).

(4) N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

(5) J. Hendrickson, D. Cram, and G. Hammond, "Organic Chemistry," 3rd ed, McGraw-Hill, New York, N. Y., 1970, p 525.

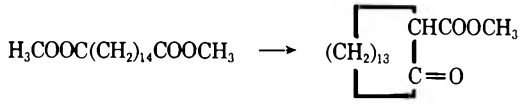
(6) S. Patai, Ed., "The Chemistry of the Carbonyl Group," Interscience, New York, N. Y., 1966, p 274.

(7) A. Liberles, "Introduction to Theoretical Organic Chemistry," Macmillan, New York, N. Y., 1968, p 550.

(8) The total synthesis of zearalanone is the subject of a paper by us in *J. Med. Chem.*, in press.

loss in yield of the desired cyclization product could be expected by way of basic attack either on the lactone function of the product or on the ester function of **2a**.

This problem was solved by substituting sodium bis(trimethylsilyl)amide, $[(CH_3)_3Si]_2NNa$ (**6**), for potassium *tert*-butoxide. Compound **6** is a strong base that is readily soluble in nonpolar organic solvents such as ether.[9] This latter property permitted us to have a homogeneous reaction system at moderate temperatures, and allowed the Dieckmann cyclization to proceed smoothly in good yield. Thus, under conditions of high dilution, a refluxing ether solution of **6** brought about cyclization of a model diester, dimethyl hexadecanedioate (**7**), into methyl 2-oxocyclopentadecanecarboxylate (**8**) in 64% yield, repeatedly.



7 **8**

This was a reproducible improvement over the 48% yield of cyclopentadecanone obtained with potassium *tert*-butoxide in refluxing xylene.[4]

Reaction of triester **2a** with **6** in reluxing ether solution resulted in a product in 77% yield. Although this product could be considered to be the 2,4-dibenzyl ether of either 5′- or 7′-carbomethoxyzearalanone[10] (**4** or **5**), we believe that it is more reasonable to consider the product as a mixture of **4** and **5**. No attempt was made to separate this mixture, since the two components are equally useful in the total synthesis of **1b**. This yield was achieved by continuous, controlled addition of a very dilute ether solution of **2a** to a refluxing ether solution of **6** during 8 hr. As expected, more rapid addition (6.5 hr) caused a drop in yield to 57%.

Base **6** exhibits high nucleophilic reactivity.[11] With esters that have a reactive α hydrogen it reacts to form a sodium enolate and bis(trimethylsilyl)amine.[9] On the other hand, esters with no α hydrogen are reported to form imidic acid derivatives.[12] With triester **2a** there is afforded to base **6** the opportunity to react in either or both of the ways just described. No evidence of an imidic acid derivative was obtained during reaction of **2a** with **6**. Isolation of the mixture of **4** and **5** demonstrated that **2a** behaved as an ester with reactive α hydrogen.

The product (**4** and **5**) was saponified to the corresponding mixture of β-keto acids and then, without isolation, this mixture was decarboxylated by warming in acid to give the 2,4-dibenzyl ether of *R,S*-zearalanone (**1b**).[8]

The ease with which these macrocyclizations were carried out, the mild reaction conditions used, and the excellent yields obtained encourage us to suggest that this reaction should be more widely investigated as a valuable tool in the synthesis of complex macrocyclic structures. Preservation of the lactone function (**4** and **5**) under basic conditions by use of **6** at moderate temperatures leads us to speculate that this adaptation of the Dieckmann reaction might be useful in the preparation of other complex macrocycles with base-reactive functions.

Thorpe–Ziegler Cyclization of 4-Cyano-1-methylbutyl 6-(5-Cyanopentyl)-2,4-bis(benzyloxy)benzoate (2b).—Fry and Fieser first applied the Thorpe–Ziegler cyclization to the synthesis of a cyclic ketone fused to an aromatic ring.[13] In our hands, their reaction conditions[14] applied to dinitrile **2b**[8] gave a very small yield of a mixture of unidentified products and an equally small recovery of unreacted **2b**.

The importance of a soluble base for good yields in the nitrile cyclization at high dilution has long been recognized.[15,16] Since the condensing agent used by Fry and Fieser proved to be insoluble in ether, we turned to the ether-soluble agent developed by Ziegler and coworkers.[16] This agent, prepared from powdered sodium (2 g-atoms), styrene (1 mol), and *N*-methylaniline (2.5 mol) in ether, gave 65% total yields of products resulting from cyclization of **2b**.

We observed that when lactone **3** was exposed to this condensing agent in refluxing ether, it was nearly all recovered after 5 hr but was substantially decomposed to at least three unidentified products after 27 hr. To define further the relationship between yield and reaction time,[17] we reexamined[18] the cyclization of a model compound, hexadecanedinitrile, into 2-amino-1-cyclopentadecene-1-carbonitrile using $NaN(CH_3)$-C_6H_5 in ether solution. For reaction times of 72, 6, and 4 hr, the yields of this cyclic enamino nitrile were 47, 34, and 20%, respectively.

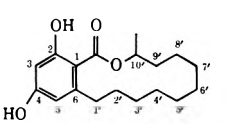
Under conditions of high dilution, an ethereal solution of 1 molar equiv of **2b** was added at a constant rate in 6 hr to a refluxing ethereal solution of 10 molar equiv of sodio-*N*-methylaniline. Two products were obtained: a monomer (mol wt 566) and a dimer (mol wt 1040) in 20 and 45% yields, respectively. It was tempting at first to consider that the monomer was the expected mixture of isomeric enamino nitriles, **9** and **10** (mol wt 524) and that the dimer was a mixture of the macrocyclic products containing two lactone and two enamino nitrile functions (mol wt 1048) resulting from intermolecular condensation of **2b**. Such was not the case, however, and each of these products will be discussed in turn.

Monomer.—Both the molecular weight and combustion analysis of the monomer agree closely with structures **9** and **10**, or any other isomeric structure.

The ir spectrum presents an ambiguous picture. Absorptions at 2180, 3390, and 3310 cm^{-1} conform to a

(9) C. R. Krüger and E. G. Rochow, *J. Organometal. Chem.*, **1**, 476 (1964).

(10) The numbering system used in this paper for the zearalane ring system is as follows.



(11) U. Wannagat and H. Niederprüm, *Chem. Ber.*, **94**, 1540 (1961).

(12) C. Krüger, E. G. Rochow, and U. Wannagat, *ibid.*, **96**, 2139 (1963).

(13) E. M. Fry and L. F. Fieser, *J. Amer. Chem. Soc.*, **62**, 3489 (1940).

(14) *N*-Methylaniline was converted to its sodium derivative with the use of naphthalene as an assistant, and this condensing agent was used in refluxing ether where it is mainly insoluble.

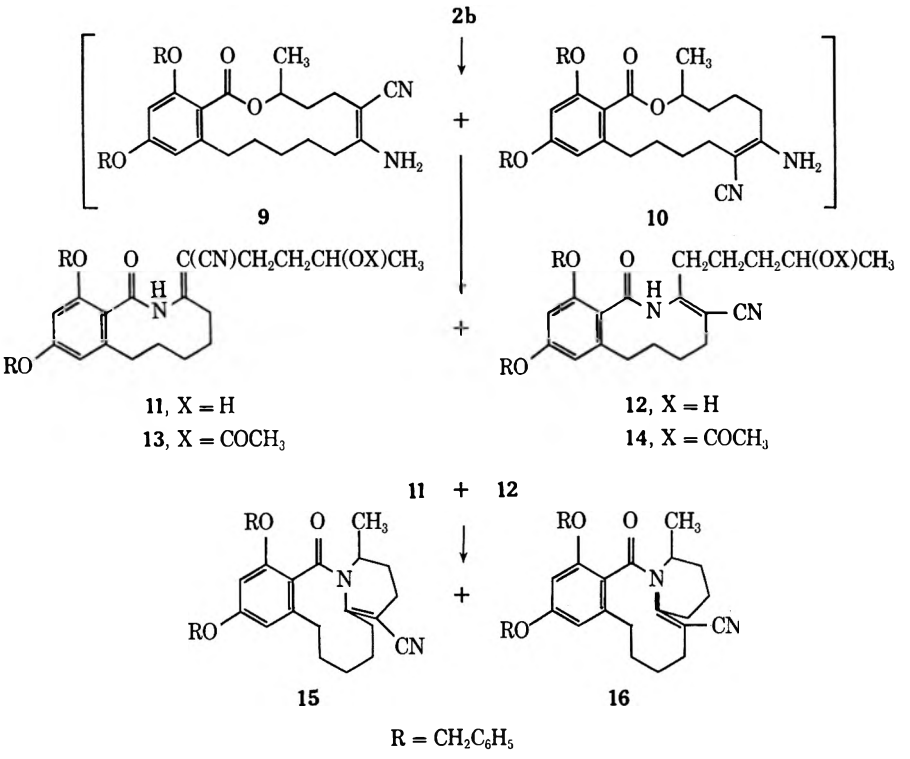
(15) K. Ziegler and H. Hall, *Justus Liebigs Ann. Chem.*, **528**, 151, 153 (1937).

(16) K. Ziegler, L. Jakob, and H. Wollthan, *ibid.*, **511**, 69, 70 (1934).

(17) Reaction time in the Thorpe–Ziegler cyclization is the time of addition, under conditions of high dilution, of a solution of the dinitrile to a refluxing solution of the condensing agent.

(18) The Thorpe–Ziegler cyclization of hexadecanedinitrile was first reported by L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **9**, 260 (1926).

SCHEME II



very characteristic pattern of absorption for enamino nitriles,[19] but that at 3390 cm^{-1} could also represent an H-bonded OH stretching frequency and the absorption at 3310 cm^{-1} might represent a secondary amide NH stretching mode. Absorption at 2220 cm^{-1} is characteristic of an α,β-unsaturated nitrile. Carbonyl absorption at 1685 cm^{-1} is only moderately intense in contrast to the very intense absorption exhibited by the lactone carbonyl functions of **1a**, **1b**, **3**, and other zearalanone derivatives.

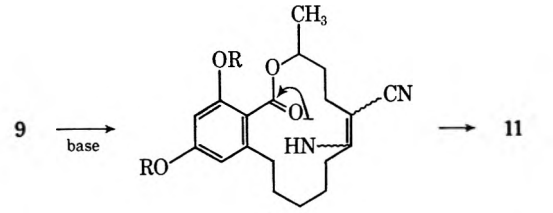
The nmr spectrum fails to support structures **9** and **10**, because there is no signal at δ 5.1, the usual position for a lactone proton, and no indication of $-NH_2$ protons, usually seen at 266 cps in enamino nitriles.[20] Instead, there is a multiplet (1 H) at δ 4.2 which disappears with D_2O, and a multiplet (1 H) at δ 3.3–3.9 which by decoupling was shown to couple with a methyl group.

This evidence suggests that the monomer has either structure **11** or **12**, its isomer (Scheme II). These structures are compatible with the known information on the monomer. In the nmr spectrum, for example, the multiplet at δ 4.2 represents –**OH** and the multiplet at δ 3.3–3.9 represents CH_3C=**H**.

We rationalize that the Thorpe reaction did occur to give the expected mixture of enamino nitriles, **9** and **10**, and that in the presence of base the lactone carbonyl in **9** and **10** each underwent nucleophilic attack by an enamino anion (such as **9a**) to give a mixture of **11** and **12**, respectively.

Structures **11** and **12** are also consistent with the chemical behavior of the monomer.

Enamino nitriles are generally hydrolyzed to the



corresponding keto nitriles or ketones under acidic conditions, although exceptions are known.[21] When the monomer is warmed to 50° for 2 hr in a mixture of acetic acid, water, and phosphoric acid, a considerably less polar product is obtained whose nitrogen content and spectra show that it is not the β-keto nitrile, β-keto amide, or ketone that would be expected from **9** or **10**. Nitrogen analysis, as well as the ir and nmr spectra, agree with acetates **13** and **14** as the products arising from treatment of alcohols **11** and **12**, respectively, with this acidic mixture.

Treatment of the monomeric mixture **11** and **12** with a warm mixture of methanol and concentrated HCl for several hours gave products for which we propose structures **15** and **16**. These fused-ring, N,N-disubstituted amides may be viewed as resulting by loss of water from hydroxy amides **11** and **12**, respectively, probably *via* an oxonium intermediate as shown in Scheme III.

Combustion analyses support these structures. A molecular weight determination (572) agrees with the view that water was lost intramolecularly and not intermolecularly by dimer formation.

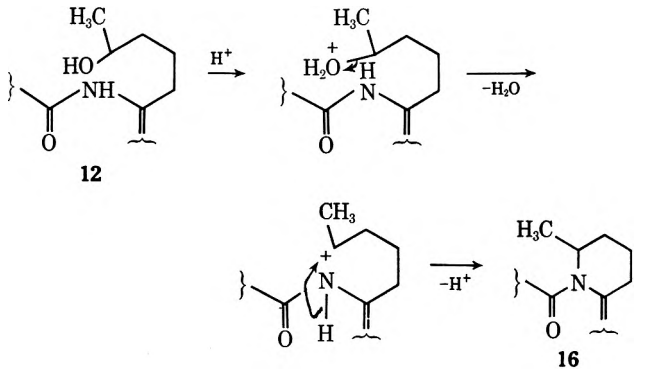
The nmr spectrum of the mixture of **15** and **16** shows that no lactone proton or other hydrogen exchangeable with D_2O is present. The methyl doublet at δ 1.2 in the mixture of **11** and **12** becomes two sets

(19) Enamino nitriles exhibit their nitrile stretching frequency at the unusually low range of 2165–2190 cm^{-1}. They also show two bands in the NH-stretching region. For a review of this topic, see E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Interscience, New York, N. Y., 1970, p 4.

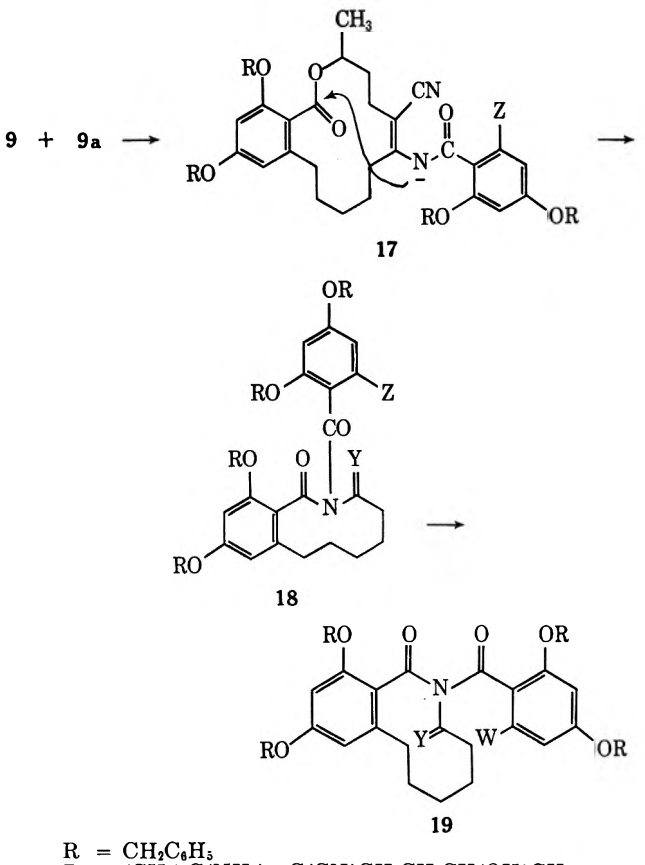
(20) S. Baldwin, *J. Org. Chem.*, **26**, 3288 (1961).

(21) Reference 19, p 60.

SCHEME III



SCHEME IV



R = $CH_2C_6H_5$
Z = $(CH_2)_5C(NH_2)=C(CN)CH_2CH_2CH(OH)CH_3$
W = $(CH_2)_5COCH(CN)CH_2CH_2CH(OH)CH_3$
Y = $C(CN)CH_2CH_2CH(OH)CH_3$

of methyl doublets at δ 1.2–1.4 (J = 6 cps) in the mixture of **15** and **16**. Possibly this change is related to the conformation of the methyl group, where it is axial in one structure and equatorial in the other one. In quite a different family of compounds, derivations of 2-methylcyclohexanone and 4-methylcyclohexanone, it has been shown[22] that axial methyl groups occur at lower field than equatorial methyl groups in nmr spectra, irrespective of their ring position.

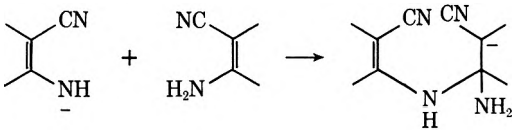
Since structures **15** and **16** contain *N*-acylenamino nitrile groups, it is pertinent to note that the products resulting from the above methanol–HCl treatment exhibit strong absorption at 2180 cm^{-1} in the ir spectrum. N,N-Disubstituted enamino nitriles are known to absorb at this wavenumber.[20]

Dimer.—The major product of the Thorpe–Ziegler cyclization exhibits an nmr spectrum very similar to that of the monomer. This fact rules out for the dimer the type of structure usually seen for this cyclization where each nitrile function of two molecules of dinitrile **2a** condenses intermolecularly to give a 28-membered ring, fused to two aromatic rings, and containing two lactone functions and two enamino nitrile groups.

The ir spectrum of the dimer also closely resembles that of the monomer, except that the carbonyl absorption at 1710 cm^{-1} is of strong rather than weak intensity.

Combustion analysis indicates that in dimerization about one-fourth of the available nitrogen is lost.

These facts also rule out for the dimer the type of structure proposed by Thompson,[23] wherein the enamino anion of one molecule of enamino nitrile nucleophilically attacks a second molecule of enamino nitrile.



A possible course for the present dimerization begins with nucleophilic attack upon the lactone carbonyl of **9** by its anion **9a** to give an intermediate dimer anion **17** (Scheme IV), which, as an *N*-acylenamino nitrile, can undergo intramolecular nucleophilic attack at the remaining lactone carbonyl to give imide **18**. Acidic hydrolysis, an opportunity for which is afforded in the processing conditions of the Thorpe–Ziegler reaction mixture, might result in hydrolysis of the unsubstituted enamino nitrile function to a β-keto nitrile function, as shown in **19**.

Although we regard structure **19** as speculative, it is in agreement with the ir and nmr spectra, the results of combustion analyses, and a determination of molecular weight of the dimer.

(22) F. Johnson, N. A. Starkovsky, and W. D. Guravitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

(23) Q. E. Thompson, *ibid.*, **80**, 5483 (1958).

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Elemental analyses were obtained in our laboratories. Melting points were taken in a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Molecular weights were determined using a Hewlett-Packard vapor pressure osmometer Model 302 calibrated with recrystallized benzil using chloroform as the solvent.

The preparation of compounds **2a** and **2b** is described in ref 8.

Mixture of the 2,4-Dibenzyl Ethers of Racemic 5′- and 7′-Carbomethoxyzearalanone, 4 and 5.—To a refluxing ethereal solution of 3.44 g (0.019 mol) of **6**[9,11] in 175 ml of dry ether, a solution of 1.85 g (0.003 mol) of triester **2a**[8] in 260 ml of dry ether was added continuously and uniformly over a period of 8 hr using the high-dilution technique described below. The reaction mixture was refluxed for an additional 15 min after addition was complete and cooled. Glacial acetic acid (25 ml) was added. The resulting mixture was washed three times with 80-ml portions of water, dried ($MgSO_4$), and stripped of ether to give 1.81 g of paste. This residue was passed through 60 g of a Silicar-CC-7 column with chloroform to obtain 1.33 g (77%) of the mixture of **7** and **8**: ir (film) 1725 (ester C=O), 1700 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 1.01–1.09 (d, 3, $-OCHCH_3$), 1.25–2.01 (m, 10, $-CH_2CH_2CHCOOCH_3$, $-CH_2CH_2CH_2CH_2CH_2C{=}O$), 2.01–3.00 (m, 4, $-CH_2C{=}O$, benzylic CH_2), 3.63 (t, 4, $-CH_2CHCOOCH_3$), 5.00 (d, 4, 2 $OCH_2C_6H_5$), 5.1–5.3 (m, 1, $-OCHCH_3$), 6.45 (s, 2, 2 aromatic H), 7.35 (d, 10, 2 $OCH_2C_6H_5$).

To achieve high dilution, the rate of addition of the ethereal solution of **2a** was controlled by addition of fine droplets of mercury from a leveling bulb through a capillary tube into a reservoir containing the solution of **2a** in essentially the same manner as described by Ziegler and coworkers.[3] The solution of **2a** flowed from this reservoir into the high-dilution mixer described by Allen and VanAllan,[24] where it was first diluted by condensed ether from the refluxing reaction mixture. From this mixer, the diluted solution of **2a** flowed into the reaction flask.

2,4-Dibenzyl Ether of *R,S*-Zearalanone (1b).—A solution of 1.5 g of KOH in 3 ml of water and 27 ml of ethanol was prepared. A 7.5-ml aliquot of this solution (containing 0.375 g of KOH) was added to 200 mg (0.339 mmol) of the mixture of **4** and **5**. The resulting reaction mixture was refluxed for 1 hr, cooled, and acidified with 6 *N* HCl. The acidified mixture was warmed to 50° for 10 min, and then diluted with 75 ml of water. The diluted mixture was thrice extracted with 30-ml portions of ether. The combined ether extracts were washed with 20 ml of 5% $NaHCO_3$, then 20 ml of water, and finally dried ($MgSO_4$). Removal of ether left 130 mg of paste, which was passed through a column of 10 g of Silicar-CC-7 with chloroform to give 100 mg of paste. This paste crystallized slowly from methanol to give 90 mg (53.1%) of white **1b**, mp 104°. No depression in melting point was observed with the natural, authentic 2,4-dibenzyl ether of *S*-zearalanone (mp 104°).[25]

Anal. Calcd for $C_{32}H_{36}O_5$: C, 76.76; H, 7.24. Found: C, 76.93; H, 7.43.

Cyclization of 4-Cyano-1-methylbutyl 2,4-Bis(benzyloxy)-6-(5-cyanopentyl)benzoate (2b).—Dinitrile **2b**[8] (3.00 g, 0.006 mol) in 250 ml of dry ether was added continuously at a uniform rate in 6 hr to a stirred, refluxing 0.67 *M* solution (90 ml) of sodio-*N*-methylaniline[16] in ether using the high-dilution technique described for the preparation of the mixture of **4** and **5**. The mixture was then cooled and 25 ml of water was added to it. Most of the product separated as a thick oil. This oil was taken up in $CHCl_3$, and the $CHCl_3$ solution was washed with 20% phosphoric acid and dried (Na_2SO_4). Removal of $CHCl_3$ left 2.77 g of glassy solid which was put on a column (80 g) of Silicar-CC-7 in $CHCl_3$. Development of the column with $CHCl_3$ resulted in separation of 0.6 g (20%) of a mixture of **11** and **12**. Further development of the column with 2% methanol in chloroform gave 1.35 g of the dimer (**19**).

Mixture of the lactams of 4,6-dibenzyloxy-2-(6-amino-7-cyano-10-hydroxy-6-undecenyl)benzoic acid (11) and 4,6-dibenzyloxy-2-(6-amino-5-cyano-10-hydroxy-5-undecenyl)benzoic acid (12) had ir (film) 1685 (C=O), 2180 (conjugated CN), 2220 (unconjugated CN), 3310 (monosubstituted amide NH), 3390 cm^{-1} (H-bonded OH); nmr ($CDCl_3$) δ 1.2 (d, 3, $-OCHCH_3$), 3.3–3.9 (m, 1, $-OCHCH_3$), 4.2 δ (m, 1, OH). In this nmr spectrum, the multiplet at δ 3.3–3.9 was shown to couple with the methyl group by decoupling, and the multiplet at δ 4.2 disappeared with D_2O.

Anal. Calcd for $C_{33}H_{36}N_2O_4$: C, 75.75; H, 6.87; N, 5.34; mol wt, 524. Found: C, 75.58; H, 7.18; N, 5.24; mol wt, 566.

Dimer 19 had ir (film) 1700 (C=O), 2180 (conjugated CN), 2220 (unconjugated CN), 3365 cm^{-1} (H-bonded OH); nmr ($CDCl_3$) δ 3.5 (m, 1), 4.1 (m, 1).

Anal. Calcd for $C_{66}H_{71}N_3O_9$: C, 75.51; H, 6.76; N, 4.00; mol wt, 1050. Found: C, 75.22; H, 6.96; N, 3.66; mol wt, 1038.

Mixture of Lactams of 4,6-Dibenzyloxy-2-(6-amino-7-cyano-10-acetoxy-6-undecenyl)benzoic Acid (13) and 4,6-Dibenzyloxy-2-(6-amino-5-cyano-10-acetoxy-5-undecenyl)benzoic Acid (14).—The mixture of **11** and **12** (200 mg, 0.003 mol) was dissolved in a solution of 12 ml of glacial acetic acid, 1 ml of water, and 6 ml of 85% phosphoric acid. The reaction mixture was heated to 55° for 2 hr, cooled, and poured over ice. The resulting mixture was extracted with ether, the extract was dried ($MgSO_4$), and ether was removed from the dried extract to leave 180 mg of paste. This residue was taken up in $CHCl_3$, and the solution was passed through a column (10 g) of Silicar-CC-7 to give a mixture of **13** and **14** as a paste. In the ir spectrum, intensity of absorption at 1700 cm^{-1} (C=O) was increased, and intensity of absorption at 2180 cm^{-1} (conjugated CN) was the same in comparison with the ir spectrum of the starting mixture of **11** and **12**; nmr ($CDCl_3$) δ 2.00 (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{35}H_{38}N_2O_5$: N, 4.94. Found: N, 4.67.

Mixture of Lactams of 4,6-Dibenzyloxy-2-[5-(5-cyano-2-methyl-1,2,3,4-tetrahydro-6-pyridyl)pentyl]benzoic Acid (15) and 4,6-Dibenzyloxy-2-[5-cyano-5-(6-methyl-2-piperidylidene)pentyl]-benzoic Acid (16).—The mixture of **11** and **12** (220 mg, 0.004 mol) was dissolved in 10 ml of methanol, concentrated hydrochloric acid (7 mmol) was added, and the resulting reaction mixture was stirred at 55° for 3 hr. Crushed ice was added, and the mixture was extracted with 5% sodium bicarbonate solution and water and then dried ($MgSO_4$). Removal of ether left a yellow, pasty residue (220 mg) which was taken up in $CHCl_3$. The $CHCl_3$ solution was passed through a 20-g column of Silicar-CC-7. Removal of $CHCl_3$ gave 180 mg of the mixture of **15** and **16**: ir (film) 1700 (weak, C=O), 2180 cm^{-1} (strong, conjugated CN); nmr ($CDCl_3$) δ 1.2–1.4 (2 d, 6, axial and equatorial CH_3 groups),[22] 4.0–4.4 (m, 1, $-CHCH_3$). The multiplet at δ 4.0–4.4 was shown to couple with the methyl group by decoupling. This nmr spectrum had no hydrogen exchangeable with D_2O.

Anal. Calcd for $C_{33}H_{34}N_2O_3$: C, 78.25; H, 6.71; N, 5.53. Found: C, 77.84; H, 6.78; N, 5.15.

Registry No.—**1b**, 37103-23-4; **11**, 37103-24-5; **12**, 37103-25-6; **13**, 37157-00-9; **14**, 37103-26-7; **15**, 37103-27-8; **16**, 37102-822; **19**, 37102-833.

Acknowledgment.—The authors wish to thank Mr. Carl Wassink and Dr. Lynn Swanson for analyses and molecular weight determinations, and express appreciation to the Department of Chemistry, Indiana State University, for use of its osmometer.

(24) C. F. H. Allen and J. A. VanAllan, *J. Org. Chem.*, **14**, 754 (1949).

(25) Unpublished data from the research laboratories of the Commercial Solvents Corp. For the preparation and other properties of *S*-zearalanone, see W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, *Tetrahedron Lett.*, 3109 (1966).

Notes

Amide Hydrofluoroborates

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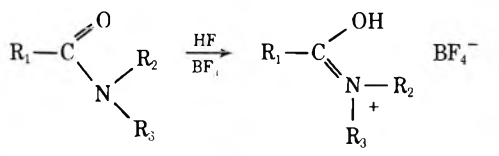
We have found that aliphatic amides (**1a–d**) react with anhydrous HF and BF_3 to give stable, isolable amide hydrofluoroborates (**2a–d**) in 40–60% yield.[2] Compounds **2a–d** were typically prepared by dissolving the amide in liquid HF at 0–15°, bubbling in BF_3, and allowing the mixture to stand for 30 min at 15–20°. They were isolated by removal of excess HF and BF_3 and purified by recrystallization.



1 **2**

a, $R_1 = C_{17}H_{35}$; $R_2 = CH_3$; $R_3 = H$
b, $R_1 = C_{17}H_{35}$; $R_2 = CH_3$; $R_3 = CH_3$
c, $R_1 = C_{15}H_{31}$; $R_2 = n\text{-}C_4H_9$; $R_3 = H$
d, $R_1 = C_7H_{15}$; $R_2 = n\text{-}C_4H_9$; $R_3 = H$

The structures of these compounds have been established by spectral data and by elemental analysis (see Experimental Section). For example, *N*-*n*-butylpalmitamide hydrofluoroborate (**2c**) shows ir bands at 3300 [OH or $(=NHR)^+$] and 1680 cm^{-1} [$(>C=N<)^+$], compared to absorptions of 3455 (–NH) and 1660 cm^{-1} (>C=O) for the starting amide. The nmr spectrum of **2c** shows two downfield singlets at 10.15 (OH) and 9.12 ppm [$(=NHR)^+$]. In addition, a quartet centered at 3.52 [$(>C=NHCH_2CH_2-)^+$] and a triplet at 2.75 ppm [$-CH_2CH_2C(=NHR)^+OH$] are in agreement with the amide hydrofluoroborate structure.[3] These data are indicative of protonation on oxygen, which has been noted in previous studies of amides in strongly acidic media.[4] The stereochemistry at the quaternary nitrogen in **2a**, **c**, and **d** is not known.

Amide hydrofluoroborates are quantitatively reconverted to the corresponding amides by treatment with H_2O and undergo partial decomposition on heating. However, they appear to be indefinitely stable in the absence of H_2O at room temperature.

In contrast to the above results, *N*-methylstearamide (**1a**) does not form stable salts with HF alone or upon treatment with HCl in CH_2Cl_2. Reaction of **1a** with BF_3 alone in CH_2Cl_2 results in the formation of a hygroscopic complex.[5] In the case of stearamide (R_1 = $C_{17}H_{35}$; R_2 = R_3 = H), reaction with HF and BF_3 yields a less stable salt, which could not be successfully separated from the starting amide. Apparently, the unsubstituted amide is less basic than either **1a** or **1b**.

Experimental Section

All reactions were performed in a graduated polyethylene bottle with an inlet tube for attachment to HF and BF_3 cylinders[6] and an exit tube protected by Drierite. The ratio of liquid HF to amide in the preparation of **2a–c** is important, since the use of a larger amount of HF results in a different reaction pathway.[7] Caution: To avoid toxicity and severe burns in the handling of HF, appropriate safety precautions should be taken.

***N*-Methylstearamide Hydrofluoroborate (2a).**—Liquid HF (6 ml) was condensed into the vessel containing *N*-methylstearamide (**1a**) (3.0 g, 0.0101 mol) at 0°. Anhydrous BF_3 was then admitted into the mixture at a moderate bubbling rate for 5 min with occasional warming to maintain solution. The mixture was allowed to stand at 15° for 30 min. Excess HF and BF_3 were removed in a stream of N_2, and the resulting solid residue was recrystallized from CH_2Cl_2 to give **2a**: 1.8 g (48%); mp 66–70° dec; ir ($CHCl_3$) 3300, 2920, 2860, 1685, 1070 cm^{-1}; nmr ($CDCl_3$) 9.45 (1 H, s), 8.75 (1 H, s), 3.10 (3 H, d), 2.72 (2 H, t), 1.4–0.9 ppm (33 H, m).

Anal. Calcd for $C_{19}H_{40}NOBF_4$: C, 59.23; H, 10.47; N, 3.64; F, 19.72. Found: C, 59.32; H, 10.31; N, 3.56; F, 19.54.

***N*,*N*-Dimethylstearamide Hydrofluoroborate (2b).**—*N*,*N*-Dimethylstearamide (2.0 g, 0.0064 mol) was suspended in liquid HF (3 ml) at 10° and anhydrous BF_3 was admitted at a moderate bubbling rate for 10 min at 10°. The mixture was then warmed briefly to achieve complete solution. After the solution had stood at 0° for 30 min, the excess HF and BF_3 were removed and the residue was crystallized from methylene chloride–hexane (1:1) to give **2b**: 1.5 g (59%); mp 61–65° dec; ir ($CHCl_3$) 3480, 2920, 2860, 1670, 1070 cm^{-1}; nmr ($CDCl_3$) 9.38 (1 H, s), 3.40 (3 H, br s), 2.85 (2, H, t), 1.8–0.9 ppm (33 H, m).

Anal. Calcd for $C_{20}H_{42}NOBF_4$: C, 60.15; H, 10.61; N, 3.51. Found: C, 60.35; H, 10.90; N, 3.30.

***N*-*n*-Butylpalmitamide Hydrofluoroborate (2c).**—*N*-*n*-Butylpalmitamide (**1c**) (3.0 g, 0.0096 mol) was dissolved in liquid HF (4 ml) at 0° and BF_3 was bubbled in at a moderate rate for 5 min. The solution was then allowed to stand at 0–15° for 30 min. The excess HF and BF_3 were removed and the crude product was recrystallized from CH_2Cl_2–hexane (3:1) to yield **2c** (hygroscopic): 1.5 g (40%); mp 55–59° dec; ir ($CHCl_3$) 3300, 2930, 2860, 1680, 1070 cm^{-1}; nmr ($CDCl_3$) 10.15 (1 H, s), 9.12 (1 H, s), 3.52 (2, H, q), 2.75 (2 H, t), 1.9–0.7 ppm (36 H, m).

Anal. Calcd for $C_{20}H_{42}NOBF_4$: C, 60.15; H, 10.60; N, 3.51. Found: C, 59.96; H, 10.42; N, 3.33.

***N*-*n*-Butyloctanamide Hydrofluoroborate (2d).**—*N*-*n*-Butyloctanamide (**1d**) (2.0 g, 0.01 mol) was dissolved in liquid HF (2 ml) at 0°. The usual procedure was then followed leaving an oily residue, which was dissolved in boiling CH_2Cl_2/hexane (1:1). On cooling, **2d** separated as an oil which was isolated, filtered to remove a very small amount of inorganic solid, and freed from residual solvent *in vacuo* at 20°. This treatment yielded 1.7 g of **2d** (58%): ir ($CHCl_3$) 3300, 2930, 2860, 1680, 1070 cm^{-1};

(1) Agricultural Research Service, U. S. Department of Agriculture.

(2) Certain other examples of isolation of amide salts have been reported. For example, see (a) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6215 (1955); (b) R. Gompper and P. Altreuther, *Z. Anal. Chem.*, **170**, 205 (1959).

(3) The corresponding quartet and triplet in *N*-*n*-butylpalmitamide occur at 3.30 and 2.25 ppm, respectively.

(4) (a) D. M. Brouwer and J. A. van Doorn, *Tetrahedron Lett.*, 3339 (1971); (b) G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, **70**, 580 (1970), and references cited therein.

(5) See E. L. Muetterties and E. G. Rochow, *J. Amer. Chem. Soc.*, **75**, 490 (1953), for previous examples.

(6) Commercial research grade BF_3 and HF were used directly.

(7) Long-chain aliphatic amides undergo chain-cleavage reactions under these conditions. We will report this in detail separately.

nmr ($CDCl_3$) 11.15 (1 H, s), 9.12 (1 H, s), 3.52 (2 H, q), 2.74 (2 H, t), 2.0–0.6 ppm (20 H, m).

Anal. Calcd for $C_{12}H_{20}NOBF_4$: C, 50.20; H, 9.13; N, 4.88. Found: C, 50.47; H, 9.33; N, 5.01.

Registry No.—2a, 36955-98-3; 2b, 36994-06-6; 2c, 36989-94-3; 2d, 36989-95-4.

Reactivity of Hydroxamic Acids. Correlation with the Two-Parameter Taft Equation

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The problem of the separation of polar, steric, and resonance effects has recently been reviewed,[1] and further testing of the range of applicability of the empirical equations as well as the assumptions underlying them deserve further testing. The two-parameter eq 1 suggested by Taft[1,2] for use with aliphatic compounds correlates the data reported below for the acidic hydrolysis of a series of aliphatic hydroxamic acids. ρ^* and δ are constants to be determined for each reaction and set of reaction conditions and represent the susceptibility of the reaction system to polar and steric effects, respectively. σ^* and E_s are polar and steric substituent constants, respectively, characteristic of each substituent and are tabulated in the literature.[1,2]

$$\log k = \rho^*\sigma^* + \delta E_s + \log k_0 \quad (1)$$

The kinetics of amide hydrolysis have been studied extensively; nevertheless, uncertainties remain, especially for the acid-catalyzed reactions.[3] Three reports, to our knowledge, of kinetic studies of hydrolysis of the related hydroxamic acids exist; two report results for benzohydroxamic acid and a few of its derivatives at moderate[4] to very high acidities[5] and the third,[6] results for acetohydroxamic acid at very low acidity (pH >0.7). Table I reports results for the acidic dependence of the hydrolysis rate of propionohydroxamic acid at moderate acidities.

Table I
Rate Constants for Propionohydroxamic Acid Hydrolysis in Aqueous *p*-Toluenesulfonic Acid at 50.2° and Ionic Strength at 0.494 *M*

$[H^+]$,[a] *M*	$10^5 k_{obsd}$[b]	$10^4 k_{obsd}/[H^+]$
0.494	22.0	4.45
0.247	9.88	4.00
0.124	5.27	4.25
		Av 4.23

[a] *p*-Toluenesulfonic acid. [b] Average pseudo-first-order rate constant, sec^{-1}.

The results of Table I are represented by eq 2, *i.e.*,

$$k_{obsd} = k_2[H^+] \quad (2)$$

the reaction is first order in catalytic acid and also in the hydroxamic acid. Equation 2 is consistent with the accepted bimolecular mechanism (eq 3 and 4) for acidic hydrolysis of benzohydroxamic acid[4,5] and amides[3] at moderate acidity. This mechanism requires k_2 to be a product of an equilibrium constant and a second-order rate constant.[4]

$$RCONHOH + H^+ \rightleftharpoons RC^+(OH)NHOH \quad (3)$$

$$RC^+(OH)NHOH + H_2O \longrightarrow \text{products} \quad (4)$$

Equation 1 should be applicable to the hydrolysis of acyl compounds following the bimolecular mechanism.[1,2] Table II lists the experimental results and log k calculated from eq 5 with the parameters determined by the method of least squares.[7] The reference substituent is methyl.

Table II
Hydrolysis Rates of Hydroxamic Acids in 0.249 *N* Aqueous *p*-Toluenesulfonic Acid at 50.5°

Hydroxamic acid	Registry no.	$10^5 k_1$[a]	$10^5 k_2$[b]	$-\log k_2$	$-\log k_2$ (calcd)[c]
Aceto-	1113-25-3	11.0	44.2	3.355	3.438
Propiono-	2580-63-4	11.2	45.0	3.347	3.434
Isobutyro-	22779-89-1	3.92	15.7	3.804	3.608
Pivalo-	29740-67-8	2.17	8.71	4.060	4.126
Phenylaceto-	5330-97-2	4.27	17.1	3.767	3.726

[a] Pseudo-first-order rate constant, sec^{-1}. [b] Second-order rate constant, l. mol^{-1} sec^{-1}, $k_1/0.249$. [c] Calculated from eq 5.

$$\log k = -0.409\sigma^* + 0.526E_s - 3.438 \quad (5)$$

Equation 5 reproduces the log k values within 1 to 5% over a σ^* range of 0.515 (from phenylaceto, 0.215, to *tert*-butyl, −0.30) and an E_s range of 1.54 (from methyl, 0.00, to *tert*-butyl, −1.54). The coefficient of multiple regression[7] is 0.920. Neither σ^* nor E_s individually provide satisfactory correlation of the log k values. A log k *vs.* σ^* plot is quite scattered while a log k *vs.* E_s plot is a curve.

These results show that polar and steric effects are of comparable magnitude in the acid-catalyzed hydrolysis of hydroxamic acids. This result is in contrast to the acidic hydrolysis of amides and esters which shows very little or no dependence on polar effects.[1,2,8] The Taft steric substituent constants, E_s, implicitly allow for hyperconjugative effects.[9] A somewhat improved correlation for acidic hydrolysis

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(2) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.
(3) C. O'Connor, *Quart. Rev., Chem. Soc.*, **24**, 553 (1970).
(4) D. C. Berndt and R. L. Fuller, *J. Org. Chem.*, **31**, 3312 (1966).
(5) A. J. Buglass, K. Hudson, and J. G. Tillett, *J. Chem. Soc. B*, 123 (1971).
(6) J. W. Munson and K. A. Connors, *J. Amer. Chem. Soc.*, **94**, 1979 (1972).
(7) D. A. Leabo, "Basic Statistics," 3rd ed, Richard D. Irvin, Inc., Homewood, Ill., 1968, Chapter 14.
(8) P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 471 (1971).
(9) C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Amer. Chem. Soc.*, **83**, 4211 (1961).

of the aliphatic amides noted above was obtained when modified E_s values were used along with a parameter explicity allowing for hyperconjugative effects[8] rather than using the single parameter, E_s.

The rate constants in Table II are overall rate constants, *i.e.*, a composite for steps 3 and 4. Buglass, *et al.*,[5] have calculated rate constants for step 4 for the acidic hydrolysis of a series of para-substituted benzohydroxamic acids and report a positive Hammett ρ value for correlation of those rate constants, a result consistent with the bimolecular mechanism. An examination of the data in their[5] Table 6 indicates at best (with the *p*-hydroxy compound excluded) only a fair correlation between the observed overall rate constants and Hammett σ constants with a negative value for ρ. This result is consistent with our negative value for ρ^* for the overall rate constants for the aliphatic compounds.

Since $\rho^* < 0$ in eq 5, electron-donating groups accelerate the rate compared to that of the reference compound, acetohydroxamic acid. This is consistent with the greater electronegativity of hydroxyl compared to hydrogen in changing from amides to hydroxamic acids, provided that the polar effect on the protonation of hydroxamic acids is greater than the polar effect for the nucleophilic attack by water on the protonated intermediate in the bimolecular mechanism. The positive value for δ means that steric effects are rate decelerating compared to acetohydroxamic acid as would be anticipated.

Experimental Section

Aceto-, isobutyro-, and pivalohydroxamic acids have been described previously.[10] Propionohydroxamic acid was prepared by adaptation of the method used for preparation of isobutyrohydroxamic acid, purified by means of the copper salt, and crystallized from ethyl acetate, mp 93.2–95.0° (lit.[11] mp 92.5–93°). Phenylacetohydroxamic acid, mp 142.7–144.0° dec (lit.[12] mp 143–144° dec), was prepared by adaptation of the method used for benzohydroxamic acid.[4]

The 0.494 *M* *p*-toluenesulfonic acid solution (Table I) was prepared by addition of the acid to distilled water and titrated with standardized base. The 0.247 and 0.124 *M* solutions were prepared from the above solution by appropriate dilutions and with potassium chloride added to maintain the ionic strength at 0.494 *M*. The 0.249 *M* *p*-toluenesulfonic acid (Table II) was prepared by addition of the acid to double distilled water and titrated as above.

Kinetic measurements were made by use of the spectrophotometric method reported previously[4] using either a photoelectric colorimeter[4] (Table I) or a Beckman DU spectrophotometer (Table II) set at 520 nm. Pseudo-first-order rate constants were obtained from the slope of the appropriate graph.[4] The rate constants reported in column two in Table I are the average of five, two, and six runs, respectively, from highest to lowest catalytic acid concentration. The rate constants in Table II are averages of duplicate or triplicate measurements. Average deviation from the mean is less than 1.7%. Temperature control was ±0.05°. Initial concentration of hydroxamic acids in the kinetic runs was 0.012 *M*.

Acknowledgment.—D. C. B. gratefully acknowledges the support of a Western Michigan University Faculty Research Fellowship as partial support of this work.

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Microbiological Reduction and Resolution of Prostaglandins. Synthesis of Natural $PGF_{2\alpha}$ and *ent*-$PGF_{2\beta}$ Methyl Esters

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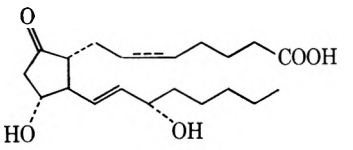
The total synthesis of racemic prostaglandins E_1 (**1**, 5,6-saturated) and E_2 (**1**, 5,6-cis double bond) and their



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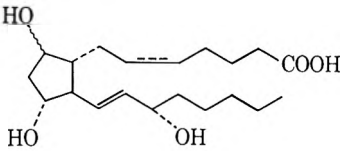

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methyl esters *via* bicyclo[3.1.0]hexane intermediates has previously been reported from these laboratories.[1] Chemical reduction of the 9-keto group of these compounds using sodium borohydride led to racemic $PGF_{1\alpha}$ (**2**, 9α,5,6-saturated), $PGF_{1\beta}$ (**2**, 9β,5,6-saturated), and $PGF_{2\alpha}$ (**2**, 9α,5,6-cis double bond), $PGF_{2\beta}$ (**2**, 9β,-5,6-cis double bond), respectively. Natural $PGF_{1\alpha}$ and $PGF_{2\alpha}$ have the 9*S* configuration while nat-$PGF_{1\beta}$ and $PGF_{2\beta}$ are 9*R*. Fermenting yeasts are known to reduce ketones to optically active secondary alcohols of the *S* configuration, the extent of stereoselectivity varying somewhat with the steric environment of the keto group.[2] Enzymatic reductions of some steroid ketones show high stereoselectivity.[3] It was thus of interest to us to determine the effect of enzymes of fermenting yeasts and other microorganisms on prostaglandins E_1 and E_2. Stereoselective microbiological reduction of a racemic prostaglandin 15-ketone **3** to **4** has recently been reported.[4]

Actively fermenting baker's yeast was found to reduce *nat*-PGE_1 and *nat*-PGE_2 slowly to $PGF_{1\alpha}$ and $PGF_{2\alpha}$, respectively. No appreciable amounts of the 9β epimers could be seen by thin layer chromatography of extracts, thus demonstrating the stereoselective

(1) (a) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Amer. Chem. Soc.*, **91**, 5372 (1969); (b) U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Commun.*, 303 (1969); (c) W. P. Schneider, *ibid.*, 304 (1969).

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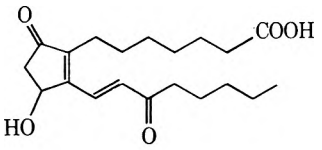

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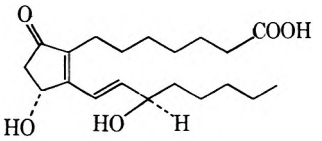

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nature of the reduction to 9-alcohols of the *S* configuration. The methyl esters of *nat*-PGE_1 and PGE_2 were slowly hydrolyzed by the same fermentation mixture prior to reduction of the 9-ketone, also producing $PGF_{1\alpha}$ and $PGF_{2\alpha}$.

When *rac*-PGE_1 methyl ester and *rac*-PGE_2 methyl esters were subjected to the same conditions, tlc spots corresponding in mobility and color reactions to both isomeric 9-alcohols (*i.e.*, $PGF_{1\alpha}$ and $PGF_1\beta$ from PGE_1 methyl ester and $PGF_{2\alpha}$, $PGF_2\beta$ from PGE_2 methyl ester) were observed. These pairs of products were produced in about equal amounts, suggesting that yeast reduced both enantiomers of the racemates, producing *nat*-$PGF_{1\alpha}$, *ent*-$PGF_1\beta$, and *nat*-$PGF_{2\alpha}$, *ent*-$PGF_2\beta$, respectively. This was confirmed by the isolation of the products from the reduction of *rac*-PGE_2 methyl ester by silica gel chromatography of their methyl esters. The $PGF_{2\alpha}$ methyl ester obtained gave a positive plain ORD curve of the same shape as that of *nat*-$PGF_{2\alpha}$ methyl ester and of nearly the same amplitude. The $PGF_2\beta$ methyl ester was crystalline, mp 85–87° (*vs.* 90–91° for *nat*-$PGF_2\beta$ methyl ester), but had an ORD curve which was the mirror image of that exhibited by *nat*-$PGF_2\beta$ methyl ester. The amplitudes of the ORD curves indicated about 85% optical purity, assuming that the only impurity is the optical antipode.

Thus, the stereoselective microbiological reduction, hydrolysis, and resolution of racemic PGE_1 and PGE_2 methyl esters has been demonstrated. The isolated yield of *nat*-$PGF_{2\alpha}$ was only about 10%, however, and the yield was not improved by the use of a special enriched growth medium.[2b] Screening of other microorganisms and conditions also failed to improve the yield, although Torulopsis yeast also reduced and hydrolyzed *rac*-PGE_2 methyl ester. These yeast reductions were quite slow, with starting PGE_2 still present after 46 hr at 25°, and undesired side reactions were evident, such as dehydration to PGA_2 and reduction of the terminal carboxyl group.

Experimental Section

Yeast Reduction of *rac*-PGE_2 Methyl Ester.—A total of 500 mg of *rac*-PGE_2 methyl ester was reduced by yeast in four identical batches, each one as follows. A mixture of 200 ml of boiled water, 25 g of sugar, and 1 cake (17.5 g) of baker's yeast was allowed to incubate at 25° for 0.75 hr, when CO_2 evolution through a water bubbler was rapid. Then a solution of 125 mg of the substrate in 5 ml of ethanol was added. The mixture was stirred and samples (10 ml) were withdrawn at intervals. These were acidified with 1 ml of 3 *N* HCl, shaken with ethyl acetate, and filtered, and the ethyl acetate layer was evaporated to leave a residue which was assayed by thin layer chromatography (silica gel plates, developed by AIX system[5] and visualized by spraying and heating with a vanillin–phosphoric acid spray[6]). After 20 hr, most of the starting PGE_2 methyl ester had been hydrolyzed to PGE_2 and minor spots corresponding in tlc mobility and color reactions to PGA_2, $PGF_{2\alpha}$, and $PGF_2\beta$ were seen, the latter two of about equal intensity. After 29 hr, 25 g more sugar was added and at 46 hr, while the $PGF_{2\alpha}$ and $PGF_2\beta$ spots had increased in intensity, there was still much PGE_2 left as judged by tlc. The mixture was worked up in the same way as for the aliquots above and the crude products were chromatographed on 50 g of acid-washed silica gel. Elution with 40–100% ethyl acetate in Skellysolve B gave 304 mg of *rac*-PGE_2 and 106 mg of material consisting of a mixture of $PGF_{2\alpha}$ and $PGF_2\beta$. This latter mixture was treated with excess ethereal diazomethane and rechromatographed on 10 g of silica gel. The column was eluted with ethyl acetate and 1 and 2% methanol in ethyl acetate. There was obtained 25 mg of noncrystalline material, homogeneous by tlc, spectrally identical with $PGF_{2\alpha}$ methyl ester (ir and nmr) and showing a plain positive ORD curve in EtOH, $[\alpha]_{589}$ +18.3°, $[\alpha]_{220}$ +440° (for *nat*-$PGF_{2\alpha}$, $[\alpha]_{589}$ +25°, $[\alpha]_{220}$ +534°, EtOH).

The more polar material (28 mg) was crystalline, and melted at 85–87° after two recrystallizations from ethyl acetate–Skellysolve B. This was spectrally (ir, nmr) identical with $PGF_2\beta$ methyl ester but had an ORD curve which is positive at long wavelengths, becoming negative below 320 nm, $[\alpha]_{589}$ +5.6°, $[\alpha]_{220}$ −995°, and is the mirror image of that of *nat*-$PGF_2\beta$ methyl ester, $[\alpha]_{589}$ −5.2°, $[\alpha]_{220}$ +1400°.

Yeast Reduction of *rac*-PGE_1 Methyl Ester.—In the same manner as the preceding experiment, 120 mg of *rac*-PGE_1 methyl ester was reduced. After 3 hr, partial hydrolysis to *rac*-PGE_1 was seen by tlc of an aliquot, and at 22 hr, additional spots corresponding in mobility and color reactions to PGA_1, $PGF_{1\alpha}$, and $PGF_1\beta$ were seen. At 29 hr, 25 g more sugar was added and the mixture was worked up as before at 50 hr. The crude residue after evaporation of extracts was chromatographed on 50 g of Silicar CC_4 (Mallinckrodt) silica gel, eluting with solvent mixtures ranging from 50% ethyl acetate–Skellysolve B to 5% methanol–ethyl acetate. Fractions 13–18 contained 10 mg of material which was partially crystalline, resembled $PGF_{1\alpha}$ on thin layer plates, and showed a positive rotation as does $PGF_{1\alpha}$, but was not further purified. Fractions 20–23 contained an equal quantity of material with thin layer behavior like that of $PGF_1\beta$, also showing a small positive rotation (*nat*-$PGF_1\beta$ has $[\alpha]^{25}D$ −20°, EtOH).[7]

Yeast Reductions of *nat*-PGE_1 and *nat*-PGE_2.[8]—In the same manner as the preceding experiment, 250 mg of *nat*-PGE_1 was incubated with fermenting yeast. After 30 hr, tlc spots corresponding in mobility and color reactions to PGA_1, PGE_1, and $PGF_{1\alpha}$ were seen, but no $PGF_1\beta$ was evident. Work-up as above, treatment with diazomethane, and chromatography on 25 g of silica gel gave 183 mg of *nat*-PGE_1 methyl ester followed by 10 mg of *nat*-$PGF_{1\alpha}$ methyl ester, identical in tlc color and mobility and ir spectra with authentic materials. Further elution of the column failed to elute any material resembling $PGF_1\beta$ methyl ester on tlc plates.

On a smaller scale, reduction of 10 mg of *nat*-PGE_2 gave material showing tlc spots corresponding in mobility and color with starting PGE_2 and $PGF_{2\alpha}$. An identical reduction of 10 mg of *rac*-PGE_2 methyl ester showed, in addition, a spot on tlc like $PGF_2\beta$ of approximately the same intensity as the $PGF_{2\alpha}$ spot. Treatment of the extract with ethereal diazomethane converted these to materials having the same mobility as that of $PGF_{2\alpha}$ and $PGF_2\beta$ methyl esters.

Registry No.—(±)-PGE_2 (Me ester), 31660-08-9; *nat*-$PGF_{2\alpha}$, 551-11-1; mirror image of *nat*-$PGF_2\beta$ (Me ester), 37107-45-2; (±)-PGE_1 (Me ester), 20993-69-5; *nat*-$PGF_{1\alpha}$, 745-62-0; *nat*-$PGF_1\beta$, 10164-73-5; *nat*-PGE_1, 745-65-3; *nat*-PGE_2, 363-24-6.

(5) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).

(6) W. J. McAleer and M. A. Kozlowski, *Arch. Biochem. Biophys.*, **66**, 120 (1957).

(7) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(8) Separation of the reduction products from PGE_1 ($PGF_{1\alpha}$ and *ent*-$PGF_1\beta$) was less readily accomplished as the free acids on this scale than was that of the methyl esters described in the preceding example.

Pyrolytic Aromatization of Dimethyl 3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate

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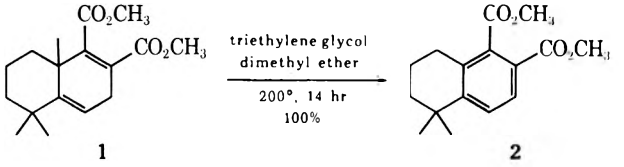
Pyrolytic aromatization reactions involving the elimination of a bridgehead methyl group are seldom of synthetic utility. Thus, the pyrolysis of steroidal 10-methyl ring A dienones to 19-norphenolic steroids are characterized by reaction temperatures between 300 and 700° and yields of less than 30%.[2] Similarly, pyrolytic aromatizations of bis-$\Delta^{5,8(9)}$-steroidal dienes to the corresponding ring B aromatic steroids are usually effected in low yields.[3-10]

We wish to report a high-yield pyrolytic aromatization involving the elimination of a bridgehead methyl group under exceptionally mild conditions. Previously unreported dimethyl 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (1), prepared in 69% yield by the Diels–Alder reaction of 1-vinyl-2,6,6-trimethylcyclohexene with dimethyl acetylenedicarboxylate, is quantitatively aromatized to dimethyl 5,6,7,8-tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate (2) by heating in triethylene glycol dimethyl ether at 200° for 14 hr. At *m/e* greater than 178 (M^+ of solvent) the mass spectra of the reaction mixture and an analytical sample of 2 were identical. The nmr spectrum of the isolated product exhibited peaks due to a trace of residual solvent but was otherwise identical with the spectrum of the analytical sample. To the extent that the results of pyrolytic aromatization studies of various methyl-substituted 1,4-cyclohexadienes[11-14] apply to the aromatization of 1, the reaction probably goes through a nonchain radical process.



1 2

Whereas 1 is a useful intermediate for the synthesis of many sesquiterpenes, 2 should prove to be useful for the synthesis of compounds such as the tanshinones[15] or 4,4-dimethyl ring B aromatic steroids.

(1) P. O. Box 33221, Central Research Laboratories, 3M Company, St. Paul, Minn. 55133.
(2) C. Djerassi, "Steroid Reactions—An Outline for Organic Chemists," Holden-Day, San Francisco, Calif., 1963, pp 382–383.
(3) A. Windaus and P. Borgeaud, *Justus Liebigs Ann. Chem.*, **460**, 235 (1928).
(4) A. Windaus and O. Linsert, *ibid.*, **465**, 148 (1928).
(5) A. Windaus and R. Langer, *ibid.*, **508**, 105 (1933).
(6) F. Schenck, K. Buchholz, and O. Wiese, *Chem. Ber.*, **69**, 2696 (1926).
(7) A. Windaus and C. Roosen-Runge, *ibid.*, **73**, 321 (1940).
(8) R. P. Jacobsen and C. Z. Nawrocki, *J. Amer. Chem. Soc.*, **62**, 2612 (1940).
(9) R. P. Jacobsen, *ibid.*, **65**, 1789 (1943).
(10) E. Mosettig and I. Scheer, *J. Org. Chem.*, **17**, 764 (1952).
(11) R. J. Ellis and H. M. Frey, *J. Chem. Soc. A*, 553 (1966).
(12) H. M. Frey and D. H. Lister, *ibid.*, 509 (1967).
(13) H. M. Frey and D. H. Lister, *ibid.*, 1800 (1967).
(14) H. M. Frey, A. Krantz, and I. D. R. Stevens, *ibid.*, 1734 (1969).
(15) A. C. Baillie and R. H. Thomson, *J. Chem. Soc. C*, 48 (1968).

Experimental Section

Dimethyl 3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-1,2-naphthalenedicarboxylate (1).—A mixture of 12.92 g (0.086 mol) of 1-vinyl-2,6,6-trimethylcyclohexene and 25 ml of dimethyl acetylenedicarboxylate was mechanically stirred and heated on a steam bath under nitrogen for 71 hr. Prolonged heating at higher temperatures causes the dimethyl acetylenedicarboxylate to tetramerize.[16] Vacuum distillation gave 17.35 g (69%) of 1 contaminated with a small amount of 2: bp 135° (0.13 mm); uv max (MeOH) end absorption; ir (neat) 1725 (C=O), 1670, 1630 (C=C), 1250 cm^{-1} (CO); nmr (CCl_4) δ 5.92–5.49 (dd, 1, J = 3.0, 2.6, 3.0 Hz, =CH), 3.70 (s, 6, OCH_3), 3.00 (d, 1, J = 5.6 Hz, =$CHCH_2$), 2.8 (d, 1, J = 3.0 Hz, =$CHCH_2$), 1.70–1.27 [m, 6, $(CH_2)_3$], 1.37 (s, 3, bridgehead CH_3), 1.17 (s, 3, geminal CH_3), 1.13 (s, 3, geminal CH_3); mass spectrum (70 eV) *m/e* (rel intensity), 292 (2), 277 (13), 260 (26), 245 (100), 233 (37), 213 (98), 163 (37).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.03; H, 8.51.

Dimethyl 5,6,7,8-Tetrahydro-5,5-dimethyl-1,2-naphthalenedicarboxylate (2).—A solution of 1 (0.5 g) in 5 ml of triethylene glycol dimethyl ether was heated at 200° for 14 hr. The reaction mixture was diluted with chloroform and extracted with water. Concentration of the dried (sodium sulfate) chloroform solution gave a quantitative yield of 2, as a pale yellow oil: uv max (pentane) 241 nm (ϵ 9400), 281 (1500), 289 (1450); ir (neat) 1725, 1735 (C=O), 1590 (aromatic CH), 1275, 1290 cm^{-1} (CO); nmr (CCl_4) δ 7.38 and 7.75 (ABq, 2, J = 9 Hz, aromatic H), 3.85 (s, 6, OCH_3), 2.86–2.54 (m, 2, benzyl CH_2), 2.13–1.50 [m, 4, $(CH_2)_2$], 1.33 [s, 6, $(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 276 (4), 261 (9), 245 (37), 244 (100), 229 (49), 213 (4), 201 (8), 186 (21), 142 (8).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 70.00; H, 7.47.

Registry No.—1, 36963-51-6; 2, 36963-52-7.

Acknowledgment.—The author acknowledges financial support from NSF Grant GP-10810 and fruitful discussions with Dr. William Reusch.

(16) E. LeGoff and R. B. LaCount, *Tetrahedron Lett.* 2333 (1967).

The Enamine as a Cyclohexylidene Source

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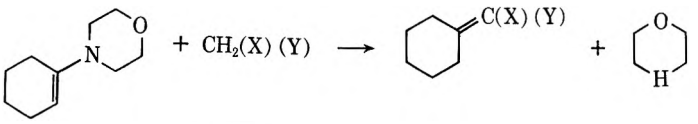
The recent observation of Alt and Gallegos[1] that enamines react with cyanoacetic acid to produce alkylidenecyanoacetic acids has led us to examine the limitations of 1-morpholino-1-cyclohexene as an intermediate for the preparation of cyclohexylidene derivatives (Knoevenagel products).

Malonic acid derivatives which contain at least one cyano group (cyanoacetic acid derivatives) react with the enamine in an exothermic reaction within 30 min, producing the expected product in at least 59% yield. On the other hand, several other compounds having active methylene groups (phenylacetonitrile, ethyl malonate, acetylacetone, chloroacetic acid, and chloroacetonitrile) failed to give a condensation product even with extensive boiling. The limitation is essentially the same as documented so carefully by Hein, Astle, and

(1) G. H. Alt and G. A. Gallegos, *J. Org. Chem.*, **36**, 1003 (1971).

TABLE I

REACTION OF 1-MORPHOLINO-1-CYCLOHEXENE WITH ACTIVE METHYLENE COMPOUNDS



Registry no.	No.	Methylene X	Methylene Y	Solvent	Reacting conditions: Temp, °C	Time	Mp or bp, °C (mm)	Yield, %	Registry no.	Ir,[a] cm⁻¹: CN	C=O	C=C	Nmr,[b] δ, CH_2 (cis)
372-09-8	1	CN	COOH	DMF	25–30	30 min	110–112[c]	81.4	37107-50-9	2230	1705	1590	2.72 (CN) 3.01 (COOH)
105-56-6	2	CN	$COOC_2H_5$	None	25–30	20 hr	152–157 (10)[d]	59.1	6802-76-2	2225	1725	1595	2.63 (CN) 2.93 ($COOC_2H_5$)
109-77-3	3	CN	CN	DMF[e]	25–30	30 min	138–146 (10–8)[f]	58.7	4354-73-8	2245		1595	2.55 (CN)
107-91-5	4	CN	$CONH_2$	Abs EtOH[g]	Reflux	10 min	105–110[g]	76.1	704-16-5	2215	1670	1585	2.62 (CN) 2.92 ($CONH_2$)
141-82-2	5	COOH	COOH	DMF	25–30	7 days	135–140	19.6[h]	4354-70-5		1690	1620	2.80 (COOH)
	6	COOH	COOH	DMF	58–65	15 hr	70–83[i]	60.0	1552-91-6		1695	1645	2.23 (H) 2.82 (COOH)
1071-46-1	7	COOH	$COOC_2H_5$	DMF	55–70	8 hr	99–103 (8)	28.7[j]	1552-92-7		1715	1650	2.17 (H) 2.84 ($COOC_2H_5$)

[a] Infrared spectra were determined in chloroform (1, 4), neat (2, 3, 7), in carbon tetrachloride (6), and as a Nujol mull (5). [b] Nmr response of methylenes cis to the substituent in chloroform (1, 4), neat (3, 7), carbon tetrachloride (2, 6), and pyridine (5). [c] Reported mp 110–110.5°: A. C. Cope, *et al.*, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 234. [d] Reported bp 98–99° (0.1 mm), ref 2. Nmr taken by T. Izewski. [e] An equivalent of acetic acid was required to buffer the mixture. Omission of the acetic acid resulted in an 83% yield of dimer, mp 107–140°. After recrystallization the melting point was 171–175°, as reported by M. R. S. Weir and J. B. Hyne, *Can. J. Chem.*, 42, 1440 (1964). [f] Reported bp 98–101° (0.08 mm), ref 2. [g] An equivalent of acetic acid was required to buffer the mixture, avoiding complex products formed in base [*cf.* F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, 99, 422 (1911)]. Product crystallized directly from reaction mixture. The reported melting point is 110.5–111.5°, ref 2. [h] A 25% excess of malonic acid was used and the dibasic acid was accompanied by an 18.9% yield of monobasic acid. Crystallization from ethyl acetate–hexane furnished purified product, mp 146–147.5°, reported mp 150° [G. A. R. Kon and E. A. Speight, *J. Chem. Soc.*, 2727 (1926)]. [i] The monbasic acid, cyclohexylideneacetic acid, was the product when the malonic acid to enamine ratio was 2:1. Crystallization from alcohol–water results in mp 90–92°, as reported by Papa and Schwenck (ref 4). [j] Ethyl hydrogen malonate was generated *in situ* by action of the potassium salt and chloroacetic acid. Ethyl cyclohexylideneacetate was the product. The reported boiling point is 88–90° (10 mm) [W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 83, 1733 (1961)].

Shelton[2] in their ion-exchange resin catalysis study of the Knoevenagel condensation.

We have, however, observed a reaction with malonic acid. If 1-morpholino-1-cyclohexene was allowed to stand with malonic acid for 7 days at room temperature a mixture of cyclohexylidenemalonic acid (20% yield) and cyclohexylideneacetic acid (19%) was obtained. By heating a 2:1 ratio of malonic acid and the enamine at 60–65° for 15 hr a good yield (60%) of cyclohexylideneacetic acid was produced. This procedure is much more effective than the direct Knoevenagel procedure said to give less than 5% yield.[3] Furthermore, the procedure is much more convenient than the Reformatsky reaction usually used.[4]

Ethyl hydrogen malonate[5] has also proved to be effective in producing ethyl cyclohexylideneacetate (29%). Here the potassium salt was more convenient and the product was apparently free of the endo isomer, ethyl 1-cyclohexenylacetate, based on nmr.

Experimental Section

All melting points and boiling points were uncorrected. A Varian A-60 nmr spectrophotometer was used for recording nmr spectra in parts per million (δ) with respect to tetramethylsilane. A Beckman IR-8 or Perkin-Elmer 337 was used to record infrared spectra.

Reaction of 1-Morpholino-1-cyclohexene with Active Methylene Compounds.—The enamine was added to an equimolar amount of active methylene compound ($CH_2(X)(Y)$) in dimethylformamide (250 ml/mol). After the exothermic reaction was over (or heating concluded), the product was treated with dilute hydrochloric acid and the reaction was worked up by extraction with ether. Acidic products were washed out with 10% sodium carbonate, precipitated with hydrochloric acid, and collected. Liquid, neutral products were distilled at reduced pressure. The results are assembled in Table I.

Registry No.—1-Morpholino-1-cyclohexene, 670-80-4.

(2) R. W. Hein, M. J. Astle, and J. R. Shelton, *J. Org. Chem.*, **26**, 4874 (1961).

(3) I. S. Dutt, *Quart. J. Chem. Soc.*, **1**, 297 (1925); *Chem. Abstr.*, **19**, 2475 (1925).

(4) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **67**, 1432 (1945); J. H. Tumlinson, *et al.*, *J. Org. Chem.*, **36**, 2616 (1971).

(5) D. S. Breslow, E. Baumgarten, and G. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1287 (1944).

^1H Nuclear Magnetic Resonance Structure Elucidation of Substituted Isoquinolines by Means of $Eu(fod)_3$[1a]-Induced Paramagnetic Shifts

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Research efforts in this laboratory have led to the synthesis of a number of substituted isoquinolines. The determination of the position of substitution in these and other heterocyclic systems is by no means a trivial task, and in many instances classical and spectroscopic determinations lead to equivocal results.

The recently developed lanthanide-induced shift reagents[2] have found extensive application in structure elucidation, and we report here the application of

(1) (a) $Eu(fod)_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane)-4,6-dionatoeuropium(III): R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971). (b) National Research Council Postdoctoral Research Associate, 1971–1972.

(2) W. DeW. Horrocks, Jr., and J. P. Sipe, III, *ibid.*, **93**, 6800 (1971), and references cited therein.

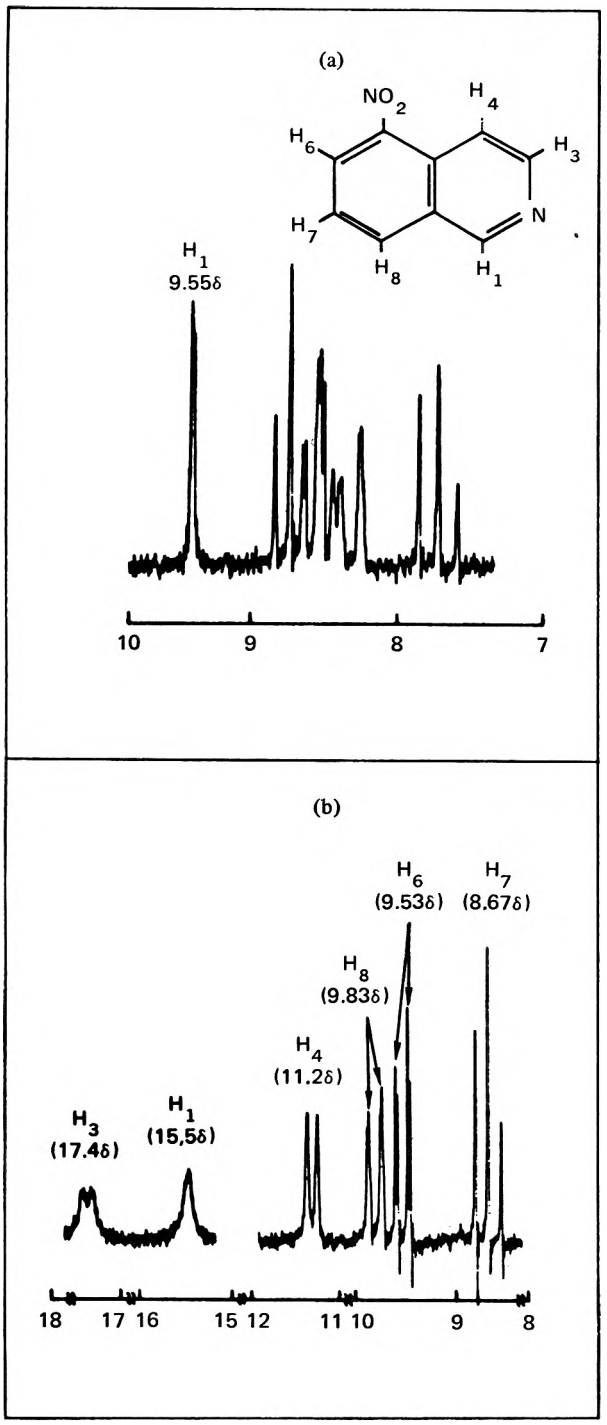

Figure 1.—60-MHz nmr spectra of 5-nitroisoquinoline (1): (a) 0.314 *M* in $CDCl_3$: (b) in the presence of 0.201 molar equiv of $Eu(fod)_3$.

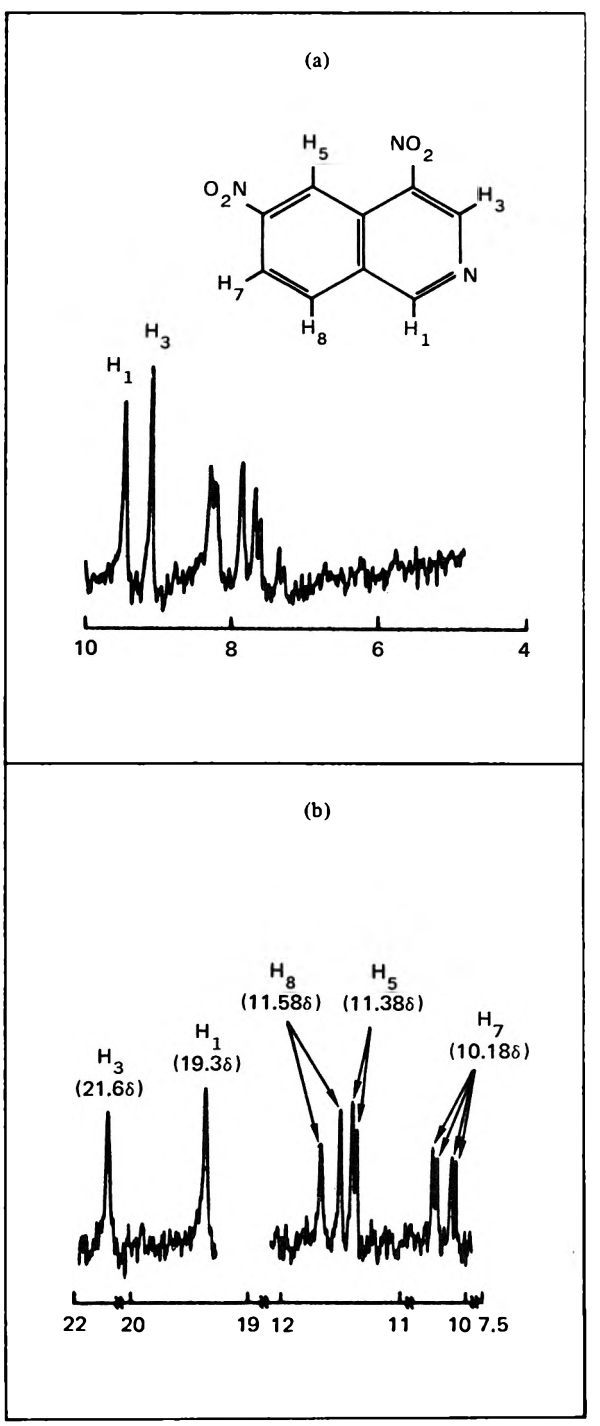

Figure 2.—60-MHz nmr spectra of 4,6-dinitroisoquinoline (2); (a) 0.640 *M* in $CDCl_3$: (b) in the presence of 0.428 molar equiv of $Eu(fod)_3$.

$Eu(fod)_3$ to a number of substituted isoquinolines, **1–8**. In every case spectral clarification was realized, and the position of substitution could be unambiguously assigned.

Figures 1 and 2 show the nmr spectra of two representative compounds. Spectrum 1a is the normal spectrum obtained at 60 MHz for 5-nitroisoquinoline, (**1**). In this spectrum only H_1 at δ 9.55 can unequivocally be assigned. The remaining protons appear as a complex series of 15 lines between δ 8.83 and 7.58. Spectrum 1b was obtained for a 0.314 *M* solution of **1** taken at 60 MHz in the presence of 0.201 molar equiv of $Eu(fod)_3$. In this spectrum the complexities of the original spectrum have been reduced to the point that a first-order analysis is possible allowing the unequivocal assignment of each resonance. The observed coupling constants are consistent with those reported for isoquinoline.[3]

Spectrum 2a was obtained for a previously unknown dinitroisoquinoline, **2**. From 2a it is not possible to distinguish the 4,6- from the 4,5-substituted isomer. Spectrum 2b was obtained for a 0.640 *M* solution of **2** in the presence of 0.428 molar equiv of $Eu(fod)_3$. The shift reagent has removed the fortuitous equivalence and overlap of chemical shifts observed in a and has made it possible to assign the structure of **2**

(3) F. Balkau and M. L. Heffernan, *Aust. J. Chem.*, **24**, 2311 (1971).

TABLE I

Δδ VALUES OBSERVED FOR COMPOUNDS 1–8 IN THE PRESENCE OF Eu(fod)$_3$

Compd	No.	Concn	Proton 1	3	4	5	6	7	8
5-Nitroisoquinoline	1	0.314	29.4	42.5	13.6			4.7	
4,6-Dinitroisoquinoline[d]	2	0.640	22.8	27.7		5.3		3.4	5.4
3,4-Dibromoisoquinoline	3	0.222	2.2						1.8
3-Methylisoquinoline	4	0.203	17.3	22.1[a]	6.1	2.6			3.2
3-Bromoisoquinoline	5	0.131	3.2		3.9				2.0
4-Bromoisoquinoline	6	0.258	29.4	37.6		5.5			6.4
1-Cyanoisoquinoline[c]	7	0.126		2.6	0.7				1.3
Isoquinoline	8	0.446	28.1	29.9	9.7				
Isoquinoline[b]	8a	0.33	23.3	24.1	6.5	3.2	0.6	0.6	3.2

[a] This entry is the gradient observed for the 3-methyl substituent. [b] Data are taken from ref 3 and are the gradients observed for the protons of isoquinoline in the presence of Eu(dpm)$_3$. [c] A. Kaufmann and P. Dändliker, *Ber.*, **46**, 2924 (1923). [d] R. A. Henry, A. T. Nielsen, and D. W. Moore, *J. Org. Chem.*, **37**, 3206 (1972).

as 4,6-dinitroisoquinoline with absolute certainty. Again, the observed coupling constants are in accord with expectations.[3]

In a similar manner, the dibromide **3** was assigned as the 3,4-dibromoisoquinoline. In this case the four protons of the B ring did not reduce to a first-order system, but appear as a complex AA'BB' system.

In all the isoquinolines examined the shift parameter Δδ [the slope of the straight line obtained by plotting the change of chemical shift in parts per million *vs.* the mole ratio of Eu(fod)$_3$ to substrate] varied monotonically with added shift reagent in the low-shift reagent to substrate domain (ratio less than 0.5). At higher ratios of shift reagent to substrate some deviations from linearity are observed, which are more pronounced for H_1 and H_3, and less severe for protons further removed from the coordination site. The methyl substituent of 3-methylisoquinoline (**4**) shows a marked deviation from linearity. The data for the shift gradients determined for compounds **1**–**8** are summarized in Table I.

Considerable line broadening was observed for resonances of protons near the coordination site. In the case of 3-methylisoquinoline the methyl resonance, which exhibits a 1.6-Hz line-width at half-height in the absence of Eu(fod)$_3$, is broadened to 22 Hz in the presence of 0.57 molar equiv of Eu(fod)$_3$. Similarly H_1 and H_3 of **1** (see Figure 1b) show extensive broadening in the presence of Eu(fod)$_3$. Protons further removed from the coordination site show little broadening.

Experimental Section

The pmr shifts were measured with a Varian HA-60-IL spectrometer. The solvent, $CDCl_3$, was dried over preheated (110° *in vacuo*) Linde 4 A Molecular Sieve to exclude water and HCl. TMS was used as an internal standard. The probe temperature was 30°. The shifted spectra were obtained by adding small increments of Eu(fod)$_3$.[4] Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,4-Dibromoisoquinoline (3).—This compound was formed in an attempt to prepare 3-bromoisoquinoline from the corresponding 3-amino derivative by using the procedure of Craig[5] for 2-bromopyridine.

3-Aminoisoquinoline (4.11 g, 0.029 mol) was dissolved with stirring and cooling in 32.5 g of 48% hydrobromic acid. Bromine (4.5 ml) was added over 40 min keeping the temperature between −5 and 0°. The perbromide which separated was initially gummy but toward the end of the addition the mass broke down to an easily dispersed orange solid. Sodium nitrite (4.9 g) in 7 ml of water was added over 50 min keeping the temperature below 0°. The mixture was stirred for an additional 2 hr (0°) and then neutralized by the dropwise addition of 11 g of sodium hydroxide in 50 ml of water. The tan product was filtered, washed well with cold water and dried, 6.5 g (80%), mp 86–87°. Recrystallization from 70% ethanol gave the product with mp 92–93°.

Anal. Calcd for $C_9H_5Br_2N$: Br, 55.69; N, 4.88; mol wt, 285. Found: Br, 56.49; N, 4.99; mol wt (mass spectrum) 285, 287, 289.

3-Bromo- and 3-Hydroxy-4-bromoisoquinoline.—The latter compound precipitated as a hydrated sodium salt in about 22% yield during the preparation of 3-bromoisoquinoline (47% yield) by the method of Case.[6] Recrystallization from 95% ethanol gave yellow needles, mp 254–256° dec.

Anal. Calcd for $C_9H_5BrNONa \cdot 1.5H_2O$: C, 39.58; H, 2.95; Br, 29.26; N, 5.13; Na, 8.42. Found: C, 40.09; H, 2.54; Br, 28.98; N, 5.09; Na, 8.29.

The pure hydroxy compound was recovered by dissolving the salt in hot water and acidifying with acetic acid. A yellow-orange solid was obtained, mp 209–211°. Its spectral properties are similar to those reported for 3-hydroxyisoquinoline.

Anal. Calcd for C_9H_6BrNO: Br, 35.66; N, 6.25; mol wt, 224. Found: Br, 35.68; N, 6.26; mol wt (mass spectrum), 223, 225. Uv (95% ethanol) 229 nm (log ϵ_{max} 4.54), 241 (4.55), 282 (3.43), 294 (3.47), 307 (2.95), 357 (3.28), 428 (3.52); ir (Nujol) C=O, 1625, 1645 cm^{-1} (sh).

The isoquinolines 1, 4, 6, and 8 were commercially available. Purities were checked by nmr and melting point.

Registry No.—**1**, 607-32-9; **2**, 35202-47-2; **3**, 36963-44-7; **4**, 1125-80-0; **5**, 34784-02-6; **6**, 1532-97-4; **7**, 1198-30-7; **8**, 119-65-3; Eu(fod)$_3$, 17631-68-4; 3-hydroxy-4-bromoisoquinoline sodium salt, 36963-49-2; 3-hydroxy-4-bromosioquinoline, 36963-50-5.

(4) Willow Brook Laboratories, Inc., Waukesha, Wis.

(5) L. C. Craig, *J. Amer. Chem. Soc.*, **56**, 231 (1934).

(6) F. H. Case, *J. Org. Chem.*, **17**, 471 (1952).

Mechanism and Stereochemistry of 1,4-Diol Ring Closure to Tetrahydrofuran

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Four principal methods have been employed for the conversion of 1,4-diols to tetrahydrofuran derivatives; the transformation has been accomplished with strong acid,[1] sulfonyl chlorides,[2] alumina,[1a,2c,3] and dimethyl

(1) (a) G. A. Haggis and L. N. Owens, *J. Chem. Soc.*, 389 (1953); (b) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1499 (1954).

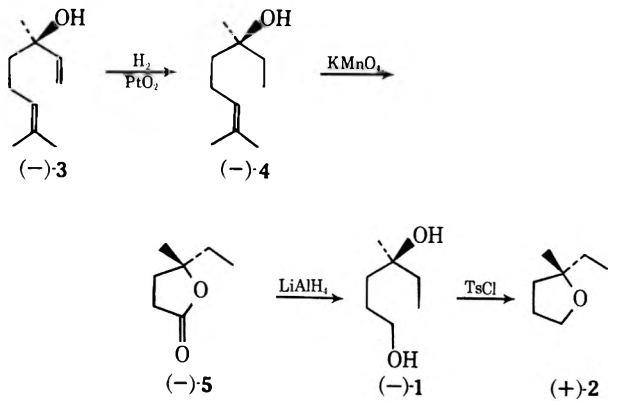
(2) (a) D. D. Reynolds and W. O. Kenyon, *J. Amer. Chem. Soc.*, **72**, 1593 (1950); (b) K. Alder and W. Roth, *Ber.*, **88**, 407 (1955); (c) E. L. Whittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 1218 (1960).

(3) R. C. Olberg, H. Pines, and V. N. Ipatieff, *ibid.*, **66**, 1096 (1944).

sulfoxide (DMSO).[4] We should like to report the mechanism and stereochemistry of each of these transformations.

Absolute Configurations of Reactants and Products. The Mechanism of Tosyl Chloride Ring Closure.—The preparations of 4-methyl-1,4-hexanediol (1) and 2-methyl-2-ethyltetrahydrofuran (2) are summarized in Chart I. Catalytic semihydrogenation[5] of (−)-(*R*)-

CHART I
PREPARATIVE SCHEME



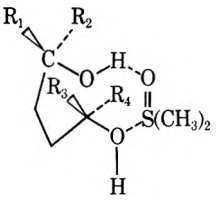
linalool (**3**),[6] with subsequent oxidation of (−)-(*S*)-**4**, afforded the levorotatory lactone (**5**) of (−)-(*S*)-4-hydroxyhexanoic acid.[5] Lithium aluminium hydride reduction of (−)-**5** yields (−)-(*S*)-4-methyl-1,4-hexanediol (**1**).

Treatment of (−)-**1** with *p*-toluenesulfonyl chloride in pyridine afforded (+)-2-methyl-2-ethyltetrahydrofuran (**2**). The absolute configuration of (+)-**2** is not known, but can be inferred from the known selectivity of tosylation reactions. Numerous examples[7] of selective tosylations are known; in general, primary alcohol functionalities form tosyl esters more readily than secondary or tertiary alcohol groups in diols. Thus, for example, 3α,24-cholanediol has been selectively monotosylated to yield 24-tosyloxy-3α-cholanol.[7b]

Granted selectivity in the tosylation of (−)-**1**, the most probable mechanism for the formation of (+)-**2** is tosylation at the primary alcohol functionality with subsequent intramolecular displacement of toluenesulfonate anion by the tertiary oxygen atom. With this sequence, retention of configuration at the chiral center is the expected result; we therefore assign the *S* configuration to (+)-**2**.

Acid-Catalyzed Ring Closure.—Reaction of (−)-(*S*)-**1** with toluenesulfonic acid in benzene with azeotropic distillation of water affords racemic **2**. The most reasonable mechanism for acid-catalyzed ring closure of **1** involves protonation at C-4 hydroxyl (tertiary), formation of an intermediate carbonium ion by loss of water, formation of an oxonium ion intermediate with C-1 hydroxyl, and proton loss. Racemization is explicable by rapid torsion about the C_3–C_4 bond of the intermediate carbonium ion.

DMSO Ring Closure.—Numerous examples of DMSO-catalyzed ring closure of 1,4-diols to THF derivatives have been reported by Gillis and Beck.[4] The mechanism chosen by these authors involved the nine-membered cyclic transition state **6**. With diol **1** two transition states based on **6** (**7** and **8**) become possible. Transition state **7** would yield **2** of retained configuration at C-2, whereas **8** should yield **2** of inverted configuration at C-2. On the basis of nonbonded interactions between reactant and DMSO, **7** should be favored over **8** if a cyclic transition state is operative. The possibility of **7** and **8** being equally probable, with resultant formation of racemic **2**, should be remote. Thus, a cyclic mechanism, if operative, should produce an excess of (+)-**2** *via* transition state **7**.



6

7, $R_1 = CH_3$; $R_2 = Et$; $R_3 = R_4 = H$
8, $R_1 = R_2 = H$; $R_3 = CH_3$; $R_4 = Et$

Heating of (−)-**1** in DMSO at 165–180° yields racemic **2**. A more prosaic alternative than the previously suggested[4] cyclic mechanism, at least for diols possessing a tertiary alcohol functionality, involves a reaction sequence similar to that proposed for acid-catalyzed ring closure. DMSO is known to promote dehydration of secondary and tertiary benzylic and tertiary aliphatic alcohols, presumably *via* intermediate cations. By analogy to simple tertiary alcohols[8] (−)-**1** should produce an achiral carbonium ion intermediate which will subsequently collapse to racemic **2**.

Alumina-Catalyzed Ring Closure.—Heating (−)-**1** with alumina (Alcoa, grade F-20) at 165–180° results in the formation of (+)-**2**, $[\alpha]^{24}D$ +0.33° (neat), *i.e.*, with net retention at C-2 of product. The most plausible rationalization of this result involves selective adsorption[9] of C-1 hydroxyl with subsequent nucleophilic displacement of hydroxide (or its equivalent) by C-4 hydroxyl.

The mechanism can be thought of as the surface equivalent of the tosylate reaction (*vide supra*). The lower degree of stereospecificity in this reaction as compared to the tosylate reaction is indicative of the incursion of minor, alternate mechanisms; the relatively high degree of stereospecificity signalizes that the selective adsorption scheme is the major pathway. This mechanism demands inversion at C-1 of the reactant (C-4 of product).

(4) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963).

(5) (a) P. Vlad and M. Soucek, *Collect. Czech. Chem. Commun.*, **27**, 1726 (1962); (b) H. Mayer, P. Schudel, R. Ruegg, and O. Isler, *Helv. Chim. Acta*, **46**, 963 (1963).

(6) The absolute configuration of **3** was determined by correlation with mevalonic acid: R. H. Cornforth, J. W. Cornforth, and V. Prelog, *Justus Liebigs Ann. Chem.*, **634**, 197 (1960).

(7) (a) I. Scheer, M. J. Thompson, and E. Mosettig, *J. Amer. Chem. Soc.*, **78**, 4733 (1956); (b) R. T. Blickenstaff and F. C. Chang, *ibid.*, **80**, 2726 (1958); (c) R. T. Blickenstaff and F. C. Chang, *ibid.*, **81**, 2835 (1959); (d) W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *ibid.*, **85**, 1409 (1963).

(8) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964), and references cited therein.

(9) L. R. Snyder, *J. Chromatogr.*, **16**, 55 (1964).

Synthetic Utility.—The yields of the ring closure of **1** with tosyl chloride, *p*-toluenesulfonic acid, DMSO, and alumina are 92, 90, 67, and 48%, respectively. Thus, for **1**, the optimal yield, both product and optical, is obtained with tosyl chloride; for the preparation of THF derivatives this route is highly recommended both on the basis of yield and ease of laboratory manipulations.

Experimental Section

Dihydrolinalool (4) was prepared as previously described, $[\alpha]^{23}D$ −2.40 ± 0.03° (neat), bp 85–90° (15 mm) (Kugelrohr) [lit.[5b] bp 88° (17 mm)].

The lactone of 4-methyl-4-hydroxyhexanoic acid (5) was prepared as previously described,[5] $[\alpha]^{24}D$ −7.73 ± 0.02° (*c* 8.2, chloroform), bp 81–82° (3 mm) (Kugelrohr) [lit.[5] bp 100° (20 mm)].

4-Methyl-1,4-hexanediol (1) was prepared by the reduction of 5.4 g (0.042 mol) of (−)-**5** with 1.6 g (0.042 mol) of lithium aluminum hydride in 100 ml of ether at 0° for 16 hr. A saturated solution of sodium sulfate in water (25 ml) was added dropwise to the reaction mixture, followed by *ca.* 10 g of anhydrous sodium sulfate. The precipitated aluminum salts were removed by vacuum filtration. Removal of ether from the filtrate under reduced pressure afforded crude 1. Kugelrohr distillation (105°, 0.4 mm) of the crude product gave 4.3 g (77%) of 1, $[\alpha]^{24}D$ −2.35 ± 0.16° (*c* 12.8, CCl_4) [lit. bp 102° (4 mm),[10] 129–130.5° (12 mm)].[11]

2-Methyl-2-ethyltetrahydrofuran (2) was prepared by the addition of a solution of 5.71 g (0.03 mol) of *p*-toluenesulfonyl chloride in 10 ml of anhydrous pyridine to an ice-cooled solution of 3.5 g (0.027 mol) of (−)-1 in 40 ml of anhydrous pyridine. The reaction mixture (0°) was stirred overnight and poured into a mixture of 100 ml of cold 10% aqueous hydrochloric acid and 100 ml of ether. The ether layer was washed with cold 10% hydrochloric acid until acidic, neutralized with aqueous saturated sodium carbonate, and dried over anhydrous magnesium sulfate. The solution was filtered and the ethyl ether was removed by distillation through a 10-cm Vigreux column. Subsequent distillation of the residue yielded 2.8 g (92%) of (+)-**2**, homogeneous by tlc and vpc analysis (FFAP, 30 ft), $[\alpha]^{24}D$ +0.44 ± 0.03° (neat),[12] bp 118–120° [lit.[12] bp 120–121° (760 mm)].

***p*-Toluenesulfonic Acid Ring Closure of** (−)-1. A solution of 3.0 g (0.023 mol) of (−)-1, $[\alpha]^{24}D$ −2.35° (CCl_4) and 0.1 g of *p*-toluenesulfonic acid in 30 ml of anhydrous benzene was refluxed into a Dean–Stark trap for 18 hr. The benzene solution was poured into 25 ml of 5% aqueous sodium bicarbonate. It was separated from the aqueous layer, washed with 30 ml of water, dried over anhydrous magnesium sulfate, filtered, and distilled. The fraction with bp 118–120° was collected (1.8 g, 90% of theoretical yield). Nmr, vpc, and tlc analysis indicated that this material was homogeneous **2**, $\alpha^{24}D$ +0.02 ± 0.03° (neat, *l* 1).

DMSO Ring Closure of (−)-1.—A solution of 5.0 g (0.038 mol) of (−)-1, $[\alpha]^{24}D$ −2.35° (CCl_4), in 34 ml of anhydrous DMSO was heated under reflux at 180° for 18 hr. The reaction mixture was poured into 100 ml of H_2O and the resultant solution was extracted with three 50-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed by distillation. The distillation residue (bp >35°) was fractionated to yield 2.9 g (67% of theoretical yield) of *dl*-**2**, bp 118–119°, $\alpha^{24}D$ −0.02 ± 0.03° (neat, *l* 1), identical in spectral parameters with an authentic sample of **2**.

Alumina Ring Closure of (−)-1.—An intimate mixture of 5.0 g (0.038 mol) of (−)-1, $[\alpha]^{24}D$ −2.35° (CCl_4), and 10 g of anhydrous alumina (Alcoa F-20) was heated at 165–180°. A mixture of **2** and olefins (nmr vinylic absorption) distilled over a period of 2 hr. The distilled material was fractionated and the material boiling at 118–120° (2.1 g, 48% of theoretical yield) was collected. The spectral properties (nmr and ir) of this material were identical with those of an authentic sample of **2**. The material exhibited $[\alpha]^{24}D$ +0.33 ± 0.02° (neat).

Registry No.—(−)-1, 37102-84-4; (+)-2, 37102-85-5.

(10) I. N. Nazarov, I. L. Kotlyarevskii, and V. F. Ryabchenko, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 960 (1956); *Chem. Abstr.*, **51**, 5019 (1957).

(11) T. A. Favorskaya and O. V. Sergievskaya, *Zh. Obshch. Khim.*, **28**, 87 (1958); *Chem. Abstr.*, **52**, 12757 (1958).

(12) The density of *dl*-**2** is 0.8562: N. I. Shuikin, L. F. Bel'skii, and R. A. Karakhanov, *Z. Chem.*, **3**, 226 (1963); *Chem. Abstr.*, **59**, 9948 (1964).

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

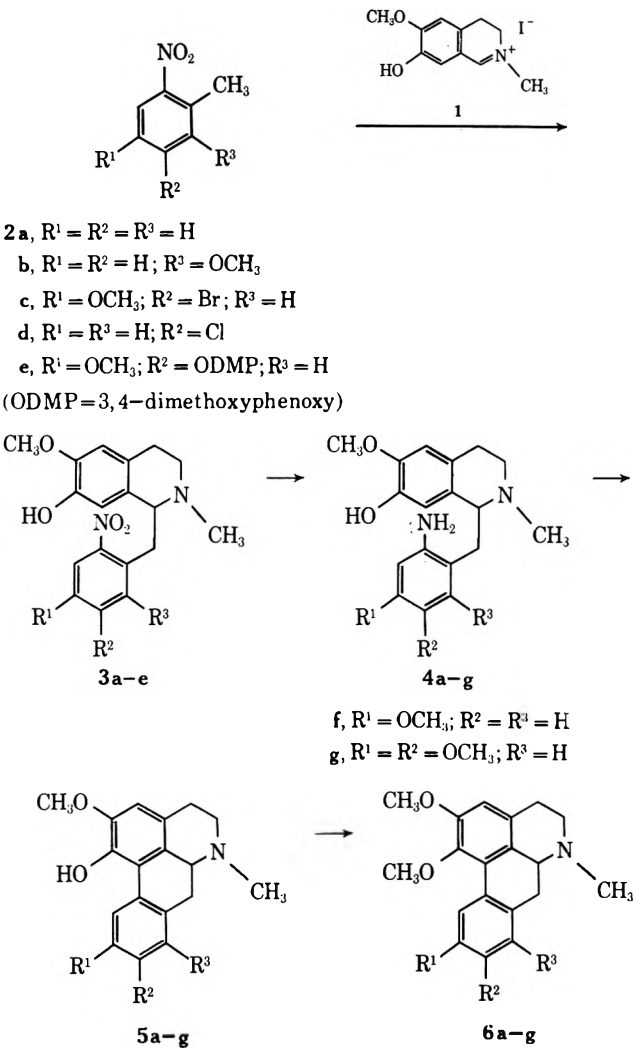
Aporphine Synthesis by Pschorr Cyclization of Aminophenols. An Improved Synthesis of a Thalicarpine Precursor[1,2]

Summary: An improved general synthesis of aporphines *via* Pschorr cyclization of 1-(2′-aminobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines has been developed and successfully applied to the synthesis of thalicmidine (**5g**), nuciferine (**6a**), glaucine (**6g**), and the thalicarpine precursor **6e**, in the highest yields reported to date.

Sir: In an earlier communication,[3] we have described a total synthesis of the tumor inhibitory alkaloid thalicarpine.[4,5] The synthesis suffered from a single low-yield (15%) step, cyclization to the intermediate **6e**. Similar problems have been encountered in the synthesis of most aporphines, and, in general, the cyclization yield decreases as the oxygenation level of the precursor increases.[6,7] This communication reports an improved synthesis of aporphines. We believe this synthesis to be of general synthetic utility.

The key step in our synthesis is the Pschorr cyclization of 1-(2′-aminobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines of type **4**. Earlier studies have demonstrated the yield enhancement by the 7-hydroxy group in mechanistically different aporphine cyclizations, but the overall synthetic sequences were not of general practicality.[8,9] In contrast, condensation of the appropriate *o*-nitrotoluenes **2a–e** with 6-methoxy-7-hydroxy-3,4-dihydroisoquinolinium methiodide[10] (1.2 mol equiv) in the presence of KO-*t*-Bu (2.2 mol equiv) in *N*,*N*-dimethylacetamide gave the 1-(2′-nitrobenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinolines **3a–e** in yields of 88–95% (Table I).[11,12] Reduction of **3a,b,e** with 5% Pd/C gave the corresponding aminophenols **4a,b,e** in yields of 87–98%. Catalytic reduction of **3c** was accompanied by hydrogenolysis to **4f**. The halogenated aminophenols **4c,d** were consequently obtained by Zn–H_2SO_4 reduction. Aminophenols **4a–f** were cyclized to the corresponding 1-hydroxyaporphines **5a–f** (35–50% yield) by diazotization in 1:1 20% H_2SO_4 and HOAc, and cyclization with copper powder. Aporphines **5a–d,f** were separated directly as crystalline salt derivatives. Hydroxyaporphine **5e** was separated as free base by chromatography, and methylation with diazomethane gave the thalicarpine precursor **6e** in 90% yield. For aporphines **6a–d,f**, it was found advantageous to proceed with diazomethane methylation of the crude hydroxyaporphines **5a–d,f**. Thus, *e.g.*, the most efficient synthesis of *dl*-nuciferine (**6a**) reported to date proceeds *via* **3a** (90%) and **4a** (87%) and cyclization–methylation to **6a** (48%).

An improved synthesis of *dl*-glaucine was effected *via* hydrogenation with 5% Pd/C of 1-(2′-nitro-4′,5′-dimethoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-



(1) Tumor Inhibitors. LXXVIII. Part LXXVII: R. J. Restivo, R. F. Bryan, and S. M. Kupchan, *J. Chem. Soc., Perkin Trans. 2*, in press.

(2) This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (T-275).

(3) S. M. Kupchan and A. J. Liepa, *Chem. Commun.*, 599 (1971).

(4) *Chem. Eng. News*, **44**, 64 (1966); J. L. Hartwell and B. J. Abbott, *Advan. Pharm. Chemother.*, **7**, 117 (1969).

(5) Clinical investigation of thalicarpine is underway, in the program of the Division of Cancer Treatment, National Cancer Institute.

(6) For a brief review of the synthesis of aporphines up to 1960, see A. R. Pinder in "Chemistry of Carbon Compounds," Vol. IV, E. H. Rodd, Ed., Elsevier, New York, N.Y., 1960, Chapter 24.

(7) S. M. Kupchan, J. L. Moniot, R. M. Kanojia, and J. B. O'Brien, *J. Org. Chem.*, **36**, 2413 (1971), and references cited therein.

(8) B. Franck and L.-F. Tietze, *Angew. Chem., Int. Ed. Engl.*, **6**, 799 (1967).

(9) R. J. Spangler and D. C. Boop, *Tetrahedron Lett.*, 4851 (1971).

(10) A. Brossi, J. O'Brien, and S. Teitel, *Org. Prep. Procedures*, **2**, 281 (1970).

(11) *Cf.* S. Narayanaswami, S. Prabhakar, B. R. Pai, and S. Shanmugasundaram, *Indian J. Chem.*, **7**, 755 (1969), and references cited therein.

(12) All new compounds were characterized by concordant analytical and spectral data.

TABLE I

YIELDS (PER CENT) AND MELTING POINTS (°C)

	3	4	5	6[a]
a	90[b,c]	87, 210–112 dec[d]	44, 269–271 dec[e]	48, 259–261 dec[e]
b	88, 167–168	93, 161–162[f]	45, 239–241 dec[e]	40, 186–187[f]
c	95, 146–147	83[b,g]	43, 241–243 dec[h]	
d	94, 127–129	77, 118–119[f,g]	50, 244–246 dec[h]	43, 260–261 dec[h]
e	92, 173–174	98[b,f]	35, 150–151[f]	23, 212–214 dec[e]
f		81, 137–138[e]	46, 219–223 dec[e]	36, 223–225 dec[e]
g		81, 177–179[d]	43, 190–192[f]	46, 191–192 dec[i]

[a] Combined yields for direct two-step conversion from 4 to 6. [b] Amorphous. [c] Characterized as the *N*-methiodide, mp 218–219°. [d] Dihydrochloride. [e] Hydrobromide. [f] Free base. [g] Reduction with $Zn-H_2SO_4$. [h] Hydrochloride. [i] Picrate.

1,2,3,4-tetrahydroisoquinoline[13] to aminophenol **4g** (81%). Cyclization of the diazonium salt of **4g** using copper powder gave *dl*-thalicmidine[13,14] (**5g**) in 43% yield. Cyclization–methylation gave *dl*-glaucine (**6g**) in 46% yield from **4g** (which was isolated as the picrate salt[15]).

(13) M. Shamma and W. A. Slusarchyk, *Tetrahedron*, **23**, 2563 (1967).

(14) S. Yunosov and N. N. Progressov, *Zh. Obshch. Khim.*, **22**, 1047 (1952); *Chem. Abstr.*, **47**, 8084 (1953); M. Shamma, M. J. Hillman, R. Charubala, and B. R. Pai, *Indian J. Chem.*, **7**, 1056 (1969).

(15) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert, and R. J. Spangler, *J. Org. Chem.* **35**, 175 (1970).

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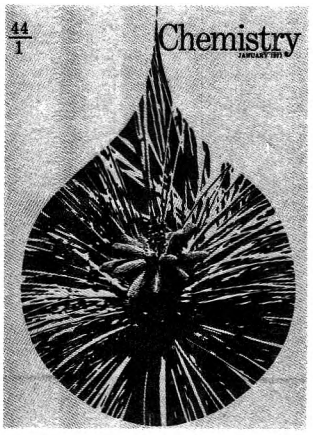
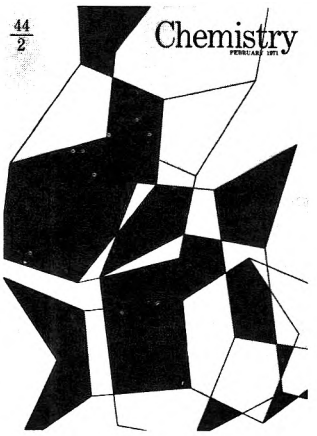
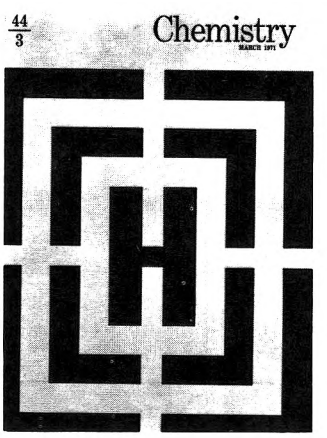
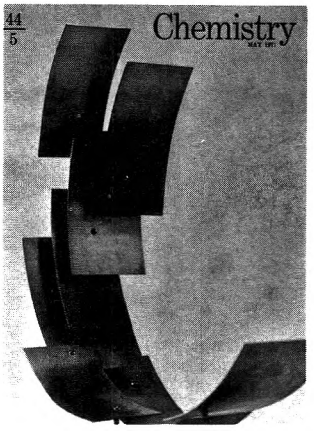
OCTOBER 11, 1972

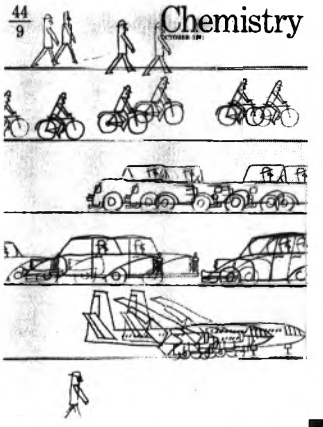


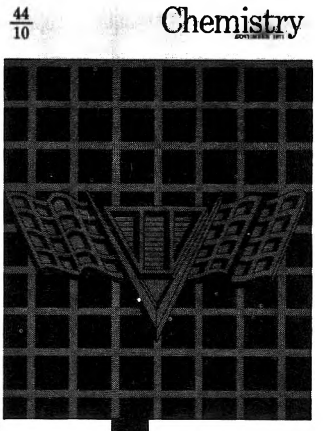


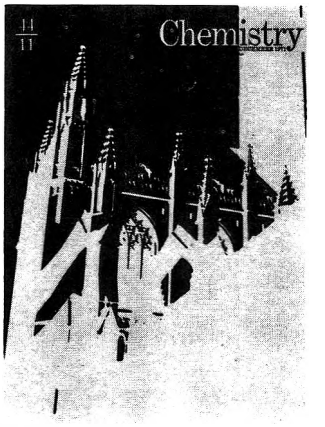




it's colorful
it's lively
it's appealing







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It is the **Aldrich tradition** to help the synthetic chemists by offering a wide variety of intermediates and reagents. Take peptide synthesis,[1] we generally offer one or two reagents for each peptide coupling method described in the literature to date. As each method or reagent has some disadvantages as well as advantages, a variety of reagents is necessary.

For the classic **"mixed anhydride" method,**[2] we offer **isobutyl** and **ethyl chloroformate.** Generally, isobutyl chloroformate is preferred for the preparation of peptides of moderate or high molecular weight, whereas ethyl chloroformate is preferred for the synthesis of dipeptides.[3] The **carbodiimide method**[2] is another versatile and convenient method. The most popular **DCC** is a highly reactive agent and can be used in solid-phase peptide synthesis (SPPS). Related reagents **1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate** and **1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride** are water-soluble diimides, which permit simplified purification of the peptide product because the corresponding ureas are water-soluble. Racemization in the DCC method can be minimized or completely suppressed by using an additive,[1] such as **N-hydroxysuccinimide, N-hydroxyphthalimide, N-hydroxypiperidine** or **1-hydroxybenzotriazole.** The latter is exceptionally good at retarding racemization, prohibiting N-acylurea formation, and at improving yields of high-purity peptides.[4] These additives, of course, can be used in SPPS.[1]

The use of **DCC-pentachlorophenol** (PCP) and **DCC-pentafluorophenol** (PFP) **complexes** in the preparation of acylpeptide-PCP and -PFP active esters,[5] and other uses[6] of DCC have been described.

Another equally versatile reagent is **EEDQ** which has many more advantages: volatile and easily removable by-products, practically no racemization, usable with O-non-protected hydroxy amino acids. **EEDQ** and its more reactive analog **IIDQ,**[7] another Aldrich first, are also good for SPPS. **Woodward's reagents K and L** offer similar advantages: high yields, water soluble by-products, and usable with O-non-protected hydroxy amino acids. An **oxidation-reduction condensation method**[8] calls for **Aldrithiol-2** (2,2'-dipyridyl disulfide) and **triphenylphosphine** as coupling reagents. This system can be used in a variety of solvents at a wide range of temperature,[8] affords high yields and little racemization,[8] and can be used in SPPS.[9]

A selection of other reagents we sell are: **pivaloyl chloride,**[10] **triphenylphosphine** with CCl_4 or CBr_4,[11] **triphenyl phosphite** and **imidazole,**[12] **carbonyldiimidazole,**[2] **α,α-dichloromethyl methyl ether,**[1] **chloroacetonitrile,***[1] **p-nitrophenyl trifluoroacetate,***[13] **2-hydroxypyridine,***[14] **2-mercaptopyridine.***[15]

*Active ester reagents

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