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VOLUME 40, NUMBER 25

DECEMBER 12, 1975

Electrochemical Reduction of α,α′-Dibromo Ketones in Acetic Acid. A Convenient Synthetic Route to Highly Branched α-Acetoxy Ketones

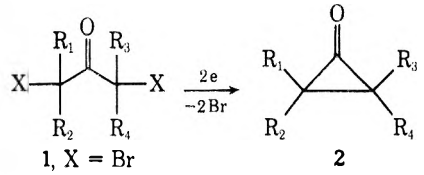
Albert J. Fry* and John J. O'Dea[1]

Hall-Atwater Laboratories of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received July 30, 1975

The electrochemical reduction of a number of α,α′-dibromo ketones (1) was carried out in acetic acid containing sodium acetate. From highly branched ketones, e.g., 2,4-dibromo-2,4-dimethyl-3-pentanone (6), the major products were α-acetoxy ketones in good yields and purity. From less highly substituted dibromo ketones, e.g., 4,6-dibromo-5-nonanone (17), the products were simply the parent (dehalogenated) ketones (3). A mechanistic scheme is presented to explain the results. It is believed that the first step is electrochemical reduction of 1 to an α-bromo enolate (33). Protonation of 33 by the solvent affords an enol allylic bromide (34), which can afford either the parent ketone, by ketonization and reduction of the resulting α-bromo ketone, or acetoxy ketone, by ionization to a hydroxyallyl cation and subsequent nucleophilic attack upon this cation by acetate ion. Substituent effects upon these competing processes are discussed.

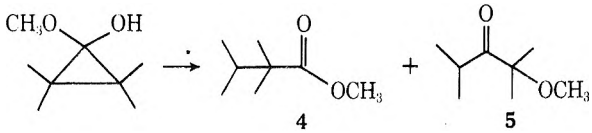
The chemistry of α,α′-dibromo ketones (1) is as rich and diversified as one would expect for such highly functionalized substances.[2] We became interested in the electrochemical behavior of this class of compounds as an outgrowth of our studies on the electrolytic reductive cyclization of 1,3-dibromoalkanes to cyclopropanes.[3] It was natural to inquire into the feasibility of conversion of dibromo ketones 1 into cyclopropanones 2, i.e.



1, X = Br
3, X = H

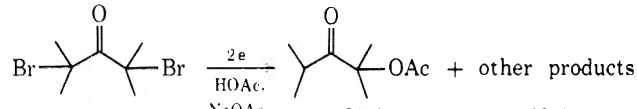
2

If feasible, we expected that this might prove to be a very general route to cyclopropanones, since a wide variety of substances 1 are available by acid-catalyzed dibromination of the parent ketones (3). Our initial foray into this field showed that 2,4-dibromo-2-methyl-3-pentanone (1, R_1 = R_2 = CH_3; R_3 = R_4 = H) is indeed converted into the corresponding cyclopropanone when electrolyzed in acetonitrile at room temperature.[4] Because of the instability of cyclopropanones under the electrolysis conditions, it proved more convenient to carry out the electrolyses in methanol, by which means it was possible to trap tetramethylcyclopropanone as its methyl hemiketal by electrolysis of the corresponding dibromide. This hemiketal is itself somewhat thermally labile, however, slowly decomposing to an ester (4) and a ketone (5).



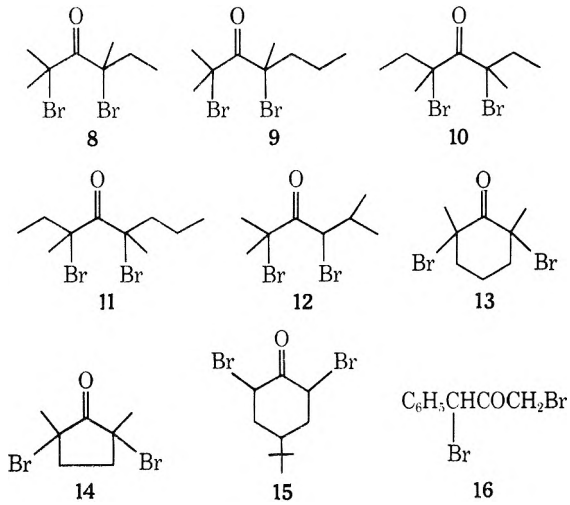
4 5

Because this decomposition promised to afford complex mixtures of products from unsymmetrical dibromo ketones, we were interested in an alternate method of intercepting intermediates in the electroreduction of dibromo ketones. We therefore carried out a preliminary electrolysis of 2,4-dibromo-2,4-dimethyl-3-pentanone (6) in acetic acid containing sodium acetate. This reaction afforded 2-acetoxy-2,4-dimethyl-3-pentanone (7) as the major product in quite good yield, along with several minor products. With

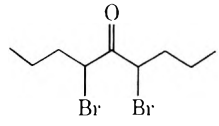


6 7 (92%) (8%)

this interesting result in hand, we carried out an extensive study of the electrochemical reduction of 6 and ten other dibromo ketones (8–17) under these conditions. We report



8 9 10 11 12 13 14 15 16



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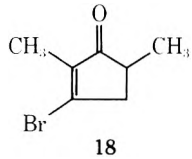
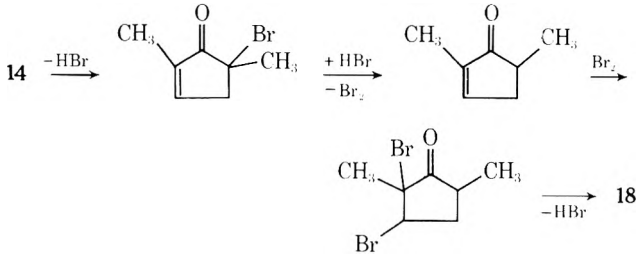
herein the results of that study, which clarify the mechanism of formation of **7** from **6** and demonstrate the scope and synthetic utility of the reaction.

Synthesis and Spectra of Dibromo Ketones. The bromination procedure of Claesson and Thalen[5] (bromine, ketone, aqueous HBr, 60°, no solvent) proved of general utility and was used for the synthesis of most of the dibromo ketones. This procedure failed notably in the case of **14**, which proved to be labile under the conditions of the Claesson–Thalen procedure. It is possible to obtain **14** in 89% yield (after distillation) by bromination in carbon tetrachloride at 0°, but upon standing at room temperature for several hours it decomposes with evolution of hydrogen bromide and bromine to afford a mixture whose principal component is 3-bromo-2,5-dimethylcyclopentenone (**18**). The structure of **18** follows from its mass spectrum [*m/e*



18

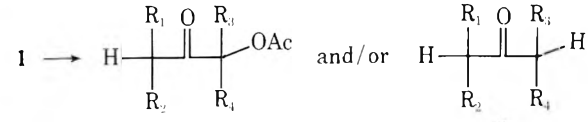
190, 188, 175, 173, and 109 (base peak)], uv spectrum (max 243 nm, log ϵ 4.09, in 95% EtOH), ir spectrum (5.85 and 6.10 μ), and NMR spectrum [d, τ 8.83 (J = 7 Hz); t, τ 8.22 (J = 2 Hz); m, τ 6.6–7.7; relative areas 3:3:3]. The long-range five-bond coupling of the allylic methyl and methylene groups has precedent in other cyclopentenone spectra;[6] coupling constants in such cases are generally ca. 2 Hz. The formation of **18** from **14** presumably involves dehydrobromination, acid-catalyzed debromination, addition of molecular bromine, and final dehydrobromination, i.e.



or a variant of this sequence.[7] 2,6-Dibromo-2,6-dimethylcyclohexanone (**13**) is somewhat labile to acid also, and probably undergoes a similar decomposition sequence, but the products of decomposition were not characterized.

The NMR spectra of several of the ketones displayed features worthy of comment here. The spectrum of **10** exhibited two peaks of almost equal height at τ 7.83 and 7.93, one presumably due to the α-methyl groups of the *dl* diastereomer and the other due to the meso diastereomer; the upfield methyl triplets at ca. τ 9 are also doubled. Presumably this indicates a ca. 1:1 mixture of diastereomers. In dibromide **11**, on the other hand, two doublets in ca. 60:40 ratio are observed at τ 7.85 and 7.93, with apparent spacings of 1.2 and 1.0 Hz, respectively. These doublets presumably are associated with the nonequivalent α-methyl groups of the erythro and threo isomers of **11**. A number of the dibromo ketones also exhibit effects associated with diastereotopic methylene and/or methyl groups. Thus, the methylene protons of **16** dxhibit an AB pattern at τ 5.85 and 6.99 (J = 13.0 Hz), and **12** exhibits two pairs of diastereotopic methyl groups: a downfield pair of singlets at τ 7.94 and 8.12 for the *gem*-dimethyl group adjacent to the carbonyl and an upfield pair of doublets (J = 6.5 Hz) at τ 8.80 and 8.96 for the terminal isopropyl group. Other features of the various NMR spectra, including other examples of such effects, are presented in the Experimental Section.

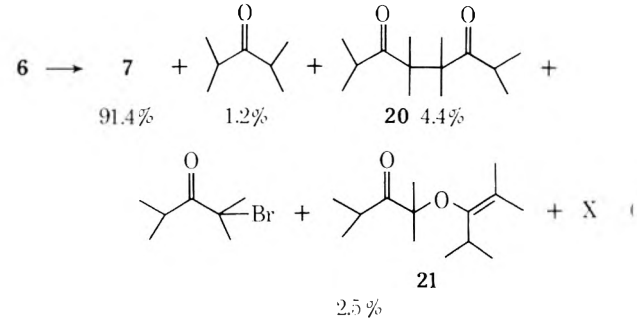
General Characteristics of the Electrochemical Reductions. The electrochemical reductions were carried under standard conditions: acetic acid containing 1.0 *M* sodium acetate, mercury cathode, 25°C, controlled potential. A few experiments were carried out under other conditions, and will be referred to at the appropriate points in the ensuing discussion. The results of the various electrolyses are summarized in Table I. The major overall reaction may be described in very general terms as



19 3

though some side products are formed, usually in low yield (see the column headed "Other" in Table I). The yields of α-acetoxy ketones are generally very good when the starting dibromo ketone is highly branched (**6**, 8–12); reduction to the parent ketone was observed with dibromo ketones **15–17**. We will return to this mechanistic dichotomy later, after discussion of the individual electrolyses.

2,4-Dibromo-2,4-dimethyl-3-pentanone (6). Only in the case of **6** were attempts made to identify all of the products of the electrolysis. Except for an unidentified trace product, these attempts were successful; the reaction stoichiometry is shown in eq 1. Acetoxy ketone **7** was iden-

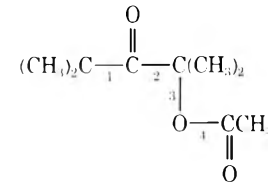


91.4% 1.2% 20 4.4%

21

2.5%

tified by comparison with an authentic sample prepared by lead tetraacetate oxidation of diisopropyl ketone.[8,9] The mass spectrum of **7** exhibited features characteristic of all of the acetoxy ketones obtained in our study. Major fragments were observed at *m/e* 172 (parent), 129, 101, 71, 59, and 43 (base). Cleavage of bonds 1 and 2 produces the



peaks at *m/e* 129, 101, 71, and 43 (the 43 peak is also formed by cleavage of bond 4). The peak at *m/e* 59 arises by cleavage of bonds 2 and 4 with concomitant hydrogen abstraction to afford a C_3H_7O fragment. This is a characteristic feature of all α-acetoxy ketones isolated (except **30**, which has an alternate decomposition path available), and proved to be very useful in locating the position of the acetoxy group when isomeric acetoxy ketones were isolated. For convenience in subsequent discussions we will refer to

Table I
Electrochemical Reduction of Dibromo Ketones in Acetic Acid–Sodium Acetate[a]

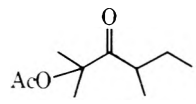
Dibromide	n[b]	Relative yields, % α-Acetoxy ketone (19)	Registry no.	Parent ketone (3)	Registry no.	Other[c]	Total yield, %[d]
6	2.18	91.9	17346-16-6	1.2	21980-75-6	6.9[e]	78
6 (cce)[f]	2.49	94.0		1.0		5.0[g]	83
8	2.21	~98[h]	56829-62-0	~1[h]	56829-69-7	~1[h]	85
9	1.98	90.6	56829-63-1	0.6	56829-70-0	8.8	85
10	2.12	89.6	56829-64-2	4.1	56829-71-1	6.3	82
11	2.07	94.7	56829-65-3	0.2	56829-72-2	5.1	86
12	2.10	76.6	56829-66-4	14.7	56829-73-3	8.7	73
13	2.21	59.1	56829-67-5	2.4	56829-74-4	38.5	68
14	1.48	0	56829-68-6	2.9	1888-57-9	56.0[i]	74
15	j	1	52113-92-5	99	98-53-3	0	90
16	j	0	54210-98-9	100	103-79-7	0	85
17	j	0	3473-24-3	100	502-56-7	0	90

[a] Mercury cathode, 25° C, −1.80 V (vs. Ag/0.1 $AgClO_4$ in HOAc). [b] Number of faradays consumed per mole of starting dibromide. [c] Side products not identified except where noted. [d] Calculated relative to the major product. [e] 4.4% **20**, 25% other (see text). [f] Constant current electrolysis. [g] 2.70% **20**, 2.3% other. [h] Starting material was a ca. 55:45 mixture of 8 and the corresponding monobromide; the actual yields were 55% acetoxy ketone, 44.7% parent ketone, and 0.3% "other". [i] 43% 32, 13% "other". [j] Not measured.

this fragmentation pattern as "double cleavage". Observation of a metastable peak in this mass spectrum at apparent *m/e* 39.2 ($M_1 \rightarrow M_2$; M_1 = 129, M_2 = 71; $M_1 - M_2$ = 58) enables us to assign the sequence of events leading to the peak at 59 as initial cleavage of bond 4, subsequent cleavage of bond 2 to generate a C_3H_6O fragment, and finally hydrogen abstraction by the latter fragment.

Dimer **20** was identified by comparison with an authentic sample prepared by the method of Hoffmann.[10] Structure **21** is tentatively assigned to one of the trace (<1%) products of the electrolysis on the basis of its mass spectrum (*m/e* 226, 183, 157, 114, 113, 71, 43; calcd for $C_{14}H_{26}O_2$, 226) and NMR spectrum (singlet τ 8.67, multiplets at τ 7.22 and 8.96). It was demonstrated that control of the cathode potential is unnecessary in these electrolyses by carrying out a constant current electrolysis of **6**, which afforded **7** in 83% (crude) yield; distillation afforded **7** of 97% purity (VPC). Thus the electrolysis does not require sophisticated equipment; in fact, the constant current electrolysis was carried out in an open beaker rather than the standard closed electrochemical cell. Temperature control is necessary, however: in an unthermostatted cell the temperature rose to 55° because of current dissipation, and the proportion of **20** in the product rose to over 10%.

2,4-Dibromo-2,4-dimethyl-3-hexanone (8). In this and subsequent electrolyses the products other than acetoxy ketones and parent ketones were not characterized. Reduction of **8** afforded an acetate fraction constituting 98% of the products from **8**, after correction for the presence of ca. 45% monobromo ketone[11] in the dibromo ketone; the monobromo ketone is reduced cleanly to parent ketone.[12] The acetate fraction is an inseparable mixture of 2-acetoxy-2,4-dimethyl-3-hexanone (**22**) and 4-acetoxy-2,4-dimethyl-3-hexanone (**23**); the fact that it is a mixture is



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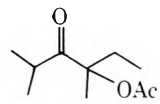
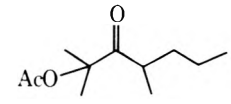


23

demonstrated by its NMR spectrum [two singlets in a ratio of 43:57 at τ 7.93 and 7.95 [–$OCOCH_3$)] and mass spectrum, which exhibited major fragments at 186 (parent), 143, 115, 101*, 85*, 73, 71, 59*, 57*, and 43 (base). (An asterisk next to a mass number denotes a fragment uniquely characteristic of **22**). The peaks at 59* and 73 arise from the "double cleavage" (see above) of **22** and **23**, respectively; the other peaks correspond to cleavage adjacent to carbonyl groups as also observed with **7**.

2,4-Dibromo-2,4-dimethyl-3-heptanone (9). The acetoxy ketone fraction from **9** accounted for 90.6% of the total product. This fraction was separable by VPC into a 62:38 mixture of 2-acetoxy-2,4-dimethyl-3-heptanone (**24**) and 4-acetoxy-2,4-dimethyl-3-heptanone (**25**). The mass spectra of **24** and **25** have several peaks in common: *m/e* 200



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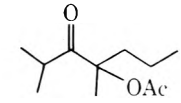
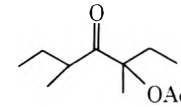


25

(parent), 157, 71, and 43, corresponding to cleavages adjacent to carbonyl groups. In addition, **24** has peaks at *m/e* 101, 99, and 59, while **25** has peaks at *m/e* 129 and 87. The peaks at *m/e* 59 for **24** and 87 for **25** are due to the so-called "double cleavage" and uniquely characterize the point of attachment of the acetoxy group in these compounds.

3,5-Dibromo-3,5-dimethyl-4-heptanone (10). The acetate fraction from **10** constituted 89.6% of the total product and was presumably an inseparable mixture of erythro and threo diastereomers of acetoxy ketone **26**. The ratio of the



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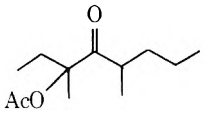
two (assuming both are present) could not be determined by NMR, since the acetyl and downfield α-methyl groups appear as singlets. The mass spectrum of **26** displays major fragments at *m/e* 200 (parent), 157, 143, 115, 85, 73, 57, and 43. Interpretation is straightforward by analogy with the spectra of the acetoxy ketones already discussed. Note particularly the fragment of *m/e* 73 corresponding to the "double cleavage" process; a metastable peak was observed at 46.2 ($M_1 \rightarrow M_2$; M_1 = 157, M_2 = 85, $M_2 - M_1$ = 72) also associated with this process (see the discussion of the mass spectrum of **7**).

3,5-Dibromo-3,5-dimethyl-4-octanone (11). The acetate fraction from electrolysis of **11** constitutes 94.7% of the total product. It is a 59:41 mixture (separable by VPC) of 3-acetoxy-3,5-dimethyl-4-octanone (**27**) and 5-acetoxy-3,5-dimethyl-4-octanone (**28**). Each acetoxy ketone can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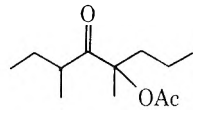
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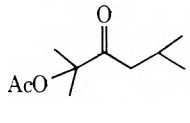
exist as two *dl* diastereomeric pairs, but neither ketone could be resolved into its respective diastereomers by VPC. The mass spectra are unexceptional [**27**, *m/e* 214 (parent)], 171, 115, 99, 73, 71, and 43; **28**, *m/e* 214, 171, 129, 87, 85, 57, and 43). The peaks at 73 and 87 in **27** and **28**, respectively, are due to the "double cleavage" process and permit the assignment of the acetoxyl group in the two isomers.

2,4-Dibromo-2,5-dimethyl-3-hexanone (12). Electrolysis of **12** under the standard conditions afforded an acetate fraction in distinctly lower yield (76.6%) and parent ketone in distinctly higher yield (14%) than with any of the dibromo ketones discussed thus far. We shall return to this significant point later. The acetate fraction consists of an inseparable mixture of 2-acetoxy-2,5-dimethyl-3-hexanone (**29**) and 4-acetoxy-2,5-dimethyl-3-hexanone (**30**). Analysis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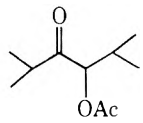
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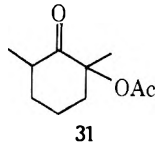
by NMR indicates an approximately 85:15 ratio of **29** to **30**. The mass spectrum of the mixture displays major fragments at *m/e* 186 (parent), 143, 115, 101*, 85*, 71, 59*, 43 (base), 42, and 41. (The peaks labeled with an asterisk denote fragments characteristic of **29**). The peak at *m/e* 59 and a metastable peak at *m/e* 50.5 are due to the "double cleavage" process of **29**. Interestingly, this process does not occur with **30**, since no major fragment is observed at *m/e* 73; instead, a strong peak is observed at *m/e* 71, i.e., cleavage between bonds 2 and 4 (see the numbering system under the discussion of **7**), followed by *loss*, not gain, of a hydrogen. Presumably the C_4H_8O fragment from **30** loses an α-hydrogen atom to give a carbonyl-containing fragment,[13] a process unavailable to the other acetoxy ketones. The other peaks in the mass spectrum are unexceptional—they arise from cleavage adjacent to various carbonyl groups.

2,6-Dibromo-2,6-dimethylcyclohexanone (13). The acetate fraction from this electrolysis constituted a smaller fraction (59.1%) of the total product than in the case of the dibromo ketones already discussed. Unlike the case of **12**, however, the decrease in yield of acetoxy ketone was not associated with an increased yield of parent ketone (only 2.4%); rather, there were a number of side products in this electrolysis, formed in total yield of almost 40%. The acetate fraction consists of an 87:13 mixture of cis and trans isomers of 2-acetoxy-2,6-dimethylcyclohexanone (**31**), but it was not possible to determine from spectral data which is the major isomer. Major mass spectral peaks for each isomer occur at *m/e* 184 (parent), 141, 113, 71, and 43, and are consistent with mass spectra of cyclic ketones.[13] The side products were not identified (there are at least six in addition to the parent ketone, all with VPC retention times shorter than that of **31**), but our observation of metallic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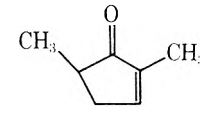
mercury in the trap during attempted preparative VPC suggests that at least one product is a thermolabile organomercurial,[14] and there is probably also some acid-catalyzed decomposition of **13** under the electrolysis as observed with **14** (see below).

Other Electrolyses. Electrolytic reduction of 2,6-dibromo-4-*tert*-butylcyclohexanone (**15**), α,α'-dibromophenylacetone (**16**), and 4,6-dibromo-5-nonanone (**17**) resulted in clean conversion to the parent ketone in each case (though a trace, ca. 1%, of acetoxy ketone was obtained from **15**). Failure to obtain acetoxy ketones from dibromides **15–17** is consistent with the mechanism we believe these reactions to follow (see next section).

Electrolytic reduction of 2,5-dibromo-2,5-dimethylcyclopentanone (**14**) afforded 2,5-dimethylcyclopentenone (**32**) as the major product (43% yield). This product was characterized by NMR, ir, uv, and mass spectroscopy (see Experimental Section) and by its 2,4-dinitrophenylhydrazone, mp 194–195° (lit.[7] mp 194–194.5°). Apparently, under the acidic conditions of the electrolysis **14** is converted into **18**, which is subsequently dehalogenated in straightforward fashion[15] to **32**.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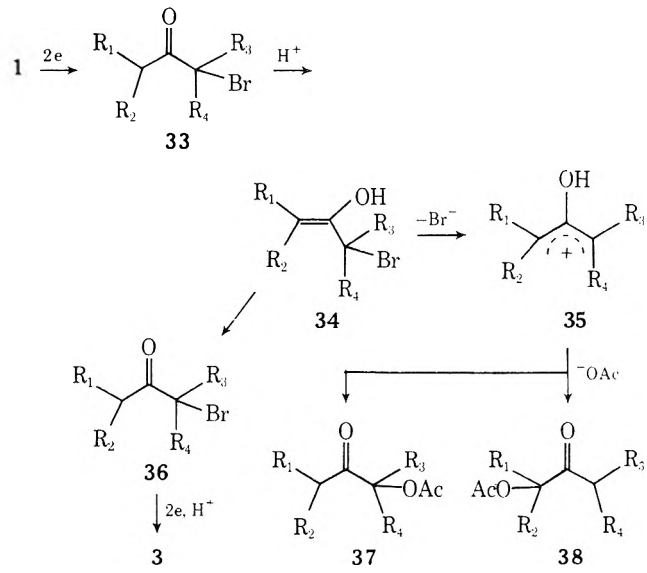
Mechanistic Discussion. The results described herein are readily understood in terms of the mechanism presented in Scheme I. There is a great deal of evidence[15] that the

Scheme I



electrochemical reduction of alkyl halides involves intermediate carbanions; hence the initial intermediate in the reaction sequence must be bromo enolate **33**. Such species have been established by Bordwell and coworkers as intermediates in the base-promoted reactions of bromo ketones.[16] (Indeed, much of Scheme I derives from the extensive studies by Bordwell et al. on the nature of such reactions). Although enolate **33** can be generated either by electrochemical reduction of a dibromo ketone (**1**) or by the action of base upon a monobromo ketone (**36**), the electrochemical reaction has the unique advantage that it may be carried out in acetic acid, where protonation of **33** ought to be rapid.[17] Hence under our conditions the observed chemistry is that of bromo enol **34**, not **33**. Protonation of **33** ought to occur faster on oxygen than on carbon;[18] hence we do not expect monobromo ketone **36** to be formed in any but very minor amounts at this stage. Ionization of the allylic bro-

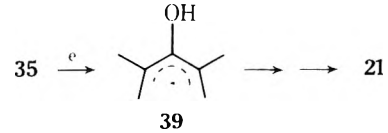
Table II

Compd	Relative solvolysis rate[a]	Compd	Relative solvolysis rate[a]
$CH_2=CHCH_2Cl$	1	$(CH_3)_2C=CHCH_2Cl$	1.5×10^7
$CH_3CH=CHCH_2Cl$	3.6×10^3	$CH_2=CHC(CH_3)_2Cl$	8×10^7
$C_6H_5CH=CHCH_2Cl$	5×10^5	$(CH_3)_2C=CHC(CH_3)_2Cl$	10^{15}[b]

[a] Formic acid. C. A. Vernon, *J. Chem. Soc.*, 423 (1954). [b] Estimated by the method of Vernon.[a]

mine of **34** to afford hydroxyallyl cation **35**, nucleophilic attack by acetate upon the latter,[19] and final ketonization will then afford a mixture of isomeric α-keto acetates **37** and **38**. Actually, it is known that monobromo ketones are reduced electrochemically to the parent ketones (**3**);[12] hence isolation of **3** in only very minor amounts (1–2%) from most of the dibromo ketones (**6**, **8–11**, and **13**) provides confirmation that the major site of protonation of **33** is on oxygen, and, further, that **34** is converted to **35** faster than it can tautomerize to **36**. Recall, however, that several dibromo ketones (**15–17**) are converted cleanly to the parent ketones under the electrolysis conditions, and that another (**12**) afforded a substantial quantity (ca. 15%) of parent ketone. It appears that the route to **3** can become predominant with certain structural types. We do not believe that branching occurs at the point of **33**, i.e., that in such cases protonation occurs on carbon. Rather, we believe that whether parent ketone **3** or acetoxy ketone (**37** and **38**) is formed depends upon the relative rates at which **34** ionizes (to **35**) or ketonizes (to **36**). The major factor of these two is probably the rate of ionization of **34**. It is known that the rates of ionization of allylic halides are extremely sensitive to alkyl substitution.[20] For example, the relative rates of solvolysis of a series of substituted allylic chlorides in formic acid show the effect clearly (Table II). Thus the bromo enols from the tetrasubstituted dibromo ketones **6**, **8–11**, and **13** ought to form far more highly stabilized hydroxyallyl cations than the bromo enols from **15**, **16**, or **17**, favoring therefore the path leading to α substitution.[21] The difference is apparently great enough that ionization of the bromo enols from ketones **15–17** is not competitive with ketonization. The bromo enol from trisubstituted ketone **12** displays intermediate behavior, as expected. The reaction between α,α'-dibromo ketones and zinc–copper couple in methanol[22] displays parallel behavior, in that increasing α-alkyl substitution favors α-substitution, but it is far less sensitive to alkyl substitution than is the electrochemical process.

The formation of diketone **20** as a by-product in the electrolysis of **6** is understandable in terms of Scheme I, by reduction of cation **35** ($R_1 = R_2 = R_3 = R_4 = CH_3$) to a hydroxyallyl radical (**39**), radical coupling to a bis enol, and



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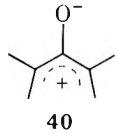
final ketonization to **20**. It is unlikely for steric reasons that **20** arises by coupling of **6** or **36** with **33**; also, were this the case, dimer formation would be more significant with the less substituted dibromo ketones, e.g., **16** or **17**. The other trace product of the electrolysis, tentatively assigned as **21**, is of less obvious origin. It might arise by O to C coupling of **39**, or might involve zwitterion **40**, the conjugate base of **35**.



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In general there seems to be no reason to suspect organomercurials[14] as significant intermediates in these reactions, although they may be minor products (cf. the discussion of by-products in the electrolysis of **13**). Indeed, **7** is still the major product when **6** is electrolyzed using a platinum cathode. Coulometric evidence (Table I) also supports the proposed mechanism: two faradays per mole of **1** are required to generate **33**,[15] and the subsequent reactions leading to acetoxy ketones consume no current.

Conclusions

Electrochemical reduction of highly substituted α,α'-dibromo ketones in acetic acid–sodium acetate affords α-acetoxy ketones in good yields and purity, and does not require sophisticated electrochemical equipment. From our inspection of the literature pertaining to the synthesis of such substances,[23] we believe that it is in fact the synthetic method of choice for highly branched α-acetoxy ketones. For example, preparation of **7** by the lead tetraacetate oxidation of diisopropyl ketone[8] affords in our hands a complex mixture including some bis-acetoxylated material, and less than 50% **7**. On the other hand, the electrochemical conversion of dibromo ketones to α-acetoxy ketones fails with less highly substituted systems, e.g., **15–17**, hence the electrochemical and conventional procedures[23] nicely complement each other. Mixtures of acetoxy ketones are formed from unsymmetrical dibromo ketones, though usually that isomer predominates in which the acetoxy group has entered the less hindered position (but note the predominance of **29** over **30** in the electrolysis of **12**). We plan to explore this point further, but it appears that the reaction will be of most synthetic utility with symmetrical ketones. No attempt was made to maximize yields in our experiments, but we expect that total yields would be higher if the electrolyses were carried out on a larger scale. Finally, we note that the mechanism outlined in Scheme I suggests that a wide variety of nucleophiles could in principle be substituted for acetate ion in this reaction. We plan to explore this possibility.[24,25]

Experimental Section

General. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian A-60A spectrometer in $CDCl_3$ relative to internal tetramethylsilane. Infrared (ir) spectra were recorded as 5.7% solutions (v/v) in CCl_4 on a Perkin-Elmer Model 457 spectrophotometer, and calibrated against a polystyrene reference. Ultraviolet (uv) spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer and calibrated against a holmium oxide glass reference (279.4 nm). Gas chromatographic separations were carried out using a Varian Series 1700 dual column thermal conductivity instrument with temperature programmer. Electrolysis mixtures were analyzed using a 0.25 in. × 8 ft column packed with 5% Carbowax 6000 on Chromosorb G, with the temperature programmed from 100 to 220° at 15°/min. Isomeric acetates were separated on a 0.25 in. × 20 ft column of 5% diethylene glycol succinate (DEGS) on Chromosorb P, in the isothermal mode, at 120°. Mass spectra were recorded (70 eV) on a Perkin-Elmer Hitachi Model RMU-6L spectrometer and were calibrated against perfluorokerosene. Electrochemical experiments were carried out using a Princeton Applied Research Model 170 electrochemistry system.

Materials. Starting ketones were all purchased from the Aldrich Chemical Co. and used without purification. Reagent grade acetic acid was purified by successive treatments with potassium

permanganate and triacetyl borate.[26] Reagent grade anhydrous sodium acetate was dried overnight at 150°.

Dibromo Ketones. The method of Claesson and Thalen[5] for dibromination of ketones was used except where noted. Where a literature reference does not appear in the following descriptions, the dibromo ketone is a new compound. Because of their slow decomposition with time, microanalyses were not obtained for such compounds, but their spectral properties, method of synthesis, and chemistry are all completely in accord with the assigned structures. They were distilled in vacuo as clear, colorless liquids before use.

2,4-Dibromo-2,4-dimethyl-3-pentanone (6) was obtained in 61% yield, bp 80° (5 mm) [lit.[5] bp 85–86.5° (10 mm)]; NMR singlet at τ 7.87.

2,4-Dibromo-2,4-dimethyl-3-hexanone (8) was obtained as a ca. 55:45 mixture of 8 and the corresponding isomeric monobromides (5), and was used as such.

2,4-Dibromo-2,4-dimethyl-3-heptanone (9) was obtained in 87% yield, bp 63° (0.6 mm). A distinctive feature of its NMR spectrum is the appearance of three downfield methyl resonances at τ 7.83, 7.87, and 7.93, two of them due to the diastereotopic methyl groups at C-2.

3,5-Dibromo-3,5-dimethyl-4-heptanone (10) was obtained in 62% yield, bp 68° (0.6 mm). For NMR spectrum see Discussion.

3,5-Dibromo-3,5-dimethyl-4-octanone (11) was obtained in 91% yield, bp 68° (0.3 mm). For NMR spectrum see Discussion.

2,4-Dibromo-2,5-dimethyl-3-hexanone (12) was obtained in 84% yield, bp 45° (0.3 mm) [lit.[27] 41° (1 mm)]. For NMR spectrum see Discussion.

2,6-Dibromo-2,6-dimethylcyclohexanone (13) was obtained in 72% yield, bp 64° (0.3 mm); it solidified in the refrigerator. Corey et al.[28] report mp 27–28° for the cis isomer. Singlets in the NMR at τ 7.98 and 8.08, ratio 85:15, suggest that our sample is a mixture of isomers.

2,5-Dibromo-2,5-dimethylcyclopentanone (14). To a solution of 0.54 g of 2,5-dimethylcyclopentanone in 10 ml of CCl_4 under nitrogen at 0° was added dropwise a solution of 0.5 ml of bromine in 10 ml of CCl_4. The orange color of the solution was discharged within 5 min after addition was complete. The solution was diluted with CCl_4, washed with saturated aqueous $NaHCO_3$, dried over magnesium sulfate, and evaporated at aspirator pressure to yield 1.16 g (89%) of a colorless oil, unstable at room temperature. Its NMR spectrum consisted of two broadened singlets at τ 7.6 and 8.0, relative areas 2:3. If this dibromide is allowed to stand overnight at room temperature, it decomposes, evolving both Br_2 and HBr. After extraction with ether, washing with sodium bisulfite and sodium bicarbonate, drying, and removal of solvent, a yellow oil was obtained. Analysis by VPC indicated a mixture of products. The major product was isolated by preparative VPC and was shown to be 3-bromo-2,5-dimethylcyclopentenone (18) (see Discussion).

Anal. Calcd for C_7M_9BrO: C, 44.47; H, 4.80. Found: C, 44.34; H, 4.79.

2,6-Dibromo-4-*tert*-butylcyclohexanone (15) was prepared by the method of Bordwell and Wellman.[29] The sample used was a mixture of stereoisomers.

1,3-Dibromo-1-phenylacetone (16)[30] was prepared by bromination of phenylacetone in acetic acid, bp 138° (1.8 mm). Its NMR spectrum consists of singlets at τ 2.63 and 4.20, and an AB quartet at τ 5.85 and 5.99 (J = 13.0 Hz), relative areas 5:1:2, respectively.

4,6-Dibromo-5-nonanone (17) was prepared by the method of Claesson and Thalen,[5] bp 70–75° (1 mm) [lit.[2c] 132–135° (20 mm)]. The NMR spectrum of this (presumably) *dl*–meso mixture exhibited a broad triplet (J = 7 Hz) near τ 5.2, in addition to the upfield alkyl absorptions.

Electrolysis of Dibromo Ketones. The electrolysis cell was of standard design.[31] The anode compartment and cell divider was a 25 × 150 mm unfired Vycor test tube immersed in the catholyte. The electrochemical cell was immersed in a Varian Model 9661-00 ultrasonic cleaner (which provided efficient stirring), filled with water and containing a copper coil and thermoregulator, both connected to a Haake Model F constant-temperature water circulator, and set to maintain the electrolysis cell at 25 ± 1°. The anolyte and catholyte solutions were both 1.0 M solutions of sodium acetate in acetic acid. The anode was a platinum gauze; the cathode was a mercury pool (ca. 10 ml of mercury). The reference electrode, constructed from heavy wall 5 m o.d. Teflon tubing closed on one end by a 3 mm o.d. plug of unfired Vycor, consisted of a silver wire immersed in a 0.1 M solution of $AgClO_4$ in acetic acid. Electrolyses of 10 mmol of dibromide were carried out at −1.8 V relative to this reference. (At this potential reduction of acetic acid is negligible). The electrolysis was terminated when the current had decayed to a constant value (ca. 2 mA). The catholyte was then separated from mercury and sodium bromide by filtration. Water (100 ml) was added, and the resulting solution was extracted with three 25-ml portions of CCl_4. The extracts were combined, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated at aspirator pressure to yield the crude product, which was then investigated by VPC. Spectral data were measured on samples purified by preparative VPC. [Satisfactory microanalyses (±0.4%) for all acetoxy ketones were submitted for review. Ed.]

Constant Current Electrolysis of 6. One electrolysis was carried out in an open beaker containing a mercury pool, 250 ml of NaOAc–HOAc solution, and the above-mentioned anode compartment. The solution was stirred magnetically and purged with nitrogen during the reduction. Temperature was not regulated, and rose as high as 55°C at one point. A constant current of 0.50 A was passed for 400 min for the electrolysis of 50 mmol of dibromo ketone. (This amount of current represents a 25% excess over the theoretical). The results of this experiment are described in the Discussion (cf. Table I).

Acknowledgments. Financial support was supplied by the National Science Foundation. Mr. Donald Albert measured the mass spectra. Undergraduates Jerry Segal and Joel Dixon examined the electrochemical behavior of **15** and **17**, respectively. We wish to acknowledge the prior work of Dirlam, Eberson, and Casanova in this area (ref 9b), although our ideas were developed independently.

Registry No.—**18**, 56829-75-5; **21**, 56829-76-6; **22**, 56829-77-7; **24**, 56829-78-8; **27**, 56829-79-9; **29**, 56829-80-2; *cis*-**31**, 56829-81-3; *trans*-**31**, 56829-82-4; **32**, 4041-11-6.

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(24) (a) We have recently found that **6** is converted to **7** cleanly and in high yield by the action of metallic mercury in acetic acid containing sodium acetate; the reaction is considerably slower than the electrode reaction, but affords **7** in purer form. We are exploring the scope and synthetic utility of this reaction. (b) Daniel Herr, unpublished research.
(25) A referee has suggested that those compounds affording parent ketones as product (**15–17**) might exhibit different *i–E* curves than those (e.g., **6**) affording acetoxy ketones. This is not the case: all dibromo ketones examined by us exhibit a single drawn-out *i–E* curve.[9b]
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Stereochemistry and Mechanism of Electrophilic Additions to Tricyclo[4.2.2.0^{2,5}]deca-3,7-diene Derivatives

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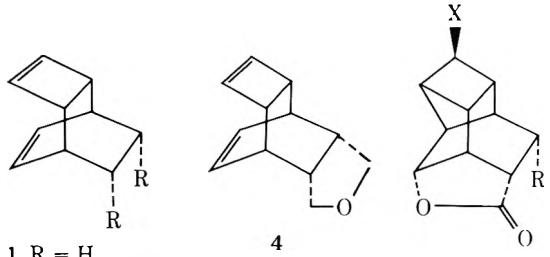
Electrophilic addition of iodine azide, mercuric acetate, nitrosyl chloride, and diborane to tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives **2**, **4**, and **5** is described. Reaction of iodine azide with diester **2** furnishes a syn azido iodide **6**. On the other hand, IN_3 addition to **4** and **5** in acetonitrile solvent results in transannular solvent participation and tetrazoles **8** and **10** are formed via Hassner–Ritter reaction. In methylene chloride solvent dienes **4** and **5** furnish the tetracyclic azido iodides **8** and **10**. Oxymercuration of **2**, **4**, and **5** with mercuric acetate yields the corresponding syn oxymercurials in high yield. The exclusive syn addition of IN_3 and $Hg(OAc)_2$ to the cyclobutene double bond of tricyclo[4.2.2.0^{2,5}]deca-3,7-dienes is interpreted in terms of the dominant role of twist strain theory. The long-range effects of substituents at C_9 and C_{10} on the reaction rates and product formation is also discussed.

Neighboring group participation by a distant double bond in carbocation reactions is now a well-established phenomenon.[2] The chemical reactivity of rigid molecules containing two isolated π bonds in favorable spatial orientation for transannular interaction provides a convenient and interesting route for generating a variety of polycyclic molecules of current interest. The addition of various electrophiles to several olefinic substrates, e.g., norbornadiene,[3] cyclic C_8,[4] C_9,[5] and C_{10}[6] 1,5-dienes, norbornadiene–cyclopentadiene adducts[7] and their chlorinated analogs (Isodrin–Aldrin series[8]), hexamethyl(Dewar benzene),[9] and 9,10-benzotricyclo[4.2.2.2^{2,5}]dodeca-3,7,9-triene,[10] has been investigated to elicit information about the nature of carbocation intermediates, proximity effects, transannular reactions, and ^1H NMR perturbations. Many of these reactions have found useful synthetic applications.[11,12] The tricyclo[4.2.2.0^{2,5}]deca-3,7-diene ring system **1** (R = H), readily available[13] from cyclooctatetraene via the diene synthesis, is endowed with a unique geometrical disposition of a strained cyclobutene double bond and a sterically shielded cyclohexene moiety, ideally suited for the study of transannular cyclizations and electrophilic additions. Furthermore, the variation of substituents at C_9 and C_{10} without altering the geometrical disposition of the double bonds provides an interesting variant for the study of long-range electronic effects. The addition of electrophiles to the dimethyl maleate adduct **2** of COT and its congeners has been studied by Reppe,[13] Nenitzescu,[14] and others[15,16] but no unambiguous structural assignments to the products were made. In a recent study, we[17] as well as others[18] have described the addition of halogens and pseudohalogens to **2** leading to the formation of tetracyclic lactones like **3** via a novel cross-type transannular cyclization. In continuation of these studies, we wish to describe here some interesting results of addition of iodine azide, mercuric acetate, diborane, and nitrosyl chloride to some derivatives of **1**. The additions of iodine azide and mercuric acetate have been found to be highly regio- and stereospecific syn additions and highlight the role of twist strain theory in electrophilic additions to strained olefins. The substrates selected for these studies were the diester **2**, ether **4**, and the dimethyl compound **5** in which the geometrical disposition of the double bonds and reacting site remains the same, while the availability of π electrons for participation by the C_7–C_8 double bond is altered owing to the presence of electron-withdrawing and -donating groups at C_9 and C_{10} endo position. The effect of this variation is distantly located substituents on the reaction rates and product formation is also discussed. The diolefinic substrates were prepared via a slight modification of literature procedures[14] and are described in the Experimental Section.



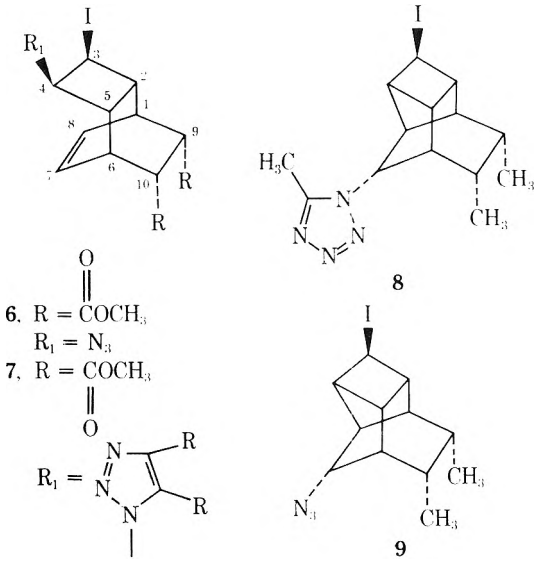
1, R = H
2, R = $COCH_3$ (‖ O)
5, R = CH_3

4

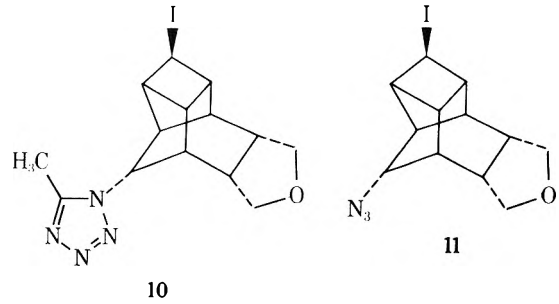
3, X = Cl, Br, etc.; R = $COCH_3$ (‖ O)

Iodine Azide Additions.[19] The reaction of diester **2** with IN_3 solution prepared in situ from excess of sodium azide and iodine monochloride in acetonitrile (−5°) according to the procedure of Fowler, Hassner, and Levy[20] afforded a crystalline azido iodide **6**, mp 137°, in near-quantitative

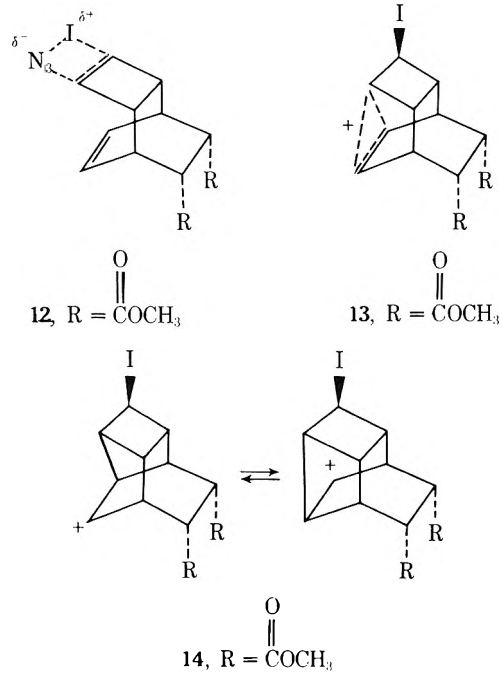
yield. The structure of the IN_3 adduct follows from the diagnostic azide absorption at 2120 cm^{-1} and the ester bands at 1740 and 1210 cm^{-1} in the ir spectrum. The ^1H NMR spectrum showed two quartets at δ 4.32 and 3.12 due to tertiary protons attached to an iodo and azido group, respectively, along with a clean triplet at δ 6.51 due to the two olefinic protons. The syn orientation of I and N_3 substituents on the cyclobutane ring follows from the relatively sharp triplet for the two olefinic protons at C_7 and C_8 arising from the near equivalence of the vinyl hydrogens and the fortuitous near equivalence of their coupling constants. Furthermore, the 1,3-dipolar addition product **7**, mp 192–194°, of **6** with dimethyl acetylenedicarboxylate also displayed, as expected, a sharp triplet at δ 6.61 for the olefinic protons. The appearance of a symmetrical triplet for the vinyl protons at C_7 and C_8 in tricyclo[4.2.2.0^{2,5}]dec-7-enes is diagnostic of symmetrical endo substitution at C_3 and C_4 and has been used for the unambiguous assignment[21,22] of configuration at C_3 and C_4. The structure of the syn addition product has been further confirmed by its correlation with the oxymercuration product of **2** (vide infra).



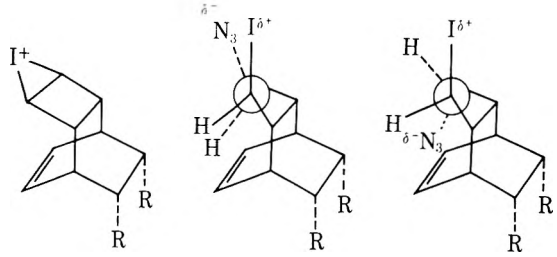
Reaction of dimethyl compound **5** with iodine azide in acetonitrile gave a crystalline solid, mp 147–148°, which analyzed for $C_{14}H_{19}N_4I$ indicating the participation of solvent in a Ritter-like reaction.[23] This product has been assigned the tetracyclic tetrazole structure **8** on the basis of spectral data. The ^1H NMR spectrum showed two singlets at δ 4.55 and 3.93 due to methine protons attached to a tetrazolyl and iodo group along with a singlet at δ 2.6 due to a tetrazolyl methyl group. The spectrum was transparent in the olefinic proton region and suggested transannular participation by the C_7–C_8 double bond.[24] The formation of **8** via cross-type cyclization[17,18] is supported by the clean singlet resonances due to C_4 and C_7 protons (expected on the basis of vicinal dihedral angles) and is in agreement with the previously assigned structure of the cyclization products[17,18] of this system. When the addition of iodine azide to the diene **5** was repeated in methylene chloride medium, an unstable azido iodide **9** was obtained in high yield as the exclusive product and is assigned structure **9** on the basis of its ir spectrum (2110 cm^{-1}, azide) and ^1H NMR spectrum (δ 4.16 and 3.75, singlets due to HCN_3 and HCl) which is analogous to **8**. The azido iodide **9** was also found to be formed, although in small quantity, along with the tetrazole **8** in acetonitrile solvent. Similarly, the addition of iodine azide to the ether **4** in acetonitrile furnished the tetrazole **10** as the major product in methylene chloride the unstable tetracyclic azido iodide **11** was obtained.



The addition of iodine azide to olefins has been shown by Hassner[25] to be a highly regio- and stereospecific process. The reaction proceeds via the electrophilic attack of IN_3 on the olefin with the formation of a three membered ring iodonium ion intermediate and preferential back-side opening resulting in the anti addition of the reagent. Numerous examples of such anti additions are recorded in the literature.[25] The formation of **6** from **2** appears to be the first example of a syn addition of IN_3 to an olefin. Several mechanistic alternatives can be considered to account for this stereospecific syn addition. These may include a concerted four-centered collapse via transition state **12**, shielding of the endo face through intervention of either a bridged ion **13** or a pair of rapidly equilibrating classical ions **14**, and dominance of twist strain factors as proposed by Traylor.[26]



The four-centered syn addition of IN_3 has been considered[25] by Hassner and rejected on the grounds that it is symmetry forbidden and the large radius of iodine precludes a syn collapse. Also, complete variation in product formation in going from **2** to **5** without any apparent change in the geometry of the olefinic moieties is not compatable with this mechanism. Therefore, we do not see any compelling reason to invoke this four-centered polarized molecular addition in the present case. The intervention of **13** or **14** is discounted on the grounds that the presence of electron-withdrawing carbomethoxy substituents at C_9 and C_{10} markedly decreases the availability of electrons from the participating C_7–C_8 double bond and should force more of the reaction of **2** through the iodonium ion **15.** This con-

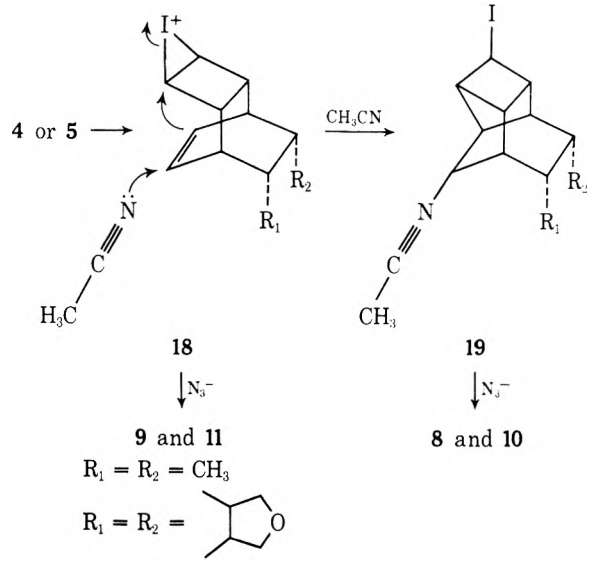


15. R = $COCH_3$ 16. R = $COCH_3$ 17, R = $COCH_3$

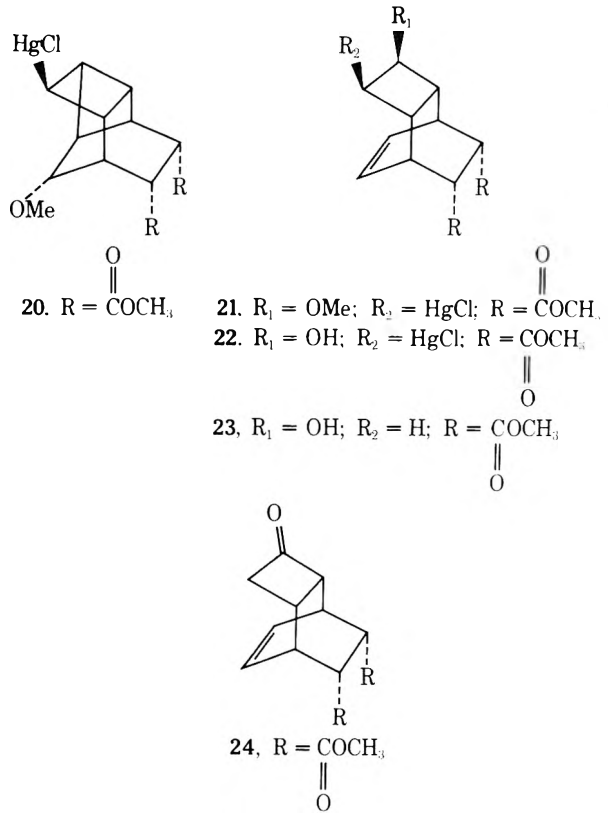
tention is supported by the fact that in the IN_3 addition to dimethyl compound **5** and ether **4**, where facile π participation and formation of ions related to **13** and **14** is possible, only cyclized tetracyclic products are formed and no syn addition product has been encountered. We, therefore, believe that the formation of syn addition product **6** is best rationalized on the basis of twist strain theory[26] and the syn transition state **16** is favored over the anti-coplanar transition state **17**. Lastly, the formation of syn product in this case, as well as in oxymercuration reaction (vide infra), cannot be attributed to steric factors (shielding of the endo face of cyclobutene by the cyclohexene moiety) as predominant formation of anti products in radical[27] and polar additions[16] to **2** is well documented.

The formation of the tetrazoles **8** and **10** from **5** and **4**, respectively, is rationalized on the basis of the solvent-assisted opening of the initially formed iodonium ion **18** to give the Ritter reaction intermediate **19**, which undergoes cycloaddition with azide ion to form the substituted tetrazoles. When the reaction is carried out in CH_2Cl_2 only the azido iodide results via the participation and nucleophilic capture by the azide ion (Scheme I).

Scheme I



Mercuric Acetate Additions. Methoxymercuration of diester **2** has been investigated by Cookson et al.,[15] resulting in the formation of a solid, mp 190–192°, to which they assigned the tetracyclic structure **20**. Repetition[28] of this methoxymercuration in our hands led to the formation of a crystalline organomercurial, mp 193–195°, whose ^1H NMR spectrum exhibited a 2 H olefinic proton triplet at δ 6.7, a 3 H methoxyl singlet at δ 3.23, and a multiplet due to a proton attached to the methoxy group at δ 3.55 along with other resonances compatible with structure **21**. Similarly, hydroxymercuration of **2** furnished the addition product

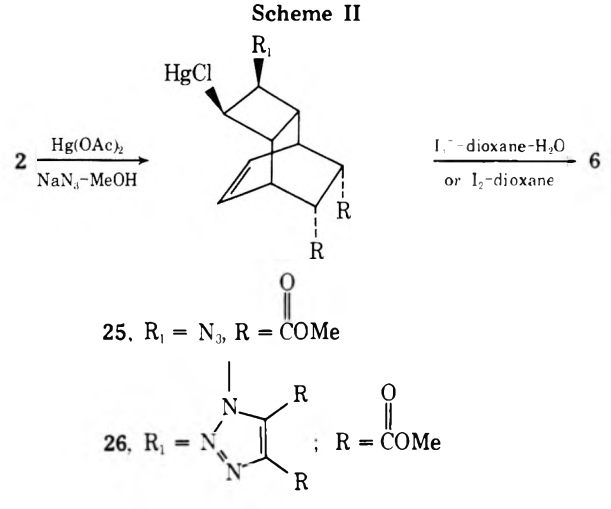


20. R = $COCH_3$

21. R_1 = OMe; R_2 = HgCl; R = $COCH_3$
22. R_1 = OH; R_2 = HgCl; R = $COCH_3$
23, R_1 = OH; R_2 = H; R = $COCH_3$
24, R = $COCH_3$

22, mp 164–165°, which displayed in its ^1H NMR spectrum a 2 H olefinic proton signal at δ 6.71 indicating addition to one of the double bonds of **2**. Regiospecific addition to the cyclobutene ring was established via hydroxymercuration–demercuration of **2** to **23** and oxidation with CrO_3–pyridine reagent to the known[29] cyclobutanone **24**. The syn stereochemistry of the oxymercuration products **21** and **22** was demonstrated on the basis of ^1H NMR data[21,22] and chemical correlation with the IN_3 adduct **8** as shown in Scheme II. Reaction of **2** with $Hg(OAc)_2$ in methanol in the pres-

Scheme II



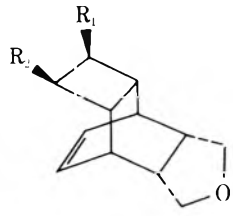
25, R_1 = N_3, R = COMe

26, R_1 = ; R = COMe

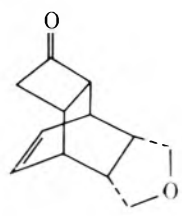
ence of azide ion furnished the azido mercurial **25**, mp 155–157°. The azido mercurial **25** as well as its dipolar addition product **26** with dimethyl acetylenedicarboxylate showed clean triplet signals for the C_7–C_8 olefinic protons. Iodination of **25** with I_2 or triiodide ion in dioxane gave a crystalline product identical in all respects with **8**. The iodination of organomercurials with triiodide ion in polar medium has been shown[30] to proceed with retention of configuration.

Methoxymercuration of ether **4** and dimethyl compound

5 proceeded rapidly and smoothly to furnish the syn methoxymercurials 27 and 28 which showed olefinic trip-



27. R_1 = OMe; R_2 = HgCl
29. R_2 = HgCl; R_1 = OH
31. R_2 = H; R_1 = OH



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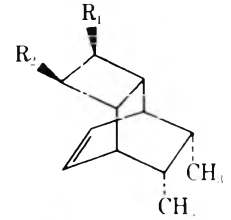
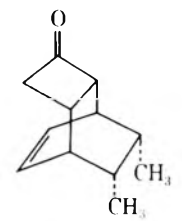


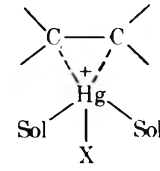
28. R_2 = HgCl; R_1 = OMe
30. R_2 = HgCl; R_1 = OH
32. R_2 = H; R_1 = OH



34

lets at δ 6.56 and 6.53, respectively. The selective addition to the cyclobutene double bond in each case was established via a reaction sequence involving hydroxymercuration to 29 and 30, demercuration with $NaBH_4$ to 31 and 32, and chromium trioxide–pyridine oxidation to cyclobutanones 33 and 34, respectively. The rate of methoxy- and hydroxymercuration of the dienes greatly increased (see Experimental Section) in going from 2 to 4 and 5, indicating a strong transannular depression in the reactivity of the cyclobutene ring as a result of variation in substituents (electron-withdrawing ester to electron-donating methyl group) at C_9 and C_{10}. Similar observation was also made in the case of IN_3 addition (see Experimental Section).

The oxymercuration of simple olefins is known to be a stereospecific anti addition.[31] On the other hand, addition of mercuric salts to strained olefins like norbornene[26,32] and bicyclo[2.1.1]hexene[33] has been shown to be a stereospecific syn addition. Several mechanistic schemes based on molecular addition, twist strain theory, torsional effects, formation of equilibrating classical ions, and nonclassical participation have been proffered to explain the formation of syn exo products, particularly in case of norbornene.[26] Among these, the last three explanations have been eliminated on the grounds that the factors controlling the stereochemistry of addition in strained olefins are not related to those governing the exo:endo rate ratios in norbornyl solvolysis.[33] Recently, Bach and Richter[34] have studied in detail the oxymercuration of bicyclo[2.2.2]oct-2-ene and explain the formation of both syn and anti addition products via a common solvated mercurinium ion intermediate 35. It has been suggested by them that syn oxymercurials may arise via the attack of displaced ligand (X^-) on 33 before the solvent separation and the anti oxymercurials result via usual back-side displacement. In the present case, oxymercuration of dienes 2, 4, and 5 with $Hg(OAc)_2$ in methanolic and aqueous medium proceeds without the formation of any detectable amounts of acetoxymercuration product and thus rules out a molecular mechanism involving the collapse of the acetate ligand on mercury in the intermediate 36 to furnish the syn products. The exclusive formation of syn products in oxymercuration of 2, 4, and 5, and the consistent absence of products arising out of either carbonium ion rearrangement or transannular participation is best rationalized in terms of the twist strain theory.[26] The syn transition state 37 is favored over the strained anticoplanar transition state 38. It is conceivable that the bond



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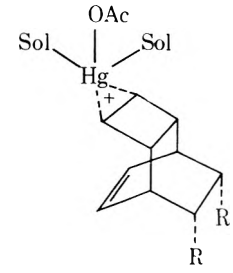

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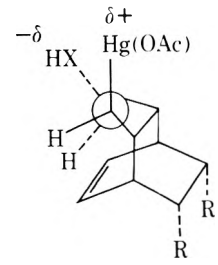

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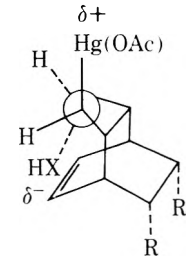

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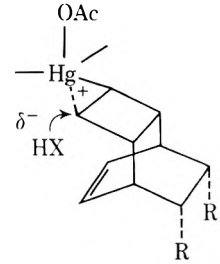
opposition inherent in the transition state for syn addition can be minimized via the conversion of 37 to an unsymmetrical ion 39. This can be expected in view of the relatively long carbon–mercury bond distance in the π complex of ~2.3 Å.[35]

The oxymercuration of dienes 2, 4, and 5 represents the first example of syn addition to a cyclobutene. The cyclobutene itself has been shown to furnish exclusively anti products[36] on oxymercuration. It is quite surprising that no transannular participation is observed during oxymercuration of our system in marked contrast to the behavior of 1,5-cyclooctadiene,[4] Dewar benzene,[37] norbornadiene,[3] and 9,10-benzotricyclo[4.2.2.$2^{2,5}$]dodeca-3,7,9-triene.[10] Further, the contrasting behavior of dienes 2, 4, and 5 toward iodine azide, halogens,[17] iodine nitrate,[17] etc. (rearrangement) on one hand and of mercuric acetate, nitrosyl chloride, benzenesulfinyl chloride,[17] etc. (no rearrangement) on the other is in agreement with Traylor's suggestion[26] that rearrangements during such additions to strained systems are governed by the nature of the electrophilic addend and its ability to stabilize the neighboring positive charge.

Miscellaneous Additions. The addition of nitrosyl chloride generated in situ with diester 2 led to the formation of unrearranged chloro ketone 40 formed through the acid hydrolysis of the oxime and no 1:1 adduct was encountered. Hydroboration of 2 in acetic acid[38] proceeded smoothly to give the alcohol 23 identical with the oxymercuration–demercuration product of 2. Finally, the addition of chlorosulfonyl isocyanate (CSI) to 2 was investigated but to our surprise[39] only the anhydride 41 was formed in this reaction in high yield.



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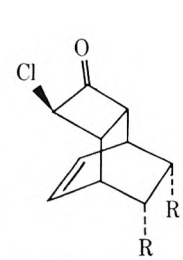
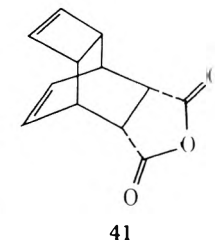


40. R = $COOCH_3$



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Experimental Section[40,41]

9,10-Dicarbomethoxytricyclo[4.2.2.0^{2,5}]deca-3,7-diene (2). This compound was prepared[13] by the reaction of COT–maleic anhydride adduct with methanol in the presence of catalytic amounts of concentrated H_2SO_4 as described in the literature. Distillation (130°, 12 mm) and crystallization from petroleum ether gave colorless crystals: mp 48°; ir (KBr) 1745 cm^{-1} (ester); ^{1}H NMR (CCl_4) δ 5.75–5.95 (olefinic, 4 H, m), 3.51 (CH_3OC=O, 6 H, s) and 2.65–2.95 (CH ring, 6 H, m).

Tricyclic Ether[14] 4. The above diester (5 g) in dry tetrahydrofuran (THF, 50 ml) was reduced with $LiAlH_4$ (2.3 g) for 8 hr at reflux temperature. Decomposition with moist ether and dilute H_2SO_4 and usual work-up furnished a diol **40** as glistening, stout needles: mp 115° (lit.[14] 117°); ir (KBr) 3300, 1040 cm^{-1} (hydroxyl); ^{1}H NMR ($CDCl_3$) δ 5.76 (olefinic, 4 H, m), 4.2 (HO–, 2 H, s), 3.56 (–CH_2OH, 4 H, m), and 2–2.8 (CH ring, 6 H, envelope). In a 250-ml round-bottom flask fitted with a Dean-Stark apparatus, diol (4.0 g) in dry benzene (50 ml) containing *p*-toluenesulfonic acid (100 mg) was placed and the mixture was refluxed for nearly 6 hr. The reaction mixture was poured into aqueous sodium bicarbonate and the benzene layer was separated. The organic phase was washed, dried, stripped of solvent, and distilled to give 3 g of **4** as a colorless, mobile liquid: bp 88–90° (3 mm); mp 38°; ir (neat) 1110 cm^{-1} (ether); ^{1}H NMR (CCl_4) δ 5.83 (olefinic, 4 H, m), 3.5 (–CH_2OCH_2–, 4 H, pair of q), and 2.17–2.73 (CH ring, 6 H, envelope).

9,10-Dimethyltricyclo[4.2.2.0^{2,5}]deca-3,7-diene (5). The diol **40** (4.0 g) in dry pyridine (25 ml) was allowed to react with an excess of methanesulfonyl chloride (7 ml) and the reaction mixture was kept in a refrigerator for 12 hr. The reaction mixture was poured into ice water and extracted with CH_2Cl_2 (2 × 50 ml). The CH_2Cl_2 extract was washed successively with dilute HCl (3 × 50 ml), sodium bicarbonate (2 × 50 ml), and brine. Drying and removal of solvent gave 5.3 g of the dimesylate: mp 136–137°; ir (KBr) 1155, 1330 cm^{-1} (sulfonate). Anal. Calcd for $C_{14}H_{20}O_6S_2$: C, 48.25; H, 5.79. Found: C, 48.85; H, 5.68.

To a stirred slurry of $LiAlH_4$ (2.5 g) in dry THF (50 ml), a solution of the dimesylate (5 g in 25 ml of THF) was added dropwise and the mixture was refluxed for 8 hr. The reaction mixture was quenched by the careful addition of moist ether followed by 25 ml of 10% dilute H_2SO_4. The organic material was extracted with petroleum ether (3 × 25 ml), washed, and dried. Removal of solvent and distillation gave 2.1 g of a colorless oil: bp 100–102° (bath, 11 mm); ir (neat) 710, 745, 770, 788 (characteristic strong bands), 1640, 3140 cm^{-1} (olefinic); ^{1}H NMR (CCl_4) δ 5.5–6.23 (olefinic, 4 H, m), 1.5–3 (CH ring, 6 H, envelope), and 0.93 (CH_3CH, 6 H, d, J = 7 Hz).

Addition of Iodine Azide to Diester 2. The procedure described by Hassner[20] was followed for the iodine azide addition reactions. To a stirred slurry of sodium azide (0.3 g, 4.8 mmol) in 10 ml of dry acetonitrile in a 50-ml round-bottom flask cooled to −5° was added freshly prepared iodine monochloride (0.8 g, 6 mmol) over a period of 5 min. The mixture was allowed to stir for a few minutes and the diester **2** (1 g, 4 mmol) in acetonitrile (5 ml) was added dropwise. After the reaction mixture was allowed to attain room temperature, the mixture was stirred for 2 hr. The brownish slurry was poured into water (50 ml) and extracted with ether (2 × 25 ml). The ethereal extract was washed with 5% sodium thiosulfate followed by brine, dried, and stripped of solvent to yield a white solid residue (1.45 g, 90%). Recrystallization from petroleum ether gave 4-azido-3-iodo-9,10-dicarbomethoxytricyclo-[4.2.2.0^{2,5}]dec-7-ene (**6**) as colorless microcrystals: mp 137°; ir (KBr) 2120 (azide), 1740 and 1210 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.5 (olefinic, 2 H, t), 4.33 (HCN_3, 1 H, q), 3.61 (CH_3OC=O, 6 H, s), 3.12 (HCI, 1 H, q), 2.65–3.55 (CH ring, 7 H, envelope). Anal. Calcd for $C_{14}H_{16}O_4IN_3$: C, 40.28; H, 3.83; N, 10.07. Found: C, 40.34; H, 3.91; N, 10.14. A mixture of **6** (0.1 g, 0.24 mmol) and dimethyl acetylenedicarboxylate (0.5 g, 3.35 mmol) in benzene (15 ml) was refluxed for 4 hr. Removal of solvent and crystallization from benzene gave the crystalline adduct **7**: mp 192–194°; ir (KBr) 1740 and 1210 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.67 (olefinic, 2 H, t), 4.73 (triazolyl methine and HCI, 2 H, m), 4.01 (CH_3OC=O of triazole, 6 H, d), 3.63 (CH_3OC=O, 6 H, s), and 2.83–3.27 (CH ring, 6 H, envelope). Anal. Calcd for $C_{20}H_{22}O_8N_3I$: C, 42.94; H, 3.97; N, 7.51. Found: C, 43.20; H, 4.15; N, 7.46.

Addition of Iodine Azide to 9,10-Dimethyltricyclo[4.2.-2.0^{2,5}]deca-3,7-diene (5). A. In Acetonitrile Solvent. Iodine azide prepared in situ by the action of iodine monochloride (0.1 g, 0.8 mmol) on sodium azide (50 mg, 0.8 mmol) in acetonitrile (5 ml) was treated with 0.1 g (0.6 mmol) of **5** at −5° for 1 hr. Usual work-up gave 0.18 g of a viscous residue. Crystallization from benzene–petroleum ether (1:4) gave 110 mg (46%) of pale needle shaped crystals of tetrazole derivative **8**: mp 147–148°; ir (KBr) 1500, 1450, 1440 cm^{-1} (characteristic –N=N– and –C=N– absorption); ^{1}H NMR ($CDCl_3$) δ 4.55 (tetrazolyl methine, 1 H, broad s), 3.93 (HCI, 1 H, s), 2.6 (tetrazolyl methyl, 3 H, s), 1.05 (CH_3CH, 6 H, m). Anal. Calcd for $C_{14}H_{19}N_4I$: C, 45.41; H, 5.18; N, 15.13. Found: C, 45.29; H, 5.3; N, 15.03. The mother liquor from the crystallization of tetrazole **8** was concentrated and its ir spectrum and TLC showed the presence of azido iodide **9**.

B. In Methylene Chloride Solvent. Iodine azide prepared in situ by the action of iodine monochloride (0.1 g, 0.8 mmol) on sodium azide (50 mg, 0.8 mmol) in methylene chloride (5 ml) at −5° was treated with dimethyl compound **5** (0.1 g, 0.6 mmol) for 2 hr. Usual work-up gave 180 mg (88%) of azido iodide **9** as a colorless oil: ir (neat) 2120 cm^{-1} (azide); ^{1}H NMR (CCl_4) δ 4.16 (HCN_3, 1 H, broad s with fine structure), 3.75 (HCI, 1 H, s), 1.16 (CH_3CH, 6 H, m), 1.9–3.6 (CH ring, 8 H, envelope).

Addition of Iodine Azide to Ether 4. A. In Acetonitrile Solvent. Iodine azide prepared in situ by the action of iodine monochloride (0.2 g, 1.6 mmol) on sodium azide (0.1 g, 1.6 mmol) in acetonitrile (5 ml) was treated with ether **4** (0.2 g, 1.1 mmol) at −20° for 1 hr. Usual work-up as described earlier furnished 0.35 g of a pale yellow liquid product. This was adsorbed on a silica gel (20 g) column and chromatographed. Elution with benzene gave 70 mg (18%) of azido iodide **11**: ir (neat) 2120 cm^{-1} (azide); ^{1}H NMR (CCl_4) δ 4.9 (HCN_3, 1 H, d, J = 2 Hz), 3.4–4.1 (HCI and –CH_2OCH_2–, 5 H, m), 1.9–3.5 (CH ring, 8 H, envelope).

Further elution of the column with benzene–ethyl acetate (1:1) furnished 250 mg (56%) of tetrazole **10**. Recrystallization from carbon tetrachloride furnished pale crystalline flakes: mp 152–153°; ir (neat) 1515, 1475, and 1400 cm^{-1} (characteristic –N=N– and –C=N– absorption); ^{1}H NMR (CCl_4) δ 4.78 (tetrazolyl methine, 1 H, broad s), 4.0 (HCI, 1 H, s), 2.5 (tetrazolyl methyl, 3 H, s), 3.4–4 (–CH_2OCH_2–, 4 H, m). Anal. Calcd for $C_{14}H_{17}N_4OI$: C, 43.76; H, 4.47; N, 14.6. Found: C, 44.09; H, 4.39; N, 14.38.

B. In Methylene Chloride Solvent. Iodine azide prepared in situ by the action of iodine monochloride (0.2 g, 1.6 mmol) on sodium azide (0.1 g, 1.6 mmol) in CH_2Cl_2 was treated at −5° with **4** (0.2 g, 1.1 mmol). Usual work-up as described earlier gave **11** as a pale oily residue (350 mg, 94%), almost single component by TLC. This was identical in all respects with the minor azido iodide formed in acetonitrile medium.

Methoxymercuration of Diester 2. To a solution of diester (0.5 g, 2 mmol) in absolute methanol (15 ml), mercuric acetate (0.7 g, 2.2 mmol) was added and the reaction mixture was stirred for 20 hr at room temperature (20°). After the reaction was complete (TLC), methanol was distilled off on a rotary evaporator and the residue was treated with a saturated sodium chloride solution (20 ml). The reaction mixture was further diluted with water (30 ml) and extracted with methylene chloride (2 × 25 ml), washed, and dried. Removal of solvent gave 1.0 g (96%) of solid methoxymercurial **21**. Recrystallization from benzene–CH_2Cl_2 furnished white crystalline flakes: mp 193–195°; ir (KBr) 1740, 1210 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.7 (olefinic, 2 H, t), 3.6 (CH_3OC=O, 6 H, s), 3.23 (CH_3OC, 3 H, s), 2.6–3.2 (CH ring, 8 H, envelope). Anal. Calcd for $C_{15}H_{19}O_5HgCl$: C, 34.95; H, 3.72. Found: C, 35.03; H, 3.86.

Hydroxymercuration of Diester 2. In a small flask, fitted with a magnetic stirrer, was placed 0.7 g (2.2 mmol) of mercuric acetate. A 1:1 mixture of water–THF (15 ml) was added followed by the diester **2** (0.5 g, 2 mmol) in THF (5 ml). The reaction mixture was stirred at room temperature (20°) for 7 hr until the yellow color was completely discharged. Treatment with saturated brine solution and work-up as described above gave 1.1 g of hydroxymercurial **22** in quantitative yield: mp 164–165°; ir (KBr) 3400 (hydroxyl), 1740 and 1210 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.71 (olefinic, 2 H, t), 4.02 (HCOH, 1 H, m), 3.61 (CH_3OC=O, 6 H, s), 2.6–3.45 (CH ring, 8 H, envelope). Anal. Calcd for $C_{14}H_{17}O_5HgCl$: C, 33.55; H, 3.41. Found: C, 33.52; H, 3.30.

Hydroxymercuration–Demercuration[42] of Diester 2. Diester (0.5 g, 2 mmol) in 1:1 water–THF (15 ml) was treated with mercuric acetate (0.7 g, 2.2 mmol) as described above. After 7 hr at 20°, a solution of 3 *N* sodium hydroxide (5 ml) followed by a mixture of sodium borohydride (50 mg) in 5 ml of 3 *N* NaOH was added. The reduction of the oxymercurial was complete in a few minutes and the mercury droplet settled on the base of the reaction flask. Sodium chloride was added to saturate the aqueous layer and extraction was carried out with ether (2 × 30 ml). Drying and removal of solvent gave 0.5 g (98%) of **23** as a colorless oil: bp 180–90° (bath, 0.5 mm); ir (neat) 3400 (hydroxyl), 1740 and 1200 cm^{-1} (ester); ^{1}H

NMR (CCl_4) δ 6.3 (olefinic, 2 H, t), 3.68 (HCOH, 1 H, m), 3.51 (CH_3OC=O, 6 H, s), 1.7–3.2 (CH ring, 9 H, envelope). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.99; H, 6.89.

Chromium Trioxide–Pyridine Oxidation[43] of 9,10-Dicarbomethoxytricyclo[4.2.2.0^{2,5}]dec-7-en-3-ol (23). A solution of alcohol **23** (0.5 g, 1.9 mmol) in pyridine (5 ml) was added dropwise to an efficiently stirred slurry of CrO_3–pyridine complex [prepared from CrO_3 (1 g) in pyridine (5 ml)] cooled in an ice bath. After stirring for 3 hr the reaction mixture was poured into water and extracted with ether (2 × 20 ml). Washing, drying, and removal of solvent gave 0.4 g (80%) of dicarbomethoxytricyclo[4.2.2.0^{2,5}]dec-7-en-3-one (**24**). Recrystallization from petroleum ether–benzene (4:1) gave white microneedles: mp 94° (lit.[29] 93–95°); ir (KBr) 1775 (cyclobutanone), 1745 and 1200 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.63 (olefinic, 2 H, t), 3.63 (CH_3OC=O, 6 H, s), 2.6–3.43 (CH ring, 7 H, envelope).

Mercuration of Diester 2 in the Presence of Azide Ion. A mixture of diester **2** (0.5 g, 2 mmol), mercuric acetate (0.7 g, 2.2 mmol), and sodium azide (0.15 g, 2.4 mmol) in methanol (15 ml) was stirred at room temperature (20°) for 15 hr. The solvent was removed under reduced pressure and the residue was treated with saturated brine solution. Extraction with CH_2Cl_2 (2 × 25 ml), removal of solvent, and crystallization from benzene–petroleum ether (4:1) gave 1 g (95%) of azido mercurial **25**: mp 155–157°; ir (KBr) 2120 (azide), 1740, 1210 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.48 (olefinic, 2 H, t), 3.82 (HCN_3, 1 H, m), 3.58 (CH_3OC=O, 6 H, s), 2.7–3.2 (CH ring, 7 H, envelope). Anal. Calcd for $C_{14}H_{16}O_4N_3HgCl$: C, 31.94; H, 3.07; N, 7.99. Found: C, 32.08; H, 3.23; N, 8.01.

A mixture of azido mercurial **25** (0.1 g, 0.2 mmol) and dimethyl acetylenedicarboxylate (0.5 g, 3.5 mmol) in dry benzene (10 ml) was refluxed for 6 hr. Removal of solvent and crystallization from benzene gave 0.11 g of the crystalline adduct **26**: mp 210–212°; ir (KBr) 1740 and 1200 cm^{-1} (ester). Anal. Calcd for $C_{20}H_{22}O_8N_3HgCl$: C, 35.93; H, 3.32; N, 6.29. Found: C, 36.18; H, 3.04; N, 6.50.

Iodination of Azido Mercurial 26 with I_2 and Triiodide Ion. To a solution of azido mercurial **26** (0.45 g, 0.9 mmol) in dioxane (10 ml) was added 300 mg of iodine crystals and the mixture was left aside at room temperature (20°) for 4 hr. The reaction mixture was poured into water, extracted with CH_2Cl_2 (2 × 25 ml), and washed successively with 10% sodium thiosulfate and brine. Removal of solvent and crystallization from petroleum ether gave 0.35 g (98%) of azido iodide **6**, mp 137°. This compound was identical (mixture melting point, ir) with the azido iodide obtained from IN_3 addition to **2**. Repetition of the above experiment in aqueous dioxane and in the presence of potassium iodide lead to exactly identical results.

Methoxymercuration of Ether 4. A mixture of ether **4** (0.1 g, 0.6 mmol) and mercuric acetate (225 mg, 0.7 mmol) in absolute methanol (5 ml) was stirred at room temperature for 1 hr. Usual work-up as described for **2** and crystallization from benzene gave 0.21 g (82%) of the methoxymercurial **27**: mp 179–180°; ir (KBr) 920, 1100 cm^{-1} (ether); ^{1}H NMR ($CDCl_3$) δ 6.56 (olefinic, 2 H, broad t), 3.53 (HCOMe, 1 H, m), 3.23 (CH_3OC, 3 H, s), 3.47 and 3.86 (–CH_2OCH_2, 4 H, a pair of t, J = 8 Hz), 2.1–3.0 (CH ring, 8 H, envelope). Anal. Calcd for $C_{13}H_{17}O_2HgCl$: C, 35.38; H, 3.89. Found: C, 35.81; H, 3.56.

Hydroxymercuration of Ether 4. A mixture of ether **4** (0.45 g, 1.5 mmol) and mercuric acetate (0.2 g, 1.1 mmol) in 1:1 water–THF (10 ml) was stirred at room temperature for 3 hr. Work-up as described earlier gave 0.4 g (81%) of hydroxymercurial **29**: mp 182–183°; ir (KBr) 3650 (hydroxyl), 1050 and 915 cm^{-1} (ether); ^{1}H NMR ($CDCl_3$) δ 6.58 (olefinic, 2 H, diffused t), 4.52 (HCOH, 1 H, q), 2.1 (–OH, 1 H, s), 3.2–4 (–CH_2OCH_2– and HCHgCl, 5 H, m), 2.3–1 (CH ring, 6 H, envelope). Anal. Calcd for $C_{12}H_{15}O_2HgCl$: C, 33.73; H, 3.55. Found: C, 34.06; H, 3.73.

Hydroxymercuration–Demercuration[42] of Ether 4. A mixture of ether **4** (0.4 g, 2.2 mmol) and mercuric acetate (0.9 g, 2.8 mmol) in 1:1 water–THF (15 ml) was stirred at room temperature for 3 hr. Sodium hydroxide (5 ml, 3 N) and sodium borohydride (125 mg) in aqueous NaOH (5 ml, 3 N) were added to the reaction mixture and stirring continued for 1 hr. Usual work-up as described above gave 0.37 g (84%) of the alcohol **31**: bp 150–160° (bath, 2 mm); mp 89–90°; ir (KBr) 3550 (hydroxyl), 910 cm^{-1} (ether). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.95; H, 8.40. Found: C, 74.69; H, 8.77.

Chromium Trioxide–Pyridine Oxidation[43] of 31. The alcohol **31** (0.25 g, 1.3 mmol) in pyridine (5 ml) was added to a stirred slurry of CrO_3–pyridine complex (prepared from 0.5 g of CrO_3 in 5 ml of pyridine) in an ice bath. The reaction was terminated after 1 hr by pouring into water and organic material was extracted with CH_2Cl_2 (2 × 25 ml). Washing, drying, and removal of solvent gave 0.2 g (80%) of ketone **33**: bp 130–135° (bath, 2 mm); mp 62°; ir (KBr) 1780 (cyclobutanone), 1020 cm^{-1} (ether). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.75; H, 7.43; Found: C, 75.90; H. 7.61.

Methoxymercuration of 9,10-Dimethyltricyclo[4.2.2.0^{2,5}]-deca-3,7-diene (5). A mixture of dimethyl compound **5** (0.1 g, 0.6 mmol) and mercuric acetate (225 mg, 0.7 mmol) in absolute methanol (5 ml) was stirred at room temperature for 1 hr. Usual work-up as already described and crystallization from benzene gave 0.22 g (82%) of the methoxymercurial **28**: mp 126–127°; ir (KBr) 1060, 1100 cm^{-1} (ether); ^{1}H NMR ($CDCl_3$) δ 6.53 (olefinic, 2 H, t), 3.5 (HCOMe, 1 H, m), 3.2 (CH_3OC, 3 H, s), 0.83 (CH_3CH, 6 H, m), 1.7–2.9 (CH ring, 7 H, envelope). Anal. Calcd for $C_{13}H_{19}OHgCl$: C, 36.52; H, 4.49. Found: C, 36.77; H, 4.38.

Hydroxymercuration of 5. A mixture of **5** (0.16 g, 1 mol) and mercuric acetate (0.35 g, 1.1 mmol) in 1:1 water–THF (10 ml) was stirred at room temperature for 3 hr. Usual work-up furnished 0.35 g (85%) of hydroxymercurial **30**: mp 137–138°; ir (KBr) 3450 and 1020 cm^{-1} (hydroxyl); ^{1}H NMR ($CDCl_3$) δ 6.55 (olefinic, 2 H, m), 4.5 (HCOH, 1 H, m), 3.9 (HCHgCl, 1 H, m), 2.03 (–OH, 1 H, s), 0.78 (CH_3CH, 6 H, J = 6.5 Hz), 1.6–3 (CH ring, 6 H, envelope). Anal. Calcd for $C_{12}H_{17}OHgCl$: C, 34.87; H, 4.15. Found: C, 35.12; H, 4.23.

Hydroxymercuration–Demercuration[42] of 5. The hydrocarbon **5** (0.35 g, 2.2 mmol) and mercuric acetate (0.8 g, 2.5 mmol) in 1:1 water–THF were stirred for 3 hr at room temperature. A 3 N solution of sodium hydroxide (5 ml) followed by sodium borohydride (75 mg) in 3 N aqueous NaOH (5 ml) was added and stirring continued for a further period of 1 hr. Usual work-up gave 0.32 g (82%) yield of 9,10-dimethyltricyclo[4.2.2.0^{2,5}]dec-7-en-3-ol (**32**): bp 120–125° (bath, 2 mm); ir (neat) 3540 cm^{-1} (hydroxyl). Anal. Calcd for $C_{12}H_{18}O$: C, 80.83; H, 10.19. Found: C, 80.51; H, 9.96.

Chromium Trioxide–Pyridine Oxidation[43] of 9,10-Dimethyltricyclo[4.2.2.0^{2,5}]dec-7-en-3-ol (32). The alcohol **32** (0.2 g) in pyridine (5 ml) was oxidized with CrO_3–pyridine reagent as described earlier. Usual work-up gave 0.16 g (80%) of 9,10-dimethyltricyclo[4.2.2.0^{2,5}]dec-7-en-2-one (**34**): bp 100–110° (bath, 2 mm); ir (neat) 1780 cm^{-1} (cyclobutanone).

Nitrosyl Chloride Addition to Diester 2. The diester **2** (1 g, 4 mmol) was dissolved in methanol (15 ml) and cooled to −5°. Isoamyl nitrite (7 ml, 16.5 mmol) was added followed by careful addition of concentrated HCl (4 ml) with vigorous stirring. The stirring was continued for 4 hr and the reaction mixture poured into ice water. Extraction with ether (2 × 25 ml), washing, and drying furnished 1.2 g (90%) of chlorocyclobutanone **40**: mp 164–165°; ir (KBr) 1780 (cyclobutanone), 1745, 1210 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 6.44 (olefinic, 2 H, t), 4.26 (HCCl, 1 H, t, J = 4 Hz), 3.7 (CH_3OC=O, 6 H, s), 2.64–3.6 (CH ring, 6 H, envelope). Anal. Calcd for $C_{14}H_{15}O_5Cl$: C, 56.28; H, 5.07. Found: C, 56.56; H, 5.40.

Hydroboration[38] of Diester 2. The diester (0.5 g, 2 mmol) in dry THF (15 ml) was cooled in an ice bath and sodium borohydride (0.2 g, 5 mmol) and acetic acid (300 mg) were added with rapid stirring. After 4 hr 20% NaOH (5 ml) and 4 ml of 30% H_2O_2 were carefully added and stirring was continued for another 1 hr. Extraction with CH_2Cl_2 (2 × 25 ml), washing, and drying gave 0.51 g (96%) of alcohol **23** identical with the oxymercuration–demercuration product of diester **2**.

Addition of Chlorosulfonyl Isocyanate to Diester 2. To a CH_2Cl_2 (5 ml) solution of diester **2** (0.3 g, 1.2 mmol) cooled in an ice bath, chlorosulfonyl isocyanate (0.3 g) in 2 ml of CH_2Cl_2 was added. The reaction mixture was stirred overnight at room temperature and CH_2Cl_2 evaporated under reduced pressure. Crystallization from acetone–benzene mixture gave 0.22 g (82%) of anhydride **41**: mp 166–167° (lit.[13] 168°); ir (KBr) 1830 and 1765 cm^{-1} (anhydride).

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Registry No.—**2**, 35211-83-7; **4**, 5773-44-4; **5**, 5773-43-3; **6**, 55999-16-1; **7**, 56116-39-3; **8**, 56689-19-1; **9**, 56689-20-4; **10**, 56689-21-5; **11**, 56689-22-6; **21**, 52730-89-9; **22**, 52730-90-2; **23**, 52748-22-

8; **24,** 56689-23-7; **25,** 56689-24-8; **26,** 56689-25-9; **27,** 56689-26-0; **28,** 56689-27-1; **29,** 56689-28-2; **30,** 56689-29-3; **31,** 10203-63-1; **32,** 10203-66-4; **33,** 56689-30-6; **34,** 56689-31-7; **40,** 56689-32-8; 9,10-bis(hydroxymethyl)tricyclo[4.2.2.0^{2,5}]deca-3,7-diene, 56711-59-2; 9,10-bis(hydroxymethyl)tricyclo[4.2.2.0^{2,5}]deca-3,7-diene dimesylate, 55054-05-2; iodine azide, 14696-82-3; dimethyl acetylenedicarboxylate, 762-42-5; mercuric acetate, 1600-27-7; nitrosyl chloride, 2696-92-6.

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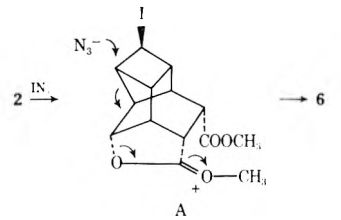

A

find that the iodolactone (**3**, X = I) related to the intermediate A is recovered unchanged when subjected to either the reaction conditions of IN_3 addition (ICl and sodium azide in acetonitrile at −5°) or more stringent conditions (sodium azide in aqueous acetonitrile reflux) for prolonged period of time. Furthermore, attempts to fragment the lactones **3** under a variety of other conditions also proved unsuccessful.[17]
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Organometallic Chemistry. VII. Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study and the Bonding Nature of the Ethylenemercurinium Ion. Preparation and Study of the Norbornadiene- and 1,5-Cyclooctadienemethylmercurinium Ions[1]

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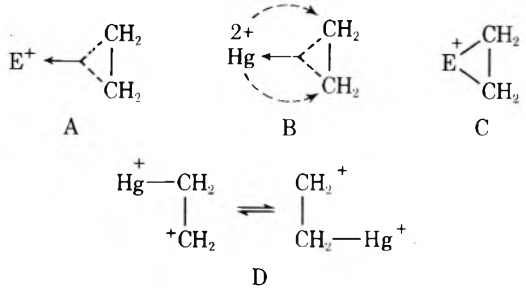
In continued study of the ethylenemercurinium ion its high-resolution carbon-13 NMR spectrum is reported. Based on the carbon chemical shift, and the carbon–proton coupling constant, the nature of bonding in the ethylenemercurinium ion is best characterized by the predominance of the forward donating σ component with a significant decrease in the electron density at the olefinic carbons. The first nonconjugated diolefin–mercurinium ion complexes, the norbornadiene- and 1,5-cyclooctadienemethylmercurinium ions, were also prepared by direct mercuration of the diolefins with methylmercuric fluorosulfate, and studied by ^1H and ^{13}C NMR spectroscopy.

In recent publications from this laboratory the first direct observation of stable mercurinium ions of monoolefins was reported.[2] We would like now to report the extension of these studies, and a better understanding of the bonding nature in the ethylenemercurinium ion **1** based on its high-resolution ^{13}C NMR spectrum, as well the preparation of first mercurinium ions formed by the direct mercuration of the nonconjugated diolefins, norbornadiene **2**, and 1,5-cyclooctadiene **3**.

Results and Discussion

Further Study of the Ethylenemercurinium Ion. The ethylenemercurinium ion **1** was prepared, as described, from the reaction of 2-methoxyethylmercuric chloride with excess HSO_3F–SbF_5 in SO_2.[3] The ^1H NMR spectrum consists of the reported singlet at δ 7.68 with satellites due to the proton–mercury coupling of $J_{^{199}Hg-H}$ = 190 Hz.[3] The proton-coupled high-resolution ^{13}C NMR spectrum consists of a triplet centered at $\delta_{^{13}C}$ 137.2 (from Me_4Si) with the proton–carbon coupling of J_{C-H} = 170 Hz.

If any electrophile E^+ approaches an olefin in electrophilic addition reactions, the intial bonding interaction was suggested to involve the formation of a molecularly bonded bridged π complex to form a two-electron, three-center bound species, as A.[4] If d, or its hydride orbitals are available in the electrophile, according to the Chatt–Dewar–Duncanson bonding description,[5] back donation becomes significant, as shown for the case of a mercurinium ion B. Subsequently, the π complex can either interact further to give a σ-bonded, three-membered ring (σ complex) C or open the three-center bond to give the corresponding β-substituted rapidly equilibrating carbenium ion D.

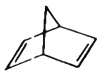


Recently, the ability of ^{13}C NMR spectroscopy to distinguish between σ- and π-complex intermediates in electrophilic addition reaction to alkenes has been demonstrated.[6,7] The ^{13}C shift and J_{C-H} coupling constants are dependent on a combination of factors.[8] A net deshielding at a nucleus is accompanied by a decrease of electron density, an increase in π character, or a decrease in the average electronic excitation energy.[9] An increase of J_{C-H} is observed when the electron density is decreased, the π character is increased, or especially a strained ring is formed. Based on both ^{13}C shifts ($\delta_{^{13}C}$ 69–74 for the parent, unsubstituted ions) and J_{C-H} values ($\simeq$187 Hz), it has been proposed that the ethylenehalonium ions[7,10,11] are best formulated as three-membered ring σ-bonded ions C. The substantial deshielding results from a decrease of π character by the formation of the bridged ion being more than compensated for by a decrease of electron density due to the polarization of positive charge on the electrophile. The increase of J_{C-H} results from a preponderant increase of ring strain by the formation of a three-membered ring cyclic ion over the decrease of electron density and of π character. An approximately linear relation between ^{13}C shifts and J_{C-H} coupling constants exists among cyclic halonium ions, ethylenearenium ions, and typical three-membered ring systems such as cyclopropane, ethylene oxide, ethylene sulfide, and *N*-methylaziridine.[10] However, the ethylenemercurinium ion falls far away from this correlation.

Recent studies indicate that isolable halogen complexes of adamantylideneadamantane are π complexes due to steric hindrance.[6] The significant deshielding observed (22–26 ppm) was proposed to result from a decrease of the electron density at the olefinic carbons predominating over a decrease of the π character. The same deshielding effect is now observed in the ethylenemercurinium ion, which is, therefore, also best formulated as the molecularly bonded π complex. The smaller deshielding (12.7 ppm) can be explained either by the weaker interaction or by the back donation of the π component in bonding as B, since back donation not only increases the total electron density but also reduces the π character of the olefinic carbons and results in an increase of shielding. Recent ^{13}C NMR studies on transition metal π complexes showed that the shielding for olefinic carbons is correlated with the relative magnitude of the π component in bonding. As the magnitude of the π component increases, a net increase in shielding is observed from Hg^+ (−12.7 ppm), Cu^+ (+28 ppm),[13] Ag^+(+14 ppm),[6,12] Pt(+39–84 ppm),[14] Rh(+61–85 ppm).[15] The present ^{13}C study, consistent with theoretical calculation,[16] indicates the predominance of the σ-bonding component in mercurinium ions due to the greater separation of the 6s and 5d orbitals in mercury.

The increase of the J_{C-H} coupling constant (13.6 Hz) in ethylenemercurinium ion is consistent with the formation of B.[12b,15] Comparison with the increase of coupling con-

Table I
Proton NMR Parameters of Methyl in Mercurinium Ions and Their Diolefinic Percursors[a]

Compd		Solvent, temp, °C	−CH=	$-CH_2-$	−CH−	CH_3Hg-
	2[b]	SO_2	6.70 (t, J = 1.9 Hz)	1.96 (t, J = 1.6 Hz)	3.53 (sep)	
	4	$CH_3HgOSO_2F-SO_2$, −70°	7.76 (t, J = 1.8 Hz)	2.17 (t, J = 1.4 Hz)	4.43 (sep)	1.37 (s)
	3[b]	SO_2	5.58 (s)	2.38 (uq)		
	5	$CH_3HgOSO_2F-SO_2$, −70°	6.67 (um)	2.73 (um)		1.23 (s)

[a] The proton NMR spectra were obtained on a Varian 56-60 instrument with a capillary of Me_4Si as reference. All chemical shifts are given relative to Me_4Si (parts per million). Multiplicity and coupling constants are given in parentheses: s, singlet; t, triplet; sep, septuplet; um, unresolved multiplet; and uq, unresolved quartet. [b] For previously reported proton NMR data, see ref 3.

stant from ethylene (J_{CH} = 157 Hz) to the highly strained cyclopropane ring (J_{CH} = 162 Hz) indicates that the even greater increase of coupling constant in ethylenemercurinium ion (J_{CH} = 170 Hz) can be due to the decrease in electron density upon complexation.[17] Unlike other intermediate complexes of olefins with electrophiles, the observed ethylenemercurinium π complex, as the preferred stable species, seems to indicate that the participation of the π back donation (although a minor contribution) prevents rehybridization and formation of σ-bonded three-membered ring ion C.

The complete ^1H and ^{13}C NMR spectra of the symmetrical ethylenemercurinium ion exclude the possibility of a static primary β-mercuryethyl cation D, even if Traylor suggested the possibility of vertical stabilization by $\sigma-\pi$ conjugation[18] (meaning electron delocalization with no subsequent molecular movement, i.e., bridging). The obtained ^{13}C NMR data do not completely rule out the possibility of a rapidly equilibrating β-mercuryethyl cation system. However, the observed $J_{^{199}Hg-H}$ coupling of 190 Hz excludes any exchange process and argues against a rapidly equilibrating open chain ion, such as D.

The ethylenemercurinium ion is thus, based on its high-resolution ^{13}C NMR spectroscopic study, a molecularly π-bonded species. As in most transition metal π complexes, both σ and π components are involved in bonding, but in the mercurinium ions the σ component is predominant. Furthermore, the electron density is reduced upon complexation and significant positive charge is developed on the carbon atoms.

Preparation and Study of Norbornadiene and 1,5-Cyclooctadienemethylmercurinium Ions. The methylmercurating agent used, methylmercuric fluorosulfate, was prepared by the reaction of a slight excess of dimethylmercury with fluorosulfuric acid in sulfur dioxide solution at −70°.[2] The lack of excess acid results in a suitable and clear system for the investigation of mercurinium ions. Norbornadienemercurinium ion **4** and 1,5-cyclooctadienemercurinium ion **5** are formed when precooled **2** or **3** in pentane solution is slowly added with vigorous stirring to methylmercuric fluorosulfate in sulfur dioxide at −78°. The proton NMR data of **4** and **5** at −60° are summarized in Table I.

Both ions show similar NMR absorptions to those of their precursors, indicating that the dienes have not isomerized in the mercurinium complexes. The ^1H NMR spectra of the mercurinium ions are deshielded, especially the olefinic protons (where the deshielding is more than 1 ppm). Except for group 1B metals, most transition metal π complexes result in net shielding of olefinic protons.[19] Whereas the silver ion complexes exhibit net deshielding,[20] the copper ion complexes are borderline cases.[13] According to Dewar–Chatt–Duncanson,[5] the bonding in transition metal π complexes is composed of σ forward donation and

Table II
Carbon-13 NMR Parameters of Mercurinium Ions and Their Precursors[a]

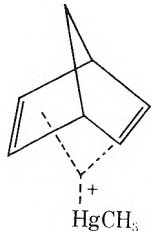
Compd		−CH=	CH_2	CH methine
	2[b]	144.26 (173.6)	74.86 (135.2)	50.23 (149.0)
	4	152.69 (180.4)	76.71 (137.2)	53.46 (158.3)
	3[c]	130.19	27.83	
	5	139.68	29.84	

[a] The spectra were recorded on a Varian HA-100 or XL-100 instrument by the Fourier transform method, at 25.2 MHz with a capillary of enriched CH_3I or Me_4Si as lock or reference at −60° in SO_2. [b] Previously reported spectra; see ref 23. [c] Previously reported spectra; see ref 14.

π back donation. The shielding effect of olefinic protons in ^1H NMR spectra has been proposed[22] to result, at least in part, from the relative contributions of the σ and π components.[20b,21] From these considerations, a greater π-bonding component results in the net shielding of the olefinic protons. The marked difference in silver ion complexes suggests that in these the σ component may predominate. Because of the greater separation of 5d and 6s orbitals of mercury, it is not surprising that the mercury π complexes consist almost entirely of the σ-bonding component. Based on molecular orbital calculations,[16] the olefin transfers electron density to mercury and a significant positive charge is developed on the olefinic carbons. Therefore, the greatest deshielding is observed in mercurinium ions (2.1–2.4 ppm for monoolefinic protons).[2] However, both ions **4** and **5** show only half of the deshielding in comparison with that observed for the mercurinium ions of monoolefins. This indicates the participation of the second olefinic bond in the mercurinium ion formation of diolefins. As no proton–mercury coupling is observed in ions **3** and **4**, it could indicate that fast exchange takes place in the system.

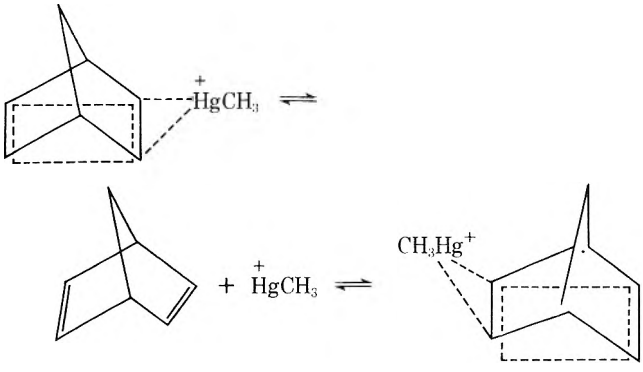
The carbon-13 NMR data of ions **4** and **5** are summarized in Table II. According to recent discussion of the carbon chemical shifts of transition metal π complexes,[13,14a,21,24] the observed deshielding of olefinic carbons upon formation of mercurinium ions, consistent with the proton NMR spectra, is best rationalized on the basis of predominance of the σ-bonding component resulting in a significant decrease in the electron density at the olefinic carbons. Generally, norbornadiene complexes with transition metals in two distinct ways:[19a] as a chelating ligand where the metal is situated in the endo position, and alternatively when the metal is situated in the exo position. When the metal is situated in the endo position, the π-electron density should concentrate between the ligand and the

metal. The electron density on the exo side decreases upon complexation, and the methylene carbons should be shielded, as observed in $C_7H_8Pt(CH_3)_2$,[25] $C_7H_8Fe(CO)_3$,[26] $C_7H_8Mo(CO)_3$,[27] and $C_7H_8Cr(CO)_3$.[27] The observed deshielding on the methylene carbons upon formation of mercurinium ions rules out the possible structure **6** to represent ion **7**. Upon further consideration an exo-bonded structure is also consistent with the known norbornadiene π complexes of group 1B metals.[28]



6

Based on the formation of nortricyclanic product upon the mercuration of 1[29] ion **3** is best rationalized by the following equilibrium.



The 1,5-cyclooctadiene–methylmercurinium ion is also considered to undergo similar equilibration. However, the small increase of J_{C-H} coupling constant (9 Hz) of the methine carbons upon formation of the mercurinium ion does not give definite proof for the homoallylic participation.

Experimental Section

Norbornadiene, 1,5-cyclooctadiene, and dimethylmercury were commercially available and used without further purification.

Methylmercuric fluorosulfate was prepared as previously described[2] except that a slight excess of dimethylmercury was used. Mercurinium ions were prepared by adding the corresponding diolefins in cold SO_2 to the stirred solution of methylmercuric fluorosulfate in SO_2 at −70°, as reported previously for alkenemercurinium ions.[2]

The ^1H NMR spectra were obtained on a Varian A56/60A ^1H NMR spectrometer.

The ^{13}C NMR spectra were obtained on a Varian XL-100 spectrometer. Fluorobenzene was used as external lock, and all chemical shifts are referred to the external Me_4Si (5% enriched) capillary.

Acknowledgment. Support of our work by the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

Registry No.—**1**, 38831-99-1; **2**, 121-46-0; **3**, 111-78-4; **4**, 56666-11-6; **5**, 56666-12-7; methylmercuric fluorosulfate, 43049-30-5.

Supplementary Material Available. The proton-coupled ^{13}C NMR spectrum of the ethylenemercurinium ion in SO_2 solution at −40° (Figure 1), the ^1H NMR spectrum of the norbornadiene methylenemercurinium ion in SO_2 solution at −70° (Figure 2), and the ^1H NMR spectrum of 1,5-cyclooctadienemethylmercurinium ion in SO_2 solution at −70° (Figure 3) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3638.

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Palladium- vs. Peroxide-Promoted Decarbonylation of Neophyl-like Aldehydes[1,2]

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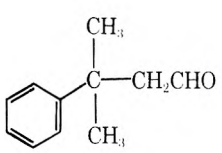
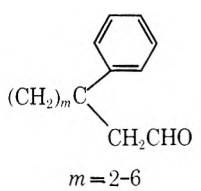
A series of 1-methylbenzocycloalkenyl-1-acetaldehydes has been synthesized, incorporating four-, five-, and six-membered alicyclic rings. Their synthesis and characterization is described. For the purpose of further distinguishing the alternative methods of aldehyde decarbonylation by peroxide vis-á-vis palladium promotion, these aldehydes were subjected to each method. The former method failed completely in the case of the cyclobutyl analogue. The other ring systems exhibited typical neophyl free radical rearrangement, giving rise to 1,1-dimethylbenzocycloalkenes and to 2-methylbenzocycloalkenes with ring expansion. The extent of neophyl rearrangement varied inversely with concentration of the aldehyde. The product from the cyclobutyl compound was a mixture that could not be characterized definitely. The palladium-promoted method succeeded in all cases, although again the cyclobutyl analogue was more resistant to reaction. In this reaction the products were *solely* the 1,1-dimethylbenzocycloalkenes, lending credence to a mechanism that does not involve free radicals, at least beyond the catalyst surface.

The observation[4] that decarbonylation of β-phenylisovaleraldehyde (1) with palladium on carbon proceeded with essentially no rearrangement contrasts markedly with its decarbonylation with di-*tert*-butyl peroxide (DTBP), where rearrangement can be extensive.[5] Furthermore, the latter type decarbonylation of aldehydes **2** is subject to a modest ring size effect, the percentage of phenyl-rearranged product decreasing as the phenyl migration becomes more stereoelectronically demanding in the smaller or more constrained rings.[6] No rearrangement, in fact, was observed in the decarbonylation of benzonorbornene-1-acetaldehyde (**3**).[7] However, no study has as yet extended the use of palladium-promoted decarbonylation to other rearrangement-prone systems.[8] With this as its background, a study was undertaken on the benzoalicyclic acetaldehydes **4-6**-CHO above to compare the rearrangement observed with the two disparate decarbonylation techniques.

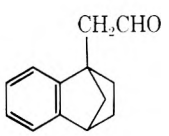


1

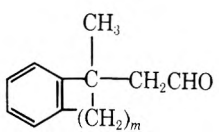


$m = 2$-6

2



3



4-CHO, $m = 1$
5-CHO, $m = 2$
6-CHO, $m = 3$

Results

The aldehydes **4-6**-CHO were synthesized by straightforward procedures which are given in the Experimental Section.

Decarbonylation studies were carried out essentially as earlier described.[8c] The results are shown in Tables I and II.

An additional study was carried out in light of the data in Table I, namely, a study aimed at trapping intermediate acyl radicals with carbon tetrachloride.[9] The results of this study are shown in Table III.

Table I
Peroxide-Induced Decarbonylations

Aldehyde	Concn, *M*	% CO[a]	% Hydrocarbon products[b]	% Rearrangement
1	6.4[c]	81	65	64
1	1.0[d]	80	69	91
4-CHO	6.0[c]	16	0	
4-CHO	1.0[d]	20	0	
5-CHO	5.9[c,e]	81	76	35
5-CHO	1.0[d]	67	38	86
6-CHO	5.6[c]	74	56	32
6-CHO	1.0[d]	79	24	74

[a] ±2%, by GLC analysis (molecular sieve column, 25°), average of several runs. [b] ±3%, by GLC analysis using calibration data with known mixtures, average of several runs. [c] Neat aldehyde heated at 160° (bath) with three equally spaced additions of DTBP (10 mol %) over 300 min. [d] As in *c*, except that the reaction was performed in chlorobenzene at 140° (bath) over 900 min. [e] Data from ref 25.

Table II
Palladium-Promoted Decarbonylations[a]

Aldehyde	Time, hr[c]	% CO[b]	% Hydrocarbon[d]
1	5	92	84, *tert*-butylbenzene
4-CHO	15	34	31, **4**-H
5-CHO	3	80	79, **5**-H
6-CHO	5	84	82, **6**-H

[a] On neat aldehyde (1–2 mmol) in the presence of palladium on carbon (5%, 100 mg) at 160° (bath). [b] Average of three separate runs, ±5%. [c] Time for disappearance of aldehyde, determined by GLC analysis. [d] Less than 1% (if any) rearranged products was present.

Discussion

The peroxide-induced decarbonylation process is believed to take the course shown in Scheme I. The reaction is well documented[5] and will not be discussed in detail here. The use of **1** along with the others in this study served to calibrate the results, and to allow a more secure comparison with earlier reported data. At 129.7° Rüchardt[10] observed 52% rearrangement to isobutylbenzene and related olefins upon reaction of neat **1** with DTBP, the extent of rearrangement rising both with dilution of **1** and the tem-

Table III
Peroxide-Induced Reaction of Aldehydes and Carbon Tetrachloride[a]

Aldehyde	% acyl radical trapped[b]
1	95
4-CHO	0
5-CHO	72
6-CHO	50

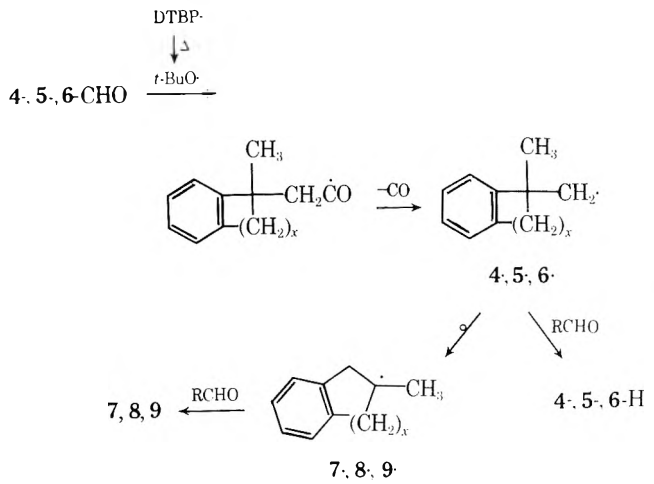
[a] Aldehyde (1 *M* in carbon tetrachloride) and benzoyl peroxide (10 mol %) were refluxed for 5 hr, after which time methanol was added and the mixture was refluxed for an additional 1 hr. [b] As the corresponding methyl ester, ±5%, the average of three separate runs.

perature used. For example, rearrangement at 129.7° rose to 84% with 1 *M* 1 in *o*-dichlorobenzene and to 71% at 144.5° with 3 *M* 1 in the same solvent. Our results with 1 seem quite comparable to these.[11] Moreover, our earlier results[4] with 1 in the palladium-promoted process were again observed here. So it is believed that the conditions and apparatus used are proper for a comparison among the aldehydes of this study in the two types of decarbonylation.

The results in the tables indicate clearly that the benzoalicyclic analogues of 1 behave less satisfactorily in all three types of reactions studied: peroxide-induced decarbonylation, palladium-promoted decarbonylation and peroxide-induced chlorination. Furthermore, while insignificant differences exist between 5- and 6-CHO in these reactions, a startling feature is the gross dissimilarity found with 4-CHO. Only small amounts of carbon monoxide were evolved in the several DTBP-induced reactions of 4-CHO attempted. No 4-H or 7 was ever observed under conditions where less than 1% of each was detectable. Control studies indicated that 60% of these hydrocarbons would be lost through decomposition under reactions conditions, but the failure to detect even 1% of these products argues against their formation at all. The only semicharacterizable product was a viscous oil obtained from chromatography of the reaction residue. Unfortunately, however, the intractable nature of the material precluded any further study.[12] Nonetheless, the acyl radicals formed from 4-CHO obviously underwent decarbonylation with difficulty for some reason, and their presence was therefore sought through chain transfer with carbon tetrachloride,[9] an efficient process with 1 (Table III). Again, a totally negative process was found with 4-CHO. Clearly, acyl radicals from surprisingly slowly (if at all) from this aldehyde. Aldehydes 5- and 6-CHO underwent either type of decarbonylation to similar extents. With both these alicyclic cases, however, the migration of the aryl group via the Ar_1-3 transition state necessary to form 8· and 9· (Scheme I) introduces additional steric strain, causing both to exhibit less rearrangement than does 1 itself in the peroxide process. The lower yield of hydrocarbon in all cases compared to carbon monoxide loss reflects the poor chain nature of these decarbonylations (chain length ~3–10). The radicals formed by loss of carbon monoxide undergo disproportionation and coupling,[10] both of which are termination steps. While it is dangerous to compare different rearrangement percentages in reactions that are not quantitative, it is felt that the rates of disproportionation and coupling in the cases of similar radicals are themselves probably similar and that therefore the rearrangement differences are real.

The mechanism of the heterogeneous palladium-promoted decarbonylation is unknown.[14] However, the results with the present aldehydes concur with the earlier suggestion[4] that neither acyl species R–CO· nor alkyl species R· intervene (at least beyond the catalytic surface), as evidenced both by the partial success of the reaction with

Scheme I



4-CHO and by the total lack of rearranged products from the sensitive precursors 1, 5-, and 6-CHO.

Summary

The present study indicated that palladium-promoted decarbonylation of aldehydes is an efficient, simple, and structurally retentive method, even in sensitive systems. The peroxide-induced technique, on the other hand, is less efficient, more complex, and (as expected) rearrangement prone. Most interestingly, the cyclobutyl analogue has been found to be unexpectedly resistant to both decarbonylation methods, completely failing in the peroxide-induced technique. Further work is needed to determine the cause(s) of this resistance.

Experimental Section

Melting points and boiling points are uncorrected. The former were taken on a Fisher-Johns block. Gas–liquid partition chromatography was performed on a Varian Aerograph A-90P with helium gas as carrier. The columns and temperatures used are cited where appropriate. The following instruments were used to obtain spectra:[17] infrared, Beckman IR 5A; nuclear magnetic resonance, Varian A-60A. The former are given in microns and only significant absorptions are listed. The latter are given in parts per million units (δ) relative to Me_4Si as internal standard. Integration of signals gave values expected for the assigned structure. The usual splitting abbreviations are used. Microanalyses were performed by G. D. Searle Analytical Department or by Micro-Tech Laboratories, both in Skokie, Ill. Spectral and analytical data, together with other selected physical data, are collected in the supplementary tables.[18]

Synthesis of Aldehydes. β-Phenylisovaleraldehyde (1). The aldehyde was available from another study,[4] as was the corresponding methyl ester.

1-Methylbenzocyclobutenyl-1-acetaldehyde (4-CHO). 1-Methylbenzocyclobutene-1-carboxylic acid[1] (0.02 mol) was heated with redistilled thionyl chloride (0.05 mol) in benzene (50 ml). Removal of excess reactants and subsequent distillation afforded the acid chloride[19] 4′- COCl, bp 65° (0.2 mm), 97% yield. Reaction of the acid chloride (0.025 mol) in dry ether (80 ml) with diazomethane (0.07 mol) in dry ether (400 ml) was complete in 2 hr at 25°. The ether was removed by rotary evaporation and the oily, residual diazoketone was dissolved in dry methanol (200 ml). Treatment of this solution with silver benzoate in triethylamine (5 g in 60 ml) over a 3-hr period, as described for this method,[20] led to evolution of nitrogen. The reaction mixture was processed to afford **methyl 1-methylbenzocyclobutenyl-1-acetate,** (4-COOMe), 79%, bp 88° (0.80 mm).[19] An alternative synthesis of this ester involved reaction of 1-methylbenzocyclobutenyl-1-carbinyl tosylate[1] (4-OTs) with sodium cyanide (1.1 equiv) in dimethyl sulfoxide (25 ml/mmol of tosylate) at 80° for ca. 12 hr. Dilution of the material with water and extraction with ether led to **1-methylbenzocyclobutenyl-1-acetonitrile,** (4-CN), 49%, bp 100–101° (1.5 mm).[19] Olefinic products which were identical with those observed[1] in the

solvolysis of 4-OTs were also formed in this reaction, rendering it a less satisfactory procedure. Methanolysis of 4-CN (0.04 mol) with water (0.04 mol) in methanol (45 ml) was achieved under reflux as dry hydrogen chloride was bubbled through the solution for 4 hr. Cold brine (50 ml) was added and the solution was extracted with ether. The ether extracts washed until neutral, dried ($MgSO_4$), and distilled. The ester 4-COOMe was obtained in 78% yield.

Saponification of this ester with 20% ethanolic sodium hydroxide and acidification then gave **1-methylbenzocyclobutenyl-1-acetic acid** (4-COOH), 97%, bp 142° (3.5 mm).[19] The acid was converted to its acid chloride as mentioned above, 97%, bp 111° (4.5 mm).[19] The acid chloride (0.04 mol) was added with stirring to a solution of ethylenimine (0.04 mol) and triethylamine (0.04 mol) in ether (20 ml) at 0°. After 30 min the solution was filtered and combined with an ether wash of the amine hydrochloride precipitate. Ethereal lithium aluminum hydride (8 ml of a 1.25 *M* solution) was then added to the combined ether solution of the aziridide dropwise at 0° over 30 min. Processing the mixture as described[21] gave aldehyde 4-CHO, 80%, bp 82–83° (0.75 mm).[19] The 2,4-dinitrophenylhydrazone was prepared in customary fashion, mp 113°.[19] Heating 4-CHO at 160° either neat or in chlorobenzene produced no significant change in its ir or NMR spectra. See ref 12.

An alternative, attempted synthesis of 4-CHO involved reduction of 4-COOH with ethereal lithium aluminum hydride to **1-methylbenzocyclobutenyl-1-ethanol** (4-CH_2OH), 98%, bp 100–101° (1.0 mm),[19] followed by conversion to its tosylate (4-CH_2OTs) with *p*-toluenesulfonyl chloride in pyridine in the usual fashion,[22] 90%. The tosylate[19] was an oil that was purified by passage through a short column of alumina. Attempted oxidation of this tosylate with sodium bicarbonate in dimethyl sulfoxide[23] failed. Only dark, ill-defined products resulted.

Another synthesis of 4-CHO proceeded by treatment of 4-COCl with lithium tri-*tert*-butoxyaluminohydride in diglyme using a literature method[24] (65% yield).

1-Methylindanyl-1-acetaldehyde (5-CHO). The aldehyde was prepared as reported.[25] Reaction of the known[25] acid with diazomethane in ether led to **methyl 1-methylindanyl-1-acetate** (5-COOMe), 94%, bp 122–123° (0.32 mm).[19]

1-Methyltetralyl-1-acetaldehyde (6-CHO). 4-Methyl-4-carboxymethyl-1-tetralone (prepared as reported,[26] 0.25 mol) was heated under reflux in a solution of potassium hydroxide (85% material, 1 mol), hydrazine hydrate (90%, 50 ml), and diethylene glycol (700 ml). Low-boiling material was allowed to escape until the temperature rose to 220°. After 12 hr at this temperature, the material was cooled and then acidified with hydrocholric acid. The solution was extracted several times with benzene and the combined extracts were dried and evaporated to produce **1-methyltetralyl-1-acetic acid** (6-COOH), 86%, mp 72–73° from methanol–water.[19] Reaction of this acid with diazomethane in ether afforded **methyl 1-methyltetralyl-1-acetate,** (6-COOMe), 94%, bp 98–99° (0.1 mm).[19]

Reduction of the above acid on a 20-mmol scale with ethereal lithium aluminum hydride in the well-known fashion gave **2-(1-methyltetralyl)ethanol** (6-CH_2OH), 91.5%, bp 143° (1.5 mm).[19] Reaction of the alcohol with *p*-toluenesulfonyl chloride in pyridine according to the published procedure[22] gave the corresponding tosylate 6-CH_2OTs, 96.5%, an oil purified by low-temperature crystallization from pentane, mp −20°.[19] Oxidation of the purified tosylate (30 mmol) was achieved by reaction with sodium bicarbonate (20 g) in dimethyl sulfoxide (150 ml) at 150°. Nitrogen was bubbled through the hot solution for 5 min and then ice water (200 ml) was added. The material was extracted with ether and processed to yield 6-CHO, 73%, bp 158–159° (10 mm).[19] The 2,4-dinitrophenylhydrazone was made in the usual fashion, mp 171–172°.[19]

Conversion of 6-COOH with thionyl chloride in benzene to the acid chloride was straightforward, 97%, bp 114–115° (0.4 mm).[19] Reaction of this acid chloride with lithium tri-*tert*-butoxyaluminohydride in the reported manner[24] gave 6-CHO in 43% yield. Reduction to 6-CHO by reaction of lithium aluminum hydride and the aziridide[21] from the acid chloride proceeded in 37% yield.

Synthesis of Reference Hydrocarbons. 1,1-Dimethylbenzocyclobutene (4-H). Reduction of 4-OTs (8.25 mmol) with lithium aluminum hydride (8.25 mmol) in ether (50 ml) was performed under reflux (5 hr). The solution was treated carefully with water followed by dilute acid and processed. Distillation afforded 4-H, 80%, bp 60–61° (20 mm), as an oil smelling like *tert*-butylbenzene.[19]

1,1-Dimethylindan (5-H)[27] and **1,1-dimethyltetralin** (6-H)[27] were obtained by the literature method cited, as were **2-methylindan** (7),[27] **2-methyltetralin** (8),[25] and **2-methylbenzsuberane** (9).[28]

Decarbonylation Studies. Peroxide-Induced. The general procedure is well documented.[10] Certain details are given in Tables I and III. All-glass apparatus[29] was used in all studies because the use of rubber or silicone septa for peroxide entry or reaction monitoring led to inconsistent results, usually evidenced by extensive induction periods and increased peroxide demand. A brief process description follows. Accurately weighed aldehyde (1–4 mmol, neat or 1 *M* in chlorobenzene) was placed in the apparatus which was then flushed with helium. Di-*tert*-butyl peroxide (10 mol %, redistilled, d_4^{24} 0.788) was added and the system was closed. The unit was placed in a 160° bath and the evolved gas collected. Volatile products were not collected but were returned to the reaction mixture. Two equal subsequent DTBP additions were made via a pressurized capillary. After the time period for study, the material in the system was analyzed by GLC: carbon monoxide was determined on a molecular sieves 13X column at 25° and the hydrocarbon products were determined on a series of columns, SE-30, Apiezon L, and Flexol 8N8. Calibration studies were done with mixtures of authentic samples. From the response curves obtained on the mixtures of known hydrocarbons, plus an accurate determination of the reaction mixture volume (±1 μl), calculations gave the amount of each substance present, excluding high molecular weight material for which no GLC data was obtained. In the case of 4-CHO, the viscous reaction residue was chromatographed on silica gel. Benzene eluted chlorobenzene (if any were used) and small amounts of unchanged 4-CHO. Methanol was necessary to elute the viscous yellow oil mentioned in the Discussion.

Because the more volatile hydrocarbon products were returned to the reaction mixture, their stability was determined under reaction conditions. The appropriate pair of hydrocarbons (e.g., 4-H and 7) were made 0.5 *M* in chlorobenzene (4 ml). Di-*tert*-butyl peroxide (0.2 mmol) and an internal standard (biphenyl or o-dichlorobenzene) was added and the mixture was heated under reflux for 5 hr. Only the mixture of 4-H and 7 showed significant transformation during this time period; 4-H unchanged, 36%; 7 unchanged, 42%. The other hydrocarbons showed minor changes.

The studies with carbon tetrachloride and benzoyl peroxide (Table III) were carried out as were the DTBP experiments. The methyl esters formed were confirmed and analyzed by GLC on a Reoplex column at 180° by comparison with authentic samples prepared as mentioned above.

Palladium-Promoted. Certain details may be found in Table II. The reactions were performed again in an all-glass apparatus.[29] After the indicated time period (when the aldehyde was consumed), carbon tetrachloride (2 ml) was added and the mixture was carefully filtered to remove the catalyst. Analyses for carbon monoxide and the hydrocarbon products were by GLC as mentioned earlier. Sensitivity experiments indicated that at least 1% (and in some cases less) of rearranged hydrocarbons could be detected on the GLC columns used.

Registry No.—4-H, 56846-74-3; 4-CO_2Me, 56846-75-4; 4-CN, 56846-76-5; 4-CO_2H, 56846-77-6; 4-COCl, 56846-78-7; 4-CHO, 56846-79-8; 4-CHO 2,4-DNP, 56846-80-1; 4-CH_2OH, 56846-81-2; 4-CH_2OTs, 56846-82-3; 5-CO_2Me, 56846-83-4; 5-CHO, 56846-84-5; 6-CO_2H, 56846-85-6; 6-CO_2Me, 56846-86-7; 6-CH_2OH, 56846-87-8; 6-CH_2OTs, 56846-88-9; 6-CHO, 56846-89-0; 6-CHO 2,4-DNP, 56846-90-3; 6-COCl, 56846-91-4; 1-methylbenzocyclobutene-1-carboxylic acid, 33223-77-7; di-*tert*-butyl peroxide, 110-05-4; palladium, 7440-05-3.

Supplementary Material Available. Tables IV and V containing physical (n_D^t and d_4^t values), spectral (functional ir and total NMR), and analytical data for compounds 4-COCl*, 4-H, 4-COOMe, 4-CN, 4-COOH, 4-COCl*, 4-CHO, 2,4-DNP of 4-CHO, 4-CH_2OH, 4-CH_2OTs*, 5-COOMe, 5-CHO, 6-COOH, 6-COOMe, 6-CH_2OH, 6-CH_2OTs*, 6-CHO, 2,4-DNP of 6-CHO and 6-COCl* [compounds with asterisk have physical and analytical data only; 5-CHO has spectral data only; the 2,4-DNP's and 6-COOH (solid) have only analytical data] will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiches, referring to code number JOC-75-3641.

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(11) Rüchardt[10] found that use of chlorobenzene as solvent in the decarbonylation complicated the rearrangement data owing to formation of *p*-chlorotoluene (from DTBP-engendered methyl radical attack). Such a problem was not observed in the cases of **4**–**6**-CHO, and was corrected in our study of **1** by use of several GLC columns which separated this contaminant from the hydrocarbon products.
(12) Benzocyclobutenes can isomerize thermally to *o*-quinodimethanes.[13] Although no gross change was apparent in the spectra of 4-CHO after heating, slight conversion to an *o*-quinodimethane (and attendant polymerization) cannot yet be totally discounted as a cause of the anomalous behavior observed with this aldehyde.
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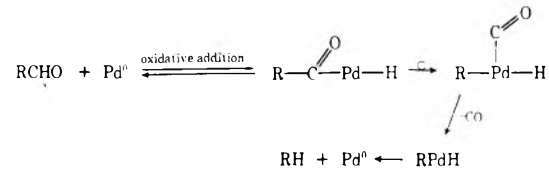

Another mechanistic possibility is a concerted, chelotropic reaction with loss of carbon monoxide and formation of hydrocarbon occuring in the allowed suprafacial manner only in the presence of transition metal catalyst (like palladium).[16]
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(29) The details of the apparatus are given in the dissertation of W.W.P., Jr.

Reaction of Organoboranes with Lithium Aldimines. A New Approach for the Synthesis of Partially Mixed Trialkylcarbinols[1]

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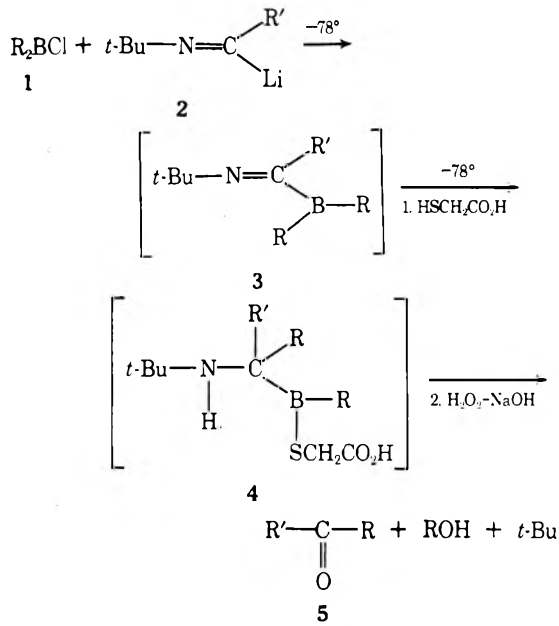
Partially mixed trialkylcarbinols are produced in good yields via the reaction of dialkylchloroboranes with lithium aldimines followed by treatment with (1) thioglycolic acid, (2) NaOH in diglyme, (3) H_2O_2–NaOH. Primary or secondary alkyl groups are introduced readily. The reaction of trialkylboranes with lithium aldimines also proceeds smoothly, affording the partially mixed trialkylcarbinols on treatment with (1) thioglycolic acid, (2) H_2O_2–NaOH.

In recent years, various procedures for the synthesis of trialkylcarbinols via organoboranes have been developed. Symmetrical trialkylcarbinols are produced from the reaction of trialkylboranes with carbon monoxide,[2] sodium cyanide,[3] or α,α-dichloromethyl methyl ether (DCME).[4] Partially mixed trialkylcarbinols are obtained by treatment of partially mixed trialkylboranes with carbon monoxide,[5] or by treatment of trialkylboranes with 1-lithio-1,1-bis(phenylthio)alkane.[6] On the other hand, totally mixed carbinols are available via the reaction of totally mixed hindered boranes with DCME,[7] or via dialkylmethylvinylboronates.[8] We now report a new approach for the synthesis of partially mixed trialkylcarbinols, where two alkyl groups of the carbinols arise from dialkylchloroboranes and the third is derived from Walborsky's masked acyl carbanions.[9]

Results and Discussion

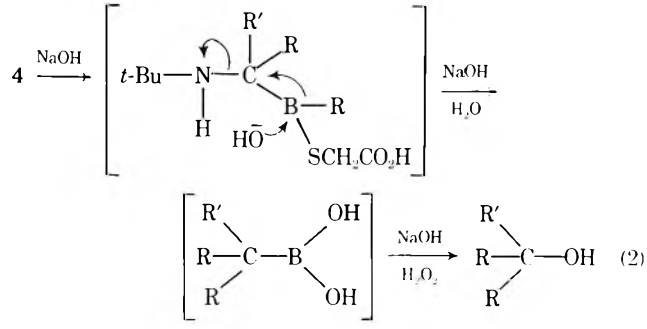
We previously reported that dialkylchloroboranes (**1**), now readily available via hydroboration with chloroborane–ethyl etherate,[10] reacted with lithium aldimines[9] (**2**) to give unsymmetrical ketones (**5**) on treatment with (1) thioglycolic acid, (2) aqueous alkaline hydrogen peroxide (eq 1).[11]



$$R'\text{—}\underset{\underset{O}{\|}}{C}\text{—}R + ROH + t\text{-}BuNH_2 \quad (1)$$

5

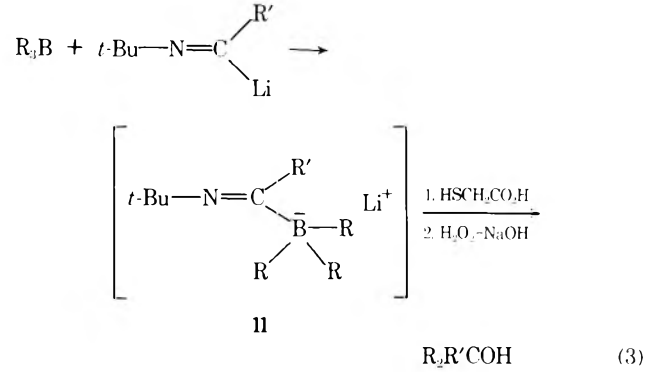
It was anticipated that the migration of an alkyl group (R) from boron to carbon in the initial intermediate (3) was induced by thioglycolic acid, leading to the intermediate borane (4). This was supported by the fact that the oxidation of 4 produced the alcohol (ROH) and *tert*-butylamine along with 5 and also by the previous results on the related reactions.[12] If so, partially mixed trialkylcarbinols may be obtained by achieving the migration of the second alkyl group (R) from boron to carbon in the intermediate (4). Accordingly, we examined the reaction of dihexylchloroborane with lithium aldimine derived from *n*-butyllithium. The yield of the product, 7-*n*-butyl-7-tridecanol (6), depended upon the reaction conditions as shown in Table I. Heating 4 at 80° in diglyme containing aqueous NaOH permitted the desired migration to produce the trialkylcarbinylborane derivatives. The alkaline hydrogen peroxide oxidation gave the partially mixed carbinols in good yields (eq 2).[13] The results are summarized in Table II.



(2)

There appears to be no difficulty in introducing primary and secondary alkyl groups. The present procedure offers the following advantages over the previous methods:[5,6] (1) the accommodation of the alkyl group such as isopropyl or methyl, which cannot be introduced via the hydroboration method,[5] (2) utilization of all three alkyl groups without loss of an alkyl group of the boranes.[6,14]

In contrast to the dialkylchloroboranes, the reaction of tri-*n*-hexylborane with the lithium aldimine prepared from *n*-butyllithium, followed by treatment with thioglycolic acid, produced, upon alkaline hydrogen peroxide oxidation, 6 in 87% yield (eq 3). The reaction could not be stopped at

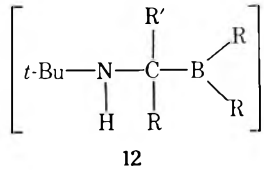


11

$R_2R'COH$ (3)

6 (R = *n*-Hex; R′ = *n*-Bu)

the stage of ketone formation (eq 1), suggesting that the migration in the borate complex (11) proceeds quite rapidly. It seems that this result is a reflection of difference between 4 and 12 which is presumably derived from 11. We



12

speculate that the trialkylborane derivative (12) undergoes the further rearrangement more easily than the dialkylborane derivative (4).[15] In fact, simple alkaline hydrogen peroxide oxidation of 11 produced 6 (19% yield) along with 5-undecanone (67% yield). Consequently, if the mildness is required, the reaction with trialkylboranes is recommended. However, the disadvantage is that the reaction uses but two of the three alkyl groups on boron. In order to overcome this difficulty and to prepare totally mixed trialkylcarbinols, the reaction of thexyldialkylboranes (thexyl-BR_2 and thexyl-BRR′) with lithium aldimines was also attempted. However, such an approach is so far unsuccessful.

Table I
Yield of 7-*n*-Butyl-7-tridecanol (6)[a]

Conditions	5-Undecanone (5), %	6, %
$HSCH_2CO_2H$, THF, reflux, 6 hr	44	
$(CF_3CO)_2O$, THF, reflux, 6 hr	16	47
$HSCH_2CO_2H$, 6 *M* NaOH, THF, reflux, 6 hr	Trace	73
$HSCH_2CO_2H$, 6 *M* NaOH, diglyme, reflux, 8 hr		87

[a] By GLC analysis. The yields were determined by the use of correction factors.

Table II
Partially Mixed Trialkylcarbinols *via* the Reaction of 1 with 2

Dialkylchloroborane	Alkyllithium	Product	Yield,[a] % (by isoln)
n-Hexyl	*n*-Butyl	7-*n*-Butyl-7-tridecanol (6)	87
n-Hexyl	Isopropyl	7-Isopropyl-7-tridecanol (7)	(75)
n-Hexyl	Methyl	7-Methyl-7-tridecanol (8)	(45)[b]
Cyclopentyl	Isopropyl	1,1-Dicyclopentyl-2-methyl-1-propanol (9)	77
n-Butyl	4-*n*-Pentenyl	5-*n*-Butyl-9-decen-5-ol (10)	(46)[b]

[a] The yields are based on GLC analysis, and are not necessarily optimum. [b] The low yield must be due to the unfavorable equilibrium of the lithium aldimine.[9]

Experimental Section

NMR spectra were recorded on a Jeol JNM-MH-60 instrument; chemical shifts (δ) are expressed in parts per million relative to Me_4Si. Ir spectra were recorded on a Hitachi 215 spectrophotometer. GLC analyses were performed on a Yanaco GCG-550T instrument, using a 2 m 10% SE-30 column. Elemental analyses were performed by Mr. Y. Harada at our Department. All temperatures were uncorrected.

Reagents. Reagent-grade solvents were purified by standard techniques and kept over a drying agent. B_2H_6–THF, BH_2Cl–OEt_2, tri-*n*-hexylborane, and dialkylchloroboranes were prepared according to the known procedures.[16] Butyllithium in hexane was a commercial product. Methyllithium in ether and isopropyllithium in pentane were prepared by standard procedures.[17] 4-*n*-Pentenyllithium was prepared from 5-bromo-1-pentene and lithium dispersion in ether at −30 to −20°.[18] The titration was performed by Gilman's[19] or Eastham's[20] method.

General Procedure. In a 200-ml flask maintained under N_2 and fitted with a septum inlet, magnetic stirrer, and reflux condenser were placed *tert*-butylisonitrile (3.6 ml, 30 mmol) and dry ether (60 ml). The solution was cooled to 0° and a solution of alkyllithium (30 mmol) was added dropwise. The mixture was stirred for 30 min at 0°, and then cooled to −78° with a dry ice–acetone bath. Dialkylchloroborane (30 mmol) was added, and the resultant

Table III
Physical Data for Alcohols[a]

Compd	Bp,° C (mm)	n^{20}D	NMR data, δ (CCl_4, 60 MHz)[b]	Ir, cm^{-1} (neat)
6	108–110 (1) 163–165 (10)[c]	1.4495 1.4489[c]	0.90 (t, 9 H), 1.21 (br s, 26 H)	3400, 1140
7	94–95 (0.2)	1.4517	0.83 (d, 6 H), 0.88 (t, 6 H) 1.26 (br s, 20 H), 1.66–2.00 (m, 1 H)	3495, 1140
8	87–88 (1) 160–162 (15)[d]	1.4450	0.89 (t, 6 H), 1.07 (s, 3 H) 1.29 (br s, 20 H)	3385, 1140
9	76–78 (0.3)	1.4967	0.93 (d, 6 H), 1.55 (br s, 16 H) 1.63–2.28 (m, 3 H)	3535, 1175
10	90–93 (1)	1.4557	0.95 (t, 6 H), 1.37 (br s, 16 H) 1.85–2.15 (m, 2 H), 4.79 (m, 1 H) 4.99–5.08 (m, 1 H), 5.34–6.15 (m, 1 H)	3400, 1639, 1130 988, 905

[a] The alcohols gave satisfactory elemental analyses the results of which have been provided to the Editor. [b] The absorption corresponding to OH is not listed; br s = broad s. [c] A. D. Petrov and M. V. Vittikh, *Bull. Acad. Sci. URSS, Cl. Sci. Chim.*, 238 (1944). [d] M. Asano and T. Yamakawa, *J. Pharm. Soc. Jpn.*, 70, 474 (1950).

mixture was kept at −78° for 30 min. Thioglycolic acid (4.2 ml, 60 mmol) was then added, and the reaction mixture was allowed to come to room temperature over 1 hr. The solvent was removed at reduced pressure and replaced with diglyme (60 ml) and 6 *M* aqueous NaOH (15 ml). The resultant mixture was refluxed for 8 hr (the temperature in the flask was at 80°). Oxidation was accomplished by the addition of 6 *M* aqueous NaOH (20 ml)–30% H_2O_2 (40 ml). Petroleum ether (60 ml) was added, and the organic phase was separated, washed with water (60 ml), and dried over anhydrous K_2CO_3. The solvents were removed and the product was obtained by distillation under reduced pressure. GLC yields were determined by the use of correction factors with appropriate hydrocarbons as an internal standard. All new products exhibited expected spectral characteristics and provided satisfactory elemental analyses (Table III).

Reaction of Dihexylchloroborane with Lithium Aldimine Derived from *n*-Butyllithium under Various Conditions. Essentially the same procedure as above was employed (10-mmol scale). Thioglycolic acid or trifluoroacetic anhydride was added at −78° after the addition of dihexylchloroborane, and the reaction was allowed to come to room temperature over 1 hr. The solvent was replaced with THF. The resultant mixture was refluxed for 6 hr, or refluxed after the addition of 6 *M* NaOH. The mixture was oxidized and analyzed with GLC (Table I).

Reaction of Trihexylborane with Lithium Aldimine Derived from *n*-Butyllithium. The lithium aldimine (3 mmol) was prepared by the same procedure as above. To the solution was added trihexylborane (0.85 g, 3.2 mmol) at 0°, and the resultant mixture was stirred for 5 hr at room temperature. Thioglycolic acid (0.85 g, 9.2 mmol) was then added at 0°, and the mixture was stirred for 2 hr at room temperature. Oxidation was accomplished by the same method as above. GLC analysis revealed the formation of **6** in 87% yield, which was determined by the use of correction factors.

Registry No.—**6**, 56846-92-5; **7**, 56846-93-6; **8**, 19016-75-2; **9**, 56846-94-7; **10**, 56846-95-8; chlorodihexylborane, 18379-62-9; chlorodicyclopentylborane, 36140-18-8; chlorodibutylborane, 1730-69-4; butyllithium, 109-72-8; isopropyllithium, 1888-75-1; methyllithium, 917-54-4; 4-*n*-pentenyllithium, 54313-25-6.

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(13) Although the intermediates in eq 2 are not isolated, the scheme is most consistent with the result.
(14) Utilization of thexyldioctylborane overcomes this difficulty.[6] However, thexylboranes containing bulky alkyl groups are relatively labile.
(15) If this speculation is correct, α-aminoalkyldialkylborane (**12**), a new class of organoboranes, may be preparable via this route. Such an attempt is now under way.
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Oxidation by Metal Salts. XIII. Oxidation of Arylcarboxylic Acids by Cobaltic Acetate

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The oxidative decarboxylation of arylacetic acids by cobaltic acetate was shown to be an electron transfer process involving aromatic radical cation intermediates, rather than the free-radical process previously assumed. Evidence for this mechanism included the realtively high ρ value of -2.9 observed for the decarboxylation of substituted arylacetic acids, the detection of aromatic radical cations by ESR spectroscopy, and the exclusive formation of γ-phenylbutyrolactone in the cobaltic oxidation of γ-phenylbutyric acids.

The oxidative decarboxylation of saturated as well as aryl-substituted carboxylic acids by either electrochemical means (Kolbe reaction)[1] or by high-valent metal ions[2-5] has been extensively studied. The mechanism generally proposed for these decarboxylations has involved homolytic decomposition of the carboxylate anion into carbon dioxide, and alkyl radical, and the reduced form of the metal oxidant. In essence, this mechanism viewed oxidative decarboxylation as an electron transfer process from the carboxylate anion to the higher valent metal ion oxidant, even in the case of arylacetic acids (eq 1).

$$RCO_2^- \xrightarrow{-e} RCO_2\cdot \longrightarrow R\cdot + CO_2 \qquad (1)$$

Recent variations[5] which describe the transition state as highly polar with extensive carbon–carbon cleavage can still be classified as oxidations of the carboxylate group by the mechanism shown above.

Our previous work on the oxidation of alkylbenzenes by cobaltic acetate[6] clearly suggests that, whereas the above mechanism may indeed be correct for the oxidative decarboxylation of saturated carboxylic acids, an entirely different mechanism should be operative in the case of aryl-substituted carboxylic acids. We now wish to report our results which clearly demonstrate that the cobaltic acetate oxidation of aryl-substituted carboxylic acids involves attack at the aromatic center rather than at the carboxylate group, as shown in the following equations for the oxidative decarboxylation of phenylacetic acid.

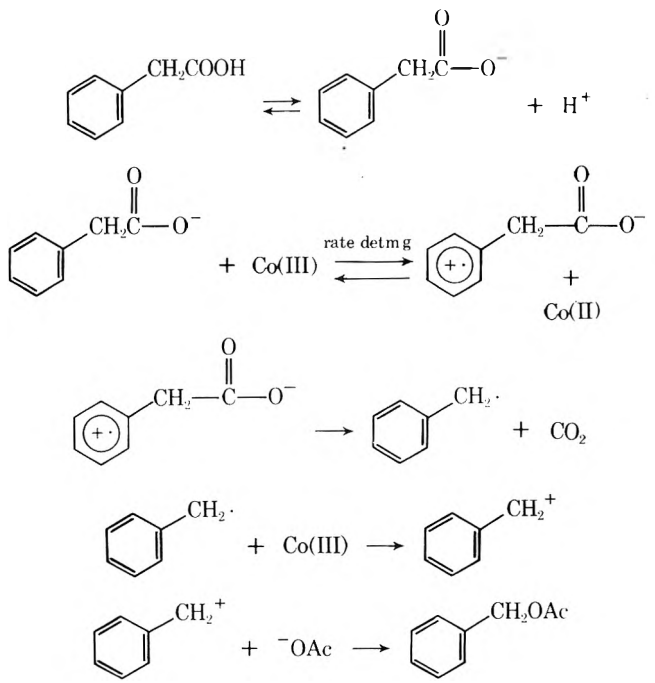


Table I
Formation of Benzylacetates from Arylacetic Acids

Arylacetic acid[a]	Acetate formed	Reaction time, min	Yield,[b] %
Phenylacetic acid	Benzyl	20	80
p-Methoxyphenylacetic	*p*-Methoxybenzyl	5	100
p-Tolylacetic	*p*-Methylbenzyl	15	90
m-Tolylacetic	*m*-Methylbenzyl	30	90
p-Chlorophenylacetic	*p*-Chlorobenzyl	30	70
m-Chlorophenylacetic	*m*-Chlorobenzyl	60	50

[a] Reaction conditions: 0.4 *M* arylacetic acid, 0.4 *M* $Co(OAc)_3$, 0.2 *M* $Cu(OAc)_2\cdot H_2O$ in refluxing HOAc. [b] Yield based on cobaltic ion, assuming 2 mol per mole of acetate produced.

Table II
Competitive Experiments[a] Relative Reactivity of Substituted Arylacetic Acids at 65°

Acid A	Acid B	k_B/k_A[b]
Phenyl	*p*-Tolyl	6.9 ± 0.15
Phenyl	*m*-Tolyl	1.75 ± 0.15
Phenyl	*p*-Chlorophenyl	0.75 ± 0.02
Phenyl	*m*-Chlorophenyl	0.17 ± 0.01
p-Tolyl	*p*-Methoxyphenyl	53. ± 5

[a] Reaction conditions: 0.5 *M* total arylacetic acids, 0.05 *M* $Co(OAc)_3$, 0.2 *M* $Cu(OAc)_2\cdot H_2O$, 65° in HOAc, reaction times 5–18 hr. [b] Values given are average of two or three independent experiments, each analyzed twice by vpc. Nonequimolar quantities of both acids were used to facilitate product analysis.

Such a mechanism has in fact been previously suggested for very special cases such as the ceric ion oxidation of methoxyphenylacetic acid[5] and the electrochemical oxidation of methoxyphenyl acetate and 10-methylanthracen-9-yl acetate;[7] although in all these cases the assertion was made that such a mechanism was not operative for simple phenylacetic acids.

The oxidative decarboxylation of arylacetic acids by cobaltic acetate in refluxing acetic acid,[8] containing added cupric acetate, resulted in the rapid formation of benzylacetates in very high yields, as shown in Table I.

In order to test our proposed mechanism, the competitive decarboxylation of a series of substituted arylacetic acids was studied. The relative rates of decarboxylation of these arylacetic acids were determined from the relative amounts of the corresponding benzylacetates produced under conditions where these acetates accounted for more than 80–90% of all products observed (Table II). These ra-

tios were essentially independent of the extent of reaction, or the amount of cupric ion added.

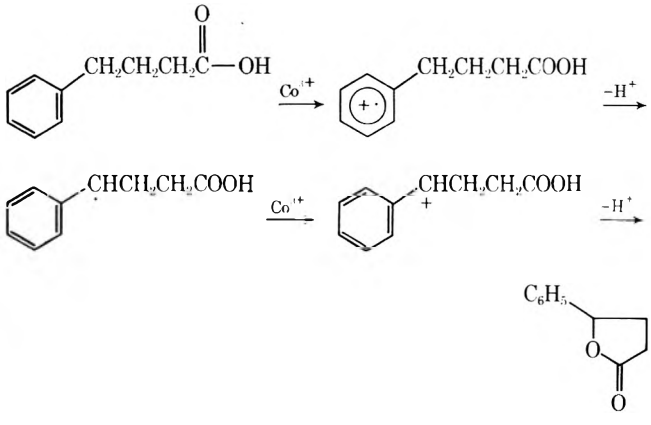
A Hammett σ–ρ plot of this data is presented in Figure 1. The good correlation with σ^+ values yielded a ρ of −2.9.

Note that the good correlation includes the data for the *p*-methoxy compound, indicating a common mechanism for all the arylacetic acids studied.

This high ρ value is inconsistent with any known free-radical process and indicates considerable positive charge development on the aromatic nucleus in the transition state. The large ρ value obtained agrees quite well with that observed by us for the cobaltic acetate oxidation of alkylaromatic hydrocarbons[6] (ρ = −2.4 at 65°), a process clearly shown to involve aromatic radical cation intermediates. The large ρ value of −2.9 stands in marked contrast to that reported[9] for the potassium persulfate promoted decarboxylation of substituted phenylacetic acids which gave a ρ of only −0.4. The small substituent effect in that case can best be rationalized by a mechanism involving the homolytic scission of a peroxidic intermediate such as $RC(=O)OOSO_3^-$ (formed by attack of a carboxylate anion on $S_2O_8^{2-}$) in a manner comparable to that suggested for the thermal decomposition of the corresponding *tert*-butyl peresters,[10] rather than by an electron transfer process, whether it be from the carboxylate anion[9] or the aromatic ring.[11]

Additional support for the intermediacy of aromatic radical cations in the cobaltic oxidation of arylacetic acids comes from the direct observation of the ESR spectrum of the *p*-methoxyphenylacetic acid radical cation in a flow system using trifluoroacetic acid.[12]

Further support for the mechanism involving initial attack at the aromatic ring in aryl-substituted carboxylic acids can be found in the products obtained from the cobaltic acetate oxidation of γ-phenylbutyric acids. Here no oxidative decarboxylation was detected and the only product observed was γ-phenylbutyrolactone, the formation of which is depicted in the mechanism shown below.



The yield of lactone was 25% based on cobaltic ion used; however, this yield could be increased to 60% by the addition of some LiCl[6] or trifluoroacetic acid,[12] reagents previously shown to accelerate the electron transfer process to cobaltic ion. The formation of a single product in the case of cobaltic acetate contrasts sharply with the variety of products obtained using lead tetraacetate which, unlike cobaltic acetate, oxidatively decarboxylates acids, including aryl-substituted acids, via a homolytic process involving alkyl free radicals.[4,13] These compounds from the reaction of lead tetraacetate included the decarboxylation products, *n*-propylbenzene and 3-phenylpropyl acetate, in addition to only a small amount of lactone formed by hydrogen abstraction[13,14] from phenylbutyric acid.

These observations clearly demonstrate that the oxidation of arylcarboxylic acids by cobaltic ion involves electron transfer from the aromatic ring as the initial step. It is quite likely that other oxidants that undergo single electron transfer[15] will also follow this mechanism.

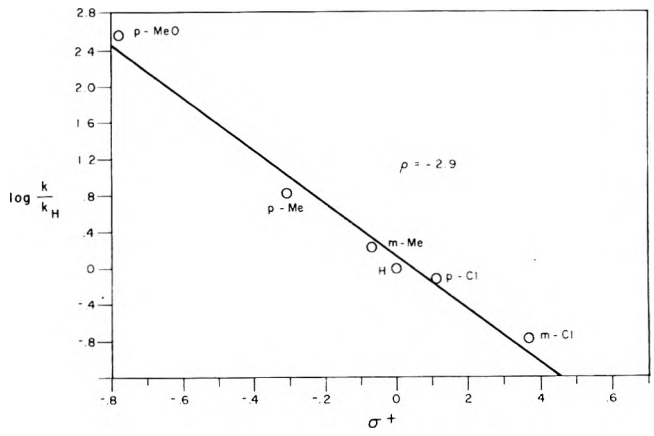


Figure 1. Relative rates of decarboxylation of arylacetic acids by cobaltic acetate at 65°.

Experimental Section

Preparation of Cobaltic Acetate Solution. A dilute stream of ozone was bubbled overnight through a solution of 375 g (1.5 mol) of $Co(OAc)_2 \cdot 4H_2O$ and 567 ml (6 mol) of acetic anhydride in 3 l. of glacial acetic acid. The resulting deep green solution was flushed with nitrogen for 2 hr and filtered. Titration of this solution by sodium thiosulfate indicated a 0.44 *M* cobaltic ion concentration.

Cobaltic Oxidation of Arylacetic Acids. Formation of Benzyl Acetates. Solutions of arylacetic acid (0.4 *M*), cobaltic acetate (0.4 *M*), and $Cu(OAc)_2 \cdot H_2O$ (0.2 *M*) in glacial acetic acid were heated at reflux under a nitrogen atmosphere for a period of 5–60 min, at which time the green color had disappeared. An internal standard was added prior to extraction and the yields of benzyl acetates formed were determined by vapor phase chromatography. Yields based on cobaltic ion consumed were calculated on the assumption that 2 equiv were required per mole of benzyl acetate formed.

Competitive Oxidations of Substituted Arylacetic Acids. Competitive oxidations of pairs of substituted arylacetic acids were conducted at 65° under nitrogen atmosphere. The solutions, 0.5 *M* in total arylacetic acids, 0.05 *M* $Co(OAc)_3$, and 0.2 *M* $Cu(OAc)_2 \cdot H_2O$ in glacial acetic acid, were heated for a period of 5–18 hr. The solutions, some of which still contained cobaltic ion, were then poured into 1 l. of water and extracted into ether. After drying, the ether layer was stripped on a rotary evaporator and the residue analyzed by vapor phase chromatography on an OV-17 column. The ratios of benzyl acetates, which represented 80–90% of the observable products, were determined from their relative areas in the chromatogram after correction for variations in molar sensitivities. To facilitate analyses, nonequimolar quantities of arylacetic acids were used in some cases, most notably in the case of *p*-methoxyphenylacetic acid where 1:4 molar ratios were used.

Cobaltic Oxidation of Phenylbutyric Acid. A solution of 5.7 g (0.035 mol) of 4-phenylbutyric acid in 50 ml of a 0.7 *M* $Co(OAc)_3$ solution was heated at reflux for 2 hr, at which time the green color had disappeared. An internal standard was added to the reaction mixture which was then extracted with ether and water. The ether layer was dried and stripped on the rotary evaporator and the residue analyzed by vapor phase chromatography on an OV-17 column. Essentially only one product was observed, γ-phenylbutyrolactone (25% yield based on cobaltic ion used), whose spectra and retention time were identical with those of an authentic sample. In a similar experiment, 7.4 g of 4-phenylbutyric acid was dissolved in 100 ml of a 0.45 *M* cobaltic acetate solution containing 7.6 g of LiCl. The reaction mixture was maintained at room temperature for 22 hr, at which time the color had changed from green to blue. Analysis of the reaction residue again indicated one product, γ-phenylbutyrolactone, now obtained in 50% yield.

Replacement of LiCl with 100 ml of CF_3COOH also yielded γ-phenylbutyrolactone in 60% yield.

Acknowledgment. The skillful technical assistance of Ms. M. Zikos is gratefully acknowledged.

Registry No.—Phenylacetic acid, 103-82-2; *p*-methoxyphenylacetic acid, 104-01-8; *p*-tolylacetic acid, 622-47-9; *m*-tolylacetic acid, 621-36-3; *p*-chlorophenylacetic acid, 1878-66-6; *m*-chlorophenylacetic acid, 1878-65-5; benzyl acetate, 140-11-4; *p*-methoxybenzyl acetate, 104-21-2; *p*-methylbenzyl acetate 2216-45-7; *m*-methylbenzyl acetate 17369-57-2; *p*-chlorobenzyl acetate, 5406-33-7; *m*-chlorobenzyl acetate, 21388-93-2; phenylbutyric acid, 1821-12-1; cobaltic acetate, 917-69-1.

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(14) The low yield of lactone produced by hydrogen abstraction was further dramatically reduced in the presence of 0.2 *M* cupric acetate, which simultaneously converted all of the propylbenzene to allylbenzene by oxidation of the intermediate 3-phenylpropyl radical.
(15) The data of ref 5, contrary to the conclusions stated therein, suggest that a similar mechanism is indeed operative in the case of ceric ion. The ρ value reported there, −2.9, is quite consistent with those we observed in the oxidation reactions of cobaltic ion. The high rate reported for the ceric oxidation of *p*-methoxyphenylacetic acid, which must have been extremely difficult to measure accurately by NMR, is just about what would have been expected for a reaction with such a large ρ. The high reactivity of the *m*-methoxy compound, which definitely does not fit the Hammett correlation (which we also found in our system, it being only slightly less reactive than *p*-tolylacetic acid), is exactly what would be expected on the basis of aromatic radical cation formation and the ease of electron transfer from anisole and its derivatives. On the basis of molecular orbital theory, it is clear that the symmetry of the highest occupied molecular orbital of the radical cation of *m*-methoxyphenylacetic acid differs from all the other derivatives in terms of electronic symmetry relative to the carboxymethylene group. Consequently, a *m*-methoxy substituent is not a minor perturbation of the aromatic ring and should not fit a Hammett plot.

Copper(I)-Induced Reductive Dehalogenation, Hydrolysis, or Coupling of Some Aryl and Vinyl Halides at Room Temperature

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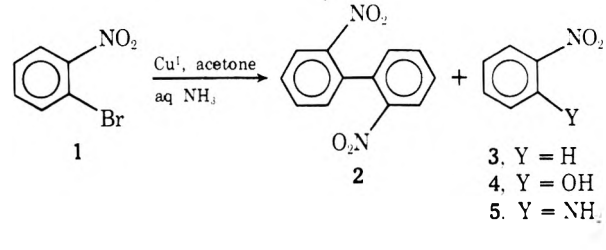
The room temperature reactions of some activated aryl and vinyl halides with acetone solutions of copper(I) trifluoromethanesulfonate, ammonia (aqueous or dry), and various quantities of copper(II) trifluoromethanesulfonate have been studied. Conditions have been found for the following conversions in good yield: *o*-bromonitrobenzene to 2,2′-dinitrobiphenyl, nitrobenzene, or *o*-nitrophenol; methyl o-iodobenzoate to methyl salicylate or methyl benzoate; diethyl iodofumarate to *trans,trans*-1,2,3,4-tetracarbethoxy-1,3-butadiene or diethyl fumarate; diethyl iodomaleate to diethyl maleate. Reductive dehalogenation and phenol formation are favored, respectively, by the presence of ammonium tetrafluoroborate and a substantial quantity of cupric ion. The retention of configuration observed for the protolysis products of the organocopper intermediates derived from the vinyl iodides has been interpreted as ruling out vinyl radicals as intermediates.

It was recently reported from this laboratory that the Ullmann coupling,[1] which is usually performed with copper powder at elevated temperatures, can, in the case of certain activated aryl halides, be performed at room temperature in homogeneous solutions containing copper(I) trifluoromethanesulfonate[2] (triflate) dissolved in equal volumes of acetone and 5% aqueous ammonia.[3] For example, while *p*-nitro- and o-fluoroiodobenzene failed to react, *o*-iodonitrobenzene and 2,4-dinitroiodobenzene coupled in a few minutes to form 2,2′-dinitrobiphenyl (**2**) and 2,2′,4,4′-tetranitrobiphenyl, respectively. However, with *o*-bromonitrobenzene (**1**) as substrate, under the same conditions, the reaction took far longer (about 24 hr) and only produced a 15% yield of biaryl (**2**) in addition to *o*-nitroaniline (**5**), the other significant product. Methyl *o*-iodobenzoate (**6**) was about as reactive as *o*-bromonitrobenzene (**1**) but, under these conditions, it produced mainly methyl anthranilate and no discernible coupling product. We summarize here a survey of reaction conditions for bromide displacement in *o*-bromonitrobenzene (**1**) and we report satisfactory conditions for the formation of good yields of any of the following products: biaryl (**2**), o-nitrophenol (**4**), or nitrobenzene (**3**). Conditions for halide displacement reactions in methyl o-iodobenzoate (**6**), diethyl iodofumarate (**10**), and diethyl iodomaleate (**13**) are also reported.

We have found that in the case of o-bromonitrobenzene far better yields of biaryl can be obtained by using a smaller volume of more concentrated aqueous ammonia. The yields can be further enhanced by the presence of a small quantity of copper(II) triflate. On the other hand, the presence of a much larger quantity of copper(II) triflate leads to a 74.6% yield of o-nitrophenol (**4**). A selection of our re-



1 2 3, Y = H 4, Y = OH 5. Y = NH_2

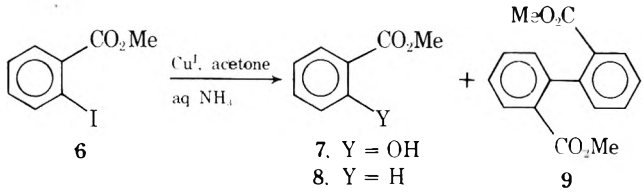
Table I
Reaction of o-Bromonitrobenzene with Copper(I) Triflate in Acetone Containing Aqueous Ammonia[a]

ml 20% aq NH_3	mmol Cu^{II}	Yields[b-d] Ar_2 (2)	ArH (3)	ArOH (4)	$ArNH_2$ (5)
25	0.20	17.5	56.0	2.5	20.5
5	0.20	70.0	9.2	18.3	3.2
4	0.20	80.7	6.4	9.7	2.6
2	0.20	62.6	0.8	32.9	
5	0.42	89.8	7.8	1.2	0.7
4	3.46	21.6	2.6	74.6	
4	5.19	18.2[e]	2.8[e]	50.8[e]	
4	11.1	10.2[f]	3.4[f]	4.1[f]	
5[g]	0.20	40.1	7.2	50.2	1.2
5[h]	0.42	16.4	80.4	*i*	0.9

[a] In all runs, 25 ml of acetone and 1.25 ml of acetonitrile were used and, unless otherwise stated, the reactions were run for 24 hr at room temperature; for other reaction conditions, see text. [b] Ar = o-nitrophenyl. [c] Gas chromatographic yields. [d] Unless otherwise indicated, not more than 1% of o-bromonitrobenzene remained unreacted. [e] 28% of unreacted aryl bromide remained. [f] 82.3% of unreacted aryl bromide remained. [g] Five hours at reflux. [h] 2.0 mmol of NH_4BF_4 was present; ref 5. [i] Not determined.

sults utilizing different quantities of 20% aqueous ammonia and of cupric triflate is shown in Table I; in all cases the copper(I) triflate was prepared by reducing 2.70 mmol of copper(II) triflate hydrate with 2.50 mmol of copper powder in a refluxing mixture of 25 ml of acetone and 1.25 ml of acetonitrile [which is required in order for the production of copper(I) to proceed], the aqueous ammonia, any extra copper(II) triflate, and the aryl bromide (0.250 mmol) were then added and, unless otherwise stated, the solution was stirred for 24 hr. Similar yields of biaryl could be obtained by using the optimum conditions of Table I [5 ml of ammonia water and 0.42 mmol of copper(II)] but replacing the acetone with 2-propanol or diglyme. A mechanistic study of the present reaction has revealed that, as in the heterogeneous Ullmann coupling,[1,4] there is an organocopper intermediate which is capturable by protonation;[5] thus, the presence of only 2.0 mmol of ammonium tetrafluoroborate causes the production of nitrobenzene in 80% yield[5] (last entry in Table I). Finally, in a preparative run, starting with a 20-fold greater quantity of o-bromonitrobenzene, a 90% crude yield and a 79% yield of recrystallized 2,2′-dinitrobiphenyl were obtained.

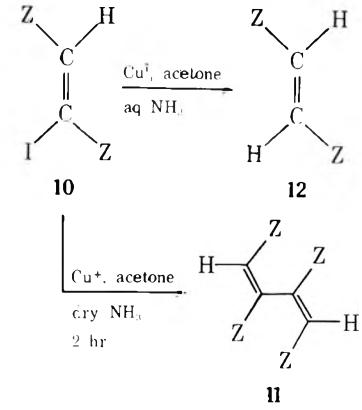
Methyl o-iodobenzoate (6), which previously yielded methyl anthranilate in the presence of 5% ammonia,[3] was found to provide mainly methyl salicylate (7), along with some dimethyl diphenate (9), in the presence of 20% aqueous ammonia. When the same reaction was performed in the presence of 3.46 mmol of copper(II) triflate (in 31.25 ml of solvent), this phenol was essentially the only product and was formed in 94% yield (GLC). In the absence of excess copper(II) triflate, but in the presence of 10.0 mmol of ammonium tetrafluoroborate, the product was entirely methyl benzoate (8), formed in 98% yield (GLC).



6 7, Y = OH 8, Y = H 9

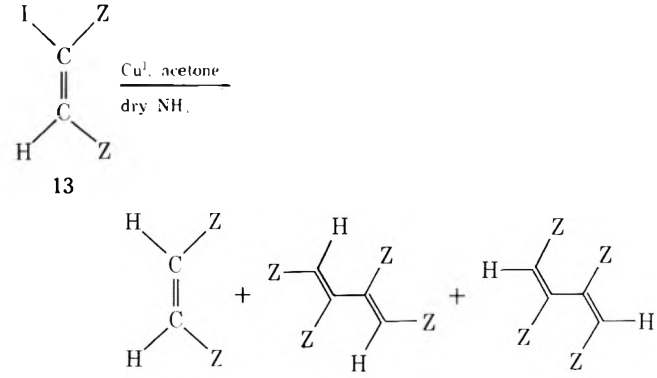
It has been shown recently that diethyl iodofumarate (10) couples to form the trans,trans tetraester 11 in good yield when heated with copper powder for 12 hr at 100°.[6]

Under the optimum conditions for coupling of o-bromonitrobenzene (fifth entry of Table I), 10 gives very little coupling product (11); the overwhelming product was diethyl fumarate (12). However, when the 25 ml of acetone and 5 ml of 20% aqueous ammonia was replaced with 20 ml of acetone and 5 ml of acetone saturated with ammonia gas, a 95% yield (GLC) of *trans,trans*-1,2,3,4-tetracarbethoxy-1,3-butadiene (11) was formed in 2 hr. From a scale-up run, this ester was isolated in 90% crude yield, from which 80% of pure crystalline material could be obtained. The crude material contained none of the geometrically isomeric dienes.[6]



Z = CO_2Et

When diethyl iodomaleate (13) was subjected to the successful coupling conditions used for the iodofumarate ester (dry ammonia) for 20 hr, 54.5% of 13 remained unreacted and 30% of diethyl maleate (14) was produced along with 8.6% of *cis,cis*-tetracarbethoxy-1,3-butadiene (15) and 2.1% of the trans,trans ester (11). When the same experiment

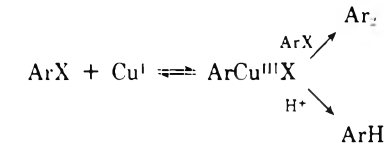


Z = CO_2Et

was performed for 10 hr at 40°, reaction was complete to yield 86% (GLC) of diethyl maleate (14). It is of interest that the reactivity sequence (trans > cis) and the stereoselectivity of the coupling process are rather comparable to those of the corresponding heterogeneous Ullmann coupling of these iodoesters.[6]

Our recent mechanistic study[5] of the homogeneous Ullmann coupling of o-bromonitrobenzene revealed that an arylcopper(III) intermediate, which is reversibly produced by oxidative addition of the CBr bond to copper(I), is capable of reacting with another aryl bromide molecule to form biaryl or of competitively becoming protonated by the medium. If these two processes are slow, it seems likely that a ligand (L) such as water or ammonia could displace the bromide in the intermediate to give another copper(III) compound which would undergo reductive elimination of copper(I) to produce the protonated phenol or aniline

(ArL). This reductive elimination is analogous to the reverse of the first step and such processes appear to be common in the mechanisms of the displacements of aryl and vinyl halides with the anions of copper(I) salts.[7] More work will obviously be required before reliable predictions can be made concerning the different reaction paths of the intermediate in an unstudied case.



$$ArCu^{III}X + L \longrightarrow X^- + ArCu^{III}L \longrightarrow ArL + Cu^I$$

Nevertheless, some synthetically useful generalizations have apparently been established. The replacement of halogen by hydrogen can be readily accomplished at room temperature by performing the reaction in the presence of ammonium ion, although in some cases this additive is not necessary; furthermore, in the case of the isomeric vinyl iodides studied, the reductive dehalogenation occurs with complete retention of configuration. Phenol production is encouraged by the presence of a fairly high concentration of copper(II). Finally, in the absence of these additives, except for a small quantity of copper(II), reductive coupling can be accomplished at room temperature in some cases, but, at least under the conditions we have investigated, not in others.

These results also provide valuable mechanistic information. Our recent mechanistic study provided strong evidence that the *o*-nitrophenyl radical is not an intermediate in the homogeneous Ullmann coupling of o-bromonitrobenzene.[5] The stereospecific reductive dehalogenation of the iodofumarate and iodomaleate esters under the same conditions constitutes completely independent evidence for the absence of radical intermediates since vinyl radicals are extremely unstable stereochemically.[6,8] The same stereochemical result obtains in the reductive dehalogenation of these esters by copper metal at elevated temperatures in the presence of benzoic acid.[6] Finally, an organocopper species has been shown to be an intermediate, not only in biaryl formation, as was demonstrated in our mechanistic study,[5] but also in phenol formation; this follows from its diversion to methyl benzoate by ammonium ion in the case of **6** which ordinarily gives mostly phenol **7**. However, the role of copper(II) in phenol formation has not yet been clarified.

Experimental Section[9]

Preparation of Solutions of Copper(I) Triflate. The procedure was the same in each case. The quantities of ingredients used in preparative experiments are specified under each preparation. The quantities that were used in gas chromatographic analytical experiments are included in the following description. A magnetically stirred mixture of copper(II) triflate (the light blue salt, $Cu(CF_3SO_3)_2 \cdot 5.5H_2O$,[3] obtained by drying the freshly prepared hydrate[2] for 1 hr at room temperature in a vacuum desiccator, 1.24 g, 2.70 mmol) and copper powder (0.159 g, 2.50 mmol) in 25 ml of acetone (except for the experiments using anhydrous ammonia, in which 20 ml of acetone was used) and 1.25 ml of acetonitrile was heated at reflux for 1 hr under a nitrogen atmosphere. The light blue mixture, which had become homogeneous, was then cooled to room temperature.

Analytical (Nonpreparative) Experiments. In all the experiments summarized in Table I, *o*-bromonitrobenzene (0.0506 g, 0.250 mmol, Eastman), the gas chromatographic standard 4,4′-dinitrobiphenyl (0.035 g, 0.125 mmol), and appropriate quantities of 20% aqueous ammonia and $Cu(CF_3SO_3)_2 \cdot 5.5H_2O$ were added to the solution of cuprous triflate and, unless otherwise specified in Table I, the solution was stirred under nitrogen for 24 hr at room temperature. In the other analytical experiments, methyl o-iodobenzoate (0.117 g, 0.500 mmol), diethyl iodofumarate (0.25 g, 0.80 mmol), or diethyl iodomaleate (0.25 g, 0.80 mmol), copper(II) triflate (0.10 g, 0.22 mmol or 1.50 g, 3.26 mmol, as specified in the Results section), and 5.0 ml of either 20% aqueous ammonia or acetone saturated with gaseous ammonia were added and the solution was allowed to stir under nitrogen for the specified time.

The solution was separated into ether-soluble and aqueous phases by a thorough extraction procedure and the ether extracts were dried (magnesium sulfate), the solvent removed, and the residue dissolved in acetone. The acetone solution was submitted to gas chromatographic analysis on a 10 ft × 0.125 in. column packed with 3% OV-17 on Gas-Chrom Q 100/120 with a program of 50–300° at 10°/min; the relative flame ionization detector response of the standard and products had been previously determined utilizing an electronic integrator. The products were identified by comparing their gas chromatographic behavior (by coinjection) with that of authentic samples. The products in the case of experiments with diethyl iodofumarate and iodomaleate were available from the previous study.[6] Other ester products were either commercially available or readily prepared by esterification (CH_3OH, HCl) of the commercially available acids.

Isolation of 2,2′-Dinitrobiphenyl. To a solution of copper(I) triflate, prepared from 3.72 g (8.10 mmol) of copper(II) triflate, 0.477 g (7.50 mmol) of copper powder, 75 ml of acetone, and 3.75 ml of acetonitrile, were added 1-bromo-2-nitrobenzene (1.01 g, 5.00 mmol) and 20% aqueous ammonia (15 ml) and the mixture was stirred under nitrogen for 24 hr. The mixture was separated into ether-soluble and aqueous phases by a thorough extraction procedure. Evaporation of the dried (magnesium sulfate) ether extract yielded 0.54 g (90%) of an orange-yellow solid; recrystallization from methanol provided 0.47 g (79%) of 2,2′-dinitrobiphenyl, mp 127.5–128.0° (lit.[10] mp 127–128°).

Isolation of *trans,trans*-1,2,3,4-Tetracarbethoxy-1,3-butadiene. To a solution of copper(I) triflate prepared from 2.5 g (5.4 mmol) of copper(II) triflate and 0.32 g (5.0 mmol) of copper powder in 35 ml of acetone and 2.5 ml of acetonitrile were added 1.00 g (3.3 mmol) of diethyl iodofumarate and 12 ml of dry acetone which had been saturated with gaseous ammonia. The solution was stirred under a nitrogen atmosphere for 4 hr. Work-up as in the preparation of 2,2′-dinitrobiphenyl yielded 0.51 g of a light yelllow oil (89% crude yield); crystallization from hexane yielded 0.46 g (80%) of the trans,trans ester, mp 41.5–43.0° (identical with that of an authentic sample[6]). The gas chromatogram of the crude material showed a single peak alone or when coinjected with an authentic sample of the trans,trans ester. The NMR spectrum of the crude product was also identical with that of the authentic sample.

Registry No.—**1**, 577-19-5; **2**, 2436-96-6; **3**, 98-95-3; **4**, 88-75-5; **5**, 88-74-4; **6**, 610-97-9; **10**, 38318-65-9; **11**, 38318-64-8; **13**, 38318-63-7; copper(I) triflate, 42152-44-3; copper(II) triflate, 34946-82-2; copper, 7440-50-8.

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Hydrogenolysis of Unsaturated Phosphate Esters

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A series of unsaturated phosphate esters has been synthesized and subjected to hydrogenolysis over Adams catalyst. It has been demonstrated that direct hydrogenolysis of vinylic esters occurs yielding the phosphoric acid and the alkene; the alkene is then further reduced to the alkane. It has also been shown that migration of a "distant" olefinic linkage to a site subject to hydrogenolysis occurs at a rate such that cleavage product may be obtained. Moreover, it has been shown that benzylic ester linkages are subject to facile hydrogenolysis over Adams catalyst but not homobenzylic ester linkages.

It had previously been reported that diethyl isopropenyl phosphate (I) absorbed 2 mol of hydrogen over Adams catalyst yielding as the observed product diethylphosphoric acid; when palladium was used as the catalyst, only 1 mol of hydrogen was absorbed and diethyl isopropyl phosphate was observed to be the product.[1] In the course of our investigations on the hydrogenolysis of aryl phosphate esters[2,3] it was observed that diethyl 1-cyclohexenyl phosphate (II) underwent hydrogenolysis over Adams catalyst with the formation of cyclohexane. With this observation it became of interest to investigate in detail the hydrogenolysis of saturated and unsaturated aliphatic phosphate esters. If a generality of reaction could be established here it would further extend the already well-known scheme of nonhydrolytic phosphate ester cleavages involving aryl and benzylic linkages.[2-6]

To test the generality of this reaction and to elucidate the sequence of reaction steps the series of vinylic phosphate esters I–V was prepared and subjected to standard hydrogenolysis conditions. In all cases direct observation of hydrocarbon product and any intermediates was attempted. In addition, reactions using deuterium were performed on the vinylic esters, their hydrocarbon cleavage products, and possible intermediates to help establish the sequence of reaction steps.

Several other molecular systems were also synthesized and subjected to hydrogenolysis conditions. First, a fully saturated compound was investigated in a consideration of two possible reaction sequences, i.e., cleavage followed by reduction as compared to initial reduction followed by cleavage. Moreover, as deuterium interchange was noted with possible intermediates containing sites of unsaturation, and as structural isomerization under hydrogenation conditions is well known,[7] it was of interest to prepare and investigate a phosphate ester with an olefinic site distant from a possible site of hydrogenolysis. Finally, benzylic and homobenzylic esters were investigated.

Experimental Section

Reagents. All reagents used in the preparation of the phosphate esters or their precursors were purchased from Aldrich Chemical Co. and used without further purification. Absolute ethanol, used as a standard solvent for the hydrogenolyses, was purchased from Commercial Solvents Corp. and used without further purification. The platinum oxide catalyst (83 ± 0.5%) was a generous gift of Engelhard Minerals and Chemicals Corp. Deuterium was from Matheson Corp. and was in excess of 99.5 atom % D.

General Synthesis of Diethyl Vinyl Phosphates. The standard reaction technique used for the Perkow reaction was followed.[8,9] To 0.20 mol of triethyl phosphite heated to 120° was added in small portions 0.20 mol of the appropriate α-chloro ketone. The reaction mixture was maintained at 120° for 1 hr after completion of the addition and then raised to 170° for an additional 1 hr, whereupon the product was vacuum distilled. Yield and analytical data are given below for each compound. Satisfactory ir, NMR, and mass spectra were obtained for all compounds, and elemental analyses for those not previously reported.[10]

Diethyl 2-Propenyl Phosphate (I):[1] yield 47%; bp 64° (0.9 Torr); mass spectrum, parent peak *m/e* 194 (25%), base peak *m/e* 99.

Diethyl 1-Cyclohexenyl Phosphate (II):[9] yield 35%; bp 105° (0.15 Torr); mass spectrum, parent peak *m/e* 234 (54%), base peak *m/e* 99.

Diethyl 1-Cyclopentenyl Phosphate (III): yield 78%; bp 83° (0.09 Torr); mass spectrum, parent peak *m/e* 220 (33%), base peak *m/e* 137. Anal. Calcd for $C_9H_{17}O_4P$: C, 48.88; H, 7.85. Found: C, 49.09; H, 7.73.

Diethyl 1-Cycloheptenyl Phosphate (IV): yield 78%; bp 80° (0.01 Torr); mass spectrum, parent peak *m/e* 248 (40%), base peak *m/e* 155. Anal. Calcd for $C_{11}H_{21}O_4P$: C, 53.56; H, 8.53. Found: C, 53.23; H, 8.47.

Diethyl α-Styryl Phosphate (V): yield 39%; bp 106° (0.04 Torr); mass spectrum, parent peak *m/e* 256 (37%), base peak *m/e* 106. Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.06; H, 6.78. Found: C, 56.21; H, 6.64.

General Synthesis of Diethyl Alkyl Phosphates. To 0.12 mol of the alcohol in 100 ml of dry benzene was added slowly 0.1 mol of sodium hydride (ether washed) and the solution was stirred for 2 hr. To this was added dropwise 0.1 mol of diethyl phosphorochloridate and the reaction mixture was stirred for several hours. There was then added 50 ml of pentane, causing precipitation of the salt, which was filtered with suction. The solvent was removed at reduced pressure and the residual phosphate was vacuum distilled. Yield and analytical data are given below for each compound.

Diethyl Cyclohexyl Phosphate (VI):[11] yield 45%; bp 103° (0.65 Torr); mass spectrum, parent peak *m/e* 236 (1%), base peak *m/e* 155.

Diethyl Benzyl Phosphate (VII):[12] yield 25%; bp 101° (0.8 Torr); mass spectrum, parent peak *m/e* 244 (67%), base peak *m/e* 91.

Diethyl 2-Phenylethyl Phosphate (VIII):[12] yield 43%; bp 147° (0.25 Torr); mass spectrum, parent peak *m/e* 256 (3%), base peak *m/e* 106.

Diethyl 5-Pent-1-enyl Phosphate (IX): yield 16%; bp 85° (0.75 Torr); mass spectrum, parent peak *m/e* 222 (12%), base peak *m/e* 99. Anal. Calcd for $C_9H_{19}O_4P$: C, 48.65; H, 8.56. Found: C, 48.93; H, 8.64.

General Procedure for 1 Atm and 4 Atm Hydrogen Reactions. The reactors and experimental conditions for hydrogenation were as previously described.[3] For the analytical experiments the reaction flask was charged with 25 ml of absolute ethanol ca. 0.020 *M* in the compound to be investigated and ca. 0.020 *M* in a reference material for gas–liquid chromatographic (GLC) analysis. For the studies involving the isolation and identification of products the concentration of the reactant was increased to ca. 1 *M*.

Deuterium Incorporation Studies. All experiments using deuterium were performed at 1 atm pressure with solutions ca. 1 *M* in phosphate ester. The extent of deuterium incorporation was determined by collection of product or "unreacted" starting material using gas–liquid chromatography and its analysis by mass spectrometry. The resultant spectra were compared with those of the corresponding undeuterated materials.

Analysis. Gas–liquid chromatographic analysis (and preparative GLC) were performed using two columns: a 10 ft × 0.25 in. column of 20% Carbowax 20M on Chromosorb W was used for analysis of reactions of III whereas a 5 ft × 0.25 in. column of 20% Apiezon L on Chromosorb W was used for all other reaction sys-

tems. For quantitative analysis all products were compared for GLC relative response factors with a reference material; cyclohexane was used as the reference material for all reaction systems except those involving II and VI and the deuteration studies, where methylcyclohexane was used as the reference material.

All ir spectra were measured using a Perkin-Elmer Model 237-B spectrometer; NMR spectra were measured using a Varian EM360 spectrometer and mass spectra were measured using a Varian MAT CH-7 instrument.

Results and Discussion

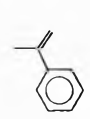
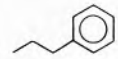
The diethyl vinyl phosphates I–V were subjected to hydrogenation in ethanol solution over Adams catalyst at 1 and 4 atm pressure of hydrogen. The products and yields (as determined by GLC) are listed in Table I. With the exception of I, where a true quantitative determination could not be made owing to volitalization of the product from the reaction mixture, quantitative or near quantitative cleavage of the vinylic ester group was observed. This is interesting as it points to the extremely facile nature of the hydrogenolysis process as compared to other possible reactions, such as olefin reduction and hydrogen exchange (vide infra). With reaction systems of II–V attempts were made to observe and isolate cleaved olefinic intermediate; GLC collection of the entire region of expected elution was performed and the effluent subjected to mass spectral analysis. No olefinic material could be observed even under these extremely sensitive conditions of analysis. Changing to a saturated hydrocarbon solvent, useful in slowing the reduction of aromatics,[2,3] again proved unsuccessful. Either the free olefinic hydrocarbon *is not* an intermediate, *or* it is formed in only low concentrations and is reduced to the alkane with a high rate. Several experiments were performed to consider these possibilities.

First, in a consideration of the possibility of initial *reduction* of the vinylic phosphate, the fully saturated system VI was prepared and subjected to the identical conditions as used for II. After 1 week using conditions of 1 atm pressure of hydrogen, diethyl cyclohexyl phosphate exhibited *no* cleavage and could be recovered unchanged. After 1 week under conditions of 4 atm pressure of hydrogen only 5% cleavage (to cyclohexane) could be observed. From this it may be concluded that initial reduction of the vinylic ester followed by hydrogenolysis does not occur.

Second, in a consideration of the possibility of the free alkene being an intermediate, but present at any one time in only low concentration, evidence of an indirect nature was gathered. Several experiments were performed using deuterium in deuterated alcohol (CH_3OD, CD_3OD, CH_3CH_2OD) and cyclohexane solvents. In these solvents with Adams catalyst and deuterium it was observed that the alkenes to be considered as intermediates underwent significant deuterium incorporation *in excess* of that expected by addition to the olefinic linkage. That this deuterium-for-hydrogen exchange occurred with the *alkene* and not its reduction product was shown by further experiments of the same type with the alkane itself; within experimental error no deuterium incorporation could be observed for the fully saturated compounds under these reaction conditions. Thereby, were the product alkane (from vinylic phosphate cleavage with deuterium) to exhibit incorporation of more than *three* atoms of deuterium it *could* be indicative of alkene intermediacy. For compound II, studied in CH_3OD and CD_3OD solution, use of deuterium for the cleavage reaction resulted in formation of cyclohexane exhibiting various quantities of deuterium incorporation, up to *seven* atoms of deuterium in significant amount. Similarly, for compound IV, studied in cyclohexane solution, incorporation of up to seven atoms of deuterium in significant amount was observed in the cycloheptane product.

Table I

$(CH_3CH_2O)_2P(=O)-OR \xrightarrow{H_2,\ PtO_2} (CH_3CH_2O)_2PO_2H + R'H$

R	Compd	Yield R'H (24 hr reaction time),[a] % 1 atm H_2	4 atm H_2
	I	>15[b]	>6[b]
	II	97.6	100.0
	III	97.3	100.0
	IV	96.7	100.0
	V	5.6	100.0
		94.4	0
	VI	0[c]	5[c]
	VII	8.6	86.0
		60.0	<1
	VIII	No hydrocarbon product	
	IX	5.0	<1

[a] Yields as measured by GLC using a calibrated internal reference. [b] Quantities as determined by GLC; these represent minimum values as significant amounts of material are lost due to volatilization of product during isolation. [c] One week reaction time.

It is critical to note here that excess deuterium incorporation can only arise with the alkene itself or a cleaved alkene–catalyst complex; mass spectral analysis of unreacted vinyl phosphate ester after reaction was allowed to proceed to more than 20% completion showed within experimental error *no deuterium incorporation*. This constitutes firm evidence that the overall mechanism of reaction involves first hydrogenolysis of the vinyl ester linkage (without catalyst-mediated hydrogen exchange) yielding the phosphoric acid and the alkene followed by reduction of the alkene to the alkane accompanied by catalyst-mediated hydrogen exchange. It should again be noted that the alkene might not be "free" but rather associated at all times after generation, prior to reduction, with the catalyst surface upon which exchange occurs. To consider this problem, fundamental to studies of catalytic surface reactions, further competitive kinetic experiments are being designed.

The selective reactivity of the vinyl phosphate ester linkage is worthy of note; while it undergoes facile hydrogenolysis, compared to ordinary alkenes it is quite unreactive toward reduction and catalyzed hydrogen exchange. This interesting nature of the linkage is to be a topic of further investigation.

Several other points may be raised by these experiments with deuterium. First, as it appears that catalyst-mediated exchange of hydrogens (and possibly thereby isomerization) occurs with ordinary olefinic linkages under these conditions at a rate competitive with reduction, there exists the possibility that a "distant" olefinic linkage in an alkyl

phosphate ester might be induced to migrate to a position from which cleavage might occur. To test this possibility the diethyl 5-pent-1-enyl phosphate (IX) was prepared and subjected to the standard conditions of hydrogenolysis. Unlike the result observed with VI, also an alkyl ester, with IX it is found that cleavage to yield pentane does occur at 1 atm pressure of hydrogen, albeit to a relatively low extent (5%), the remaining material being the reduced phosphate ester; complete reaction is obtained within 6 hr. Only reduction is observed at 4 atm pressure of hydrogen over extended periods of time.

Moreover, these results raise questions concerning the required location of the site of unsaturation if cleavage is to occur. The capability of a vinyl phosphate ester to undergo cleavage *without* isomerization is shown by the hydrogenolysis of compound I and the lack of deuterium incorporation into the unreacted vinyl phosphate esters. This does not eliminate the possibility that a more distant olefinic site might also be subject to hydrogenolysis; allylic and benzylic phosphate linkages are subject to hydrogenolysis over palladium catalysts, and in the present effort have been found to be subject to cleavage over Adams catalyst as well. Efforts to investigate the nature of allylic and benzylic ester cleavage over Adams catalyst have not proven fruitful; with the ester linkage being primary or secondary they are capable of undergoing hydrogen exchange (and isomerization) both prior to and after hydrogenolysis yielding no data of significance (for the current question) from their cleavage with or without deuterium. Tertiary esters would be unsatisfactory as they cleave by other routes.[13]

Summary

Vinyl phosphate esters undergo hydrogenolysis over Adams catalyst to yield the phosphoric acid and the alkene, the latter being reduced to the alkane. Olefinic linkages in other positions can undergo migration to the vinylic (or allylic) site by hydrogen exchange on the catalytic surface; once the site of unsaturation is in the vinylic ester position no further hydrogen exchange occurs. Benzylic, but not homobenzylic, phosphate esters also undergo hydrogenolysis over Adams catalyst.

Acknowledgment. This work was performed under support from a CUNY FRAP research grant.

Registry No.—I, 5954-28-9; II, 4452-32-8; III, 30842-23-0; IV, 31327-27-2; V, 1021-45-0; VI, 7301-86-2; VII, 884-90-2; VIII, 56830-42-3; IX, 56830-43-4; 1-chloro-2-propanone, 78-95-5; 2-chlorocyclohexanone, 822-87-7; 2-chlorocyclopentanone, 694-28-0; 2-chlorocycloheptanone, 766-66-5; 2-chloro-1-phenyl-1-ethanone, 532-27-4; triethyl phosphite, 122-52-1; cyclohexanol, 108-93-0; benzyl alcohol, 100-51-6; benzeneethanol, 60-12-8; 4-penten-1-ol, 821-09-0; diethyl phosphorochloridate, 814-49-3.

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Addition of Trichloroacetic Acid to 8-Methylcamphene

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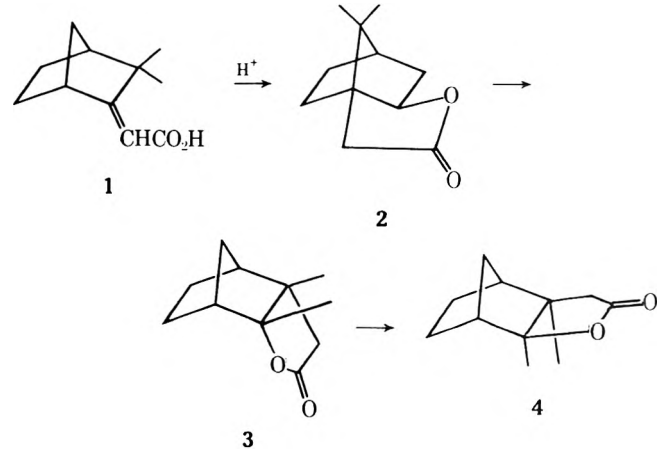
The reaction of 8-methylcamphene (5) with haloacetic acids gives a mixture of isobornyl esters which on hydrolysis followed by dehydration with phosphorus oxychloride in pyridine affords a mixture of 8-methylcamphene (5), 9-methylcamphene (8), and 10-methylcamphene (7). Authentic samples of 8-methylisoborneol (15) and 10-methylisoborneol (19) on dehydration with phosphorus oxychloride in pyridine gave 10-methylcamphene (7) and 8-methylcamphene (5), respectively, demonstrating that dehydration occurs by way of a Wagner–Meerwein shift without the intervention of 3,2-alkyl shifts.

The facile and sequential conversion of 8-camphenecarboxylic acid (1) to lactone **2**, endo lactone **3**, and exo lactone **4**[2] led us to investigate the action of acids on 8-methylcamphene (5) in order to determine whether similar alkyl shifts would provide a simple entry to the β-santalene ring system.[3]

A mixture of 8-methylcamphenes **5** and **6**[4] was obtained in 36% overall yield by the sequence shown in Chart I. Gas chromatographic analysis indicated the presence of *anti*-**5** and *syn*-**6** in a ratio of 93:7.[5]

The action of stannic chloride on **5** and **6** gave recovered starting material or polymer depending on conditions, while sulfuric acid produced polymers. Oxalic acid or cupric acetate in acetic acid[6] gave no rearrangement,[7] while pyruvic acid at 160° for 6 hr afforded 7% of isomerized olefins.[7] Subsequent to the completion of this work Vaughan[8]



1 2 3 4

Chart I

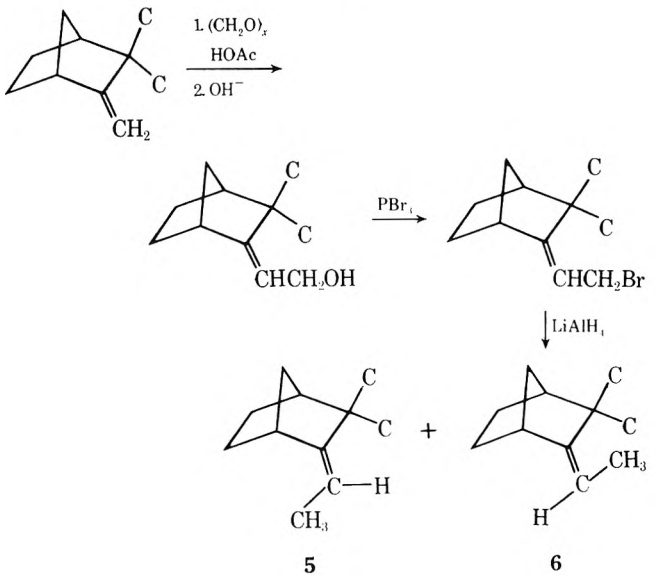


Table I
Reaction of 8-Methylcamphene with Organic Acids Followed by Hydrolysis and Dehydration[a]

Acid	Conditions	% 5 and 6	% 7 and 8
CH_3CO_2H + 0.5% H_2SO_4	60°, 30 hr	75	25
$ClCH_2CO_2H$	100°, 24 hr	80	20
Cl_3CCO_2H 1 equiv	100°, 24 hr	64	36
5 equiv	100°, 24 hr	50	50
10 equiv	100°, 24 hr	42	58

[a] NMR analysis by comparison of peak areas of the overlapping quartets at 4.90 ppm for olefins 5 and 6 and the pair of identical singlets at 4.42 and 4.66 ppm for olefins 7 and 8.

reported a 4% conversion of 5 to 10-methylcamphene (7) after heating with pyruvic acid for 7 hr in acetonitrile and that pure 7 gave 38% of 5 under the same conditions.

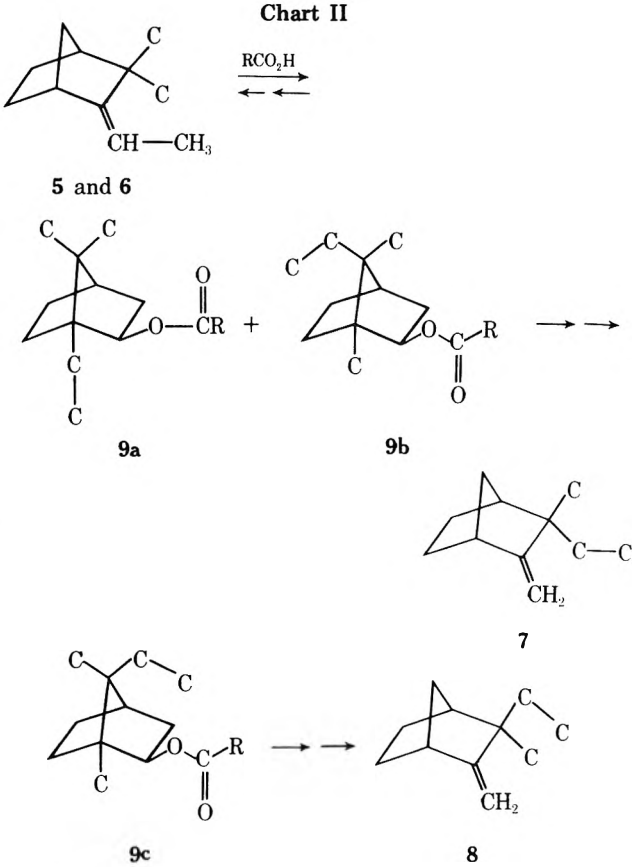
The action of strong organic acids such as trichloroacetic acid on 5 and 6 gave a mixture of isobornyl esters 9a–c for which a convenient method of separation was not found. The ester mixture was hydrolyzed and the resulting alcohols were dehydrated with phosphorus oxychloride in pyridine to a mixture of olefins 5, 6, 7, and 8 (See Chart II and Table I). It was independently established that dehydration of isoborneol derivatives with phosphorus oxychloride in pyridine proceeds by way of a Wagner–Meerwein shift without the intervention of 6,2-hydride or 3,2-methyl or ethyl shifts; consequently, the proportion of each olefin formed by dehydration provides a measure of the amount of the corresponding isoborneol derivative present in the original mixture.

Treatment of 9-methylcamphene (8) with trichloroacetic acid gave an ester mixture which was hydrolyzed and dehydrated to a mixture of 40% 5, 30% 7, and 30% 8.

A mixture of isobornyl esters was also obtained by heating pure trifluoroacetate 9b with a small amount of trifluoroacetic acid.

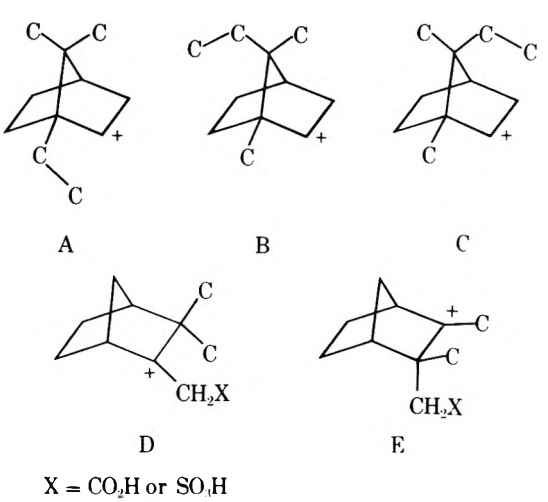
It is apparent that Wagner–Meerwein, 6,2-hydride, and 3,2-alkyl shifts occur competetively when the methylcamphenes or methylisobornyl trihaloacetates are heated in a haloacetic acid and that an acid-catalyzed isomerization of an 8-alkylcamphene derivative as a selective entry to the β-santalene system must fail since there appears to be little difference in stability between ions A, B, or C which are likely intermediates in these transformations. These results

Chart II



are in sharp contrast to those observed with pyruvic acid. Pyruvic acid apparently avoids trapping ions A, B, or C and favors the formation of the more thermodynamically stable 8-methylcamphene (5 and 6). The lack of rearrangement of the 8-alkylcamphenes claimed by Ritter[9] is suspect, since hydrogen chloride addition followed by base-catalyzed dehydrochlorination should parallel the behavior of trichloroacetic acid and afford rearranged olefins.

Finally, the difference in behavior of olefin 5, lactone 2, and camphene sultone[10] in strong acids derives from the proximity of the electron-withdrawing substituents to the carbonium ion center in the latter cases (ion D) which raises their energy considerably by comparison with that of ion E.



X = CO_2H or SO_3H

To confirm the stereochemical assignments of the isoborneols and characterize their mode of dehydration, authentic samples of 10-methylcamphene (7), 8-methylisoborneol (15), and 10-methylisoborneol (19) were prepared as illustrated in Charts III and IV.

Chart III

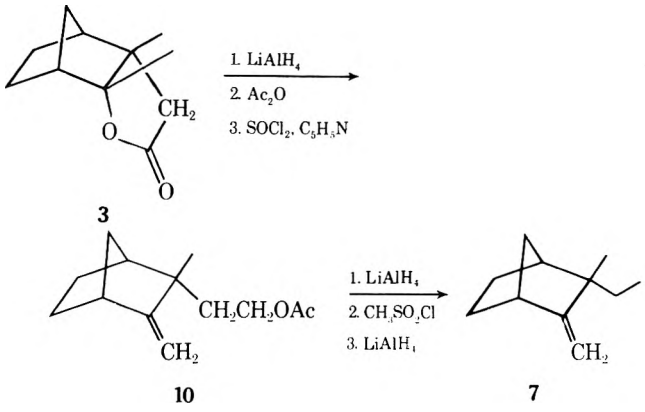
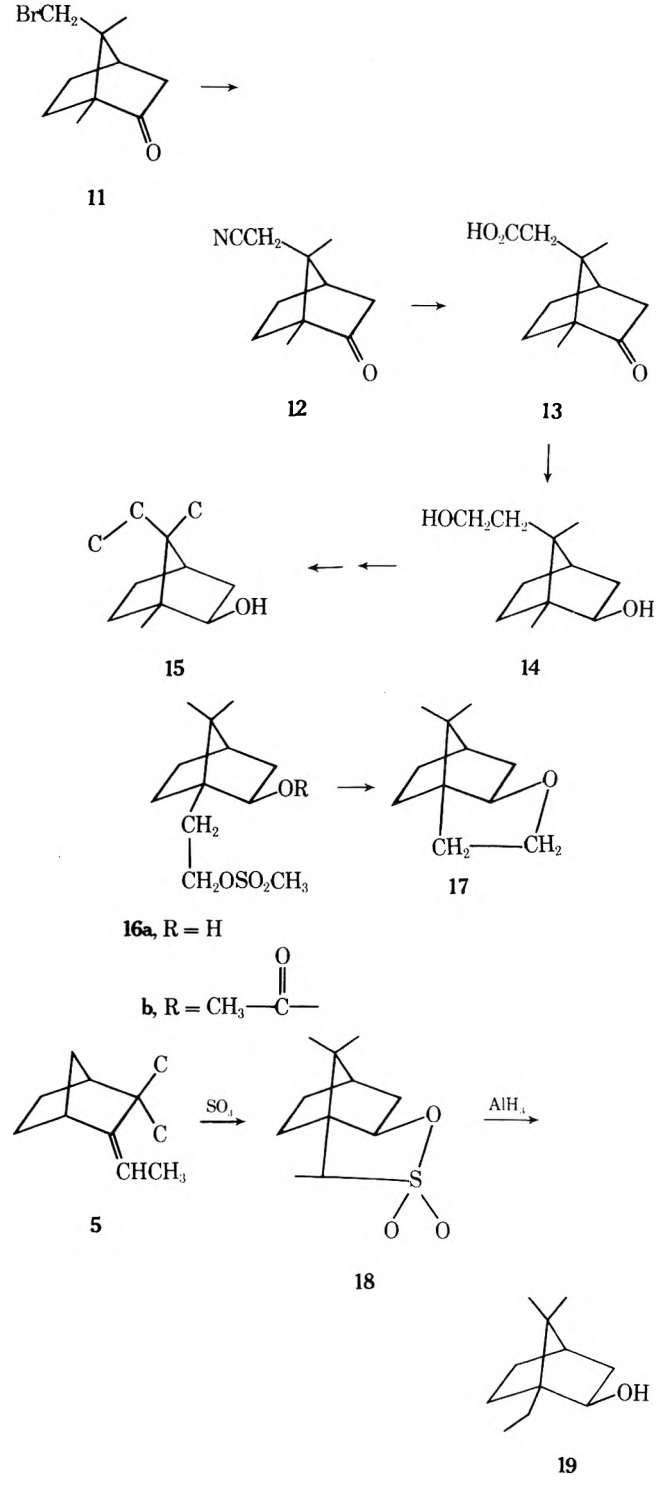


Chart IV



8-Cyanocamphor (**12**) was prepared from 8-bromocamphor (**11**)[11] in 40% yield by heating with potassium cyanide in Me_2SO. Hydrolysis of **12** gave camphor-8-carboxylic acid (**13**), which was reduced with lithium aluminum hydride in THF to 8-hydroxymethylisoborneol (**14**) which was freed of a small amount of 8-hydroxymethylborneol by recrystallization. Diol **14** was converted to a monotosylate derivative which was transformed into 8-methylisoborneol (**15**) by reduction with lithium aluminum hydride.

A variety of attempts to prepare 10-methylisoborneol (**19**) were unsuccessful. For example, hydride reduction of monomesylate **16a** or its acetate derivative **16b** afforded tricyclic ether **17**. 10-Methylisoborneol (**19**) was finally obtained by sulfonation of 8-methylcamphene (**5**) followed by aluminum hydride reduction of sultone **18**.[12]

Dehydration of 8-methylisoborneol (**15**) with phosphorus oxychloride in pyridine gave 10-methylcamphene (**7**), while dehydration of 10-methylisoborneol (**19**) afforded 8-methylcamphene (**5**). Further evidence[13] for the absence of 6,2-hydride or 3,2-alkyl shifts in these dehydrations was provided by the formation of optically active camphene on dehydration of (−)-isoborneol. It is reasonable to assume that dehydration of 9-methylisoborneol would lead exclusively to 9-methylcamphene (**8**), although a sample was not prepared to check this.

Experimental Section[14]

8-Methylcamphene (5 and 6). To a stirred slurry of 5 g (0.13 mol) of lithium aluminum hydride in 50 ml of dry ether at 0° was added (0.5 hr) a solution of 11.0 g (0.046 mol) of 8-bromomethylcamphene[2] [bp 68–72° (0.5 mm), $n^{20}D$ 1.5282] in 20 ml of ether. The mixture was stirred at ambient temperature for 48 hr and the excess hydride was destroyed by the addition of 25 ml of ethyl acetate. The salts were removed and washed with ether and the ether solution was washed with water, dried ($MgSO_4$), and evaporated to yield 5.6 g (85%) of 8-methylcamphene: ir 5.96 and 11.35 μ; NMR ($CDCl_3$) 0.98 and 1.00 (s, 6, CH_3CCH_3), 1.60 (d, 3, J = 7 Hz, C=CHC**H**$_3$), 2.92 (m, 1), and 4.96 ppm (q, 1, J = 7 Hz, –C=C**H**CH$_3$); mass spectrum m/e (rel intensity) 150 (39), 135 (100), 121 (42), 107 (89), 93 (43), 91 (17), 79 (23), 67 (20), and 41 (23).

GLC using a 6-ft 15% Carbowax 20M column at 95° indicated the presence of two isomers in a ratio of 13:1. The minor isomer was collected (retention time 28 min vs. 23 min for **5**) and exhibited ir ($CHCl_3$) 5.98 μ; NMR ($CDCl_3$) 1.13 and 1.18 (s, 6, CH_3CCH_3), 1.62 (d, 3, J = 6.5 Hz, C=CHC**H**$_3$), 2.49 (m, 1), and 5.12 ppm (q, 1, J = 6.5 Hz, C=C**H**CH$_3$).

10-Acetoxymethylcamphene (10). A solution of 2.0 g (11.1 mol) of endo lactone 3[2] was reduced with 0.6 g (15.8 mmol) of lithium aluminum hydride in ether. Work-up in the usual manner and recrystallization from hexane afforded 1.22 g of *exo,exo*-2,3-dimethyl-*endo*-3-(2-hydroxyethyl)-*endo*-2-norbornanol: mp 78–81°; NMR ($CDCl_3$) 0.95 (t, 3, CH_3C–), 1.18 (s, 3, CH_3CO–), 4.58 (m, 2, –CH_2O–), and 5.0–5.5 ppm (m, 2, –OH).

A solution of 1.20 g of the diol in 30 ml of acetic anhydride containing 0.3 ml of pyridine was kept at 50° overnight. Water (20 ml) was added and the mixture was heated for 1 hr, cooled, and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated, and the residue was taken up in methylene chloride, cooled to 0°, and treated with 10 ml of thionyl chloride in 10 ml of pyridine. The mixture was stirred for 30 min, poured over ice, and extracted with ether. The ether was washed with dilute hydrochloric acid and water, dried ($MgSO_4$), and evaporated to yield 1.18 g of crude unsaturated acetate **10**. A pure sample of **10** was obtained by GLC using a 15% SE-30 column at 145°: ir (CCl_4) 5.70, 6.00, and 11.34 μ; NMR (CCl_4) 1.02 (s, 3, CH_3C–), 1.92 (s, 3, CH_3CO–), 2.65 (m, 1), 4.03 (t, 2, –CH_2O–), and 4.45 and 4.68 ppm (s, 2, –C=C**H**$_2$).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.92.

10-Methylcamphene (7). Lithium aluminum hydride reduction of 1.00 g of unsaturated acetate **10** gave 0.8 g of 10-hydroxymethylcamphene: ir 2.95, 6.02, and 11.40 μ; NMR ($CDCl_3$) 1.02 (s, 3,

CH_3C–), 2.66 (m, 1), 3.68 (m, 2, $-CH_2O$), and 4.50 and 4.73 ppm (s, 2, $-C{=}CH_2$).

To an ice-cold solution of 0.8 g of 10-hydroxymethylcamphene in 20 ml of dry pyridine was added 1.6 g of mesyl chloride. The solution was kept at −20° for 24 hr and then poured onto ice and extracted with a mixture of ether and methylene chloride. The extracts were washed with 10% hydrochloric acid and water, dried ($MgSO_4$), and evaporated to yield an oil which could not be induced to crystallize. The crude mesylate was dissolved in 10 ml of ether and added to a slurry of 0.6 g of lithium aluminum hydride in ether. After stirring at ambient temperature for 18 hr, work-up in the usual manner yielded 0.70 g of an oil. An analytical sample of 10-methylcamphene (**7**) was obtained by GLC using a 15% SE-30 column at 90°: ir (neat) 6.05 and 11.31 μ; NMR (CCl_4) 0.97 (s, 3, CH_3C–), 2.65 (m, 1), and 4.42 and 4.66 (s, 2, $-C{=}CH_2$); mass spectrum *m/e* (rel intensity) 150 (14), 121 (100), 93 (95), 91 (30), 79 (53), 77 (30), 67 (35), 55 (28), 41 (51), and 39 (30).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.95; H, 12.19.

(±)-8-Cyanocamphor (12). A stirred mixture of 20 g (0.087 mol) of (±)-8-bromocamphor (**11**)[11] and 13 g (0.20 mol) of potassium cyanide in 150 ml of dimethyl sulfoxide was heated at 100° overnight. The solution was diluted with water and extracted with ether. The organic solution was dried ($MgSO_4$) and evaporated to leave a white solid which yielded 6.0 g (39%) of (±)-8-cyanocamphor after two recrystallizations from hexane: mp 163.5–165° [lit.[11b] (+)-**12**, mp 168°]; NMR 0.95 and 1.05 ppm (s, 6, 2 CH_3C–); mass spectrum *m/e* (rel intensity) 177 (26), 133 (100), 109 (28), 108 (23), 95 (72), 93 (23), 81 (54), 67 (26), and 41 (23).

(±)-Camphor-8-carboxylic Acid (13). A mixture of 5.8 g of 8-cyanocamphor (**12**), 5.6 g of potassium hydroxide, and 150 ml of water was heated at reflux for 44 hr. The mixture was cooled and extracted with ether. The aqueous solution was acidified with dilute sulfuric acid and extracted with a mixture of ether and methylene chloride. The organic solution was washed with water, dried ($MgSO_4$), and evaporated to yield 6.3 g (100%) of crude (±)-camphor-8-carboxylic acid (**13**). An analytical sample was prepared by sublimation in vacuo and showed mp 140–141°; ir ($CHCl_3$) 3.0–4.0, 5.73, and 5.83 μ; NMR ($CDCl_3$) 0.94 and 1.02 (s, 6, 2 CH_3C–) and 11.10 ppm (s, 1, $-CO_2H$).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.10; H, 8.25.

(±)-8-Hydroxymethylisoborneol (14). A mixture of 6.25 g of keto acid **13** and 2.60 g of lithium aluminum hydride in 50 ml of ether was refluxed for 24 hr. The usual work-up afforded 3.10 g of a mixture whose NMR spectrum indicated the presence of 80% of 8-hydroxymethylisoborneol (**14**) and 20% of 8-hydroxymethylborneol. Acidification of the residual salts obtained during reaction work-up gave a mixture of what appeared to be isoborneol and borneol-8-carboxylic acid which was not examined further. When the $LiAlH_4$ reduction was conducted in THF for 44 hr at reflux the yield of diols rose to 86%.

Pure diol **14** was obtained by recrystallization from ether–hexane and displayed mp 135–136°; NMR ($CDCl_3$) 0.90 and 1.02 (s, 6, 2 CH_3C–) and 3.3–3.9 ppm (m, 5, CH_2OH and CHOH); mass spectrum *m/e* (rel intensity) 184 (1), 166 (15), 140 (42), 139 (36), 125 (47), 121 (29), 111 (22), 107 (24), 96 (28), 95 (100), 93 (33), 81 (29), 67 (34), 55 (36), 43 (36) and 41 (44).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.79; H, 11.21.

(±)-8-Methylisoborneol (15). To an ice-cold solution of 5.25 g (28.6 mmol) of diol **14** in 50 ml of pyridine was added 6.55 g (57 mmol) of methanesulfonyl chloride. The reaction mixture was kept at −20° for 36 hr and yielded 5.30 g of an oil after usual work-up.

Attempted reduction using lithium aluminum hydride in ether at ambient temperature for 18 hr gave back the monomesylate. The mesylate was then heated with $LiAlH_4$ in THF for 36 hr. The usual work-up afforded 3.0 g (62%) of 8-methylisoborneol (**15**). An analytical sample of **15** was obtained by two sublimations in vacuo and showed mp 81–84°; NMR (CCl_4) 0.86 (m, 6, CH_3CH_2 superimposed on CH_3C–), 0.96 (s, 3, CH_3C–), 3.10 (s, 1, –OH), and 3.55 ppm (t, 5, 1, –CHO); mass spectrum *m/e* (rel intensity) 168 (3), 150 (12), 139 (30), 121 (32), 96 (25), 95 (100), 93 (25), 55 (28), 43 (30), 41 (42), and 39 (17).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.48; H, 12.20.

(±)-8-Methylcamphor. To an ice-cold solution of 300 mg of diol **14** in acetone was added 3 ml of Jones reagent.[15] After standing for 30 min the excess oxidant was destroyed by adding isopropyl alcohol. Removal of the salts by filtration and evaporation of the solvent left 290 mg of a yellow oil. Sublimation in vacuo gave pure 8-methylcamphor: mp 61–62°; ir (CCl_4) 5.71 μ; NMR (CCl_4) 0.86 (m, 6, CH_3CH_2– superimposed on CH_3C–), 0.98 (s, 3, CH_3C–), and 2.0–2.2 ppm (m, 2, $-CH_2CO$); mass spectrum *m/e* (rel intensity) 166 (29), 122 (20), 109 (31), 95 (100), 81 (23), 67 (30), 55 (31) and 41 (35).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.46; H, 10.74.

8-Methylisobornyl Trifluoroacetate (9b). A solution of 1.85 g (11.0 mmol) of 8-methylisoborneol (**14**) in 6 ml of trifluoroacetic anhydride was kept at ambient temperature for 22 hr. Ice was added cautiously and after stirring for 10 min the mixture was extracted with ether. The ether was washed with aqueous sodium carbonate, dried, and evaporated to yield 2.76 g (95%) of trifluoroacetate **9b**: ir 5.59, 8.2, and 8.52–8.68 μ; NMR (CCl_4) 0.90 (s, 3, CH_3C–), 0.97 (s and t, 6, CH_3C– and CH_3CH_2–), and 4.86 ppm (m, 1, CHO–); mass spectrum *m/e* (rel intensity) 264 (2), 150 (39), 121 (100), 95 (45), 93 (50), 79 (22) and 69 (29).

Anal. Calcd for $C_{13}H_{19}O_2F_3$: C, 59.08; H, 7.36; F, 21.56. Found: C, 59.13; H, 7.36; F, 21.60.

Attempted Preparation of 10-Methylisoborneol via 10-Hydroxymethylisoborneol. To an ice-cold solution of 1.0 g (5.45 mmol) of 10-hydroxymethylisoborneol,[2] mp 91.5–92.5°, in 25 ml of dry pyridine was added 1.25 g (10.9 mmol) of methanesulfonyl chloride. The mixture was kept at −25° for 23 hr and worked up to afford an oil which showed an NMR signal at 2.86 ppm and ir bands at 8.4, 8.5, and 12.6 μ characteristic of a mesylate. The only product isolated when this mesylate was treated with lithium aluminum hydride was 10,10-dimethyltricyclo[4.3.1^{1,7}.0^{1,5}]-4-oxadecane (**17**): mp 136–137° (lit.[16] mp 129–130°); NMR ($CDCl_3$) 0.84 and 1.14 (s, 6, CH_3CCH_3) and 3.58–4.20 ppm (m, 3, $-CH_2OCH$–).

Attempts to react the mesylate with sodium methyl mercaptide or sodium iodide gave tricyclic ether **17**. Acetylation of the mesylate using acetyl chloride and magnesium, followed by lithium aluminum hydride, also gave ether **17**.

Dehydration of 8-Methylisoborneol (15). To an ice-cooled solution of 346 mg (2.06 mmol) of 8-methylisoborneol (**15**) (containing ca. 20% of 8-methylborneol) in 10 ml of pyridine was added 1.0 ml of phosphorus oxychloride. The solution was stirred at 25° for 6 hr and at 100° for 2 hr. The mixture was cooled, cautiously poured onto ice, and extracted with ether. The ether was removed, affording 260 mg of a clear oil which showed a single peak on GLC using a 150-ft UCON-P capillary column at 120°. The ir, NMR, and GLC retention time were identical with those of an authentic sample of 10-methylcamphene (**7**).

Dehydration of 10-Methylisoborneol (19). Dehydration of 256 mg of 10-methylisoborneol (**19**) by the procedure described above gave 189 mg (80.5%) of 8-methylcamphene (**5** and a trace of **6**).

Dehydration of (−)-Isoborneol. Dehydration of (−)-isoborneol, prepared by lithium aluminum hydride reduction of (+)-camphor ($[\alpha]^{24}D$ +44.6°) containing a small amount of borneol, gave 463 mg of camphene, mp 51–52°, $[\alpha]^{24}D$ .96.7° (*c* 1.23, EtOH).

Dehydration of borneol under the same conditions afforded 45% of camphene and 45% of recovered borneol.

General Procedure for Reaction of 8-Methylcamphene with Trichloroacetic Acid. A mixture of 1.0 g (6.67 mmol) of 8-methylcamphene (**5** and **6**) and 5.6 g (33.2 mmol) of trichloroacetic acid was heated at 40° for 4 days. The mixture was cooled, poured into water, and extracted with ether. The ether solution was washed with water and saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated to give 1.4 g of a mixture of isobornyl trichloracetates.

The trichloracetate mixture was refluxed for 6 hr with 4 g of potassium hydroxide in ethanol. The solution was cooled, poured into water, and extracted with ether. The ether solution was washed with water, dried ($MgSO_4$), and evaporated to yield ca. 1.0 g of a semisolid mixture of isoborneols. This mixture was dehydrated using 2.0 g of phosphorus oxychloride in 10 ml of pyridine to afford a mixture of **5**, **6**, **7**, and **8** which was analyzed by NMR or GLC using a 150-ft UCON-P capillary column.

Reaction of 9-Methylcamphene (8) with Trichloroacetic Acid. A mixture of 600 mg (4 mmol) of 9-methylcamphene (**8**)[2] and 900 mg (5.5 mmol) of trichloroacetic acid was heated at 100° for 24 hr and worked up, hydrolyzed, and dehydrated as described above to yield a mixture of 55% of 9- and 10-methylcamphene (**7** and **8**) and 45% of 8-methylcamphene (**5**) as indicated by NMR analysis. Analysis using a 150-ft UCON-P capillary column indicated the presence of 40% of **5**, 30% of **7**, and 30% of **8**.

8-Methylisobornyl Trifluoroacetate (9b) and Trifluoroacetic Acid. A mixture of 831 mg (3.15 mmol) of trifluoroacetate **9b** and 75 mg (0.67 mmol) of trifluoroacetic acid was heated at 100° for 24 hr. The mixture was hydrolyzed and dehydrated in the usual manner to yield 321 mg of a mixture containing 74% of 8-methylcamphene (5) and 26% of 9- and 10-methylcamphenes (7 and 8).

Registry No.—**3**, 56906-70-8; **5**, 54382-52-4; **6**, 54382-53-5; **7**, 54345-89-0; **9b**, 56817-46-0; **10**, 56817-47-1; **11**, 3751-96-0; **12**, 56906-71-9; **13**, 56817-48-2; **14**, 56817-49-3; **15**, 56817-50-6; **16a**, 56817-51-7; **17**, 56906-72-0; **19**, 56817-52-8; 8-bromomethylcamphene, 6090-21-7; *exo,exo*-2,3-dimethyl-*endo*-3-(2-hydroxymethyl)-*endo*-2-norbornanol, 56817-53-9; 10-hydroxymethylcamphene, 56817-54-0; potassium cyanide, 151-50-8; 8-methylcamphor, 56817-55-1; trifluoroacetic anhydride, 407-25-0; (−)-isoborneol, 10334-13-1; (+)-camphene, 5794-03-6; trichloroacetic acid, 76-03-9; 10-hydroxymethylisoborneol, 56817-56-2; methanesulfonyl chloride, 124-63-0.

References and Notes

(1) Abstracted from part of the thesis submitted by E. J. E. in partial fulfillment of the requirements for the Ph.D. degree, Purdue University, June 1972.
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(5) The configurations of **5** and **6** are tentatively assigned on the basis of the C-9 and C-10 methyl shifts which appear at 1.13 and 1.18 ppm for **6** and at 0.97 and 0.99 ppm for **5**. The syn C-8 methyl in **6** should reduce the anisotropic shielding of the C-9 and C-10 methyl groups by the carbon–carbon double bond and result in a downfield shift from the corresponding methyl signals of *anti*-**5** and camphene (1.02 and 1.05 ppm).
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(14) All melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord. NMR spectra were measured with a Varian Associates A-60 spectrometer. Optical rotations were measured with a Zeiss polarimeter. Mass spectra were determined by the Purdue University Spectral Service employing a Hitachi RMU-6A spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.
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Bicyclic Amino Alcohols. The Isomeric 2-Dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-enes

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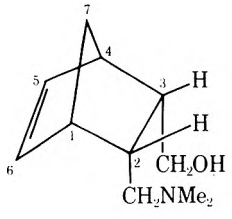
Preparation of the four isomeric 2-dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-enes is reported and characterization of the stereochemistry of each by NMR techniques is discussed. The cis isomers (**1** and **2**) were prepared from the cyclopentadiene–maleic anhydride Diels–Alder adduct, by reaction with dimethylamine, followed by reduction with $LiAlH_4$. The trans compounds (**3** and **4**) were prepared from appropriate adducts of cyclopentadiene and fumaric acid derivatives. Stereochemistry was assigned by NMR spin–spin decoupling techniques and use made of the anisotropic effects of the 5,6 unsaturation on the C-2 or C-3 methylene protons and on H-2, H-3.

Derivatives of amino alcohols in bicyclic systems have provided a number of interesting structures useful for the study of conformational and steric aspects of the action of drugs related to neurotransmitters, especially acetylcholine and its congeners. Previously, derivatives of the 2-alkylamino-3-hydroxybicyclo[2.2.2]octanes[1-3] and of boranes[4,5] have been reported. More recently, analogs of cholinergic drugs have been studied in semirigid butane systems, e.g., from *cis*- and *trans*-1-dimethylaminomethyl-2-hydroxymethylcyclopropane[6] and certain *cis*- and *trans*-2-butenes.[7]

We have prepared isomeric 2-dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-enes (**1**–**4**) to provide



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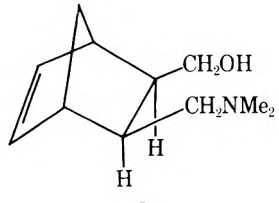

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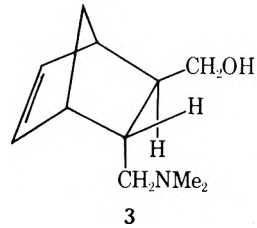

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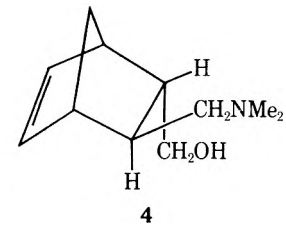
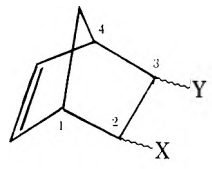


4

precursors for preparation of analogs of a muscarinic ganglionic stimulant, McN-A-343.[7,8] In this paper the synthesis of these amino alcohols is reported and facile characterization of the stereochemistry of each is demonstrated by use of NMR spectroscopic techniques.

Our initial efforts were concerned with the preparation of the three isomeric 2,3-di(hydroxymethyl)bicyclo[2.2.1]hept-5-enes (**8**, **11**, and **14**), available from the Diels–Alder adducts of cyclopentadiene with maleic anhydride or with dimethyl fumarate. Endo anhydride **5**, the kinetic product of the former addition,[9] was readily converted at 190° to a mixture of anhydrides from which exo anhydride **6** was obtained by crystallization.[10] 2-*endo*-3-*exo*-Dicarbomethoxybicyclo[2.2.1]hept-5-ene (**7**) was prepared by the



cis

	C-2	C-3
8	X = *endo*-CH_2OH	Y = *endo*-CH_2OH
9	X = *endo*-CH_2OH	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl
10	X = *endo*-CH_2OTs	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl
11	X = *exo*-CH_2OH	Y = *exo*-CH_2OH
12	X = *exo*-CH_2OH	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
13	X = *exo*-CH_2OTs	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
	trans	
14	X = *endo*-CH_2OH	Y = *exo*-CH_2OH
15	X = *endo*-CH_2OH	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
16	X = *endo*-CH_2OTs	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
17	X = *exo*-CH_2OH	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl
18	X = *exo*-CH_2OTs	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl

method of Koch.[11] The isomeric cis hydroxymethyl compounds 8 and 11 and trans hydroxymethyl compound 14 were then prepared by hydride reduction.

Since our interests in this system ultimately required carbamate derivatives of the bicyclic amino alcohols as potential muscarinic, ganglionic stimulants, we converted the diols into mono-*N*-(4-chlorophenyl)carbamates. These carbamate derivatives (**9, 12, 15, 17**) were also advantageous because they are relatively inert to functionalizing the other hydroxyl group and can be readily removed by $LiAlH_4$ reduction, thus facilitating the preparation of other esters of the amino alcohols.

The cis diols, **8** and **11**, were readily converted to their monocarbamate esters, **9** and **12**, then to the corresponding tosylates, **10** and **13**. Attempted displacement of the tosylate group with dimethylamine failed, even at 80°, probably partly owing to steric hindrance to approach presented by the cis carbamate ester adjacent to the tosylate in this system.

Even though this process failed, the same transformations were attempted in the trans series because it was thought that the lack of an adjacent cis substituent would present less steric hindrance to the displacement. Diol **14** was converted to a mixture of monocarbamates (**15** and **17**), which were partially separated by column chromatography.

The NMR spectra were extremely useful in monitoring this separation. As noted previously in bicyclo[2.2.1]hept-5-enes, an exo proton at H-2 (or H-3) is downfield from one in the endo position on the same carbon in the skeleton.[12] This shielding effect of the 5,6 double bond on endo protons and slight deshielding effects for exo protons have been noted in related systems.[13] Even the methyl esters derived from anhydrides **5** and **6**, and of **7**, show different methyl resonances, with the exo ester group being downfield.[14,15]

Early chromatographic fractions contained primarily the 3-*endo*-methylene carbamate, **17**, as evidenced by the doublets at δ 3.90 and 3.64 assigned to methylenes at C-3 and C-2, respectively (Figure 1). Decoupling of H-3 at δ 1.95 and H-2 at δ 1.2 confirmed these assignments. As expected the exo methine proton H-3 is downfield from the endo methine proton, H-2.

Later fractions showed two additional methylene doublets, one further downfield at δ 4.17 and one upfield at δ 3.40 assigned to methylenes at C-3 and C-2 in compound **15**. Decoupling experiments performed on a nearly pure fraction of **15** confirmed these assignments.

It is therefore readily apparent that the compound hav-

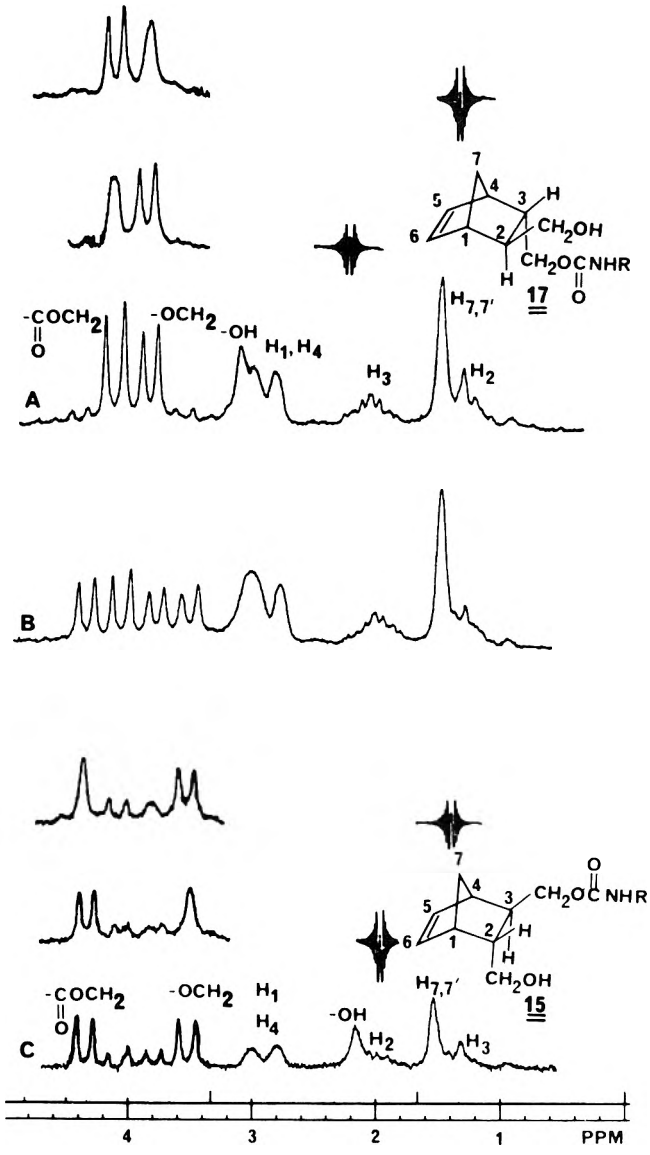
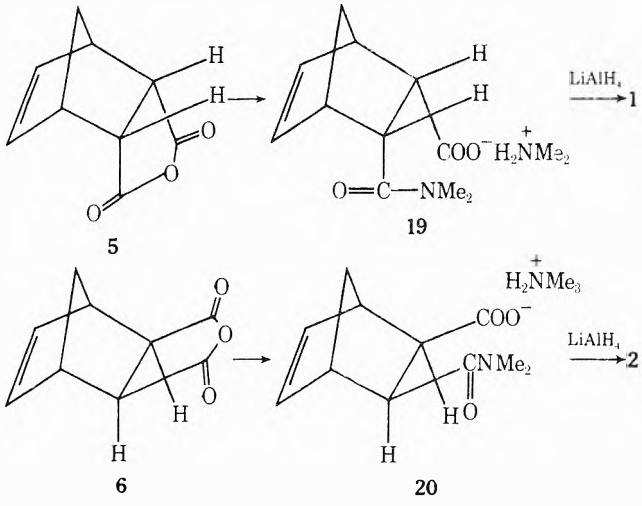


Figure 1. Portions of the 60-MHz ($CDCl_3$) NMR spectra of fractions from the chromatographic separation of **17** from **15**: A, early fraction containing nearly pure **17**; B, fraction containing nearly equal amounts of **17** and **15**; C, last fraction containing mostly **15**.

ing the methylene adjacent to the carbamate further downfield in the NMR would have the *exo-N*-(4-chlorophenyl)carbamoyloxymethylene substituent at C-3. Consequently, the hydroxymethylene group would be in the endo position and further upfield. These assignments are consistent with the spectrum for the later eluted compound, **15.**

The purified carbamate **17** was converted to its tosylate ester and displacement attempted with dimethylamine. After an attempt to displace the tosyl group under mild conditions failed, more drastic conditions of temperature and time were attempted, 100° in a bomb for 3 days. Only *N,N*-dimethyl-*n'*-(4-chlorophenyl)urea, a result of aminolysis of the carbamate ester, was isolated. This scheme was abandoned.

A more direct method was found for preparation of the desired bicyclic amino alcohols. The isomeric endo and exo anhydrides (**5** and **6**) were converted to the salts of the corresponding monoamide monocarboxylic acids (**19** and **20**) using excess dimethylamine. Attempted isolation of the



5 **19** **6** **20**

free amide acids by neutralization of the salts with hydrochloric acid resulted in re-formation of the anhydrides.

Direct $LiAlH_4$ reduction on the salts produced the desired amino alcohols. In this reduction, usually only amino alcohols were isolated. However, in the reduction of **20** small amounts of the diamine were formed, as evidenced by obtaining a small amount of the bis quaternary ammonium salt after reaction with methyl iodide. The diamine is the result of attack of dimethylamine on an aldehyde intermediate in the hydride reduction.

Preparation of the trans compounds **3** and **4** was pursued by a similar procedure. This process required preparation of the two possible isomeric monoamide monoesters of the Diels–Alder adduct of a furmaric acid derivative and cyclopentadiene (**27** and **28**). It was believed that this could be readily accomplished by an appropriate choice of the sequence of synthetic steps.

We expected the reaction of the Diels–Alder adduct of cyclopentadiene and fumaryl chloride (**24**) with 1 equiv of methanol to provide a mixture of monoester monoacid chlorides **25** and **26** consisting primarily of exo ester **25.** This strategy is consistent with other reports concerning steric preferance for attack at an exo position over the endo one in related bicyclic systems.[16-18]

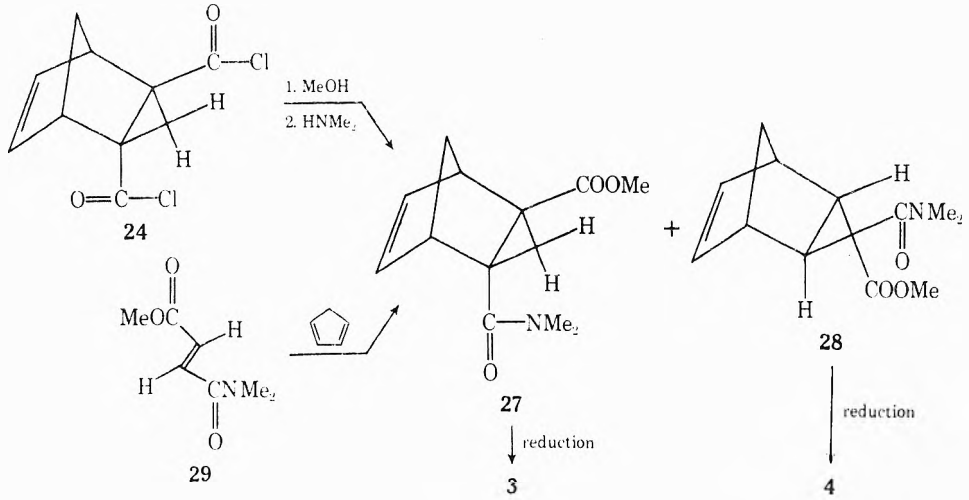
From diacyl chloride **24** was obtained a 2:1 ratio of exo ester **25** to endo ester **26.** Subsequent reaction of this mixture with dimethylamine afforded a similar ratio of **27** to **28.**

We also reasoned that the Diels–Alder addition of cyclopentadiene to the methyl ester of *N,N*-dimethylfumaramic acid (**29**) would afford primarily exo amide **28** based on steric effects (bulkier amide function) and/or electronic effects.[19,20] Although this process was successful, affording a 1:2 ratio of **27** to **28,** there appears to be no real consistencies in the prediction of exo:endo ratio of products obtained from the addition of α,β-difunctional dienophiles to cyclopentadiene. Predictions based on steric size and/or electronic considerations have provided variable results.[19-22]

Separation of **27** and **28** was readily accomplished by column chromatography using ether as eluent and NMR spectra to monitor the process. As previously noted in 2-*endo*-3-*exo*-dicarbomethoxybicyclo[2.2.1]hept-5-ene (**7**), the exo ester methyl group is consistently downfield from the endo one.[14,15] Similar results have been noted in the 2-exo and 2-endo methyl esters of 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid.[13] In this case, the MeO groups were at δ 3.66 for the endo ester (exo amide) of **28** and δ 3.73 for the exo ester (endo amide) of **27.**

Hydride reduction of the individual ester amides, **27** and **28,** afforded amino alcohols **3** and **4,** respectively. Double irridiation of the NMR signals of the methine multiplets due to H-2 and H-3 confirmed the stereochemical assignments. Irradiation of the downfield exo proton, H-3 in compound **4,** caused collapse of the two downfield multiplets of the hydroxymethylene protons into essentially two doublets. Correspondingly, irradiation of the upfield signal of the endo C-3 methine proton in **3** causes collapse of the hydroxymethylene multiplets into two doublets, J_{gem} = 10 Hz.

In both trans amino alcohols (**3** and **4**) the hydroxymethylene protons were observed as two separate multiplets,



24 **29** **27** **28** **3** **4**

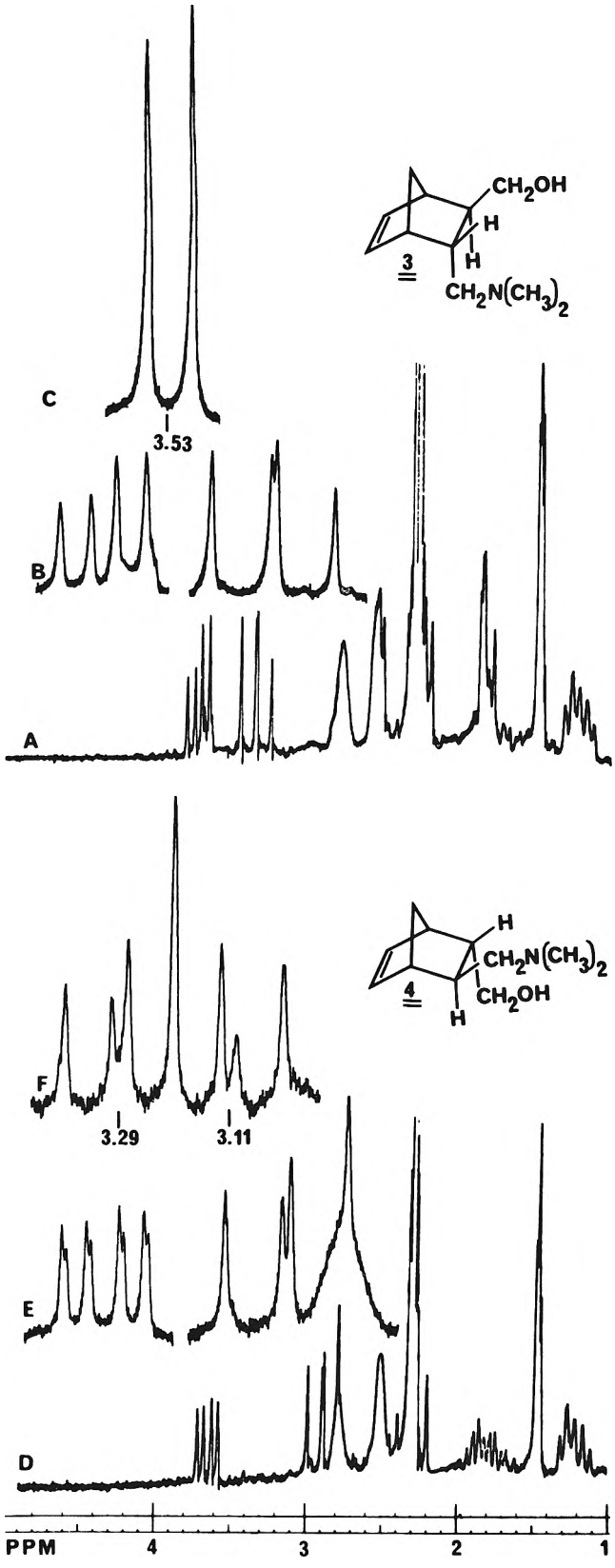


Figure 2. Portions of the 100-MHz NMR spectra of amino alcohols 3 and 4: A, amino alcohol 3, 1000-Hz sweep width, in $CDCl_3$; B, 250-Hz sweep width expansion of CH_2OH protons, in $CDCl_3$; C, 250-Hz sweep width expansion of CH_2OH in acetone-d_6–D_2O (9:1); D, amino alcohol 4, 100-Hz sweep width, in $CDCl_3$; E, 250 Hz sweep width expansion of CH_2OH protons, in $CDCl_3$; F, 250-Hz sweep width expansion of CH_2OH protons, in acetone-d_6–D_2O (9:1).

$J_{gem} \simeq$ 9–10 Hz (Figure 2). Additional vicinal coupling constants of J = 10–11 and 4–5 Hz were observed. These protons are diastereotopic, being adjacent to an asymmetric center; thus a difference in chemical shift is not unexpected. However, the observation of different vicinal coupling constants suggests a conformational preference. Models show one or more conformations where intramolecular hydrogen bonding between the hydroxyl and amine moieties accommodate the observed differences in coupling constants.

Changes observed in polar solvents are consistent with this explanation. In hydroxylic solvents, methanol or acetone–water (9:1), the hydroxymethylene protons in 3 have identical chemical shifts and collapse into a doublet at δ 3.53, J = 7.5 Hz (Figure 2). In the spectrum of 4 in acetone–water (9:1), these protons appear as overlapping quartets at δ 3.29 and 2.11, J_{gem} = 10 and J_{vic} = 8 Hz, indicating different chemical shifts, but averaged coupling constants indicating no conformational preference. However, in the presence of less water, 5% in acetone, these changes are not complete, as evidenced by quartets at δ 3.32 and 3.05, J_{gem} = 9.5, J_{vic} = 6.5 and 8 Hz.

Of the cis compounds only endo compounds 1 showed behavior in $CDCl_3$ similar to the trans compounds. However, in polar solvents the multiplets due to the CH_2OH in 1 and 2 do not change significantly, probably because of stronger intramolecular hydrogen bonding.

The preparation of amino alcohols 1–4 will allow for further work related to semirigid cholinergic ligands, which will be the subject of another publication.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded using Varian A-60, T-60, and HA-100 spectrometers using tetramethylsilane as internal standard. Notations used in the NMR descriptions are s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet. Mass spectra were obtained on the SRI-Biospect mass spectrometer operated in the CI mode using methane as carrier gas. Microanalyses were performed by F. B. Strauss, Oxford, England, and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

2-*endo*-3-*endo*-Bicyclo[2.2.1]hept-5-enedicarboxylic Anhydride (5). Anhydride 5 was prepared as described by Kloetzel,[9] and was obtained in 94% yield as needles, mp 164–166° (benzene–petroleum ether, bp 30–60°) (lit.[9] mp 164–165°).

The dimethyl ester was prepared from 5 using MeOH and a catalytic quantity of BF_3-Et_2O and was obtained as an oil: NMR (CCl_4) δ 6.15 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 1.5 Hz), 3.57 (s, 6, OCH_3), 3.23 (m, 2, H_2 and H_3, W_h = 4 Hz), 3.10 (m, 2, H_1 and H_4, W_h = 6 Hz), 1.37 (m, 2, 2 H_7, W_h = 4 Hz).

2-*exo*-3-*exo*-Bicyclo[2.2.1]hept-5-enedicarboxylic Anhydride (6). This compound was prepared in 49% yield from 5 by the method of Craig,[10] mp 141–143° (benzene) (lit.[10] mp 142–143°).

The dimethyl ester was prepared from 6, using MeOH and a catalytic quantity of BF_3-Et_2O, and was obtained as an oil: NMR (CCl_4) δ 6.22 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 3.67 (s, 6, OCH_3), 3.12 (m, 2, H_1 and H_4, W_h = 5 Hz), 2.62 (d, 2, H_2 and H_3, $J_{2,1}$ ($J_{3,4}$) = 2 Hz), 2.14 (d, 1, H_7-syn, J_{gem} = 9 Hz), 1.50 (dt, 1, $H_{7\text{-anti}}$, $J_{7,1} = J_{7,4}$ = 2, J_{gem} = 9 Hz).

2-*endo*-3-*exo*-Dicarbomethoxybicyclo[2.2.1]hept-5-ene (7).[11] Reaction of dimethyl fumarate with cyclopentadiene followed by distillation produced 7 in 71% yield, obtained as an oil: bp 80–85° (1 mm) [lit.[23] bp 119–120° (4 mm)]; NMR ($CDCl_3$) δ 6.22 (dd, 1, H_6, $J_{6,1}$ = 3, $J_{6,5}$ = 6 Hz), 6.00 (dd, 1, H_5, $J_{5,4}$ = 2, $J_{5,6}$ = 6 Hz), 3.70 (s, 3, exo $COOCH_3$), 3.62 (s, 3, endo $COOCH_3$), 3.1–3.4 (m, 2, H_2 and H_4), 3.07 (m, 1, H_1), 2.58 (d, 1, H_3, $J_{3,2}$ = 4 Hz), 1.2–1.8 (m, 2, 2 H_7).

2-*endo*-3-*endo*-Di(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (8). To 100 mg (2.6 mmol) of $LiAlH_4$ in 25 ml of anhydrous Et_2O was added dropwise, with stirring, a solution of 200 mg (0.95 mmol) of the dimethyl ester of 5 in 10 ml of Et_2O. The reaction was refluxed for 24 hr and after cooling was carefully treated with H_2O. The white solid was removed by suction filtration and

washed with EtOAc, and the combined organic filtrate was dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield 145 mg (99%) of a colorless oil which solidified upon standing: mp 79–82°; infrared (neat) 2.98 (s), 3.24 (w), 3.36, 6.10 (w), 6.90, 7.45, 7.98, 8.07 (w), 8.28 (w), 8.56, 9.00 (br), 9.57 (s), 9.76 (s), 10.14, 10.35 (w), 10.93, 11.26, 11.80 (w), 12.11 (w), 12.33 (w), 12.84, 13.47, and 13.84 (br); NMR ($CDCl_3$) δ 6.05 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 4.00 (s, 2, OH), 3.2–3.8 (m, 4, OCH_2), 2.77 (m, 2, H_1 and H_4, W_h = 8 Hz), 2.3–2.7 (m, 2, H_2 and H_3), 1.40 (t, unsymmetrical, 2, 2 H_7, $J_{7,1}$ and $J_{7,4}$ = 1.5 Hz).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.84; H, 9.05.

2-*endo*-Hydroxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (9). To a stirred solution of 1.90 g (12.3 mmol) of diol 8 in 100 ml of anhydrous Et_2O was added dropwise a solution of 1.70 g (11.0 mmol) of 4-chlorophenyl isocyanate in 20 ml of Et_2O. The reaction mixture was stirred at room temperature for 2 days and the Et_2O removed by rotary evaporation. The residue was dissolved in benzene and the insoluble *N,N'*-di(4-chlorophenyl)urea removed by suction filtration. The carbamate, **9**, was crystallized from a benzene–petroleum ether (bp 30–60°) mixture to yield 1.60 g (48%) of white crystals: mp 117–119°; infrared (KBr) 2.88, 3.03, 3.18 (w), 3.22, 3.33, 5.85 (s), 6.24, 6.47 (s), 6.70, 7.11, 7.46 (w), 7.52, 7.62, 7.78, 7.90 (w), 8.09 (s), 8.51 (w), 8.94 (w), 9.14, 9.38, 9.52, 9.73, 9.90, 10.05 (w), 10.70 (w), 10.96 (w), 11.22, 12.10, 13,00, 13.51, 13.92, and 14.60 μ; NMR ($CDCl_3$) δ 7.32 (s, 4, ArH), 7.11 (s, 1, NH), 6.18 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 1.5 Hz), 3.98 (d, 2, ester OCH_2, $J_{H,3}$ = 7 Hz), 3.40 (d, 2, OCH_2, $J_{H,2}$ = 5 Hz), 2.94 (m, 2, H_1 and H_4, W_h = 7 Hz), 2.50 (m, 2, H_2 and H_3, W_h = 11 Hz), 2.10 (s, broad, 1, OH, W_h = 7 Hz), 1.2–1.7 (m, 2, 2 H_7).

Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.68; H, 5.65; N, 4.60.

2-*endo*-Tosyloxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (10). To a cold (4°) solution of 200 mg (0.55 mmol) of alcohol **9** in 3 ml of anhydrous pyridine was added 200 mg (1.04 mmol) of *p*-TsCl. The reaction mixture was stored at 4° for 2.5 days and then diluted with 40 ml of ice water. This mixture was extracted with Et_2O (4 × 20 ml) and the combined Et_2O extract washed with aqueous 1 *N* HCl and with H_2O. After drying ($MgSO_4$) the Et_2O was removed by rotary evaporation to yield 300 mg (98%) of a light brown oil which was used without further purification: infrared 2.95, 3.18 (w), 3.24, 3.33, 5.82 (s), 6.24, 6.52 (s), 6.70, 6.88 (w), 7.13, 7.38 (s), 7.66, 7.77, 8.18 (s), 8.41, 8.50 (s), 8.80 (w), 8.95, 9.13, 9.45 (br), 9.88, 10.50 (br, s), 11.20, 11.56, 12.10 (br), 12.89, 13.47, 14.24 (w), 14.60, 14.92, and 15.18 μ; NMR ($CDCl_3$) δ 7.82 and 7.32 (two d, 4, Ts-ArH, J = 8 Hz), 7.30 (s, 4, ArH), 6.97 (s, 1, NH), 6.18 and 5.96 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 3.5–4.1 (m, 4, $TsOCH_2$ and ester OCH_2), 2.90 (m, 2, H_1 and H_4, W_h = 8 Hz), 2.3–2.7 (m, 2, H_2 and H_3, overlapping signals), 2.43 (s, 3, $ArCH_3$), 1.2–1.6 (m, 2, 2 H_7).

2-*endo*-(*N,N*-Dimethylcarboxamido)-3-*endo*-carboxybicyclo[2.2.1]hept-5-ene Dimethylamine Salt (19). To a cold (0°), stirred solution of 2.00 g (12 mmol) of anhydride **5** in 75 ml of Et_2O was added 1.40 g (31 mmol) of anhydrous $(CH_3)_2NH$. The reaction mixture was stirred at 0° for 1 hr and then stirred at room temperature overnight. The white precipitate was collected by suction filtration and washed with Et_2O to yield 3.00 g (97%) of a white solid: mp 100–105° dec; infrared (KBr) 2.90, 3.17, 3.38, 6.20 (s), 6.33 (s), 6.70 (w), 6.85 (w), 7.14 (s), 7.46 (w), 7.79 (w), 7.88, 8.05, 8.22, 8.70, 9.45 (w), 9.70, 11.10, 11.69 (w), 11.86 (w), 12.42, 13.47, 14.04, and 14.81 μ; NMR (D_2O) δ 6.38 (dd, 1, H_6, $J_{6,5}$ = 6, $J_{6,1}$ = 3 Hz), 5.98 (dd, 1, H_5, $J_{5,6}$ = 6, $J_{5,4}$ = 3 Hz), 4.74 (s, 2, $-^+NH_2$), 3.32 (m, 2, H_1 and H_4, overlapping signals), 3.17 (m, 2, H_2 and H_3, overlapping signals), 2.97 and 2.80 [two s, 6, amide $N(CH_3)_2$], 2.73 [s, 6, $-^+N(CH_3)_2$], 1.38 (m, unsymmetrical, 2, 2 H_7, $J_{7,1}$ and $J_{7,4}$ = 1.5 Hz).

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.13; H, 8.50; N, 11.39.

2-*exo*-(*N,N*-Dimethylcarboxamido)-3-*exo*-carboxybicyclo[2.2.1]hept-5-ene Dimethylamine Salt (20). To a stirred, water–ice bath cooled solution of 800 mg (4.9 mmol) of anhydride **6** in 50 ml of Et_2O was added 1.40 g (31 mmol) of anhydrous $(CH_3)_2NH$. The reaction mixture was allowed to stand at room temperature overnight. The white precipitate was collected by suction filtration and washed with Et_2O to yield 1.22 g (98%) of the salt **20**, mp 81–84°, although it was sometimes obtained as an oil: infrared (KBr) 2.90 (s), 3.37 (s), 3.57, 6.25 (s), 6.70, 7.20 (s), 7.75 (w), 7.92, 8.54, 8.73, 9.02, 9.45 (w), 9.72, 9.92 (w), 11.09, 11.92, 12.13 (w), 12.61, 13.23, 13.94 (s), and 14.58 μ; NMR (D_2O) δ 6.32 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 4.77 (s, 2, $-^+NH_2$), 3.03 and 2.88 [two s, 6, amide $N(CH_3)_2$], 2.73 [s, 6, $^+N(CH_3)_2$], 2.67 and 2.92 (two m, 2, H_1 and H_4, overlapping signals), 2.05 and 2.20 (two m, 2, H_2 and H_3, W_h = 4 Hz), 1.2–1.7 (m, 2, 2 H_7).

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.05; H, 8.52; N, 10.95.

2-*endo*-Dimethylaminomethyl-3-*endo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (1). To 2.00 g (53 mmol) of $LiAlH_4$ in 150 ml of anhydrous THF was added dropwise, with stirring, a solution of 1.90 g (7.5 mmol) of **19** in THF. The reaction mixture was refluxed for 3 days and after cooling was carefully treated with H_2O. The white solid was removed by suction filtration and washed with THF, and the combined filtrate was dried (Na_2SO_4). The THF solvent was removed by rotary evaporation to give an oil which solidified upon standing. Recrystallization from benzene provided 0.70 g (52%) of white, granular crystals: mp 94–96°; infrared (KBr) 3.1–3.6 (br), 3.14, 3.38 (s), 3.52, 6.85, 7.34 (w), 7.48, 7.81, 7.98, 8.23, 8.54, 8.92 (w), 9.06, 9.58 (s), 9.90, 10.97, 11.15 (w), 11.70 (w), 11.87, 12.18, 12.52, 12.89, 13.50 (w), and 13.94 μ (s); NMR ($CDCl_3$) δ 6.82 (s, broad, 1, OH), 6.03 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 3.50 (dd, 1, OCH, J_{gem} = 11.5, $J_{H,3}$ = 2.5 Hz), 3.18 (dd, 1, OCH′, J_{gem} = 11.5, $J_{H',3}$ = 10.5 Hz), 2.72 (m, 2, H_1 and H_4, overlapping signals), 2.46 (m, 2, H_2 and H_3, overlapping signals), 2.07–2.42 [overlapping signals, 8, NCH_2 and $N(CH_3)_2$], 1.41 (t, 2, 2 H_7, $J_{7,1}$ and $J_{7,4} \simeq$ 1.5 Hz). In acetone-d_6–D_2O (9:1), the CH_2OH signals appear at δ 3.40 (dd, 1, OCH, J_{gem} = 11.5, $J_{H,3}$ = 4 Hz) and 3.15 (dd, 1, OCH, J_{gem} = 11.5, $J_{H,3}$ = 10.5 Hz). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$. Mass spectrum (methane, CI), 182 (M + 1).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.89; H, 10.43; N, 7.77.

The methiodide salt was prepared, mp 214–216° dec (MeOH–Et_2O).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.30; H, 6.89; N, 4.39.

2-*exo*-Dimethylaminomethyl-3-*exo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (2). To 800 mg (21 mmol) of $LiAlH_4$ in 60 ml of anhydrous THF was added dropwise, with stirring, a solution of 620 mg (2.4 mmol) of amine salt **20** in 30 ml of THF. The reaction mixture was refluxed for 60 hr and after cooling was carefully treated with H_2O. The white solid was removed by suction filtration and washed with THF. The combined THF filtrate was dried (Na_2SO_4) and rotary evaporated to give 300 mg (68%) of a light brown oil: infrared (neat) 2.90 (s), 3.33 (s), 6.78 (s), 7.06, 7.14, 7.50, 7.70 (w), 7.96, 8.08, 8.50 (w), 8.86 (w), 9.24 (w), 9.61 (w), 10.32 (s), 10.63, 11.18 (s), 11.45, 13.17, 13.80, and 14.38 μ; NMR ($CDCl_3$) δ 6.20 (t, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 5.28 (s, broad, 1, OH, W_h = 20 Hz), 3.60 (m, unsymmetrical, 2, OCH_2, $J_{H,3}$ = 6 Hz), 2.1–2.8 (m, 2, NCH_2, overlapping signals), 2.43 (m, 2, H_1 and H_4, W_h = 7 Hz), 2.27 [s, 6, $-N(CH_3)_2$], 1.5–2.0 (m, 2, H_2 and H_3, overlapping signals), 1.1–1.5 (m, 2, 2 H_7, overlapping signals). In CD_3OD the CH_2OH signals appear at δ 3.60 (m, 2, OCH_2), and in acetone-d_6–D_2O (9:1) at δ 3.62 (m, complex, 2, OCH_2). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$.

A sample of crude amine was allowed to react with methyl iodide. Two salts were obtained, a small amount of the bis quaternary salt, mp 265–266° dec, and the methiodide of the amino alcohol, mp 180–182° dec (MeOH–Et_2O). Samples of the amine were also purified by chromatographing on silica gel, eluting with EtOAc–methanol: mass spectrum (methane CI), 182 (M + 1).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.83; H, 7.11; N, 4.49.

2-*endo*-3-exo-Di(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (14). The trans diol **14** was prepared in a manner similar to preparation of cis diol **8** using 1.00 g (4.8 mmol) of diester **7**, 500 mg (13 mmol) of $LiAlH_4$, and 150 ml of anhydrous Et_2O. This procedure afforded 720 mg (98%) of colorless oil: infrared (neat) 2.95 (s), 3.23 (w), 3.35 (s), 3.44, 6.10, 6.38 (w), 6.98 (br), 7.28, 7.48, 7.85 (w), 7.98 (w), 8.23 (w), 8.40 (w), 8.57 (w), 8.88, 9.13, 9.42 (s), 9.74 (br, s), 10.08, 10.22, 11.07 (w), 11.28 (w), 11.92 (w), 12.35 (w), 12.93 (w), and 13.93 μ (s); NMR ($CDCl_3$) δ 6.25 and 6.00 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 4.06 (s, broad, 2, 2 OH, W_h = 9 Hz), 2.9–3.9 (m, 4, OCH_2, overlapping signals), 2.84 (m, 1, H_1, W_h = 8 Hz), 2.60 (m, 1, H_4, W_h = 7 Hz), 1.7–2.1 (m, 1, H_2), 1.43 (m, 2, 2 H_7, W_h = 5 Hz), 1.0–1.5 (m, 1, H_3, overlapping signals).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.80; H, 9.20.

2-*endo*-Hydroxymethyl-3-*exo*-*N*-(4-chlorophenyl)carba-

moyloxymethylbicyclo[2.2.1]hept-5-ene (15) and 2-*exo*-Hydroxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (17). To a stirred solution of 2.10 g (14 mmol) of cis diol **14** in 20 ml of anhydrous Et_2O was added dropwise a solution of 2.00 g (13 mmol) of 4-chlorophenyl isocyanate in 25 ml of Et_2O. The reaction mixture was stirred at room temperature for 8 hr and the Et_2O removed by rotary evaporation. The residue was redissolved in benzene and the insoluble *N,N'*-di(4-chlorophenyl)urea removed by suction filtration. The benzene was removed by rotary evaporation to give 3.80 g (95%) of a brown oil consisting of the dicarbamate of **14** and monocarbamates **15** and **17**.

A 1.9-g sample of this mixture was chromatographed on a 4.5 × 50 cm column of silica gel (400 g) using a benzene–Et_2O (3:2) mixture as eluent. The fractions collected between 100 and 300 ml of eluted solvent contained 450 mg of the dicarbamate ester of **14**, 170 mg of nearly pure isomer **17** obtained between 1600 and 1700 ml eluent, 180 mg of a 3:1 mixture of **17**:**15** between 1700 and 1760 ml, 500 mg of a 1:1 mixture of **17** and **15** between 1760 and 1880 ml, and 50 mg of nearly pure isomer **15** between 1880 and 1940 ml of eluted solvent. The purification was monitored by NMR spectroscopy. After rotary evaporation, the fractions containing **17** collected were colorless oils which solidified upon standing: mp 99–100°; infrared (KBr) **17**, 2.91, 3.00, 3.19 (w), 3.23, 3.33, 5.86 (s), 6.24, 6.46 (s), 6.70, 6.80 (w), 7.11, 7.63, 7.77, 8.05 (s), 8.50 (w), 8.92 (w), 9.14, 9.40 (s), 9.87, 10.13 (w), 11.03 (w), 11.28 (w), 12.10, 12.92, 13.89, and 14.59 μ; NMR ($CDCl_3$) δ 7.50 (s, 1, NH), 7.32 (s, 4, ArH), 6.28 and 6.03 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 3.90 (d, 2, $COOCH_2$, $J_{H,3}$ = 8 Hz), 3.64 (d, 2, OCH_2, $J_{H,2}$ = 7 Hz), 2.94 (s, broad, 1, OH, W_h = 7 Hz), 2.85 and 2.66 (two m, 2, H_1 and H_4, W_h = 8 Hz), 1.7–2.2 (m, 1, H_3), 1.43 (m, 2, 2 H_7, W_h = 5 Hz), 1.0–1.5 (m, 1, H_2, overlapping signals with H_7). Compound **15** was never obtained totally free of **17**: infrared (KBr) **15**, 2.92, 3.07, 3.13 (w), 3.20 (w), 3.25, 3.35, 5.87 (s), 6.22, 6.45, 6.70, 6.81 (w), 7.11, 7.61, 7.98, 8.50 (w), 8.92 (w), 9.13, 9.35, 9.42, 9.87, 10.14, 10.90 (w), 11.00 (w), 11.29 (w), 12.00, 12.96, 13.90, and 14.58 μ; NMR ($CDCl_3$) δ 7.30 (s, 4, ArH), 7.04 (s, broad, 1, NH, W_h = 7 Hz), 6.0–6.4 (m, 2, H_5 and H_6), 4.17 (d, 2, $COOCH_2$, $J_{H,3}$ = 7 Hz), 3.40 (d, 2, OCH_2, $J_{H,2}$ = 8 Hz), 2.88 and 2.70 (two m, 2, H_1 and H_4, W_h = 8 Hz), 2.08 (s, broad, 1, OH, W_h = 6 Hz), 1.7–2.1 (m, 1, H_2, overlapping signals with OH), 1.50 (m, 2, 2 H_7, W_h = 5 Hz), 1.0–1.5 (m, 1, H_3, overlapping signals with H_7).

Anal. Calcd for $C_{16}H_{18}NO_3Cl$ (**17**): C, 62.44; H, 5.89; N, 4.55. Found: C, 62.02; H, 6.17; N, 4.94.

2-*exo*-Tosyloxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (18). The trans tosylate **18** was prepared in the same manner as cis tosylate **10** using 170 mg (1.55 mmol) of alcohol **17**, 200 mg (1.04 mmol) of *p*-TsCl, and 3 ml of anhydrous pyridine to yield 200 mg (79%) of tosylate **18** as a light brown oil which was used without further purification: infrared (neat) 2.96, 3.06 (w), 3.27, 3.35, 5.79 (s), 6.25, 6.53, 6.70, 6.96, 7.13, 7.36, 7.65, 7.77 (w), 8.19 (s), 8.42, 8.50 (s), 8.95 (w), 9.14, 9.38, 9.88, 10.10 (w), 10.50 (s), 11.26 (w), 11.46 (w), 11.57 (w), 12.08 (s), 12.29, 12.73, 13.01, 13.40, 14.23 (s), 14.60, and 15.06 μ; NMR ($CDCl_3$) δ 7.80 and 7.32 (two d, 4, TsArH, J = 8 Hz), 7.30 (s, 4, ArH), 7.18 (s, 1, NH), 6.0–6.4 (m, 2, H_5 and H_6), 3.5–4.2 (m, 4, $TsOCH_2$ and ester OCH_2, overlapping signals), 2.80 and 2.63 (two m, 2, H_1 and H_4, W_h = 7 Hz), 2.44 (s, 3, $ArCH_3$), 1.8–2.2 (m, 1, H_3), 1.40 (m, 2, 2 H_7, W_h = 6 Hz), 1.1–1.7 (m, 1, H_2, overlapping signals with H_7).

Reaction of Dimethylamine with 2-*exo*-Tosyloxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo-[2.2.1]hept-5-ene (18). To a cold (4°) solution of 200 mg (0.43 mmol) of tosylate **18** in 20 ml of benzene was added 700 mg (15.5 mmol) of anhydrous $(CH_3)_2NH$. This reaction mixture was heated in a bomb at 100° for 3 days, after which the cooled benzene solution was decanted from the insoluble residue. The benzene and excess $(CH_3)_2NH$ were removed by rotary evaporation to give a brown oil which was crystallized and recrystallized from $CHCl_3$ yielding white needles. These crystals were identified as *N,N*-dimethyl-*N'*-(4-chlorophenyl)urea by ir and NMR spectroscopy, mp 170–172° (lit.[24] 170–171°).

2-*endo*-3-*exo*-Di(chloroformyl)bicyclo[2.2.1]hept-5-ene (24). Cyclopentadiene was distilled from pyrolysis of the dimer into a stirred, water–ice bath cooled solution of 150 g (0.98 mol) of fumaryl chloride[25] in 100 ml of anhydrous Et_2O. The distillation was continued for 8 hr to allow approximately 77 g (1.2 mol) of cyclopentadiene to distil into the reaction solution. The reaction mixture was stirred at room temperature overnight and then the Et_2O was removed by rotary evaporation. The residue was vacuum distilled, yielding 122 g (57%) of a colorless oil, bp 60–62° (0.2–0.3 mm) [lit.[23] 114–118° (11 mm)].

2-*endo*-Chloroformyl-3-*exo*-carbomethoxybicyclo-[2.2.1]hept-5-ene (25) and 2-*exo*-Chloroformyl-3-*endo*-carbomethoxybicyclo[2.2.1]hept-5-ene (26). To a stirred, water–ice bath cooled solution of 60.0 g (0.27 mol) of acid chloride **24** in 100 ml of benzene was added dropwise a solution of 8.7 g (0.27 mol) of MeOH in 100 ml of benzene. The reaction mixture was stirred at room temperature overnight and then the benzene was removed by rotary evaporation. The residue was vacuum distilled to yield 48.5 g (83%) of a colorless oil consisting of a mixture of acid chloride esters **25** and **26** (2:1 **25**:**26**), as shown by NMR. This mixture was used without further purification: bp 80–82° (0.2–0.4 mm); infrared (neat) 3.24 (w), 3.32, 3.45 (w), 5.57 (s), 5.78 (s), 6.98, 7.30, 7.51, 7.64, 7.91, 8.03, 8.28, 8.35, 8.48, 8.98, 9.37, 9.78 (s), 10.04 (w), 10.19 (w), 10.78 (w), 11.02, 11.29, 11.65, 11.92 (w), 12.15, 12.71, 12.94, 13.50, 14.33, and 14.64 μ; NMR ($CDCl_3$) δ 6.0–6.6 (m, 2, H_5 and H_6), 3.0–4.0 (m, 4, H_1, H_2, H_3, and H_4, overlapping signals for isomeric mixture), 3.78 and 3.70 (two s, 3, exo OCH_3 and endo OCH_3 protons from isomeric mixture), 2.73 (m, 1, endo H_3, W_h = 8 Hz), 1.64 (m, 2, 2 H_7, W_h = 8 Hz).

***trans*-β-Carbomethoxy-*N,N*-dimethylacrylamide (29).** To a stirred, water–ice bath cooled solution of 78.0 g (0.52 mol) of *trans*-β-carbomethoxyacrylyl chloride, prepared by the method of Lutz,[26] in 100 ml of benzene was added dropwise a solution of 50.0 g (1.10 mol) of anhydrous $(CH_3)_2NH$ in 100 ml of benzene. The reaction mixture was stirred at room temperature overnight and then treated with 200 ml of H_2O. The organic phase was separated and washed consecutively with portions of aqueous 1 *N* HCl, H_2O, aqueous 0.5 *M* Na_2CO_3, and H_2O. After drying ($MgSO_4$) the benzene was removed by rotary evaporation and the residue vacuum distilled. The first fraction of the distillate solidified in the condenser (dimethyl fumarate) followed by 5.5 g (7%) of amide **29** collected as a colorless oil: bp 76–80° (0.2–0.3 mm); infrared (neat) 3.30, 3.38, 5.80 (s), 6.10 (br, s), 6.70, 6.97, 7.16 (s), 7.63 (s), 7.81 (s), 8.34, 8.51, 8.76, 9.43 (w), 9.68, 9.91, 10.25, 10.70, 11.33 (w), 11.62 (w), 12.12 (w), 13.11, 14.22, and 14.58 μ (w); NMR ($CDCl_3$) δ 7.48 and 6.76 (two d, 2, H_α and H_β, $J_{\alpha,\beta}$ = 14 Hz), 3.83 (s, 3, OCH_3), 3.17 [s, broad, 6, $N(CH_3)_2$, W_h = 9 Hz].

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.59; H, 7.05; N, 8.91. Found: C, 53.23; H, 6.84; N, 8.75.

2-*endo*-(*N,N*-Dimethylcarboxamido)-3-*exo*-carbomethoxybicyclo[2.2.1]hept-5-ene (27) and 2-*exo*-(*N,N*-Dimethylcarboxamido)-3-*endo*-carbomethoxybicyclo[2.2.1]hept-5-ene (28). A. Diels–Alder Addition of 29 with Cyclopentadiene. Cyclopentadiene was added to a stirred solution of 4.8 g (30 mmol) of amide ester **29** in 50 ml of benzene. The distillation of cyclopentadiene dimer was continued for 50 min to allow approximately 8.0 g (120 mmol) of cyclopentadiene to distil into the reaction solution. The reaction mixture was stirred at room temperature overnight and then the benzene was removed by rotary evaporation. The residue was vacuum distilled, affording 5.4 g (80%) of a yellow oil consisting of a mixture of the isomeric amide esters **27** and **28** (2:1 **28**:**27**) as shown by NMR, bp 107–112° (0.1 mm).

A 3.4-g sample of this mixture was chromatographed on a 2.5 × 33 cm silica gel column using Et_2O as eluent. The fractions collected between 250 and 325 ml of eluted solvent contained 1.7 g of the pure exo amide endo ester **28**, 0.6 g of mixed isomers between 325 and 375 ml, and 0.5 g of pure endo amide exo ester **27** between 375 and 500 ml of eluted solvent. The purification was monitored by NMR spectroscopy. Both purified isomers **27** and **28** were obtained as colorless oils.

B. Reaction of 25 and 26 with Dimethylamine. To a stirred, water–ice bath cooled solution of 21.0 g (0.47 mol) of anhydrous $(CH_3)_2NH$ in 50 ml of benzene was added dropwise a solution of 45.0 g (0.21 mol) of the mixture of acid chlorides, **25** and **26**, in 75 ml of benzene. The reaction mixture was stirred at room temperature overnight and the white precipitate which formed removed by suction filtration. The benzene was removed from the filtrate by rotary evaporation and the residue vacuum distilled affording 18.5 g (40%) of a colorless oil consisting of a mixture of isomeric amide esters **27** and **28** (2:1 **27**:**28**), bp 130–132° (0.3 mm).

A 3.0-g sample of this mixture was chromatographed on silica gel as previously described, providing 0.40 g of pure exo amide endo ester **28** and 1.0 g of pure endo amide exo ester **27**: infrared (neat), **28**, 2.84 (w), 3.23 (w), 3.37, 5.78 (s), 6.10 (s), 6.68, 6.88, 6.97, 7.07, 7.13, 7.38, 7.49, 7.65, 7.90 (s), 8.30 (s), 8.51, 8.70, 8.95, 9.40 (br), 9.75, 10.00, 10.99, 11.52, 11.85 (w), 12.48 (w), 12.68 (w), 12.97 (w), 13.80, 14.06, and 14.57 μ; NMR ($CDCl_3$), **28**, δ 6.38 and 6.13 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 3.66 (s, 3,

$COOCH_3$), 3.5–3.7 (m, 1, H_3, overlapping signals with $COOCH_3$), 2.8–3.4 (m, 3, H_1, H_2, and H_4, overlapping signals), 3.15 and 3.00 [two s, 6, $N(CH_3)_2$], 1.92 (d, unsymmetrical, 1, H_7, J_{gem} = 9 Hz), 1.40 (d, unsymmetrical, 1, H_7, J_{gem} = 9 Hz); infrared (neat), **27**, 2.84 (w), 3.24 (w), 3.37, 5.79 (s), 6.10 (s), 6.67, 6.88, 6.97, 7.08, 7.13, 7.36, 7.48, 7.67, 7.90 (s), 8.04, 8.25, 8.38, 8.53 (s), 8.71 (s), 9.00, 9.42, 9.76, 9.98, 10.52, 10.75, 11.20, 11.61, 11.88 (w), 12.18, 12.68 (w), 13.35, 13.76, 14.17, and 14.55 μ; NMR ($CDCl_3$), **27**, δ 6.38 and 6.05 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 7 Hz), 3.73 (s, 3, $COOCH_3$), 3.4–3.7 (m, 1, H_2, overlapping signals), 2.9–3.4 (m, 3, H_1, H_3, and H_4, overlapping signals), 3.20 and 2.97 [two s, 6, $N(CH_3)_2$], 1.3–1.9 (m, 2, 2 H_7).

Anal. Calcd for $C_{12}H_{17}NO_3$ (**28**): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.47, H, 7.74; N, 6.38.

Anal. Calcd for $C_{12}H_{17}NO_3$ (**27**): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.31; H, 7.69; N, 6.46.

2-*exo*-Dimethylaminomethyl-3-*endo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (4). To a stirred solution of 7.00 g (35 mmol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, Red-al, Aldrich) in 75 ml of anhydrous benzene was added dropwise a solution of 1.00 g (4.5 mmol) of amide ester **28** in 25 ml of benzene. The reaction mixture was refluxed for 24 hr and after cooling was slowly treated with 150 ml of aqueous 2.5 N NaOH. The organic phase was separated and the aqueous layer extracted with $CHCl_3$ (3 × 50 ml). The combined organic extract was washed with H_2O, dried ($MgSO_4$), and rotary evaporated to yield 0.60 g (74%) of a light yellow oil: infrared (neat) 2.90 (br), 3.23 (w), 3.34 (s), 3.46, 3.52, 3.58, 6.12 (w), 6.37 (w), 6.83 (s), 7.27, 7.47, 7.69 (w), 7.97, 8.23, 8.50, 8.57, 8.68, 8.88 (w), 9.06, 9.17, 9.42 (s), 9.70 (s), 10.98 (w), 11.08 (w), 11.25 (w), 11.98, 12.54 (w), 12.90, 13.23 (w), and 13.93 μ (s); NMR (100 MHz) ($CDCl_3$) δ 6.20 and 5.94 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 4.50 (s, broad, 1, OH, W_h = 5 Hz), 3.62 (ddd, 1, OCH, $J_{H,3}$ = 4, J_{gem} = 9.5, J_w = 0.5 Hz), 2.87 (t, 1, OCH′, $J_{H',3}$ = 11, J_{gem} = 9.5 Hz), 2.77 (m, 1, H_4, W_h = 8 Hz), 2.50 (m, 1, H_1, W_h = 8 Hz), 2.22–2.36 [overlapping signals, 8, NCH_2 and $N(CH_3)_2$], 1.82 (m, 1, H_3, W = 19 Hz), 1.46 (m, 2, 2 H_7, W_h = 4 Hz), 1.16 (m, 1, H_2, W = 20 Hz). In acetone-d_6–D_2O (9:1), the CH_2OH signals appear at δ 3.29 (dd, 1, OCH, J_{gem} = 10, $J_{H,3}$ = 8 Hz) and 3.11 (dd, 1, OCH′, J_{gem} = 10, $J_{H',3}$ = 8 Hz). In acetone-d_6–D_2O (19:1), the CH_2OH signals appear at δ 3.32 (dd, 1, OCH, J_{gem} = 9.5, $J_{H,3}$ = 6.5 Hz) and 3.05 (dd, 1, OCH′, J_{gem} = 9.5, $J_{H',3}$ = 8 Hz). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$. Mass spectrum (methane-CI) 182 (M + 1).

For an analytical sample, the methiodide salt was prepared, mp 148–150° (MeOH–Et_2O).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.31; H, 6.90; N, 4.11.

2-*endo*-Dimethylaminomethyl-3-*exo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (3). Amino alcohol **3** was prepared in a manner similar to compound **4** using 3.50 g (17 mmol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, Red-al), 0.54 g (2.4 mmol) of amide ester **27**, and 75 ml of anhydrous benzene. This procedure provided 0.40 g (91%) of amino alcohol **3** as a light yellow oil: infrared (neat) 2.90 (br), 3.36 (s), 3.58, 6.86, 7.28 (w), 7.48, 7.95, 8.22, 8.58, 8.70, 8.92 (w), 9.13, 9.40, 9.62 (s), 9.80, 11.74 (w), 12.00, 12.38, 12.91, and 14.96 μ (s); NMR (100 MHz) ($CDCl_3$) δ 6.23 and 5.94 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 4.82 (s, 1, OH), 3.69 (dd, 1, OCH, $J_{H,3}$ = 5, J_{gem} = 9 Hz), 3.30 (t, 1, OCH′, $J_{H',3}$ = 11, J_{gem} = 9 Hz), 2.75 (m, 1, H_1, W_h = 8 Hz), 2.52 (m, 1, H_4, W_h = 8 Hz), 2.26–2.31 [overlapping signals 8, NCH_2 and $N(CH_3)_2$], 1.80 (m, 1, H_2), 1.47 (m, 2, 2 H_7, W_h = 4 Hz), 1.20 (m, 1, H_3, W = 18 Hz). In CD_3OD the OCH_2 protons appear at δ 3.53 (d, 2, OCH_2, $J_{H,3}$ = 7.5 Hz). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$. Mass spectrum (methane CI), 182 (M + 1).

For an analytical sample, the methiodide salt was prepared, mp 180–182° (MeOH–Et_2O).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.20; H, 6.87; N, 4.08.

Acknowledgments. This investigation was supported in part by a U.S. Public Health Service Career Development Award (5-K4-GM-70,023) to W.L.N. from the National Institute of General Medical Sciences. We acknowledge support of D.S.F. by the American Foundation for Pharmaceutical Education through the Josiah Kirby Lilly Memorial Fellowship, 1972–1974.

Registry No.—**1**, 56679-25-5; **1** methiodide, 56689-38-4; **2**, 56679-26-6; **2** methiodide, 56679-27-7; **2** bis quaternary salt, 56679-28-8; **3**, 56711-26-3; **3** methiodide, 56760-97-5; **4**, 56711-27-4; **4** methiodide, 56711-28-5; **5**, 129-64-6; **5** dimethyl ester, 39589-98-5; **6**, 2746-19-2; **6** dimethyl ester, 7184-07-8; **7**, 3014-58-2; **8**, 699-97-8; **9**, 56679-29-9; **10**, 56679-30-2; **14**, 699-96-7; **15**, 56711-29-6; **17**, 56711-30-9; **18**, 56711-31-0; **19**, 56679-32-4; **20**, 56679-34-6; **24**, 4582-21-2; **25**, 56679-35-7; **26**, 56711-32-1; **27**, 56679-36-8; **28**, 56711-33-2; **29**, 23743-87-5; dimethyl fumarate, 624-49-7; cyclopentadiene, 542-92-7; 4-chlorophenyl isocyanate, 104-12-1; *p*-toluenesulfonyl chloride, 98-59-9; dimethylamine, 124-40-3; *trans*-β-carbomethoxyacrylyl chloride, 17081-97-9.

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Cyclohexenone Photochemistry. Photogeneration of Methyl Radicals from *tert*-Butyl Alcohol during Photolysis of 3-Cyano-4,4-dimethylcyclohex-2-en-1-one[1]

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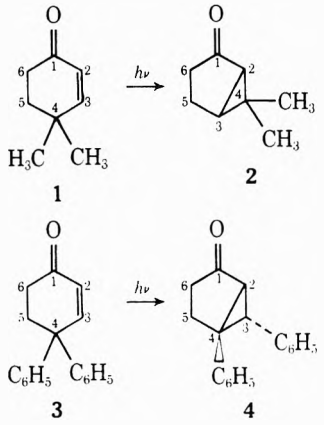
The irradiation of 3-cyano-4,4-dimethylcyclohex-2-en-1-one (**10**) in *tert*-butyl alcohol under conditions favoring intramolecular photorearrangement afforded no rearranged product. Instead, a novel methyl radical substitution reaction occurred to give 3-cyano-2,4,4-trimethylcyclohex-2-en-1-one (**11**). Formation of 3-cyano-2-perdeuteriomethyl-4,4-dimethylcyclohex-2-en-1-one (**12**) on irradiation of **10** in *tert*-butyl alcohol-d_9 showed the source of the incorporated methyl group to be *tert*-butyl alcohol. These observations necessitate qualification of assumptions regarding the suitability of *tert*-butyl alcohol as an inert solvent for photochemical studies of α,β-unsaturated ketones. The role of *tert*-butyl alcohol was confirmed by effecting the substitution reaction thermally using di-*tert*-butyl peroxide as the methyl radical source.

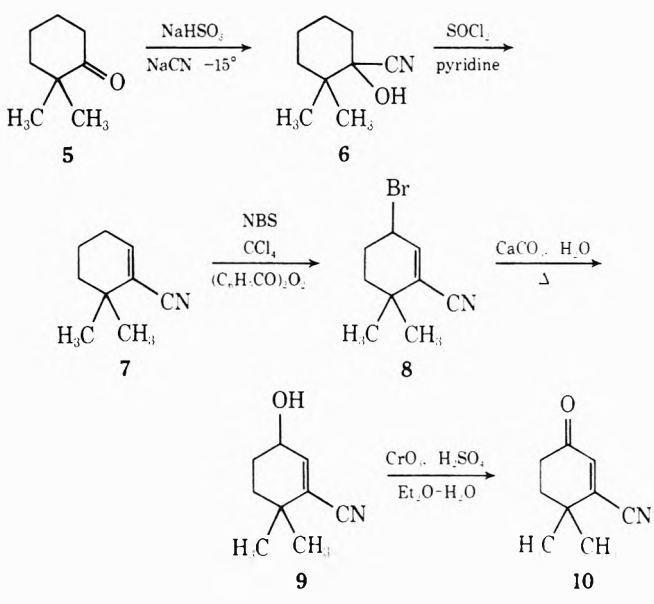
The intramolecular photorearrangements of 2-cyclohexenones show a striking dependence on the type and position of the ring substituents. The two most common types of phototransformations, skeletal rearrangement and aryl group migration, are exemplified by 4,4-dimethyl-2-cyclohexenone (**1**)[2] and 4,4-diphenyl-2-cyclohexenone (**3**),[3] respectively. Whereas the rearrangement of **1** to **2** involves 4,5-bond cleavage with 3,5- and 2,4-bond formation, **3** rearranges to **4** via 4,3-phenyl migration and direct 2,4 bonding without skeletal rearrangement.



A major point of mechanistic interest regarding the above transformations is the electronic character at the β carbon of the excited-state cyclohexenone. The results of numerous investigations of both the rearrangement and migration processes[4] leave controversy regarding the dipolar or diradical nature of the rearranging species. Although the photochemical aryl migration reactions of systems specifically designed to test the electronic character of the β carbon[5] suggest that this process occurs via a photoexcited diradical species, the validity of conclusions regarding the electronic nature of C-3 during skeletal rearrangement based on the results of aryl migration studies is at best tenuous, particularly in view of recent evidence[6,7] that these two processes occur from different excited states whose electronic distributions are quite possibly dissimilar.

The above questions regarding the mechanism involved in cyclohexenone photorearrangements suggested the introduction of a substituent at C-3 of the enone moiety which would be sensitive to the electronic character of this position upon photoexcitation. The cyano group seemed well suited for this purpose. This group is generally recognized as a powerful electron-withdrawing substituent,[8] both by inductive and resonance mechanisms. In reactions

Scheme I



which proceed via a carbonium ion, such as electrophilic aromatic substitution, a cyano substituent retards the rate of attack by an electrophile and destabilizes positive charge developed in the transition state. The opposite effect is to be expected for cyano-substituted molecules undergoing carbanionic or radical reactions, in which an electron-rich transition state (or intermediate) is involved. It was thus anticipated that the cyano group would influence the course of the photorearrangement in a manner indicative of the electronic nature of the rearranging species.

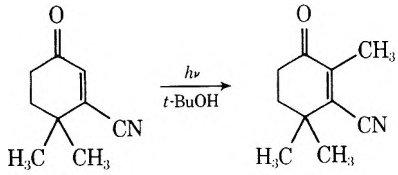
A comprehensive study[9] of the alkyl substituent requirements for intramolecular photorearrangement of 2-cyclohexenones has shown that the fourth carbon atom of the cyclohexenone ring must be fully alkyl substituted. As discussed above, aryl substituents at this position result in 4,3 migration with no skeletal rearrangement. With this knowledge in hand, a procedure was developed for the synthesis of 3-cyano-4,4-dimethylcyclohex-2-en-1-one (**10**) from 2,2-dimethylcyclohexanone (**5**). The multiple-step route is outlined in Scheme I.

Results

Irradiation of **10** in *tert*-butyl alcohol afforded a product mixture which contained one volatile photoproduct in 15% yield (VPC analysis). A comparison of the NMR spectra of

10 and the photoproduct indicated that the olefinic proton of 10 had been replaced by a methyl group. Since the chemical shift positions, multiplicities, and peak areas of all other protons in both spectra were identical, it was concluded that skeletal rearrangement had not occurred. On the basis of additional spectral and elemental analyses the photoproduct was identified as 3-cyano-2,4,4-trimethylcyclohex-2-en-1-one (11). The presence of a methyl group at C-2 in 11 is further indicated by the red shift of 11 nm in the π,π^* absorption maximum in the uv spectrum of 11 relative to that of 10.

In addition, careful VPC and mass spectral analyses of 10 showed that it contained virtually no 11 before irradiation, and the NMR spectrum of the crude photolysate after solvent removal but before steam distillation or VPC analysis contained all peaks which appeared in the product NMR spectra after separation and purification. Thus 11 is a true photoproduct of 10 under these irradiation conditions.

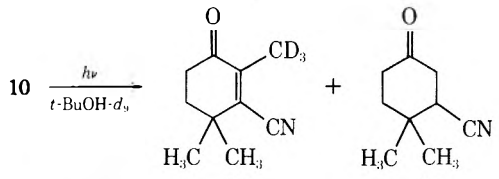


10 11

Since there is no precedent in the literature for the occurrence of this type of alkyl substitution reaction during photolysis of a 2-cyclohexenone, the source and mechanism of incorporation of the C-2 methyl group in 11 remained open to question. The combined amounts of 10 and 11 recovered from the photolysate were less than 50% of the original charge of 10. There are thus two possible sources of methyl groups: degraded molecules of 10 or the solvent, *tert*-butyl alcohol.

Irradiation of a solution of 10 in cyclohexane resulted in rapid destruction of starting material (VPC analysis); however, no volatile photoproducts were produced. This result indicated that formation of 11 quite likely involves *tert*-butyl alcohol, and it further showed that photorearrangement of 10 does not occur under conditions employing two quite different solvent media.

A more definitive test to determine the origin of the C-2 methyl group involved the use of *tert*-butyl alcohol-d_9. Irradiation of 10, in this solvent afforded one new volatile component whose VPC retention time corresponded to that of 11. This component was isolated by preparative VPC and identified by high-resolution mass spectrometry as 3-cyano-2-perdeuteriomethyl-4,4-dimethylcyclohex-2-en-1-one (12). The mass spectrum of 12 also exhibited an



12 13

intense peak at *m/e* 151.0997, which does not correspond to $(M - CH_3)^+$ (see Experimental Section); rather, this peak indicated an ion having the formula $C_9H_{13}NO$. In light of the starting material employed in this reaction and previous examples of similar systems in which hydrogen abstraction produces the saturated analogue of the cyclohexenone employed,[9] the most reasonable structure corresponding to $C_9H_{13}NO$ would be 3-cyano-4,4-dimethylcyclohexanone (13). Further evidence that the *m/e* 151 peak results from a molecular ion was provided by field ionization mass spectral analysis of the component containing 12. VPC studies utilizing independently synthesized 13 confirmed the possibility that this compound would have eluted simultaneously with 12 under the conditions employed for isolation of the latter compound.

The results obtained show that *tert*-butyl alcohol is indeed the source of the methyl group which replaces the C-2 hydrogen of 10 in its photoconversion to 11. The probable presence of 13 in the product mixture further suggests that 10 may be involved in hydrogen abstraction from the solvent and/or the intermediate involved in the formation of 11. The mechanistic implications of these results will be discussed later.

Since it appeared that formation of 11 results from attack of 10 by photochemically generated methyl radicals, the possibility that the same result could be effected with thermally generated methyl radicals was explored. Di-*tert*-butyl peroxide is known[10] to decompose at elevated temperature to give *tert*-butoxy radicals which undergo C–C bond scission to afford acetone and methyl radicals. Heating of a mixture of 10 and di-*tert*-butyl peroxide in *tert*-butyl alcohol gave 11 in 46% yield plus 8% of a compound whose mass and NMR spectra were consistent with the structure 3-cyano-2,4,4-trimethylcyclohexanone (14), the saturated analogue of 11.

14

Discussion

The results obtained from the photolysis of 10 in *tert*-butyl alcohol are consistent with the stepwise mechanism outlined in Scheme II. Hydrogen abstraction by excited-state 10 produces a *tert*-butoxy radical which decomposes to give acetone[11] and a methyl radical (step 1). The role of 10 in this process is supported by the formation of undeuterated 13 during irradiation of 10 in *tert*-butyl alcohol-d_9 and by the lack of previous reports of unimolecular photodecomposition of *tert*-butyl alcohol during irradiation at >290 nm.

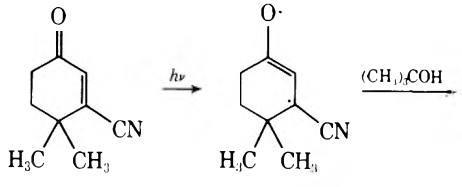
The next step in this sequence is attack at the C-2 position of 10 by methyl radical to give the α-cyano radical, 16. The facile formation 11 during thermolysis of di-*tert*-butyl peroxide provides substantial evidence for the occurrence of this process. In the particular case of 10 this step is promoted by the cyano group at C-3, since cyano-substituted olefins are greatly activated for donor (e.g., alkyl) radical attack,[12] and the resulting radical (16) would be stabilized by delocalization involving the cyano substituent.

Abstraction of the C-2 hydrogen of 16 is the necessary third and final step for the formation of 11. The process by which this occurs remains debatable since no one species has been identified as the abstracting agent. Inclusion of intermediate 15 as shown in Scheme II accounts for the formation of 13 during photolysis of 10 in *tert*-butyl alcohol-d_9.

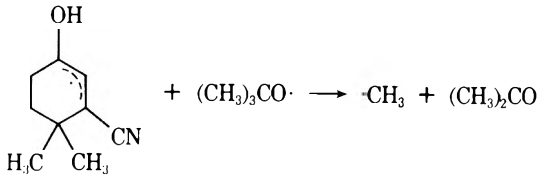
In the absence of quantum yield and reaction rate data for the conversion of 10 to 11 the relative efficiencies of methyl radical substitution in 10 vs. skeletal rearrangement

Scheme II

Step 1



10



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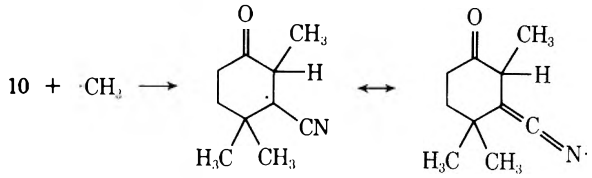
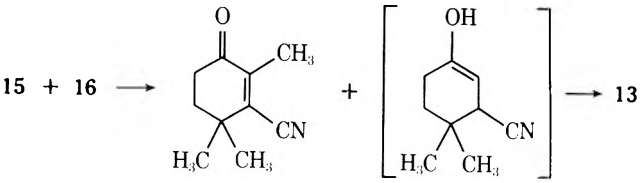
Step 2



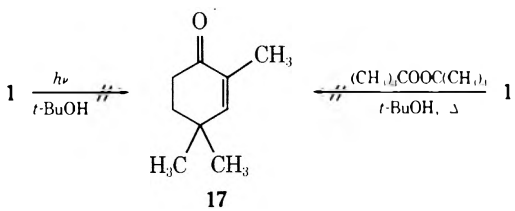
16

Step 3



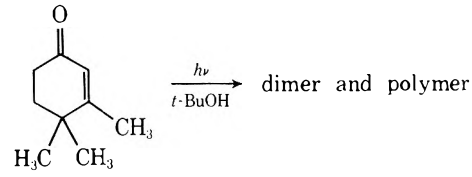
11

in cyclohexenones such as **1** cannot be determined. It is clear, however, that any preference for methyl radical attack of **10** does not control the mode of reaction, since **10** does not photorearrange in cyclohexane, a medium in which methyl substitution does not occur. The cyano substituent in **10** thus effectively quenches skeletal rearrangement. At the same time it is obvious that the cyano group is directly responsible for methyl radical substitution in **10**, since analogous compounds such as **1** do not form substitution products [e.g., 2,4,4-trimethylcyclohex-2-en-1-one (**17**)] during irradiation[2,13] in *tert*-butyl alcohol or when heated with di-*tert*-butyl peroxide in *tert*-butyl alcohol (see Experimental Section).



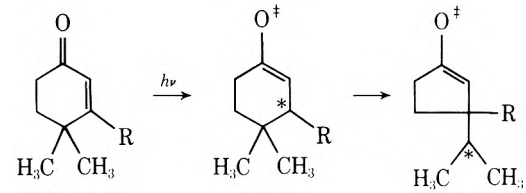
17

Steric inhibition toward photorearrangement resulting from the relatively small, cylindrical cyano group is not likely to be significant. A more pronounced effect is to be expected from the electronic influences of this group on the photoexcited species. In the case of **10**, quenching of skeletal rearrangement does not provide a clue to the electronic nature of C-3 after photoexcitation. While the failure of excited-state **10** to undergo rearrangement may suggest destabilization of positive character at C-3 by the cyano substituent, the behavior of 3,4,4-trimethylcyclohex-2-en-1-one (**18**), which gives only dimer and polymer upon photolysis,[9] does not support this argument, since the methyl group at C-3 of **18** would be capable of stabilizing cationic character at that position.



18

The inertness of both **10** and **18** toward photorearrangement may be explained in terms of the relative energies of the reactive intermediates, regardless of electronic distribution. Excitation of **10** or **18** would afford **19**, which contains a tertiary cationic or radical moiety at C-3. Rearrangement to **20** would create another tertiary cation or radical; no increased stability would obtain from this isom-

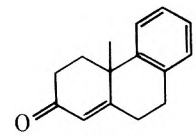


1, R = H
10, R = CN
18, R = CH_3

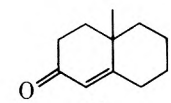
19 **20**

‡ = · or −
* = · or +

erization. On the other hand, in cyclohexenones such as **1** this rearrangement step may find its driving force in the conversion of a secondary cation or radical to a more stable tertiary cation or radical. Unfortunately, the facile photorearrangement of 3,4,4-trisubstituted fused-ring enones such as **21**[14] and **22**[15] to bicyclic products is inconsistent with this picture.



21



22

Conclusion

Although the photochemistry of **10** does not allow a choice to be made regarding the mechanism of cyclohexenone photorearrangement, the photoinitiated methyl substitution of **10** represents a previously unobserved radical substitution reaction of α,β-unsaturated ketones. It is evident that radical attack is promoted by the electron-withdrawing cyano substituent which also serves to stabilize the intermediate α-cyano radical through induction and resonance involving the cyano group directly. The role of *tert*-butyl alcohol as the source of methyl radicals also points out the need for reassessment of assumptions[4b,16] regarding the inertness and consequent suitability of this solvent for studies of α,β-unsaturated ketone photochemistry.

Experimental Section

Instruments and Methods. All melting points are corrected. NMR spectra were measured on Varian A-60, Hitachi Perkin-Elmer RE-20, and Varian HR-220 spectrometers. Ultraviolet spectra were recorded on a Beckman DK-2A spectrophotometer and, unless otherwise noted, were obtained in 95% ethanol. Mass spectra were measured at 70 eV on CEC 21-103C, CEC 21-110B, Hitachi Perkin-Elmer RMU-6, and Finnigan Model 3000 spectrometers. VPC analyses were performed on Varian Model 202b, 1525c, 90P-3, and 1400 instruments. Separations were effected with the following columns: (A) 5 ft × 0.125 in. 3% SE-30 on 100–120 mesh

Aeropak 30; (B) 5 ft × 0.25 in. 20% SE-30 on 60–80 mesh Chromosorb W; (C) 20 ft × 0.375 in. 15% SE-30 on preparative grade Chromosorb W; (D) 6 ft × 0.25 in. 5% LAC-446 on 80–100 mesh Chromosorb P; (E) 5 ft × 0.125 in. 3% OV-1 on 60–80 mesh Gas-Chrom Q. Flame ionization was employed for analyses with column A; column E was used only in conjunction with the Finnigan Model 3000 mass spectrometer; thermal conductivity was used with all other columns.

2,2-Dimethylcyclohexanone (5). Conversion of 2-methylcyclohexanone to **5** was carried out according to published procedures.[17] Purification was accomplished by distillation through a 1-m annular Teflon spinning band still.

1-Cyano-6,6-dimethylcyclohexene (7). A mixture of 148 g (1.17 mol) of **5** and 114.7 g (2.34 mol, 100% excess) of sodium cyanide in 300 ml of water was stirred at −15° (ice–salt bath). A solution of 226.7 g (2.18 mol) of sodium bisulfite in 500 ml of water was added slowly and the mixture was vigorously stirred for an additional 4 hr. The mixture was then filtered, and the filtrate was extracted with four 300-ml portions of ether. The etherate was dried over magnesium sulfate and filtered, and the ether was distilled under reduced pressure. The solid crude **6** weighed 174.5 g (1.14 mol, 97.5%).

To a solution of the crude **6** in 225 ml of pyridine and 200 ml of dry, reagent-grade benzene stirred at −15° was added a solution of 259.5 g (2.18 mol) of thionyl chloride in 200 ml of dry benzene at a rate which maintained the temperature at 10°. After addition was complete the mixture was slowly warmed and finally stirred at the reflux temperature for 1 hr.

The cooled mixture was poured onto 1 l. of cracked ice. The resulting mixture was divided into two equal portions, and each portion was extracted with four 250-ml portions of ether. The combined extracts were washed with dilute hydrochloric acid, 5% sodium carbonate solution, and finally water.

After drying over sodium sulfate, the etherate was filtered and the solution was concentrated. Distillation of the residue under reduced pressure afforded 135.9 g (1.01 mol, 86.1%) of **7**: bp 59–60° (2.2 mm) [lit.[18] 102–104° (26 mm)]; ir (neat) 1635 (C=C) and 2260 cm^{-1} (C≡N); NMR (CCl_4) δ 6.37 (t, 1, J = 5 Hz, C=CH), 2.13 (m, 2, C=CHCH_2), 1.88–1.50 (m, 4), and 1.15 (s, 6, CH_3).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.03; H, 9.70; N, 10.53.

1-Cyano-3-bromo-6,6-dimethylcyclohexene (8). A mixture of 135 g (1.00 mol) of **7**, 195.8 g (1.10 mol) of *N*-bromosuccinimide, 0.25 g of benzoyl peroxide, and 1.0 l. of reagent-grade carbon tetrachloride was stirred at the reflux temperature for 12 hr. The mixture was then cooled in an ice bath; the succinimide was removed by filtration, and the filtrate was concentrated. Reduced-pressure distillation of the residue through a 10-cm Vigreux column gave 177.4 g (0.83 mol, 83%) of **8**: bp 83° (0.60 mm); ir (neat) 1625 (C=C) and 2230 cm^{-1} (C≡N); NMR (neat) δ 6.53 (d, 1, J = 4.5 Hz), 4.80 (m, 1), 1.45–2.32 (m, 4), 1.20 (s, 3), and 1.12 (s, 3). This compound was insufficiently stable for microanalysis even when stored under nitrogen at 0°.

3-Cyano-4,4-dimethylcyclohex-2-en-1-ol (9). A mixture of 177.4 g (0.83 mol) of **8**, 91 g (0.91 mol, 10% excess) of calcium carbonate, and 900 ml of water was stirred at the reflux temperature for 24 hr. The cooled mixture was filtered into a separatory funnel and the solid material was washed with water and ether. The combined filtrate and washings were extracted with three 300-ml portions of ether. The combined ether extracts were dried over sodium sulfate, filtered to remove drying agent, and concentrated. Distillation of the residue yielded 102.9 g (0.681 mol, 82%) of **9**: bp 89–91° (0.225 mm); ir (neat) 3500 (OH), 2227 (C≡N), and 1635 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.46 (d, 1, J = 3.0 Hz, C=CH), 4.23 (br m, 1, HCOH), 2.65 (s, 1, OH), 1.40–2.17 (m, 4, CH_2CH_2), 1.20 (s, 3, CH_3), and 1.18 (s, 3, CH_3).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.27. Found: C, 71.05; H, 8.74; N, 9.53.

3-Cyano-4,4-dimethylcyclohex-2-en-1-one (10). A solution of 116.9 g (0.39 mol) of sodium dichromate dihydrate in 65 ml (1.22 mol) of 96% sulfuric acid diluted to 500 ml was added over a period of 4 hr to a stirred solution of 102.9 g (0.681 mol) of **9** in 300 ml of ether. During the addition the mixture was maintained at <10°; the mixture was then allowed to stir at room temperature for 2 hr.

The aqueous and organic layers were then separated; the aqueous layer was extracted with three 250-ml portions of ether. The organic portion and the ether extracts were combined and washed with 250 ml of 10% potassium bicarbonate solution and water and dried over magnesium sulfate. The etherate was filtered and the filtrate was concentrated. Distillation of the residue afforded 82.8 g (0.556 mol, 81.6%) of **10**: bp 64–66° (0.45 mm); ir (CCl_4) 1600 (C=C), 1688 (C=O), and 2220 cm^{-1} (C≡N); NMR ($CDCl_3$) δ 6.38 (s, 1, C=CH), 2.55 (m, 2, CH_2CH_2CO), 1.95 (m, 2, CH_2CH_2CO), and 1.35 (s, 6, CH_3); uv λ_{max} 237 nm (ε 13600), 350.5 (28); mass spectrum (70 eV) m/e 149 (M^+).

Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.33; H, 7.73; N, 9.61.

When cooled to 0°, **10** solidified as greenish-white crystals, mp 25.5–27.0°. The 2,4-dinitrophenylhydrazone was obtained from a 95% ethanol solution as canary yellow crystals, mp 219–221° (slight dec).

3-Cyano-4,4-dimethylcyclohexanone (13). **13** was prepared according to a published procedure[19] for the preparation of 3-cyanocyclohexanone from 2-cyclohexenone. From 68.9 g (0.556 mol) of **1**[13] was obtained 43.5 g (0.288 mol, 51.8%) of **13**, bp 120–122° (0.20 mm), mp 80–81.5°. The white, crystalline product was sublimed at 55° (0.13 mm): mp 84.0–84.5°; ir (CCl_4) 1725 (C=O) and 2245 cm^{-1} (C≡N); NMR (CCl_4) δ 2.18–3.00 (m, 5), 1.55–1.90 (m, 2), 1.28 (s, 3, CH_3), and 1.23 (s, 3, CH_3); mass spectrum (70 eV) m/e 151 (M^+), 136 [$(M - CH_3)^+$], 123 [$(M - CO)^+$], and 108 [$(123 - CH_3)^+$].

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.27. Found: C, 71.60; H, 8.76; N, 9.15.

Irradiation of 10 in *tert*-Butyl Alcohol. The apparatus consisted of a 2.0-l. cylindrical irradiation vessel equipped with a water-cooled internal Pyrex immersion well containing a 550-W uv lamp and fitted with provisions for maintaining a slow stream of nitrogen through the solution, and for magnetic stirring. In a typical run, 3.00 g (0.0201 mol) of **10** and 2.0 l. of *tert*-butyl alcohol freshly distilled from potassium metal were placed in the vessel. Deoxygenation was accomplished by bubbling nitrogen through the stirred solution for 1.5 hr prior to commencing the irradiation (commercial tank nitrogen was prepurified by passage through three wash bottles of Fieser's solution,[20] one bottle of saturated lead acetate solution, and finally a drying tower containing anhydrous calcium sulfate). Nitrogen was slowly bubbled through the solution during the irradiation.

Irradiation was terminated after 100 hr. The *tert*-butyl alcohol was distilled under reduced pressure, leaving 3.8 g of an amber-colored viscous oil. VPC analysis of this oil revealed the presence of a trace of residual solvent, as well as two volatile components. The volatile components were separated from the total mixture by steam distillation. The aqueous distillate was extracted with four 125-ml portions of ether. The combined ether extracts were washed with water and dried over sodium sulfate. Filtation and distillation of solvent under reduced pressure yielded 1.38 g of bright yellow oil. Analysis of the oil by VPC (column D at 135°) showed the presence of two components in a ratio of 36:64. Both components were isolated by preparative scale VPC (column C at 160°). The major component (64%) was shown by NMR and ir analyses to be unchanged **10** (29.4% recovery). Based on spectral and elemental analyses, the other component was assigned structure **11**: yield 9.50 g (0.0030 mol, 14.9% based on initial **10**; 21.1% conversion from **10**); ir (CCl_4) 1608 (C=C), 1689 (C=O), and 2212 cm^{-1} (C≡N); NMR ($CDCl_3$) δ 2.55 (m, 2, CH_2CH_2CO), 2.04 [s, 3, $C(CH_3)$=C], 1.93 (m, 2, CH_2CH_2CO), 1.33 [s, 6, $C(CH_3)_2$]; uv λ_{max} 248 nm (ε 13500), 323 (28), and 348 (sh, 25); mass spectrum (70 eV) m/e 163 (M^+).

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.58; H, 8.10; N, 8.56.

Determination of the Purity of the Stock Sample of 10. VPC Analysis. A sample of **10** was analyzed by VPC (column B at 140°); the highest detector sensitivity was used. No peaks other than that corresponding to **10** were observed. A 9:1 (v/v) mixture of **10** and **11** was prepared. Analysis of this mixture under conditions identical with those used for the pure sample showed the presence of two peaks, corresponding to **10** and **11**, in a ratio of 8.9:1.1.

Mass Spectral Analysis. A sample of **10** was analyzed by mass spectrometry. The relative intensities of the molecular ion peaks of **10** and **11** were 1254.3 and 2.0 units, respectively. Assuming equal mass spectrometer sensitivities for both compounds and comparable intensities for the molecular ions, the amount of **11** in the stock sample of **10** is no greater than 0.16%.

Irradiation of 10 in *tert*-Butyl Alcohol-d_9. A mixture of 69.6 mg (0.467 mmol) of **10** and 4.28 g of *tert*-butyl alcohol-d_9 was placed in a 15 × 75 mm Pyrex tube to which a ⅋ 14/20 outer joint was sealed. The contents were deoxygenated with ultrahigh purity nitrogen for 5 min, after which the tube was tightly capped with a ⅋ 14/20 stopper. The tube was clamped against the outer surface

of a vertical Pyrex cooling well containing the 550-W Hg lamp. The sample was irradiated for 143.5 hr. VPC analysis (column A at 105°) of the crude photolysate showed, in addition to solvent, the presence of two major peaks. After distillation of the *tert*-butyl alcohol-d_9 at atmospheric pressure, the two volatile components were isolated by preparative VPC (column C at 162°). High-resolution mass spectral analysis of the component corresponding to **10** showed a molecular ion at *m/e* 149.0842 (M^+ calcd for **10**: *m/e* 149.0840). The major fragment ions at *m/e* 134, 121, 107, and 79 are also consistent with the structure of **10**. Analysis by high-resolution mass spectrometry of the other component (whose VPC retention time corresponded to that of **11**) showed a molecular ion at *m/e* 166.1185 (M^+ calcd for $C_{10}H_{10}D_3NO$: *m/e* 166.1186) as well as peaks at *m/e* 165.1128 (calcd for $C_{10}H_{11}D_2NO$: *m/e* 165.1123) and 163.0997 (calcd for $C_{10}H_{13}NO$: *m/e* 163.0996). This component was assigned structure **12**.

The above spectrum also exhibits an intense peak at *m/e* 151.0997, which does not correspond to $(M - CH_3)^+$ for **12** (calcd for $C_9H_7D_3NO$: *m/e* 151.0951). Rather, this peak corresponds to $C_9H_{13}NO$ (calcd *m/e* 151.0996). Analysis by field ionization mass spectrometry also showed an intense *m/e* 151 peak, suggesting a molecular ion. Under the conditions employed for VPC isolation of **12**, any **13** present in the reaction mixture could have eluted simultaneously.

Irradiation of 10 in Cyclohexane. A solution of 2.0 g (0.013 mol) of **10** in 750 ml of cyclohexane (Matheson Spectroquality) was placed in an apparatus similar to that described for the irradiation of **10** in *tert*-butyl alcohol. Deoxygenation was effected by bubbling nitrogen through the solution for 3 hr prior to and during the irradiation. The reaction was monitored by VPC (column A at 98°); 80% of the initial **10** had been consumed after 4.5 hr. Prolonged irradiation (44.5 hr) did not result in further destruction of starting material. Inspection of the solution surface of the lamp well revealed the presence of a coating of ivory-colored solid (accounting for the lack of complete destruction of **10**); this solid was non-VPC volatile. VPC analysis (column A at 98°) of the crude photolysate did not indicate the presence of any components which were not present in the initial mixture. Distillation of the solvent under reduced pressure afforded a residue of extremely viscous, honey-colored syrup; repeated extraction of this material with hexane and reduced-pressure distillation of hexane from the combined extracts resulted in isolation of a very small amount of **10**. No other low molecular weight compounds could be isolated.

Reaction of 10 with Di-*tert*-butyl Peroxide in *tert*-Butyl Alcohol. To a solution of 5.0 g (0.034 mol) of **10** in 1.0 l. of *tert*-butyl alcohol contained in a 2-l. glass-lined autoclave was added 4.96 g (0.034 mol) of di-*tert*-butyl peroxide. The autoclave was purged with nitrogen and sealed, and the contents were heated at 120° for 65 hr, during which an internal pressure of 70 psig was observed.

After distillation of solvent from the cooled reaction mixture under reduced pressure there remained a dark yellow oil. VPC analysis of this oil (column A at 100°) showed the presence of 14 components (in addition to residual di-*tert*-butyl peroxide), of which six accounted for greater than 98% of the total peak area. No absorption below δ 4.0 was detected in the NMR spectrum ($CDCl_3$) of this mixture, although a strong singlet absorption at δ 2.0 indicated the possible presence of **11** as a major component of the mixture. The complexity of the δ 0.7–1.6 region indicated the presence of an appreciable amount of polymeric material. The volatile components were removed from this mixture by steam distillation. The aqueous distillate was extracted with chloroform and the combined extracts were dried over magnesium sulfate. Filtration and removal of solvent under reduced pressure yielded 3.31 g of a light yellow oil which by VPC analysis (column B at 130°) was found to contain six components. The mass spectra of these components were determined by eluting the separated components from the VPC (column E, programmed from 80 to 120° at 6°/min) into the mass spectrometer. The data obtained are given in Table I. The mass spectrum of component A exhibited gradually decreasing peak intensities up to about *m/e* 180; no discrete molecular ion or fragmentation pattern was observed. The fragmentation pattern of component B was essentially identical with that of **10**, as was the VPC retention time. This component thus corresponds to unreacted **10**. Component C was isolated by preparative VPC (column B at 130°). The mass, ir, and NMR spectra were identical with those of **11**. The mass spectrum of component D indicated a molecular weight of 165, with major fragments at *m/e* 150 $[(M - CH_3)^+]$, 137 $[(M - CO)^+]$, and 122 $[(150 - CO)^+]$; this spectrum has the same general appearance as the mass spectrum of **13**. The NMR spectrum exhibited complex multiplets at δ 2.15–2.90, 1.45–2.10, and 1.09–1.43. The sharp singlet at δ 2.04 corresponding to $CH_3C{=}C$ in **11** was not present in this spectrum. The above data suggest that component D is **14**. This compound was not analyzed further. The fragmentation pattern in the mass spectrum of component E (M^+ 179) is identical with that of D, with all *m/e* values 14 units higher. Further analyses of components E and F were not carried out.

Table I

Component	Retention time, min[a]	Parent ion, *m/e*	mmol	% yield[b]
A	4.5	*c*		
B (**10**)	5.6	149	0.44	1.3[d]
C (**11**)	6.8	163	15.29	45.6
D	8.2	165	2.69	8.0
E	9.8	179	0.92	2.8
F	14.4	*c*	0.40	1.2

[a] Column B at 130°. [b] Based on initial moles of **10**. [c] Uncertain. [d] Unreacted **10**.

Heating of 1 with Di-*tert*-butyl Peroxide in *tert*-Butyl Alcohol. To a solution of 1.00 g (8.1 mmol) of **1** in 650 ml of *tert*-butyl alcohol contained in a 2-l. glass-lined autoclave was added 1.18 g (8.1 mmol) of di-*tert*-butyl peroxide. The solution was purged with ultrahigh purity nitrogen and the autoclave was immediately sealed. The contents were heated at 120° for 60 hr.

Analysis of the cooled mixture by VPC (column B at 120°) revealed that no new components were present in the mixture. Removal of solvent under reduced pressure yielded a light yellow oil which by VPC and NMR analyses was shown to be unreacted **1** contaminated with a small amount (<10%) of nonolefinic polymeric material. This oil was not analyzed further.

Heating of 10 with *tert*-Butyl Alcohol in the Absence of Di-*tert*-butyl Peroxide. A solution of 1.0 g (6.7 mmol) of **10** in 600 ml of *tert*-butyl alcohol was heated for 60 hr under conditions identical with those described above for **1**, except that no di-*tert*-butyl peroxide was added. The cooled solution was distilled under reduced pressure to remove solvent. Analysis of the residual yellow oil by VPC (column A at 104°) revealed that no new monomeric material had been formed. No further analyses were performed.

Registry No.—**1**, 1073-13-8; **5**, 1193-47-1; **7**, 56830-35-4; **8**, 56830-36-5; **9**, 56830-37-6; **10**, 54303-58-1; **10** 2,4-DNP, 56830-38-7; **11**, 56830-39-8; **12**, 56830-40-1; **13**, 56830-41-2; sodium cyanide, 143-33-9; *N*-bromosuccinimide, 128-08-5; *tert*-butyl alcohol, 75-65-0; *tert*-butyl alcohol-d_9, 25725-11-5.

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Synthesis, Photooxygenation, and Diels–Alder Reactions of 1-Methyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene and 1,4a-Dimethyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene

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The model dienes 1,4a-dimethyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (**1b**) and 1-methyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (**1a**) were synthesized. The intermediate, 2-bromo-*trans*-4,10-dimethyl-*trans*-3-decalone (**5b**), was prepared by bromination of the corresponding decalone, whereas 2-bromo-4-methyl-*trans*-3-decalone (**5a**) was made by a method involving the bromination of the kinetically produced 1-methyl-2-trimethylsilyl enol ether 1,4,4a,5,6,7,8,8a-*trans*-octahydronaphthalene (**4**). Dehydrobromination, followed by reduction, and then alumina dehydration, yielded the dienes **1a** and **1b**. Dye-sensitized photooxygenation of **1a** yielded as the major product the peroxide adduct. Dye-sensitized photooxygenation of **1b** gave products derived exclusively from an "ene" allylic hydrogen abstraction and shift of double bond. Reaction of the dienophile 4-phenyl-1,2,4-triazoline-2,5-dione with **1a** yielded exclusively the Diels–Alder adduct, while reaction with **1b** afforded a mixture of Diels–Alder adduct and product derived from allylic hydrogen abstraction and shift of double bond.

The study of the steric effects of axial, angular methyl groups on ring A of sesquiterpenes and related compounds led us to synthesize model compounds **1a** and **1b**. The route chosen for the synthesis was designed to serve as a model for the reexamination of 3-keto steroid bromination. The position of bromination of these steroids is determined by the stereochemistry of the A–B ring junction, and by the presence of α substituents.[1] Earlier attempts by Gunstone[2] and Yanagita[3] to brominate **3b** yielded a mixture of nonisolable products, and it was concluded, on the basis of their dehydrobromination, that the chief product was the 4-bromo derivative. Corey's bromination of tetrahydrosantonin[4] gave the 2-bromide.

Decalones **3a** and **3b** are obtained, respectively, from the reduction of octalones **2a**[5] and **2b**[6] (Scheme I). Bromination of **3b** at 0° yields exclusively 2α-bromo-*trans*-3-decalone **5b** as a white solid. The assignment of the bromine to the 2α position, on the basis of its NMR, is consistent with published results ($J_{ax,ax}$ = 13, $J_{ax,eq}$ = 6 Hz, similar to coupling constants for 2α-bromocholestanone).[7] Attempts at direct bromination of decalone **3a** gave poor yields (less than 6%) of the 2-bromo analog. The 4-bromide is the major product, indicating the important steric effects of the angular methyl group. Bromination of **3a** to yield the 2-bromide is obtained in good yield from the silyl enol ether **4**.[8] Dehydrobromination with lithium carbonate in dimethylformamide, followed by reduction of the resulting unsaturated ketone with aluminum isopropoxide, gives the respective epimeric alcohols **7a** and **7b**. Dehydration of **7b** yields only one diene, **1b**; dehydration of **7a** gives two products, separable by vapor gas chromatography. The major product (85%) is the desired diene **1a** (Scheme I). Structure proof of **1a** was accomplished by conversion of its photooxygenation products to known derivatives.

Photooxygenation.[9] The photooxygenation of dienes **1a** and **1b** yields differing results.

With diene **1b**, the crude product obtained is identified as the mixture of hydroperoxides **9** and **10**. The lack of peroxide formation, which would have resulted from the Diels–Alder type, [4 + 2] addition, is based upon the following observations: first, the NMR of the crude product shows the angular methyl group shifted downfield to δ 1.05, as the geometry of the molecule forces it into the deshielding region of the π system of the cross-conjugated double bonds in compound **9**; second, the NMR does not reveal any peaks in the region where the "expected" peroxide should occur [cf. NMR of ascaridole (Varian, spectrum 276)]; and finally, the conversion of the crude product to a known derivative. In **9** and **10** it is assumed that, because of steric hindrance, oxygen has approached from below the plane of the molecule, justifying the stereochemistry as shown. The results of photooxygenation of **1b**, and proof of structure, are shown in Scheme II.

Attempts at product separation by column chromatography failed, perhaps owing to the thermal instability of the hydroperoxides and to their ease of dehydration and/or rearrangement. The hydroperoxide mixture is oxidized with the Sarett[10,11] reagent to yield ketones **11** and **12**, which are easily separable by vapor phase chromatography. The major product **11** (85–90%) is identical with an authentic sample prepared by an alternative method.[12] Thus, the photooxygenation of **1b** proceeds exclusively by the "ene" path, abstracting a hydrogen with a shift of a double bond.

Photooxygenation of **1a** yields a mixture of products separable by silica gel column chromatography. Scheme III shows the various products formed, and proof of their structure.

On the reasonable assumption that **13** and **16** are derived from peroxide **14**, it can be seen that photooxygenation of **1a** yields at least 80% of the [4 + 2] adduct. Since there is no steric restriction to the approach of oxygen from either side, a mixture of two diastereomeric peroxides is obtained. Mild reduction of **14** yields the diastereomeric dialcohols **17**; oxidation with the Sarett reagent affords the keto alcohol **16**, which is also obtained from the rearrangement of **14** on basic alumina. Final proof is confirmed by aromatizing the keto alcohol to the naphthol derivative **18**. This also indicates that the starting diene is **1a**, rather than **8**, its iso-

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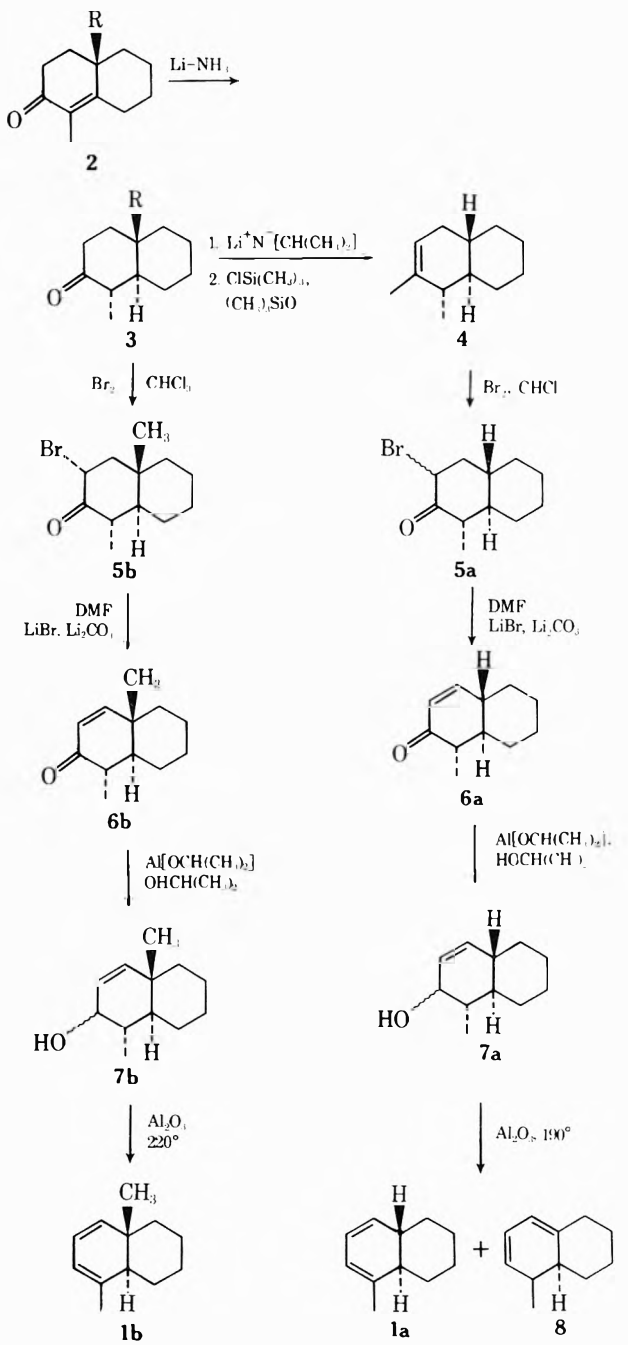
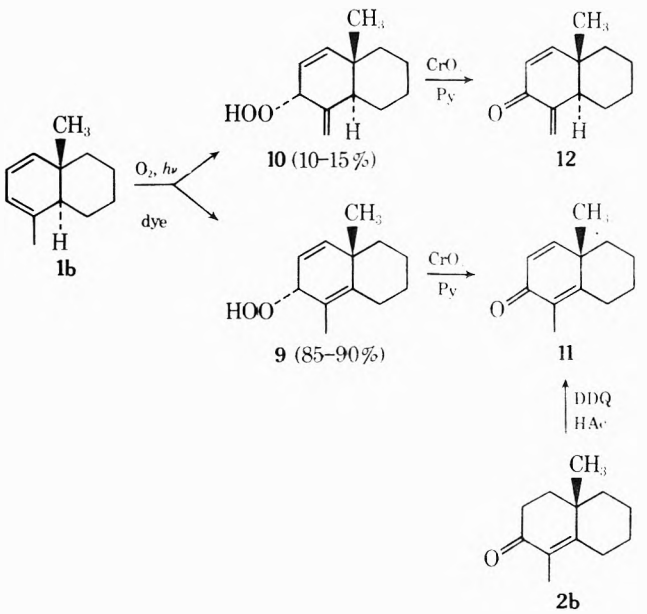
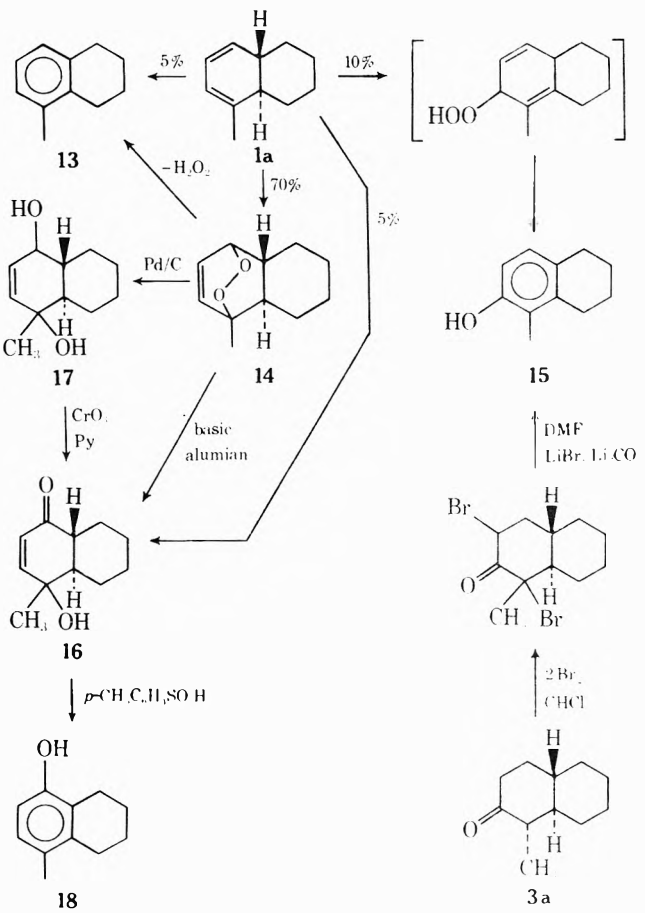
Scheme I



Scheme II
Photooxygenation of 1,4a-Dimethyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (1b)



Scheme III
Photooxygenation of 1-Methyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (1a). Proof of Structures

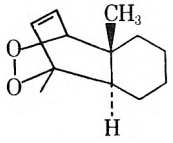


mer. The melting point of 18 and that of its acetate agree with published melting points.[13] The isomeric tetrahydronaphthol 15, which is obtained in low yield, can be considered as being derived from an allylic "ene" reaction, followed by dehydration; its structure is established by synthesizing a sample by a different route, and comparing spectra, melting points, and mixture melting points. Final proof of the identities of the two tetrahydronaphthols 15 and 18 is obtained by comparing their NMR spectra before and after the addition of the shift reagent Pr(fod)$_3$-d_{27}. Before adding the reagent, the two NMR spectra are almost identical; upon the addition of the reagent to 15 the ortho proton shifts upfield 20 Hz; the methyl group shifts 19 Hz upfield. Addition of the same quantity of the shift reagent to 18 causes a shift of the σ proton about 20 Hz upfield, while the methyl group shifts only 1 Hz upfield.

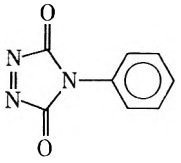
Further elution of the silica gel column with ether yields about 10% of a mixture, which was not characterized further.

The divergence in the course of reaction between dienes 1a and 1b can be attributed to the effect of the angular

methyl group. **1a** reacts by the "normal" cycloaddition, yielding a peroxide as the major product, with the minor product resulting from a concerted "ene" abstraction of a hydrogen with a shift of a double bond. Diene **1b** has a methyl group at the 4a position, which sterically prevents approach of oxygen from above the plane, thus hindering the formation of a C–O bond. Approach from below the plane of the molecule would yield a bicyclic compound with a strong 1,3-diaxial interaction between the angular methyl group and an ethylenic bridge.

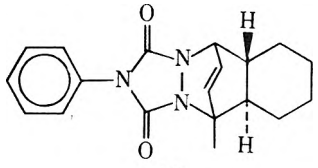


Diels–Alder Reactions. Since dienes **1a** and **1b** show different modes of reaction toward singlet oxygen, which is considered a weak dienophile, it becomes interesting to compare their reactions with a more potent dienophile, 4-phenyl-1,2,4-triazoline-3,5-dione (**19**).



19

Reaction of **1a** and **19** proceeds smoothly and rapidly, as expected, and the crimson-red color of **19** disappears instantly. The only product isolated is the Diels–Alder adduct **20**. The assignment of the structure is based upon the



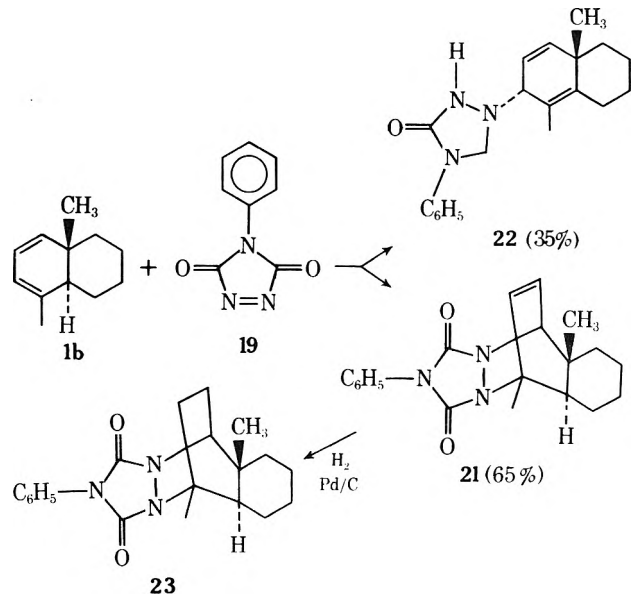
20

following: no N–H stretch in the ir spectrum; the disappearance of the 262-nm uv peak of the diene; the appearance of two olefinic protons in the NMR spectrum, δ 6.1–6.7 (six peaks), similar to those of the photooxygenation product **14**; the NMR shows also two kinds of methyl groups, at δ 1.90 and 1.85, consistent with the diastereomeric nature of the product; finally, the mass spectrum shows a molecular ion peak at *m/e* 323, exhibiting a loss of 82 at *m/e* 241, which arises from a retro-Diels–Alder reaction involving the loss of cyclohexene.

The reaction of diene **1b** with **19** also proceeds rapidly at 0°; two products are isolated by column chromatography, as shown in Scheme IV. The first product (65%) is identified as the Diels–Alder adduct **21**, based upon the following: lack of N–H stretch in the ir, two olefinic protons in the NMR at δ 5.65 and 6.15, the disappearance of the diene uv absorption at 264 nm, and a molecular ion peak M^+ at *m/e* 337. Upon hydrogenation of **21**, 1 mol of hydrogen is taken up, and the mass spectrum has molecular ion peak M^+ at *m/e* 339, with a loss of 97, corresponding to a loss of a hydrogen atom and methylcyclohexene.

The second fraction (35%) is identified as the cross-conjugated diene **22**; ir shows an N–H stretch at 3100 cm^{-1}; also, NMR shows two vinylic hydrogens at δ 5.65, and a shifted angular methyl group to δ 1.02; its molecular ion peak M^+ is at *m/e* 337, and the uv absorption of diene **1b** at 264 nm has disappeared. In **22** and **21**, it is assumed that attack is from the less hindered side, below the plane of the molecule.

Scheme IV
Diels–Alder Reactions of 1b



It is interesting to note here that **20** is such a potent dienophile that it gives a Diels–Alder adduct, even at the expense of a 1,3-diaxial interaction in **1b**. Conversely, **1b** is one of the few cis-conjugated dienes that gives a product, **22**, that is not a result of a [4 + 2] addition.

The exact mode of attack leading to product **22**, namely, the abstraction of a hydrogen with a shift of a double bond, is not yet known fully, but it is assumed here that the reaction proceeds by an "ene" concerted fashion, rather than by a radical process. This is analogous to the reaction of singlet oxygen, and of diethyl azodicarboxylate. An attempt was made to carry out a reaction of **1b** with maleic anhydride. Although not as potent as **19**, this dienophile is very reactive, more so than dimethyl acetylenedicarboxylate.[14] It reacts at room temperature with cyclohexadiene,[15] yielding the Diels–Alder adduct exclusively. However, when maleic anhydride was refluxed in benzene with **1b** up to 48 hr, the starting compounds were recovered unchanged.

Experimental Section

All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer 137 spectrophotometer. The ultraviolet spectra were measured on a Cary 14 spectrophotometer. The NMR spectra were obtained with a Varian A-60 spectrometer; tetramethylsilane was used as an internal standard for all compounds. Mass spectra were obtained on A. E. I. MS-902 mass spectrometer.

VPC analyses were performed on a Varian Model 90-P instrument employing helium as the carrier gas. Retention times are reported in minutes from the air peak and are designated as t_R, helium flow 60 ml/min except where indicated. Column A refers to a 10 ft × 0.25 in. o.d. column of 20% Carbowax on Chromosorb W. Column B refers to a 10 ft × 0.25 in. o.d. column of 10% SE-30 on Chromosorb W. Thin layer chromatograms (TLC) were made with EM reagents silica gel GF-254 (Type 60) and developed with ether in benzene. For column chromatograms, Fisher silica gel (28–200 mesh) or Fisher alumina (80–200 mesh) was used.

Isolation involved dissolving in the indicated solvent, washing with brine, drying with magnesium sulfate, and evaporation of solvent on a rotary concentrator. Elemental analysis were performed by the Baron Consulting Co., Orange, Conn. *trans*-1,4a-Dimethyloctahydro-*trans*-2-naphthalenone (**3b**) and methyloctahydro-*trans*-2-naphthalenone (**3a**) were prepared by reduction of the corresponding octalones **2b**[6] and **2a**[5] with lithium in ammonia.[16]

***trans*-1,4a-Dimethyl-3α-bromooctahydro-*trans*-2-naphthalenone (5b).** A solution of decalone **3b** (54.0 g, 0.30 mol) in 1500 ml of chloroform at 0° was treated, all at once, with a solution of 2.00 *M* bromine in chloroform (155 ml, 0.31 mol). After an in-

duction period of 45 min, the red color disappeared. Stirring was continued at 0° for an additional 45 min. Addition of water, followed by washing with saturated sodium bicarbonate, then brine, separation of layers, and evaporation of the chloroform yielded a yellow oil, to which hexane (200 ml) was added and the solution was stored overnight under refrigeration. The resulting solid (45.1 g, 52%) was filtered and recrystallized from pentane–ether. It was identified as the 3α-bromo derivative: mp 70–71°; *m/e* molecular peak at 258.0583 (calcd, 258.0616); ir ($CHCl_3$) ν 1720 cm^{-1}; NMR ($CHCl_3$) δ 1.0 (d, 3 H, J = 6 Hz, CH_3-1), 4.80 (1 H, four lines, CHBr, $J_{3a,4a}$ = 13, $J_{3a,4e}$ = 6 Hz). Dehydrohalogenation of 1.0 g of the mother liquor showed (GLC) a mixture of starting decalone **3b**, Δ^1-octalone (**6b**), and Δ^4-octalone (**2b**) in approximately equal quantities.

Anal. Calcd for $C_{12}H_{19}OBr$: C, 55.61; H, 7.39. Found: C, 55.95; H, 7.58.

***trans*-1,4a-Dimethyl-4a,5,6,7,8,8a-hexahydro-*trans*-2(1*H*)-naphthalenone (6b).** The procedures of Holysz[17] and Corey[4] were followed. To a stirred suspension of dry lithium bromide (30.0 g) and lithium carbonate (50.0 g) in 300 ml of dimethylformamide (purified by distilling from benzene) at 125° (oil bath temperature) under nitrogen was added 24.0 g (0.15 mol) of bromo ketone **5b**. Stirring was continued for 3 hr. The reaction mixture was then cooled and filtered, and the solid was washed with hexane; to the combined filtrate and washings, brine was added, then it was extracted with hexane. Isolation by vacuum distillation (108–110°, 5 mm) gave a colorless oil in 80% yield (21.6 g): ir (film) ν 1680 (C=O), with inflection at 1610 cm^{-1} (C=C). NMR exhibits the AB pattern as two doublets, J = 9.5 Hz [centered at (CCl_4) δ 5.72 and 6.65]; also, δ 1.08 (s, 3 H, CH_3-4a), 0.94 (d, J = 6 Hz, CH_3-1). This compound was judged pure (over 98%) by GLC (column A, 160°; t_R 14.5 min).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.68; H, 9.95.

1-Methyl-4a,5,6,7,8,8a-hexahydro-*trans*-2(1*H*)-naphthalenone (6a). To 55.6 ml of a 1.8 *M* ether solution of methyllithium (100 mmol) (Alfa Inorganics, Inc.) at 0°, under nitrogen, was added, dropwise with stirring, 10.10 g (100 mmol) of diisopropylamine[18] (purified by distilling from calcium hydride) in 50 ml of dry ether, containing 20 mg of bipyridyl as indicator. To this deep-red solution of lithium diisopropylamide was added, dropwise over a period of 15 min, 16.3 g (99.8 mmol) of decalone **3a**, until the color turned faint pink. The solution was stirred for an additional 2 min; to this cold (0°) lithium enolate solution was added rapidly a quenching solution of chlorotrimethylsilane [prepared from 30 ml of freshly distilled chlorotrimethylsilane (Aldrich Chemicals) added to 10 ml of anhydrous triethylamine and 50 ml of dry ether, and filtered through a sintered glass funnel]. Within 1 min after addition, a white precipitate (LiCl) began to separate. The mixture was allowed to warm to room temperature, refluxed for 1 hr, and stirred for an additional 2 hr at room temperature. It was then partitioned between pentane and cold $NaHCO_3$. The organic layer was dried, concentrated, and distilled through a short Vigreux column to give a colorless liquid, which on GLC (column A, 160°, t_R 6.5 and 12.0 min) showed a mixture of 85–90% trimethylsilyl enol ether **4** and 10–15% starting decalone **3a**. 1-Methyl-2-trimethylsilyl enol ether 1,4,4a,5,6,7,8,8a-*trans*-octahydronaphthalene (**4**) was isolated by passing the mixture through a column of neutral alumina, eluting with pentane, and fractionally distilling (98–100°, 2 mm).

The pure (less than 2% of isomer) trimethylsilyl enol ether exhibited a mass spectrum *m/e* molecular peak at 238.1755 (calcd, 238.1752) with fragment peaks at 223 ($-CH_3\cdot$), 75 [HO^+=$Si(CH_3)_2$], and 73 [$Si^+(CH_3)_3$]; ir (film ν 1675 (sh, C=C), 750 cm^{-1} (br); NMR (CCl_4) δ 0.0 [s, 9 H, $Si(CH_3)_3$], 0.88 (d, J = 6 Hz, CH_3-1), and 4.65 (m, 1 H, CH-3).

To 19.0 g (0.080 mol) of enol ether **4** in 200 ml of chloroform containing 6.5 g (0.080 mol) of sodium acetate at −20° was added 40 ml of a 2.00 *M* Br_2–$CHCl_3$ solution (0.080 mol) in one portion. The red bromine color disappeared instantly. The mixture was stirred for 5 min, then poured into a cold saturated sodium bicarbonate solution and isolated as a light yellow oil. It was characterized as a mixture of 4:1 3β-bromide (NMR δ 4.42, m) to 3α-bromide (δ 4.78, four lines). The solution was directly dehydrobrominated in dry dimethylformamide, as above. Isolation yielded 10.5 g (80% from the decalone) of 1-methyl-4a,5,6,7,8,8a-hexahydro-*trans*-2(1*H*)-naphthalenone (**6a**): ir (film) ν 1680 (C=O), with inflection at 1610 cm^{-1} (C=C); NMR (CCl_4) δ 1.04 (d, J = 6 Hz, 3 H, CH_3-1), 5.80 (d, J = 9 Hz, 1 H, exhibiting long-range coupling, J = 2 Hz, CH-3), 6.64 (two multiplets, J = 9 Hz, 1 H, CH-4). This compound was judged over 95% pure by GLC (column A, 160°; t_R 14.0 min).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.39; H, 9.79. Found: C, 80.44; H, 9.82.

***trans*-1,4a-Dimethyl-2-hydroxy-1,2,4a,5,6,7,8,8a-*trans*-octahydronaphthalene (7b).** To a freshly distilled (40.0 g) portion of aluminum isopropoxide and 500 ml of dry isopropyl alcohol was added 17.8 g of the octalone **6b** in a 1-l. flask fitted with a long Vigreux column.[19] The mixture was allowed to boil gently, the solvent being allowed to escape slowly from the reaction mixture. After 12 hr, the distillate was tested with a solution of 2,4-dinitrophenylhydrazine, the test indicating that no more acetone was being formed. After cooling, the solution was concentrated to ca. a 50-ml volume, and cold 10% hydrochloric acid was added. The resulting acidic solution was extracted with ether and neutralized with bicarbonate. Isolation gave a pale yellow viscous oil, which was distilled at 103–105° (0.5 mm) to give 15.2 g (85%) of the alcohol **7b**, which solidified on standing: ir ($CHCl_3$) ν 3550 cm^{-1} (s, COH). NMR ($CDCl_3$) exhibited the isomeric nature of the product, δ 5.40 and 5.60 (two singlets, vinyl protons), 3.62 and 3.24 (2 m, 1 H, CHOH).

1-Methyl-2-hydroxy-1,2,4a,5,6,7,8,8a-*trans*-octahydronaphthalene (7a). This was prepared as above. Thus 5.0 g of 1-methyl-4a,5,6,7,8,8a-hexahydro-*trans*-2(1*H*)-naphthalenone (**6a**) yielded 4.30 g (85%) of the alcohol **7a** in an isomeric mixture (bp 95–97°, 92 mm): ir ($CHCl_3$) ν 3550 cm^{-1} (strong, COH); NMR ($CDCl_3$) δ 5.50 and 5.65 (two singlets, vinyl protons), 3.70 and 3.78 (2 m, 1 H, CHOH). Upon taking up in pentane, one of the two isomers crystallized, mp 86–87°.

1,4a-Dimethyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (1b). A finely ground mixture of 500 mg of the dimethyl alcohol **7b** and 1.5 g of alumina (Woelm, grade I, neutral) which had been previously treated with 2% (v/w) of pyridine,[20] in a 10 ml flask under nitrogen, was introduced into a preheated oil bath (220°) for 5.5 min. The oil bath was then removed, and the flask immediately cooled in a beaker of cold water. The combined products obtained from four runs were extracted with ether, and the solvent removed on a steam bath. Chromatography on alumina with pentane as eluent yielded the diene as a colorless liquid. (Further elution of the column with benzene gave starting alcohol.) The diene **1b** was distilled (130–132°, 65 mm) giving 920 mg (52%), *m/e* 162.1394 (calcd, 162,1404), judged over 98% pure by GLC (column B, 125°, t_R 12.0 min) at a flow rate of 30 ml helium: uv λ_{max} (95% ethanol) 264 nm (ϵ 5000); ir (film) ν 1650 (w), 1590 (w), 840 (m), 720 cm^{-1} (s); NMR (CCl_4) δ 0.82 (s, 3 H, CH_3-4a), 5.65 (m, 3 H).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.60; H, 11.25.

1-Methyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (1a). A finely ground mixture of 300 mg of the related 1-methyl alcohol **7a** and 1.2 g of the pyridine-treated alumina in a 10-ml flask under nitrogen was introduced in a preheated oil bath (190°) for 4.0 min. The combined products obtained from six runs were extracted with ether, and the ether evaporated on a steam bath. It was then passed through an alumina column, eluted with pentane, to yield 480 mg (28%) of a colorless liquid. (Further elution of the column with benzene gave starting alcohol.) GLC showed a mixture of two dienes which were separated (column B, 125°, flow rate 30 ml/min He, at 9.5 and 12.0 min). The first product (15%) was identified as the isomeric 1-methyl-1,5,6,7,8,8a-hexahydronaphthalene, **8**: uv λ_{max} (95% EtOH) 267 nm (ϵ 4800); ir (film) ν 1650 (w), 1690 (w), 700 cm^{-1} (s); NMR (CCl_4) δ 1.05 (d, J = 6 Hz, 3 H, CH_3-1) and 5.6 (m, 3 H). The second product (85%) was identified as the desired trans diene **1a**, which exhibited uv λ_{max} (95% EtOH) 262 nm (ϵ 4900); ir (film) ν 1650 (w), 1580 (w), 760 (m), 700 cm^{-1} (s); NMR (CCl_4) δ 1.80 (s, 3 H, CH_3-1) and 5.65 (m, 3 H).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.30; H, 10.72.

Photooxygenation of 1-Methyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (1a). A solution of 450 mg (3.05 mmol) of the diene and 30 mg of sensitizer (methylene blue or eosin Y) in 300 ml of 95% ethanol was irradiated with a 300-W light bulb, while a finely dispersed (through a bubbler) stream of oxygen was bubbled through the reaction mixture. A cold water finger was used to keep the temperature of the reaction vessel below 25°. The reaction was complete in 50 min when methylene blue was used as sensitizer, while the use of eosin Y required 12 hr. The solvent was then removed on a rotovap, keeping the temperature below 30°. The resulting product (510 mg) was chromatographed on 20 g of silica gel, using 25% hexane in benzene as eluent, to give five separate components. The first compound to be eluted (25 mg, 5%) was a liquid, identified as 1-methyl-5,6,7,8-tetrahydronaphthalene (13):

ir (film) ν 1610, 1440, 760, 720 cm^{-1} (identical with spectrum in Sadtler, prism 8214); NMR (CCl_4) δ 2.15 (s, 3 H, CH_3-1) and 6.88 (s, 3 H, aromatic protons).

The next component (310 mg, 70%) was a pale yellow oil, identified as the diastereomeric mixture of peroxides **14**, *m/e* molecular peak at 180.1152 (calcd, 180.1142) with abundance at 146 − (O_2 + H_2); ir (film) ν 1440, 1360, 1060, 890, 755, 705 cm^{-1}; NMR ($CDCl_3$) δ 1.28 and 1.30 (2 s, 1.2 H and 1.8 H, CH_3-1), 4.28 and 4.30 (2 m, 1 H), 6.0–6.9 (six lines, 2 H).

The third component to be eluted (45 mg, 10%) solidified upon evaporation of eluent. It was recrystallized from petroleum ether, and identified as 1-methyl-2-hydroxy-5,6,7,8-tetrahydronaphthalene (**15**), mp 113–114°, identical with sample prepared from dibromination–dehydrobromination of parent decalone **3a** (undepressed mixture melting point).

The fourth component (25 mg, 5%) was identified as the keto alcohol **16**, identical (spectra, TLC) with ketol obtained from further treatments of the peroxide (see below), crystallized from hexane, mp 58–60°.

Further elution with ether produced 40 mg (10%) of a mixture of at least two products (TLC), which from their retention time and spectra (ir) might contain a hydroperoxide and were not investigated any further.

Structure Proof of Peroxide 14. A. Rearrangement of Peroxide 14 to the Hydroxy Ketone 16. Peroxide **14** (50 mg) was well mixed with 1.5 g of alumina (Woelm, basic, activity I)[21] in a test tube, saturated with ether, and stored at room temperature for 24 hr. The mixture was then transferred to a porous thimble of a Soxhlet extractor, and continuously extracted with ether for 24 hr. Solvent evaporation gave 40 mg (80%) of the hydroxy ketone, identical with **16** (see below).

B. Reduction of Peroxide 14 to the Dialcohol 1,4-Dihydroxy-1-methyl-1,4,4a,5,6,7,8,8a-octahydronaphthalene (17). A solution of 200 mg (1.11 mmol) of peroxide **14** in 10 ml of absolute ethanol was stirred for 8 hr with 2.0 g of 10% palladium on charcoal[10] at room temperature. The mixture was then filtered, and the filtrate concentrated. Crystallization of the residue from ether–pentane afforded 125 mg (63%) of the dialcohol **17**: mp 131–133°; *m/e* M^+ at 182.1320 (calcd, 182.1306), showing abundant fragments at 164 (− H_2O), 146 (− $2H_2O$); ir (KBr) ν 3250, 1440 (inflection 1450), 1060, 1040, 1000, 910, 875, 780, 760, 700 cm^{-1}; NMR (acetone-d_6) δ 1.02 and 1.14 (equatorial and axial CH_3), 3.60 and 3.70 (2 m, 1 H), 5.65 and 5.72 (two kinds of vinyl protons, 2 H).

Chromatography of the mother liquor yielded a mixture of starting peroxide and 1-methyl-5,6,7,8-tetrahydronaphthalene (**13**).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.54; H, 9.96. Found: C, 72.13; H, 9.67.

C. Oxidation of Dialcohol 17 to the Hydroxy Ketone 16. A solution of 100 mg of dialcohol **17** in 3 ml of pyridine was added to the Sarett reagent[11] (prepared from 80 mg of chromium trioxide added to 5 ml of pyridine). After 7 hr of stirring at room temperature, the solution was diluted with ether, and the chromium trioxide–pyridine complex was filtered and washed with ether. The combined organic layers were washed with brine, dried, and concentrated, the last traces of pyridine removed on a vacuum pump, to leave an oil which solidified on standing (90 mg, 90%). The keto alcohol was crystallized from hexane, mp 58–60°, and proved to be identical (similar spectra, and similar aromatic product) with previous keto alcohol: ir (KBr) ν 3400 (s), 1650 (s) (inflection at 1620), 810 (m), 785 (m), 760 cm^{-1} (m); NMR ($CDCl_3$) δ 1.30 and 1.38 (two kinds of CH_3), 5.75 (1 H, d, J = 10 Hz) (two kinds), and 6.62 (1 H, d, J = 10 Hz) (two kinds).

D. Aromatization of Hydroxy Ketone 16. To 75 mg (0.42 mmol) of ketol **16** in 10 ml of benzene was added 30 mg of *p*-toluenesulfonic acid monohydrate,[22] and the mixture was refluxed for 2 hr. After cooling, the solution was poured into a column of 4 g of acid-washed alumina. Elution with benzene gave 40 mg (53%) of 1-hydroxy-4-methyl-5,6,7,8-tetrahydronaphthalene (**18**), recrystallized from petroleum ether: mp 87–88° (reported[13] mp 87.5–88.5°); acetate, mp 81–82° (reported[13] mp 82°); ir (KBr) ν 3300 (s), 1580 (m), 800 (s), 730 cm^{-1} (m); NMR ($CDCl_3$) δ 1.75 (unresolved, 4 H), 2.12 (s, 3 H, CH_3-4), 2.60 (broad, 4 H), 6.47 (1 H, d, J = 7 Hz, ortho proton), and 6.80 (1 H, d, J = 7, meta proton).

Addition of the shift reagent Pr(fod)$_3$-d_{27} caused the σ hydrogen to shift upfield 20 Hz, while the methyl group shifts upfield 1 Hz. The amount of reagent added is equal to about 20% by weight of tetralone.

Synthesis of 1-Methyl-5,6,7,8-tetrahydro-2-naphthol (15). To 166 mg (1 mmol) of decalone **3a** in 10 ml of $CHCl_3$ was added 2.01 ml (2.01 mmol) of a solution of 2.00 *M* bromine in chloroform. The crude bromide was collected as a light brown oil, and dehydrobrominated as before to yield an oil which solidified on standing. Recrystallization from petroleum ether yielded 1-methyltetrahydro-2-naphthol: mp 112–113° (reported[24] mp 113–114°); ir (KBr) ν 3300 (s), 1580 (s), 1580 (m), 800 (s), 725 cm^{-1} (m); NMR ($CDCl_3$) δ 1.76 (broad, 4 H), 2.10 (s, 3 H, CH_3-1), 2.67 (broad, 4 H), 6150 (1 H, d, J = 8 Hz), and 6.80 (1h, d, J = 8 Hz). This phenol was identical with compound **15**, undepressed mixture melting point.

Addition of the shift reagent Pr(fod)$_3$-d_{27}, about 15% by weight of tetralone, caused the σ hydrogen to shift 12 Hz upfield, while the methyl singlet shifts 11 Hz upfield. Further addition to up to 20% by weight caused the σ hydrogen to shift 20 Hz upfield, while the methyl singlet shifts 19 Hz upfield.

Photooxygenation of 1,4a-Dimethyl-4a,5,6,7,8,8a-*trans*-hexahydronaphthalene (1b). Diene **1b** (500 mg, 3.1 mmol) in 300 ml of 95% ethanol was photooxygenated as above, using 25 mg of methylene blue as sensitizer, for 1 hr, the disappearance of the 264-nm peak on uv being noted (the same result is obtained if the reaction is run for 12 hr, sensitized with eosin Y). NMR of the crude product did not show any formation of a peroxide (no peaks between δ 6 and 7), but rather it showed a singlet at δ 5.75, suggesting hydroperoxide formation with shift of double bond. Also, the C-4a methyl group has shifted to δ 1.05. Attempts at column chromatographic separation yielded no peroxide, but a mixture of hydroperoxide and dehydration products (conjugated ketone) (ir, NMR).

The crude hydroperoxide (530 mg) has *m/e* molecular peak at 193.1222 (calcd, 193.1228), with abundant fragments at 175 (− H_2O).

Structure Proof of Hydroperoxides 9 and 10. Hydroperoxide mixture (300 mg) in 5 ml of pyridine was added to the Sarett reagent[23] (made from 250 mg of chromium trioxide to 10 ml of pyridine). The solution was stirred at room temperature for 10 hr. Ether was then added, and the solid chromium trioxide–pyridine complex was filtered and washed with ether. The combined etheral layers were washed with brine and dried. Isolation of the light brown residue by distillation (110–112°, 1 mm) gave a colorless oil (250 mg), shown to be (GLC, column B) a mixture of two major components in a 90:10 ratio, totaling 98% of the total products (two other minor peaks, about 2% total, also appeared). Separation of the two major peaks (column B, 110°, t_R 12.0 and 16.0 min) yielded as the first product (10%) a colorless oil, identified as 1-*exo*-methylene-4a-methyl-4a,5,6,7,8,8a-hexahydro-*trans*-2(4a*H*)-naphthalenone (**12**): ir (film) ν 1660, 1610, 840, 750 cm^{-1}; NMR (CCl_4) δ 0.95 (s, 3 H, CH_3-4a), 5.08 and 5.88 (2 H), 5.90 and 6.70 (2 H, 2 d, J = 10 Hz); uv λ_{max} (95% EtOH) 240 nm (ϵ 9600).

The second compound, also a colorless oil (90%), was identified as the cross-conjugated ketone 1,4a-dimethyl-5,6,7,8-tetrahydro-2(4a*H*)-naphthalenone (**11**): uv λ_{max} (95% ethanol) 238 nm (ϵ 11000); *m/e* molecular peak at 176.1201 (calcd, 176.1201); ir (film) ν 1110, 1620, 1610 cm^{-1}; NMR (CCl_4) δ 1.25 (s, 3 H, CH_3-4a), 1.95 (s, 3 H, CH_3-1), 6.20 and 6.78 (two doublets, J = 10 Hz, CH-3 and CH-4).

This ketone was identical (GLC coinjection, spectra) with an authentic sample prepared from published procedures.[24]

Diels–Alder Reactions. 4-Phenyl-1,2,4-triazoline-3,5-dione[25] with Diene 1b. To 162 mg (1.0 mmol) of diene **1b** in 10 ml of acetone, at 0° with stirring, was added dropwise a solution of 175 mg (1.0 mmol) of the dienophile in 3 ml of acetone; the red color of the dienophile disappeared instantly. At the end of the addition, the solution (faint pink) was stirred for an additional 5 min at 0°, and the solvent was removed under vacuum. Uv shows the disappearance of the diene peak at 264 nm; TLC (85:15 ether–benzene with a drop of triethylamine) showed two spots, R_f 0.71 and 0.58. Chromatography on a column of alumina and elution with ether gave as the first fraction (165 mg, 65%) the Diels–Alder adduct **21**, recrystallized from methanol: mp 142–144° dec; ir (KBr) ν 1750 and 1700 (C=O, strong), 1580 (w), 1390 (s), 775 (s), 740, 730, 690 cm^{-1}; NMR (Me_2SO-d_6, 50°) δ 1.04 (s, 3 H), 1.75 (s, 3 H), 4.40 (d, 1 H, J = 6 Hz), 5.65 (four lines, 1 H), 6.15 (d, 1 H, J = 8 Hz), 7.4 (s, 5 H); mass spectrum M^+ 337.1788 (calcd, 337.1790).

Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.24; H, 6.82; N, 12.46. Found: C, 70.98; H, 6.91; N, 12.33.

The second fraction (90 mg, 35%) was recrystallized from 95% ethanol: mp 184–185°; ir (KBr) ν 3100 (N–H stretch), 1750 and 1700 (C=O), 1490, 1410, 760, 750, 710, and 690 cm^{-1}; NMR (Me_2SO-d_6, 50°) δ 1.10 (s, 3 H), 1.70 (s, 3 H), 5.0 (m, 1 H), 5.65 (four lines, 2 H), 7.40 (s, 5 H); mass spectrum M^+ 337.1788 (calcd. 337.1790). It was identified as 1,4a-dimethyl-2-(4-phenylurazole)-2,4a,5,6,7,8-hexahydronaphthalene (**22**).

Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.24; H, 6.87; N, 12.46. Found: C, 71.33; H, 6.86; N, 12.60.

Hydrogenation of **21** in 95% ethanol with 5% Pd/charcoal as catalyst yielded, after evaporation of solvent, a solid, mp 164–166°, whose mass spectrum has molecular ion peak *m/e* 339.1946 (calcd for **23**, 339.1946) with abundant fragments at 242.

Infrared shows no peak from 3600 to 3100 cm^{-1} (no N–H stretch), and NMR shows no peak from δ 4.5 to 7.5 (no vinylic protons).

4-Phenyl-1,2,4-triazoline-3,5-dione with Diene 1a. To 74 mg (0.50 mmol) of diene **1a** in 5 ml of acetone, at 0°, was added dropwise a solution of 88 mg (0.5 mmol) of the dienophile in 2 ml of acetone. The red color disappeared instantly. The diene peak at 262 nm disappeared on the uv, and TLC (85:15 ether–benzene, with a drop of triethylamine) showed only one spot, R_f 72. Evaporation of solvent and recrystallization from ether–pentane yielded one product in quantitative yield, mp 143–145°, identified as the Diels–Alder adduct, **20**: ir (KBr) ν 1750 (s), 1700 (s), 1440 (m), 1390 (s), 765 (s), 750 (m), 725 (m), and 690 cm^{-1} (m); NMR (acetone-d_6) δ 1.90 and 1.85 (2 s, 3 H, CH_3-1, two kinds), 4.55 and 4.62 (2 m, 1 H), 6.1–6.8 (six lines, 2 H), 7.40 (s, 5 H); mass spectrum M^+ 323.1633 (calcd, 323.1636) exhibiting retro-Diels–Alder reaction at *m/e* 241 (− cyclohexene).

Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.62; H, 6.55; N, 13.00. Found: C, 70.30; H, 6.51; N, 12.72.

Acknowledgment. We thank Professor Robert B. Fairweather for stimulating discussions concerning this project and help in spectra interpretations.

Registry No.—**1a**, 54306-51-3; **1b**, 54306-52-4; **3a**, 21102-88-5; **3b**, 22738-31-4; **4**, 56770-99-1; **5b**, 56763-83-8; **6a**, 56771-00-7; **6b**, 56763-86-1; **7a** isomer A, 56771-01-8; **7a** isomer B, 56771-02-9; **7b** isomer A, 56771-03-0; **7b** isomer B, 56771-04-1; **8**, 56771-05-2; **11**, 707-11-9; **12**, 56771-06-3; **13**, 2809-64-5; **14** isomer A, 56771-07-4; **14** isomer B, 56816-07-0; **15**, 56771-15-4; **16** isomer A, 56771-08-5; **16** isomer B, 56771-09-6; **17**, 56771-10-9; **18**, 4242-05-1; **19**, 4233-33-4; **20**, 56771-11-0; **21**, 56771-12-1; **22**, 56771-13-2; **23**, 56771-14-3.

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A Synthesis and X-Ray Structure Determination of the Photoproducts of *A*-Homocholestan-3-one

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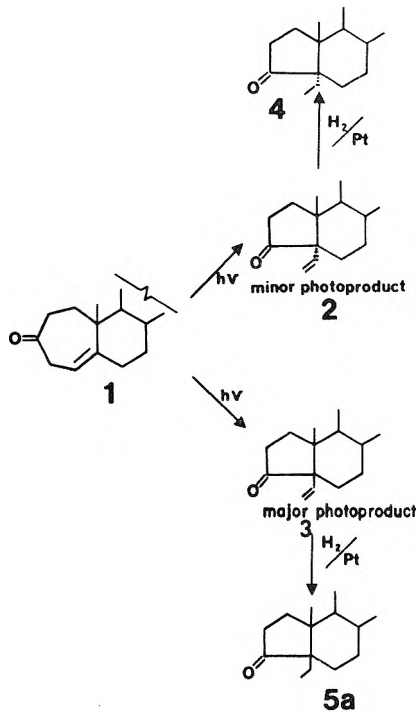
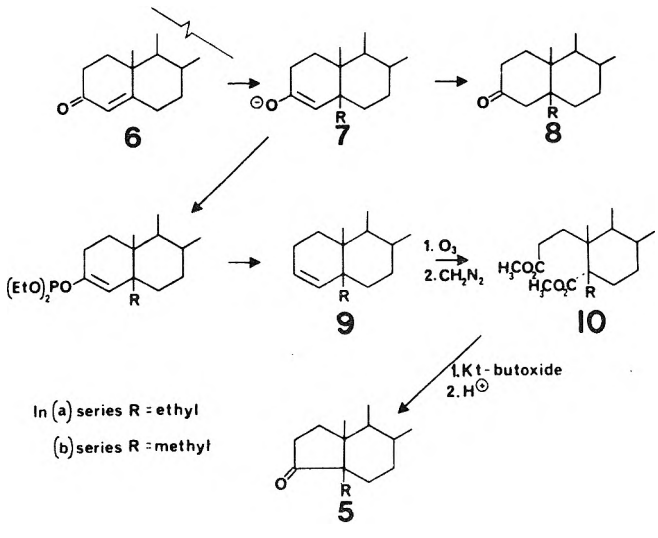
The stereochemistry assigned to the major (3) and minor (2) photoproducts of *A*-homocholest-4a(5)-en-3-one has been reinvestigated. The synthesis of 5β-ethyl-*A*-norcholestan-3-one is described; the compound is shown to be identical with the dihydro derivative of the major photoproduct. The synthesis of 5β-methyl-*A*-norcholestan-3-one is also described. The minor photoproduct, $C_{28}H_{46}O$, 5α-vinyl *A*-norcholestan-3-one, crystallizes in space group $P2_1$ with cell dimensions a = 10.429 (1), b = 7.369 (1), c = 15.605 (2) Å, β = 94.28 (2)°, and Z = 2. The structure was solved via the calculation of structure invariants and has been refined to a conventional R factor of 0.036. The relation of the absolute stereochemistry and the sign of the CD curves of the major and minor photoproducts and their dihydro derivatives are discussed.

The photochemistry of *A*-homocholest-4a(5)-en-3-one (1) and its photoproducts **2** and **3** have proven to be a rich source of mechanistic photochemical information.[2] The specificities of the observed oxadi-π-methane rearrangements and photoisomerizations of the β,γ-unsaturated ketones are summarized in Scheme I and are important in understanding the stereochemical consequences of these photoisomerizations. An essential aspect of these mechanistic evaluations centers on the stereochemical assignment of the major (3) and minor (2) photoproducts from the direct irradiation of 1. A previous study of this system by Fisher and Zeeh[3] in 1969 led them to a set of structural assignments based on interpretations of the NMR and CD spectra of the photoproducts. In order to determine the stereochemistry of these compounds unequivocally, parallel studies of the synthesis of **5a** and an X-ray crystallographic structure determination of the minor photoproduct (2) were undertaken.

Scheme I



Scheme II



Synthesis. The syntheses of 5β-ethyl-*A*-norcholest-3-one (**5a**) and 5β-methyl-*A*-norcholestan-3-one (**5b**) followed the same general procedure and are shown in Scheme II. The key feature of these syntheses is the stereoselective introduction of the β-alkyl substituent at C-5 by the addition of a lithium dialkylcopper reagent to Δ^4-cholesten-3-one (**6**). While the factors which govern the stereochemistry of this addition are not completely understood, Ireland et al.[4] have shown that the addition of lithium dimethylcopper to **6** results in the formation of only the 5β-methyl derivative **8b**. That lithium diethylcopper introduces a 5β-ethyl group was proven by comparison of the CD curves of **8a** and **8b** (Table I) formed by quenching intermediates **7a** and **7b**, respectively, with water. Alternatively, treating **7a,b** with diethyl phosphochloridate followed by reduction of the intermediate phosphonate gave **9a,b** with the established 5β-alkyl configuration. Subsequent steps in the syntheses (ozonolysis, esterification, Dieckmann condensation, hydrolysis, and decarboxylation) do not affect the configuration at C-5. A comparison of

Table I
CD Data in Methanol

Compd	CD θ	CD (λ)	Comp	CD θ	CD (λ)
2	−13400	(300)	5b	+3960	(300)
3	+10000	(300)	8a	−950	(290)
4	−4200	(295)	8b	−1075	(240)
5a	+2620	(305)			

spectral characteristics and physical properties of **5a** and the dihydro derivative of **3** showed them to be identical and quite different from the dihydro derivative of **2**. These assignments *contradict* those made previously by Fisher and Zeeh.[3]

X-Ray Structure of the Minor Photoproduct. The bond lengths, valence angles, and torsion angles for the minor photoproduct are shown in Figures 1–3. Esd's for heavier atom bond lengths are <0.003 Å except for C(25)–C(26), 0.004 Å, and C(25)–C(27), 0.005 Å. The corresponding angular esd's are <0.2°. Despite the possible distortion introduced by the change of the A ring to a cyclopentanone ring with substituents on the bridgehead atoms, the compound is in many ways a very typical steroid. The C-17 side chain is extended and all substituents, including hydrogen atoms, are placed so as to achieve relatively good gauche conformations. A gauche conformation is also present on all methyl substituents and gives a satisfactory minimization of close hydrogen contacts. The moderately high thermal motion of the terminal atoms of the C-17 side chain has produced apparent bond lengths shorter than the standard 1.54 Å and the consistent decrease in apparent bond length with position along the chain is in accord with the thermal parameters which, in their turn, are what one might expect from packing considerations.

Including atoms C(1)–C(20), the average sp^3 C–C bond length is 1.542 Å and the observed significant deviations from the mean are not unusual in steroids. The average sp^3–sp^2 C–C bond length is 1.528 Å. The longest bonds, C(5)–C(10) and C(13)–C(17), are between those carbon atoms with the greatest number of carbon substituents. Aside from the modification of the A ring, the parameters of the remainder of the molecule are remarkably similar to the "standard values" obtained by averaging appropriate steroid molecules.[5] The B and C rings show the typical steroid expansion of bond angles from the tetrahedral value, the average angles being 111.0 and 111.2°, respectively, and the average torsion angles in these rings are therefore reduced to 56.0 and 55.4° from the 60° of an undistorted symmetrical cyclohexane "chair" molecule.

The A ring, with both bridgehead atoms quaternary, has corresponding internal angles of 100°, and the D ring, with only one quaternary bridgehead atom, has an internal angle at the quaternary atom of 100° and the other angle is about 104°. The external angles between the rings follow the usual pattern. Very little conformational strain appears to have been introduced by the modification of the A ring. Although the angle between the mean planes of the A ring and the B ring is 1.7° and the corresponding angle for the C ring and the D ring is 5.7°, there does not appear to be any trend to a division of the nucleus into two units with different mean planes.

The torsion angles of the two five-membered rings are somewhat different. In terms of Altona, Geise, and Romer's[5] cyclopentane parameters Δ and θm, the values for the A ring are 10.7 and 47.9°, while those for the D ring are 15.1 and 46.3°. Since the value of Δ for the conformation of cyclopentane described as "half-chair" [2 symmetry] is 0°

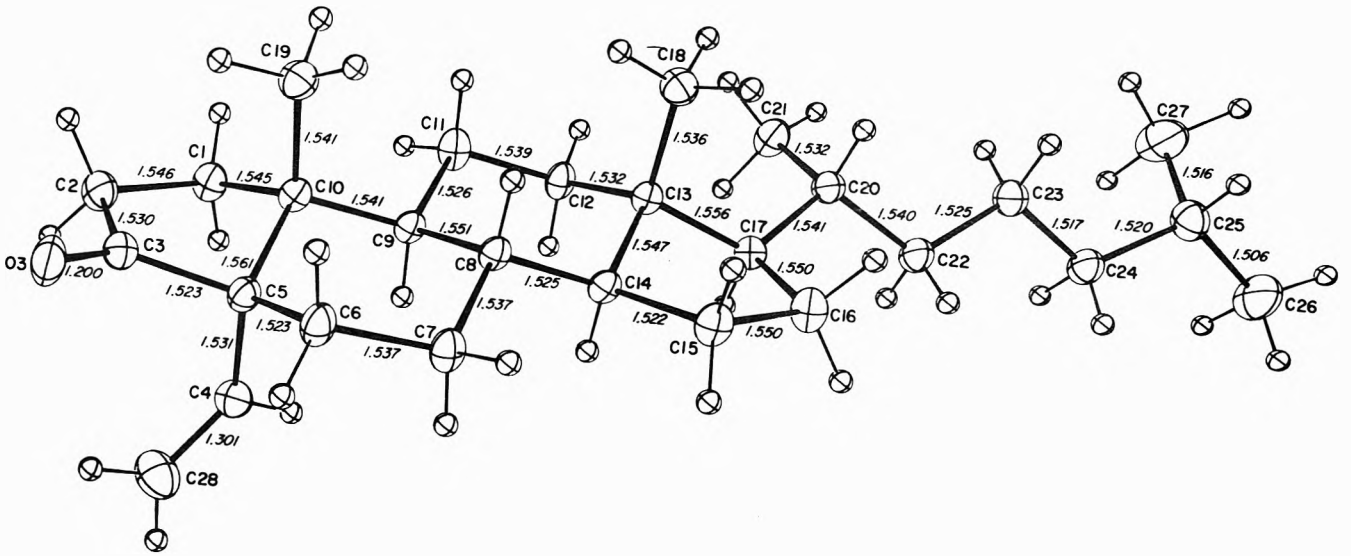


Figure 1. Bond lengths and thermal ellipsoids for the minor photoproduct **2**. The ellipsoids for the heavier atoms indicate 50% probability while those for hydrogen atoms are diagrammatic. Drawings were produced by ORTEP.[18]

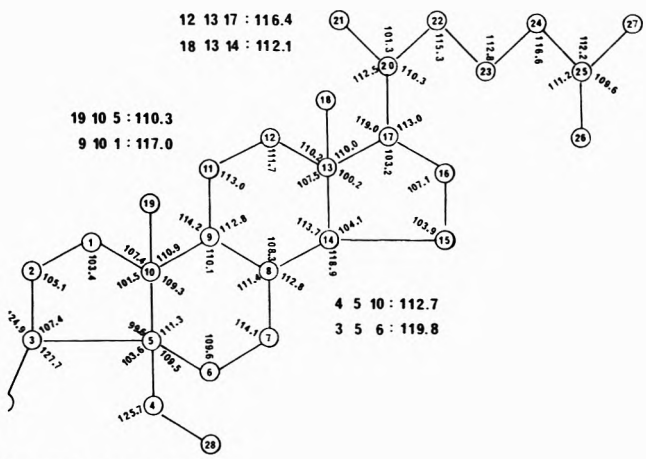


Figure 2. Bond angles.

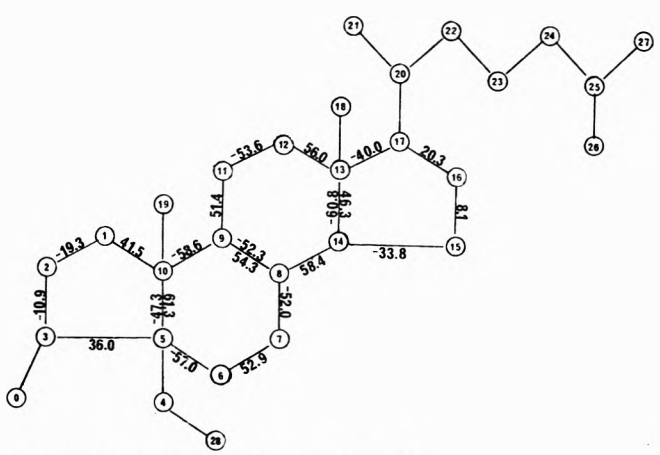


Figure 3. Torsion angles in the nucleus of **2**.

and that for the "envelope" [m symmetry] is 36°, the cyclopentane rings are intermediate between the two extreme forms; again not an unusual result in steroids without severe perturbing influences. The A ring, being a cyclopentanone ring, could be expected to adopt a conformation nearer to a "half-chair", as calculations on unsubstituted cyclopentanone[6] suggest, and the observed conformation is closer to this form than to the other; however, the Δ angle is quite large. It should be noted that ring D in 1-bromoestrone[7] is known to exist essentially in the "envelope" conformation with a Δ value of 32.2°, but that in 3α-ol-5α-androstan-17-one[8] is nearly "half-chair" with Δ = 7.9°.

The molecular packing is shown in Figure 4; it is that of a typical steroid crystallizing in $P2_1$. No intermolecular distances are significantly shorter than normal and the molecule appears to have been able to adopt a conformation of minimal energy without much crystal packing distortion.

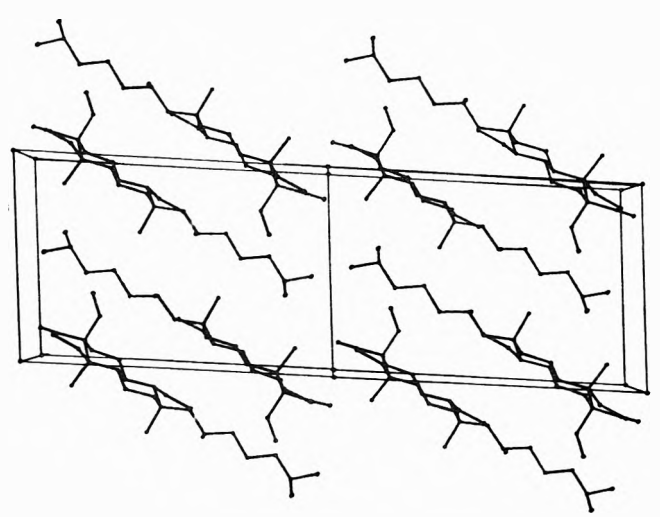


Figure 4. Packing diagram. The direction of projection is b and two unit cells are indicated.

Discussion

The synthesis of **5a** and the X-ray analysis of **2** unambiguously define the structures of both photoproducts formed in the direct irradiation of **1**. In view of the importance of the interpretation of the CD curves of **2** and **3** in the original[3] stereochemical assignment, the interpretation was reexamined.

Moscowitz, Djerassi, and Mislow have described a rule[9b] (MDM rule) relating the sign of the chiroptical effect to the molecular geometry of β,γ-unsaturated ketones. This rule was derived for and used to evaluate β,γ-unsaturated ketones possessing the specific spatial arrangement of unsaturated centers shown in Figure 5A,B. The application of the MDM rule to **2** and **3** is difficult, as these compounds are not constrained to a single fixed conformation. The orientation of the double bond of **2** is given in Figures 1–3.

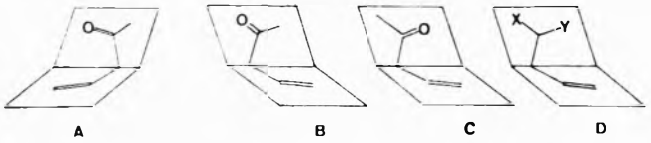


Figure 5. β,γ-Unsaturated ketones as disymmetric chromophores: A, MDM rule for positive Cotton effect; B, MDM rule for negative Cotton effect; C, relation of carboxyl and double bond in 2; D, general description where X or Y can equal O.

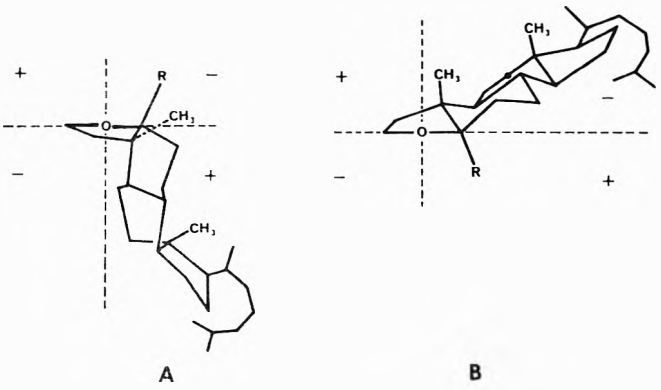


Figure 6. Octant diagrams for ketones 2–5: A, 3 (R = vinyl) and 5 (R = ethyl); B, 2 (R = vinyl) and 4 (R = ethyl).

The conformation shown is likely to be that preferred in solution, since rotation of the double bond toward the steroid skeleton (i.e., so that its projection overlays the steroid skeleton) results in an increase in nonbonded interactions. For analogous reasons it is likely that a projection of **3** would show the double bond in a similar position. Thus, the vinyl and carbonyl groups in **2** and **3** do not have the spatial arrangements shown in either Figure 5A or 5B and the MDM rule is not applicable. The relation of the vinyl and carbonyl groups in **2** is given in Figure 5C. If the bond linking the α carbon and the carbonyl group in Figure 5C is rotated 180°, a figure is generated which is identical with Figure 5B. As **2** possesses a negative Cotton effect, and the MDM rule predicts a negative effect for Figure 5B, a relationship may exist between Figure 5B and 5C shown in Figure 5D, where either X or Y represents the carbonyl oxygen. The significance of this suggestion needs to be explored by theoretical calculations and examination of additional model compounds.

Alternatively, the CD of β,γ-unsaturated ketones may be considered as a special case of the ketone octant rule where the double bond has the effect of increasing the magnitude of the chiroptical effect;[9a] i.e., the olefin may be a "super-substituent". The octant rule for ketones **2–5** is shown in Figure 6 and the CD values for these compounds are listed in Table I. The structural assignments which follow the X-ray analysis and the syntheses are consistent with the octant rule, since the contribution of the steroid skeleton is greater than the contribution of R.

However, the amplitude of the chiroptical effect of **4** (−4000) is approximately one-fifth that of its unsaturated relative **2** (−13400) although the substituent group R is shown to be in a positive octant in Figure 6B. If the double bond is a "super-substituent", the CD of **2** should be more positive than that of **4**. This dilemma can be resolved by realizing that the vinyl group can make a significant contribution to the optical activity via a front octant where sign reversal for substituents has been demonstrated for saturated ketones.[10] An equivalent conclusion obtains from an analysis of the CD curves of **3** and **5**.

In conclusion, the above synthesis of **5a** and the X-ray determination of **2** unequivocally establish the structure of the photoproducts obtained from **1**. Although considerable evidence exists for interaction between the carbonyl and the double bond in **2** and **3**, the previous structural assignments were based on an inappropriate use of the MDM rule. The correct sign of the CD bands of **2–5** can be obtained using a modification of the octant rule in which the sign of the CD band is determined by the octant occupied by the double bond and the bulk of the steroid nucleus.

Table II
Crystal and Refinement Data

Molecular formula	$C_{28}H_{46}O$	Habit	Monoclinic plates elongation *b*
Formula weight	398.67	Crystal size	0.7 × 0.25 × 0.08 mm
		X-Radiation	Cu Kα (graphite monochromator)
a	10.429 (1) Å		
b	7.369 (1) Å	λ	1.5418 Å
c	15.605 (1) Å	Diffractometer	Nonius CAD-4
β	94.28 (2)°	Reflections	2270 (observed)
V	1195.2 Å³		276 (unobserved 1σ)
Z	2	μ	4.9 cm⁻¹
*D*x	1.107 g/cm³	Function minimized	$\Sigma w\Delta^2$
*D*m (flotn in aq KI)	1.09 (1) g/cm³	Weighting	Peterson and Levy[19]
Space group	$P2_1$ (no. 4)	Refinement	Full-matrix least squares (partitioned)

Experimental Section

X-Ray Structure Determination. The minor photoproduct (**2**), obtained from the irradiation of **1**, crystallized from methanol–water as monoclinic prisms and was chosen for X-ray analysis since it gave considerably better crystals than the major product. Cell dimensions were determined by least-squares refinement using Bragg angles measured at ±θ. Lorentz and polarization corrections were applied by local programs but no absorption corrections were made or considered necessary (azimuthal scans of several reflections showed no significant variation). The basic experimental data are given in Table II. During data collection, three standard reflections were measured after every 50 reflections and no evidence of crystal deterioration was seen.

Many attempts were made to solve this structure by the symbolic addition procedure of Karle and Karle[11] but, in all cases, the *E* maps contained one single very large peak; while molecular fragments could apparently be seen, extension by the tangent formula[12] failed. In retrospect, it is considered that the source of the problem was the fact that definition of the enantiomorph in $P2_1$ is frequently difficult. The structure was finally solved by means of the MDKS and triple product formulae of Hauptman followed by his technique of "strong enantiomorph discrimination"[13] and application of the tangent formula. Two *E* maps were obtained; in one of them, the whole of the modified steroid skeleton was visible, although evidence for the substituents was somewhat nebulous. Refinement by least-squares techniques followed by difference maps resulted in the location of the missing heavier atoms and of all hydrogen atoms of the molecule. Final refinement utilized anisotropic temperature factors for the heavier atoms and isotropic factors for the hydrogen atoms, and was carried out by the full-matrix least-squares technique although, because of the size of the molecule, partitioning was necessary. The final conventional *R* factor was 0.036.[21] The direct methods calculations used programs developed by Weeks et al.;[14] all other calculations mentioned were carried out by the XRAY72 system of Stewart et al.[15] Scattering factors for carbon and oxygen were taken from the International Tables for X-Ray Crystallography,[16] and those for hydrogen from Stewart, Davidson, and Simpson.[17] In view of the absence of heavy atoms or a large fraction of oxygen atoms, we did not attempt to determine the absolute configuration by X-ray methods but, given the known stereochemistry of the parent steroid, the absolute

Table III
Atomic Parameters for Oxygen and Carbon Atoms (× 10^4)[a]

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O 3	1497 (2)	7333	155 (1)	916 (11)	731 (12)	496 (8)	124 (10)	274 (7)	163 (8)
C 1	632 (2)	3947 (3)	1604 (1)	670 (10)	374 (11)	459 (10)	70 (10)	126 (9)	−53 (9)
C 2	1242 (2)	4446 (3)	765 (1)	652 (13)	559 (13)	443 (10)	91 (11)	95 (9)	−78 (10)
C 3	1276 (2)	6448 (3)	762 (1)	526 (11)	601 (14)	413 (10)	99 (10)	84 (8)	34 (10)
C 4	2222 (2)	6860 (3)	2198 (1)	519 (11)	526 (13)	517 (10)	8 (10)	30 (8)	−15 (10)
C 5	951 (2)	7064 (3)	1648 (1)	494 (10)	380 (10)	395 (9)	44 (9)	71 (7)	44 (8)
C 6	425 (2)	8903 (3)	1761 (1)	649 (12)	360 (10)	494 (11)	30 (10)	162 (9)	89 (9)
C 7	5 (2)	9114 (3)	2679 (1)	639 (12)	279 (9)	509 (10)	−18 (9)	168 (9)	11 (8)
C 8	9075 (2)	7687 (2)	2946 (1)	472 (9)	259 (9)	368 (8)	23 (7)	67 (7)	8 (7)
C 9	9608 (2)	5829 (3)	2789 (1)	457 (9)	280 (9)	358 (8)	22 (7)	55 (7)	−2 (7)
C 10	9940 (2)	5644 (2)	1848 (1)	488 (10)	308 (10)	355 (8)	24 (8)	37 (7)	−16 (7)
C 11	8742 (2)	4380 (3)	3093 (1)	689 (13)	256 (10)	508 (10)	−46 (9)	189 (9)	−68 (8)
C 12	8389 (2)	4633 (3)	4025 (1)	623 (12)	283 (9)	475 (10)	1 (8)	162 (8)	22 (8)
C 13	7808 (2)	6446 (2)	4162 (1)	438 (9)	306 (9)	359 (8)	−5 (7)	56 (7)	−28 (7)
C 14	8784 (2)	7824 (2)	3888 (1)	458 (9)	280 (9)	375 (8)	8 (8)	38 (7)	−7 (7)
C 15	8279 (2)	9548 (3)	4217 (1)	645 (12)	296 (9)	501 (10)	2 (8)	132 (9)	−54 (8)
C 16	7677 (2)	9036 (3)	5060 (1)	664 (12)	384 (11)	489 (11)	−40 (10)	175 (9)	−90 (9)
C 17	7684 (2)	7010 (3)	5110 (1)	426 (9)	381 (10)	379 (8)	−27 (8)	45 (7)	−32 (7)
C 18	6501 (2)	6611 (3)	3646 (1)	468 (10)	592 (13)	439 (9)	−21 (9)	19 (7)	−43 (9)
C 19	8726 (2)	5829 (3)	1229 (1)	528 (10)	646 (15)	416 (9)	23 (10)	−5 (8)	−56 (9)
C 20	3430 (2)	1270 (3)	4404 (1)	454 (10)	513 (12)	408 (9)	52 (9)	67 (7)	23 (9)
C 21	3455 (2)	9264 (3)	4400 (1)	755 (14)	518 (13)	527 (11)	174 (11)	225 (10)	21 (10)
C 22	3342 (2)	1944 (3)	3472 (1)	539 (10)	568 (13)	433 (9)	73 (10)	117 (8)	57 (9)
C 23	4556 (2)	1711 (4)	2997 (1)	543 (11)	636 (14)	457 (10)	13 (10)	122 (8)	26 (10)
C 24	4375 (2)	2248 (3)	2060 (1)	603 (11)	596 (14)	484 (10)	78 (11)	148 (9)	72 (10)
C 25	5580 (2)	2350 (4)	1571 (1)	651 (13)	790 (18)	529 (11)	−37 (13)	180 (10)	35 (12)
C 26	5279 (3)	3027 (6)	673 (2)	1054 (21)	1334 (32)	707 (16)	236 (22)	390 (15)	402 (20)
C 27	6259 (3)	599 (6)	1537 (2)	1021 (21)	1299 (34)	858 (20)	526 (22)	446 (17)	284 (21)
C 28	3355 (2)	7262 (5)	1962 (2)	560 (13)	922 (22)	822 (16)	108 (14)	66 (11)	−98 (16)

[a] No esd is given for the oxygen *y* parameter since it was used to define the origin. The temperature factor used had the form exp $2\pi^2 (\sum_i \sum_j U_{ij} a_i^* a_j^* h_i h_j)$.

Table IV
Atomic Parameters for Hydrogen Atoms (× 10^3)

Atom	x/a	y/b	z/c	U	Atom	x/a	y/b	z/c	U
1A	132 (2)	365 (4)	206 (2)	62 (8)	1B	999 (2)	296 (4)	152 (2)	73 (8)
2A	70 (3)	412 (5)	25 (2)	80 (8)	2B	212 (3)	407 (5)	72 (2)	91 (9)
4A	220 (3)	648 (5)	280 (2)	95 (10)	6A	967 (3)	910 (4)	132 (2)	69 (7)
6B	108 (3)	971 (5)	164 (2)	85 (9)	7A	956 (2)	25 (4)	274 (2)	65 (8)
7B	79 (2)	907 (4)	310 (2)	75 (8)	8A	823 (2)	783 (4)	260 (2)	64 (7)
9A	43 (2)	576 (4)	317 (1)	54 (7)	11A	796 (3)	436 (4)	274 (2)	71 (8)
11B	918 (3)	322 (5)	303 (2)	82 (9)	12A	781 (3)	365 (4)	417 (2)	72 (8)
12B	922 (3)	450 (4)	441 (2)	73 (8)	14A	959 (2)	763 (4)	424 (1)	60 (7)
15A	758 (2)	1003 (4)	380 (2)	71 (8)	15B	892 (2)	38 (5)	429 (2)	75 (8)
16A	677 (3)	943 (5)	503 (2)	76 (8)	16B	815 (3)	947 (5)	559 (2)	93 (10)
17A	154 (2)	167 (4)	457 (2)	56 (7)	18A	654 (2)	643 (5)	307 (2)	73 (8)
18B	603 (3)	782 (5)	373 (2)	93 (10)	18C	590 (3)	580 (5)	384 (2)	79 (9)
19A	896 (3)	585 (4)	61 (2)	81 (9)	19B	813 (3)	489 (5)	128 (2)	97 (10)
19C	816 (3)	679 (5)	129 (2)	90 (8)	20A	425 (2)	166 (4)	469 (2)	59 (7)
21A	372 (3)	884 (5)	500 (2)	84 (9)	21B	403 (3)	877 (4)	401 (2)	85 (9)
21C	251 (3)	880 (5)	426 (2)	94 (10)	22A	314 (3)	319 (5)	346 (2)	82 (9)
22B	264 (2)	146 (5)	315 (2)	78 (9)	23A	486 (2)	56 (4)	303 (2)	74 (8)
23B	535 (3)	223 (4)	334 (2)	79 (8)	24A	371 (3)	136 (5)	174 (2)	93 (10)
24B	393 (3)	330 (4)	202 (2)	89 (9)	25A	622 (3)	321 (6)	195 (2)	114 (12)
26A	459 (3)	215 (6)	38 (2)	121 (12)	26B	478 (3)	413 (6)	62 (2)	115 (11)
26C	599 (3)	312 (6)	29 (2)	113 (11)	27A	714 (3)	96 (5)	130 (2)	106 (10)
27B	661 (3)	37 (5)	220 (2)	109 (10)	27C	546 (3)	971 (5)	123 (2)	115 (10)
28A	418 (3)	718 (5)	234 (2)	107 (10)	28B	348 (3)	759 (5)	137 (2)	117 (10)

stereochemistry is that shown in Figure 1. The stereochemistry of the A/B ring junction is trans and therefore *opposite* to that assigned by Fisher and Zeeh.[3] The atomic parameters for heavier atoms are given in Table III and those for hydrogen atoms in Table IV.

5β-Methylcholestan-3-one (8b). The enolate **7b** was prepared by the addition of lithium dimethylcopper to **6** as described by Muchmore;[4b] quenching with water yielded **8b**, mp 82–83° (lit.[20] 88–89°).

5β-Methylcholest-3-ene (9b). The olefin **9b** was prepared as described by Muchmore;[4b] however, the final purification employed column chromatography on silica gel in lieu of vacuum distillation. Spectral properties were identical with those reported.

5β-Methyl-*A*-norcholestan-3-one (5b). A solution of 471 mg of **9b** in 50 ml of 1:1 ethyl acetate–acetic acid was treated with excess ozone at −10 to 0° until GC analysis indicated that no starting material remained. Hydrogen peroxide (0.5 ml, 30%) was added and the mixture was allowed to stand for 24 hr at room temperature. The solvent was removed under reduced pressure, and ether was added. The resulting mixture was washed with water, sodium bicarbonate, water, and brine, dried ($MgSO_4$), and evaporated in vacuo, giving 501 mg of crude diacid which was crystallized from ethyl acetate, mp 166–170° (lit.[4b] mp 168–172°).

The crude diacid was esterified with excess diazomethane and the crude ester purified via column chromatography: NMR ($CDCl_3$) δ 3.62 (s, 6 H, CO_2CH_3), 0.85 (s, 3 H, CH_3), 0.65 (s, 3 H, CH_3); ir (CCl_4) 1733, 1748 cm^{-1}. To the diester **10b** (50 mg) in 15 ml of benzene, 120 mg of freshly sublimed potassium *tert*-butoxide

was added and the mixture refluxed for 12 hr. The reaction mixture was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The organic phase was washed with water, aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in a 3:1 mixture of acetic acid and concentrated hydrochloric acid and refluxed for 5 hr. The cooled reaction mixture was made basic with aqueous sodium bicarbonate and extracted with ether. The ether layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to yield a yellow solid which was purified by column chromatography over silica gel, mp 82–84° from methanol: NMR ($CDCl_3$, 220 MHz) 145 (s, 3 H), 175 (s, 3 H), 185 (s, 3 H), 495 Hz (m, 2 H); ir (CCl_4) 1748 cm^{-1}. Anal. Calcd for $C_{27}H_{40}O$: C, 83.87; H, 11.99. Found: C, 83.90; H, 12.40.

5β-Ethylcholestan-3-one (8a). To a solution of lithium diethylcopper in ether, prepared from 3.0 g (15. 7 mmol) of cuprous iodide and 42 ml (31.2 mmol) of 0.736 *M* ethyllithium, was added a solution of 2.0 g (5.2 mmol) of **6** in ether at 0°. The enolate **7a** was hydrolyzed as described for **8b** to yield **8a** from methanol, mp 85–87°, ir (CCl_4) 1723 cm^{-1}. Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.13; H, 12.17.

5β-Ethyl-*A*-norcholestan-3-one (5a). A sample of 5β-ethyl-*A*-norcholestan-3-one (**5a**) was prepared from **6** using lithium diethylcopper in the same sequence as described for **5b**. The intermediates **9a**, NMR ($CDCl_3$, 220 MHz) 1240 (t of d, J = 2.5, 10 Hz), 1165 (d, J = 10 Hz), 140 Hz (s, 3 H), and **10a**, ir (CCl_4) 1733, 1747 cm^{-1}, NMR ($CDCl_3$, 220 MHz) 802 (s, 6 H), 145 Hz (s, 3 H), were colorless oils and were obtained in yields of 80 and 87%, respectively. The sample of **5a** prepared in this manner was identical in all physical properties with the dihydro derivative of the major photoproduct 3 of 1.

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Registry No.—1, 51355-04-5; **2**, 19682-31-6; **3**, 19594-90-2; **4**, 19682-32-7; **5a**, 19682-33-8; **5b**, 39932-87-1; **6**, 601-57-0; **7a**, 56829-83-5; **7b**, 56829-84-6; **8a**, 51355-05-6; **8b**, 13163-71-8; **9a**, 51355-07-8; **9b**, 23931-38-6; **10a**, 56829-85-7; **10b**, 56829-86-8.

Supplementary Material Available. A diagram showing deviations of atoms from mean planes and a listing of structure factor amplitudes will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3675.

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Synthesis and C-25 Chirality of 26-Hydroxycholesterols

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Samples of cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether were prepared via hydroboration of cholest-5,25-dien-3β-ol tetrahydropyranyl ether with (a) disiamylborane, (b) (+)-diisopinocampheylboranes (DIPCB), and (c) (−)-(DIPCB). The 26-hydroxy compounds were converted first to cholest-4-en-3-on-26-ol *p*-bromobenzoates and then to cholest-4-ene-3β,26-diol 26-*p*-bromobenzoates. Authentic (25*R*)- and (25*S*)-cholest-4-ene-3β,26-diol *p*-bromobenzoates were prepared from kryptogenin and from (25*S*)-cholest-4-en-3-on-26-ol *p*-bromobenzoate, respectively. The magnitudes of the Cotton effects of the 25*R* and 25*S* samples were the same but of the opposite sign. The 25*R* compound had a negative Cotton effect while the 25*S* compound had a positive Cotton effect. Both compounds were assumed to be optically pure (100%). The CD spectra of the corresponding analogs derived from the hydroboration of the C-25 olefin were recorded. Based on the sign and amplitude of their Cotton effects, their stereochemistry and optical purity at C-25 was defined.

For studies of the stereochemistry of the reduction of the C-24 double bond of lanosterol in the course of the biosynthesis of cholesterol in the S-10 fraction of rat livers[3–5] we required samples of (25*R*)- and (25*S*)-26-hydroxycholestenone.[4–5] The attempted preparation of these compounds via the selective hydroboration of cholesta-5,25-dien-3β-ol

3-tetrahydropyranyl ether (3-THP ether)[6] with (−)- and (+)-diisopinocampheylborane[7-9] is the subject of this communication.

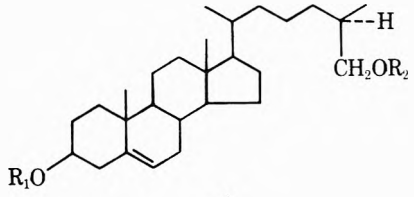
Experimental Section

Materials. Tetrahydrofuran and boron trifluoride etherate were purified by procedures previously described.[7] Sodium borohydride (minimum 98% pure) was supplied by Fisher Scientific Co. The previously used samples of (+)- and (−)-α-pinene were employed in the present study.[9]

Physical Measurements. Melting points were taken on a hot-stage apparatus and are corrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 237 spectrophotometer as KBr wafers. Ultraviolet spectra were measured on a Perkin-Elmer 202 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian DA60 spectrometer at 60 MHz. Chemical shifts are quoted in parts per million downfield from internal tetramethylsilane. Coupling constants are quoted in hertz. Mass spectra were measured on a Varian Associates M-66 instrument. A Hilger MK-III instrument was used for the measurement of all optical rotations.[4] The optical rotations of the samples of cholest-4-en-3-on-26-ols were also recorded on a Rudoph and Son's photoelectric polarimeter.[4] The CD measurements were carried out on a Jasco J-40 instrument.

Chromatography. Gas chromatographic (GLC) analyses were performed on a Perkin-Elmer Model 811 instrument equipped with a flame ionization detector. A 3-ft silanized glass column of 3% XE-60 on Chromosorb at 240–250° was used for all analyses. Silica gel (Merck $HF_{254+366}$) was used for preparative and analytical TLC in the indicated solvent systems. The products were detected under ultraviolet light and by color reactions with phosphomolybdic acid. Radiochromatograms were scanned on a Vanguard automatic chromatogram scanner (Model 880).

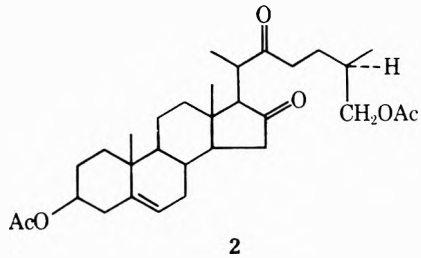
Preparation of (25*R*)-Cholest-5-ene-3β,26-diol (1a) from Kryptogenin Diacetate (2). A specimen of kryptogenin diacetate (**2**) was purified by preparative TLC [ethyl acetate–benzene (1:4)] and crystallized from ethyl acetate–hexane to give needles: mp 148–151°; $[\alpha]^{21}D$ −176.3 ± 0.5° (*c* 4.84, $CHCl_3$) [reported $[\alpha]^{20}D$ −167° ($CHCl_3$[10])]; $[\alpha]^{23}D$ −182° (c 0.08, dioxane; from ORD measurement[11]).



1

25*R*, derived from **2**

a, R_1 = H, R_2 = H
b, R_1 = $C(C_6H_5)_3$; R_2 = $C(C_6H_5)_3$
c, R_1 = H; R_2 = $C(C_6H_5)_3$
d, R_1 = Ac; R_2 = $C(C_6H_5)_3$
e, R_1 = Ac; R_2 = Ac
f, R_1 = Ac; R_2 = H

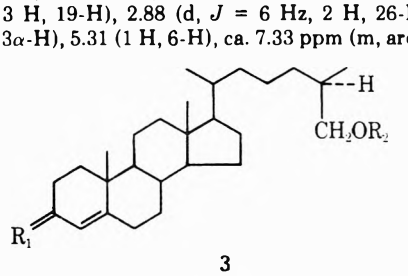


2

The diacetate (>90% pure) was subjected to Clemmensen reduction.[12] The ir spectrum of the crude product revealed complete reduction of the side-chain carbonyl (1710 cm^{-1}). The material was then further reduced by the Huang-Minlon procedure[12] and the resulting mixture was crystallized from ethyl acetate, giving needles. Trace impurities were removed by preparative TLC and the purified material was recrystallized to give (25*R*)-cholest-5-ene-3β,26-diol (**1a**): mp 172–173°; $[\alpha]^{21}D$ −27.7 ± 1.4° (*c* 1.65, DMF); $[\alpha]^{21}D$ −26.3 ± 1.6° (c 1.22, dioxane); $[\alpha]^{21}D$ −33.5 ± 1.3° (c 1.5, $CHCl_3$) [reported[12] mp 177–178°, $[\alpha]^{20}D$ −30° (c ~1, $CHCl_3$)].

(25*R*)-Cholest-5-ene-3β,26-diol 26-Triphenylmethyl Ether (1c) (Derived from Kryptogenin). A solution of the diol **1a** (700 mg, 1.75 mmol) and purified triphenylchloromethane (532 mg, 1.93 mmol) in dry pyridine (20 ml) was refluxed for 3 hr.[13] The reaction was terminated by pouring into water and the products were extracted with ether. The organic phase was washed several times with a solution of KH_2PO_4 and then with water. The solution was dried (Na_2SO_4) and the solvent was removed to furnish a noncrystalline product, which was purified by chromatography on a column of silica (40 g). Elution with hexane–benzene (1:4, 700 ml) furnished an amorphous powder (130 mg) considered from its spectral properties to be the dityrityl ether **1b**. Elution of the column with benzene (800 ml) gave triphenylmethylcarbinol and subsequent use of ether–benzene (1:9, 1.8 l.) yielded the 26-monotrityl ether **1c** (520 mg) as an amorphous solid [ir ν_{max} (KBr) 3380 cm^{-1} (OH) and aromatic absorption bands]. Finally, elution of the column with methanol–ether (1:49, 600 ml) furnished the unreacted diol **1a** (190 mg) having the same optical rotation as the starting material. Treatment of this diol (190 mg) as described above gave an additional 102 mg of monotrityl ether **1c**.

(25*R*)-Cholest-4-en-3-on-26-ol (3a). The ether **1c** was further purified by preparative TLC [ethyl acetate–benzene (1:1)] to give an amorphous powder, characterized by its NMR spectrum ($CDCl_3$): 0.67 (s, 3 H, 18-H), 0.93 (d, *J* = 6.5 Hz, 6 H, 21- and 27-H), 0.99 (s, 3 H, 19-H), 2.88 (d, *J* = 6 Hz, 2 H, 26-H), ca. 3.50 (broad, 1 H, 3α-H), 5.31 (1 H, 6-H), ca. 7.33 ppm (m, aromatic H).



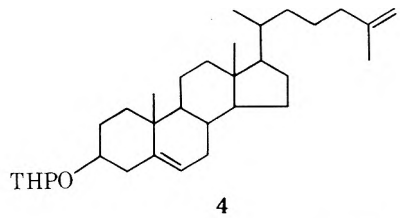
3

25*R*, derived from **1**

a, R_1 = O: R_2 = H;
b, R_1 = O; R_2 = *p*-BrC_6H_4CO
c, R_1 = β-OH; R_2 = *p*-BrC_6H_4CO

A mixture of the monotrityl ether **1c** (520 mg), toluene (125 ml), and cyclohexanone (2.5 ml) was stirred and distilled until 50 ml of toluene was collected. Aluminum isopropoxide (300 mg) was added and the mixture was refluxed with the exclusion of moisture (18 hr). After cooling, the solution was treated with a saturated solution of potassium hydrogen tartrate (20 ml) and the product was isolated in the conventional manner. The volatile components were distilled under reduced pressure, and the resulting oily residue was refluxed (2.5 hr) with 85% aqueous acetic acid (20 ml). The reaction mixture was poured into water and the product was extracted with ether. The extract was processed in the usual manner to yield an oily residue which was fractionated by TLC [ethyl acetate–benzene (1:3)] and (25*R*)-cholest-4-en-3-on-26-ol (**3a**) was isolated. Crystallization from ethyl acetate–hexane furnished needles (180 mg): mp 129–131°; ν_{max} (KBr) 3380 (OH), 1663 (C=O), 1615 cm^{-1} (C=C); λ_{max} (EtOH) 241 nm (ε 15800); $[\alpha]^{21}D$ +84.5 ± 0.8° (c 2.5, $CHCl_3$) and $[\alpha]^{22}D$ +85.6 ± 0.5° (c 5.3, $CHCl_3$); homogenous by GLC (250°; t_R 24 min).

(25*RS*)-Cholest-5-ene-3β,26-diol 3-Tetrahydropyranyl Ether (5a) (Hydroboration of 4 with (+)-Diisopinocampheylborane). A mixture of sodium borohydride (1.5 mmol, 57.0 mg) and (−)-α-pinene (4.4 mmol, 0.70 ml) in tetrahydrofuran (10 ml) was stirred and cooled to 0° as previously described.[7-9] Boron trifluoride etherate (2 mmol, 0.25 ml) was added dropwise from a syringe in 2 min and the mixture was stirred at 0–2° for 3.5 hr. A solution of cholest-5,25-dien-3β-ol tetrahydropyranyl ether[6a] (**4**, 240 mg) in tetrahydrofuran (5–10 ml) was then added during 5 min. The mixture was stirred for 2.5 hr at 0–2° and allowed to warm up to room temperature. Then 3 *N* NaOH (3.0 ml) and 30% H_2O_2 (3.0 ml) were added and the stirring was continued for 1.5 hr at ~40°. The product was recovered with ether and the volatile components were removed under reduced pressure at 70–80°. The residue was chromatographed on a column of silica gel (20 g). Elution with benzene (150 ml) furnished starting material (**4**, 45 mg) and elution with methanol–dichloromethane (1:9, 200 ml) gave (25*RS*)-cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether (**5a**, 180 mg). The ir spectrum of **5a** and its chromatographic properties were identical with those of the 25*S* isomer (**6a**) (23% optical purity described previously[6a,b]) (see below).



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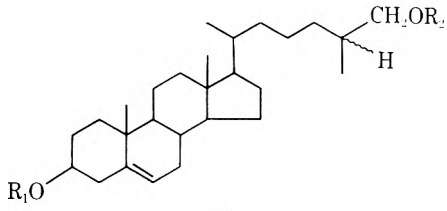


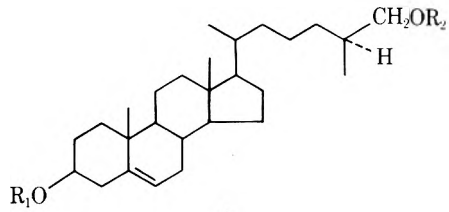
5

25*RS*

a, hydroboration of 4 with (+)-DIPCB; R_1 = THP; R_2 = H
b, from **5a**; $R_1 = R_2$ = H
c, from **5b**; R_1 = H; $R_2 = C(C_6H_5)_3$
d, from acid **9c**; $R_1 = R_2$ = H
e, from acid **9d**; $R_1 = R_2$ = H
f, [25-^{3}H]; $R_1 = R_2$ = H

(25*RS*)-Cholest-5-ene-3β,26-diol (5b) (from 5a). The above material (**5a**, 150 mg) was dissolved in methanol (15 ml), *p*-toluenesulfonic acid (5 mg) was added, and the mixture was refluxed for 1 hr. The solution was diluted with water and extracted with ether. The ether solution was washed with dilute NaOH and water and dried (Na_2SO_4) and the solvent was evaporated. Crystallization of the residue from ethyl acetate–hexane (1:1) gave needles (100 mg), mp 171.5–172.5°. A portion of the crystalline material was further purified by TLC [ethyl acetate–benzene (1:1)] and crystallized to furnish needles of (25*RS*)-cholest-5-ene-3,26-diol (**5b**), mp 171.5–172.5°, $[\alpha]^{25}D$ −35 ± 1.33° (*c* 1.51, $CHCl_3$). The product was homogeneous by GLC analysis.

(25*S*)-Cholest-5-ene-3β,26-diol (6b) (ca. 23% Optical Purity) (Hydroboration of 4 with Disiamylborane). The preparation of 4 and its selective hydroboration with disiamylborane to yield **6a** was carried out exactly as previously described.[6a] The obtained 3-THP ether **6a** was then hydrolyzed to the 3,26-diol **6b**, mp 168.5°, $[\alpha]^{25}D$ −35.9 ± 1.53° (*c* 1.31, $CHCl_3$).



6

25*S*, ca. 23% optical purity

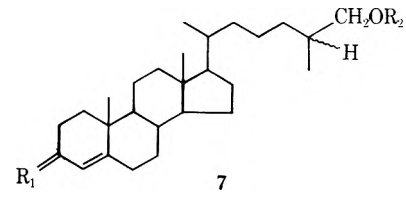
a, hydroboration of 4 with disiamylborane; R_1 = THP; R_2 = H
b, from **6a**; $R_1 = R_2$ = H
c, from **6a**; R_1 = THP; R_2 = Ac
d, from **6c**; R_1 = H; R_2 = Ac

25*S*, ca. 83% optical purity

e, hydroboration of 4 with (−)-DIPCB; R_1 = THP; R_2 = H
f, from **6e**; $R_1 = R_2$ = H
g, from **6f**; R_1 = H; $R_2 = C(C_6H_5)_3$

(25*S*)-Cholest-5-ene-3β,26-diol (6f) (ca. 83% Optical Purity) (Hydroboration of 4 with (−)-Diisopinocampheylborane). The reaction was performed in the manner described for the hydroboration with (+)-diisopinocampheylborane except that (+)-α-pinene was used for the preparation of the (−)-DIPCB reagent. The 26-hydroxytetrahydropyranyl ether (**6e**) was isolated, purified, and converted as above to the (25*S*)-cholest-5-ene-3β,26-diol (**6f**). mp 171–172°, $[\alpha]^{25}D$ −38.0 ± 1.16° (*c* 1.72, $CHCl_3$).

(25*RS*)-Cholest-4-en-3-on-26-ol (7a) (from 5b). The 25*RS* diol **5b** was converted through the 26-monotrityl ether **5c** to (25*RS*)-cholest-4-en-3-on-26-ol (**7a**) by the procedure described above. The product was homogeneous by TLC and GLC and showed $[\alpha]^{22}D$ +87.4 ± 0.8° (*c* 2.7, $CHCl_3$) and $[\alpha]^{22}D$ +85.9 ± 0.5° (*c* 4.3, $CHCl_3$).



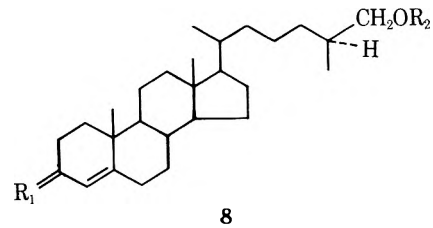
7

25*RS*, derived from 5a

a, R_1 = O; R_2 = H
b, R_1 = O; R_2 = *p*-BrC_6H_4CO
c, R_1 = β-OH; R_2 = *p*-BrC_6H_4CO

(25*S*)-Cholest-4-en-3-on-26-ol (8a) (ca. 23% Optical Purity) (from 6a). A solution of (25*S*)-cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether (**6a**, 1.35 g) in pyridine (5 ml) and acetic anhydride (0.2 ml) was kept at 25° overnight and the product was worked up in the conventional manner to give the 3-THP 26-acetate **6c** (1.45 g). This compound was dissolved in 90% ethanol (50 ml) and treated with 2 *N* HCl (0.25 ml) under reflux for 5 min. The usual work-up procedure furnished 1.21 g of material which was chromatographed on silica gel (50 g). Elution of the column with ethyl acetate–benzene (1:9, 450 ml) gave 180 mg of a mixture containing starting material and the required 26-acetoxy-3β-alcohol (**6d**). Further elution (4.0 l.) furnished (25*S*)-cholest-5-ene-3β,26-diol 26-acetate (**6d**), ν_{max} (KBr) 3415 (OH) and 1740 cm^{-1} (–$OCOCH_3$).

Oxidation of the hydroxy acetate (150 mg) with aluminum isopropoxide (170 mg) and cyclohexanone (0.75 ml) in dry toluene (20 ml) at reflux (7 hr) was performed as described for **3a**. The oily product was dissolved in a mixture of 5% aqueous Na_2CO_3 in methanol (18 ml) and stored for 16 hr at 25°. Water was added and the product was isolated with ether. The residue (129 mg) was fractionated by preparative TLC to give (25*S*)-cholest-4-en-3-on-26-ol (**8a**) (23% optical purity) (75 mg), which was crystallized from ethyl acetate–hexane: mp 140.5–145.5°; λ_{max} (EtOH) 241 nm (ε 16400); $[\alpha]^{21}D$ +80.4 ± 0.4° (*c* 2.58, $CHCl_3$) and $[\alpha]^{22}D$ +82.4 ± 0.4° (*c* 5.6, $CHCl_3$); mass spectrum *m/e* 400 (M^+), 358 (M − 42) 277, 229, 124 (base peak).



8

25*S*, ca. 23% optical purity; derived from 6a

a, R_1 = O; R_2 = H
b, R_1 = O; R_2 = *p*-BrC_6H_4CO
c, R_1 = β-OH; R_2 = *p*-BrC_6H_4CO

25*S*, ca. 83% optical purity; derived from 6e

d, R_1 = O; R_2 = H
e, R_1 = O; R_2 = *p*-BrC_6H_4CO
f, R_1 = β-OH; R_2 = *p*-BrC_6H_4CO

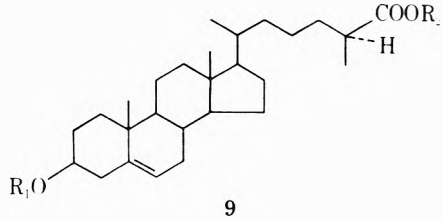
25*S*, 100% optical purity; derived from the incubation of cholesterol with *M. smegmatis*

g, R_1 = O; R_2 = *p*-BrC_6H_4CO
h, R_1 = β-OH; R_2 = *p*-BrC_6H_4CO

(25*S*)-Cholest-4-en-3-on-26-ol (ca. 83% Optical Purity) (8d) (from 6e). The 25*S* diol **6f** was converted via **6g** to the 25*S* keto alcohol **8d**, $[\alpha]^{22}D$ +74.8 ± 0.8° (c 2.5, $CHCl_3$).

(25*S*)-3β-Tetrahydropyranyloxycholest-5-en-26-oic Acid (ca. 23% Optical Purity) (9a). A solution of (25*S*)-cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether (**6a**) (23% optical purity) (250 mg) in pyridine (5 ml) was added to a magnetically stirred mixture

of pyridine (20 ml), chromic oxide (1.0 g), and water (0.3 ml) at 0°. The mixture was stirred (4 hr) at 25°, then poured into water (150 ml) and the product recovered with ether. The organic phase was washed with cold dilute HCl, 5% NaOH, and water and dried (Na_2SO_4). Evaporation of the solvent gave a neutral material (110 mg), ν_{max} (KBr) 1700 and 1730 cm^{-1}, which was not further investigated. The alkaline extract was cooled in ice and acidified with dilute HCl. The product was extracted with ethyl acetate–ether (1:1). The extract was washed and dried (Na_2SO_4) and the solvent was removed. The obtained sold (141 mg) was crystallized from acetone to give (25*S*)-3β-tetrahydropyranyloxycholest-5-en-26-oic acid (**9a**): mp 158.5–160.5°; ν_{max} (KBr) 3500–3100 (COOH), 1725, 1700 cm^{-1} (C=O).



9

a, R_1 = THP; R_2 = H [derived from 25*S* (**6a**), ca. 23% optical purity]
b, R_1 = R_2 = H
c, R_1 = R_2 = H; 25ξ, recovered from crystalline quinine salt
d, R_1 = H; R_2 = H; 25ξ, recovered from the mother liquor of crystallization of the quinine salt
e, methyl ester of 9b; R_1 = H; R_2 = CH_3

(25*S*)-Cholest-5-en-3β-ol-26-oic Acid (ca. 23% Optical Purity) (9b). A solution of the 25*S* 3-ether acid **9a** (350 mg) and *p*-toluenesulfonic acid (10 mg) in methanol (10 ml) was stored at 25° for 18 hr. The solvent was then removed in a stream of nitrogen. The residue was taken up in ether, washed with water, and dried and the solvent was removed. TLC and the ir spectrum indicated that the residue was a mixture of the hydroxy acid **9b** and the 26-methyl ester. The crude material was saponified with 5% methanolic KOH (reflux, 1 hr). The solution was acidified and the product recovered with ether. Two crystallizations from ethyl acetate furnished plates of (25*S*)-cholest-5-en-3β-ol-26-oic acid (**9b**): mp 170–172.5° (reported for 25*RS* acid 176–178° uncorrected[14] and 173–175[15]); $[\alpha]^{22}D$ −23.9 ± 0.9° (*c* 2.21, CH_3OH) and −21.7 ± 2° (*c* 1.0, CH_3OH); ν_{max} (KBr) 3400 (OH), 1700 cm^{-1} (C=O).

The mother liquors of crystallizations were combined (98 mg) and recrystallized to give a second sample of the acid **9b**, mp 169–171°, $[\alpha]^{22}D$ −23.0 ± 1.4° (*c* 1.4, CH_3OH). Both specimens were homogeneous by TLC (ethyl acetate).

A portion of **9b** was treated with ethereal diazomethane and the product crystallized from methanol to give the methyl ester **9e**: mp 99–101° (reported for 25*RS* 26-Me ester 100–103° uncorrected[14] and 102–103[15]); ν_{max} (KBr) 3430 (OH), 1730 cm^{-1} (ester).

Attempted Resolution of the Quinine Salt of (25*S*)-Cholest-5-en-3β-ol-26-oic Acid (ca 23% Optical Purity) (9b). Attempts to resolve the acids using the systems brucine–methanol, brucine–acetone, or strychnine–ethanol were not successful. However, it appears that at least a partial resolution was obtained using (−)-quinine–methanol.

A mixture of the 25*S* hydroxy acid **9b** (113.5 mg, 0.272 mmol) and (−)-quinine (88.0 mg, 0.272 mmol) was dissolved in hot methanol and stored at 0–5° overnight. The obtained salt was filtered (126 mg), dissolved in methanol (3.0 ml), and stored at 0–5° for 5 hr. The crystals were collected (89 mg) and the salt was decomposed by shaking with a mixture of ether (75 ml) and 1 *N* HCl (30 ml). The ether layer was washed, dried, and concentrated to yield the acid **9c** (47 mg), which was recrystallized from ethyl acetate–hexane as needles, $[\alpha]^{22}D$ −27.2 ± 1.1° (*c* 2.2, CH_3OH) and −25.3 ± 1.8° (*c* 0.9, CH_3OH).

The mother liquors of crystallization of the quinine salt were combined and the salt was decomposed as described above to give the acid **9d** (62 mg) which was crystallized from ethyl acetate–hexane. The product showed $[\alpha]^{22}D$ −19.1 ± 1.1° (*c* 1.9, CH_3OH).

A sample of the acid **9c** from a duplicate experiment showed $[\alpha]^{22}D$ −27.3 ± 1.4° (*c* 1.4, CH_3OH). Following preparative TLC and crystallization **9c** had $[\alpha]^{22}D$ −25.3 ± 1.1° (*c* 1.9, CH_3OH). The acid **9d** (from the duplicate experiment) showed $[\alpha]^{22}D$ −20.8 ± 1.4° (CH_3OH). After preparative TLC and crystallization this specimen of **9d** had $[\alpha]^{22}D$ −21.9 ± 1.1° (*c* 1.9, CH_3OH); NMR spectrum (in dimethylformamide-d_7) 0.71 (s, 3 H, 18-H), 1.00 (s, 3 H, 19-H), 1.11 (d, *J* = 7.0, 3 H, 27-H), ca. 3.38 (broad, 1 H, 3α-H), and 5.30 (1 H, 6-H).

(25ξ)-Cholest-5-ene-3β,26-diol (5d) from Acid 9c. A mixture of the acid **9c** (from the duplicate experiment), $LiAlH_4$, and dry tetrahydrofuran was refluxed in an atmosphere of dry nitrogen. The recovered product was purified by TLC [ethyl acetate–benzene (1:1)] and crystallized from ethyl acetate. The (25ξ)-cholest-5-ene-3β,26-diol (**5d**) showed $[\alpha]^{22}D$ −30.4 ± 3.0° (*c* 0.66, DMF), $[\alpha]^{21}D$ −27.1 ± 1.8° (*c* 1.18, dioxane), and $[\alpha]^{21}D$ −33.7 ± 1.8° (*c* 1.2, $CHCl_3$).

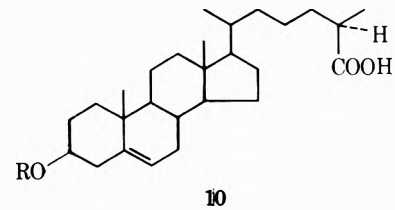
(25ξ)-Cholest-5-en-3β,26-diol (5e) from Acid 9d. The acid **9d** (from the duplicate experiment) was reduced with $LiAlH_4$ as described above. The obtained (25ξ)-cholest-5-ene-3β,26-diol (**5e**) showed $[\alpha]^{21}D$ −31.9 ± 2.2° (*c* 1.12, DMF), $[\alpha]^{21}D$ −33.3 ± 2.0° (*c* 1.0, dioxane), and $[\alpha]^{22}D$ −37.8° (*c* 1.1, $CHCl_3$).

(25*R*)-Cholest-5-en-3β-ol-26-oic Acid 3-Acetate (10a). A mixture of the 26-trityl ether **1c** (derived from kryptogenin) (1 g), pyridine (10 ml), and acetic anhydride (2 ml) was stored for 16 hr at ambient temperature. The product was recovered in the conventional manner to yield **1d**, ir no OH band, 1730 cm^{-1} (acetate), aromatic absorption bands.

A solution of (25*R*)-3β-acetoxycholest-5-ene 26-trityl ether (**1d**, 2.93 g) in 90% aqueous dioxane (60 ml) containing concentrated HCl (0.5 ml) was heated at 50–60° for 2 hr. The solution was diluted with water and extracted with ether. The organic phase was washed with dilute $NaHCO_3$ and water, and, after drying, the solvent was removed.

The resulting residue was adsorbed on a silica gel (100 g) column. Elution with benzene (2.7 l.) gave triphenylmethanol and some (25*R*)-cholest-5-ene-3β,26-diol diacetate (**1e**), mp 125.5–127.5° [reported[12] (for 25*R* diacetate) 128–129° (uncorrected)]. Subsequent elution with ethyl acetate–benzene (3:97, 1.8 l.) furnished (25*R*)-cholest-5-ene-3β,26-diol 3-acetate (**1f**, 952 mg). Crystallization from ethyl acetate gave plates: mp 130.5–131.5°; $[\alpha]^{24}D$ −35.6° (*c* 3.0, $CHCl_3$); ν_{max} (KBr) 3360 (OH) and 1735 cm^{-1} (acetate); NMR spectrum ($CDCl_3$) 0.68 (s, 3 H, 18-H), 0.91 (d, *J* = 6.5 Hz, 6 H, 21- and 27-H), 1.03 (s, 3 H, 19-H), 2.03 (s, 3 H, $-OOCCH_3$), 3.46 (c, *J* = 5 Hz, 2 H, 26-H), ca. 4.57 (broad, 1 H, 3α-H), and 5.37 (d, *J* = 5 Hz, 1 H, 6-H). Further elution of the column with ethyl acetate–benzene (3:7) gave (25*R*)-cholest-5-ene-3β,26-diol (**1a**) (410 mg), mp 167–168°.

The 3-acetoxy-26-alcohol **1f** (770 mg) in acetone (80 ml) was oxidized with Jones reagent at ambient temperature for 3 min. Conventional work-up gave a crystalline residue (728 mg), which was shown by TLC to contain mainly the required acetoxy acid (**10a**). Purification by preparative TLC [ethyl acetate–benzene (2:3)] and crystallization of the major product from ether–hexane gave (25*R*)-cholest-5-en-3β-ol-26-oic acid 3-acetate (**10a**): mp 142.5–149° (mostly 148–149°); ν_{max} (KBr) 3600–3000 (broad, -COOH) and 1725 cm^{-1} (C=O, acid and ester); $[\alpha]^{24}D$ −45.9 ± 1.3° (*c* 2.44, $CHCl_3$).



10

a, R = Ac [derived from 25*R* (**1f**) (100% optical purity)]
b, R = H
c, b recovered from crystalline quinine salt
d, b recovered from mother liquor of quinine salt

(25*R*)-Cholest-5-en-3β-ol-26-oic Acid (10b), 10c, and 10d. A. (25*R*)-Cholest-5-en-3β-ol-26-oic acid 3-acetate (**10a**, 650 mg) was dissolved in a mixture of ether (50 ml) and a saturated solution of Na_2CO_3 in 80% methanol (440 ml). After 24 hr at room temperature the solution was acidified with concentrated HCl (Congo Red) and the volume of solvent was reduced under vacuum at 35°. The residue was diluted with water, and the product was extracted with ether and worked up as usual to give a crystalline residue (620 mg). Two crystallizations from ethyl acetate furnished needles (400 mg) of (25*R*)-cholest-5-en-3β-ol-26-oic acid (**10b**), mp 168–170°, $[\alpha]^{24}D$ −34.1° (*c* 2.0, CH_3CH). From the mother liquor a second crop (125 mg) was obtained: $[\alpha]^{24}D$ −33.5° (*c* 2.0, CH_3OH) [reported for 25*RS* acid mp 176–178°[14] (uncorrected) and 173–175°;[15] $[\alpha]^{20}D$ −30.6° (no solvent or concentration reported)].

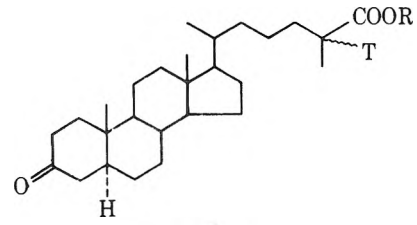
B. The above (25*R*)-cholest-5-en-3β-ol-26-oic acid (**10b**, 113.5

mg) (prepared in A) was subjected to resolution in the (−)-quinine–methanol system described previously. The twice-crystallized salt and the mother liquors were decomposed to give acids **10c** (71 mg) and **10d** (38 mg), respectively. Both samples had $[\alpha]^{24}D$ −33.6° (*c* 2.0, CH_3OH). Hence the acids **10** derived from kryptogenin are apparently optically pure 25*R* acids.

[25-^{3}H]-5α-Cholestane-3β,26-diol (12). A specimen of [25-^{3}H]cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether[6] (255 μg, 3.8 μCi) was mixed with nonradioactive material (500 mg) and converted to [25-^{3}H]cholest-5-ene-3β,26-diol (**5f**) as previously described.[6] The product was crystallized from ethyl acetate to constant specific activity.

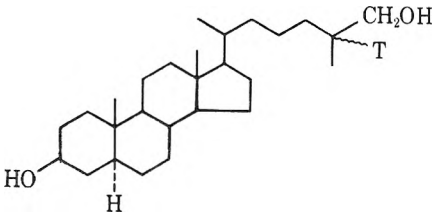
The [25-^{3}H]cholest-5-ene-3β,26-diol (**5f**, 400 mg) was hydrogenated in ethyl acetate–perchloric acid.[6] The partially acetylated reduced residue was treated with 1 *N* methanolic KOH (75 ml) at 25° for 18 hr. The product **12** was isolated and recrystallized from methanol. The specific activity was unchanged, mp 166.5–171°, $[\alpha]^{24}D$ +23.6 ± 1.2° (*c* 1.7, $CHCl_3$) [reported[12] for *R* diastereomer, 179–181° uncorrected, $[\alpha]^{20}D$ +28° (ca. 1%, $CHCl_3$)].

[25-^{3}H]-5α-Cholestane-3β,26-diol (**12**, 200 mg) in acetone (75 ml) was treated with Jones reagent (0.75 ml) dropwise at room temperature for 5 min. The usual work-up procedure gave a homogeneous product which was crystallized from ethyl acetate–hexane to give [25-^{3}H]-5α-cholestan-3-on-26-oic acid (**11a**). The specific activity of **11** remained unchanged.



11

a, R = H
b, R = CH_3



12

We repeated the oxidation of **12** with the pyridine (20 ml)–chromic acid (1 g)–water (0.3 ml) reagent. The resulting **11a** retained all the tritium.

The 3-keto 26-acid **11a** showed mp 145–147.5° [reported[12] for the 25*R* diastereomer 156–158° (uncorrected)]; ν_{max} (KBr) 3680–3640 and 1715 cm^{-1} (–COOH); $[\alpha]^{24}D$ +39.8 ± 1.3° (*c* 1.5, $CHCl_3$) [reported[12] for 25*R* (**11a**) $[\alpha]^{20}D$ +32° (c ~1, $CHCl_3$)].

Equilibration of [25-^{3}H]-5α-Cholestan-3-on-26-oic Acid (11a) and 26-Methyl Ester (11b) with Base. A. The keto acid **11a** (100 mg) was treated with a saturated solution of Na_2CO_3 in 80% methanol (25 ml) for 24 hr at room temperature. Isolation of the product and crystallization from ethyl acetate–hexane gave **11a** which showed an unchanged specific activity and $[\alpha]^{24}D$ +40.1° (c 1.6, $CHCl_3$).

B. A specimen of the acid **11a** (50 mg) was refluxed with 5% KOH in aqueous ethanol (1:9, 10 ml) for 20 hr. The product was isolated and crystallized from ethyl acetate–hexane. No loss of tritium occurred.

C. The material from experiment B was refluxed with KOH (600 mg) in propylene glycol (10 ml) and water (2 ml) for 20 hr. The product was isolated, purified by TLC [ethyl acetate–benzene (1:2)], and crystallized. The specific activity remained unchanged.

D. Another specimen of the keto acid **11a** (40 mg) was esterified with diazomethane. The resulting 26-methyl ester **11b** (38 mg) was added to a solution of sodium methoxide in dry methanol (860 mg of Na in 25 ml of MeOH) and the mixture was refluxed (6 hr) under N_2. Water (3 ml) was then added and the solution was refluxed for a further 2.5 hr. The product was isolated in the usual manner and after purification by TLC [ethyl acetate–benzene (1:3)] the keto acid **11a** was crystallized. The specific activity remained unchanged.

Preparation of Cholest-4-en-3-on-26-ol *p*-Bromobenzoates. The 26-*p*-bromobenzoates **3b** (derived from kyptogenin), **7b** (derived from hydroboration of Δ^{25} with (+)-diisopinocampheylborane), **8b** (derived from hydroboration of Δ^{25} with disiamylborane), and **8e** (derived from hydroboration of Δ^{25} with (−)-diisopinocampheylborane) were prepared as previously described.[4,16]

Preparation of Cholest-4-en-3β,26-diol 26-*p*-Bromobenzoates. (25*S*)-Cholest-4-en-3-on-26-ol *p*-bromobenzoate (**8g**, ca. 5 mg) [derived from microbially prepared 26-hydroxycholest-4-en-3-one] was dissolved in 0.5 ml of ether and treated with 1.5 mg of lithium aluminum tri-*tert*-butoxyhydride at 0°. The suspension was kept at 0° for 16 hr. The reaction mixture was poured into ice–water and extracted with ether. The crude product obtained after evaporation of the solvent was purified by preparative TLC [$CHCl_3$–MeOH (24:1)] and afforded ca. 1.8 mg of cholest-4-ene-3β,26-diol 26-*p*-bromobenzoate (**8h**): uv (MeOH) 245 nm (ε ca. 20000); NMR ($CDCl_3$) 0.70 (s, 3 H, 18-H), 0.94 (d, *J* = 6.5 Hz, 3 H, 21-H), 1.01 (d, *J* = 6.5 Hz, 3 H, 27-H), 1.04 (s, 3 H, 19-H), ca. 4.1 (broad, 1 H, 3α-H), 4.15 (2 H, 26-H), 5.27 (s, 1 H, 4-H), 7.59 and 7.90 ppm (4 H, benzoate protons) (the NMR spectrum was obtained on a Jeolco PS-100 instrument by the Fourier transform method).

The 26-*p*-bromobenzoate **8h** was further purified by liquid chromatography on a Waters-Alc instrument equipped with two linearly connected Corasil columns (3 ft × 0.375 in. each). The column was percolated with hexane–2-propanol (199:1) at a rate of 3 ml/min. A small amount of starting material (retention time 23 min) and a trace of an impurity were removed. The required 3β-ol-4-ene **8h** showed a retention time of 35 min.

The four remaining cholest-4-ene-3β,26-diol 26-*p*-bromobenzoates were prepared in a similar manner.

Results and Discussion

Our approach to the synthesis of 26-hydroxycholesterol analogs was the same as that previously used.[6] We planned to hydroborate[7-9] selectively the 25 double bond of the 5,25-diene 3-THP ether **4** and oxidize the resulting product with $NaOH–H_2O_2$ to yield the 26-hydroxycholesterol 3-tetrahydropyranyl ether (THP ether). The 26-hydroxy 3-THP ether could then be manipulated to give the required products.

It was considered likely that hydroboration of **4** with the achiral disiamylborane will give racemic (or nearly so) (25*RS*)-26-alcohol.[6a,b] On the other hand, hydroboration of **4** with (+)-diisopinocampheylborane (DIPCB) [derived from (−)-α-pinene] and (−)-DIPCB [derived from (+)-α-pinene] should result in 26-alcohols enriched with 25*R* and 25*S* isomers, respectively. These projections were based on certain generalizations on the possible orientation of the substrate (**4**) and the hydroborating reagents in the transition state.[7-9] The C-25(26) methylene moiety is located at the end of the aliphatic side chain and is removed from the chiral centers of **4**. We therefore considered it likely that the hydroboration of the C-25(26) double bond will be minimally influenced by the chiral centers of **4**. In essence, we thought that the reaction will proceed in a manner similar to that of a straight-chain aliphatic compound with a terminal methylene[7-9] moiety.

As reference we have synthesized (25*R*)-cholest-5-ene-3β,26-diol (**1a**) from kryptogenin diacetate[12] (**2**), which is known to have the 25*R* stereochemistry.[17] Authentic (25*S*)-cholest-4-en-3-on-26-ol was obtained from the incubation of cholesterol with *M. smegmatis*.[4,16,18] The 25*S* stereochemistry of the microbially obtained product was determined by X-ray crystallography[16a] of its 26-*p*-bromobenzoate (**8g**).

The determination of the C-25 stereochemistry (and eventually optical purity) of the 26-hydroxy specimens obtained via hydroboration of **4** was to be carried out by the circular dichroism (CD) method on the 26-*p*-bromobenzoates[19]. The CD spectra of these derivatives were to be

Table I
Circular Dichroism (CD) Data of Samples of Cholest-4-ene-3β,26-diol 26-*p*-Bromobenzoates[a]

Entry	Compd	Chirality	Estimated optical purity at C-25,[b] %	Origin of sample	CD	
					Δε	λ, nm
1	**8h**	25*S*		Microbial transformation	+0.78	244
2	**3c**	25*R*		Kryptogenin	−0.80	244
3	**7c**	25*RS*	0	Hydroboration[c] with (+)-DIPCB		
4	**8f**	25*S*	83	Hydroboration[c] with (−)-DIPCB	+0.64	245
5	**8c**	25*S*	23	Hydroboration[c] with disiamylborane	+0.18	243

[a] The spectra were recorded in methanol–dioxane (9:1) solutions. [b] Calculated on the basis of Δε of **8h** and **3c**, which were assumed to be optically pure (100%). [c] The substrate for hydroboration was the 25(26)-olefin **4**.

compared with that of the (25*S*)-*p*-bromobenzoate **8g** whose 25*S* chirality was rigorously established. At this point we had two options, either to convert the microbially prepared (25*S*)-26-hydroxycholestenone to the (25*S*)-26-hydroxycholesterol analog, or convert the other chemically prepared compounds to the 26-hydroxycholestenones. Because of the scarcity of the microbially prepared material we chose to convert all the products to the 26-hydroxycholestenone analogs.

The transformation of the samples of 26-hydroxycholesterols to 26-hydroxycholestenones was carried out by two procedures. When the 26-hydroxycholesterol was the starting material (**1a**, **5b**, and **6f**) the 26-hydroxyl was selectively protected by tritylation.[13] Treatment of **1a** with $(C_6H_5)_3CCl$ and pyridine gave the 26-trityl ether **1c**, which was separated from the accompanying 3,26-ditrityl ether **1b**. The formation of a ditrityl ether involving a primary and secondary hydroxyl was previously noted.[13] Oppenauer oxidation of **1c** and mild acid hydrolysis of the product provided the required **3a**. A similar sequence of transformations was used for the preparation of **7a** (from **5b** via **5c**) and of **8d** (from **6e** via **6f** and **6g**).

In the case of the 26-hydroxy 3-THP ether **6a** the 26-hydroxyl was acetylated and the resulting **6c** was treated with acid to yield the 3-hydroxy 26-acetate **6d**. The obtained **6d** was oxidized by the Oppenauer procedure to give 26-acetoxycholestenone, which was saponified to the required 26-hydroxycholestenone (**8a**).

The four samples of 26-hydroxycholestenone, 25*R* (**3a**), 25*RS* (**7a**), 25*S* (23% optical purity) (**8a**), and 25*S* (83% optical purity) (**8d**), were treated with *p*-bromobenzoyl chloride and pyridine to yield the 26-hydroxycholestenone 26-*p*-bromobenzoates **3b**, **7b**, **8b**, and **8e**, respectively. Attempts to determine the C-25 stereochemistry of these compounds by CD failed, since all gave essentially identical curves. The dominating effect of the 4-en-3-one chromophore obviously obscured the CD differences emanating from the stereochemical variations at C-25. To obviate this difficulty it was necessary to eliminate the 4-en-3-one chromophore. This was accomplished by reduction of the conjugated ketone to an allylic alcohol. Thus, treatment of the pertinent 26-hydroxycholestenone 26-*p*-bromobenzoates with $LiAlH(t\text{-}BuO)_3$ gave the required Δ^4-3β-ol-26-*p*-bromobenzoates **3c**, **7c**, **8c**, and **8f**. In a similar manner, reduction of the (25*S*)-26-hydroxycholestenone *p*-bromobenzoate **8g** (derived from the microbial preparation) gave **8h**.

The CD spectra of all samples were recorded in methanol–dioxane (9:1) solutions. Although the observed Cotton effects were not large, they sufficed for assigning the configurations[19] at C-25 (Table I). It is evident that the **8h** obtained microbiologically and **3c** obtained from kryptogenin gave CD Cotton effects of the same magnitude but of the opposite sign (entries 1 and 2). While the **8h** whose 25*S* configuration was determined by X-ray crystallography has a positive CD Cotton effect (Table I, entry 1), the 25*R* analog **3c** derived from kryptogenin has a negative CD Cotton effect (Table I, entry 2).[20] Rather unexpectedly, the derivative **7c** obtained by "asymmetric" hydroboration of **4** with (+)-DIPCB did not show a Cotton effect and proved to be racemic (25*RS*) (Table I, entry 3). In contrast, **8f**, which was derived from hydroboration of **4** with (−)-DIPCB, has a positive CD Cotton effect (Δε +0.64) for the 25*S* isomer. Assuming a 100% optical purity for **8h**, it follows that the optical purity of **8f** is ca. 83%. Finally, hydroboration of **4** with the achiral disiamylborane gave the 25*S* isomer **8c** which had an optical purity of ca. 23%.

The C-25 stereochemistry of the hydroboration products was unexpected and difficult to rationalize. However, the results become accountable if a "25*S*-inducing effect" is assigned to the steroidal moiety. The hydroboration of **4** with the achiral disiamylborane gave the 25*S* product (23% optical purity) due to the "25*S*" influence of the steroidal nucleus. The hydroboration of **4** with the (−)-DIPCB was expected to yield the 25*S* isomer and this was seemingly potentiated by the "inducing effect" of the steroidal molecule; hence **8f** shows a fairly high "25*S*" character (ca. 83% optical purity). In contrast, the (+)-DIPCB was expected to yield the 25*R* isomer, but this was counteracted by the influence of the steroidal moiety and resulted in the racemic (25*RS*) **7c**. Presumably the side chain of **4** is coiled during hydroboration so that the steroidal skeleton exerts a chiral (25*S*) influence.

In the initial stages of the study it was considered likely that **6a**, obtained via hydroboration of **4** with disiamylborane, is racemic.[6a,b] Attempts to resolve the 26-alcohol 3-THP ether **6a** with different reagents were not successful. Consequently we decided to convert the alcohol to a 25-carboxylic acid and resolve the acid.

We have previously proven[6a] that the transformation of [25-^{3}H]cholest-5-ene-3β,26-diol (**5f**) via [25-^{3}H]-5α-cholestane-3β,26-diol (**12**) to [25-^{3}H]-5α-cholestan-3-on-26-oic acid (**11a**) proceeds without epimerization at C-25 as evidenced by the retention of all the tritium in the acid (**11a**). We repeated the sequence of reactions except that the oxidation was carried out with the CrO_3–pyridine–water reagent.[21] Again no loss of tritium was observed. Since one of the steps in the projected preparation of the 26-acids involved saponification, we tested also the influence of common bases in protic solvents on the chirality at C-25. Under the conditions of equilibration tested (see Experimental Section) **11a** and **11b** retained all the tritium, indicating that epimerization at C-25 did not occur. Consequently, **6a** was oxidized under the same conditions (CrO_3–pyridine–water), to yield the acid **9a**, which was hydrolyzed to **9b**. The obtained acid **9b** was treated with (−)-quinine and the resulting salt was crystallized from methanol. The acid **9c** ($[\alpha]^{22}D$ −27.2°, −25.3°) was recovered from the crystalline quinine salt. The acid **9d** ($[\alpha]^{22}D$ −19.1°) was obtained from the mother liquor of crystallization of the quinine salt. It seems therefore that at least a partial resolution of

the acids was achieved by the procedure employed. The acids **9c** and **9d** were reduced ($LiAlH_4$) to the 26-alcohols **5d** and **5e**, respectively.

The authentic 25*R* acid **10b** was prepared from **1a** derived from kryptogenin. The diol **1a** was converted to the 26-trityl ether **1c** and acetylated to **1d**. Acid hydrolysis provided the 3-acetoxy-26-hydroxy **1f** which was oxidized to **10a** and saponified to **10b**. To test the optical purity of **10b** attempts were made to resolve it via the quinine salt as described above. However, both the acid **10c** recovered from the crystalline salt and the acid **10d** recovered from the mother liquor had the same $[\alpha]^{24}D$ −33.6°. No further attempts were made to determine the configurations of the acids **9c** and **9d** and the configurations of the derived alcohols **5d** and **5e**, respectively.

The identity of the $[\alpha]D$ of **10c** and **10d** tends to indicate their near 100% "optical purity" and consequently the near "optical purity" of **1a** and of the kryptogenin diacetate **2**.

Registry No.—**1a**, 20380-11-4; **1c**, 56792-57-5; **1f**, 56845-81-9; **2**, 56792-58-6; **3a**, 56792-59-7; **3c**, 56792-60-0; **4**, 24583-89-9; **5a**, 24583-90-2; **5b**, 13095-61-9; **6a**, 56845-82-0; **6b**, 56845-83-1; **6d**, 56906-69-5; **7a**, 19257-21-7; **7c**, 56845-84-2; **8a**, 41530-25-0; **8b**, 41530-31-8; **8c**, 56792-61-1; **9a**, 56792-62-2; **9b**, 56845-85-3; **9c**, 6561-58-6; **9e**, 56845-86-4; **10a**, 56792-63-3; **10b**, 56845-87-5; **11a**, 24583-91-3; **12**, 54575-47-8; triphenylchloromethane, 76-83-5; [25-^{3}H]cholest-5-ene-3β,26-diol 3-tetrahydropyranyl ether, 56792-64-4.

References and Notes

(1) (a) Worcester Foundation for Experimental Biology. (b) Postdoctoral Fellow, 1966–1969. (c) Postdoctoral Fellow, 1970–1972. (d) The work at the Worcester Foundation was supported by Grants AM 12156 and GM 19882 from the National Institutes of Health.

(2) (a) Columbia Univeristy. (b) The work at Columbia University was supported by Grant AI 10187 from the National Institutes of Health.

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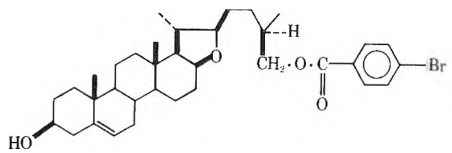
(20) A word of caution is in order. The presence of other chiral centers in the side chain will influence significantly the CD spectra of 26-*p*-bromobenzoates as exemplified by the CD of the dihydrodiosgenin derivative which showed $\Delta\epsilon_{245}$ −1.74 (MeOH).



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Diterpenoid Total Synthesis, an A → B → C Approach. VII. Total Synthesis of DL-Sugiol, DL-Ferruginol, and DL-Nimbiol[1]

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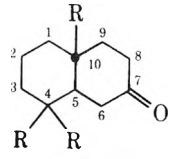
Cyanoethylation of 2,2,6-trimethylcyclohexanone followed by saponification affords 3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propionic acid (**5**), the carboxyl of which is converted to acetyl (**9**) either by treatment of **5** with methyllithium or by sequential exposure to oxalyl chloride, diazomethane, hydrogen chloride, and zinc–acetic acid. Reaction of **5** with thionyl chloride affords chloro lactone **10** rather than the normal acid chloride. Pyrrolidine-catalyzed cyclodehydration of diketone **9** produces 4,4,10-trimethyl-Δ^5-7-octalone, which undergoes hydrogenation to a 4:1 mixture of the corresponding trans and cis decalones (**12** and **13**). Decalone **12** is also available from 10-cyano-4,4-dimethyl-*trans*-7-decalone by the sequence ketalization, lithium aluminum hydride reduction of cyano to imino, Huang-Minlon reduction of imino to methyl, and ketal hydrolysis, or from 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone by the sequence ketalization, lithium aluminum hydride reduction, Sarett oxidation to the angular aldehyde, Huang-Minlon reduction, and ketal hydrolysis. 4,4,10-Trimethyl-*trans*-decalin was prepared by reduction of **12**. Condensation of **12** with ethyl formate affords exclusively the 8-hydroxymethylene derivative, which is dehydrogenated by 2,3-dichloro-5,6-dicyanoquinone to form the $\Delta^{8,9}$-unsaturated keto aldehyde **23**. Michael addition of the sodium enolate of *tert*-butyl isovalerylacetate or *tert*-butyl propionylacetate produces adducts **24**, which in the presence of *p*-toluenesulfonic acid in acetic acid undergo *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration, thereby forming the tricyclic enediones **25a** and **25b**, respectively. On the basis of ^1H NMR data these are tentatively assigned the trans-syn-cis configuration, and the adducts **24** are formulated with a 9α side chain. Exposure of the enediones to pyridine hydrobromide perbromide in acetic acid brings about aromatization of ring C to form DL-sugiol and DL-nimbiol, respectively. Hydrogenolysis of the former affords DL-ferruginol.

Earlier we described a general scheme of synthesis which was planned to allow stereoselective construction of a variety of polycyclic members of the diterpenoid family of natural products.[1b] In essence this involves preparation of a 4,4,10-trisubstituted *trans*-7-decalone (**1**)[2] which is to become the A/B ring system of the terpenoid, followed by attachment of a C ring which carries the appropriate carbon substituents and functional groups. In this paper we de-

scribe details of adaptation of this sequence for synthesis of several typical tricyclic diterpenoids in which the three substituents at C-4 and C-10 are methyl and in which the C ring is a 12-phenol, DL-sugiol (**2a**),[3] DL-nimbiol (**2b**),[4] and DL-ferruginol (**2c**).[5]



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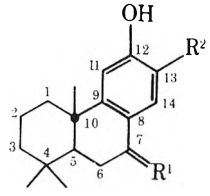
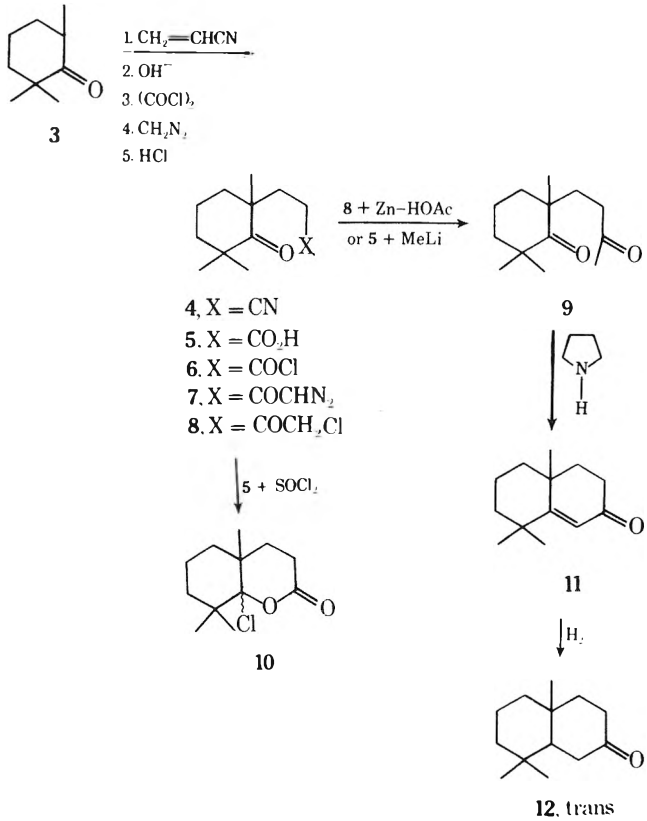


2a, $R^1 = O$; $R^2 = CH(CH_3)_2$
b, $R^1 = O$; $R^2 = CH_3$
c, $R^1 = H_2$; $R^2 = CH(CH_3)_2$

4,4,10-Trimethyl-*trans*-7-decalone (12). The appropriate *trans*-7-decalone (**1**) for use in preparation of these and many other terpenoids by this sequence is the 4,4,10-trimethyl derivative **12**.[6-8] One might visualize its preparation in a manner analogous to that used for synthesis of its angular cyano[1b] and angular carbethoxy[9] counterparts, viz., by condensation of 2,2,6-trimethylcyclohexanone (**3**) with methyl vinyl ketone to produce octalone **11**, followed by stereospecific hydrogenation. However, Michael–Robinson annulations of simple cyclohexanones such as **3** in which the appropriate α hydrogen is not activated by a second electron-withdrawing group often proceed poorly, particularly when the ketone is sterically hindered,[10] and such was the case with this system. Under none of the conditions we examined[10,11] were more than meager yields of the octalone or an intermediate ketol produced, and consequently more circuitous syntheses of octalone **11**[12,13] were explored (Scheme I).

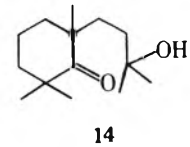
Scheme I



At least part of the difficulty in methyl vinyl ketone addition to trimethylcyclohexanone seemed to originate from competitive self-condensation of methyl vinyl ketone or further condensation of methyl vinyl ketone with the initial Michael adduct, and thus we initially turned to an alternate Michael acceptor which could still lead through diketone **9** to octalone **11**. Cyanoethylation of trimethylcyclohexanone proceeds excellently, and saponification of keto nitrile **4** affords the corresponding keto acid **5** in 76% overall yield. However, exposure of the keto acid to thionyl chloride does not produce the keto acid chloride **6**, but an isomeric substance with a single carbonyl absorption at 5.68 μ rather than two near 5.5 and 5.9 μ. Several features in its ^{1}H NMR spectrum differ sufficiently from those in spectra of keto nitrile **4**, keto acid **5**, diazo ketone **7**, chloro ketone **8**, and diketone **9** (see below) to suggest that this product is not a structural analog of those substances. For example, in spectra of all five of these monocyclic compounds the resonance patterns from the $CH_2C{=}O$ protons and the other methylene protons show considerable similarity to one another both in chemical shift and spin-splitting fine structure, while the corresponding resonances of the thionyl chloride product are quite different in both respects. Also, the three methyl resonances of the thionyl chloride product are clearly separated from one another, while in spectra of the five monocyclic derivatives the methyl resonances are either all superimposed or two are superimposed with the third no more than a few hertz removed at 60 MHz. From these data this substance is formulated as one of the diastereomeric chloro lactones **10**, presumably formed from the normal acid chloride under the influence of acid.[14] This derivative is stable toward dimethylcadmium. Although methyllithium and the Grignard reagent were considered as alternative reagents for converting it to the desired diketone, these reactions have not been explored.

Exposure of the sodium salt of keto acid **5** to oxalyl chloride, conditions which avoid the presence of a proton donor, forms the normal acid chloride **6**. This was treated sequentially with diazomethane, hydrogen chloride, and zinc–acetic acid[14] to produce diketone **9** in 79% yield.

A shorter preparation of the diketone was found in direct treatment of the keto acid with methyllithium.[15] While yields of diketone from this reaction were lower than from the foregoing sequence, and varied considerably from run to run (generally 30–50%), the majority of the remaining material was starting keto acid which could be reused. Usually only minor amounts of by-products were evident in gas chromatograms of the total neutral product, although occasionally substantial quantities of one or more other substances were found. These were not isolated nor definitely characterized, but spectroscopic properties of such mixtures suggested that at least the ketol **14** was among the capricious contaminants. Seldom when the methyllithium for this reaction was freshly prepared from methyl iodide[15] was evidence for significant formation of the isomeric ketol **15**, diol **16**, hydroxy acid **17**, or its lactone **18** encountered (but see Experimental Section for a comment on use of commercial methyllithium). It certainly appears, as was anticipated, that steric hindrance to ketone attack is substan-



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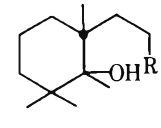
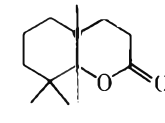


15, R = $COCH_3$
16, R = $C(CH_3)_2OH$
17, R = CO_2H



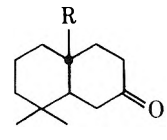
18

tial, and allows selective reactivity at the carboxyl group. Detailed development of this reaction for synthetic purposes was not pursued in light of developments discussed below, but it appears capable of improvement by careful study of reaction conditions.

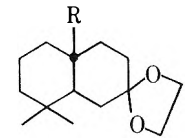
Pyrrolidine-catalyzed cyclodehydration[9] smoothly converts diketone **9** into the corresponding octalone **11**,[12,13] the overall yield from trimethylcyclohexanone being 60% through the diazo ketone or 52% by the methyllithium route (taking recovered keto acid into account).

The enone was subjected to palladium-catalyzed hydrogenation. Such reduction of the analogous 10-cyano-[1b] and 10-carbethoxy-4,4-dimethyloctalones[9] had been completely stereospecific, affording only the trans decalones, so it was with some surprise that we isolated a mixture of decalones in the present instance (Scheme I). From the relative intensities of the methyl resonances in ^{1}H NMR spectra and from GLC analysis it is apparent that the two isomers are formed in an approximately 4:1 ratio. The major product proved to be identical with the product subsequently derived from cyano decalone **19a** (below), and it has ir and ^{1}H NMR spectra which are superimposable on those of the levorotatory degradation product of dehydroabietane.[8] It is thus the trans-fused racemate. The minor hydrogenation product, by exclusion, is the cis decalone. The results of this hydrogenation[16] reaffirm that 4,4-dimethyl substitution may not play as important a steric role in directing catalyst approach as has been often assumed.[17] The angular functions obviously contribute a significant directive influence in reduction of the angular cyano and carbethoxy octalones,[1b,9] just as they are known to do in hydrogenation of 10-substituted octalones devoid of 4,4-dimethyl groups.[17f,18]

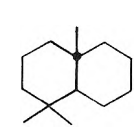
The lack of stereoselectivity in hydrogenation of trimethyloctalone **11**, combined with the difficulty in purifying the trans decalone from the isomer mixture, made this route to decalone **12** less than attractive for synthetic purposes. One of the reasons the cyano decalone **19a** had been chosen for initial investigation was the potential synthetic versatility of the cyano group.[1b] Inasmuch as the cyano decalone can be synthesized stereoselectively in good overall yield,[1b] it was of interest to examine its reduction to the trimethyldecalone. Ketalization, lithium aluminum hydride reduction of its cyano group to imino,[19] direct Huang-Minlon reduction of the imine without prior hydrolysis to the aldehyde,[20] and ketal hydrolysis (**19a** → **20a** → **20b** → **20c** → **12**) proceed in nearly quantitative yield to afford the crystalline trans trimethyldecalone, which is thus available in 52% overall yield from 2,2-dimethylcyclohexanone. This decalone is also obtained efficiently (68% overall) from its angular carbethoxy counterpart **19b**[9] by the sequence ketalization, lithium aluminum hydride reduction, Sarett oxidation, Huang-Minlon reduction, and ketal hydrolysis (**19b** → **20d** → **20e** → **20f** → **20c** → **12**). The alternate sequence $RCO_2Et \rightarrow RCH_2OH \rightarrow RCH_2OTs \rightarrow RCH_3$ to convert the angular ester of **20d** to a methyl was unsatisfactory, however, because lithium aluminum hydride reduction of the *p*-toluenesulfonate **20g** resulted only in S–O bond cleavage, regenerating alcohol **20e**. It may be noted that these interconversions, together with ultimate transformation of trimethyldecalone **12** to natural products of known trans A/B configuration, serve to substantiate the assignment of a trans configuration to all of these derivatives. Inasmuch as 4,4,10-trimethyl-*trans*-decalin (**21**) promised to be potentially useful as a reference substance for the determination of configuration of other trimethyldecalin derivatives in our own and other laboratories, a sample of this hydrocarbon[7,21] was prepared by Huang-Minlon reduction of the corresponding decalone **12**.



19a, R = CN
b, R = CO_2Et



20a, R = CN
b, R = CH=NH
c, R = CH_2
d, R = CO_2Et
e, R = CH_2OH
f, R = CHO
g, R = CH_2OTs



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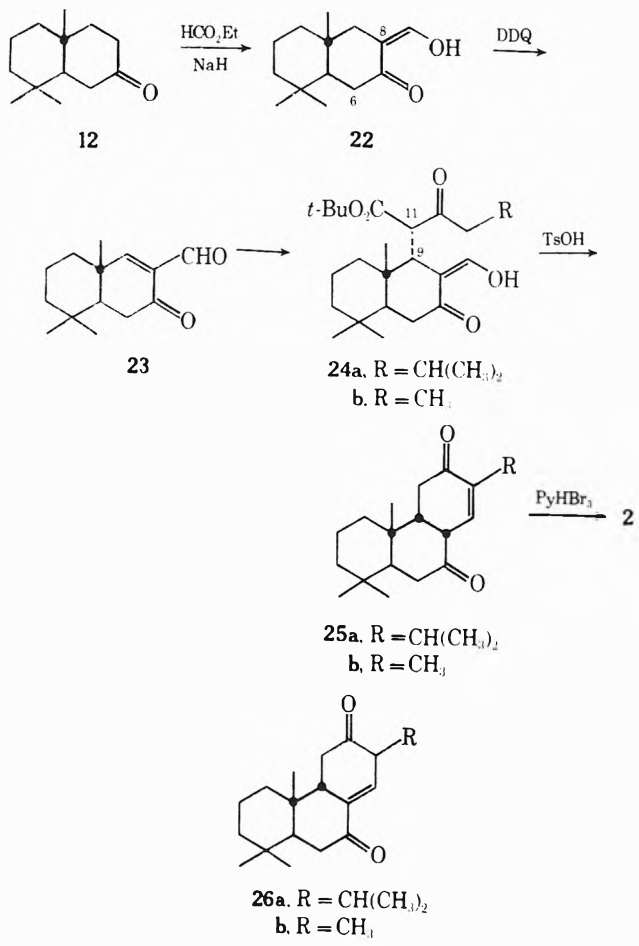
Addition of the C Ring. Condensation of trimethyldecalone **12** with ethyl formate produces exclusively one α-hydroxymethylene ketone in 92% yield. That this is the 8-hydroxymethylene derivative **22** (Scheme II), rather than the 6-substituted isomer, is clear from the appearance in its ^{1}H NMR spectrum of resonances from four rather than three protons of the type =C–CH and from the properties of subsequent reaction products. Such selectivity in this condensation is not unanticipated. Base-catalyzed acylations of this type are often reversible and thus thermodynamically controlled,[22] and the enolate of a hydroxymethylene substituent at C-6 would experience destabilizing nonbonded interactions with the 4α-methyl which are not present in the 8-hydroxymethylene isomer. However, it should be noted that the same result would be predicted if in this instance the controlling factor were condensation through the more stable enolate of decalone **12**, for the conformationally favored enolization of trans β-decalones in this direction is well known.[23] Indeed, inasmuch as it is presumably in large measure the nonbonded interaction between the syn-axial 4 and 10 substituents which preferentially destabilizes the Δ^6 enol compared to the Δ^7 enol,[23,24] selectivity should be enhanced in systems such as **12** with axial methyls at *both* C-4 and C-10. Even if the relative stabilities of the Δ^6 and Δ^7 enolates were also not important, in this system one would expect kinetic factors to favor Δ^7 enolate production and substitution. Approach of a base to the 6β-axial position is sterically hindered by two syn-axial methyls whereas only one methyl hinders axial approach to C-8. The same substituents would preferentially inhibit axial approach of ethyl formate to the 6β position of the enolate, and owing to the conformational restrictions placed on ring B by the trans fusion of the rings, transition states with proper stereoelectronic properties (orbital overlap)[25] for 6α-attack of the formic ester on the Δ^6 enolate or of a base on the ketone would need to approach true boat character whereas those for 8α-attack can be twist–boat in form. Thus both thermodynamic and kinetic factors should favor condensation at C-8 of decalone **12**, and the 5,6 double bond which was present in the model system[1b] is not necessary to control the regioselectivity of this process.

Dehydrogenation of hydroxymethylene ketone **22** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[1b,26] affords unsaturated keto aldehyde **23** in excellent yield. The appearance of resonance from one vinyl proton in its ^{1}H NMR spectrum confirms location of the formyl group at C-8 rather than C-6. By virtue of its double conjugation the olefinic bond of this aldehyde is unusually reactive toward nucleophilic addition, for the product is the resonance-stabilized enolate of a hydroxymethylene ketone.[1b] Thus Michael addition of the sodium enolates of *tert*-butyl isovalerylacetate and *tert*-butyl propionylacetate leads rapidly and in good yield to the adducts **24a** and **24b**, respectively. In each instance the ^{1}H NMR spectrum of the adduct contains two *tert*-butyl resonances, two C-11 H resonances,

Scheme II



and two CHOH resonances, indicating the product to be a mixture of two diastereomeric racemates. These were not separated, nor were the adduct mixtures purified, but direct exposure of the crude adducts to *p*-toluenesulfonic acid in glacial acetic acid induces cleavage of the *tert*-butyl group, decarboxylation, and cyclodehydration with efficient production of a single crystalline enedione (**25a** and **25b**) in each instance. Inasmuch as both diastereomers of each adduct **24** lead to the same enedione and it seems unlikely that the acidic cyclization conditions should produce a change in configuration at C-9 in either the adduct or the enedione, the diastereomers of adducts **24** are considered to differ from one another only in their relative configurations at C-11. Subsequent demonstration that the enediones **25** are of the trans-syn-cis configuration supports this deduction, for if any 9β-alkyl adduct had been formed, or if acid-catalyzed 9-epimerization had occurred, the cyclization product would have been expected to contain the thermodynamically preferred trans-anti-trans enedione.

The overall yield of this four-stage C-ring elaboration sequence, from decalone **12** to enedione **25**, was 60% in the sugiol series (**25a**) and 63% in the nimbiol series (**25b**). It would thus seem that the general sequence may offer an attractive addition to the variety of other methods for constructing functional six-membered rings in organic synthesis. The scope and limitations of this sequence are presently under study.

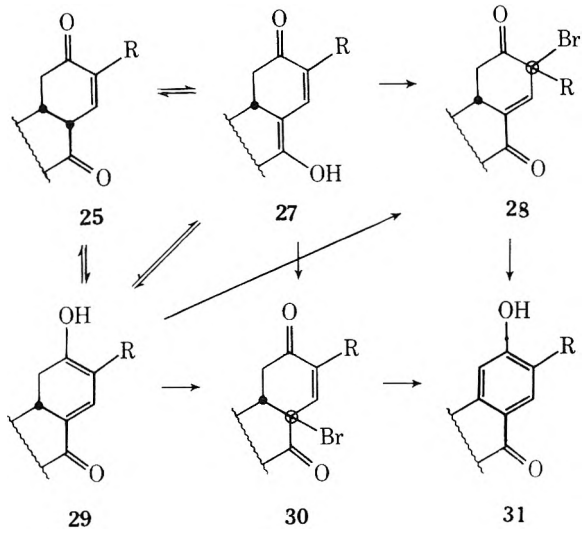
The double bond location and 9 configuration in enediones **25** were tentatively assigned on the basis of ^{1}H NMR data.[27] Both the τ 8.20 chemical shift of the 13-methyl and its long-range coupling with the vinyl proton (J = 1 Hz) indicate that the methyl is allylic and that the 13-methyl compound must have the $\Delta^{13,14}$ structure **25b** rather than the isomeric $\Delta^{8,14}$ structure **26b**. The decision is not as clear from spectra of the 13-isopropyl enedione. Both structures **25a** and **26a** are consistent with the observed long-range coupling (J = 0.9 Hz) between the 14-vinyl proton and *one* allylic proton (C-9 H in **26** or the isopropyl methine in **25**), and the resonances of both C-9 H and the isopropyl methine proton are obscured by other resonances in the 60-MHz spectrum so one cannot observe which of these shows an allylic chemical shift and the 0.9-Hz coupling. Thus the structure of this enedione was tentatively assigned by analogy with the methyl derivative; the general similarity of ^{1}H NMR and uv spectra of the two compounds lends credence to this formulation.[28]

Two new asymmetric centers have been produced in the enedione, those at C-8 and C-9, and thus the cyclization products **25a** and **25b** correspond to one of four possible diastereomeric racemates (trans-anti-trans, trans-anti-cis, trans-syn-trans, or trans-syn-cis). In many of these structures the dihedral angular relationships among the B- and C-ring protons are quite different, and should give rise to significantly different spin-coupling constants. Of these couplings $J_{8,14}$ is clearly discernible from the H-14 resonance even in 60-MHz spectra of the two enediones; it is approximately 6 Hz in each compound, which corresponds to a dihedral angle near either 25 or 125°.[29] Examination of Dreiding models of the reasonable conformations for each of the four enedione configurations, including those with nonchair forms of rings B and C (which might be significant in view of the location of trigonal carbon in those rings),[30] indicates that in no case can an appropriate 8,14 dihedral angle near 125° be attained, and only three possible structures incorporate an angle sufficiently near 25° to accommodate the observed 6-Hz coupling. One of these structures is a trans-anti-cis form and the other two are trans-syn-cis conformers. However, the configuration of the enedione at C-8 should certainly be the more stable of the two possibilities, for the acidic conditions under which it was formed would have led to equilibration at that site through enolization of the vinylogous β-diketone system. The trans-anti-cis form which satisfies the required dihedral angle relationship contains a B-ring boat conformation with a very severe eclipsed (or nearly eclipsed) interaction between the angular methyl and C-11 as well as a 5,8 prow–stern interaction. There is thus no reason to expect it to be lower in energy than its C-8 epimer (trans-anti-trans), and hence it should not be present after C-8 equilibration. Accordingly, the trans-syn-cis configuration is tentatively assigned to the enediones,[27] and their precursors, the adducts **24**, are considered to contain a 9α (axial) side chain. It may furthermore be recalled that in a related series, Michael addition of a β-keto ester to an unsaturated keto aldehyde similar to **23** but containing a 5,6 double bond led to a product from double Michael addition at both C-9 and C-5.[1b] This could only have occurred if the additions were α; the corresponding product from β-addition would contain an energetically prohibitive (and unknown) *trans*-bicyclo[4.2.0]octanone system as part of its skeleton.

These results indicate that Michael addition of the enolate to the unsaturated keto aldehyde **23** is kinetically controlled (the 9β equatorial configuration of the bulky side chain would certainly be the product of thermodynamic control), and that it occurs with complete stereoselectivity from the α face of the molecule. This stereoselectivity is in fact that expected on the basis of either stereoelectronic control (axial approach of the nucleophile) or steric approach control (approach of the nucleophile from the less hindered direction).

Ring C in the enediones is but one oxidation level below that of the phenolic natural products. In our earlier work,[1b] C-ring dehydrogenation to form a 7-keto-12-phenol was

brought about by DDQ, albeit in disappointing yield. Considerable examination of reaction conditions for this aromatization has been conducted in this series and several others. Catalytic dehydrogenation over palladium on carbon, either with or without maleic acid as an acceptor, is no more efficacious than the DDQ process. However, exposure to pyridine hydrobromide perbromide in acetic acid[31] converts the enediones **25a** and **25b** rapidly and almost quantitatively to the corresponding keto phenols DL-sugiol (**2a**) and DL-nimbiol (**2b**). Presumably this facile aromatization proceeds by initial bromination of one or both of the enolic forms of the enedione (**27** and **29**) to form bromo enediones **28** and/or **30.** In both of these substances further enolization of the enedione system is blocked, and either 1,2-dehydrobromination of **30** or 1,4-dehydrobromination of **28** to the keto phenol is the only available course of reaction. On the other hand, we have no evidence to rule out initial addition to form a dibromide followed by a double dehydrobromination.

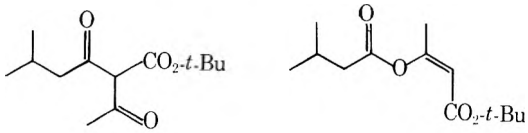


25 27 28

29 30 31

Hydrogenolysis of DL-sugiol (**2a**) over 30% palladium on carbon[32] removes the benzylic ketone and produces DL-ferruginol (**2c**).[5] Infrared and/or ^{1}H NMR spectra of these substances are superimposable on those of authentic natural products or identical with those reported in the literature for the natural enantiomers or suitable derivatives.[33,34] Total synthesis of the racemates of sugiol,[3] ferruginol,[5] and nimbiol[4] is thus confirmed.

For elaboration of the C ring, the *tert*-butyl β-keto esters **34** and **35,** which contain the ultimate 13-alkyl group of the natural products, needed to be prepared. *tert*-Butyl propionylacetate (**35**) was synthesized by condensation of *tert*-butyl acetate with *p*-diphenyl propionate in analogy to the reported preparation of the corresponding ethyl ester.[35] Synthesis of keto ester **34** proceeded through acylation of the sodium enolate of *tert*-butyl acetoacetate by isovaleryl chloride to form the diketo ester **32**,[36] sodium hydride



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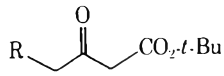

34, R = $CH(CH_3)_2$
35, R = CH_3

being used as the base. This compound is readily separated from the small amount of O-acylation product **33** by basic extraction. Ammonolysis has been reported[37] as a procedure for selectively cleaving the acetyl group in analogous diketo esters, but we have found that 1% aqueous sodium hydroxide is faster and at least equally selective,[37,38] affording the γ-substituted β-keto ester **34** in high yield.

Experimental Section

Spectra were obtained using Perkin-Elmer Models 137, 137G, and 337 (ir), Cary Model 14 (uv), and Varian A-60 (^{1}H NMR) spectrometers. The ^{1}H NMR reference was Me_4Si as an internal standard, with chemical shifts reported in τ units and coupling constants (J) in hertz. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E double-focusing spectrometer with direct sample introduction at an ionization potential of 80 eV; data is in the form *m/e* (percent base peak intensity). Glc was conducted on a 2-m 10% silicone gum SE-30 on Chromosorb W column at the indicated temperature, using an F & M Model 609 chromatograph with N_2 as carrier gas and with a hydrogen flame ionization detector. Melting points and boiling points are uncorrected. Microanalyses are by Alfred Bernhardt, Mulheim, Germany. Unless indicated otherwise the drying agent for organic solutions was $MgSO_4$. When no temperature is specified, the reaction was conducted at room temperature, ca. 23°.

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionitrile (4). In an adaptation of an analogous procedure[39] a solution of 74.2 g (1.40 mol) of freshly distilled acrylonitrile in 100 ml of MeOH was added over 1 hr to an ice-cold mixture of 300 ml of MeOH and 6.72 g of a 55% dispersion of NaH in mineral oil (0.15 mole of NaH) in a N_2 atmosphere. The mixture was stirred for 1 hr in the cold to form β-methyoxypropionitrile, and 28.0 g (0.20 mol) of 2,2,6-trimethylcyclohexanone,[40] bp 176–178°, was slowly added. The solution was stirred at ca. 23° for 4 hr and under reflux for 4.5 days, neutralized with glacial HOAc, and concentrated at reduced pressure, and the residue was poured onto ice and extracted with ether which was washed with brine, dried, and evaporated in vacuo. The residue was distilled to yield a forerun of 83 g of an approximately equimolar mixture (GLC, 150°) of reactants followed by 22.8 g (59%) of keto nitrile **4** as a colorless oil, bp 136–145° (1.5 mm). Redistillation yielded 20.6 g (54%) of pure **4**: bp 104–105° (0.3 mm); ir (film) 4.43, 5.90 μ; uv max (95% EtOH) 244 nm (ϵ 21), 295 (26); ^{1}H NMR (CCl_4) τ 8.86 (s, 6 H), 8.94 (s, 3 H).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.61; H, 9.84; N, 7.25. Found: C, 74.44; H, 9.57; N, 7.40.

The combined foreruns of two such reactions were subjected to reaction with fresh acrylonitrile to afford an additional 18.9 g of once-distilled **4**, bp 135–145° (1.5–2.0 mm) (total conversion 84%).

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionic Acid (5). A mixture of 150 g of 15% aqueous KOH and 10.0 g (0.052 mol) of keto nitrile **4**, bp 104–105° (0.3 mm), was refluxed under N_2 for 24 hr, cooled, washed with ether, and acidified with concentrated HCl. The precipitate was extracted into ether which was washed with water, dried, and removed in vacuo to afford 10.7 g (97%) of a viscous yellow oil. Crystallization from pentane yielded 9.0 g (82%) of keto acid **5** as white prisms: mp 48–49°; ir (CCl_4) 5.83 μ; uv max (95% EtOH) 305 nm (ϵ 26); ^{1}H NMR (CCl_4) τ −1.83 (s, 1 H), 8.94 (s, 9 H). Concentration and crystallization of the mother liquors yielded an additional 1.0 g of **5**, mp 47–48° (total yield 91%).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.99; H, 9.27.

3-(1′,3′,3′-Trimethyl-2′-chloro-2′-hydroxycyclohexyl)propionic Acid Lactone (10). Over a 1.0-hr period 5.36 g (0.045 mol) of purified[41a] $SOCl_2$ was added to 6.36 g (0.030 mol) of keto acid **5**, mp 46–47°, at 0° under N_2. The solution was stirred in the cold for 0.5 hr, heated at 60° for 2 hr, and excess $SOCl_2$ was removed by codistillation with C_6H_6 to leave a yellowish crystalline mass with ir (CCl_4) 5.68 (s), 5.90 μ (w). Recrystallization from pentane yielded chloro lactone **10** as white prisms: mp 59–60°; ir (CCl_4) 5.68 μ; ^{1}H NMR ($CDCl_3$) τ 8.68 (s, 3 H), 8.75 (s, 3 H), 8.78 (s, 3 H); positive Beilstein test for halogen.

Anal.[42] Calcd for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.30. Found: C, 62.61; H, 7.93.

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionyl Chloride (6). The procedure was adapted from one by Stork and Clarke.[14] A solution of 2.14 g (0.025 mol) of $NaHCO_3$ and 5.28 g (0.025 mol) of keto acid **5**, mp 45–46°, in 15 ml of water was washed with ether and evaporated to dryness in vacuo. The salt was dried over $CaSO_4$

at 0.5 mm for 24 hr, suspended in 75 ml of ether, treated with 0.75 ml of pyridine, and cooled in ice, and 12 ml of oxalyl chloride was added during 45 min. The mixture was stirred for 1.0 hr in the cold, filtered, and solvent was removed in vacuo to afford acid chloride **6** as an oil, ir (CCl_4) 5.55, 5.90 μ, in quantitative yield. The near absence of chloro lactone **10** was indicated by very weak absorption at 5.68 μ.

4-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)-2-butanone (9). A. Diazo Ketone Route. Procedures were adapted from Stork and Clarke.[14] An ice-cold solution of crude acid chloride **6** [freshly prepared from 9.42 g (0.045 mol) of keto acid **5**, mp 46–47°] in 100 ml of ether was added over 20 min to a cold solution of CH_2N_2 [prepared from 60 g (0.58 mol) of *N*-methyl-*N*-nitrosourea[43a] and dried over KOH[43b]] in 400 ml of ether, and the solution was allowed to stand in the cold for 1.5 hr. Diazo ketone **7** could be obtained as a pale yellow oil, ir (CCl_4) 4.74, 5.90, 6.06 μ, ^{1}H NMR (CCl_4) τ 4.83 (s, 1 H), 8.93 (s, 6 H), 8.95 (s, 3 H), by evaporation of solvent; in general, however, the solution was directly treated with dry HCl at 0° until N_2 evolution ceased, approximately 15 min being required. Evaporation of solvent in vacuo afforded crude chloro ketone **8** as an orange oil: ir (CCl_4) 5.78, 5.90 μ; ^{1}H NMR (CCl_4) τ 4.72 (s, 2 H), 8.93 (s, 6 H), 8.96 (s, 3 H). Crude **8** and 135 g of Zn dust were added to a mixture of 27 g of KI in 350 ml of glacial HOAc in a N_2 atmosphere, stirred for 10 hr, treated with 70 ml of water, stirred for 11 hr, and filtered. The filtrate was concentrated in vacuo, diluted with water, and extracted with ether which was washed with water, dried, and removed in vacuo to afford 8.29 g (88%) of crude diketone **9** as a pale yellow oil which was 90% pure (GLC, 150°). A small sample was evaporatively distilled at 125–135° (bath temperature, 2 mm) to afford a spectrally pure sample of colorless **9**: ir (CCl_4) 5.80, 5.90 μ; ^{1}H NMR ($CDCl_3$) τ 7.90 (s, 3 H), 8.93 (s, 9 H).

B. Methyllithium Route. The procedure was adapted from one by Tegner.[15] During 2.5 hr 420 ml of a 0.48 *M* solution of MeLi in ether (0.20 mol of MeLi freshly prepared from MeI[15]) was added to a solution of 21.1 g (0.10 mol) of keto acid **5**, mp 46–47°, in 170 ml of ether. The solution was refluxed for 10 min, decomposed with 20 ml of water,[44] washed with water, dried, and evaporated in vacuo to afford 12.1 g (58%) of a pale yellow oil which consisted predominantly of diketone **9** (GLC assay). Distillation afforded 6.90 g (33%) of nearly pure **9** as a colorless oil, bp 90–95° (0.55 mm), with an ir spectrum nearly identical with that of the sample described above.

Acidification of the combined aqueous phases with dilute HCl precipitated 11.0 g (52%) of **5** identified by its ir spectrum.

When commercial MeLi in ether (Foote Mineral Co.) was used in the above procedure, a mixture of products was obtained. From 20.04 g (0.0945 mol) of keto acid **5**, mp 46–47°, there was obtained 8.1 g of a pale yellow neutral oil. Crystallization from pentane afforded 1.43 g (7%) of white needles, mp 84.0–84.5°, identified spectrally as ketol **15**: ir ($CHCl_3$) 2.76, 5.79 μ; ^{1}H NMR ($CDCl_3$) τ 7.88 (s, 3 H), 8.87 (s, 3 H), 8.92 (s, 3 H), 9.00 (s, 3 H), 9.08 (s, 3 H). The remainder of the neutral product mixture was not further investigated.

4,4,10-Trimethyl-Δ^5-octaloue-7 (11). A solution of 2.32 g (0.011 mol) of crude (90%) diketone **9** and 1.56 g (0.022 mol) of freshly distilled pyrrolidine in 25 ml of C_6H_6 was refluxed for 20 hr under a Dean-Stark trap[9] and poured into brine. The C_6H_6 layer was washed with 4% HCl, aqueous phases were acidified with 3 ml of concentrated HCl and extracted with ether, and the aqueous phase was neutralized with solid NaOH[45] and extracted with ether. The combined organic phases were washed with 4% HCl and brine, dried, and evaporated in vacuo to afford 2.08 g (98%) of a pale yellow oil which was distilled in a microstill to afford 1.79 g (85%) of enone **11** as a colorless oil, bp 90–100° (0.6 mm), homogeneous by GLC (185°): ir (film) 6.00, 6.26 μ; ^{1}H NMR ($CDCl_3$) τ 4.10 (s, 1 H), 8.65 (s, 3 H), 8.82 (s, 3 H), 8.87 (s, 3 H); uv max (95% EtOH) 242 nm (ϵ 13400) [lit. bp 129–130° (10 mm);[13] uv max (95% EtOH) 240 nm (ϵ 13000);[12] uv max (95% EtOH) 242 nm (ϵ 13700)[13]].

4,4,10-Trimethyl-5α-decalone-7 (12) and 4,4,10-Trimethyl-5β-decalone-7 (13). A mixture of 1.41 g (0.0073 mol) of enone **11**, bp 90–100° (0.6 mm), and 67 mg of 30% Pd/C in 30 ml of 95% EtOH was hydrogenated at 1 atm until absorption ceased (ca. 30 min). Filtration of catalyst and distillation of solvent in vacuo left 1.40 g (98%) of a partially crystalline oil: ir (film) 5.83 μ, no OH absorption; ^{1}H NMR ($CDCl_3$) τ 8.88 (s, 3 H), 9.15 (s, 6 H) (major component), and 8.80 (s, 3 H), 9.08 (s, 3 H), 9.17 (s, 3 H) (minor component). Low-temperature crystallization from pentane afforded 1.16 g (83%) of the decalone mixture as white needles which partially liquefied at room temperature. Repeated recrystallization from pentane afforded a small quantity of a pure sample of the preponderant isomer, mp 39–40°, which was identical with **12** described below. Chromatography over neutral alumina failed to give a satisfactory separation of the two isomers, although enriched samples could be obtained. From the relative intensities of methyl resonances in ^{1}H NMR spectra of the hydrogenation mixture the ratio of trans to cis decalones was approximately 4:1.[47]

10-Cyano-4,4-dimethyl-7,7-ethylenedioxy-5α-decalin (20a). A mixture of 4.0 g (0.02 mol) of cyano decalone **19a**,[1b] mp 58–60°, 3.0 ml of ethylene glycol, and 0.05 g of TsOH in 100 ml of C_6H_6 was refluxed with azeotropic separation of water for 9.5 hr. Pyridine (0.5 ml) was added and the solution was poured into 50 ml of 2 *N* KOH and extracted with ether which was washed with water and brine, dried, and removed in vacuo to afford 5.2 g (107%) of ketal **20a** as a white solid. Fractional sublimation at reduced pressure afforded 4.8 g (99%) of **20a** as white needles: mp 116–117°; ir ($CHCl_3$) 4.49 μ; ^{1}H NMR ($CDCl_3$) τ 6.07 (s, 4 H), 8.97 (s, 3 H), 9.10 (s, 3 H).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.29; H, 9.24; N, 5.62. Found: C, 72.14; H, 9.27; N, 5.85.

4,4-Dimethyl-7,7-ethylenedioxy-10-formimidoyl-5α-decalin (20b). A suspension of 1.71 g (0.045 mol) of $LiAlH_4$ in 225 ml of tetrahydrofuran (THF) was added over 45 min to an ice-cold solution of 4.0 g (0.016 mol) of cyano ketal **20a** in 50 ml of redistilled THF in a N_2 atmosphere.[19,20] The mixture was stirred in the cold for 1.5 hr and at ca. 23° for 5.0 hr, decomposed with aqueous saturated potassium sodium tartrate, and extracted with $CHCl_3$ which was washed with brine, dried, and removed in vacuo to afford 4.3 g (106%) of imino ketal **20b** as a colorless oil: ir (CCl_4) 2.93–3.10, 6.15 μ; ^{1}H NMR ($CDCl_3$) τ 1.52 (s, 1 H), 6.07 (s, 4 H), 9.10 (s, 3 H), 9.27 (s, 3 H).[48]

4,4-Dimethyl-7,7-ethylenedioxy-10-formyl-5α-decalin (20f). A solution of 343 mg (0.00135 mol) of distilled alcohol **20e**[30] in 6 ml of pyridine (dried over KOH) was added to a slurry of CrO_3–pyridine complex, prepared from 343 mg (0.00515 molar equiv) of CrO_3 and 3.4 ml of pyridine.[49] After being stirred for 20 min and refluxed for 4.5 hr (reaction time is critical), the mixture was diluted with 25 ml of water, shaken with 10 ml of ether, and filtered through Celite to remove inorganic salts. The aqueous phase was extracted with ether which was washed with water, dried, and evaporated under a N_2 stream on a steam bath, with the final traces of solvent being removed in vacuo at ca. 23° to afford 296 mg (86%) of aldehyde **20f** as a moist, pale yellow solid: ir ($CHCl_3$) 5.83, 9.05 μ; ^{1}H NMR ($CDCl_3$) τ −0.05 (s, 1 H), 6.05 (s, 4 H), 9.08 (s, 3 H), 9.25 (s, 3 H).

The instability of aldehyde **20f** precluded further purification and necessitated its use within 1 day.

7,7-Ethylenedioxy-4,4,10-trimethyl-5α-decalin (20c). A. From Imino Ketal 20b. The general procedure of Nagata[19] was adapted. A solution of 7.0 g (0.028 mol) of crude imino ketal **20b**, 9 g (0.16 mol) of KOH, and 60 ml (1.5 mol) of 80% aqueous N_2H_4 [from addition of 10 ml of water to 50 ml of 95(+)% N_2H_4] in 300 ml of triethylene glycol in a N_2 atmosphere was heated at 70° for 1 hr. The internal temperature was raised over 5 hr to 145°, distillation began, and 60 ml of distillate was collected in an attached Dean-Stark trap as the temperature was slowly raised to 210° where it was held for 10 hr. The colorless solution was cooled, poured into 400 ml of brine, and extracted with ether which was washed with brine and water and dried. The distillate was extracted with ether which was combined with the main organic fraction. Solvent was removed in vacuo to leave 6.6 g (100%) of ketal **20c** as a pale yellow oil with spectral properties identical with those of an analytical sample prepared as a colorless oil by evaporative distillation in a microstill, ^{1}H NMR (CCl_4) τ 6.08 (s, 4 H), 9.05 (s, 3 H), 9.15 (s, 3 H), 9.20 (s, 3 H).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.61; H, 10.92. Found: C, 75.37; H, 11.00.

B. From Formyl Ketal 20f. Reduction of 4.2 g (0.017 mol) of crude aldehyde **20f**, using 5.0 g (0.089 mol) of KOH and 40 ml (1.2 mol) of N_2H_4 [Eastman 95(+)%] in 350 ml of triethylene glycol was conducted as described for **20b** but with reaction conditions as follows: 130° for 1.5 hr, raise to 230° over 7 hr (distillation), 230° for 2 hr. Isolation as described afforded 4.0 g (100%) of ketal **20c** as a pale yellow oil which was spectrally indistinguishable from the sample described above.

4,4,10-Trimethyl-5α-decalone-7 (12). A solution of 158 mg (0.67 mmol) of crude ketal **20c**, 5 drops of water, and 2 drops of concentrated H_2SO_4 in 5 ml of acetone was refluxed for 4 hr, solvent was removed in vacuo, 20 ml of brine was added, and the product was extracted with $CHCl_3$ which was washed with 5%

$NaHCO_3$ and water, dried, and evaporated to leave 123 mg (95%) of ketone **12** as a yellowish oil spectrally indistinguishable from the analytical sample. Distillation (80°, 0.2 mm) followed by fractional sublimation at reduced pressure afforded pure **12** as colorless needles: mp 39–40°; ir (CCl_4) 5.88 μ; ^1H NMR ($CDCl_3$) τ 8.88 (s, 3 H), 9.15 (s, 6 H) [reported[7] bp 125–128° (5 mm)]. Ir and ^1H NMR spectra of this sample were superimposable on those of the authentic (−) enantiomer which were kindly provided by Professor Wenkert.[8]

Anal. Calcd for $C_{13}H_{22}O$: C, 80.41; H, 11.34. Found: C, 80.20; H, 11.30.

4,4,10-Trimethyl-5α-decalin (21). Reduction of 1.0 g (0.0052 mol) of distilled decalone **12** using 1.5 g (0.27 mol) of KOH and 10 ml of 90% N_2H_4 in 75 ml of triethylene glycol was conducted as described for **20b** but with reaction conditions as follows: 60° for 1 hr, raise to 210° over 9 hr (10 ml of distillate collected), 210° for 12 hr. Isolation as described for **20c** afforded 95 mg (10%) of decalin **21** as a yellow oil which was distilled from Na to afford a colorless oil, 70 mg, bp 45° (0.2 mm) [lit. bp 105–110° (17 mm),[21] 60–65° (0.2 mm)[7]]. A second vacuum distillation in a micro-Hickman flask afforded the analytical sample: ir (film) 3.42, 6.78, 6.85, 7.15, 7.25 μ; ^1H NMR ($CDCl_3$) τ 9.00 (s, 3 H), 9.18 (s, 3 H), 9.22 (s, 3 H); mass spectrum *m/e* 180 (4), 165 (100).

Anal. Calcd for $C_{13}H_{24}$: C, 86.74; H, 13.41. Found: C, 86.56; H, 13.41.

8-Hydroxymethylene-4,4,10-trimethyl-5α-decalone-7 (22). A mixture of 1.23 g (0.0064 mol) of trans decalone **12**, mp 39°, 0.94 g (0.0127 mol) of ethyl formate, bp 52°, and 0.79 g of a 58% dispersion of NaH in mineral oil (0.019 mol of NaH) in 50 ml of C_6H_6 was stirred for 24 hr under N_2,[1b] treated with 100 ml of water, and extracted with 1% NaOH. The aqueous extracts were washed with ether, acidified with concentrated HCl, and extracted with ether which was washed with water, dried, and evaporated in vacuo to afford 1.30 g (92%) of hydroxymethylene ketone **22** as pale yellow crystals: mp 29–31°; ir (CCl_4) 6.12, 6.34 μ; ^1H NMR ($CDCl_3$) τ −4.20 (s, 1 H), 1.63 (s, 1 H), 9.13 (s, 9 H).

8-Formyl-4,4,10-trimethyl-Δ⁸-5α-octalone-7 (23). The procedure is a modification of one developed by Shew in these laboratories. A solution of 2.7 g (0.012 mol) of DDQ and 25 drops of glacial HOAc in 25 ml of dioxane was added dropwise over 15 min to a stirred solution of 2.6 g (0.012 mol) of crude hydroxymethylene ketone **22** in 25 ml of dioxane. After 15 min the mixture was filtered into 300 ml of $CHCl_3$ which was washed with 10% $NaHCO_3$ until the wash was colorless and then with water. Drying and evaporation of solvent afforded 2.5 g (97%) of formyl enone **23** as an orange oil: ir (CCl_4) 5.87, 5.92, 6.21 μ; ^1H NMR ($CDCl_3$) τ −0.03 (s, 1 H), 2.58 (s, 1 H), 8.85 (s, 3 H), 9.05 (s, 3 H), 9.08 (s, 3 H). The ^1H NMR spectrum showed no significant resonance from contaminants. Attempts to further purify this substance were unsuccessful.

7,12-Diketo-Δ¹³-5α,8β,9β-abietene (25a). A mixture of 351 mg (1.75 mmol) of *tert*-butyl isovalerylacetate, bp 97–98° (2.6 mm), and 91 mg of a 58% dispersion of NaH in mineral oil (2.2 mmol of NaH) in 10 ml of C_6H_6 was stirred under N_2 for 15 min and a solution of 366 mg of crude keto aldehyde **23** (ca. 85% purity, 1.41 mmol; estimated to contain ca. 15% of **22** from its ^1H NMR spectrum) in 20 ml of C_6H_6 was added. The mixture was stirred for 2 hr, neutralized to pH 6 with glacial HOAc, poured into water, and extracted with $CHCl_3$ which was washed with brine, dried, and removed in vacuo to afford 694 mg of adduct **24a** as a pale yellow oil: ir (CCl_4) 5.72, 5.85, 6.07, 6.27 μ; ^1H NMR (CCl_4) τ 1.63 (s) and 1.70 (s) (total 1 H), 6.47 (d, *J* = 8 Hz) and 7.05 (d, *J* = 8 Hz) and 6.80 (s) (total 2 H), 8.57 (s) and 8.58 (s) (total 9 H).

A solution of the crude adduct in 30 ml of glacial HOAc containing ca. 20 mg of TsOH was refluxed under N_2 for 3.5 hr, treated with NaOAc, and evaporated at reduced pressure. The residue was partitioned between water and $CHCl_3$ which was washed with 1% NaOH and brine, dried, and removed in vacuo to afford 287 mg (67% based on aldehyde **23**) of enedione **25a** as pale yellow crystals. Recrystallization from EtOAc yielded pure **25a** as fine white needles: mp 147–148°; ir ($CHCl_3$) 5.87, 5.99 μ; uv max (95% EtOH) 232 nm (ε 8000); ^1H NMR ($CDCl_3$) τ 3.22 (dd, 1 H, *J* = 6 and 0.9 Hz), 6.40 (dd, 1 H, *J* = 5 and 6 Hz), 8.70 (s, 3 H), 8.94 (d, 3 H, *J* = 7 Hz), 8.97 (d, 3 H, *J* = 7 Hz), 9.10 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.47; H, 9.93. Found: C, 79.35; H, 10.03.

DL-Sugiol (2a). A solution of 102 mg (0.339 mmol) of enedione **25a**, mp 145°, and 111 mg (0.346 mmol) of pyridine hydrobromide perbromide[41b] in 7 ml of glacial HOAc was allowed to stand for 0.5 hr.[31] Addition of 7 ml of water, filtration, and recrystallization from MeOH afforded 95 mg (93%) of DL-sugiol as white needles: mp 269–270° [reported for (+)-sugiol[3a] 295–297°]; ir (KBr) 3.25 (broad), 6.12, 6.41 μ; ^1H NMR (CD_3COCD_3) τ 2.18 (s, 1 H), 3.13 (s, 1 H), 8.77 (d, 3 H, *J* = 6.5 Hz), 8.79 (d, 3 H, *J* = 6.5 Hz), 8.79 (s, 3 H), 8.98 (s, 3 H), 9.05 (s, 3 H).

Acetylation according to the procedure of Brandt and Thomas[3a] afforded a colorless oil which did not crystallize; its ^1H NMR spectrum was identical with that reported[33] for the acetate of (+)-sugiol.

DL-Ferruginol (2c). A mixture of 48 mg (0.16 mmol) of DL-sugiol, mp 269–270°, 34 mg of 30% Pd/C, and 1 drop of concentrated H_2SO_4 in 8 ml of EtOAc was hydrogenated at 1 atm for 3.0 hr.[32] Catalyst was removed by filtration through Celite, and the filtrate was washed with water, dried, and evaporated in vacuo to yield DL-ferruginol[5] as a pale yellow resin: ir ($CHCl_3$) 2.78 μ; ^1H NMR ($CDCl_3$) τ 3.22 (s, 1 H), 3.42 (s, 1 H), 8.80 (d, 6 H, *J* = 7 Hz), 8.87 (s, 3 H), 9.08 (s, 6 H). The ^1H NMR spectrum was identical with that of a redistilled authentic sample of (+)-ferruginol.[34]

7,12-Diketo-13-methyl-Δ¹³-5α,8β,9β-podocarpene (25b). A mixture of 247 mg (1.28 mmol) of redistilled *tert*-butyl propionylacetate and 54 mg of a 58% dispersion of NaH in mineral oil (1.28 mmol of NaH) in 15 ml of C_6H_6 was stirred until the evolution of H_2 ceased (0.5 hr).[1b] A solution of 222 mg (1.01 mmol) of crude keto aldehyde **23** in 5 ml of C_6H_6 was added, and after 4.0 hr the mixture was neutralized with glacial HOAc and processed as described for adduct **24a** to afford 467 mg (118%) of a pale yellow oil consisting of adduct **24b** contaminated with some *tert*-butyl propionylacetate: ir (CCl_4) 5.85, 6.10, 6.29 μ; ^1H NMR (CCl_4) τ 1.65 (s) and 1.75 (s) (total 1 H), 6.42 (d, *J* = 8 Hz) and 7.05 (d, *J* = 8 Hz) and 6.78 (s) (total 2 H), 8.58 (s) and 8.60 (s) (total 9 H).

The crude adduct was cyclized in 20 ml of glacial HOAc containing ca. 5 mg of TsOH as described for preparation of enedione **25a** to afford 196 mg (71%) of crystalline, yellow enedione **25b**. Recrystallization from EtOAc afforded pure **25b** as fine, white needles: mp 209–210°; ir ($CHCl_3$) 5.85, 5.97 μ; uv max (95% EtOH) 231 nm (ε 9070); ^1H NMR ($CDCl_3$) τ 3.22 (dq, *J* = 5.5 and 1 Hz, 1 H), 8.20 (t, 3 H, *J* = ca. 1 Hz), 8.69 (s, 3 H), 9.10 (s, 3 H), 9.12 (s, 3 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.83; H, 9.49. Found: C, 78.76; H, 9.53.

DL-Nimbiol (2b). A solution of 95 mg (0.347 mmol) of enedione **24b**, mp 209°, and 114 mg (0.356 mmol) of pyridine hydrobromide perbromide,[41b] mp 132°, in 7 ml of glacial HOAc was treated as described for synthesis of DL-sugiol. Recrystallization of the crude product from MeOH afforded 42 mg (45%) of pure DL-nimbiol as white needles: mp 237.0–237.5°; ir ($CHCl_3$) 2.79, 6.02, 6.23, 6.35 μ; ^1H NMR ($CDCl_3$) τ 2.20 (s, 1 H), 3.26 (s, 1 H), 7.80 (s, 3 H), 8.81 (s, 3 H), 9.03 (s, 3 H), 9.11 (s, 3 H). The ir spectrum of this sample was identical with that of the (+) enantiomer.[34]

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.20; H, 9.08.

***tert*-Butyl α-Isovalerylacetoacetate (32).**[50] In an adaptation of an analogous procedure[36] 13.2 g (0.084 mol) of redistilled *tert*-butyl acetoacetate[51] in 100 ml of C_6H_6 was added over 0.5 hr to 5.5 g of a 58% dispersion of NaH in mineral oil (0.13 mol of NaH) in 200 ml of C_6H_6 and the mixture was stirred until evolution of H_2 ceased (2.0 hr). A solution of 10.0 g (0.084 mol) of isovaleryl chloride,[52] bp 113–114°, in 100 ml of C_6H_6 was added over 0.5 hr, and the mixture was stirred under N_2 for 18 hr, treated with 1 equiv of glacial HOAc, washed with brine, and dried. Distillation of solvent left 27.6 g (113%) of crude diketo ester **32** as a pale yellow oil. Distillation of a small portion through a spinning band column afforded a sample of bp 110–120° (4–5 mm) the ^1H NMR spectrum of which indicated the presence of 95% of the C-acylation product **32** [^1H NMR ($CDCl_3$) τ 7.72 (s, 3 H), 8.45 (s, 9 H), 9.02 (d, 6 H, *J* = 7 Hz); ir (film) 5.78, 6.23 μ], containing about 5% of the O-acylation product **33** [^1H NMR ($CDCl_3$) τ 4.23 (q, 1 H, *J* = 1 Hz), 8.07 (d, 3 H, *J* = 1 Hz), 8.59 (s, 9 H)]. Complete separation could not be achieved by distillation.

Five grams of the crude acylation product in 25 ml of ether was extracted with five portions of 1% NaOH, each extract being immediately neutralized with 10% HCl and extracted with ether which was washed with saturated aqueous $NaHCO_3$ and water and dried. Evaporation in vacuo afforded 3.13 g (63%) of a pale yellow oil devoid of the O-acylation product (^1H NMR assay). Distillation through a spinning band column afforded pure **32** as a colorless liquid, bp 114–118° (1–2 mm) [lit.[36] bp 126° (12.5 mm)].

***tert*-Butyl Isovalerylacetate (34).**[53] A solution of 13.5 g (0.0560 mol) of diketo ester **32**, bp 106–113° (0.5–0.8 mm), and 22.3 g of 1% aqueous NaOH (0.00560 mol of NaOH) in 150 ml of MeOH was held at ca. 23° under N_2 for 2.5 hr, acidified with 5 ml of 5% HCl, MeOH was distilled in vacuo, 100 ml of ether was added, and

the mixture was washed with brine and dried. Evaporation afforded 9.6 g (86%) of crude product which was distilled to give 83% of pure 34 as a colorless oil, bp 94–99° (1 mm). The analytical sample from microredistillation had ir (film) 5.75, 5.81, 6.06 μ; ^{1}H NMR (CCl_4) τ 6.80 (s, 2 H), 8.57 (s, 9 H), 9.09 (d, 6 H, J = 7 Hz).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.98; H, 10.07. Found: C, 65.97; H, 9.94.

***tert*-Butyl Propionylacetate (35).** An analogous procedure of Abramovitch and Hauser[35] was modified. A solution of 0.05 mol of Ph_3CNa in 700 ml of ether under N_2 was cooled in a salt–ice bath, and 6.0 g (0.052 mol) of *t*-BuOAc, bp 96–97°, was added. The deep red color faded after 15 sec and a solution of 11.5 g (0.051 mol) of *p*-diphenyl propionate,[35] mp 96–97°, in 250 ml of ether was added. The mixture was stirred in the cold for 1.75 hr and at ca. 23° for 0.5 hr, treated with 5 ml of glacial HOAc, washed with water and 10% aqueous Na_2CO_3, and dried, and solvent was distilled at atmospheric pressure. The residue was twice evaporatively distilled to afford 1.05 g (12%) of pure **35** as a colorless liquid: ^{1}H NMR ($CDCl_3$) τ 6.66 (s, 2 H), 7.45 (q, 2 H, J = 7 Hz), 8.52 (s, 9 H), 8.90 (t, 3 H, J = 7 Hz).

Registry No.—**2a**, 10219-81-5; **2b**, 56760-98-6; **2c**, 10219-82-6; **3**, 2408-37-9; **4**, 56666-13-8; **5**, 56666-14-9; **6**, 56666-15-0; **7**, 56666-16-1; **8**, 56666-17-2; **9**, 56666-18-3; **10**, 56666-19-4; **11**, 56666-20-7; **12**, 16892-22-1; **13**, 56712-05-1; **15**, 56666-21-8; **19a**, 56666-22-9; **20a**, 56666-23-0; **20b**, 56666-24-1; **20c**, 56666-25-2; **20f**, 56712-04-0; **21**, 16886-12-7; **22**, 56666-26-3; **23**, 56666-27-4; (*R**)-**24a**, 56666-28-5; (*S**)-**24a**, 56666-29-6; (*R**)-**24b**, 56666-30-9; (*S**)-**24b**, 56666-31-0; **25a**, 56781-34-1; **25b**, 56666-32-1; **32**, 56666-33-2; **34**, 39140-54-0; **35**, 33400-61-2; acrylonitrile, 107-13-1; oxalyl chloride, 79-37-8; diazomethane, 334-88-3; methyllithium, 917-54-4; ethyl formate, 109-94-4; *tert*-butyl acetoacetate, 141-97-9; isovaleryl chloride, 108-12-3.

References and Notes

(1) (a) Supported by Grants AM-4215 and AM-10123 from the National Institute of Arthritis and Metabolic Diseases; the uv, ^{1}H NMR, and mass spectrometers were obtained with partial support of National Science Foundation Grants GP-8286, GP-3655, and GP-6978 respectively. (b) Part VI: W. L. Meyer, R. W. Huffman, and P. G. Schroeder, *Tetrahedron*, **24**, 5959 (1968). (c) Preliminary communication: W. L. Meyer, G. B. Clemans, and R. W. Huffman, *Tetrahedron Lett.*, 4255 (1966). (d) Abstracted in part from the Ph.D. Dissertation of R.A.M., University of Arkansas, 1971.

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(16) Subsequent to our work Mukhopadhyay and Dutta[7] reported this hydrogenation to afford only the trans decalone **12**, which in their hands was noncrystalline. It may be that the difference in catalysts (10% vs. 30% palladium on carbon) leads to a difference in stereoselectivity, but no evidence was cited to demonstrate the purity of their sample, and it would appear that their procedures could well have failed to detect as much as 20% of the cis isomer.

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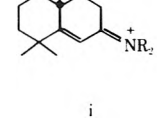
(44) Variation of the reaction time failed to reproducibly improve the yield of diketone, and in some instances led to increased formation of neutral by-products.

(45) Prior to basification a considerable proportion of the potential enone remains unextractable from the acidic aqueous phase, presumably as the unhydrolyzed eniminium salt i or perhaps as a β-ammonium ketone ii.[46] The free enone is instantaneously liberated in base. Analogous results have also occasionally been obtained with the cyclization described in ref 9.



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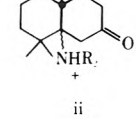

ii

(46) Cf. T. A. Spencer and K. K. Schmiegel, *Chem. Ind. (London)*, 1765 (1963); T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Lett.*, 3839 (1965).

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(48) Yields are substantially lower and the product much less pure if the $LiAlH_4$ used in this reaction is not of high quality; cf. P. G. Schroeder, M.S. Thesis, University of Arkansas, 1968.
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(51) We thank the Eastman Chemical Co. for a generous sample of this compound.
(52) Several commercial samples of isovaleric acid were contaminated with an unidentified impurity which we were unable to remove. Consequently the isovaleric acid for this work was prepared by carbonation of the isobutyl Grignard reagent by adapting the general procedure of H. Gilman and R. H. Kirby in "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1932, p 361. It was converted to its acid chloride by the method of H. C. Brown, *J. Am. Chem. Soc.*, **60**, 1325 (1938).
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Structures of Some *Knightia deplanchei* Alkaloids[1]

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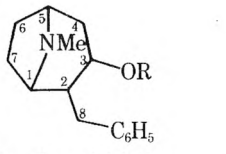
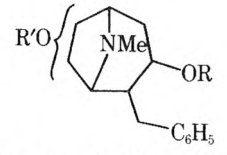
^{13}C NMR spectroscopy is utilized for the determination of the stereostructures of five alkaloids of the 2-benzyltropine type. Intramolecular hydrogen bonding by 6β- or 7β-hydroxy groups is shown to alter the normal conformation of the tropane *N*-methyl group. This phenomenon is modified greatly in a protic medium.

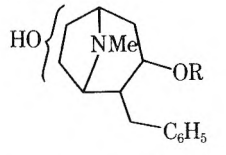
Several tropane alkaloids have been isolated recently from the New Caledonian plant *Knightia deplanchei* Vieill. ex Brongn. et Gris. Two compounds were shown to be 2-benzyltropanol derivatives **1a** and **1b** by spectral analyses[2,3] and synthesis,[4] while three others, **2a**, **3a**, and **4**, were described as oxygenated variants of their congeners.[2,3] A ^{13}C NMR spectral study now has been undertaken in order to determine the complete structures of the last three substances and the stereochemistry of all five tropane bases.



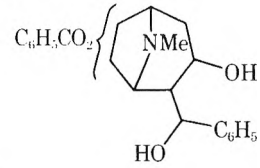
1a, R = COC_6H_5
b, R = Ac
c, R = H



2a, R = H; R′ = COC_6H_5
b, R = R′ = COC_6H_5
c, R = R′ = H



3a, R = *trans*-$COCH{=}CHC_6H_5$
b, R = H



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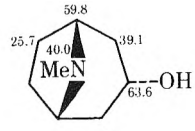
A previous investigation has revealed the carbon shifts of structurally simple tropanes, tropine (**5**), pseudotropine (**6**), and their benzoates (**7** and **8**, respectively) (δ values depicted on the formulas), and related alkaloids.[5] While the shift data could serve the present study well, their value was obscured in part by a recent report by Simeral and Maciel in which the assignment of the C(2), C(4) shifts of tropine (**5**) had been allotted to C(6), C(7).[7] Since, further, the tropine (**5**) spectrum had been taken in water solution, while the earlier δ values were obtained on deuteriochloroform solutions, a shift reevaluation had to precede the alkaloid structure study.



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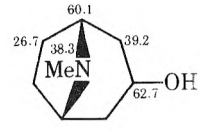

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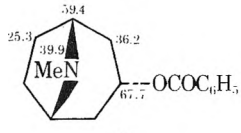

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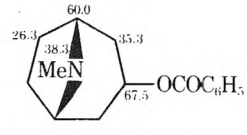

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The coupling characteristics of the two carbon pairs were utilized to determine unambiguously the proper shift assignment. A series of off-resonance decoupling experiments designed to optimize possible carbon–hydrogen virtual coupling of C(6) were performed on deuteriochloroform solutions of tropine (**5**) and pseudotropine (**6**). The combination of strong residual coupling between C(6) and H(6α), but weak C(6)–H(7α) interaction and strong H(6α)–H(7α) coupling due to the identity of the two hydrogen shifts was expected to lead to virtual coupling of this ABX system.[8,9] The strong dissimilarity of the H(2) shifts from the resonances of the vicinal hydrogens precludes any C(2) virtual coupling. The observation of second-order coupling in the C(6) signal showed the earlier shift assignment[5] for compounds **5**–**8** to be correct. Furthermore, a similar observation in off-resonance decoupled spectra of an aqueous tropine (**5**) solution indicated the need for the reversal of the recent shift designation of C(2), C(4) and C(6), C(7).[7,10]

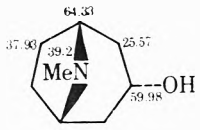
Close inspection of the fully proton-decoupled ^{13}C NMR spectrum of an aqueous solution of tropine (**5**) showed all lines except the oxymethine signal to be broad, the *N*-methyl and C(2), C(4) centers revealing the largest linewidths. While the broad 60.1-ppm signal was less intense than the 64.3-ppm resonance, the former covered an area nearly twice as large, showing it to constitute a two-carbon signal.[11] As a consequence the Simeral and Maciel assignment of the former resonance to C(3) and the latter to C(1), C(5)[7] needs reversal. The new assignment was confirmed by the residual coupling characteristics of the two resonances. A single-frequency, off-resonance decoupled (sford) spectrum in which the decoupling frequency was localized at the upfield end of the ^1H NMR spectrum exhibited expectedly lower residual coupling of the aminometh-

Table I
Chemical Shifts[a]

	1a	1b[b]	1c	2a	2b	2c	3a[c]	3b	4
C(1)	63.2	63.3	63.8	64.2	63.5	62.8	70.7	71.6	62.5
C(2)	45.8	45.4	46.3	44.9	44.3	40.0	38.6	40.1	49.4
C(3)	69.7	69.3	65.6	65.4	69.3	66.0	69.3	66.1	64.6
C(4)	37.0	37.0	39.9	36.9	34.0	32.7	31.0	34.4	36.0
C(5)	59.6	59.8	60.0	66.5	65.8	67.4	58.3	58.8	66.3
C(6)	25.3	25.3	25.3	80.5	80.0	76.2	40.9	40.8	80.3
C(7)	21.9	21.6	21.8	32.2	32.7	37.1	72.8	73.3	33.1
C(8)	35.2	35.1	35.4	35.2	35.1	35.1	35.0	35.1	74.2
i-C	139.0	139.2	140.1	140.0	138.7	139.8	138.9	139.8	142.7
o-C	127.9	128.1	127.9	128.1	128.1	128.3	127.9	128.3	126.4
m-C	128.7	128.7	128.7	128.8	128.7	128.7	128.7	128.7	128.4
p-C	125.7	125.8	125.5	125.7	126.0	125.8	126.0	125.8	127.8
NMe	40.3	40.4	40.3	40.6	40.6	36.8	36.7	37.1	40.3

[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] The methyl and carbonyl shifts of the acetyl group are 21.3 and 169.9 ppm, respectively. [c] The cinnamyl group possesses the following shifts: C=O 165.6, α-C 118.0, β-C 144.8, *ipso*-C 134.0, o-C 128.7, *m*-C 128.3, and *p*-C 130.2 ppm.

ine doublet than the oxymethine doublet.[8] Thus the former carbon shifts for tropine (**5**) in water illustrated on formula **9**[7] have been revised to the δ values portrayed on formula **10**.[12]



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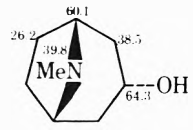
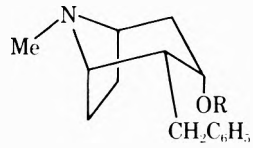


10

With the earlier chemical shift assignment of tropine (**5**)[5] and hence of pseudotropine (**6**) and their benzoates (**7** and **8**, respectively) reaffirmed, the ^{13}C NMR spectral analysis of the *Knightia deplanchei* could be undertaken. The introduction of a benzyl group at C(2) of either of the benzoates of tropine (**7**) or pseudotropine (**8**) can be expected to cause deshielding of all nonaromatic methines except C(5). This fact and the strong dissimilarity of the substituents at C(1), C(2), and C(3) permits the shift designation of all methines of alkaloid **1a**. The differentiation of the methylenes of the latter is based on the recognition of the benzylic methylene from its residual coupling characteristics (vide supra) and of C(6) and C(7) through their virtual coupling behavior (vide supra) as well as on C(7) being shielded by the proximate benzyl group. The benzoate carbons of compounds **1a, 2a, 2b,** and **4** exhibit the following signals: C=O 165.8 ± 0.4 ppm, *ipso*-C 130.3 ± 0.2 ppm, o-C 129.2 ± 0.1 ppm, *m*-C 128.1 ± 0.1 ppm, and *p*-C 132.7 ± 0.2 ppm. Both alkaloids **1a** and **1b** have been shown to yield the same hydrolysis product (**1c**).[2] The ^{13}C NMR analysis of **1b** and **1c** follow arguments similar to those for **1a** above. The chemical shifts of all compounds **1** are listed in Table I.

The C(6) and *N*-methyl resonances are diagnostic of the C(3) stereochemistry of tropine benzoate (**7**) and its C(3) epimer **8**. Similarly, the C(3) configuration of the two esters is reflected in the dissimilar C(3) as well as C(4) shift difference between esters **7** and **8** and alcohols **5** and **6**, respectively. Thus the C(3) and C(4) Δδ (**7**–**5**) are 4.1 and −2.9 ppm, respectively, and the corresponding Δδ(**8**–**6**) values are 4.8 and −3.9 ppm, respectively. On this basis alkaloid **1a** possesses the C(3) stereochemistry of tropine benzoate (**7**) and the chair conformation of its piperidine ring. The close similarity of the C(4) shift of **1a** with that of **7** and the appreciable shielding of C(7) by the benzyl group indicate the latter to be equatorially oriented and hence cis to the C(3) substituent. As a consequence compounds **1a, 1b,** and **1c** possess stereostructures **11a, 11b,** and **11c**, respectively.

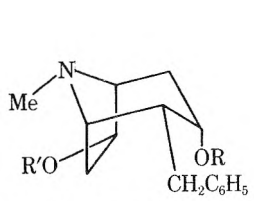


11a, R = COC_6H_5
b, R = Ac
c, R = H

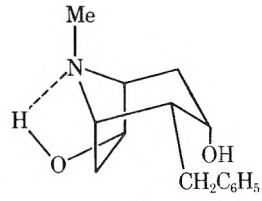
Inspection of the ^{13}C NMR spectra of alkaloid **2a** and its derivatives **2b** and **2c** reveals the effect of the substitution of a methylene group by an oxymethine function in the tropine nucleus of **1**. Comparison of the field positions and residual couplings (vide supra) of the methines of **2a** distinguishes its oxymethines from the aminomethines and C(2). In view of the close similarity of one of the oxymethine shifts with the C(3) shift of **1c** the 80.5 ppm signal can be allotted to the new oxymethine. Furthermore, the closeness of one of the aminomethine shifts to that of C(1) of **1c** and the strongly lower field position of the remaining aminomethine permits differentiation between the two methines and placement of the benzoyloxy group at C(6) of the tropine nucleus. In contrast to the behavior of compounds **1** the alkaloid **2a** reveals in its sford spectrum a methylene group with grossly magnetically nonequivalent hydrogens which as a consequence of the distant, new oxymethine cannot be the benzylic methylene function. Recognition of the latter is based on its larger residual coupling (vide supra) among the two remaining methylene signals. Carbons 4 and 7 can be distinguished from each other by the C(4) shift perturbation encountered on benzoylation of the 3-hydroxy group (cf. **2b**).

In view of the δ values of C(3) and C(8) being nearly identical in **2a** and **1c** as well as in **2b** and **1a** the stereochemistry of C(2) and C(3) must be the same in compounds **2** as in substances **1**. The C(6) configuration is based on an interpretation of the dramatic shift alteration in glycol **2c**, the product of hydrolysis of alkaloid **2a**. The ^{13}C NMR spectra of **2c** show strong shielding of C(2), C(4), and the *N*-methyl group, characteristic of reciprocal γ effects. Since the *N*-methyl inversion, leading to 1,3-diaxial interactions with H(2β) and H(4β), can be justified only on the basis of hydrogen bonding between the nitrogen electron pair and the 6-hydroxy group, the latter must possess an exo orientation. Thus **2a** and **2b** are represented by stereostructures **12a** and **12b**, respectively, while **2c** can be depicted by **13**. The chemical shifts of all three substances are listed in Table I.[13]

Previous work has shown that the hydrolysis product

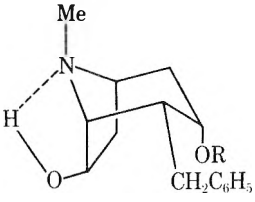


12a, R = H; R′ = COC_6H_5
b, R = R′ = COC_6H_5

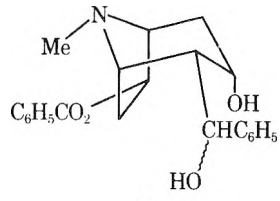


13

(**3b**) of alkaloid **3a** is an isomer of glycol **2c**.[2] The ^{13}C NMR spectra of **3a** and **3b** verify this fact and from the high-field position of the signals of the *N*-methyl group, C(2) and C(4) reveal the extra hydroxy group to occupy a 7β site of the tropine skeleton. In contrast to the behavior of **2c**, glycol **3b** feels a β effect at C(1) from the adjacent hydroxy group and reveals the presence of nonequivalent hydrogens at C(6). The fact of the C(3) and C(8) shifts being nearly identical in glycols **2c** and **3b** proves the identity of the C(2) and C(3) configurations in alkaloid **3a** with those of the natural bases **1a**, **1b**, and **2a**.[15] Thus substances **3a** and **3b** are represented fully by formulas **14a** and **14b**, respectively. Their chemical shifts are listed in Table I.



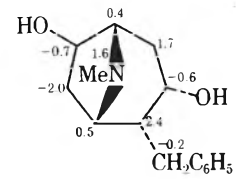
14a, R = COCH=CHC_6H_5-*t*
b, R = H



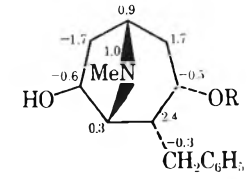
15

The determination of the location of the benzoyloxy unit of alkaloid **4** is based on consideration of the aminomethine shifts. The C(1) resonance is expected to be upfield that of compounds **1c**, **2a**, and **2b** owing to the γ effect exerted by the 8-hydroxy group in the case of the benzoyloxy moiety being located at C(6) and upfield of the C(1) shift of **3a** and **3b** in the event of the pyrrolidino substituent being held at C(7). Carbon 5 can be expected to be unaffected by the 8-hydroxy group and therefore to reflect the placement of the benzoyloxy function directly through its δ value. These arguments lead to the deposition of the benzoyloxy group at C(6) and the nearly identical C(5) and C(6) shifts of **4** and **2a** suggest an exo configuration for the substituent. The *N*-methyl shift of alkaloid **4** shows the nitrogen substituent to be equatorially disposed to the piperidine ring and supports the presence of a tropine (**5**), rather than pseudotropine (**6**) structure. Finally, the only slight perturbation of the C(4) shift of **4**, compared with **2a**, indicates the hydroxybenzyl group to possess an equatorial conformation. As a consequence the stereostructure of **4** is **15**. Its carbon shifts are depicted in Table I.

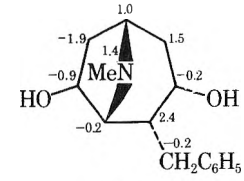
As the conformational behavior of compounds **2c** (**13**), **3a** (**14a**), and **3b** (**14b**) reveals, the introduction of 6β- or 7β-hydroxy groups into the tropane skeleton produces intramolecular hydrogen bonding forcing the *N*-methyl group into an axial orientation with respect to the piperidine ring. This phenomenon would be expected to be modified in protic media in which competition with intermolecular hydrogen bonding could take place. This change can be observed through the ^{13}C NMR spectra of several of the above compounds in 25% methanol–deuteriochloroform solution. While alcohols **1c** and **2a** show only minimal shift changes of up to 0.5 ppm, dramatic alterations occur in compounds **2c**, **3a**, and **3b**. The $\Delta\delta$ values [δ(MeOH–$CDCl_3$) – $\delta(CDCl_3)$], depicted on **16**, **17**, and **18**, respectively, exhibit deshielding of C(2) and C(4) in all three substances and simultaneous shielding of C(7) in **2c** and C(6) in **3a** and **3b**, characteristic of the *N*-methyl group assuming an increasing equatorial conformation with respect to the piperidine ring.



16



17, R = COCH=CHC_6H_5-*t*



18

Experimental Section

All carbon shifts were recorded on a Varian XL-100-15 NMR spectrometer operating at 25.20 MHz in the Fourier transform mode. The shifts on formulas **10** and iii are referenced to internal dioxane [$\delta(Me_4Si)$ = δ(dioxane) + 67.4 ppm]. The shift differences denoted on formulas **16**, **17**, **18**, i, ii, and v are with reference to internal methanol [$\delta(Me_4Si)$ = δ(MeOH) + 49.5 ppm].

Registry No.—**1a**, 50656-86-5; **1b**, 50656-87-6; **1c**, 56816-03-6; **2a**, 50656-88-7; **2b**, 56761-52-5; **2c**, 56761-53-6; **3a**, 56761-54-7; **3b**, 56761-55-8; **4**, 55249-52-0.

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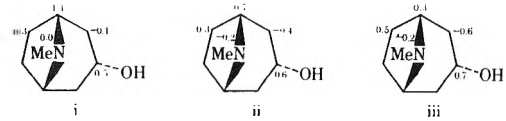
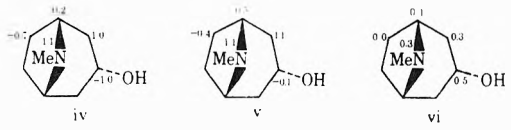
(1) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXVI. For the preceding paper see B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, E. Wenkert, and F. Näf, *Helv. Chim. Acta*, **58**, 1567 (1975).
(2) C. Kan-Fan and M. Lounasmaa, *Acta Chem. Scand.*, **27**, 1039 (j973).
(3) M. Lounasmaa, *Planta Medica*, **27**, 83 (1975).
(4) M. Lounasmaa and C.-J. Johansson, *Tetrahedron Lett.*, 2509 (1974).
(5) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974).[6]
(6) In the description of the carbon shifts of pseudotropine (**6**) those of the *N*-methyl group and of C(2), C(4) had been mixed up inadvertently.
(7) L. Simeral and G. E. Maciel, *Org. Magn. Reson.*, **6**, 226 (1974).
(8) E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gašić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, "Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances", in G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy", Vol. II, Wiley, New York, N.Y., in press.
(9) The same argument applies to the ABX system of C(6), H(6β), and H(7β).
(10) The shift reversal probably applies also to the δ values presented for an aqueous solution of atropine.[7]
(11) Whereas in Fourier transform spectroscopy the signal area loses much of its diagnostic value for carbon counting, it is still applicable in those cases in which the carbon sites to be compared are substituted by an equal number of hydrogens and thus, to a first approximation, the carbon relaxation times are similar.
(12) Tropine (**5**) shows unusual shift perturbations in a variable solvent, temperature, and concentration study. While at 29° the base shows line broadening in water solution, it retains sharp lines in deuteriochloroform, methanol, and 20% water–methanol solutions. The $\Delta\delta$ values [δ(solvent) – $\delta(CDCl_3)$] depicted on i, ii, and iii indicate the shift variations at



i ii iii

different carbon sites in methanol, water–methanol, and water solutions, respectively. Lowering of the temperature causes all signals except the oxymethine resonance to broaden and finally to resharpen at new field positions. Contrastingly, the ^1H NMR spectrum in deuteriochloroform solution remains nearly unaffected through the same temperature range. The temperature of greatest linewidth of the carbon signals is −15 to −23° in deuteriochloroform and 0 to −11° in 20% water–

methanol solutions. The $\Delta\delta$ values [$\delta(-30°) - \delta(29°)$] for the two solutions are portrayed on formulas iv and v, respectively. A threefold dilu-



iv v vi

tion of a 2 *M* deuteriochloroform solution which had yielded the shifts denoted on formula **5** leads to the $\Delta\delta$ values [δ(dil) − δ(concd)] illustrated on formula vi.

(13) Curiously, the introduction of the benzoyloxy group at C(6) shields C(2) and C(4), the latter twice as much as the former. Since the 6-oxy substituent is γ-equatorially oriented to C(4) within the cycloheptane nucleus, part of its shielding may be due to the effect recently noted in six-membered ring systems.[14]

(14) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, W. M. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).

(15) The shift alterations in the pyrrolidine ring on introduction of a 6β-hydroxy group (**1c** → **2c**) can be used to confirm the pyrrolidine carbon shifts in a 7β-hydroxy compound (**3b**). The $\Delta\delta$(**2c** − **1c**) values for C(5), C(6), C(7), and C(1) are 7.4, 50.9, 15.3, and −1.0 ppm, respectively. Their sequential application to C(1), C(7), C(6), and C(5) of **3b** yields the theoretical values of 71.2, 72.7, 40.6, and 59.0 ppm, respectively, in close agreement with the found shifts.

Sulfur-Containing Polypeptides. XVIII. Unambiguous Synthesis of the Parallel and Antiparallel Isomers of Some Bis-Cystine Peptides[1-3]

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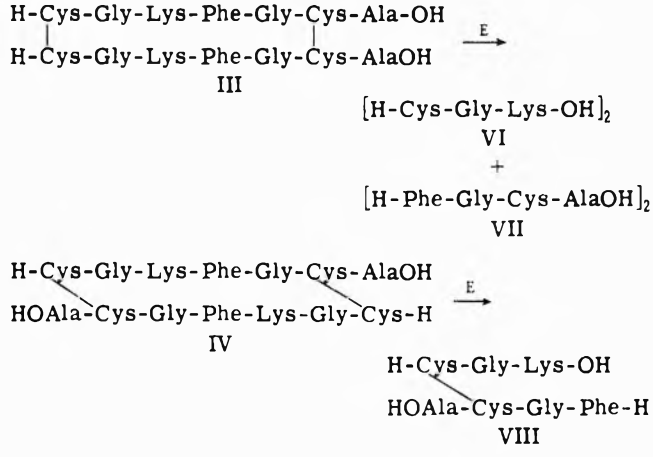
The synthesis of the parallel (III) and antiparallel (IV) isomers and cyclic monomer (V) of the L-cystylglycyl-L-lysyl-L-phenylalanylglycyl-L-cystyl-L-alanine system via the thiocyanogen–sulfenyl thiocyanate method is described. Enzymic degradation of III and IV using trypsin and α-chymotrypsin were employed to establish the pairing of the cystine residues. The thiocyanogen–sulfenyl thiocyanate method has been shown to proceed without intermediate disulfide interchange.

As part of a program directed toward the development of methods for the laboratory synthesis of polypeptides containing several cystine residues,[1] unequivocal methods for the stepwise and selective conversion of various S-protected cysteine thiols to cystine residues with the desired sulfur pairing have been studied. A route which indicated some promise[4] has been the utilization of *S*-trityl and *S*-benzhydryl thioethers of cysteine and subsequent selective oxidative removal of these protective groups by thiocyanogen or sulfenyl thiocyanates of cysteine, the former group being removed without catalysis, the latter requiring acidic conditions.

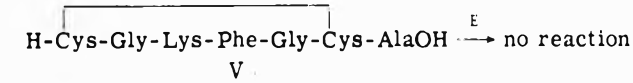
Unfortunately, the isomeric parallel (I) and antiparallel (II) bis-cystine dimers prepared by the sulfenyl thiocyanate method exhibited virtually identical physical properties and appeared to differ only in the magnitude of their optical rotations (the parallel dimer of the L-peptide having the greater negative rotation). Furthermore, the parallel and antiparallel dimers of a particular series could not be distinguished by thin layer or column chromatography.[4,5] In view of the possibility that the acid conditions[4] required for oxidative removal of the *S*-benzhydryl groups (or a thiol–disulfide interchange process as shown in Scheme I) could in fact lead to equilibration of the dimers, which could not be distinguished analytically, a bis-cystine system in which the purity of the isomeric dimers could be unequivocally established was developed.

The peptides of choice were the molecules III–V; treatment of III with trypsin should yield two cleavage products (VI, VII). Similar treatment of IV with trypsin would afford only VIII. Enzymic digestion with α-chymotrypsin should lead to a similar situation with cleavage occurring at the amide bond between Phe-Gly in both III and IV.

Relatively little is known of the parameters which effect enzymic cleavage of cystine containing peptides. Schally and Barrett[6] demonstrated that the antiparallel dimer of [Lys^8] vasopressin (40-membered ring) was cleaved at the



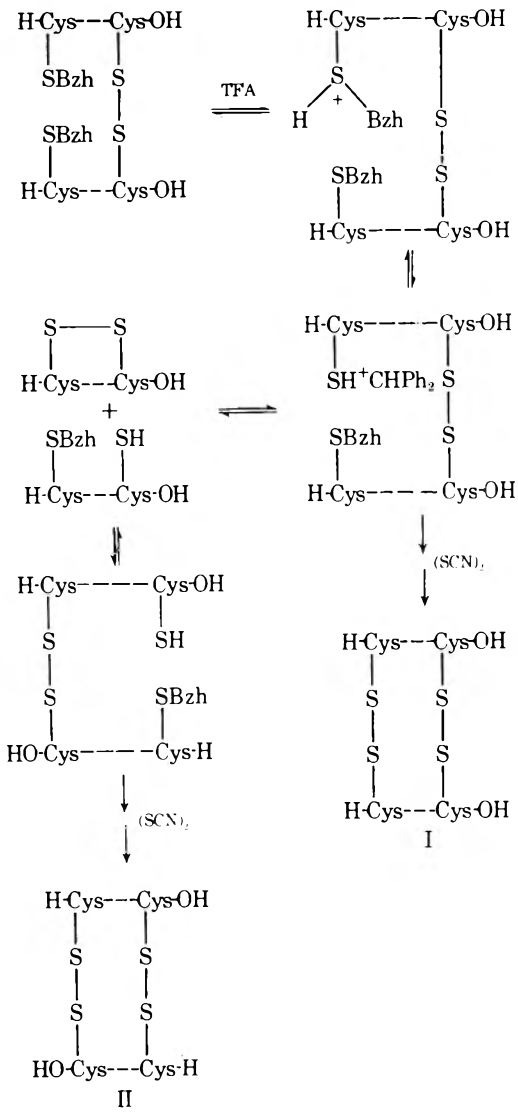
Phe-Gln bond by α-chymotrypsin. Walter and Hoffman[7] showed that oxytocin, lysine vasopressin, and arginine vasopressin (20-membered rings) were resistant to the action of α-chymotrypsin at an enzyme–substrate ratio of 1:300, whereas the corresponding S-alkylated nonapeptides were smoothly cleaved by the enzyme. The cyclic pentapeptide cyclo(Gly-Lys-Gly-Lys-Gly) is resistant to trypsin hydrolysis (15-membered ring) although the linear system is cleaved.[8] The cyclic monomer V (20-membered ring) was therefore expected to be inert to either the action of trypsin or α-chymotrypsin. If these expectations were realized III,



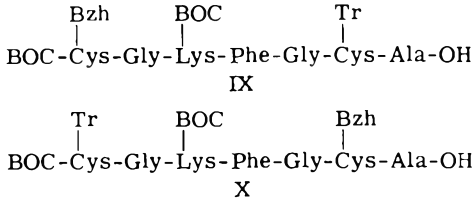
IV, and V could be distinguished from one another (since cyclic monomers have different TLC mobilities than bis dimers) and the specificity of the thiocyanogen–sulfenyl thiocyanate reaction could be established.

The heptapeptide derivatives required for the synthesis

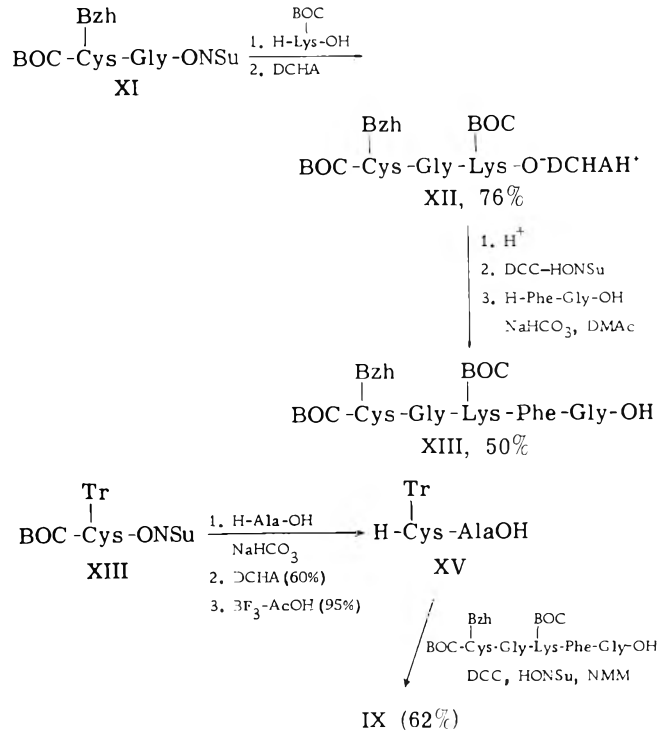
Scheme I



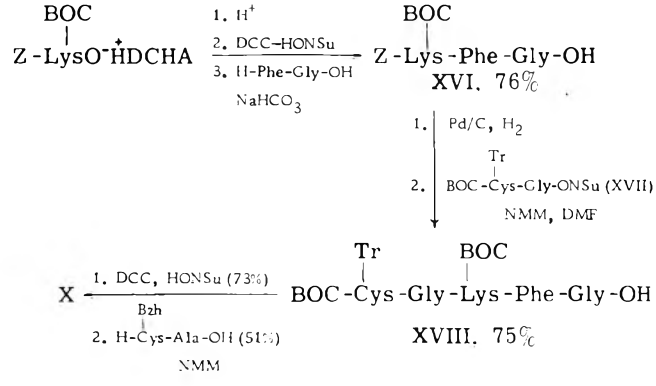
of III–V were *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-*N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-*S*-trityl-L-cysteinyl-L-alanine (IX) and the isomeric peptide derivative, X. The route developed for the



synthesis of the N-terminal pentapeptide portion of IX involved the conversion of XI to XIII. The protected dipeptide required for the elongation of XIII to IX was obtained in low yield (40%) by the DCC coupling of *N,S*-ditrityl-L-cysteine and *tert*-butyl L-alaninate; the preparation was always contaminated with *N*-acylurea and unreacted ester and was difficult to purify owing to the similarity in solubility between reactants and products. These difficulties could be circumvented by preparation of *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-alanine (XIV) and conversion of this substance to the free base, *S*-trityl-L-cysteinyl-L-alanine (XV). The coupling reaction between the crude *N*-hydroxysuccinimide ester of XIII and XV proceeded smoothly to provide IX in 62% yield.



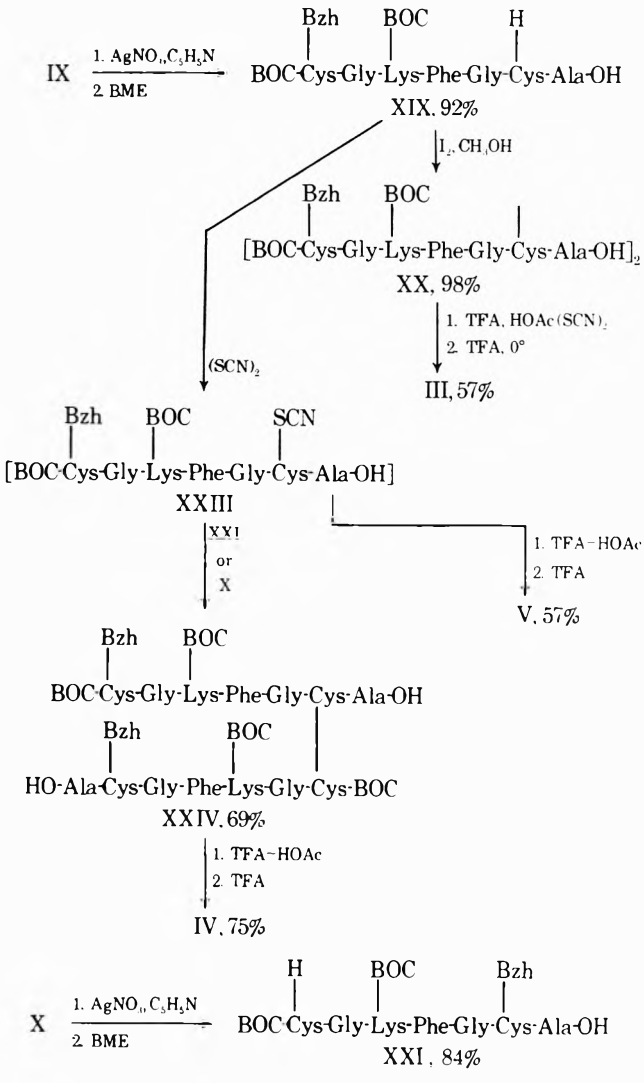
The synthesis of the isomeric heptapeptide derivative, X, was initially attempted via coupling of the *N*-hydroxysuccinimide ester of *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteinylglycine (XVII) and ϵ-*tert*-butyloxycarbonyl-L-lysine. The reaction did not proceed cleanly and the desired tripeptide was invariably contaminated with unreacted dipeptide; similar results were obtained with the mixed anhydride method of coupling. These problems likely reflected the solubility differences of the reactants. The successful synthetic route involved the formation of *N*-carbobenzyloxy-*N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycine (XVI). Removal of the *N*-carbobenzyloxy group fol-



lowed by coupling with the *N*-hydroxysuccinimide ester (XVII) provided the protected pentapeptide (XVIII) in 75% yield. Conversion of XVIII to the *N*-hydroxysuccinimide active ester followed by coupling with *S*-benzhydryl-L-cysteinyl-L-alanine provided the desired heptapeptide derivative, X.

The preparation of the required bis-cystine dimers III and IV was achieved by the thiocyanogen method (Scheme II). Treatment of IX with a solution of silver nitrate in pyridine[9,10] allowed selective removal of the *S*-trityl group and afforded the thiol XIX in high yield; oxidation of XIX with iodine provided the disulfide XX. The heptapeptide X was converted to the thiol XXI in the same manner. Iodine oxidation of XXI provided the isomeric disulfide XXII. Treatment of XX (5×10^{-4} *M*) with freshly prepared thiocyanogen solution at 0° provided the crude parallel bis dimer III

Scheme II



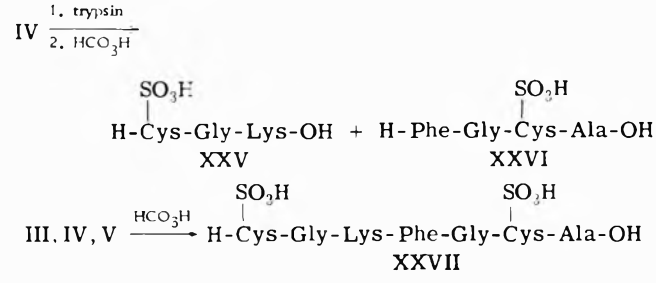
from which the BOC groups had been partially removed. Complete removal of the BOC groups was accomplished by the action of trifluoroacetic acid at 0°. The crude dimer preparation indicated no contamination by cyclic monomer V; however, the preparation invariably contained bound metal ions (probably calcium) as indicated by a residue after elemental analysis. In an attempt to minimize metal ion incorporation all solvents used for thiocyanogen generation were freshly distilled and glassware was carefully cleaned. The resulting crude parallel bis dimer preparation was chromatographed on Bio-Rex-70, a weak cation resin, with a linear gradient of aqueous acetic acid (1–80%). Elemental analysis of the first peak eluted indicated the presence of fluoride ion and inorganic residue. Amino acid and elemental analysis of this fraction were consistent with a monocalcium tetratrifluoroacetate salt of III. The second peak eluted (57%) was homogeneous on TLC and electrophoresis, did not contain metal ions, and gave an acceptable amino acid analysis for the desired parallel dimer, III.

The cyclic monomer V was prepared via the sulfenyl thiocyanate XXIII, generated by addition of XIX in acetic acid to thiocyanogen in ethyl acetate at 0°. A mixture of trifluoroacetic acid–acetic acid (1:3 v/v) was added to the reaction mixture; a concentration of 1.1×10^{-3} *M* was used to maximize intramolecular cyclization. The amino protective groups were completely removed with TFA at 0° and the crude product was purified on Bio-Rex-70. The cyclic monomer V was homogeneous on TLC and electrophoresis and could be distinguished from IX on TLC; no inorganic residue was observed in any preparation of V.

Preparation of the antiparallel bis-cystine dimer IV required the initial formation of the unsymmetrical cystine derivative XXIV. The conditions finally adopted depended on maximizing the solubility of the reactants; preparation of the thiocyanogen solution in chloroform rather than ethyl acetate improved the solubility of the reaction mixture. The thiol XIX in a mixture of acetic acid–chloroform was added to a solution of thiocyanogen in chloroform to generate the sulfenyl thiocyanate XXIII. Treatment of XXIII with either the *S*-trityl heptapeptide X or the corresponding thiol XXI provided the unsymmetrical disulfide XXIV. The material was contaminated with small amounts of unreacted starting materials, symmetrical disulfide XX, and thiocyanogen polymer; these could be removed by recrystallization to yield XXIV, homogeneous by TLC. The conversion of XXIV to IV was achieved as previously described. Chromatography on Bio-Rex-70 indicated a small amount of tetratrifluoroacetate salt of IV containing calcium ion, and a major peak (75%) corresponding to a residue-free sample of IV. The parallel and antiparallel bis-cystine dimers III and IV exhibited identical mobilities on TLC and paper electrophoresis; the parallel dimer exhibited a specific rotation of greater negative magnitude than that of the antiparallel isomer ($[\alpha]^{25}D$ −62.3, −46.4°, respectively) as previously observed.[4]

The conversion of bis-cystine peptides to the corresponding cyclic monomers under alkaline conditions has been previously reported.[4] A preliminary study indicated that III and IV were stable at pH 7.1 for at least 24 hr and that base-catalyzed disulfide interchange leading from III or IV to V would be negligible under these conditions. Hydrolysis of III with trypsin was performed at pH 7.1 and the reaction mixture was analyzed by paper electrophoresis. The tryptic digest exhibited two peptide fragments well separated by electrophoresis; no unreacted III was observed and subsequent studies showed that under these conditions (enzyme–substrate ratio 1:20 w/w) III was completely hydrolyzed in 5 min. Preparative paper electrophoresis, elution of the two spots, and amino acid analysis of each of the oxidized peptide acid hydrolysates indicated that the two open-chain symmetrical cystine peptides VI and VII were produced.

The tryptic hydrolysis of the antiparallel bis-cystine peptide IV was performed under the same conditions. Paper electrophoresis of the reaction mixture indicated that only one product, ultimately shown to be the unsymmetrical open-chain cystine peptide VIII, was produced. The electrophoretic migration distance of the bis dimer IV and the peptide VIII were similar and additional evidence for the identity of VIII was desirable. The peptides IV and

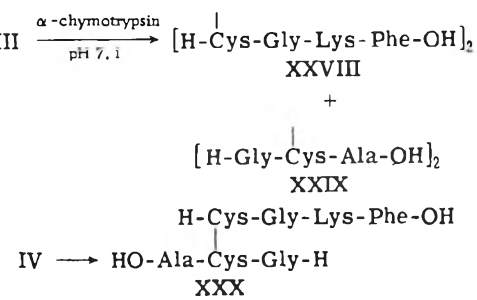


VIII could be distinguished by performic acid oxidation of the tryptic hydrolysis mixture resulting from IV; two ninhydrin positive products were observed corresponding to XXV and XXVI. A spot corresponding to XXVII produced by independent oxidations of III–V was not observed. Thus

the complete tryptic conversion of IV to VIII with no trace of VI or VII was established.

The cyclic monomer V was unaffected by the action of trypsin at pH 7.1 for 2 hr, although prolonged digestion or digestion at pH 8.6 produced some cleavage and a spot corresponding to VIII could be observed. The stability of cyclic cystine derivatives of this type to trypsin and chymotrypsin has been previously noted.[7]

The peptides III–V were also cleaved with α-chymotrypsin at substrate–enzyme ratios of 50:1 (w/w). The results of this study were similar to those obtained with trypsin. Digestion of III with α-chymotrypsin produced the peptides XXVIII and XXIX. Similar treatment of the antiparallel isomer IV provided only XXX. The open-chain unsymmetrical cystine derivative XXX could be distinguished from IV by performic acid oxidation of the enzymic digest. The cyclic monomer was inert to the enzyme at pH 7.1 but was slowly hydrolyzed at pH 8.6.



These experiments establish the purity of the parallel and antiparallel bis-cystine peptides III and IV. In addition these degradations provide independent support for the structural assignments of III and IV and hence for the reliability of the use of thiocyanogen and sulfenyl thiocyanates for the stepwise synthesis of peptides containing several cystine residues.

Experimental Section

General. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga., and Micro-Tech Laboratories, Skokie, Ill. Controlled pH reactions were operated with a Radiometer pH titrator and magnetic valve. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Amino acid analyses were performed on a Beckman Model 116 unit.

Trypsin (bovine pancreas) was obtained from Sigma Chemical Co.; α-chymotrypsin (bovine pancreas) was the product of Worthington Biochemical Corp. Bio-Rex 70 was purchased from Bio-Rad Laboratories.

Thin layer chromatograms were performed on microscope slides or 5 × 20 cm plates uniformly coated with silica gel GF-254. Spots were visualized with iodine vapor or a spray reagent of ninhydrin. The following solvent systems were used: chloroform–methanol (9:1, system A); chloroform–methanol (19:1, system B); chloroform–methanol–acetic acid (8:1:1, system C); chloroform–methanol–acetic acid (18:1:1, system D); chloroform–methanol–28% ammonia (24:6:1, system E); chloroform–methanol–28% ammonia (12:6:1, system F); 1-butanol–acetic acid–H_2O (4:1:5, system G); *tert*-butyl alcohol–1-butanol–H_2O (4:3:3, system H); 2-butanone–acetic acid–H_2O (6:1:3, system I).

Electrophoresis was performed with a Gilson high voltage electrophorator Model D on Whatman No. 3 MM chromatograph paper (46 × 57 cm). Chromatography was carried out in a pH 3.7 buffer solvent system (pyridine–acetic acid–water, 1:10:289 v/v) at 3000 V (110 mA) from 60 to 80 min. The paper was allowed to dry in air or in the oven (80°) for 15 min, and spots were visualized with ninhydrin (0.2% in acetone) spray reagent.

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-*N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysine *N*,*N*-Dicyclohexylammonium Salt (XII).** A mixture of 3.2 g (13 mmol) of *N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysine[11] and 1.82 g (13 mmol) of potassium carbonate in 2.5 ml of water was treated with a solution containing 5.5 g (10 mmol) of XI[12] in 2.5 ml of DME. The reaction mixture was stirred for 2 hr and neutralized with 20% acetic acid, and the solvent was removed in vacuo. The oil was extracted with ethyl acetate and the organic layer was washed with water and saturated brine. Removal of the solvent and treatment of an ether solution of the foam with *N*,*N*-dicyclohexylamine (4 ml, 20 mmol) provided a crystalline salt, recrystallized from methanol–ether: 6.48 g (76%); mp 107–110°; $[\alpha]^{23}D$ −9.93° (*c* 1, DMAc); homogeneous (system C).

Anal. Calcd for $C_{46}H_{71}N_5O_8S$: C, 64.68; H, 8.38; N, 8.20; S, 3.75. Found: C, 64.43; H, 8.27; N 7.86; S, 3.73.

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-*N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycine (XIII).** A solution of the oil obtained by neutralization of 2.1 g (2.5 mmol) of XII and 0.322 g (2.8 mmol) of *N*-hydroxysuccinimide in 10 ml of DME was cooled to −10° and treated with 0.53 g (2.8 mmol) of DCC. The solution was stirred for 12 hr, the DCU removed, and the solvent evaporated. The resulting oil was dissolved in 5 ml of DMAc and added to a solution containing 0.63 g (2.6 mmol) of L-phenylalanylglycine[12] and 0.44 g (5.2 mmol) of sodium bicarbonate in 5 ml of water. The reaction mixture was stirred for 12 hr, neutralized with 1 *N* sulfuric acid, and extracted with chloroform. The extract was washed with 1 *N* sulfuric acid, water, and brine and dried. Removal of the solvent and addition of ether provided a white solid which was crystallized from acetone to provide 1.03 g (50%) of the pentapeptide derivative: mp 165–167°; $[\alpha]^{23}D$ −25.0° (c 1.03, DMAc); homogeneous (system D).

Anal. Calcd for $C_{45}H_{60}N_6O_{10}S$: C, 61.62; H, 6.90; N, 9.58; S, 3.65. Found: C, 61.55; H, 6.97; N, 9.62; S, 3.55.

Amino acid analysis of an acid hydrolysate without performic acid oxidation: $Gly_{2.0}$, $Phe_{1.0}$, $Lys_{1.06}$.

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-alanine *N*,*N*-Dicyclohexylammonium Salt (XIV).** A solution of the oil obtained from neutralization of 12.56 g (20 mmol) of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine *N*,*N*-dicyclohexylammonium salt[12] and 2.76 g (24 mmol) of *N*-hydroxysuccinimide in 30 ml of DME at −10° was treated with 5 g (24 mmol) of DCC. The reaction mixture was stirred for 2 hr at −10° and overnight at room temperature. The DCU was removed and the solvent was evaporated to yield a foam which was dissolved in ethyl acetate and washed with saturated sodium bicarbonate, water, and saturated brine. The solvent was removed and the resulting oil was dissolved in DME and treated with a solution containing 2.23 g (25 mmol) of L-alanine and 5.1 g (50 mmol) of potassium bicarbonate in 50 ml of water. After 4 hr the pH was adjusted to 3.0 with 1 *N* sulfuric acid and the precipitated solid was extracted into ethyl acetate. The solution was washed with water and saturated brine, dried, and evaporated to a foam. The foam was dissolved in 30 ml of ether and treated with 6.0 ml (30 mmol) of *N*,*N*-dicyclohexylamine to yield a crystalline solid (7.92 g, 60%): mp 153–154°; $[\alpha]^{26}D$ +15.4° (c 1, DMF); hydrogeneous (system C).

Anal. Calcd for $C_{42}H_{57}N_3O_5S$: C, 70.44; H, 8.01; N, 5.86; S, 4.47. Found: C, 70.20; H, 8.04; N, 5.86; S, 4.57.

***S*-Trityl-L-cysteinyl-L-alanine (XV).** A solution containing 1.372 g (2 mmol) of the above salt in 10 ml of glacial acetic acid was treated with 0.87 ml (6 mmol) of boron trifluoride etherate. The solution was stirred for 1 hr at room temperature and poured into a solution of 5 g of sodium acetate in 70 ml of water. The white solid was collected and washed with water and ether to yield 0.897 g (95%) of XV: mp 216–218°; $[\alpha]^{25}D$ −2.35° (c 0.98, DMF); homogeneous (system C, E).

Anal. Calcd for $C_{25}H_{26}N_2O_3S \cdot 2H_2O$: C, 63.70; H, 6.40; N, 5.91; S, 6.80. Found: C, 64.55; H, 6.37; N, 5.90; S, 6.90.

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-*N*$^{\epsilon}$-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-*S*-trityl-L-cysteinyl-L-alanine (IX).** To a solution of 2.17 g (2.48 mmol) of XIII and 0.862 g (7.5 mmol) of *N*-hydroxysuccinimide in 10 ml of DMF at −10° was added 0.612 g (3 mmol) of DCC. The reaction mixture was stirred for 2 hr at −10° and overnight at 0°. After removal of DCU the filtrate was poured into 400 ml of ether. The precipitate was suspended in hot 2-propanol, cooled to room temperature, and collected. The active ester (2.0 g, 85%) was used without further purification.

The solution of the active ester in 20 ml of DMF was added to a solution containing 1.04 g (2.4 mmol) of XV and 0.25 g (2.4 mmol) of *N*-methylmorpholine in 8 ml of DMF. The solution was stirred for 24 hr and poured into cold 1 *N* sulfuric acid (500 ml), and the white solid was collected. The solid was washed with 1 *N* sulfuric acid and water and dried. The white powder was stirred in ether, filtered, and precipitated two times from acetic acid by addition of ether. Recrystallization from 2-propanol provided 1.61 g (62%) of

white powder IX: mp 189–191° dec; $[\alpha]^{25}D$ −26.89° (c 0.5, DMF); homogeneous (system D).

Anal. Calcd for $C_{70}H_{84}N_8O_{12}S_2$: C, 65.02; H, 6.55; N, 8.67; S, 4.96. Found: C, 64.89; H, 6.63; N, 8.61; S, 5.03.

The amino acid analysis of a performic acid oxidized acid hydrolysate was: $CySO_3H_{1.74}$, $Gly_{2.0}$, $Ala_{0.91}$, $Phe_{1.3}$, $Lys_{0.97}$.

N^{α}-Carbobenzyloxy-N^{ϵ}-*tert*-butyoxycarbonyl-L-lysyl-L-phenylalanylglycine (XVI). A solution of N^{α}-carbobenzyloxy-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysine *N*-hydroxysuccinimide ester[13] (2.77 g, 5.8 mol) in DME (25 ml) was added to L-phenylalanylglycine (1.81 g, 7.54 mmol) and sodium bicarbonate (1.35 g, 16 mmol) in water (20 ml). The reaction mixture was stirred for 24 hr, acidified with cold 1 *N* sulfuric acid, and extracted with ethyl acetate (200 ml). The extract was washed with water and saturated brine, dried over magnesium sulfate, filtered, and evaporated to a white solid. The crude compound was stirred with ether and filtered three times to yield 2.56 g (76%) of product: mp 120–123°; $[\alpha]^{26}D$ −32.7° (c 0.505, MeOH); homogeneous (system F, G).

Anal. Calcd for $C_{30}H_{40}N_4O_8$: C, 61.62; H, 6.89; N, 9.58. Found: C, 61.61; H, 6.94; N, 9.54.

N^{ϵ}-*tert*-Butyloxycarbonyl-L-lysyl-L-phenylalanylglycine was prepared by passing hydrogen gas through a mixture of XVI (2.56 g, 4.38 mmol) and glacial acetic acid (3 ml) in methanol (30 ml) in the presence of 0.3 g of 10% palladium on charcoal catalyst. After 4 hr, the solution was filtered and evaporated to a solid which was dissolved in methanol and precipitated by the addition of ether. The precipitate was collected and yielded 1.94 g (99%) of solid: mp 181–184° dec; $[\alpha]^{26}D$ +21.2° (c 0.5, HOAc); homogeneous (system G).

Anal. Calcd for $C_{22}H_{34}N_4O_6$: C, 58.64; H, 7.61; N, 12.43. Found: C, 58.77; H, 7.66; N, 12.29.

N-*tert*-Butyloxycarbonyl-S-trityl-L-cysteinylglycyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycine (XVIII). A solution of XVII (463.5 mg, 0.75 mmol) in DMF (1 ml) was added to a mixture of N^{ϵ}-*tert*-butyloxycarbonyl-L-lysylphenylalanylglycine (225.3 mg, 0.5 mmol) and *N*-methylmorpholine (56 mg, 0.5 mmol) in DMF (3 ml). The reaction mixture was stirred for 24 hr and poured into ether (100 ml). The white precipitate was collected by filtration, washed with 1 *N* sulfuric acid and water, and dried in vacuo. Two crystallizations from 2-propanol gave a solid (450 mg). The solid was dissolved in DMF (2 ml) and applied to a silica gel (40 g) column in chloroform. Elution with 19:1 (v/v) chloroform–methanol removed the DMF and unreacted dipeptide XVI as the first fractions. Further elution provided the product XVIII. Two recrystallizations of the material from methanol–ether afforded a white solid (362 mg, 77%): mp 180–181° dec; $[\alpha]^{25}D$ −5.58° (c 0.555, DMF); homogeneous (system D).

Anal. Calcd for $C_{51}H_{64}N_6O_{10}S$: C, 64.25; H, 6.77; N, 8.81; S, 3.36. Found: C, 64.17; H, 6.92; N, 8.70; S-3.45.

N-*tert*-Butyloxycarbonyl-S-benzhydryl-L-cysteinyl-L-alanine *N,N*-Dicyclohexylammonium Salt. A solution of the oil obtained from the neutralization of 22.76 g (40 mmol) of N-*tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteine *N,N*-dicyclohexylammonium salt and 5.52 g (48 mmol) of *N*-hydroxysuccinimide in 40 ml of DME was cooled to −10° and treated with 9.9 g (48 mmol) of DCC. The reaction mixture was stirred for 2 hr at −10° and overnight at room temperature. DCU was removed by filtration and the remaining solution was evaporated to a foam which was dissolved in ether and washed with saturated sodium bicarbonate, water, and brine, dried over magnesium sulfate, filtered, and evaporated to a foam. The foam was dissolved in 100 ml of DME and added to a solution of 4.46 g (50 mmol) of L-alanine and 10.2 g (100 mmol) of potassium bicarbonate in 100 ml of water. After 17 hr, the pH was adjusted to 3 with 1 *N* sulfuric acid and the precipitated solid was extracted into ether (500 ml). The ether solution was washed with water and brine, dried over magnesium sulfate, filtered, and treated with *N,N*-dicyclohexylamine (12 ml, 60 mmol). After cooling, a white solid was collected to yield 18.4 g (77%) of product, mp 157–158°, $[\alpha]^{25}D$ −17.3° (c 1, DMF).

Anal. Calcd for $C_{36}H_{53}N_3O_5S$: C, 67.56; H, 8.35; N, 6.57; S, 5.01. Found: C, 67.45; H, 8.40; N, 6.44; S, 5.03.

S-Benzhydryl-L-cysteinyl-L-alanine-½-Trifluoroacetate. The above salt (9 g, 0.014 mol) was neutralized with 1 *N* sulfuric acid. The resultant foam was dissolved in 40 ml of chloroform and treated with 40 ml of trifluoroacetic acid. The solution was stirred for 30 min and evaporated in vacuo. A solution of the residue in chloroform was treated with a mixture of ether–petroleum ether (1:1 v/v). The precipitate was collected by filtration, washed with ether, and dried in vacuo to give 5.1 g (80%) of product: mp 156–157° dec; $[\alpha]^{26}D$ −5.05° (c 0.99, DMF); homogeneous (system C).

Anal. Calcd for $C_{19}H_{22}N_2SO_3 \cdot \frac{1}{2}F_3C_2O_2H$: C, 57.05; H, 5.37; N, 6.63; S, 7.62; F, 6.77; residue, 1.2. Found: C, 56.91; H, 5.30; N, 6.55; S, 7.65; F, 6.74; residue, 1.14.

N-*tert*-Butyloxycarbonyl-S-trityl-L-cysteinylglycyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-S-benzhydryl-L-cysteinyl-L-alanine (X). A solution of 5.86 g (5.96 mmol) of the pentapeptide derivative XVIII and 2.07 g (18 mmol) of *N*-hydroxysuccinimide in DMF (30 ml) at 10° was treated with 1.47 g (7.2 mmol) of DCC. The reaction mixture was allowed to stir for 2 hr at −10° and overnight at 0°. DCU was removed by filtration and the remaining solution was poured into ether (600 ml). The precipitate was collected by filtration, washed with hot 2-propanol (80 ml) twice, and dried in vacuo to give a white solid (4.3 g, 73%). The active ester was used without further purification.

The active ester (4.5 g, 4.3 mmol) was dissolved in 10 ml of DMF and added to a solution containing 3.7 g (7 mmol) of *S*-benzhydryl-L-cysteinyl-L-alanine-½-trifluoroacetate salt and 1.42 g (14 mmol) of *N*-methylmorpholine in 20 ml of DMF. The solution was stirred for 24 hr and the resulting precipitate was filtered, washed with ether, 1 *N* sulfuric acid, and water, and dried. The solid was dissolved in acetic acid and precipitated with water twice and once with ether. The compound was dissolved in 10 ml of DMF and applied to a silica gel (300 g) column poured with chloroform. Elution with chloroform–methanol–acetic acid (18:1:1 v/v) provided a white solid. The solid was recrystallized twice from methanol–ether to provide the pure heptapeptide derivative, X (2.8 g, 51%): mp 180–181.5° dec; $[\alpha]^{25}D$ −17.60° (c 0.5, DMF); homogeneous (system D).

Anal. Calcd for $C_{70}H_{84}N_8S_2O_{12}$: C, 64.97; H, 6.54; N, 8.66; S, 4.96. Found: C, 64.73; H, 6.64; N, 8.50; S, 4.89.

Amino acid analysis of a performic acid oxidized acid hydrolysate gave $CySO_3H$, 1.68; Gly, 2; Ala, 1.1; Phe, 0.98; Lys, 1.1.

N-*tert*-Butyloxycarbonyl-S-benzyhydryl-L-cysteinylglycyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-L-cysteinyl-L-alanine (XIX) was prepared by treatment of a solution of IX (1.56 g, 1.2 mmol) in DMF (10 ml) and methanol (5 ml), contained in a round-bottom flask wrapped in aluminum foil, with a solution of silver nitrate (0.61 g, 3.6 mmol) and pyridine (0.3 ml, 36 mmol) in methanol (36 ml). The reaction mixture was stirred for 4 hr. Addition of ether (500 ml) to the reaction mixture precipitated a gelatinous solid which was collected by filtration, washed with ether, and dried. Mercaptoethanol (1.3 ml, fivefold excess) was added to a suspension of the silver mercaptide in 1:1 methanol–DMF (30 ml). The reaction mixture was stirred for 1 hr. The yellow precipitate was removed by filtration and the filtrate was poured into deoxygenated water (500 ml). The precipitate was collected, washed, and dried to yield 1.15 g (92%) of solid: mp 175–177° dec; $[\alpha]^{26}D$ −15.8° (c 0.5, DMF); homogeneous (system C, D).

Anal. Calcd for $C_{51}H_{70}N_8O_{12}S_2$: C, 58.44; H, 6.73; N, 10.41; S, 6.11. Found: C, 58.32; H, 6.92; N, 10.34; S, 6.11.

N-*tert*-Butyloxycarbonyl-L-cysteinylglycyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-S-benzhydryl-L-cysteinyl-L-alanine (XXI) was prepared by treatment of a solution of 129.4 mg (0.1 mmol) of X in 2 ml of DMF with a solution of silver nitrate (51 mg, 0.3 mmol) and pyridine (0.03 ml, 0.3 mmol) in methanol (2 ml) in the dark. The reaction mixture was stirred for 4 hr and ether (50 ml) was added. The precipitate was collected and dried. The silver mercaptide in DMF (2 ml) was treated with mercaptoethanol (0.1 ml, fivefold excess) and stirred for 1 hr. The reaction mixture was filtered and the filtrate was poured into water (50 ml). The precipitate was collected and washed with ether. Recrystallization from methanol–ether gave a white solid (84 mg, 84%): mp 184–186° dec; $[\alpha]^{27}D$ −29.4° (c 0.5, DMF); homogeneous (system C, D).

Anal. Calcd for $C_{51}H_{70}N_8O_{12}S_2$: C, 58.44; H, 6.73; N, 10.41; S, 6.11. Found: C, 58.18, H, 6.82; N, 10.45; S, 5.95.

S,S-Bis(N-*tert*-butyloxycarbonyl-S-benzhydryl-L-cysteinylglycyl-N^{ϵ}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-L-hemicystyl-L-alanine) (XX). A solution of 800 mg (0.38 mmol) of XIX in 20 ml of a DMF–methanol (1:1 v/v) mixture was titrated with 0.1 *N* iodine in methanol until a yellow color persisted. After stirring for 10 min, 2 drops of a 0.1% aqueous solution of sodium thiosulfate solution was added and the reaction mixture was poured into 500 ml of water. The precipitate was collected by filtration, dried in vacuo, and washed with ether to give 780 mg (98%) of the disulfide: mp 193–194° dec; $[\alpha]^{25}D$ −34.0° (c 0.5, DMF); homogeneous (system C, D).

Anal. Calcd for $C_{102}H_{138}N_{16}O_{24}S_4$: C, 58.33; H, 6.62; N, 10.67; S, 6.11. Found: C, 58.43; H, 6.65; N, 10.83; S, 6.25.

Preparation of Thiocyanogen Solution. The reagent was prepared by modification of the method of Wood.[14] All glassware was dried at 110° prior to use. The bromine was weighed into ethyl acetate or chloroform to give a solution of the appropriate concentration. The desired amount of bromine solution was added to a 25% excess of lead thiocyanate suspended in ethyl acetate or chloroform in a round-bottom flask wrapped in aluminum foil equipped with a calcium chloride drying tube. The reaction mixture was stirred until the bromine color disappeared. The colorless solution was taken with a pipet equipped with an inverted sinter funnel. This reagent was always prepared immediately before use.

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-*N*^{t}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-*S*-(*N*-*tert*-butyloxycarbonyl-L-cysteinylglycyl-*N*^{t}-*tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycyl-*S*-benzhydryl-L-cysteinyl-L-alanine)cysteinyl-L-alanine (XXIV).** A solution of XIX (262.8 mg, 0.25 mmol) in glacial acetic acid (40 ml) and chloroform (20 ml) was added dropwise to thiocyanogen solution (6.0 ml, 0.3 mmol) in chloroform at 0° in the dark. The reaction mixture was stirred for 30 min at 0°. A solution of 323.4 mg (0.25 mmol) of the *S*-trityl heptapeptide X in 10 ml of acetic acid was added to the reaction mixture and stirred for 27 hr at 0° in the dark. Chloroform was removed by evaporation and the remaining solution was poured into water (500 ml). The precipitate was coagulated by adding solid sodium chloride, collected by filtration, and dried in vacuo. The crude product was washed with ether, ethyl acetate, and chloroform. Two recrystallizations from methanol–ethyl acetate provided a pure compound XXIV (360 mg, 69%): mp 185–186° dec; $[\alpha]^{25}D$ −54.08° (c 0.49, DMF); homogeneous (system E).

Anal. Calcd for $C_{102}H_{138}N_{16}O_{24}S_4$: C, 58.33; H, 6.62; N, 10.67; S, 6.11. Found: C, 58.06; H, 6.81; N, 10.47; S, 5.98.

***S*,*S*-*S*′,*S*′-Bis(L-hemicystylglycyl-L-lysyl-L-phenylalanylglycyl-L-hemicystyl-L-alanine) (III).** A solution of XX (158 mg, 0.075 mmol) in 150 ml of trifluoroacetic acid–acetic acid (1:3 v/v) was treated with 1.9 ml (0.094 mmol, 25% excess) of a thiocyanogen solution in ethyl acetate at 0° in the dark and stirred for 48 hr. The reaction was lyophilized to a pink, fluffy powder which was treated with trifluoroacetic acid (5 ml) at 0° and stirred for 2 hr. The product was precipitated with ether and collected by filtration. The solid was dissolved in acetic acid and precipitated with ether. The crude product (110 mg) showed one spot (system I) and a lower faint streak.

A 1.5 × 60 cm column of Bio-Rex 70 (200–400 mesh) was used for purification. The column was freshly prepared before each run and equilibrated with 1% (v/v) aqueous acetic acid. The sample was dissolved in 1% acetic acid (1 ml) and applied to the column. A linear gradient of acetic acid (from 1% to 80%) was used for elution with a flow rate of 20 ml/hr. Fractions (3 ml) were collected in each tube. The effluent was examined by the Folin–Phenol reagent and monitored by absorbancy at 700 nm. Appropriate fractions were pooled and lyophilized.

The first peak was collected and lyophilized to give a white, fluffy powder (12.3 mg). TLC and paper electrophoretic mobilities of the material were identical with those exhibited by the material in the second peak (III). The electrophoretic pattern of the trypsin digest of the material was also the same as the pattern exhibited by III.

Anal. Calcd for $C_{56}H_{84}N_{16}O_{16}S_4 \cdot 2C_2F_3OOH \cdot Ca(C_2F_3O_2)_2 \cdot 4H_2O$: C, 39.72; H, 4.89; N, 11.59; S, 6.70; F, 11.70; residue calculated as CaO, 2.84; Ca^{2+}, 2.01. Found: C, 38.32; H, 4.66; N, 11.30, S, 7.52; F, 11.13; residue, 3.18; Ca^{2+}, 2.25.

Amino acid analysis of a performic acid oxidized acid hydrolysate gave $CySO_3H_{1.87}$, $Gly_{2.0}$, $Phe_{0.98}$, $Ala_{0.97}$, $Lys_{0.94}$.

The second peak was collected and lyophilized to give a white powder, III (58 mg, 57%): mp 160–169° dec; $[\alpha]^{25}D$ −63.26° (c 0.49, H_2O); homogeneous (system I); single spot on paper electrophoresis.

Anal. Calcd for $C_{56}H_{84}N_{16}O_{16}S_4 \cdot 4H_2O$: C, 46.60; H, 6.53; N, 15.40; S, 8.90. Found: C, 46.02; H, 6.50; N, 14.93; S, 8.63.

Amino acid analysis of a performic acid oxidized acid hydrolysate gave $CySO_3H_{2.0}$, $Gly_{2.04}$, $Ala_{1.0}$, $Phe_{0.92}$, $Lys_{1.0}$.

***S*,*S*′-L-Hemicystylglycyl-L-lysyl-L-phenylalanylglycyl-L-hemicystyl-L-alanine (V).** A solution of XIX (250 mg, 0.25 mmol) in acetic acid (20 ml) was added dropwise to a thiocyanogen solution (10 ml, 3.1 mmol, 25% excess) in ethyl acetate for 10 min at 0° in the dark and stirred for 20 min. The reaction mixture was diluted with 330 ml of trifluoroacetic acid–acetic acid (1:3 v/v) and stirred for 48 hr at 0° in the dark. Lyophilization gave pink, fluffy powder which was treated with 5 ml of trifluoroacetic acid at 0° and stirred for 2 hr. The product was precipitated with cold ether and collected. The solid was dissolved in water and filtered, and the remaining solution was lyophilized to a solid (140 mg) which exhibited one spot on TLC (system I) and a faint streak below the major spot. Purification of the product was carried out using chromatography on Bio-Rex 70 resin with a linear gradient of acetic acid (1% to 80%). Appropriate fractions were pooled and lyophilized to give a white, fluffy powder, V (100 mg, 59%): mp 173–182° dec; $[\alpha]^{25}D$ −16.00° (c 0.5, H_2O); homogeneous (system I); single spot on paper electrophoresis.

Anal. Calcd for $C_{28}H_{42}N_8O_8S_2 \cdot CH_3COOH \cdot 2H_2O$: C, 46.33; H, 6.40; N, 14.25; S, 8.25. Found: C, 46.69; H, 6.04; N, 13.90; S, 8.30.

Amino acid analysis of a performic acid oxidized acid hydrolysate gave $CySO_3H_{2.0}$, $Gly_{2.1}$, $Ala_{0.94}$, $Phe_{0.93}$, $Lys_{1.0}$.

***S*,*S*‴-L-Hemicystylglycyl-L-lysyl-L-phenylalanylglycyl-*S*″-(L-cysteinyl-glycyl-L-lysyl-L-phenylalanylglycyl-L-hemicystyl-L-alanine)-L-cysteinyl-L-alanine (IV).** A solution of 180 mg (0.086 mmol) of XXIV in 200 ml of trifluoroacetic acid–acetic acid (1:3 v/v) was treated with a thiocyanogen solution (2.16 ml, 0.108 mmol, 25% excess) in ethyl acetate at 0° in the dark and stirred for 48 hr. The reaction mixture was lyophilized to a pink, fluffy powder which was treated with trifluoroacetic acid (5 ml) at 0° and stirred for 2 hr. The product was precipitated with ether and collected by filtration. The solid was dissolved in water and filtered, and the remaining solution was lyophilized to a solid (130 mg) which exhibited one spot on TLC (system I) with a slight streak; no loop disulfide (V) was detected. Final purification was carried out using chromatography on Bio-Rex 70 resin with linear gradient of acetic acid (1% to 80%). Appropriate fractions were pooled and lyophilized to give a fluffy powder (15.5 mg) which exhibited mobilities on TLC and paper electrophoresis and an electrophoretic pattern of the tryptic digest identical with the second peak.

Anal. Calcd for $C_{56}H_{84}N_{16}O_{16}S_4 \cdot 2C_2F_3OOH \cdot Ca(C_2F_3OO)_2 \cdot 4H_2O$: C, 39.72; H, 4.89; N, 11.59; S, 6.70; F, 11.70; residue calculated as CaO, 2.84; Ca^{2+}, 2.01. Found: C, 38.02; H, 4.48; N, 10.90; S, 6.98; F, 11.71; residue 2.37; Ca^{2+}, 1.70.

Amino acid analysis of a performic acid oxidized acid hydrolysate gave $CySO_3H_{1.95}$, $Gly_{2.0}$, $Ala_{1.0}$, $Phe_{0.84}$, $Lys_{0.91}$.

The eluent of the second peak was collected and lyophilized to give a fluffy, white powder, IV (85 mg, 75%): mp 178–186° dec; $[\alpha]^{25}D$ −46.4° (c 0.5, H_2O); homogeneous (system I); one spot on paper electrophoresis.

Anal. Calcd for $C_{56}H_{84}N_{16}S_4O_{16} \cdot 2CH_3COOH$: C, 48.45; H, 6.25; N, 15.07; S, 8.70. Found: C, 48.09; H, 6.38; N, 14.86; S, 9.08.

Amino acid analysis of a performic acid oxidized acid hydrolysate gave $CySO_3H_{2.0}$, $Gly_{2.04}$, $Ala_{1.0}$, $Phe_{0.92}$, $Lys_{1.0}$.

Trypsin Digest Studies. A. Preparation of Enzyme Reagent. A 0.2% (w/v) solution of the enzyme reagent was prepared by dissolving trypsin (10 mg) in hydrochloric acid (5 ml, 0.001 *N*).[14]

B. Preparation of Substrate. A 0.5% (w/v) solution of the substrate was prepared by dissolving the cystine peptide (2 mg) in buffer solution (0.4 ml).[15] Enzyme digestion of the substrate was performed at pH 7.1 (0.2 *M*, sodium phosphate buffer solution). pH 6.3 (0.2 *M*, sodium phosphate buffer solution), and pH 8.6 (1 *M*, ammonium bicarbonate).

C. Hydrolytic Digestion. The enzyme reagent (0.05 ml, 0.1 mg of trypsin) was added to the substrate solution (2 mg in 0.4 ml of buffer solution) at room temperature and the reaction was allowed to proceed for 2 hr.

1. Bis Dimer III. Hydrolysis of III was performed at both pH 7.1 and 6.3. Two spots were detected at both reaction mixtures on paper electrophoresis. Spot 1, VI, migrated 40 cm (80 min); spot 2, VII, migrated 18 cm (80 min). Hydrolysis was complete after 5 min at pH 7.1. [The bis dimer III migrated 32 cm (80 min).]

2. Bis Dimer IV. Hydrolysis of IV was performed at both pH 7.1 and 6.3. One spot, VIII, detected on paper electrophoresis, migrated 29 cm (80 min) [bis dimer IV showed one spot, migrated 32 cm (80 min)].

3. Monomer V. Hydrolysis of V was performed at pH 7.1 for 2 hr. On paper electrophoresis, no change of V was detected. On prolonged digestion, a new minor spot, VIII [migrated 29 cm (80 min)], was shown above the major spot, V [migrated 28 cm (80 min)]. Two faint spots, 1, VI [migrated 40 cm (80 min)] and 2, VII [migrated 18 cm (80 min)], were also shown. When hydrolysis of V was performed at pH 8.6, in addition to the major spot [migrated at 28 cm (80 min)], three more minor spots were observed [migrated 29, 18, 40 cm (80 min)].

D. Performic Acid Oxidation. Performic acid was prepared by

mixing one part of 30% hydrogen peroxide and nine parts of formic acid (v/v) and allowing the mixture to stand at room temperature for 1 hr before use.[16]

1. Oxidation of Cystine Peptides. The cystine peptide (2 mg) was dissolved in performic acid (0.1 ml) and kept at 0° for 1 hr. The solution was diluted with water (10 ml) and lyophilized. On paper electrophoresis, the oxidative products of III, IV, and V all exhibited one spot, XXVII, migrated 3 cm (80 min).

2. Oxidation of Enzymic Hydrolysis Products. The digested samples of III and IV were acidified to pH 2.2 with hydrochloric acid (1 *N*), diluted with water, and lyophilized. The residues were dissolved in performic acid (0.1 ml) and kept at 0° for 1 hr. The solution was diluted with water (10 ml) and lyophilized. On paper electrophoresis, both of the samples of the oxidized tryptic digests of III and IV exhibited two spots. Spot 1, XXV, migrated 15 cm (80 min). Spot 2, XXVI, remained at the origin.

E. Isolation of Trypsin Hydrolysis Products of III. The digested sample III was acidified to pH 2.2 with hydrochloric acid (1 *N*), diluted with water, and lyophilized. The residue was dissolved in water (0.1 ml) and applied to Whatman no. 3 MM paper (46 × 57 cm) as a narrow band (3 cm). Electrophoresis was performed as described above. Spot visualization was achieved by cutting a strip from the edge of the narrow band on the dried paper, spraying with ninhydrin reagent, and drying. Comparison with the ninhydrin test strip allowed the isolation of each spot by cutting the area corresponding to the spot from the paper. Descending chromatography with aqueous acetic acid (5%, 20 ml) provided a solution of each compound which was lyophilized and assayed by amino acid analysis.

Amino Acid Analysis. Spot 1, VI [migrated 40 cm (80 min)]. Calcd: $CysSO_3H$, 1.0; Gly, 1.0; Lys, 1.0. Found: $CysSO_3H$, 1.02; Gly, 1.0; Lys, 1.01.

Spot 2, VII [migrated 18 cm (80 min)]. Calcd: $CysSO_3H$, 1.0; Gly, 1.0; Phe, 1.0; Ala, 1.0. Found: $CysSO_3H$, 0.97; Gly, 1.0; Phe, 0.93; Ala, 0.94; Lys, 0.

Chymotrypsin Digest Studies. A. Preparation of Enzyme Reagent. A 0.3% (w/v) solution of the enzyme reagent was prepared by dissolving α-chymotrypsin (3 mg) in hydrochloric acid (1 ml, 0.001 N).[15]

B. Preparation of Substrate. The preparation followed the procedure used on trypsin digest studies.

C. Hydrolytic Digestion. The enzyme reagent (0.015 ml, 0.04 mg of chymotrypsin) was added to the substrate solution (2 mg of substrate in 0.04 ml of buffer solution) at room temperature and the reaction was allowed to proceed for 2 hr.

1. Bis Dimer III. Hydrolysis of III was performed at pH 7.1. On paper electrophoresis, the hydrolytic sample exhibited two spots. Spot 1, XXVIII, migrated 34 cm (80 min); spot 2, XXIX, migrated 20 cm (80 min).

2. Bis Dimer IV. Hydrolysis of IV was performed at pH 7.1. On paper electrophoresis, the hydrolytic sample exhibited one spot, XXX, migrated 29 cm (80 min) [bis dimer IV showed one spot, migrated 32 cm (80 min)].

3. Monomer V. Hydrolysis of V was performed at pH 7.1 for 2 hr. On paper electrophoresis, no change of V was observed. When hydrolysis of V was carried out at pH 8.6, a minor new spot, XXX [migrated 29 cm (80 min)], above the major spot, V [migrated 28 cm (80 min)], was observed Possibly two other spots, XXVIII [migrated 34 cm (80 min)] and XXIX [migrated 20 cm (80 min)], were visible, though the spots were very faint.

D. Oxidation of Enzyme Hydrolysis Products. The reaction followed the procedure used for the trypsin digest studies. The oxidative products of the digested sample of III and IV exhibited two spots on paper electrophoresis. Spot 1 (oxidation of XXVIII) migrated 14 cm (80 min); spot 2 (oxidation of XXIX) showed very faint color at origin.

E. Isolation of Chymotrypsin Hydrolysis Products of III. The experimental procedure followed the method used for the trypsin digest studies.

Amino Acid Analysis. Spot 1, XXVIII, migrated 34 cm (80 min). Calcd: $CysSO_3H$, 1; Gly, 1; Lys, 1; Phe, 1. Found: $CysSO_3H$, 0.81; Gly, 1.0; Lys, 0.94; Phe, 1.11. Spot 2, XXIX, migrated 20 cm (80 min). Calcd: $CysSO_3H$, 1; Gly, 1; Ala, 1. Found: $CysSO_3H$, 0.89; Gly, 1.0; Ala, 0.88; Lys, 0.

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Registry No.—III, 56678-69-4; IV, 56689-35-1; V, 56689-37-3; IX, 56678-70-7; X, 56678-71-8; XI, 33515-73-0; XII, 56678-73-0; XIII, 56678-74-1; XIV, 56678-75-2; XV, 56678-76-3; XVI, 56678-77-4; XVII, 56678-78-5; XVIII, 56678-79-6; XIX, 56678-80-9; XX, 56678-81-0; XXI, 56678-82-1; XXIV, 56678-83-2; *N'-tert*-butyloxycarbonyl-L-lysine, 2418-95-3; L-phenylalanylglycine, 721-90-4; *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteine *N,N*-dicyclohexylammonium salt, 26988-59-0; L-alanine, 56-41-7; N^{α}-carbobenzyloxy-*N'-tert*-butyloxycarbonyl-L-lysine *N*-hydroxysuccinimide ester, 3338-34-9; *N'-tert*-butyloxycarbonyl-L-lysyl-L-phenylalanylglycine, 56678-84-3; *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteinyl-L-alanine *N,N*-dicyclohexylammonium salt, 56678-75-2; *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteine *N,N*-dicyclohexylammonium salt, 26988-51-2; *S*-benzyhydryl-L-cysteinyl-L-alanine-½-trifluoroacetate, 56678-86-5.

References and Notes

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(2) Abstracted in part from a dissertation by C. Li submitted in partial fulfillment of the requirements for the Ph.D., University of North Carolina at Chapel Hill, 1973.
(3) The following abbreviations have been employed in the text: BOC = *tert*-butyloxycarbonyl; Bzh = benzhydryl; Tr = trityl; DCHA = *N,N*-dicyclohexylamine; DCC = *N,N'*-dicyclohexylcarbodiimide; DCU = *N,N'*-dicyclohexylurea; HONSu = *N*-hydroxysuccinimide; NMN = *N*-methylmorpholine; BME = β-mercaptoethanol; DME = 1,2-dimethoxyethane; DMF = *N,N*-dimethylformamide; DMAc = *N,N*-dimethylacetamide.
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Synthesis of 3,6-Dideoxy-D-*erythro*-hexos-4-ulose (3,6-Dideoxy-4-keto-D-glucose)[1]

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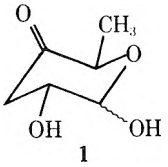
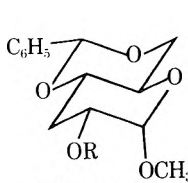
The synthesis of 3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranoside (**14**) starting from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (**2**) and from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*xylo*-hexopyranoside (**16**) is described. An attempt to prepare **14** by the direct isopropylidation of the known 3,6-dideoxy-D-*xylo*-hexose (**29**) was unsuccessful as the major product formed in this reaction was a furanose derivative, **30**. Oxidation of **14** with ruthenium tetroxide in carbon tetrachloride gave the keto sugar derivative **32** which was hydrolyzed with Dowex-50 (H^+) to give 3,6-dideoxy-D-*erythro*-hexos-4-ulose (3,6-dideoxy-4-keto-D-glucose, **1**), an important intermediate in the biosynthesis of several biologically important 3,6-dideoxy hexoses. The identification of the natural product with the synthetic material **1** has already been recorded.

Elucidation of the biochemical pathways for the formation of the biologically important 3,6-dideoxy hexoses, which contribute to the serological specificity of many immunologically active lipopolysaccharides,[2] has been the subject of several investigations.[1,3,4] Abequose, paratose, and ascarylose were shown to originate from cytidine 5′-diphosphate-6-deoxy-4-keto-D-glucose which in turn was formed from cytidine 5′-diphosphate-D-glucose. It was established recently that 3,6-dideoxy-D-*erythro*-hexos-4-ulose (**1**) as its cytidine diphosphate nucleotide conjugate is the intermediate between cytidine 5′-diphosphate-6-deoxy-4-keto-D-glucose and the 3,6-dideoxy hexoses in *Pasteurella pseudotuberculosis* type V strain VO.[1,7] The biological importance of this keto sugar **1** has been increased by the finding that its L isomer (3,6-dideoxy-L-*erythro*-hexos-4-ulose) occurs in nature as part of the antibiotic cinerubine B.[8] In this paper we describe the total synthesis of the free keto sugar **1**. The preparation of the α-methyl glycoside of **1** by another route was recently reported by Paulsen and co-workers.[9]

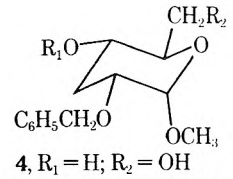


1

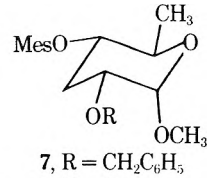
Methyl 3-deoxy-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranoside[10,11] (**2**) was prepared according to the method of Hedgley et al.[11] Conversion of **2** to the benzyl ether **3** followed by removal of the benzylidene protection by acid hydrolysis provided methyl 2-*O*-benzyl-3-deoxy-α-D-ribohexopyranoside (**4**). Treatment of **4** with excess of methanesulfonyl chloride in pyridine gave the dimesylate **5**. Selective displacement of the primary methanesulfonate group to obtain the 6-iodo derivative **6** was achieved by the treatment of **5** with 1.1 equiv of potassium iodide in refluxing 2-butanone for 90 hr. Hydrogenation of **6** in the presence of triethylamine and 10% Pd/C using ethanol as solvent provided the 3,6-dideoxy sugar derivative, **7**.



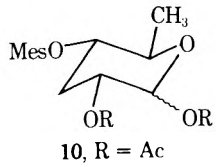
2, R = H
3, R = $CH_2C_6H_5$



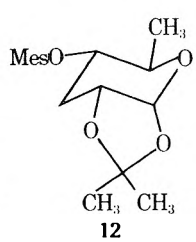
4, R_1 = H; R_2 = OH
5, R_1 = Mes; R_2 = OMes
6, R_1 = Mes; R_2 = I



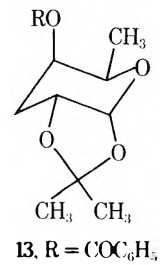
7, R = $CH_2C_6H_5$
8, R = H
9, R = Ac



10, R = Ac
11, R = H



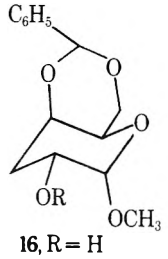
12



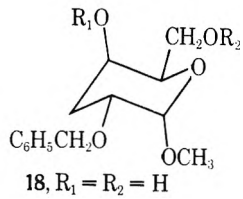
13, R = COC_6H_5
14, R = H
15, R = Tos

As a keto sugar is usually very sensitive toward acids, it was necessary to change the protection of the hydroxyl group at position 1 from the methyl glycoside (which requires very strong acid conditions for hydrolysis) to a group that can be easily converted to the free sugar after a carbonyl function is introduced in the molecule. An isopropylidene derivative was considered appropriate as it would protect both the 1 and 2 hydroxyl groups and can be hydrolyzed under very mild acid conditions. To this end, compound **7** was debenzylated by hydrogenation in the presence of 10% Pd/C and hydrogen chloride as catalysts to give methyl 3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (**8**). Although acid hydrolysis of this methyl glycoside **8** would be expected to provide the free sugar **11** easily, in practice this reaction was not clean and the product **11** was obtained only in a low yield. The free sugar **9** was, therefore, prepared by the following method. Acetylation of **8** with acetic anhydride in pyridine to give **9** and subsequent treatment of **9** with acetic acid and acetic anhydride in the presence of sulfuric acid provided 1,2-di-*O*-acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-D-*ribo*-hexopyranose (**10**) as a mixture of anomers from which the pure α isomer (**10a**) was obtained by fractional crystallization. Saponification of the mixture of diacetates **10** with sodium methoxide in methanol gave the free sugar **11** as a gum. Conversion of **11** to the isopropylidene derivative **12** was accomplished by the treatment of **11** with 2,2-diethoxypropane in acetone in the presence of *p*-toluenesulfonic acid as a catalyst. An attempt at the direct oxidation of **12** to the ketone **32** using dimethyl sulfoxide[12] in collidine was not successful owing to a competing elimination reaction of the sulfonyloxy group and difficulty in the separation of the product from dimethyl sulfoxide. Mesylate **12** was therefore converted to the easily oxidizable alcohol, **14**, by the treatment of **12** with sodium benzoate in dimethylformamide to give **13** and subsequent deacylation with sodium methoxide in methanol.

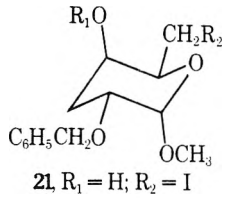
Compound **14** was also obtained by a series of reactions starting from methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*xylo*-hexopyranoside[13,14] (**16**). Treatment of **16** with benzyl chlo-



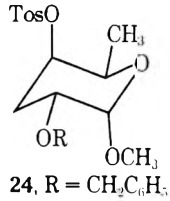
16, R = H
17, R = $CH_2C_6H_5$



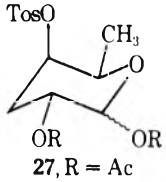
18, $R_1 = R_2 = H$
19, $R_1 = R_2$ = Mes
20. $R_1 = H$; R_2 = Tos



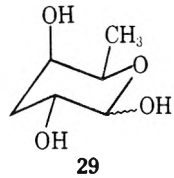
21, $R_1 = H$; $R_2 = I$
22, $R_1 = R_2 = H$
23. R_1 = Ac; $R_2 = H$



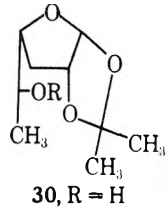
24, R = $CH_2C_6H_5$
25, R = H
26, R = Ac



27, R = Ac
28, R = H



29

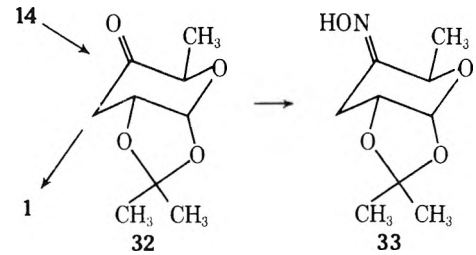


30, R = H
31, R = Mes

ride in the presence of sodium hydroxide to give **17** followed by hydrolysis of the benzylidene group gave the diol **18** which was characterized as the crystalline dimesylate **19.** Selective esterification of the primary hydroxyl group of **18** with *p*-toluenesulfonyl chloride in a mixture of pyridine and chloroform at low temperature yielded the 6-tosylate **20.** Displacement of the sulfonyloxy group with iodide anion to give **21** and subsequent reduction of the 6-iodo derivative by hydrogenation in the presence of 10% Pd/C and triethylamine provided the 3,6-dideoxy sugar derivative **22** as an oil which was characterized as the crystalline acetate **23.** In order to protect the 4-OH group in **22** it was treated with *p*-toluenesulfonyl chloride in pyridine. The tosylate **24** thus obtained was debenzylated by catalytic hydrogenation to give **25,** which was characterized as the acetate **26.** Acetolysis of **25** with acetic acid and acetic anhydride in the presence of sulfuric acid provided the 1,2-diacetate **27** as a mixture of anomers. The free sugar **28** was obtained as a viscous syrup by saponification of **27** with barium methoxide in methanol. Treatment of **28** with 2,2-diethoxypropane in acetone in the presence of *p*-toluenesulfonic acid gave the isopropylidene derivative, **15.** Removal of the sulfonyloxy group from **15** to obtain **14** was accomplished by the treatment of **15** with sodium naphthalenide reagent in tetrahydrofuran.[15]

An attempt to prepare **14** by direct isopropylidation of the free sugar, 3,6-dideoxy-D-*xylo*-hexose[16,17] (**29**), was unsuccessful. The major product obtained was the furanose derivative[18] **30,** with less than 10% of the required material, **14.** The structure of **30** was established by the preparation of its crystalline mesylate **31** having the same characteristics as reported by Antonakis.[19]

Oxidation of **14** with ruthenium tetroxide[20,21] in carbon tetrachloride provided the ketone **32** in excellent yield. Compound **32** was also characterized as its crystalline oxime, **33.** Hydrolysis of **32** to the keto free sugar **1** was accomplished by stirring **32** with Dowex-50 (H^+) in water at room temperature. Free sugar **1** was characterized by converting it back to the isopropylidene derivative, **32,** followed by preparation of **33.** The identification of the natu-



32 33

ral product isolated from *Pasteurella pseudotuberculosis* type V strain VO with the synthetic material, **1**, has already been described.[1]

Experimental Section

Melting points were determined on either a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. Thin layer chromatography (TLC), both analytical and preparative, was performed on glass plates coated with silica gel G from Brinkmann Instruments or Quantagram precoated plates containing fluorescent indicator. Compounds were detected by absorbance at 256 nm using an ultraviolet source when applicable and/or by spraying with 50% sulfuric acid followed by baking at 120°. Gas chromatographic analyses were conducted on a F & M Model 810 instrument equipped with dual flame ionization detectors. A 10 ft × 0.25 in. 3% ethylene glycol succinate on Chromosorb W column was used. NMR spectra were taken on a Varian A-60, T-60, or T-60A spectrometer using tetramethylsilane as an internal standard. The infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Specific rotations were measured using a Perkin-Elmer Model 141 polarimeter. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (3). A mixture of 50 g (0.19 mol) of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside[10,11] (**2**) in 2.0 l. of toluene and 80 g (2.0 mol) of powdered potassium hydroxide was stirred and heated under reflux using a Dean-Stark trap for 1 hr. Benzyl chloride (200 ml, 1.8 mol) was added dropwise over a period of 3 hr and the mixture was heated under reflux for an additional 12 hr. Water was added and excess benzyl chloride was removed by steam distillation under reduced pressure. When all the volatile materials were removed, the mixture was cooled, and the crystalline material formed was filtered, washed with water, and dried. It was dissolved in 95% ethanol, decolorized using Norit, and recrystallized to give 62.0 g (92%) of **3,** mp 103–104°, $[\alpha]^{24}D$ +23.1° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.87; H, 6.89

Methyl 2-*O*-Benzyl-3-deoxy-α-D-*ribo*-hexopyranoside (4). A solution of 50 g (0.14 mol) of **3** in 980 ml of 95% ethanol and 12.5 ml of concentrated HCl in 196 ml of water was stirred and heated under reflux for 1 hr. The ethanol was removed under vacuum and the residue was diluted with 1300 ml of water. The acid was neutralized by stirring with solid $NaHCO_3$ and the mixture was steam distilled under reduced pressure to remove the benzaldehyde. The mixture was extracted with 6 × 250 ml of $CHCl_3$, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from benzene to give 34.5 g (88%) of **4,** mp 105–106°, $[\alpha]^{25}D$ +67.4° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.60, H, 7.69.

Methyl 2-*O*-Benzyl-3-deoxy-4,6-di-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (5). A solution of 47.0 g (175 mmol) of **4** in 260 ml of pyridine was cooled in an ice bath and 30 ml (0.39 mol) of methanesulfonyl chloride was added dropwise with stirring over a period of 1 hr. The mixture was allowed to warm up to room temperature and stirring was continued overnight. The mixture was poured onto ice water, and the solid formed was filtered, washed with water, dried, and recrystallized from methanol to give 67.6 g (91%) of **5,** mp 78–79°, $[\alpha]^{27}D$ +60.7° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_9S_2$: C, 45.27; H, 5.69; S, 15.10. Found: C, 45.45; H, 5.65; S, 14.85.

Methyl 2-*O*-Benzyl-3,6-dideoxy-6-iodo-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (6). A solution of 25 g (59 mmol) of **5** and 10.6 g (65.3 mmol) of potassium iodide in 800 ml of 2-butanone was heated under reflux for 5 days. The mixture was cooled and the precipitated sodium mesylate removed by filtration. The filtrate was evaporated to dryness, and the residue was

dissolved in $CHCl_3$, washed with $NaHCO_3$ solution followed by 20% aqueous sodium thiosulfate solution and water, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from absolute ethanol to give 22.6 g (84%) of **6**, mp 86–87°, $[\alpha]^{25}D$ +71.9° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{21}IO_6S$: C, 39.48; H, 4.63; I, 27.81; S, 7.02. Found: C, 39.61; H, 4.62; I, 27.59; S, 7.07.

Methyl 2-*O*-Benzyl-3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (7). A solution of 50.0 g (0.11 mol) of **6** in 1 l. of ethanol and 51.4 ml of triethylamine was mixed with 5.0 g of 10% Pd/C and hydrogenated under atmospheric pressure until hydrogen uptake was complete. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in $CHCl_3$, washed successively with 1.0 *N* HCl, 10% $KHCO_3$ solution, 20% $Na_2S_2O_3$ solution, and water, dried (Na_2SO_4), and evaporated to dryness. The solid residue was recrystallized from CH_2Cl_2–hexane to give 34.1 g (94%) of **7**, mp 95–96°, $[\alpha]^{25}D$ +70.9° (c 0.9 $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71; S, 9.70. Found: C, 54.32; H, 6.84; S, 9.46.

Methyl 3,6-Dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (8). A solution of 25.0 g (75.7 mmol) of **7** in 125 ml of tetrahydrofuran and 225 ml of ethanol containing 1.0 g of 10% Pd/C and 25 drops of concentrated HCl was hydrogenated under atmospheric pressure until there was no more hydrogen uptake. The catalyst was filtered off, the filtrate was neutralized with Dowex-1 (OH^-), and the solution was evaporated to dryness. The residue was recrystallized from methylene chloride–ether–pentane to give 16.8 g (93%) of **8**, mp 88–89° $[\alpha]^{27}D$ +162.3° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_8H_{16}O_6S$: C, 39.99; H, 6.71; S, 13.34. Found: C, 40.26; H, 6.68; S, 13.10.

Methyl 2-*O*-Acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranoside (9). A solution of 10 g (41.6 mmol) of **8** in 100 ml of pyridine and 15 ml of acetic anhydride was stirred at room temperature overnight. The mixture was poured onto ice water and extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with cold 3 *N* HCl followed by 10% $KHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. The oily residue was crystallized from ether–hexane to give 10.9 g (92%) of **9**, mp 68–69°, $[\alpha]^{27}D$ + 127.7° (c 0.95, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_7S$: C, 42.54; H, 6.43; S, 11.36. Found: C, 42.50; H, 6.14; S, 11.14.

1,2-Di-*O*-acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranose (10a). A solution of 10.0 g (35.4 mmol) of **9** in 200 ml of acetic acid and 50 ml of acetic anhydride was mixed with 40 drops of a cold solution of 1:1 H_2SO_4 and acetic anhydride. After the solution was stirred overnight at room temperature, it was poured onto crushed ice with stirring. When all the ice was melted, the solid formed was filtered, washed with cold water, and dried. The filtrate was extracted with $CHCl_3$, washed with 20% $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness. The residue was combined with the air-dried solid to give 10.64 g (96%) of 1,2-di-*O*-acetyl-3,6-dideoxy-4-*O*-methylsulfonyl-D-*ribo*-hexopyranose (**10**) as a mixture of α and β anomers. Several recrystallizations of this material from methylene chloride–hexane provided pure **10a**, mp 159–160°, $[\alpha]^{25}D$ +98.8° (c 0.85, $CHCl_3$).

Anal. Calcd for $C_{11}H_{18}O_8S$: C, 42.57; H, 5.85; S, 10.33. Found: C, 42.47; H, 5.82; S, 10.40.

3,6-Dideoxy-1,2-*O*-isopropylidene-4-*O*-methylsulfonyl-α-D-*ribo*-hexopyranose (12). A solution of 5.44 g (17.5 mmol) of **10** in 500 ml of methanol was cooled in an ice bath, 200 ml of 0.1 *N* sodium methoxide in methanol was added, and the mixture was stirred at 0° for 45 min. As a TLC analysis indicated that the deacetylation was complete, the reaction mixture was carefully neutralized with Dowex-50 (H^+). After removal of the Dowex by filtration, the filtrate was evaporated to dryness to give 4.24 g of 3,6-dideoxy-4-*O*-methylsulfonyl-D-ribohexose (**11**) as a white gum. This material was treated with 500 ml of anhydrous acetone, 50 g of freshly distilled 2,2-diethoxypropane, and 250 mg of anhydrous *p*-toluenesulfonic acid and the mixture was stirred at room temperature for 24 hr. The reaction mixture was neutralized by stirring with solid $NaHCO_3$ and filtered and the filtrate was concentrated under vacuum to give 4.64 g of a yellow oil. Column chromatography of this material over alumina using benzene–chloroform (1:1) and $CHCl_3$ as eluents gave 3.6 g of a light yellow oil which crystallized from ether–hexane to give 2.77 g of **12**, mp 59–60°, $[\alpha]^{25}D$ +32.1° (c 1.0, $CHCl_3$). Preparative TLC of the mother liquors provided an additional 113 mg for a total yield of 50% for the two steps starting from **10**.

Anal. Calcd for $C_{10}H_{18}O_6S$: C, 45.10; H, 6.81; S, 12.04. Found: C, 45.00; H, 6.56; S, 11.82.

4-*O*-Benzoyl-3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (13). A mixture of 500 mg (1.9 mmol) of **12** in 50 ml of DMF and 810 mg (5.6 mmol) of sodium benzoate was heated at 130–135° with stirring for 24 hr. The solvent was removed under vacuum and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by preparative TLC (ether–hexane, 1:1 system) and the product crystallized from pentane to give 220 mg (40%) of **13**, mp 76–77°, $[\alpha]^{24}D$ −28.7° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.88; H, 7.09.

Methyl 2-*O*-Benzyl-4,6-*O*-benzylidene-3-deoxy-α-D-*xylo*-hexopyranoside (17). Compound **16** (67.0 g, 0.25 mol) was benzylated as described for the preparation of **3** to give 71.4 g (80%) of **17**, mp 73–74°, $[\alpha]^{24}D$ +43.6° (c 0.9, $CHCl_3$).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.56; H, 6.64.

Methyl 2-*O*-Benzyl-3-deoxy-α-D-*xylo*-hexopyranoside (19). A solution of 48.7 g (0.14 mol) of **17** in 955 ml of 95% ethanol and 191 ml of water containing 12.2 ml of concentrated HCl was stirred and heated under reflux for 1 hr. The ethanol was evaporated in vacuo, 1270 ml of water was added, and the benzaldehyde formed was removed by steam distillation under reduced pressure. The residue was extracted with $CHCl_3$, dried (Na_2SO_4), and evaporated to dryness to give 38.7 g (65%) of **18** which failed to crystallize. It was therefore characterized as its dimesylate as follows. Treatment of 500 mg (1.87 mmol) of **18** with excess of methanesulfonyl chloride in pyridine followed by the usual work-up and recrystallization from 95% ethanol gave 530 mg (67%) of methyl 2-*O*-benzyl-3-deoxy-4,6-di-*O*-methylsulfonyl-α-D-*xylo*-hexopyranoside (**19**), mp 97–98°, $[\alpha]^{25}D$ +32.8° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_9S_2$: C, 45.27; H, 5.70; S, 15.11. Found: C, 45.13; H, 5.80; S, 14.92.

Methyl 2-*O*-Benzyl-3-deoxy-6-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranoside (20). A solution of 38.7 g (0.14 mol) of **18** in 240 ml of pyridine was cooled to 0° and mixed with 28.7 g (0.15 mol) of *p*-toluenesulfonyl chloride in 120 ml of $CHCl_3$, also cooled to 0°. The mixture was kept at 5° for 3 days, when an additional 2.6 g of *p*-toluenesulfonyl chloride was added and the mixture was kept at 5° for 2 more days. After the standard work-up, a yellow syrup was obtained which was crystallized from methylene chloride–ether–hexane to give 34.0 g (59% for two steps) of **20**, mp 108–109°, $[\alpha]^{25}D$ +45.4° (c 0.9, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_7S$: C, 59.70; H, 6.20; S, 7.59. Found: C, 59.43; H, 6.14; S, 7.38.

Methyl 2-*O*-Benzyl-3,6-dideoxy-6-iodo-α-D-*xylo*-hexopyranoside (21). A solution of 35.3 g (83.7 mmol) of **20** in 1 l. of 2-butanone and 17.7 g (118 mmol) of NaI was stirred and heated under reflux for 4 days. The sodium tosylate formed was filtered and the filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$, washed with 20% sodium thiosulfate solution followed by water, dried (Na_2SO_4), and concentrated under vacuum. The yellow syrup obtained crystallized on standing and was recrystallized from methylene chloride–hexane to give 28.5 g (90%) of **21**, mp 90–91°, $[\alpha]^{25}D$ +83.9° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{14}H_{19}IO_4$: C, 44.46; H, 5.06; I, 33.55. Found: C, 44.59; H, 5.12; I, 33.71.

Methyl 2-*O*-Benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (22). A solution of 27.7 g (73.3 mmol) of **21** in 750 ml of methanol and 12 ml of triethylamine was hydrogenolyzed in the presence of 5.0 g of 10% Pd/C. When the hydrogen uptake ceased, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in $CHCl_3$, washed successively with 3 *N* H_2SO_4, $NaHCO_3$ solution, 20% sodium thiosulfate, and water, dried (Na_2SO_4), and concentrated in vacuo to give 18.4 g (99.6%) of **22** which failed to crystallize. It was therefore characterized as its 4-acetyl derivative by treating 200 mg (0.8 mmol) of **22** with excess of acetic anhydride in pyridine. The standard work-up provided 221 mg of a colorless gum which was purified by preparative TLC (ether–benzene, 1:1 system) and subsequently crystallized from pentane to give 108 mg (46%) of methyl 4-*O*-acetyl-2-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (**23**), mp 36–37°, $[\alpha]^{23}D$ +33.5° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.45; H, 7.41.

Methyl 2-*O*-Benzyl-3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-

***xylo*-hexopyranoside (24).** A solution of 18.4 g (73 mmol) of **22** in 100 ml of pyridine was treated with 17.0 g (89.2 mmol) of *p*-toluenesulfonyl chloride at room temperature for 3 days. As a TLC analysis indicated that the reaction was complete, the mixture was poured into ice water, and the crystals formed were collected, washed with water, and dried to give 25.7 g (86%) of **24**. A small portion was recrystallized from methylene chloride–hexane for analysis, mp 105–106°, $[\alpha]^{25}D$ +28.8° (c 1.6, $CHCl_3$).

Anal. Calcd for $C_{21}H_{26}O_6S$: C, 62.05; H, 6.45; S, 7.89. Found: C, 61.96; H, 6.36; S, 7.70.

Methyl 2-*O*-Acetyl-3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranoside (26). A solution of 25.4 g (62.6 mmol) of **24** in 150 ml of THF and 360 ml of 95% ethanol was mixed with 45 drops of concentrated HCl and 3.0 g of 10% Pd/C and hydrogenated at atmospheric pressure. When a TLC analysis showed that the debenzylation was complete, the catalyst was filtered and the filtrate concentrated under vacuum. The residue was dissolved in $CHCl_3$, washed with sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to dryness to give 19.7 g (99.6%) of methyl 3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranoside (**25**) as a glassy material which did not crystallize. This substance (900 mg, 2.85 mmol) was acetylated with acetic anhydride in pyridine and the mixture poured onto ice–water. The crystals were collected and recrystallized from CH_2Cl_2–ether–pentane to give 0.9 g (89%) of **26**, mp 92–93°.

Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19; S, 8.94. Found: C, 53.69; H, 6.31; S, 8.81.

3,6-Dideoxy-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexose (28). A solution of 19.2 g (60.8 mmol) of **25** in 225 ml of acetic acid and 60 ml of acetic anhydride was mixed with a solution of 3.75 ml of concentrated H_2SO_4 in 37.5 ml of acetic acid. The mixture was stirred at room temperature for 24 hr, poured onto crushed ice, extracted with $CHCl_3$, washed with water and $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to dryness to give 23.0 g (98.1%) of 1,2-di-*O*-acetyl-3,6-dideoxy-4-*O*-*p*-toluylsulfonyl-D-*xylo*-hexopyranose (**27**) as a colorless, partially gummy and partially crystalline material, a mixture of α and β anomers. This substance (23.0 g) was dissolved in 200 ml of CH_3OH and treated with 5 ml of a 1.5 *N* barium methoxide solution in methanol. When a TLC analysis indicated the absence of starting material, the solution was neutralized with Dowex-50 X 2 (H^+), and after filtration of the Dowex, the filtrate was evaporated to dryness to give 17.5 g (97.2%) of the free sugar **28** as a colorless, viscous syrup.

3,6-Dideoxy-1,2-*O*-isopropylidene-4-*O*-*p*-toluylsulfonyl-α-D-*xylo*-hexopyranose (15). A mixture of 17.5 g (58 mmol) of **28**, 700 ml of acetone, 100 ml of freshly distilled 2,2-diethoxypropane, and 500 mg of anhydrous *p*-toluenesulfonic acid was stirred at room temperature for 3 hr. As a TLC analysis showed only a trace of the starting material left, the acid was neutralized by stirring with solid $NaHCO_3$, the inorganic materials were filtered off, and the filtrate was evaporated to dryness to yield a dark brown oil. Column chromatography over 400 g of silica gel using hexane–ether (19:1) as eluent provided 9.886 g (50%) of **15**, homogeneous by TLC, $[\alpha]^{26}D$ +2.2° (c 0.9, $CHCl_3$).

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (14). A. By the Detosylation of 15. A solution of 9.0 g (26.3 mmol) of **15** in 250 ml of THF was treated with a solution of sodium naphthalenide[15] (prepared from 3.45 g of Na and 20.0 g of naphthalene) in THF under a nitrogen atmosphere until the green color of the reagent remained. The excess reagent was decomposed by the addition of water, and the solvents were evaporated in vacuo. A TLC analysis showed seven spots for the product with **14** as the major component. A rapid column chromatography to remove the naphthalene followed by a careful column chromatography over 100 g of silica gel with ether–hexane (1:3) as eluent gave 1.65 g (33.4%) of an oil which was crystallized from ether–pentane to give 1.30 g (26.3%) of **14**, mp 49–50°, $[\alpha]^{27}D$ −47.3° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.70; H, 8.57.

B. By the Debenzoylation of 13. A solution of 320 mg (1.1 mmol) of **13** in 15 ml of methanol and 15 ml of 0.1 *N* sodium methoxide in methanol was stirred at room temperature overnight. Solid $NaHCO_3$ was added to neutralize the base and after filtration of the inorganic materials, the solution was evaporated to dryness. The residue was extracted with hexane to remove any methyl benzoate and the remainder recrystallized from benzene–pentane to give 185 mg (88%) of **14**, mp 49–50°. A mixture melting point with the analyzed sample from A was unchanged.

Condensation of 3,6-Dideoxy-D-*xylo*-hexose (29) with Acetone. A solution of 1.0 g (6.76 mmol) of **29** in 50 ml of dry acetone and 50 mg of *p*-toluenesulfonic acid was stirred at room temperature for 21 hr. As TLC analyses indicated no further reaction, the mixture was neutralized by stirring with $BaCO_3$. The inorganic materials were removed by filtration, the filtrate was evaporated to dryness, and the residue was dissolved in $CHCl_3$ and washed with water to remove the unreacted starting material, **29** (recovered 305 mg, 30.5%). The $CHCl_3$ solution was dried (Na_2SO_4) and concentrated in vacuo to give 870 mg of a yellow oil. Separation by preparative TLC using 3-pentanone–2,4-dimethyl-3-pentanone–ligroin (6:3:1) as solvent gave 92 mg (7%) of **14** and 435 mg (35%) of 3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose[18] (**30**), each fraction containing a small percentage of the other. Preparative gas chromatography (F&M Model 775 instrument, 8 ft × 2.5 in. 3% ethylene glycol succinate column) of the major fraction followed by recrystallization from ether–pentane provided pure **30**, mp 47–48°, $[\alpha]^{25}D$ −35.0° (c 1.0, CH_3OH).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.31; H, 8.62.

Treatment of 80 mg (0.42 mmol) of **30** with methanesulfonyl chloride in pyridine followed by the standard work-up gave 75 mg (67%) of 3,6-dideoxy-1,2-*O*-isopropylidene-5-*O*-methylsulfonyl-α-D-*xylo*-hexofuranose[19] (**31**), mp 104–105°, $[\alpha]^{25}D$ −88° (c 0.5, $CHCl_3$).

Anal. Calcd for $C_{10}H_{18}O_6S$: C, 45.10, H, 6.81; S, 12.04. Found: C, 45.10; H, 6.90; S, 12.10.

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexos-4-ulose (32). A solution of 452 mg (2.4 mmol) of **15** in 20 ml of CCl_4 was stirred at 0° and a solution of ruthenium tetroxide[12,21] in CCl_4 was added dropwise until the yellow color of RuO_4 remained. A GC analysis indicated that the oxidation was complete. The excess RuO_4 was destroyed by adding a few drops of 2-propanol, the precipitated RuO_2 was removed by filtration, the solvent was evaporated at reduced pressure, and the residue was distilled in vacuo to give 364 mg (82%) of **32** as a colorless liquid, bp 47–49° (0.3 mm Hg), $[\alpha]^{27}D$ +166.3° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.76; H, 7.60.

Oxidation of 266 mg (1.0 mmol) of the mesylate **12** in 7 ml of Me_2SO and 0.13 ml of dry collidine at 125° for 20 hr showed that a significant amount of the ketone **32** was formed by a GC analysis. The mixture was poured onto ice and extracted with $CHCl_3$ to give 486 mg of a dark yellow oil containing Me_2SO, ketone **32**, and a by-product, probably an unsaturated compound formed by the elimination of mesylate. However, neither distillation nor preparative TLC was effective in separating **32** from Me_2SO and therefore this method was abandoned.

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-hexos-4-ulose Oxime (33). A mixture of 50 mg (0.27 mmol) of **32** in 2.5 ml of ethanol and 2.5 ml of pyridine and 200 mg (2.9 mmol) of hydroxylamine hydrochloride was heated on a steam bath overnight. The solvents were removed under reduced pressure, and the residue was dissolved in water and extracted thoroughly with ether. The ether solution was dried (Na_2SO_4) and evaporated to dryness and the residue was recrystallized from hexane to give 32 mg (60%) of **33**, mp 132–134°, $[\alpha]^{27}D$ +159.3° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.75; H, 7.51; N, 6.80.

3,6-Dideoxy-D-*erythro*-hexos-4-ulose (3,6-Dideoxy-4-keto-D-glucose 1). A solution of 95 mg (0.5 mmol) of **32** in 10 ml of water was stirred with 1.0 g of prewashed Dowex-50 X 2 (H^+) (100–200 mesh) at room temperature for 24 hr. A TLC analysis (solvent EtOAc) showed that the hydrolysis was complete. The Dowex was removed by filtration and the solution lyophilized at 0.02 mm Hg to give 75.4 mg (95%) of **1** as a white gum. An NMR in Me_2SO-d_6–D_2O showed two anomeric protons at τ 4.85 ($J_{1,2}$ = 7 Hz) and 5.15 ($J_{1,2}$ = 3 Hz) in a 1:1 ratio indicating that the free sugar was a 50:50 mixture of β and α anomers. The other peaks in the NMR spectrum were consistent with the structure.

A mixture of 75.4 mg (0.48 mmol) of **1**, 10 ml of dry acetone, 1 ml of 2,2-diethoxypropane, and 5 mg of *p*-toluenesulfonic acid was stirred at room temperature for 2 hr. A TLC analysis (solvent EtOAc) showed that the free sugar was converted to the isopropylidene derivative, **32**. The acid was neutralized with solid $NaHCO_3$ and filtered, and the filtrate was evaporated, the residue was extracted with ether, and the ether was removed in vacuo to give 107 mg of **32**, over 90% pure by GC. A portion (50 mg) of this material was converted to the crystalline oxime as described earlier to give

27 mg (50%) of **33**, mp 132–133°. A mixture melting point of the two samples of **33** was unchanged.

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Registry No.—**1**, 56783-59-6; **2**, 40773-64-6; **3**, 50272-14-5; **4**, 50272-15-6; **5**, 50272-16-7; **6**, 50272-17-8; **7**, 50272-18-9; **8**, 50272-19-0; **9**, 50421-06-2; **10a**, 50272-20-3; **10** isomer A, 56783-60-9; **12**, 50272-21-4; **13**, 50272-22-5; **14**, 50272-23-6; **15**, 56783-61-0; **16**, 20196-81-0; **17**, 56783-62-1; **18**, 56783-63-2; **19**, 56783-64-3; **20**, 56783-65-4; **21**, 56783-66-5; **22**, 56783-67-6; **23**, 56783-68-7; **24**, 56783-69-8; **25**, 56783-70-1; **26**, 56783-71-2; **28**, 56783-72-3; **29**, 56816-60-5; **30**, 22395-75-1; **31**, 56783-73-4; **32**, 50272-24-7; **33**, 50272-13-4; benzyl chloride, 100-44-7; methanesulfonyl chloride, 124-63-0; *p*-toluenesulfonyl chloride, 98-59-9; acetone, 67-64-1.

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Imidazo[1,2-*c*]pyrimidine Nucleosides. Synthesis of N-Bridgehead Inosine Monophosphate and Guanosine Monophosphate Analogues Related to 3-Deazapurines[1]

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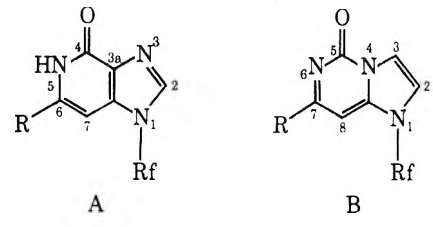
The first chemical syntheses of imidazo[1,2-c]pyrimidine nucleosides are described. Cyclization of 4-amino-6-chloro-2-pyrimidinol (**2**) with bromoacetaldehyde diethyl acetal gave 7-chloroimidazo[1,2-*c*]pyrimidin-5-one (**3**). Direct glycosylation of the trimethylsilyl derivative of **3** with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile gave an anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (**12**) which on deacetylation and separation of anomers furnished 7-chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**10**) and its α anomer (**11**). However, the glycosylation of Me_3Si-**3** with tetra-*O*-acetyl-β-D-ribofuranose in dichloroethane containing stannic chloride, followed by aminolysis, gave only the β anomer **10**. Catalytic dehalogenation of **10** and **11** furnished the 3-deazainosine analogue, 1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**15**), and its α anomer (**17**), respectively. Amination of **10** gave 7-amino-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**13**), an analogue of 3-deazaguanosine possessing a bridgehead nitrogen atom. Phosphorylation of **15**, **17**, and **13** gave 1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate (**16**), the IMP analogue, its α anomer (**18**), and 7-amino-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate (**14**), the GMP analogue, respectively. The assignment of site of ribosylation has been determined unequivocally by using ^{13}C NMR spectroscopy and the anomeric configurations have been established by using ^1H NMR of the 2′,3′-*O*-isopropylidene derivatives of **10** and **11**.

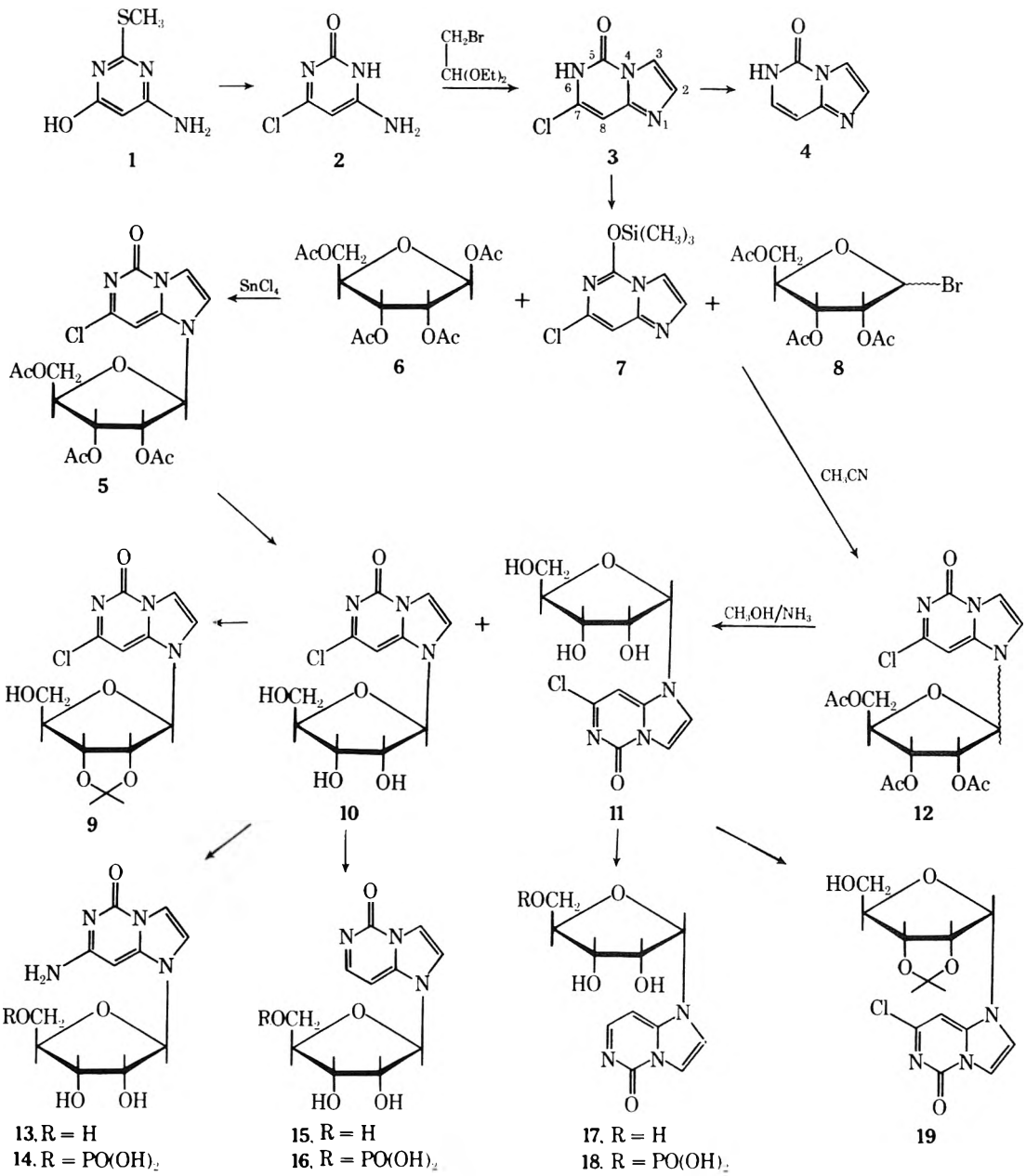
It is well established that alterations of either the furanose or the base moiety of naturally occurring purine nucleosides may produce analogues that exert interesting biological effects.[2] The role of the various nitrogen atoms of purine nucleosides as binding sites for important enzymes in biological systems has become the subject of considerable interest.[3] The isolation of a number of antibiotics of the deazapurine series (e.g., viomycin,[4] tubercidin,[5] toyocamycin[6]) which are isomeric or isosteric with purine are of particular interest because of their structural uniqueness and their biological properties.[6b,7] Since the majority of purine-type ribosides exist in the anti conformation (some exist in the syn conformation in the solid state[8]), 3-deazapurine nucleosides deserve special attention because N_3 of purine nucleosides is presumed to be involved in stabilizing the syn conformation through intramolecular hydrogen bonding [5′-OH···N_3H].[9] The syntheses of several 3-deazapurine nucleosides[10] and nucleotides[10f,g,11] (A) have been



Rf = -β-D-ribofuranosyl

reported. Some of these 3-deazapurine derivatives have demonstrated significant antibacterial,[12] anticancer,[10b,e] and antiviral[10g] activity. The imidazo[1,2-*c*]pyrimidine ring system (B), which has not been explored appreciably, may be regarded as 3-deazapurine with a bridgehead nitrogen atom in which N_3 and C_{3a} are interchanged. The nucleoside analogues of imidazo[1,2-c]pyrimidine have the potential, therefore, either to emulate or to antagonize the functions of the naturally occurring nucleosides and nucleotides.

Scheme I



These nucleoside analogues are also of particular interest since they lack an N(H) function at position 1 of purine; hydrogen bonding of the Watson–Crick type, therefore, would not be possible.

For these reasons we pursued the synthesis of 3-deaza analogues with a bridgehead nitrogen atom of some naturally occurring nucleotides, inosine monophosphate and guanosine monophosphate. The complete synthetic route consists of three parts: synthesis of an appropriate imidazo[1,2-c]pyrimidine; conversion of the starting imidazo[1,2-c]pyrimidine to the required nucleoside; and finally, the phosphorylation of the nucleoside to the corresponding 5′-monophosphate.

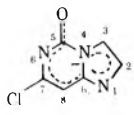
The most frequently encountered procedure for the synthesis of imidazo[1,2-c]pyrimidines involves the cyclization of 4(6)-aminopyrimidine derivatives with an α-halocarbonyl compound.[13] The possibility of utilizing this approach was investigated for the synthesis of 7-chloroimidazo[1,2-c]pyrimidin-5(6*H*)-one (**3**). Compound **3** was particularly elected as the starting material, since the halogen group is known to deactivate its neighboring nitrogen in a glycosylation reaction[14] thereby producing the requisite N_1 glycosyl derivative. The logical key intermediate, 4-amino-6-chloro-2-pyrimidinol[15] (**2**), was prepared in 83% yield in one step from 2-methylthio-4-amino-6-pyrimidinol[16] (**1**) (Scheme I). Compound **1** was chlorinated with phosphorus oxychloride and without isolation of the intermediate, 2-methylthio-4-amino-6-chloropyrimidine, the acidic aqueous solution was heated on a steam bath to obtain crystalline **2**. Ring closure of **2** with bromoacetaldehyde diethyl acetal in aqueous media at reflux gave exclusively 7-chloroimidazo[1,2-c]pyrimidin-5-one (**3**) in 86% yield. The assignment of this structure is based on the fact that the ^{1}H NMR (Me_2SO-d_6–NaOD) spectrum of **3** revealed a singlet at δ 6.46 (C_8H) in addition to two doublets at δ 7.54 (J = 2 Hz, C_2H) and 7.24 (J = 2 Hz, C_3H). Catalytic dehalogenation of **3** with 10% palladium on carbon in a hydrogen atmosphere readily gave imidazo[1,2-c]pyrimidin-5-one (**4**). The identity of this compound was confirmed by rigorous comparison of the physicochemical data reported[13e] for **4**, thereby confirming the structure of **3**. It is of particular interest to note that earlier attempts[17] to remove the chloro groups of 5-substituted 2,7-dichloroimidazo[1,2-c]pyrimidines by hydrogenation were unsuccessful.

The glycosylation of 3 was next considered. Treatment of 7-chloroimidazo[1,2-c]pyrimidin-5(6*H*)-one with hexamethyldisilazane in the presence of ammonium sulfate, according to the general procedure described by Wittenburg,[18] gave the trimethylsilyl derivative (7) which without further purification was treated with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (8) in acetonitrile at room temperature as described previously.[14,19] Under these conditions a 93% yield of an anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (12) was obtained, which resisted our efforts to separate the pure anomers by silicic acid column chromatography. Deacetylation of the anomeric mixture 12 with methanolic ammonia at ambient temperature gave 7-chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (10) and its α anomer (11). The anomeric nucleosides were separated by fractional crystallization using methanol as the solvent; the less soluble α anomer 11 crystallizes first, the anomeric ratio being almost 1:1. The purity of these nucleosides was assured by elemental analysis and by ^{1}H NMR spectroscopy. The formation of 11 is not surprising, since a number of exceptions to the Baker "trans" rule have been reported.[20] The formation of 10 established the retainment of the 7-chloro group, and confirmed the directive effect of the halogen group to give exclusively the N_1 glycosyl derivative.

In an effort to improve the yield of the β anomer 10 we have examined the use of Friedel–Crafts catalyzed glycosylation procedure.[21] Thus, treatment of 1 equiv of the trimethylsilyl derivative of 3 (7) in 1,2-dichloroethane with 1 equiv of fully acylated ribofuranose (6) and 1.44 molar equiv of stannic chloride afforded, after silicic acid column chromatography, a 64% yield of 7-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (5) as light yellow foam. Nucleoside 5 was the only nucleoside product which could be detected by TLC or column chromatography procedures. Aminolysis of 5 with methanolic ammonia at ambient temperature gave an 81% yield of 10.

Although the anomeric configuration of 10 and 11 could tentatively be assigned as β and α, respectively, on the basis of several empirical rules,[22] and by a large negative specific rotation for 10 ($[\alpha]^{25}$D −39.5°) and positive specific rotation for 11 ($[\alpha]^{25}$D +34.07°), this could not be used for the unequivocal assignment of anomeric configuration, since there are no imidazo[1,2-c]pyrimidine N_1 ribosides available for comparison. Therefore, a more rigorous proof was in order for this unusual heterocyclic nucleoside series. The ^{1}H NMR spectra of 10 and 11 in Me_2SO-d_6 revealed a doublet (for C_1'H) centered at δ 5.85 and 6.23, respectively, with a $J_{1,2}$ of approximately 4.5 Hz, which contemplated the preparation of the 2',3'-*O*-isopropylidene derivative in order to reduce the magnitude of the coupling constant to within the acceptable limits.[23] Isopropylidenation of 10 and 11 with 70% perchloric acid and 2,2-dimethoxypropane in acetone furnished 7-chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (9) and the α anomer (19) in good yield. The ^{1}H NMR spectrum of 9 in Me_2SO-d_6 revealed a doublet centered at δ 6.13 with a $J_{1,2}$ of 3.5 Hz indicating the β configuration. The spectrum also revealed the difference between the chemical shift of the two methyl signals of isopropylidene group to be 0.23 ppm, a difference characteristic of the β configuration.[24] Similarly, the ^{1}H NMR spectrum of 19 in Me_2SO-d_6 revealed the difference in proton chemical shifts between the isopropylidene methyl groups to be almost 0.0 ppm, indicating the α configuration.[24] Based on this data, the anomeric configuration for 9 and 19, and hence for 10 and 11, were unequivocally assigned as β and α, respectively.

Table I
Comparison of ^{13}C Chemical Shifts for the Anion of 7-Chloroimidazo[1,2-c]pyrimidin-5-one (C) and its Nucleosides (10 and 11)

Compd	Chemical shift, δ, ppm[a]					
	C_2	C_3	C_5	C_7[b]	C_8	C_b[b]
 C	129.4	109.4	150.9	147.2	92.2	148.4
10	118.9	111.0	155.3	148.0	89.6	144.6
11	121.3	109.9	154.7	148.2	86.2	144.6
ΔδC-10	10.5	−1.6	−4.4	−0.8	2.6	3.8
ΔδC-11	8.1	−0.5	−3.8	−1.0	6.0	3.8

[a] Chemical shifts are measured from Me_2SO-d_6, converted to Me_4Si scale using the relationship $\delta_{Me_4Si} = \delta_{Me_2SO\text{-}d_6} + 39.5$ ppm. [b] Assignments tentative.

The site of ribosylation was established by using ^{13}C NMR spectroscopy. The use of ^{13}C chemical shifts for the determination of glycosylation site in nucleosides of fused nitrogen heterocycles has recently been documented.[25] The assignments were made on the basis of the α and β substitution shifts observed when the ribofuranosyl derivatives were compared with the corresponding ionized base.[26] The pertinent ^{13}C chemical shifts of the anion of 3 and its ribosylated derivatives are summarized in Table I. The assignment of various carbons was obtained through examination of the multiplicity patterns in the proton-coupled spectra as well as comparisons of the ^{13}C chemical shifts with related compounds.[25] By comparing the ^{13}C chemical shifts of the anion of 3 (C), 10, and 11, we note that upfield shifts of 10.5 and 3.8 ppm were observed for C_2 and C_b (α carbons to N_1) and a downfield shift of 1.6 ppm was observed for C_3 (β carbon to N_1) for the nucleoside 10; similar substitution shifts were observed for the nucleoside 11. These changes in chemical shifts are consistent with the large upfield α shifts and small downfield β shifts predicted for the nucleosides, which leads to the conclusion that N_1 is the ribosylation site. The downfield shifts observed for the C_5 and C_7 (α carbons to N_6) in 10 and 11 also indicate that ribosylation has not occurred at the N_6 position. Additional support for the site of ribosylation was also obtained by the direct comparison of the reported ultraviolet absorption spectra of 6-methylimidazo[1,2-c]pyrimidin-5-one[27] or the fluorescent 6-ribosylimidazo[1,2-c]pyrimidin-5-one[28] [λ_{max} (0.05 *N* HCl) 248 s, 288, 302 nm s (ε 4.4, 12.3, 7.0 × 10^3); λ_{max} (pH 7) 272, 281 s, 292 nm s (ε 11.7, 11.1, 6.7 × 10^3); λ_{max} (0.05 *N* NaOH) 272, 281 s, 292 nm s (ε 12.0, 10.9, 5.3 × 10^3)] with the ultraviolet absorption spectra observed for 15 and 17 (see Experimental Section), which conclusively established that the ribosylation has not taken place at N_6.

Catalytic dehalogenation of 10 and 11 with 10% palladium on carbon in a hydrogen atmosphere at room temperature gave the 3-deazainosine analogue 1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (15) in 65% yield, and the corresponding α anomer (17) in 68% yield, respectively. Treatment of 10 with anhydrous methanol containing liquid ammonia at elevated temperature and pressure furnished a 64% yield of 7-amino-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (13), the 3-deazaguanosine analogue possessing a bridgehead nitrogen atom in which N_3 and C_{3a} are interchanged. Typical of most of the compounds in the present work, 13, 15, and 17 were obtained as well-defined crystalline products. Phosphorylation[29] of unprotected 15 with phosphorus oxychloride using trimethyl

phosphate as solvent at ambient temperature provided a rather low yield of N-bridgehead IMP analogue, 1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate (16), which was isolated in the free acid form. Similarly, the nucleoside 17 was phosphorylated to 1-α-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate (18). Direct phosphorylation of 13 in the manner as described above provided the GMP analogue with a bridgehead nitrogen atom, 7-amino-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one 5′-monophosphate, isolated as the free acid after ion-exchange chromatography. The structure of these IMP and GMP analogues was confirmed by ^{1}H NMR spectra and elemental analyses. The purity was assured by the homogeneity in several thin layer systems and on paper electrophoresis.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in Me_2SO-d_6 or D_2O using DSS as an internal standard. A Bruker HX-90 NMR spectrometer operating at 22.62 MHz in the Fourier transform mode was used to obtain the ^{13}C NMR spectra (20% solutions in Me_2SO-d_6). A Fabri-Tek 1074 signal averager with 4096 word memory was used for data accumulation and a Digital PDP-8/e computer for data processing. Ultraviolet spectra (uv, $\epsilon \times 10^{-3}$, s = shoulder) were recorded on a Cary Model 15 spectrometer and infrared spectra (ir) on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Chromatography solvent mixtures were by volume and the systems used were: D, ethyl acetate–water–1-propanol (4:2:1, upper phase); E, ethyl acetate–ethanol–water (4:2:1); F, 2-propanol–concentrated ammonium hydroxide–water (7:1:2). Evaporations were carried out under reduced pressure with bath temperature below 30°.

4-Amino-6-chloro-2-pyrimidinol (2). To a suspension of dry 2-methylthio-4-amino-6-pyrimidinol[16] (1, 20.0 g, 127 mmol) in phosphorus oxychloride (100 ml) was added with agitation *N,N*-diethylaniline (10 ml) and the mixture was gently refluxed for 6 hr. The excess phosphorus oxychloride (about 65 ml) was removed in vacuo, and the residual syrup poured over crushed ice (200 g) with stirring. The cold mixture was slowly brought to room temperature with continuous stirring, during which time nearly all insoluble material went into solution. The clear solution was decanted from a small amount of insoluble gum and was heated on a steam bath overnight. After refrigeration the solid that crystallized out was collected to give 19.9 g of the HCl salt. The salt was dissolved in hot water (1 l.), treated with charcoal, and filtered, and the hot filtrate was adjusted to pH 6–7 with 40% aqueous sodium hydroxide solution. After cooling the crystalline solid was collected and dried to yield 15.4 g (83%) of 2, mp >300° (lit.[15] mp >300°).

7-Chloroimidazo[1,2-c]pyrimidin-5-one (3). To a suspension of 4-amino-6-chloro-2-pyrimidinol (2, 19.0 g, 130 mmol) in water (400 ml) was added bromoacetaldehyde diethyl acetal (26.0 g, 132 mmol). The mixture was refluxed with stirring for 1.5 hr and then an additional 26.0 g of bromoacetaldehyde diethyl acetal was added. Refluxing was continued until solution was complete (2–3 hr). The heating mantle was replaced with an ice bath, and the brown solution was immediately neutralized with solid sodium bicarbonate. The cooled mixture was filtered, and the solid was washed with cold water, then acetone, and finally with ether. The tan-colored solid, weighing 19.1 g (86%), was used directly without further purification. A small sample was crystallized from water to afford an analytical sample: mp >300°; ^{1}H NMR (Me_2SO-d_6–NaOD) δ 6.46 (s, C_8H), 7.24 (d, J = 2.0 Hz, C_3H), 7.54 (d, J = 2.0 Hz, C_2H); uv λ_{max} (pH 1) 260 nm s (ε 5.5), 292 (12.8), 304 s (7.3); λ_{max} (pH 7) 265 nm s (ε 6.2), 292 (13.5); λ_{max} (pH 11) 283 nm (ε 12.4), 301 s (7.2); ir 1680 (C=O), 3110 cm^{-1} (NH).

Anal. Calcd for $C_6H_4ClN_3O$ (169.57): C, 42.50; H, 2.38; N, 24.78. Found: C, 42.25; H, 2.26; N, 24.59.

Imidazo[1,2-c]pyrimidin-5-one (4). 7-Chloroimidazo[1,2-c]pyrimidin-5-one (3, 2.0 g, 11.8 mmol) was dissolved in 50% aqueous ethanol (200 ml) containing concentrated ammonium hydroxide (5 ml), and to this solution was added 10% palladium on carbon (0.20 g). The mixture was shaken under hydrogen (45 psi) at room temperature for 1.5 hr. The mixture was filtered through a Celite pad and the filtrate concentrated to 20 ml. After cooling, the crystalline solid was collected by filtration and dried to give 1.46 g (93%). A small sample was recrystallized from water to give pure 4: mp 278° dec (lit.[13e] mp 272–274°); ^{1}H NMR (Me_2SO-d_6) δ 6.63 (d, J = 8.0 Hz, C_8H), 7.32 (d, J = 8.0 Hz, C_7H), 7.45 (d, J = 2.0 Hz, C_3H), 7.82 (d, J = 2.0 Hz, C_2H), 11.90 (broad, NH); uv λ_{max} (pH 1) 248 nm s (ε 5.4), 282 (10.4), 297 s (5.8); λ_{max} (pH 7) 267 nm (ε 11.3), 275 s (10.0), 287 s (5.0); λ_{max} (pH 11) 276 nm (λ 11.1), 294 s (5.7); ir 1720 cm^{-1} (C=O).

Anal. Calcd for $C_6H_5N_3O$ (135.12): C, 53.33; H, 3.73; N, 31.09. Found: C, 53.14; H, 3.66; N, 30.96.

7-Chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (12). Methylene chloride (30 ml) saturated with anhydrous hydrogen bromide at −20° was added to a solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (5.7 g, 17.5 mmol) in dry methylene chloride (30 ml) at −20°. The solution was protected from moisture and allowed to warm to 0°. The excess HBr and solvents were removed on a rotary evaporator, and the residual syrup was coevaporated with dry toluene (3 × 50 ml). This syrupy 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (8) was dissolved in "nanograde" acetonitrile[30] (85 ml) and added to the trimethylsilyl compound (7) obtained by refluxing 3 (2.77 g, 16.3 mmol) in hexamethyldisilazane (HMDS, 10 ml) in the presence of a catalytic amount of ammonium sulfate for 14 hr, under anhydrous conditions, and distilling off the excess HMDS in vacuo. The flask was stoppered and stirred at room temperature for 3.5 days. The reaction mixture was filtered to remove 0.15 g of unreacted 3. The dark filtrate was evaporated to dryness, and the residue was dissolved in chloroform (150 ml), washed with saturated aqueous sodium bicarbonate solution (2 × 50 ml) followed by water (2 × 50 ml), and then dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness and the residual foam was chromatographed on silica gel (400 g) prepacked in ethyl acetate and eluted with solvent D. The band carrying the products was collected and evaporated to dryness, leaving 6.15 g (93%, based on the recovery of unreacted 3) of a yellow foam: uv λ_{max} (pH 1) 250 nm (ε 4.3), 292 s (11.7), 302 (14.5), 313 s (10.6); λ_{max} (pH 7) 253 nm (ε 4.5), 304 (16.1), 313 s (14.1); λ_{max} (pH 11) 253 nm (ε 4.5), 304 (16.1), 313 s (14.1); ir 1670 (C=O of heterocycle), 1750 cm^{-1} (OAc of sugar moiety).

7-Chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (5). To a solution of 7 [prepared from 3.5 g (20.6 mmol) of 3] in anhydrous 1,2-dichloroethane (125 ml) was added 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (6, 5.6 g 20.6 mmol) followed by stannic chloride (7.9 g, 29.8 mmol). The reaction mixture was protected from moisture and stirred for 24 hr at ambient temperature. The reaction solution was then poured into 120 ml of saturated aqueous sodium bicarbonate solution with stirring. The resulting emulsion was filtered through Celite, and the organic layer was washed with water (50 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated to a light brown foam which was chromatographed on silica gel (600 g) prepacked in ethyl acetate and eluted with solvent D–ethyl acetate (1:1). The band containing the requisite product was evaporated to leave 5.6 g (64%) of light yellow foam: uv λ_{max} (pH 1) 250 nm (ε 4.3), 292 s (11.8), 302 (14.6), 313 s (10.6); λ_{max} (pH 7) 253 nm (ε 4.6), 304 (16.2), 313 s (14.1); λ_{max} (pH 11) 253 nm (ε 4.6), 304 (16.2), 313 s (14.1); ir 1670 (C=O of heterocycle), 1750 cm^{-1} (OAc).

7-Chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (10) and 7-Chloro-1-α-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (11). The anomeric mixture of 7-chloro-1-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)imidazo[1,2-c]pyrimidin-5-one (12, 6.7 g, 15.3 mmol) was dissolved in methanolic ammonia (150 ml, saturated at 0°) and the solution was allowed to stand at room temperature overnight. The volume of the reaction solution was reduced to about 75 ml and the solution was kept at room temperature for 4 hr. The tan-colored solid that crystallized was collected by filtration (G) and dried to give a chromatographically homogenous sample of the α anomer (11), 1.96 g (42%), mp 206–208°. Recrystallization from aqueous methanol afforded an analytically pure sample: mp 209°; $[\alpha]^{25}$D +34.07° (c 1.0, Me_2SO); ^{1}H NMR (Me_2SO-d_6) δ 6.23 (d, J = 4.5 Hz, C_1H), 6.86 (s, C_8H), 7.77 (d, J = 1.5 Hz, 2 H, C_2H and C_3H); uv λ_{max} (pH 1) 250 nm s (ε 4.2), 289 s (13.3), 299 (14.9), 312 s (9.8); λ_{max} (pH 7) 253 nm (ε 4.2), 302 (16.4), 311 s (14.7); λ_{max} (pH 11) 253 nm (ε 4.2), 302 (16.4), 311 s (14.7); ir 1645 cm^{-1} (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{12}ClN_3O_5$ (301.69): C, 43.79; H, 4.01, N, 13.92. Found: C, 43.40; H, 3.85; N, 13.78.

The filtrate from above (G) was allowed to stand in an open beaker until crystals began to form; then the container was covered and refrigerated. The crystalline solid was collected and dried to give 2.25 g (48%) of the β anomer (**10**), mp 190–191°. An analytical sample was obtained by recrystallization from aqueous ethanol: mp 192°; $[\alpha]^{25}D$ −39.6° (*c* 1.0, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 5.85 (d, *J* = 4.5 Hz, C_1·H), 6.95 (s, C_8H), 7.83 (d, *J* = 3.0 Hz, C_3H), 7.98 (d, *J* = 3.0 Hz, C_2H); uv λ_{max} (pH 1) 250 nm (ε 4.4), 293 s (14.2), 301 (15.4), 312 s (11.5); λ_{max} (pH 7) 253 nm (ε 5.5), 303 (17.1), 312 s (15.7); λ_{max} (pH 11) 253 nm (ε 5.5), 303 (17.1), 312 s (15.7); ir 1650 cm^{-1} (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{12}ClN_3O_5$ (301.69): C, 43.79; H, 4.01, N, 13.92. Found: C, 43.52; H, 3.76; N, 13.78.

7-Chloro-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (10). A solution of 7-chloro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (**5**, 3.5 g, 8.15 mmol) in methanolic ammonia (80 ml, saturated at 0°) was allowed to stand at room temperature overnight. The volume was reduced to about 35 ml, and the solution was decolorized with carbon and chilled. The colorless crystals that separated were collected and dried to afford 1.98 g (81%): mp 192°; $[\alpha]^{25}D$ −40.06° (c 1.0, Me_2SO); uv, ir, and ^1H NMR identical with those of **10** prepared as above.

7-Chloro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (9). 2,2-Dimethoxypropane (0.5 ml) and 70% perchloric acid (0.5 ml) were added to dry acetone (120 ml). The mixture was protected from moisture and stirred at room temperature for 5 min before 7-chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**10**, 0.40 g, 1.33 mmol) was added in one portion. The mixture was stirred for 3 hr and pyridine (0.5 ml) was added. The volume was reduced to about 15 ml, 10% aqueous potassium carbonate solution (15 ml) was added, and the remaining acetone was removed. Cold water (15 ml) was added to the aqueous solution, which was then left at 5° overnight. The crystals that deposited were collected and recrystallized from aqueous ethanol to yield 0.34 g (73%) of **9**: mp 191–192°; $[\alpha]^{25}D$ −29.5° (*c* 1.0, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 1.36 (s, CH_3), 1.59 (s, CH_3), 6.13 (d, *J* = 3.5 Hz, C_1·H), 6.88 (s, C_8H), 7.82 (d, *J* = 2.5 Hz, C_3H), 7.93 (d, *J* = 2.5 Hz, C_2H); uv λ_{max} (pH 1) 249 nm (ε 2.7), 292 s (7.9), 302 (8.9), 314 s (6.2); λ_{max} (pH 7) 253 nm (ε 4.1), 304 (11.4), 313 s (10.0); λ_{max} (pH 11) 253 nm (ε 3.4), 304 (9.8), 313 s (9.3).

Anal. Calcd for $C_{14}H_{16}ClN_3O_5 \cdot 0.5H_2O$ (350.75): C, 47.93; H, 4.88; N, 11.98. Found: C, 48.14; H, 4.52; N, 11.96.

7-Chloro-1-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)imidazo[1,2-*c*]pyrimidin-5-one (19). Isopropylidenation of 7-chloro-1-α-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**11**, 0.40 g, 1.33 mmol) according to the procedure as described for **9** furnished 0.28 g (60%) of **19** after recrystallization from aqueous ethanol as needles: mp 202°; $[\alpha]^{25}D$ −45.8° (c 1.0, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 1.28 (s, 6 H of 2 CH_3, *J* = 0.0 Hz), 6.34 (d, *J* = 5.1 Hz, C_1·H), 6.87 (s, C_8H), 7.72 (d, *J* = 2.3 Hz, C_3H), 7.78 (d, *J* = 2.3 Hz, C_2H); uv λ_{max} (pH 1) 249 nm (ε 4.4), 292 s (13.5), 301 (15.5), 313 s (10.7); λ_{max} (pH 7) 252 nm (ε 6.3), 303 (17.4), 312 s (15.7); λ_{max} (pH 11) 252 nm (ε 5.3), 303 (16.8), 312 s (15.3).

Anal. Calcd for $C_{14}H_{16}ClN_3O_5 \cdot 0.5H_2O$ (350.75): C, 47.93; H, 4.88; N, 11.98. Found: C, 48.17; H, 4.45; N, 11.99.

1-β-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (15). 7-Chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**10**, 1.6 g, 5.32 mmol) was dissolved in 50% aqueous ethanol (120 ml) containing a few drops of concentrated ammonium hydroxide. To this solution was added 10% palladium on carbon (0.40 g) and the mixture was hydrogenated at 40 psi at room temperature for 1 hr. The mixture was filtered through a Celite pad and washed with hot water (2 × 10 ml). The combined filtrate and washings were concentrated to about 20 ml in vacuo. The white crystalline solid that separated was collected and dried to yield 0.92 g (65%) of **15**. It was recrystallized from ethanol as colorless needles: mp 196–197°; $[\alpha]^{25}D$ −52.4° (c 1.0, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 5.86 (d, *J* = 5.2 Hz, C_1·H), 6.73 (d, *J* = 6.1 Hz, C_8H), 7.84 (d, *J* = 3.0 Hz, C_3H), 7.98 (d, *J* = 3.0 Hz, C_2H), 8.05 (d, *J* = 6.1 Hz, C_7H); uv λ_{max} (pH 1) 244 nm (ε 5.0), 285 s (12.1), 292 (12.3), 305 s (7.9); λ_{max} (pH 7) 251 nm (ε 6.4), 302 (14.9), 309 s (12.8); λ_{max} (pH 11) 251 nm (ε 6.3), 302 (15.5), 309 s (14.1); ir 1645 cm^{-1} (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{13}N_3O_5$ (267.23): C, 49.43; H, 4.90; N, 15.73. Found: C, 49.20; H, 4.78; N, 15.49.

1-α-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (17). 7-Chloro-1-α-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**11**, 1.8 g, 6.0 mmol) was catalytically dehalogenated according to the procedure described for **15** to afford 1.08 g (68%) of (**17**). An analytical sample was obtained by recrystallization from aqueous ethanol: mp 208° dec; $[\alpha]^{25}D$ +63.7° (c 1.0 Me_2SO); ^1H NMR (Me_2SO-d_6) δ 6.26 (d, *J* = 6.5 Hz, C_1·H), 6.67 (d, *J* = 7.1 Hz, C_8H), 7.74 (d, *J* = 2.5 Hz, C_3H), 7.85 (d, *J* = 2.5 Hz, C_2H), 8.01 (d, *J* = 7.1 Hz, C_7H); uv λ_{max} (pH 1) 246 nm (ε 4.4), 283 s (10.9), 292 (11.6), 304 s (7.0); λ_{max} (pH 7) 251 nm (ε 5.5), 300 (13.2); λ_{max} (pH 11) 251 nm (ε 5.9), 301 (14.5); ir 1647 cm^{-1} (C=O of heterocycle).

Anal. Calcd for $C_{11}H_{13}N_3O_5$ (267.23): C, 49.43; H, 4.90; N, 15.73. Found: C, 49.26; H, 5.14; N, 15.65.

7-Amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one (13). A suspension of 7-chloro-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**10**, 1.5 g, 49.9 mmol) in anhydrous methanol–liquid ammonia (3:1, 70 ml) was heated in a sealed steel reaction vessel at 100–105° for 45 hr. The resulting dark solution was evaporated to dryness and the residue was chromatographed on silica gel (250 g) prepacked in ethyl acetate and eluted with solvent E. The band containing the requisite product was collected and evaporated to dryness and the residue was triturated with hot ethanol (30 ml) and refrigerated. The solid was collected and dried to yield 0.89 g (64%) of **13**. A small sample was crystallized from water: mp >300° dec (sinters at 215°); $[\alpha]^{25}D$ −20.4° (c 1.0, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 5.53 (d, *J* = 5.5 Hz, C_1H), 5.62 (s, C_8H), 6.73 (broad, s, NH_2), 7.46 (d, *J* = 2.0 Hz, C_3H), 7.56 (d, *J* = 2.0 Hz, C_2H); uv λ_{max} (pH 1) 265 nm (ε 9.2), 301 (22.1); λ_{max} (pH 7) 293 nm (ε 22.6); λ_{max} (pH 11) 292 nm (ε 22.9): ir 1635 (C=O of heterocycle), 3349 cm^{-1} (NH_2).

Anal. Calcd for $C_{11}H_{14}N_4O_5$ (282.25): C, 46.80; H, 4.99; N, 19.85. Found: C, 46.56; H, 4.82; N, 19.60.

1-β-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-Monophosphate (16). Freshly distilled phosphorus oxychloride (0.80 g) and trimethyl phosphate (8 ml) were cooled to <5° in an ice-bath. Dry 1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**15**, 0.80 g, 3 mmol) was added all at once. The mixture was stirred at 0–10° until solution was complete (35 min), and then refrigerated at 3° for 4.5 hr. The reaction mixture was poured into ice–water (20 ml) containing sodium bicarbonate (1.0 g), with stirring. The cold solution was kept in an ice bath for 1 hr with occasional stirring, adding solid sodium bicarbonate periodically to keep the pH 5–6. The pH-stabilized solution was extracted with ether (2 × 15 ml) and the aqueous phase concentrated in vacuo until salts began to crystallize. Enough water was added to complete solution, the pH was checked at 6–7, and the solution was applied to a Barneby Cheney[31] charcoal column (80 g). The charcoal was washed with water (4 l.) to remove inorganic salts, and the product was eluted with water–methanol–concentrated ammonium hydroxide (45:45:10). The solution containing the product was concentrated in vacuo, acidified with Dowex 50 (H^+) resin (10 ml), and filtered. The filtrate was frozen and lyophilized to afford 0.105 g (10.0%) of light, fluffy powder: mp >148° dec; $[\alpha]^{25}D$ −30.2° (c 1.0, H_2O); ^1H NMR (D_2O) δ 6.17 (d, *J* = 5.2 Hz, C_1·H), 7.24 (d, *J* = 8.0 Hz, C_8H), 8.00 (d, *J* = 8.0 Hz, C_7H), 8.13 (d, *J* = 1.8 Hz, C_3H), 8.21 (d, *J* = 1.8 Hz, C_2H); uv λ_{max} (pH 1) 244 nm (ε 2.9), 292 (7.8), 305 s (4.8); λ_{max} (pH 7) 249 nm (ε 4.2), 300 (8.7); λ_{max} (pH 11) 249 nm (ε 3.6), 300 (9.9), 309 s (8.7).

Anal. Calcd for $C_{11}H_{14}N_3O_8P$ (347.22): C, 38.04; H, 4.07; N, 12.10. Found: C, 37.74; H, 4.11; N, 11.90.

1-α-D-Ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-Monophosphate (18). 1-α-D-Ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**17**, 0.79, 2.95 mmol) was phosphorylated with phosphorus oxychloride (0.9 g) using trimethyl phosphate (9.5 ml) as the solvent. It was treated as described in **16** to yield 0.125 g (12.2%) of **18**: mp >183° dec; $[\alpha]^{25}D$ +17.2° (c 1.0, H_2O); ^1H NMR (D_2O) δ 6.51 (d, *J* = 6.0 Hz, C_1·H), 7.10 (d, *J* = 8.0 Hz, C_8H), 7.92 (d, *J* = 8.0 Hz, C_7H), 8.01 (d, *J* = 2.5 Hz, C_3H), 8.09 (d, *J* = 2.5 Hz, C_2H); uv λ_{max} (pH 1) 244 nm (ε 3.2), 291 (7.8), 305 s (4.5); λ_{max} (pH 7) 250 nm (ε 3.9), 297 (8.9); λ_{max} (pH 11) 250 nm (ε 3.9), 298 (9.7), 310 s (8.9).

Anal. Calcd for $C_{11}H_{14}N_3O_8P \cdot H_2O$ (365.23): C, 36.17; H, 4.41; N, 11.50. Found: C, 35.80; H, 4.30; N, 11.12.

7-Amino-1-β-D-ribofuranosylimidazo[1,2-*c*]pyrimidin-5-one 5′-Monophosphate (14). Redistilled phosphorus oxychloride (0.80 g) and trimethyl phosphate (8 ml) were cooled to <0° in an ice bath. Dry 7-amino-1-β-D-ribofuranosylimidazo[1,2-c]pyrimidin-5-one (**13**, 0.70 g, 2.48 mmol) was added and the mixture was stirred at 0–5° for 1 hr until solution was almost complete. The mixture was then stored at 3° for 3 hr with occasional agitation. The light brown solution (a small amount of solid remained undissolved) was poured into ice–water (30 ml) containing sodium carbonate (1:1 g) with stirring and external cooling. The mixture was occasionally stirred in an ice bath for 1 hr, and the pH was monitored at 5–6 by adding solid sodium carbonate when needed. The pH-stabilized solution was extracted with ether (2 × 15 ml) and

the aqueous phase was concentrated in vacuo until salts began to crystallize. Enough water was added to complete solution, the pH was adjusted to 6–7, and then the solution was applied to a column containing Dowex 1 × 2 (100–200 mesh, formate form, 40 ml). The resin was washed with water (2 l.) to remove unreacted **13** and the inorganic salts. The compound was obtained by gradient elution (0.1 *M* formic acid to H_2O). The eluent containing the compound was pooled, frozen, and lyophilized to yield 0.24 g (23.5%) of **14**, mp >169° dec. This was slightly impure, so 0.17 g of this product was passed through a column containing the same resin as above (15 ml), to give 0.11 g of pure (**14**) after work-up as above: mp >172° dec; $[\alpha]^{25}D$ −62.9° (*c* 1.0, H_2O); ^1H NMR (D_2O) δ 5.71 (d, J = 5.5 Hz, C_1-H), 7.50 (s, 2 H, C_2H and C_3H); uv λ_{max} (pH 1) 265 nm (ϵ 8.4), 302 (19.4); λ_{max} (pH 7) 293 nm (ϵ 19.9); λ_{max} (pH 11) 292 nm (ϵ 20.3).

Anal. Calcd for $C_{11}H_{15}N_4O_8P \cdot 1.5H_2O$ (389.25): C, 33.94; H, 4.66; N, 14.39. Found: C, 34.14; H, 4.38; N, 14.54.

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Registry No.—**1**, 1074-41-5; **2**, 3289-35-8; **3**, 56817-09-5; **4**, 55662-66-3; **5**, 56817-10-8; **6**, 13035-61-5; **7**, 56817-11-9; **9**, 56817-12-0; **10**, 56817-13-1; **11**, 56817-14-2; **β-12**, 56817-10-8; **α-12**, 56817-15-3; **13**, 56817-16-4; **14**, 56817-17-5; **15**, 56817-18-6; **16**, 56817-19-7; **17**, 56817-20-0; **18**, 56817-21-1; **19**, 56817-22-2; 2,2-dimethoxypropane, 77-76-9; phosphorus oxychloride, 10025-87-3; 7-chloroimidazo[1,2-*c*]pyrimidin-5-one anion, 56817-23-3.

References and Notes

(1) Part of this material was presented at the 170th National Meeting of the American Chemical Society, Chicago, Ill., August 1975, Abstract MEDI-55.

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Pyrimido[4,5-*b*][1,4]oxazines, 8-Oxadihydropteridines[1]

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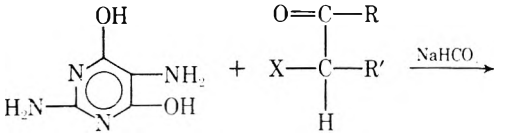
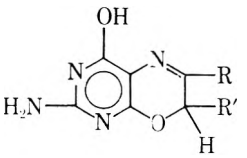
The synthesis and characterization of several 2-amino-4-hydroxy-6- and/or -7-(substituted)pyrimido[4,5-*b*]-[1,4]oxazines (8-oxadihydropteridines) have been accomplished. These compounds are homeosteric analogues of the 7,8-dihydropteridine moiety and were produced by the condensation of 2,5-diamino-4,6-pyrimidinediol and an α-halo ketone. Hydrogenation of the N_5–C_6 double bond in formic acid produced a mixture of cis and trans isomers when both the 6 and 7 positions were substituted. An analysis of their NMR spectra indicated a preference for cis isomer formation.

Homeosteric[2] replacement of the N_8 nitrogen in the pteridine nucleus by oxygen has not been widely studied. However, synthesis of the pyrimido[4,5-*b*][1,4]oxazine (8-oxadihydropteridine) ring system has been accomplished by cyclization of 5-(chloroacetamido)-4-methyl-2,6-pyrimidinediol to give 2,6-dihydroxy-4-methyl-8-oxadihydropteridine.[3,4] More recently, another route has been reported by the reaction of an α-halo ketone and 2,4,5-triamino-6-pyrimidinol to yield 2,4-diamino-8-oxadihydropteridine derivative.[5] Unfortunately, this method often yielded a pteridine as the major product in preference to a 8-oxadihydropteridine derivative. A synthesis of the 8-oxadihydropteridine ring system was then attempted by the condensation of an α-halo ketone and 2,5-diamino-4,6-pyrimidinediol.[1] In con-

trast to previous reported procedures,[5] this route yields unambiguous products, and the physical and spectral proper-





1

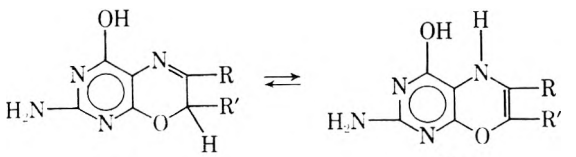
ties of a number of 6- and/or 7-(substituted) analogues have been examined. Since characteristic reactions of this ring system are of interest, several 8-oxadihydropteridines were hydrogenated, and the stereochemistry of the resulting derivatives identified.

Results and Discussion

2-Amino-4,6-pyrimidinediol was produced by the reaction of guanidine with diethyl malonate.[6] Nitrosation of the 5 position under acidic conditions followed by reduction with dithionite gave 2,5-diamino-4,6-pyrimidinediol.[7,8] Condensation of an α-halo ketone and 2,5-diamino-4,6-pyrimidinediol in the presence of sodium bicarbonate yielded 2-amino-4-hydroxy-8-oxadihydropteridine derivatives. Yields varied between 52 and 70%. All of the compounds decomposed around 250°C and were only sparingly soluble in common solvents. The analogues were characterized through elemental analyses, ultraviolet spectra, and nuclear magnetic resonance studies.

Characteristic uv spectra for acid solutions of the 8-oxadihydropteridines possess two major maximum absorption peaks at 264 and 361 nm. Substituent groups at either the 6 or 7 positions did not affect the uv spectra significantly. However, reduction to the corresponding 8-oxatetrahydropteridine resulted in loss of the absorption peak at 361 nm. This is analogous to the spectral properties of 2,6-diamino-4-hydroxy-7,8-dihydropteridine in acid solutions, where maximum absorption peaks at 280 and 330 nm were reported. The corresponding tetrahydropteridine has only one absorption at 280 nm.[9]

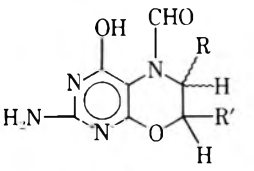
8-Oxadihydropteridines which possess a hydrogen in the 7 position can exist in two tautomeric forms. It has been re-



2 3

ported that form 2 is most favored by 2,4-diamino-8-oxadihydropteridines[5] and the structurally similar pyrimido[4,5-*b*][1,4]thiazines (8-thiodihydropteridines).[10] Both 2-amino-4-hydroxy-6,7-dimethyl-8-oxadihydropteridine (**1a**) and 2-amino-4-hydroxy-6-phenyl-7-methyl-8-oxadihydropteridine (**1e**) possess NMR spectra showing the 7 hydrogen split into a quartet by the adjacent methyl group, and the 7 methyl split into a doublet by the adjacent hydrogen (Table II). Thus, in this case structure 2 also appears to be the preferred isomer at least in trifluoroacetic acid solutions.

The N_5–C_6 double bond readily underwent hydrogenation, and if formic acid was used as a solvent, the N_5 position was concurrently formylated to produce 5-formyl-8-oxatetrahydropteridines.[4]



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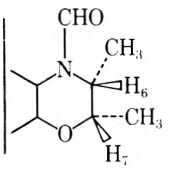
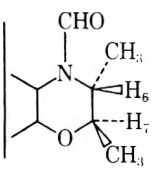
Theoretically, hydrogenation of a 6,7-disubstituted 8-oxadihydropteridine should produce a mixture of cis and trans isomers. If the hydrogen atoms come in from the same side as the 7 substituent, then the trans isomer will be produced, and if they come in from the opposite side, the cis isomer will be produced. However, reaction from the same side should be sterically more difficult and approach from the opposite side might be preferred. Thus, the majority of the hydrogenated product should be cis isomer.



cis

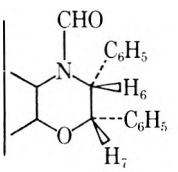


trans

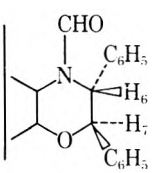
The NMR spectra of 2-amino-4-hydroxy-5-formyl-6,7-dimethyl-8-oxatetrahydropteridine (**4a**) shows four peaks for the 6 and 7 hydrogens. The cis isomer has two at δ 4.16 and 4.84, and the trans isomer has two at δ 3.68 and 4.56. A cis to trans ratio of 70:30 was estimated from the peak areas. For both isomers, the 7 hydrogen, which is closer to the more electronegative oxygen, appears downfield from the 6 hydrogen.

In the cis isomer, the 6 and 7 hydrogens are in an equatorial, axial conformation. The typical coupling constants of cyclohexane hydrogens in this conformation are usually small (i.e., 2–3 Hz).[11] Repulsion between the cis 6 and 7 methyl groups could cause an even greater dihedral angle between the 6 and 7 hydrogens, and from the Karplus relation, coupling constants even smaller than those in cyclohexane could result.[12] Indeed, it appears that the 6 and 7 hydrogens couple to a small degree (ca. <2 Hz) as only quartets were observed at δ 4.16 and 4.84.

In the trans isomer, the 6 and 7 methyls are probably in an equatorial, equatorial conformation, and this means that the 6 and 7 hydrogens will be axial, axial. Cyclohexane axial, axial hydrogens have a large average coupling of about 8–10 Hz,[11] and the 8-oxatetrahydropteridine 6 and 7 hydrogens also exhibit a large coupling (ca. 8–10 Hz) which produces pentuplets at δ 3.68 and 4.56.



cis



trans

The NMR spectra of 5-formyl-6,7-diphenyl-8-oxatetrahydropteridine (**4c**) is much simpler because only two doublets are observed. The 7-hydrogen doublet is at δ 6.10 and the 6-hydrogen doublet is at δ 5.82. Apparently, only cis isomer is formed since the coupling constant observed for each of the doublets was 3.5 Hz. This is consistent with the 6 and 7 hydrogens being in an equatorial, axial conformation, but not the axial, axial arrangement required by the trans isomer.

In a similar manner, the 6-phenyl-7-methyl derivative (**4e**) was found to possess a cis to trans ratio of 60:40, and the 6-methyl-7-phenyl analogue (**4f**) was found to consist

Table I[a]
2-Amino-4-hydroxy-7*H*-pyrimido[4,5-*b*][1,4]oxazines (1)

Compd	No.	Yield, %	Mp, °C	Formula	Uv spectrum: 2 *N* HCl λ_{max}, nm	Log ϵ	2 *N* NaOH λ_{max}, nm	Log ϵ
6,7-Dimethyl-	1a	70	>320	$C_8H_{10}N_4O_2 \cdot H_2O$	267	4.35	268	3.99
					341	4.47	311	3.94
6-Methyl-	1b	65	>320	$C_7H_8N_4O_2 \cdot 2H_2O$	266	3.87	267	3.77
					347	4.05	311	3.71
6,7-Diphenyl-	1c	69	294–296 dec	$C_{18}H_{14}N_4O_2$	258	4.32	279	3.82
					353	4.13	366	3.92
6-Phenyl-	1d	64	303–305 dec	$C_{12}H_{10}N_4O_2$	258	4.16	275	3.71
					391	4.07	361	4.01
6-Phenyl-7-methyl-	1e	59	298–299 dec	$C_{13}H_{12}N_4O_2$	272	4.27	279	3.84
					384	4.37	362	4.32
6-Methyl-7-phenyl-	1f	52	314–316 dec	$C_{13}H_{12}N_4O_2 \cdot {}^1/_2H_2O$	262	4.11	264	3.63
					351	3.87	319	3.46

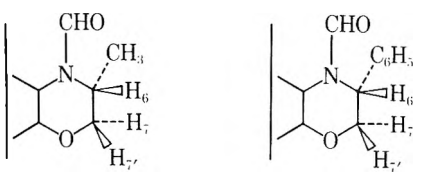
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed in this table.

Table II
NMR Spectra[a] of 2-Amino-4-hydroxy-7*H*-pyrimido[4,5-*b*][1,4]oxazines (1)

Compd	
6,7-Dimethyl- (1a)	δ 1.92 (d, 3 H, 7-CH_3), 2.82 (s, 3 H, 6-CH_3), 5.88 (q, 1 H, –H), 7.90 (s, 2 H, $-NH_2$)
6-Methyl- (1b)	δ 2.70 (s, 3 H, $-CH_3$), 5.62 (s, 2 H, $-CH_2-$), 7.68 (s, 2 H, $-NH_2$)
6,7-Diphenyl- (1c)	δ 2.78 (s, 1 H, –H), 7.82 [m, 12 H, 2($-C_6H_5$), $-NH_2$]
6-Phenyl- (1d)	δ 6.08 (s, 2 H, $-CH_2-$), 7.78 (m, 7 H, $-C_6H_5$, $-NH_2$)
6-Phenyl-7-methyl- (1e)	δ 1.88 (d, 3 H, $-CH_3$), 6.70 (q, 1 H, –H), 8.16 (m, 7 H, $-C_6H_5$, $-NH_2$)
6-Methyl-7-phenyl- (1f)	δ 2.66 (s, 3 H, $-CH_3$), 6.64 (s, 1 H, –H), 7.68 (m, 7 H, $-C_6H_5$, $-NH_2$)

[a] Solvent CF_3COOH.

only of cis isomer. These observed isomer distributions do not appear to have resulted from acid-catalyzed ring opening and ring closing of the reduced product. A sample of 5-formyl-6,7-diphenyl-8-oxatetrahydropteridine (**4c**) dissolved in 97% formic acid showed no appearance of trans isomer over a 24-hr period.



No geometrical isomers are possible in the case of the 6-methyl- or 6-phenyl-5-formyl-8-oxatetrahydropteridines (**4b, 4d**), but the NMR spectra are still informative. The 6, 7, and 7′ hydrogens in the 6-methyl analogue (**4b**) form an $ABCX_3$ system. LAOCOON III computer analysis[13] of the resulting NMR patterns gave the following coupling constants: $J_{6,7} = 8.80$, $J_{6,7'} = 0.01$, $J_{7,7'} = -12.00$, and $J_{6\text{-}CH_3} = 2.40$ Hz.

The 6, 7, and 7′ hydrogens in the 6-phenyl derivative (**4d**) form an ABX system. Computer analysis[13] gave the following coupling constants: $J_{6,7} = 10.00$, $J_{6,7'} = 1.10$, and $J_{7,7'} = -13.10$ Hz. These results support the previous NMR assignments, as the trans 6 and 7 hydrogens have much larger coupling constants than the cis 6 and 7′ hydrogens.

Experimental Section

Melting points were determined in a capillary melting point apparatus and are uncorrected. Uv spectra were determined with a Beckman DB-GT grating spectrophotometer. NMR spectra were carried out on a Jeol PS-100 high-resolution NMR at 100 MHz using tetramethylsilane as internal standard. Microanalyses were performed either by Heterocyclic Chemical Co., Harrisonville, Mo., or Midwest Microlab, Indianapolis, Ind.

α-Halo Ketones. These compounds were purchased from commercial sources except for α-chloro-α-phenylacetophenone, which was synthesized by the procedure of Ward,[14] and 1-chloro-1-phenyl-2-propanone, which was prepared by the procedure of Bordwell and Scamehorn.[15]

2-Amino-4,6-pyrimidinediol. The following synthesis is a modification of a previously reported procedure.[6] Sodium (12.0 g, 0.52 mol) was dissolved in 300 ml of ethanol, guanidine hydrochloride (48.0 g, 0.50 mol) was added, and the solution was filtered. Another sodium ethoxide solution was prepared by dissolving sodium (23.0 g, 1.0 mol) in 500 ml of ethanol, to which was added diethyl malonate (80.0 g, 0.50 mol) and the guanidine solution prepared above. The resulting reaction mixture was heated under reflux for 1 hr. After evaporation to dryness in vacuo, the residue was taken up in water, and the pH adjusted to 6 with acetic acid. The precipitate which formed was filtered, washed with ethanol and ether, and finally dried for 12 hr at 60°C in vacuo: yield 58.0 g, 91.3%; mp >300°C; uv (0.1 *N* HCl) λ_{max} 255 nm (log ϵ 4.03) [Davoll and Laney[16] give uv (0.1 *N* HCl) λ_{max} 256 nm (log ϵ 3.98)].

2,5-Diamino-4,6-pyrimidinediol. The following synthesis is a combination of two previously reported procedures[7,8] with modifications. Finely ground 2-amino-4,6-pyrimidinediol (25.4 g, 0.2 mol) was suspended in a mixture of 300 ml of water, 300 ml of ethanol, and 20 ml of acetic acid. Sodium nitrite (13.8 g, 0.2 mol), dissolved in 50 ml of water, was added in several portions with stirring. The resulting mixture was stirred for an additional 0.5 hr at room temperature, and the reddish nitrosopyrimidine which formed was filtered. The solid was suspended in 400 ml of warm water, heated to 75°C, and sodium dithionite added in small portions until the color of the reaction mixture changed to a light yellow. The suspension was maintained at 70–80°C for 20 min and then cooled in an ice bath. Concentrated sulfuric acid (50 ml) was carefully added and the mixture again cooled. The precipitated pyrimidine hemisulfate was filtered and dried in vacuo overnight. The crude solid was suspended in 100 ml of water, the pH was adjusted to 8 with 2 *N* sodium hydroxide, and the free base was filtered and added immediately to 300 ml of 6 *N* hydrochloric acid. The resulting solution was treated with charcoal and filtered, ethanol (600 ml) was added to the filtrate, and the solution was cooled overnight. 2,5-Diamino-4,6-pyrimidinediol hydrochloride crystallized as white needles which were filtered and dried in vacuo: yield 23.3 g, 59.0%; mp >300°C; uv (2 *N* HCl) λ_{max} 256 nm (log ϵ 4.03) [Bendrich and Clements[17] give uv (0.25 *N* HCl) λ_{max} 253 nm (ϵ not reported)]. The compound gave a strongly positive alkaline phosphomolybdate test, confirming that a 5-amino group was present.[17]

Table III[a]
2-Amino-4-hydroxy-5-formyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines (4)

Compd	No.	Yield, %	Mp, °C	Formula	Uv spectrum: 2 *N* HCl λ_{max}, nm	2 *N* HCl Log ϵ	2 *N* NaOH λ_{max}, nm	2 *N* NaOH Log ϵ
6,7-Dimethyl	4a	89	272–274 dec	$C_9H_{12}N_4O_3$	259	4.01	253	4.31
6-Methyl[b]	4b	85	286–288 dec	$C_8H_{10}N_4O_3 \cdot {}^1/_2H_2O$	258	3.82	249	4.35
6,7-Diphenyl-	4c	86	315–318 dec	$C_{19}H_{16}N_4O_3$	266	3.87	253	4.21
6-Phenyl-	4d	92	273–274 dec	$C_{13}H_{12}N_4O_3 \cdot 2H_2O$	255	4.06	256	4.35
6-Phenyl-7-methyl-	4e	84	310–313 dec	$C_{14}H_{14}N_4O_3 \cdot {}^1/_2H_2O$	261	3.86	256	4.19
6-Methyl-7-phenyl-	4f	85	>320	$C_{14}H_{14}N_4O_3 \cdot {}^1/_2H_2O$	258	4.10	260	4.33

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed in this table. [b] Analytical sample obtained after recrystallization from boiling water.

Table IV
NMR Spectra of 2-Amino-4-hydroxy-5-formyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines (4)

6,7-Dimethyl-[a] (4a)	δ 1.46 [m, 6 H, 2($-CH_3$)]; 3.68 (p, trans isomer), and 4.16 (q, cis isomer) (1 H, 6 hydrogen); 4.56 (p, trans isomer) and 4.84 (q, cis isomer) (1 H, 7 hydrogen); 7.15 (sharp s overlapping broad s, 3 H, $-NH_2$, –CHO)
6-Methyl-[b,c] (4b)	δ 1.65 (d, 3 H, $-CH_3$); 4.20 (m, 1 H, 6 hydrogen), 4.61 (t, 1 H, 7 hydrogen trans to 6 hydrogen); 4.87 (d, 1 H, 7 hydrogen cis to 6 hydrogen); 7.32 (sharp s overlapping broad s, 3 H, $-NH_2$, –CHO)
6,7-Diphenyl-[a] (4c)	δ 5.82 (d, 1 H, 6 hydrogen); 6.10 (d, 1 H, 7 hydrogen); 7.12 [m, 13 H, 2($-C_6H_5$), $-NH_2$, –CHO]
6-Phenyl-[b,c] (4d)	δ 4.90 (AB portion of ABX pattern, 2 H, 7 and 7′ hydrogen); 5.94 (X portion of ABX pattern, 1 H, 6 hydrogen); 7.29 (m, 8 H, $-C_6H_5$, $-NH_2$, –CHO)
6-Phenyl-7-methyl- (4e)[b]	δ 1.08 (m, 3 H, $-CH_3$); 4.26 (m, trans isomer) and 4.59 (m, cis isomer) (1 H, 7 hydrogen); 4.78 (d, trans isomer) and 5.55 (s, cis isomer) (1 H, 6 hydrogen); 7.10 (m, 8 H, $-C_6H_5$, $-NH_2$, –CHO)
6-Methyl-7-phenyl- (4f)[b]	δ 0.92 (d, 3 H, $-CH_3$); 5.00 (m, 1 H, 6 hydrogen); 5.43 (d, 1 H, 7 hydrogen); 7.21 (m, 8 H, $-C_6H_5$, $-NH_2$, –CHO)

[a] Solvent CF_3COOH. [b] Solvent 97% HCOOH. [c] Second-order patterns subjected to LAOCOON III computer analysis.[13]

Anal. Calcd for $C_4H_6N_4O_2 \cdot HCl \cdot 1{}^1/_2H_2O$: C, 23.35; H, 4.90; N, 27.24. Found: C, 23.37; H, 4.70; N, 27.55.

7*H*-Pyrimido[4,5-*b*][1,4]oxazines (8-Oxadihydropteridines) (1). All of these derivatives were synthesized by comparable procedures. Individual physical data and uv spectra are summarized in Table I. 2,5-Diamino-4,6-pyrimidinediol hydrochloride (2.06 g, 0.01 mol) was suspended in a solvent containing 250 ml of water and 250 ml of ethanol. The resulting mixture was heated to reflux and the appropriate α-halo ketone (0.02 mol), dissolved in 25 ml of ethanol, was added dropwise. After 10–15 min sodium bicarbonate (1.68 g, 0.02 mol), dissolved in 25 ml of water, was added dropwise with continued heating. After 6 hr, heating was discontinued and the mixture was cooled overnight. A precipitate formed which was filtered and dried in vacuo. In those instances where no precipitate formed, the reaction mixture was reduced in volume in vacuo to produce a solid product. Ir spectra obtained for the various 8-oxadihydropteridines are all very similar and showed typical maximum absorptions at (Nujol) 3390, 1650, 830, 770, and 660 cm^{-1}. NMR spectra are given in Table II.

Hydrogenation of the 7*H*-Pyrimido[4,5-*b*][1,4]oxazines (4). The reduction procedures used for all of the analogues studied are comparable. Individual physical data and uv spectra are summarized in Table III. The appropriate 8-oxadihydropteridine (0.5 g) was dissolved in 150 ml of 88% formic acid, platinum oxide (10 mg) was added, and the reaction mixture was shaken under hydrogen pressure (50 lb) for 2 hr at room temperature. The catalyst was filtered, the filtrate was concentrated in vacuo, and ether was added. After cooling overnight, the resulting precipitate was filtered and dried in vacuo to give the corresponding 6,7-dihydro-5-formyl-5*H*-pyrimido[4,5-*b*][1,4]oxazine (4). NMR spectra are given in Table IV.

Acknowledgment. This study was supported in part by the Robert A. Welch Foundation (B-342) and the North Texas State University Faculty Research Fund. D.L.D. holds the Samuel R. Noble Foundation Fellowship, 1974–1975. We are indebted to Gary P. Holmes for technical assistance in the preparation of some compounds used in this study.

Registry No.—**1a**, 56830-44-5; **1b**, 56830-45-6; **1c**, 56830-46-7; **1d**, 56830-47-8; **1e**, 56830-48-9; **1f**, 56830-49-0; *cis*-**4a**, 56830-50-3; *trans*-**4a**, 56830-51-4; **4b**, 56830-52-5; **4c**, 56830-53-6; **4d**, 56830-54-7; *cis*-**4e**, 56830-55-8; *trans*-**4e**, 56830-56-9; **4f**, 56830-57-0; 2-amino-4,6-pyrimidinediol, 56-09-7; guanidine hydrochloride, 50-01-1; diethyl malonate, 105-53-3; 2,5-diamino-4,6-pyrimidinediol hydrochloride, 56830-58-1.

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Reaction of 5-Diazouracils with Pyridines

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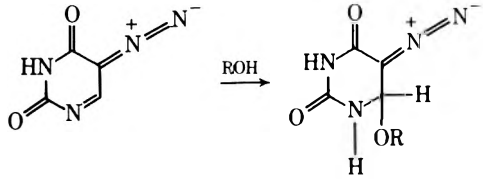
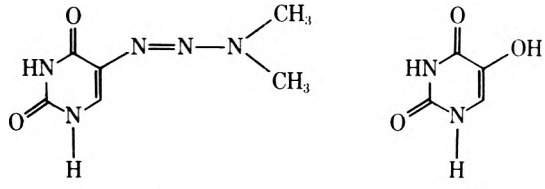
5-Diazouracil reacts thermally with pyridine, methyl isonicotinate, and 4-methoxypyridine to form 2- and 3-pyridyl derivatives of 5-substituted uracils. The ratio of 2:3 substituted pyridyluracils is the same for pyridine and methyl isonicotinate (1:2), while the 3-substituted pyridyluracil is the sole product when 4-methoxypyridine is used. A 5,5′-uracil dimer is a minor product in these thermal reactions. A uracil carbene is suggested as the intermediate in these reactions.

Some of the chemistry of 5-diazouracil (1) has been examined by Townsend and co-workers.[1-3] These researchers have shown that the compound has structure 1 and is readily covalently hydrated, or methanolated to form compounds 2 and 3. Compound 3 reacts readily with dimethyl-



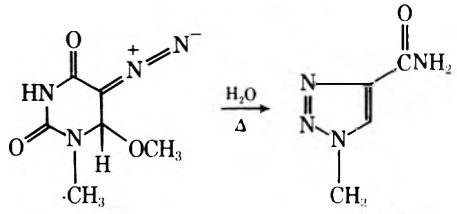
1 2, R = H 3, R = CH_3

amine to form 5-(3,3-dimethyl-1-triazeno)uracil (4) and is converted to compound 5 by aqueous dilute hydrochloric



4 5

acid.[4] The N-methylated compound 6, when heated in water, undergoes a ring contraction to the triazole 7.[3]



6 7

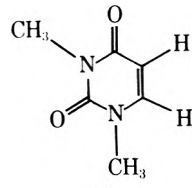
We now wish to describe the thermal reaction of 5-diazouracil (1), its covalently hydrated product (2), and its covalently methanolated derivative 3 with pyridine.

All three of these compounds afforded identical mixtures of isomeric materials (^1H NMR spectral and elemental analyses) analyzing for pyridyluracils and uracil.

When the reaction was done under more concentrated conditions, an additional compound analyzing for a uracil dimer was obtained.

Since it was impossible to separate the mixture of pyridyluracils by either column or high-pressure liquid chromatography, the mixture was treated with diazomethane. The resulting compounds were separated by column chromatography to yield two different dimethyl pyridyluracils, along with some *N,N′*-dimethyluracil (8).

The latter compound was identified by a comparison with an authentic sample. The isomeric dimethyl pyridyluracils may have several possible structures. In order to establish the site of substitution on the uracil ring (9 or 10),



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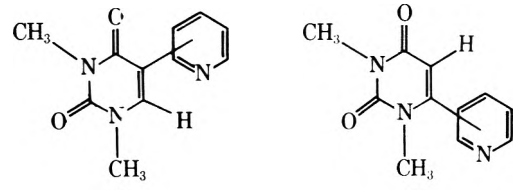
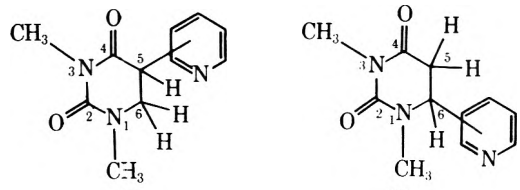


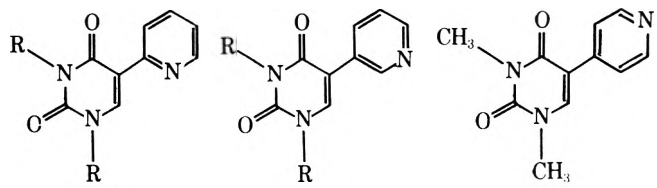
9 10

the compounds were catalytically reduced to dihydro derivatives (11 or 12). If the pyridine ring is at position 5 (structure 9) we would expect the H-5 proton in the dihydro derivative (11) to be subject to facile base-catalyzed H → D exchange, while, if the dihydro derivative 12 were formed, the two protons of C-5 would be subject to base-catalyzed H → D exchange. In fact, only one proton of the dihydro compounds (11a,b) is exchanged for deuterium in the presence of base. This exchange phenomenon is also observed in the dihydro compound 16 where the methylene protons



11 12

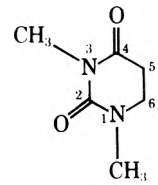
a. α-substituted pyridyl
b. β-substituted pyridyl



13 14 15

13 a, R = H b, R = CH_3

14 a, R = H b, R = CH_3



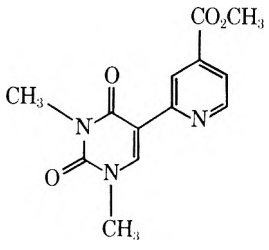
16

at C-5 are readily exchanged by deuterium in the presence of dilute base.[7] Consequently, substitution of the uracil ring at C-5 is confirmed. It now remains to establish the sites of substitution on the pyridine ring (structures **13b, 14b,** and **15** are possible). The ^{1}H NMR spectrum of the compound formed in higher yield (41%, **14b**) has a singlet at τ 2.55 which is no longer present as such in the dihydro derivative (**11b,** see Experimental Section). The remaining spectrum consists of an ABX system (τ 2.04, 2.67, 1.48) as well as a broad singlet at τ 1.34. The coupling constants in a 3-substituted pyridine, e.g., β-substituted picoline, are J_{45} = 6.8–9.1, J_{56} = 4.0–5.7, J_{24} = 0–2.5, and J_{46} = 0–2.5 Hz. The ABX pattern of the above compound has the following coupling constants: J_{45} = 8.0, J_{56} = 4.6, and J_{46} = 2.0 Hz. Thus, not only the multiplicity pattern, but also the coupling constants prove that the major pyridyluracil product obtained in these reactions has structure **14** (a 3-substituted pyridine).

The other pyridyluracil (**13b**), formed in 21% yield, has a ^{1}H NMR spectrum composed of a singlet at τ 1.61 which is no longer present in the dihydro derivative (**11a,** see Experimental Section) and is consequently due to the uracil proton H_6 in structure **13b.** In addition to this singlet, an ABCD pattern is evident (τ 1.65, 2.30, 2.82, 1.50). The various coupling constants are J_{45} = 7.5, J_{56} = 5.0, J_{46} = 1.9, J_{34} = 7.8, J_{35} = 1.3, J_{36} = 1.2 Hz. A comparison of these values with those of α-substituted pyridines, e.g., α-picoline (J_{45} = 6.8–9.1, J_{56} = 4.0–5.7, J_{46} = 0–2.5, J_{34} = 6.8–9.1, J_{35} = 0.5–1.8, J_{36} = 0–2.3 Hz), along with the ABCD pattern itself, identifies the compound as an α-pyridyl derivative (**13b**).

In order to examine the effect that substituents on the pyridine ring have upon the isomer distribution, the thermal reactions of the diazouracil derivative **3** with 4-methoxy- and 4-carbomethoxypyridine were studied. Again, to facilitate isomer separation, the reaction mixture was treated with diazomethane and the resulting *N,N'*-dimethyl derivatives were examined.

In the case of the 4-methyl isonicotinate reaction, two isomeric products were again obtained. Their structures were established by an analysis of their ^{1}H NMR spectra in a manner similar to that described for the pyridyl isomers. Interestingly, while the overall yield of the isomers is less in the 4-methyl isonicotinate reaction, the relative percentages of the 2- vs. the 3-substituted isomers (1:2) (**17** and **18,**



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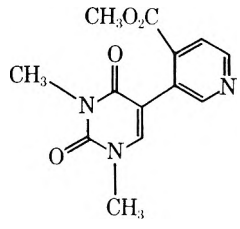

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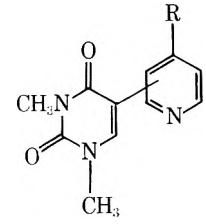
respectively) are the same as in the pyridine instance (**13** and **14**).

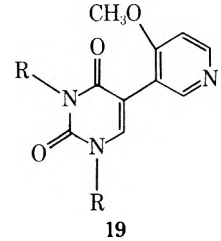
The reaction of **3** with 4-methoxypyridine and methylation of the resulting products with diazomethane afforded, in addition to uracil, a uracil dimer and two compounds, each giving an elemental analysis for $C_{12}H_{13}N_3O_3$. The compound formed in higher yield (**19**) has a ^{1}H NMR spectrum whose major salient feature is the presence of two fairly deshielded protons (τ 1.52, 1.63). The more deshielded of these protons is a broad singlet, while the other is part of an AB system (see Table I). A singlet at τ 2.68 is clearly due to the proton at C-6 of the uracil ring, and has a chemical shift similar to that proton in the 3-pyridyl derivative **14** (τ 2.55). Thus, we can conclude that this compound has structure **19.**

Table I
^{1}H NMR Data of Various Uracil Derivatives[a]



Compd[b]	Chemical shifts, τ					
	H_2	H_3	H_4	H_5	H_6	$H_{6'}$
2-Pyridyl, R = H (13b)		1.65	2.30	2.82	1.50	1.61
3-Pyridyl, R = H (14b)	1.34		2.04	2.67	1.48	2.55
2-Isonicotinate, R = CO_2Me (17b)		1.50		2.31	1.31	2.65
3-Isonicotinate, R = CO_2Me (18b)	1.06			2.27	1.36	1.58
3-(4-Methoxypyridyl), R = CH_3O (19b)	1.63			3.12	1.52	2.68
3-(*N*-Methyl-4-pyridonyl (20)	1.44			3.56	2.28	0.96

[a] Dilute solutions in $CDCl_3$. [b] The chemical shifts of the *N*-methyl protons are 6.50 ± 0.15. The pyridyl proton coupling constants are typical for pyridine derivatives.



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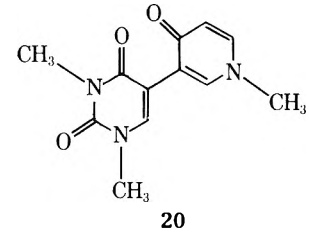
a, R = H
b, R = CH_3

The compound, $C_{12}H_{13}N_3O_3$, formed in lower yield, could also be obtained by sublimation of compound **19.** Thus, one can strongly suggest that it has structure **20.**



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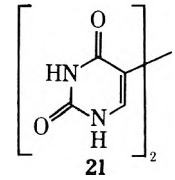
This is confirmed by a comparison of its ^{1}H NMR spectrum with that of *N*-methyl-4-pyridone (see Table I).

The structure of the uracil dimer obtained in this reaction is readily established by the observation that the ^{1}H NMR spectrum shows the presence of only one highly deshielded proton (τ 1.55). Thus, the dimer must be a symmetrical one and have structure **21.**



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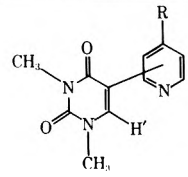
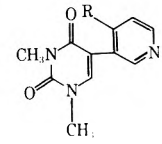
The yields of the various products for the different reactions are given in Table II.

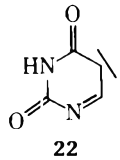
Table II
Product Distribution of Various Pyridyluracils

Reagents	Substituent (R)	Compd	%	Substituent (R)	Compd	%
1, 2, or 3 + pyridine[a]	H	13b	21	H	14b	41
3 + 4-methyl isonicotinate	CO_2Me	17b	4	CO_2Me	18b	8
3 + 4-methoxypyridine	OCH_3		0	OCH_3[a]	19b + 20[a]	20

[a] A small amount of *O*-methylated products (10%) was also obtained. [b] Includes the percentage of *N*-methylpyridone derivative 20 obtained.

The formation of these pyridyluracils can, perhaps, be best explained by assuming the initial formation of the singlet, highly electrophilic carbene **22**.[6] Attack of this species



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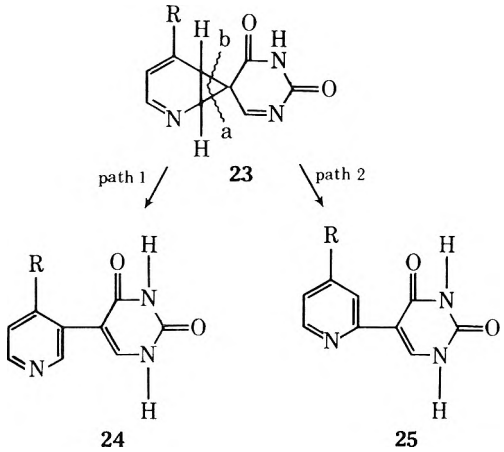
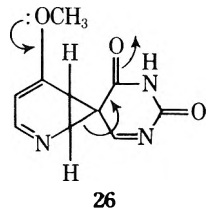
at the C_2–C_3 bond of the pyridines employed in this reaction would generate the intermediate cyclopropane **23**, which can form the 2- or 3-substituted pyridyluracil by either bond b or bond a cleavage, respectively, along with the



24 **25**

appropriate proton transfer to the sp^2-hybridized pyrimidine nitrogen. If R = OCH_3, the substituent will greatly facilitate formation of the 3-pyridyluracils (arrows in **26**). This is again in accordance with the experimental results.



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On the other hand, if R = CO_2CH_3, a deactivation of the C_2–C_3 bond in pyridine toward attack by the carbene (**22**) is to be expected. Thus, the considerably decreased yield when methyl isonicotinate is used instead of pyridine is understandable. If R = CO_2CH_3 in structure **23**, the ratio of paths 1 vs. 2 should not be altered significantly in comparison to the case where R = H. Thus, the observation that the 2:3-substitution ratio is the same when methyl isonicotinate is used as it is in the pyridine instance is consistent with the experimental results.

Experimental Section

The 5-diazouracils **1** and **3** were prepared by the method of Thurber and Townsend.[1] The 5-diazouracil derivative **2** was prepared by recrystallization of compound **3** from 85° H_2O.[5] Pyridine was stored over type 4A molecular sieves.

Ultraviolet spectra were recorded on a Cary 14 spectrometer. Infrared spectra were determined on a Beckman Acculab 3 spectrometer, ^1H NMR spectra were recorded with a Varian HA-100, and mass spectra with a Hitachi Perkin-Elmer RMU-6M instrument. Melting points, determined with a Thomas-Hoover capillary melting point apparatus, are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama.

Reaction of the Diazouracils 1, 2, and 3 with Pyridine. In a typical experiment 1.25 g (~7.5 mmol) of **1**, **2**, or **3** was added to 40 ml of dry pyridine in a round-bottom flask equipped with a magnetic stirrer and reflux condenser. The reaction mixture was refluxed for 4 hr and allowed to come to room temperature. The pyridine was evaporated in vacuo and the residue was triturated with 50 ml of ether. The resulting solid was sublimed at 260° (0.2 Torr), recrystallized from boiling H_2O, and dried in vacuo to give 850 mg (60%) of the 5-pyridyluracils **13a** and **14a**: mp 330–335°; ir (Nujol) 1710 and 1670 cm^{-1} (amide C=O); uv (95% ethanol) λ_{max} 240 and 279 nm. Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.09; H, 3.85; N, 22.18.

Preparation of 1,3-Dimethyl-5-pyridyluracils 13b and 14b. To 800 mg (4.2 mmol) of a mixture of 5-pyridyluracils **13a** and **14a** was added 25 ml of absolute CH_3OH. Excess CH_2N_2 ether solution (0.01–0.02 mol) was added with shaking for 1 hr. The solution was stirred overnight, boiled with charcoal, filtered, and evaporated in vacuo. The residue was chromatographed on neutral alumina (grade III) with benzene–methylene chloride (1:1) to give 180 mg of **13b** (21%), 30 mg of 1,3-dimethyluracil (5%), 370 mg of **14b** (41%), and 90 mg of several O-methylated 5-pyridyluracils (10%). Compounds **13b** and **14b** could be sublimed or recrystallized from benzene–hexane (1:1). Compound **14b**: mp 200–201°; ir (Nujol) 1705 and 1660 cm^{-1} (amide C=O); uv λ_{max} (95% ethanol) 243 nm (ϵ, 4600), 286 (6400); mass spectrum *m/e* (rel intensity) 217 (100), 202 (3), 189 (2), 159 (95), 132 (18), 119 (35), 103 (13). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.15; N, 19.34. Found: C, 60.94; H, 5.22; N, 19.29. Compound **13b**: mp 119–121°; ir (Nujol) 1695 and 1650 cm^{-1} (amide (C=O); uv λ_{max} (95% ethanol) 244 nm (ϵ 10800), 301 (11800); mass spectrum *m/e* (rel intensity) 217 (100), 202 (7), 189 (18), 132 (64), 131 (19), 117 (10). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.15; N, 19.34. Found: C, 60.95; H, 5.16; N, 19.25.

Reduction of the 1,3-Dimethyl-5-pyridyluracils 13b and 14b. In a typical experiment 150 mg (0.7 mmol) of sublimed **14b** was dissolved in 70 ml of 95% ethanol. A catalytic amount of palladium on charcoal was added and the reaction mixture was heated at 50°C under a H_2 pressure of 50 psi for 3 hr in a Paar apparatus. The reaction mixture was allowed to come to room temperature and the excess H_2 removed with a H_2O aspirator. The catalyst was removed by filtration and washed with two 10-ml portions of 95% ethanol and the ethanol was evaporated in vacuo to give an oil which was chromatographed on neutral alumina (grade III) with 1:1 acetonitrile–benzene to give 110 mg (75%) of **11b**. Compounds

11a and 11b were oils that crystallized on long standing. **11b:** ir (Nujol) 1705, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) τ 1.48 (d, 2 H), 2.47 (d, 1 H), 2.74 (q, 1 H), 6.06 (q, 1 H), 6.44 (m, 2 H), 6.88 (s, 3 H), 6.95 (s, 3 H); mass spectrum M^+ 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98. Found: C, 60.55; H, 6.08. **11a:** ir (Nujol) 1705, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) τ 1.47 (d, d, 1 H), 2.36 (1, d, 1 H), 2.78 (m, 2 H), 6.03 (m, 2 H), 6.35 (q, 1 H), 6.80 (s, 3 H), 7.00 (s, 3 H); mass spectrum M^+ 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.19; H, 6.08; N, 19.06.

Reaction of Diazouracil 3 with Methyl Isonicotinate. To 17.40 g (0.12 mol) of methyl isonicotinate was added 1.40 g (8.0 mmol) of diazouracil 3. The stirred reaction mixture was heated at 130° for 2 hr, allowed to come to room temperature, and added to 50 ml of hot H_2O. This suspension was continuously extracted with $CHCl_3$ for 48 hr. The H_2O suspension was evaporated in vacuo and the resulting residue was treated with excess CH_2N_2 in benzene. The resulting solution was treated with charcoal, evaporated in vacuo, and chromatographed on neutral alumina (grade III) with benzene–acetonitrile (9:1) to give 180 mg of **18b** (8%), 90 mg of **17b** (4%), 50 mg of 8 (5%), and mono-O-methylated products (3%). Compound **18b:** mp 233–234°; ir (Nujol) 1730, 1700, 1655 cm^{-1} (C=O); mass spectrum M^+ 275. Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.72; H, 4.76; N, 14.98.

Reaction of Diazouracil 3 with 4-Methoxypyridine. To 10 ml (0.10 mol) of 4-methoxypyridine was added 1.50 g (9.0 mmol) of diazouracil 3. The stirred solution was heated at 130–135° for 3 hr. The crude reaction mixture was allowed to cool and added to 35 ml of hot H_2O. This brown slurry was continuously extracted with $CHCl_3$ for 48 hr. The H_2O suspension was evaporated in vacuo and the resulting solid dried in vacuo at 90°C for 1 hr. This residue showed molecular ions at *m/e* 222, 219, and 112. The residue was transferred with a small amount of CH_3OH and methylated with excess CH_2N_2–benzene. After shaking for 1 hr and standing overnight, the reaction mixture was treated with charcoal and chromatographed on neutral alumina (grade III) with benzene–acetonitrile progressing to ethanol to give 170 mg of 8 (13%), 290 mg of **19b** (13%), 140 mg of **20** (7%), 25 mg of **21b** (2%), and mono-O-methylated products (5%). In addition, some *N*-methyl-4-pyridone was also obtained. Compounds **20** and **21b** could be sublimed but **19b** partially (40–50%) rearranged to **20** on sublimation. Compound **19b:** mp 175° dec; ir (Nujol) 1695, 1655 cm^{-1} (C=O); mass spectrum M^+ 247. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.02; H, 5.42; N, 17.15. Compound **20:** mp 257–260°; ir (Nujol) 1685, 1645, 1555 cm^{-1} (C=O); mass spectrum M^+ 247. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.18; H, 5.35; N, 16.91. Compound **21b:** mp 254–256°; ir (Nujol) 1695, 1650 cm^{-1} (C=O); mass spectrum M^+ 278. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.75; H, 5.08; N, 20.18.

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Registry No.—**1**, 2435-76-9; **2**, 38099-09-1; **3**, 35124-90-4; **11a**, 56817-24-4; **11b**, 56817-25-5; **13a**, 56817-26-6; **13b**, 56817-27-7; **14a**, 56817-28-8; **14b**, 56817-29-9; **17b**, 56817-30-2; **18b**, 56817-31-3; **19b**, 56817-32-4; **20**, 56817-33-5; **21b**, 7033-42-3; pyridine, 110-86-1; methanol, 67-56-1; methyl isonicotinate, 2459-09-8; 4-methoxypyridine, 620-08-6.

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Carbon-13 Fourier Transform Nuclear Magnetic Resonance Spectroscopy of Indolo[2,3-*a*]quinolizidines. Specific Deuteration and Relaxation Methods in Structure Assignments[1]

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The carbon-13 chemical shifts of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**), confirmed by selective deuteration, and the observed chemical shift differences between trans and cis C/D quinolizidine ring fusion in the 2-*tert*-butyl derivatives (**2** and **3**) are discussed in terms of steric compression and electronic effects. A two-bond deuterium-induced ^{13}C relaxation effect on the signal of nonprotonated carbons is observed and used for chemical shift assignments. The spin-lattice relaxation (T_1) times of **1** are an independent means of assigning chemical shifts, especially for nonprotonated carbons, and the results show that all of the carbons in **1** are relaxed primarily by the dipolar mechanism.

The past five years have seen enormous advances in the application of carbon-13 NMR spectroscopy to the structure elucidation and analysis of organic molecules.[6] Included in this array of compounds are plant indole alkaloids, which have recently been examined[7] by ^{13}C NMR, using the signal assignment techniques[6] of selective and off-resonance decoupling, lanthanide chelation, spectral comparison, and chemical shift considerations.

We wish to report a ^{13}C NMR study of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine[8] (**1**) (*Dracontomelum mangiferum*) using the techniques of carbon deuteration[9] and spin-lattice relaxation times[7b,10] to assign chemical shifts and to study relaxation pathways, and to report a study of the effect of ring conformation on the ^{13}C chemical shifts in the 2-*tert*-butyl derivatives **2** and **3**,[11] which have trans and cis C/D ring fusions, respectively.

The synthetic accessibility[8b] of **1** and its deuterated[8b,12] and alkyl[11] derivatives makes this alkaloid ideal for a ^{13}C NMR study as a simple model for the general class of *Corynanthe-Yohimbe* indole alkaloids.

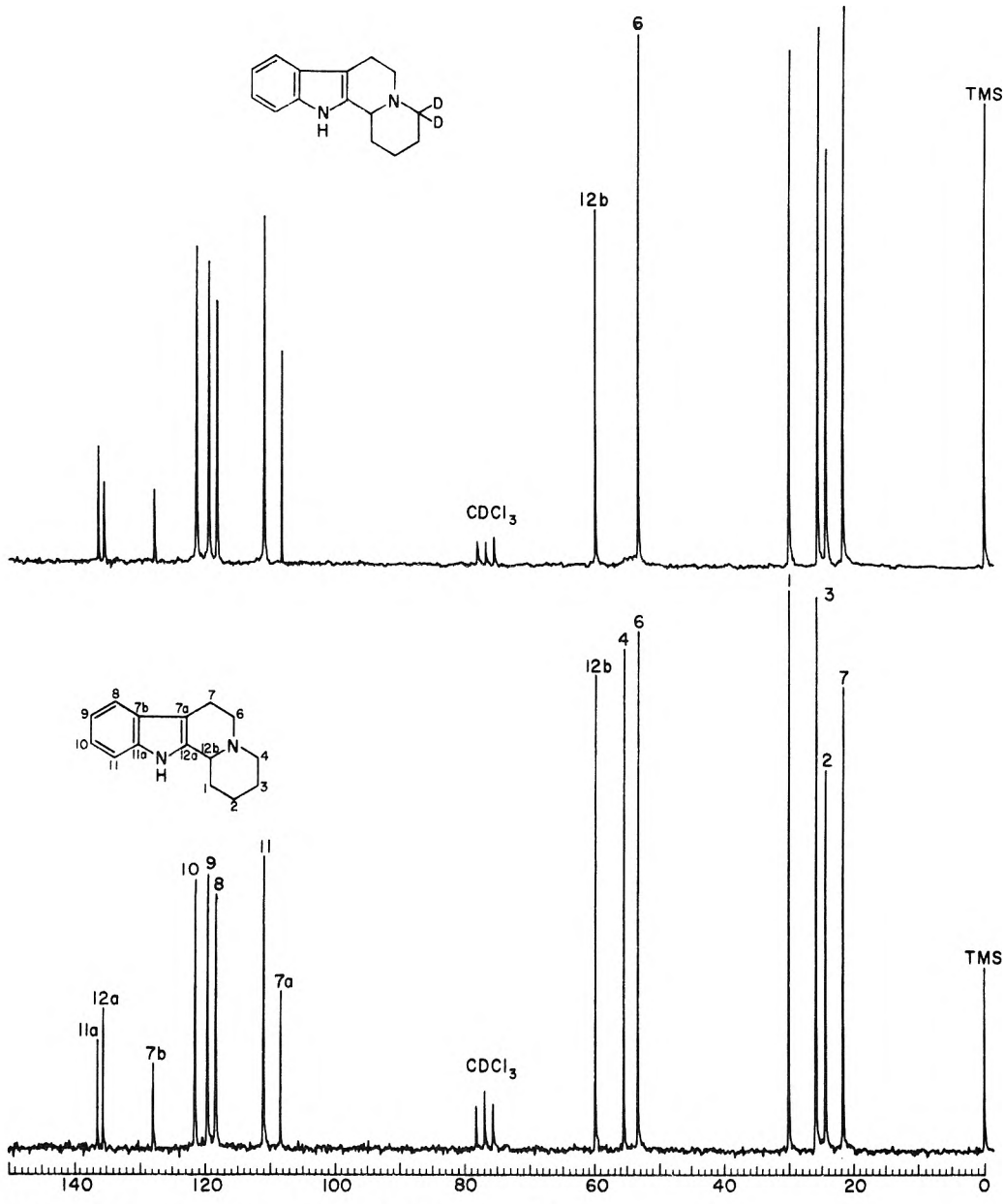


Figure 1. 25.2-MHz ^{13}C FT NMR spectrum of **1** (bottom) and **1**-*4*-d_2 (top) in $CDCl_3$.

1

2 (12bα-H; cis)
3 (12bβ-H; trans)

Results and Discussion

Chemical Shifts. 1 and Deuterated Derivatives. The fully proton-decoupled pulse and Fourier transform ^{13}C spectrum of **1** is shown in Figure 1 and the chemical shifts of **1** and the deuterated derivatives **1**-*1*-d_2, **1**-*3*-d_2, **1**-*4*-d_2, **1**-*6*-d_2, **1**-*7*-d_2, **1**-*12b*-d_1, and **1**-*9*-d_1 are tabulated in Table I.[13,14]

The methylene (C-1, C-2, C-3, C-4, C-6, C-7) and methine (C-12b) carbons corresponding to the seven well-separated upfield signals (Figure 1) can be unambiguously assigned in the order of increasing chemical shift, C-7 < C-2 < C-3 < C-1 < C-6 < C-4 < C-12b because complete replacement of hydrogen by deuterium on a carbon atom causes that ^{13}C signal to disappear. This follows from the increased spin-lattice relaxation time (T_1) of the deuterated carbon,[9a] which under typical short pulse intervals of 0.4–0.8 sec leads to saturation of the signal. One also expects increased complexity and decreased intensity from ^{13}C–D splitting and a decreased nuclear Overhauser effect.

The chemical shifts of the nondeuterated carbons are unchanged except for the carbons adjacent to the deuterated ones which show a uniform upfield shift of −0.1 to −0.2 ppm. This agrees with the reported second-atom deuterium shifts in deuteriobenzenes.[9d,15] For example, in **1**-*7*-d_2 the signal for C-6 is shifted upfield (−0.11 ppm) while that for C-4 remains essentially unchanged (+0.03). In **1**-*4*-d_2 the signal for C-3 is shifted upfield by −0.20 ppm. In **1**-*3*-d_2 both C-2 (−0.16 ppm) and C-4 (−0.09 ppm) are more shielded than nonflanking carbons. It is interesting to note that in **1**-*1*-d_2 not only are the two flanking carbons, C-2 (−0.21 ppm) and C-12b (−0.08 ppm), shifted upfield, but so is C-12a (−0.15 ppm), which represents a large third-atom deuterium shift.

The unusual feature of the seven-signal aliphatic portion

Table I
^{13}C Chemical Shifts of 1 and Deuterated Derivatives[a]

Carbon	1	1-*1*-d_2	1-*3*-d_2	1-*4*-d_2	1-*6*-d_2	1-*7*-d_2	1-*12b*-d_1	1-*9*-d_1
1	29.96	*b*	29.95	29.96	29.82	29.94	29.75	30.11
2	24.31	24.10	24.15	24.29	24.24	24.31	24.24	24.44
3	25.74	25.69	*b*	25.54	25.66	25.73	25.68	25.87
4	55.75	55.75	55.65	*b*	55.62	55.77	55.53	55.75
6	53.51	53.57	53.57	53.46	*b*	53.40	53.35	53.53
7	21.62	21.61	21.63	21.66	21.35	*b*	21.55	21.77
12b	60.27	60.19	60.28	60.22	60.11	60.26	*b*	60.27
8	118.06	118.00	118.11	118.08	117.94	118.09	118.10	117.97
9	119.31	119.39	119.35	119.31	119.16	119.29	119.38	*b*
10	121.20	121.19	121.24	121.19	121.04	121.19	121.28	121.15
11	110.75	110.80	110.75	110.79	110.72	110.74	110.94	110.76
7a	108.11	108.12	108.12	108.11	107.91	*c*	108.00	108.28
7b	127.59	127.56	127.55	127.63	127.47	127.54	127.32	127.86
11a	136.08	136.14	136.07	136.18	136.05	136.03	135.89	136.41
12a	135.24	135.09	135.20	135.33	135.23	135.23	135.33	135.44

[a] In $CDCl_3$ solution (except 1-*12b*-d_1, which was in $CDCl_2CDCl_2$). Chemical shifts downfield from Me_4Si in parts per million, ±0.03–0.05 ppm. [b] A low-intensity multiplet could sometimes barely be discerned. [c] The signal is very weak (see text).

of the ^{13}C spectrum of 1 is the high field position of C-7, appearing at higher field than what one might predict for a benzylic-type methylene carbon. This pronounced shielding, which is also seen in the ^{13}C spectra of 3-methylindole[16] and o-alkylanilines,[17,18] probably reflects the increased electron density at the (enamine) carbon C-7a in 1, and the cyclohexene-like half-chair conformation of ring C (vide infra).

The remaining six aliphatic ^{13}C chemical shifts are consistent with those reported for simple piperidines.[7h,19] The downfield position of C-1 relative to C-3 is due to the β effect[20] of C-12a. Carbon 6 is found to be more shielded than C-4. This is probably due in part to the half-chair conformation of ring C, which introduces eclipsing[26,27] between C-6 protons and C-7 protons. This effect is analogous to the shielding observed[21] (−4.3 ppm) for the methylene carbons in *cis*-1,4-di-*tert*-butylcyclohexane, which exists in a twist–boat conformation with eclipsed methylene groups. Likewise, C-4 in cyclohexene (−4.7 ppm) and cyclopentane (−1.3 ppm) (eclipsed hydrogens) is shielded relative to cyclohexane (staggered hydrogens).[22]

The four protonated aromatic carbons in 1 are assigned in the order of increasing chemical shift, C-11 < C-8 < C-9 < C-10, based partially on the assignments reported[16] for indole and methyl-substituted indoles, and on the disappearance of the signal at 119 ppm in 1-*9*-d_1. Our assignments for C-9 and C-10 differ from those normally reported for these carbons in indoles[16] and indole alkaloids.[7] We believe that the original assignments[16] for C-5 and C-6 in indoles are incorrect and should be reversed.[23]

The four signals with reduced intensity are assigned to the four nonprotonated carbons in the order of increasing chemical shift: C-7a < C-7b < C-12a < C-11a. The low-field peaks at 135.24 and 136.08 ppm are assigned to the carbons adjacent to the indole nitrogen, C-12a and C-11a, with the lower field signal assigned to the benzene carbon C-11a.[24] This also follows from the shifts observed in pyrroles[25] and indoles.[7a] The distinction between the C-12a and C-11a assignment is confirmed by the results with 2 and 3 and relaxation measurements (vide infra).

The remaining two nonprotonated carbons C-7a and C-7b are assigned to the signals at 108.11 and 127.59 ppm, respectively. The increased electron density in the π orbital on C-7a, due to the enamine character of the indole double bond, accounts for the pronounced shielding of C-7a. An olefinic analogue such as the α carbon in α-methylstyrene absorbs at 142.4 ppm.[26]

A striking feature in the spectrum of 1-*7*-d_2 is the greatly reduced signal for C-7a. We ascribe this to the fact that C-7a is primarily relaxed by the C-7 protons (vide infra) and substitution of deuterium at C-7 leads to a relative saturation of the C-7a signal. The signal for C-7 itself is eliminated by the effect of the directly bonded deuteriums.

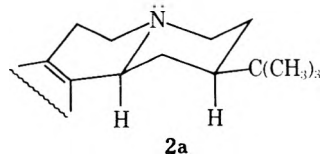
Table II
^{13}C Chemical Shifts of 1, 2, and 3[a]

Carbon	1	2	3	δ (2 → 3)
1	29.96	31.05	28.72	−2.33
2	24.31	46.65	41.03	−5.62
3	25.74	26.72	26.42	−0.30
4	55.75	56.09	50.82	−5.27
6	53.51	53.11	45.83	−7.28
7	21.62	21.76	16.78	−4.98
12b	60.27	60.31	54.30	−6.01
8	118.06	118.14	118.07	−0.07
9	119.31	119.38	119.53	+0.15
10	121.20	121.27	121.52	+0.25
11	110.75	110.79	111.09	+0.30
7a	108.11	108.06	107.61	−0.45
7b	127.59	127.58	127.74	+0.16
11a	136.08	136.12	135.90	−0.22
12a	135.24	135.29	132.85	−2.44
2α		32.4	32.0	−0.4
2β		27.5	27.3	−0.2

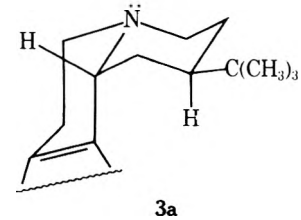
[a] See Table I.

An independent method for identifying nonprotonated carbons is to use two pulse intervals as shown in Figure 2 for 1-*6*-d_2. The short pulse interval effectively suppresses the four nonprotonated carbons C-7a, C-7b, C-11a, C-12a, as well as the $CDCl_3$ and Me_4Si lines (long T_1's) and the CD_2 multiplet. The long pulse interval increases the intensity of the lines of the nonprotonated carbons to the point where they nearly match the intensity of the protonated carbons. The integral trace in Figure 2 shows this clearly.

Chemical Shifts. 2-*tert*-Butyl Derivatives. The ^{13}C chemical shifts of the *cis*- and *trans*-2-*tert*-butyl derivatives of 1 (2 and 3) are tabulated in Table II and the spectra shown in Figure 3. The dominant conformations are **2a** (≥95%) and **3a** (>99.9%).[11] The *tert*-butyl holding group



2a



3a

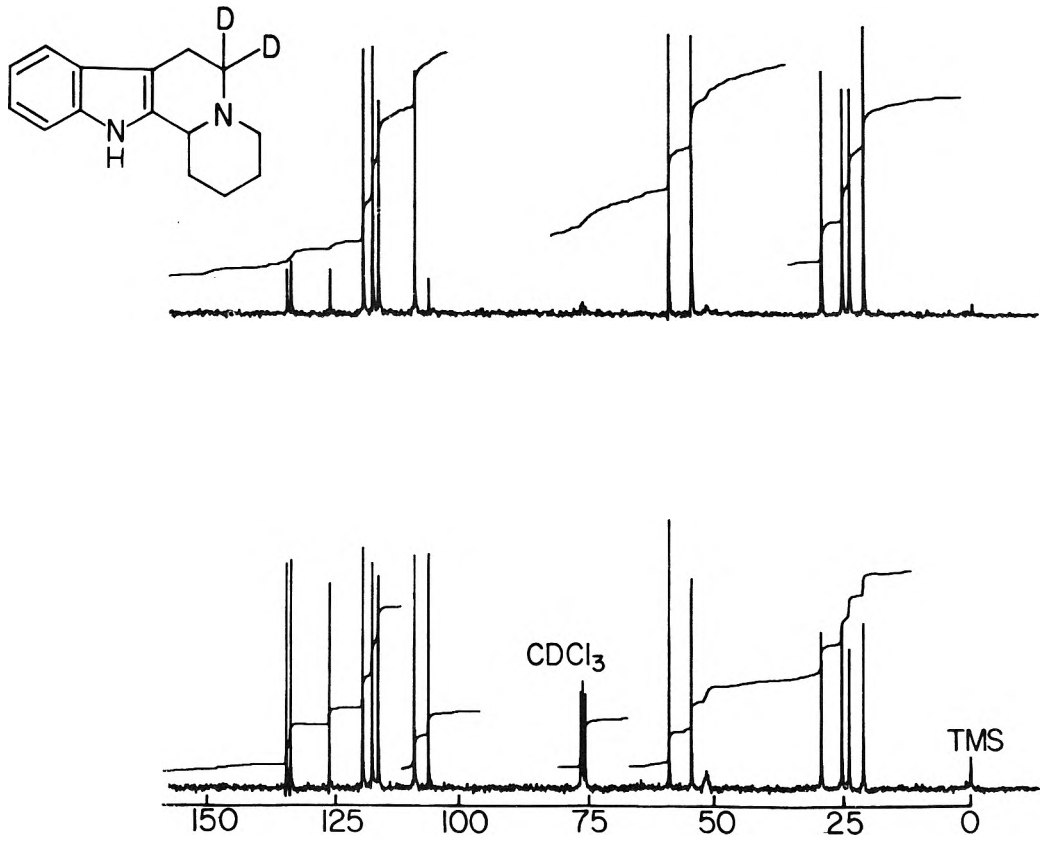


Figure 2. 67.9-MHz ^{13}C FT NMR spectrum of 1-*6*-d_2: (top) 300 90° (34 μsec) pulses, repetition time 1 sec; (bottom) 120 90° pulses, repetition time 20 sec. Each spectrum 15 kHz, 16K transform.

allows one to study the effect of C/D ring fusion on ^{13}C chemical shifts without itself perturbing the ^{13}C spectrum, since a *tert*-butyl group largely affects only the directly attached carbon (α effect).[21]

The chemical shifts of the six benzene carbons (C-7b, C-8, C-9, C-10, C-11, C-11a) show virtually no change in **1**–**3**, and the chemical shifts of the *tert*-butyl group carbons, C-2α and C-2β, are very similar in **2** and **3**.

In general, the other carbons in **1** and **2**, which both have a trans C/D ring fusion,[11] have the same chemical shift (Table II). The only exceptions are C-2 in **2**, which experiences an α effect of the *tert*-butyl group of +22.34 ppm (downfield), and C-1 and C-3, which each experience the β effect of a *tert*-butyl group of +1.09 and +0.97 ppm, respectively. The corresponding α and β effects of the *tert*-butyl group on a cyclohexane ring are +21.2 and +0.5 ppm, respectively.[21]

The remaining carbons in the C and D rings (C-4, C-12b, C-6, C-7, C-7a, C-12a) show little chemical shift differences between **1** and **2**, perhaps indicating the absence of significant ring distortion induced by the *tert*-butyl group.

In contrast, the cis-fused system **3** shows striking chemical shift differences in the ^{13}C spectrum (Table II). The signals for C-3 in **2** and **3** are essentially the same, as expected, since the immediate steric environments of the C-3 protons are the same in each isomer. However, C-4, C-6, C-7, and C-12b are all shifted upfield in the spectrum of **3**: −5.27, −7.28, −4.98, and −6.01 ppm, respectively. A Dreiding model of **3** shows a 1,4-gauche interaction between the C-4 axial proton and the C-7 pseudoaxial proton (~1.7–1.8 Å), leading to shielding of both carbons. By comparison, the reported steric-induced shielding of the 3,5 ring carbons in axial-methyl cyclohexanes (γ_a effect) is −5.4 ppm,[28] and the empirically derived shift is calculated to be −5.24 ppm (r_{HH} = 1.88 Å).[27]

The upfield shift of −2.33 ppm for C-1 in **3** relative to **2** perhaps reflects the difference between an equatorial and an axial effect (−3.7 ppm in methylcyclohexanes),[28] and a steric compression between the equatorial C-1 proton and the N–H (~2.4 Å) in **3**.

The upfield shifts of C-2, C-4, and C-12a (−5.62, −5.27, and −2.44 ppm) in **3** relative to **2** may be partially due to steric compression[27,28] between the axial C-2 and C-4 protons and the indole π orbital on C-12a ($r_{HC} \simeq 2.5$ Å). This specific shielding of C-12a in **3** provides an independent method for distinguishing it from C-11a and from the other nonprotonated carbons.

It is difficult to rationalize the upfield shifts of C-6 and C-12b (−7.28 and −6.01 ppm, respectively) in terms of steric compression, since no significant interaction appears to be present in **2** or **3** involving these protons. Therefore, the shielding of C-6 and C-12b in **3** relative to **2** may be due in part to a reduction in overlap between the nitrogen lone pair and the antibonding orbital of an adjacent axial C–H bond—an interaction in trans-fused quinolizidines such as **2** that has been suggested to account for both infrared "Bohlmann bands" [11,29a] and the shielding of protons that are trans diaxial to a nitrogen lone pair.[11,29] Thus, in **2** the carbons α to the nitrogen (C-6, C-12b) may actually be *deshielded* relative to **3** which does not have protons on C-6 and C-12b trans diaxial to the nitrogen lone pair.[30]

Relaxation Studies. The spin-lattice relaxation times (T_1) and the nuclear Overhauser effects (NOE) were measured for all of the carbons in **1** and for the unsaturated carbons in **1**-*7*-d_2 and **1**-*12b*-d_1 (Table III).

The T_1 values for all of the protonated carbons in **1** are found to be less than 1 sec. The NOE's are found to be close to the maximum theoretical value (η = 1.988), and therefore the dominant mechanism for the relaxation of the protonated carbons is clearly the ^{13}C–^{1}H dipolar–dipolar mechanism.[31] The methylene carbon T_1's are all approximately 0.3 sec, about twice as fast as the methine carbon

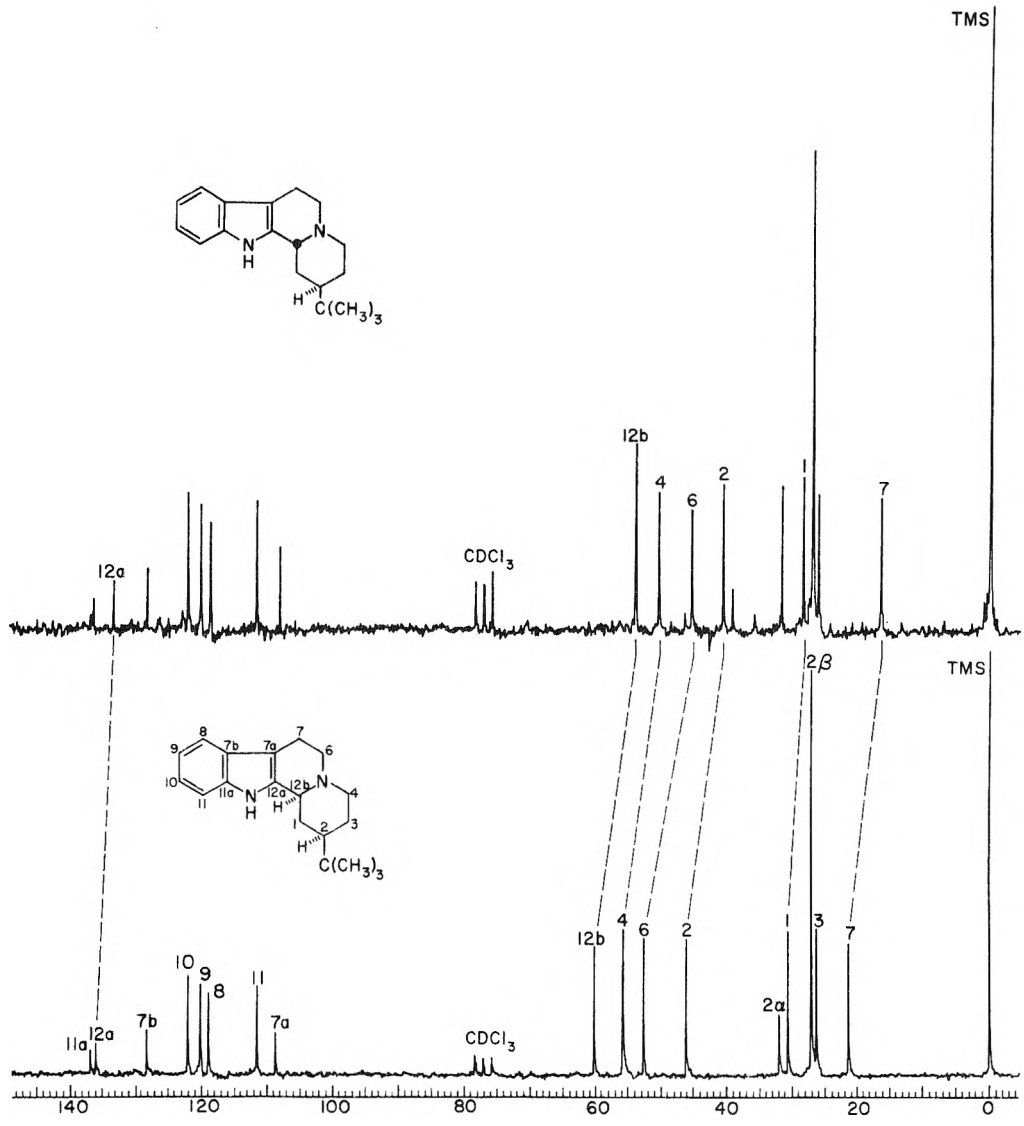


Figure 3. 25.2-MHz ^{13}C FT NMR spectrum of **2** (bottom) and **3** (top) in $CDCl_3$.

Table III
Spin-Lattice Relaxation Times for 1, 1-7-d_2 and 1-12b-d_1[a]

	1					
Carbon	T_1	NOE (η)	T_1^{DD}	T_1^{DD} (calcd)	1-7-d_2 T_1	1-12b-d_1 T_1
1	0.31					
2	0.32					
3	0.31					
4	0.28					
6	0.30					
7	0.31					
12b	0.67					
8	0.60	2.0			0.77[b]	0.75[b]
9	0.52	2.0			0.77[b]	0.75[b]
10	0.54	2.0			0.77[b]	0.75[b]
11	0.60	1.8			0.77[b]	0.75[b]
7a	7.7	1.8	8.5	12	~22	9.9
7b	10.2	1.7	11.9	25	~22	12.1
11a	7.0	1.5	9.3	18	14.6	9.7
12a	5.7	1.6	7.6	11	12.2	11.2

[a] All T_1's in sec (±10–15%), determined at 25.2 MHz and 38°C. [b] T_1's ±10–20%.

T_1's (Table III), indicating that the molecule is undergoing largely isotropic molecular motion.[31,32]

The NOE's for the four nonprotonated carbons indicate that those carbons are also largely relaxed by the dipolar mechanism involving nearby protons. This is also the case in other large molecules such as cholesteryl chloride,[32] mescaline,[31] and codeine,[7b] where overall molecular motion is slow. The T_1^{DD} contribution to the T_1^{obsd} can be calculated[31] from eq 1, where η is the observed NOE. These values are shown in Table III.

$$T_1^{DD} = T_1^{obsd} \frac{1.988}{\eta} \quad (1)$$

The longer T_1's for the protonated carbons in 1-7-d_2 and 1-12b-d_1 result from solution viscosity effects. The two specifically deuterated samples were run at significantly lower concentrations; the lower viscosities of the solutions resulted in more rapid molecular tumbling. The ratios 0.77/0.56 and 0.75/0.56 (≈1.4) correspond to the differentials for molecular tumbling.

The large increase in T_1 for the nonprotonated carbons in 1-7-d_2 (e.g., 22 sec for C-7a and C-7b, Table III) clearly implicates the protons on C-7 as those responsible in part for relaxing C-7a, C-7b, C-11a, and C-12a by the dipolar mechanism. As would be predicted, the closest nonprotonated carbon to C-7, C-7a, is affected more than the other carbons and, in fact, its signal disappears completely with normal pulse intervals (vide supra). Likewise, the T_1 values for 1-12b-d_1 indicate that the C-12b proton relaxes C-12a more than C-7a and that C-7b and C-11a are not appreciably relaxed by this proton.

We have measured the distances from the four nonproto-

nated carbons to nearby protons (≤4.0 Å) using Dreiding models and have calculated[31-33] (eq 2) the T_1^{DD}'s using $\tau_c = 7.8 \times 10^{-11}$ sec (calculated using the average T_1 from the 11 protonated carbons and $r = 1.09$ Å). These calculated T_1^{DD}'s (Table III) are in only fair agreement with T_1^{DD}, as might be expected from the sensitivity of T_1^{DD} to the internuclear distance and to τ_c, but the parallel nature of the two sets of values (C-7b > C-11a > C-7a > C-12a) is informative. Thus, one can immediately distinguish C-11a and C-12a, which have very similar chemical shifts, from the different relaxation times due to their local environment (C-11a has two protons within 3 Å whereas C-12a has six protons within 3 Å).

$$\frac{1}{T_1^{DD}} = \frac{h^2}{2\pi}\gamma_H^2\gamma_C^2\sum_i r_{CH_i}^{-6}\tau_c \qquad (2)$$

These results show that (1) deuterium substitution, when synthetically convenient, is a powerful tool for assigning ^{13}C chemical shifts to directly bonded carbons as well as to adjacent carbons (two-bond deuterium isotope effect[15]), (2) the striking chemical shift differences between trans and cis C/D ring fusion (**2** and **3**) allows ^{13}C NMR to be used as a method for establishing the stereochemistry of unknown indole or quinolizidine alkaloids, and (3) spin-lattice relaxation times, coupled with deuterium substitution, are a powerful probe for chemical shift assignments, especially for nonprotonated carbons, for which other techniques (e.g., the various proton decoupling methods) are not generally useful.

Experimental Section

Compounds. The syntheses of **1**, **1**-*3*-d_2, **1**-*4*-d_2, **1**-*6*-d_2, **1**-*7*-d_2, **1**-*12b*-d_1, **2**, and **3** have been described.[8b,11,12]

1,1-Dideuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**-*1*-d_2) was prepared from *N*-[2-(3-indolyl)ethyl]-2-piperidone[34] by a seqence involving K_2CO_3-catalyzed deuterium exchange,[12] $POCl_3$ cyclization,[34] and $NaBH_4$ reduction.[8b,11,12]

9-Deuterio-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**-*9*-d_1) was prepared from 5-bromoindole by a sequence involving *n*-butyllithium–D_2O (5-deuterioindole), oxalyl chloride–ammonia–$LiAlH_4$ (5-deuteriotryptamine), and glutaraldehyde–$NaBH_4$.[8b]

NMR Spectra. Carbon-13 Fourier transform spectra (0.1–0.5 *M* $CDCl_3$ with added Me_4Si as an internal chemical shift reference) were run on a Varian XL-100-15 NMR spectrometer at 25.2 MHz, except for **1**-*6*-d_2 and **1**-*9*-d_1, which were run on a Bruker HX-270 spectrometer at 67.9 MHz. In general, 8K free induction decays (FID's) were acquired over spectral widths of 5 kHz. Some spectra were obtained with short (≤1 sec) pulse intervals while other spectra were acquired using pulse intervals of 4–10 sec; in both cases the H_1 pulse widths used were <90°.

Spin-Lattice Relaxation Measurements. Carbon-13 T_1's were determined by the inversion-recovery pulse sequence as modified by Freeman and Hill.[35] T_1 measurements were separately performed on the aliphatic and unsaturated carbon regions, because the available H_1 field was not large enough to allow T_1 measurements over 4–5 kHz. T_1's were determined from semilogarithmic plots in the usual way.[31,35] No sample degassing was used since ^{13}C T_1's <10 sec are not significantly affected by 0.2 atm of O_2. T_1's reported in this study of 10–20 sec include minor contributions from dissolved air.

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Registry No.—**1**, 4802-79-3; **1**-*1*-d_2, 56817-44-8; **1**-*3*-d_2, 51263-49-1; **1**-*4*-d_2, 51263-50-4; **1**-*6*-d_2, 51263-51-5; **1**-*7*-d_2, 51263-52-6; **1**-*9*-d_1, 56817-45-9; **1**-*12b*-d_1, 34388-09-5; **2**, 40587-68-6; **3**, 40587-69-7; *N*-[2-(3-indolyl)ethyl]-2-piperidone, 38199-31-4; 5-bromoindole, 10075-50-0.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Charge-Transfer Complexes[1a]

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High-resolution ^{13}C pulse Fourier transform nuclear magnetic resonance has been used to study the effects of charge-transfer complexation between trinitrobenzene (1) and aromatic donor molecules: benzene (2), mesitylene (3), naphthalene (4), and anthracene (5). Plots of the chemical shifts of the donor carbons as a function of acceptor concentration allows the ready determination of the association constants, K_{AD}, and the bound shifts of the donor carbons in the pure 1:1 complexes, Δ_0. The Δ_0 values so obtained indicate that diamagnetic ring anisotropy and transfer of charge are as phenomenologically important to ^{13}C as to ^1H NMR for aromatic molecules.

There has been an upsurge of interest in molecular complexes of the donor–acceptor type during the last two decades,[2] because of the pronounced electronic changes induced in both donor and acceptor moieties, their unusual physical properties, and the possible importance of charge-transfer complexation to the interactions of biological systems. Whereas the geometries of a substantial number of complexes in the solid state are known from X-ray diffraction data, relatively little is known about their structures in solution. ^1H and ^{19}F nuclear magnetic resonance have been demonstrated to be important methods for the study of molecular complexation in solution,[3] because these techniques provide a simple way for obtaining information on complex composition and thermodynamic data on complex formation equilibria by using the Hanna–Ashbaugh–Foster–Fyfe (HAFF) equation or modification thereof.[4] Much important information has been obtained by these techniques, but they are, for the most part, applicable to simple symmetric systems, and not to the study of larger unsymmetrical donors and acceptors, because of the inherent complexity of the ^1H and ^{19}F NMR absorptions. It has long been recognized that ^{13}C NMR investigations could be important in this connection, as the chemical shifts at all unique positions of a complex donor or acceptor molecule could be determined simultaneously; however, the low sensitivity of carbon magnetic resonance signals and the difficulty in obtaining accurate measurements of small chemical-shift changes has thus far made such studies difficult. The recent advent of pulsed Fourier transform NMR spectrometers has helped to alleviate these difficulties and permitted a study of the 1:1 charge-transfer complexes of the strong acceptor 1,3,5-trinitrobenzene (1) with benzene (2), mesitylene (3), naphthalene (4), and anthracene (5) acting as donor molecules. All of these complexes have been previously well characterized by investigations utilizing other techniques.[2]

Experimental Section

The carbon-13 spectra were taken with our Brukarian[5] DFS-60 pulse Fourier transform modified spectrometer operating at 15.09 MHz with field stabilization via internal deuterium lock, and with full proton noise decoupling. The temperature was maintained at 28.5° with a Bruker B-ST 100/700 temperature controller.

The solvents, ethylene dichloride and chloroform, were MCB "spectroquality", as was the benzene and mesitylene, and were used without further purification. The naphthalene (MCB), anthracene (MCB), and 1,3,5-trinitrobenzene (Eastman) were recrystallized to constant melting point each of which was in accord with literature values.

The sample concentrations were prepared to four-digit accuracy in a 10-mm tube fitted with a vortex plug and a 3-mm coaxial insert filled with D_2O to establish the deuterium lock.

The carbon-13 chemical shifts in each case were measured in hertz relative to the major constituent of the solvent which was demonstrated to be affected less than ±0.1 Hz over the entire concentration range of added trinitrobenzene. This procedure was superior to the use of a small amount of an internal reference such as tetramethylsilane, $CHCl_3$, or CCl_4, as the induced shifts of the reference were quite large (0.4–0.8 Hz).

Results and Discussion

There are several detailed accounts of how to relate nuclear magnetic resonance chemical shifts under conditions of fast exchange to the thermodynamic properties of complexation, the most common treatment utilizing the so-called HAFF equation,[2,3,4] and these will be given only very limited attention here. Because in ^{13}C studies we are primarily interested in the variation of chemical shifts of the donor species with increased acceptor concentration, the opposite situation of nearly all the reported ^1H or ^{19}F NMR studies, we have utilized the inverse of the derived HAFF expression. Thus, for a 1:1 molecular complex AD

$$K_{AD} = \frac{[AD]}{[A][D]} \text{ and } \frac{\Delta}{[A]} + \Delta K_{AD} = \Delta_0 K_{AD}$$

where Δ is the donor chemical shift observed (δ_{obsd}) minus the chemical shift of the uncomplexed donor (δ_0), and Δ_0 is the chemical shift of the donor in the pure 1:1 complex relative to δ_0. Thus, a plot of Δ vs. $\Delta/[A]$ for a given resonance will be a straight line with $-K_{AD}$ as the slope, and Δ_0 (the chemical shift of the resonance in the pure 1:1 complex) as the intercept under the condition that $[A] \gg [D]$.

The advantage of the ^{13}C technique over ^1H and ^{19}F lies in the ability to determine multiple resonances in symmetrical or unsymmetrical donors simultaneously so that we could obtain multiple equiparallel data sets. To analyze these data mathematically, we have set up equations for determining the best fit of the slope (m) and intercepts (b_j) for $j = 1$ to n in a series of n parallel sets of data. If the measured values of the ordinate and coordinate are $y_i^{(j)}$ and $x_i^{(j)}$, respectively, and the best predicted value of the ordinate is $\bar{y}_i^{(j)}$, then we may write

$$\bar{y}_i^{(j)} = m x_i^{(j)} + b_j$$

where the parallel slopes are all given by a single value for m, and the various intercepts by b_j. If k_j is the number of data points in each subsets j, and n is the number of subsets, then the best values for m and b_j may be obtained using standard least-squares techniques. Defining the sum of squares of the deviations from perfect fit as

$$\delta = \sum_j^n \sum_i^{k_j} (y_i^{(j)} - \bar{y}_i^{(j)})^2$$

and minimizing with respect to $m, b_1, b_2, \ldots, b_n$ yields $n + 1$ simultaneous equations of the following form.

Table I
Δ ^{13}C Chemical Shift Values for 0.333 *M* Benzene, Mesitylene, and Naphthalene as a Function of 1,3,5-Trinitrobenzene Concentration

Trinitrobenzene, mol l.$^{-1}$	Benzene,[a,b] Δ, Hz		Mesitylene,[a,b] Δ, Hz		Naphthalene,[b,c] Δ, Hz	
0.667	C_1	+2.0	C_1	+1.0	C_9	+6.3
			C_2	+2.5	C_1	+3.1
			CH_3	+3.5	C_2	−2.1
1.000	C_1	+2.8	C_1	+1.5	C_9	+8.3
			C_2	+3.5	C_1	+4.1
			CH_3	+4.5	C_2	−2.5
1.333	C_1	+3.6	C_1	+2.0	C_9	+9.4
			C_2	+4.3	C_1	+4.8
			CH_3	+5.5	C_2	−2.9
1.667	C_1	+4.4	C_1	+2.5	C_9	+10.5
			C_2	+5.0	C_1	+5.6
			CH_3	+6.5	C_2	−3.2
2.000	C_1	+4.8	C_1	+3.0	C_9	+12.0
			C_2	+5.5	C_1	+6.0
			CH_3	+7.5	C_2	−3.2
2.333	C_1	+5.3	C_1	+3.4	C_9	+12.6
			C_2	+6.0	C_1	+6.6
			CH_3	+8.0	C_2	−3.2

[a] In CH_2ClCH_2Cl at 28.5°. [b] Positive shifts are to higher field. [c] In 9:1 $CHClCH_2Cl$–$CHCl_3$ at 28.5°.

$$\frac{\partial\delta}{\partial m} = 0 = \sum_j^n \sum_i^{k_j} x_i^{(j)} (y_i^{(j)} - m x_i^{(j)} - b_j)$$

$$\frac{\partial\delta}{\partial b_1} = 0 = \sum_i^{k_1} (y_i^{(1)} - m x_i^{(1)} - b_1)$$

$$\frac{\partial\delta}{\partial b_2} = 0 = \sum_i^{k_2} (y_i^{(2)} - m x_i^{(2)} - b_2)$$

$$\vdots \qquad \vdots$$

$$\frac{\partial\delta}{\partial b_n} = 0 = \sum_i^{k_n} (y_i^{(n)} - m x_i^{(n)} - b_n)$$

Solving for m, and the n different b_j's yields

$$m = \frac{\sum_j^n \sum_i^{k_j} (x_i^{(j)} y_i^{(j)}) - \sum_j^n \left(\sum_i^{k_j} y_i^{(j)}\right)\left(\sum_i^{k_j} x_i^{(j)}\right)\Big/ k_j}{\sum_j^n \sum_i^{k_j} (x_i^{(j)})^2 - \sum_j^n \left(\sum_i^{k_j} x_i^{(j)}\right)^2 \Big/ k_j}$$

$$b_j = \frac{\left(\sum_i^{k_j} y_i^{(j)}\right) - m\left(\sum_i^{k_j} x_i^{(j)}\right)}{k_j}$$

for each j set of data. The standard deviation (σ) of the fit is given for

$$N = \sum_j n_j$$

total pieces of data is:

$$\sigma = \frac{\delta}{N - n - 1}$$

where $(N - n - 1)$ is the number of degrees of freedom not used to set the $n + 1$ parameters ($m, b_1, b_2, \ldots, b_n$). These equations have been incorporated in a computer program for rapid analysis of the ^{13}C chemical shift data.

The ability to utilize this type of analysis is crucial for the carbon resonances exhibiting relatively small shifts as the parallelization procedure can give reasonably accurate b_j values for a given subset, even though the error for that subset is much larger than in the other subsets, and in addition, the error in K_{AD} is clearly lower than what is achievable from measurement of a single resonance.

Table II
Δ ^{13}C Chemical Shifts and Δ/[A] Values for 0.167 *M* Anthracene as a Function of 1,3,5-Trinitrobenzene Concentration

TNB[A], mol l.$^{-1}$	Δ, Hz		Δ/[A], Hz l. mol^{-1}
0.333	C_{11}	+6.2	18.60
	C_1	+5.3	15.90
	C_9	+3.9	11.70
	C_2	−4.5	−13.50
0.500	C_{11}	+7.9	15.80
	C_1	+6.5	13.00
	C_9	+5.1	10.20
	C_2	−5.4	−10.80
0.667	C_{11}	+9.2	13.80
	C_1	+7.5	11.25
	C_9	+5.8	8.70
	C_2	−6.4	−9.60
0.833	C_{11}	+10.1	12.12
	C_1	+8.4	10.08
	C_9	+6.4	7.68
	C_2	−6.8	−8.16
1.000	C_{11}	+11.1	11.10
	C_1	+9.2	9.20
	C_9	+7.0	7.00
	C_2	−7.4	−7.40
1.167	C_{11}	+11.8	10.11
	C_1	+9.8	8.40
	C_9	+7.3	6.26
	C_2	−7.8	−6.69
1.333	C_{11}	+12.4	9.30
	C_1	+10.0	7.58
	C_9	+7.6	5.70
	C_2	−8.4	−6.30

The chemical-shift assignments are well documented for these molecules.[6] A discrepancy with the early values reported[7] for anthracene was discovered, but this has subsequently been corrected in the literature.[8]

Table I contains the carbon-13 chemical-shift differences (Δ) for 0.333 *M* solutions of the donor molecules, benzene (**2**), mesitylene (**3**), and naphthalene (**4**), as a function of the acceptor concentration [A] of 1,3,5-trinitrobenzene (**1**), relative to the chemical-shift values of 0.333 *M* solutions in the absence of **1**, at 28.5°. Because of the relative insolubility of anthracene (**5**), similar experiments were performed at 0.167 *M* anthracene concentration and in a 2:1 mixture of $CHCl_3$–CH_2ClCH_2Cl at 28.5°. The results of these experiments are recorded in Table II. Positive values of Δ refer to shifts to higher field (shielding) and negative values refer to shifts to lower field (deshielding).

A typical plot of Δ, the observed ^{13}C chemical shifts vs. Δ/[A] is given in Figure 1 for 0.167 *M* solutions of 1,3,5-trinitrobenzene concentration [A]. The lines have the slopes (m) and intercepts (b_j) obtained from the least-squares computer analysis of the data. It is apparent from Figure 1 that the K_{AD} values are extremely well determined from the slope of the ^{13}C data, and the extrapolations from the data points to intercepts yield very reliable values for Δ_0.

The first thing to be noted from Tables I and II is that the induced chemical shifts due to charge-transfer complexation are reasonably large, even for the weak complex between benzene and trinitrobenzene. A second, and perhaps more important, observation is that for donors with

Table III
Maximum Observed Shifts, Δ_{max}, Calculated Shifts for the Pure Complexes, Δ_0, and Association Constants, K_{AD}, for 1,3,5-Trinitrobenzene Donor Complexes at 28.5°

Donor	Solvent		Δ_{max}, Hz	Δ_0, Hz	K_{AD}, l. mol^{-1}
Benzene	CH_2ClCH_2Cl	C_1	+5.3	+15.9	0.22
Mesitylene	CH_2ClCH_2Cl	C_1	+3.4	+6.3	0.37
		C_2	+6.0	+13.0	
		CH_3	+8.0	+17.0	
Naphthalene	9:1 CH_2ClCH_2Cl–$CHCl_3$	C_9	+12.6	+20.2	0.69
		C_1	+6.6	+10.3	
		C_2	−3.2	−5.9	
Anthracene	2:1 $CHCl_3$–CH_2ClCH_2Cl	C_{11}	+12.4	+17.7	1.64
		C_1	+10.1	+14.7	
		C_9	+7.6	+11.1	
		C_2	−8.4	−12.1	

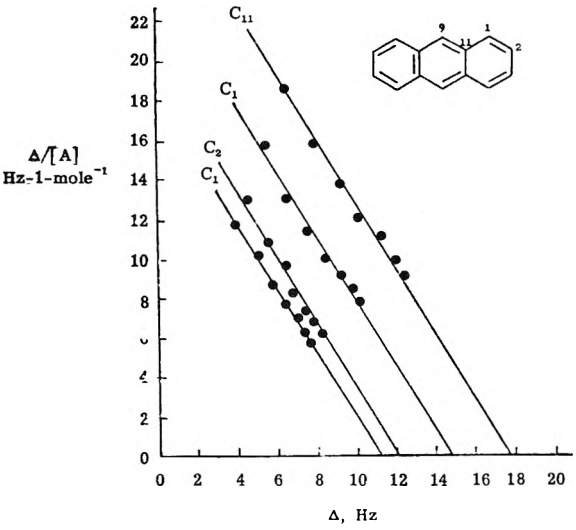

Figure 1. A plot of Δ vs. Δ/[A] for 0.167 *M* anthracene as a function of 1,3,5-trinitrobenzene concentration. The *negative* Δ shifts for C_2 have been reflected into the *positive* quadrant.

magnetically different carbons, the corresponding resonances gave distinct differential shifts, which opens up possibilities for obtaining information on the magnitude of aromatic shieldings and charge-transfer effects, the preferred sites of interaction, and spacings between donor–acceptor pairs.

For **2** and **3**, positive shifts (shielding) are observed at all carbon resonances, as is the case in the proton NMR of all known simple benzenoid complexes,[2b] and commonly attributed to the predominance of ring-current induced diamagnetic shielding effects from the opposing benzene ring in the favored equiplanar geometry. With the polycyclics, **4** and **5**, similar effects are observed, except for the peripheral C-2 carbons, which display negative shifts. A similar feature had been noted previously for ^{1}H NMR studies of **4** and **5** in which the α H's were shifted upfield to a greater extent than the β H's at high trinitrobenzene concentrations.[2b]

The maximum observed shifts, Δ_{max}, the mean values of the association constant, K_{AD}, and the chemical shifts of the carbons in the pure 1:1 complexes, Δ_0, computed from the data in Tables I and II by the least-squares procedure, are summarized in Table III. The association constants obtained in the present study are in accord with those obtained by optical[9] and ^{1}H NMR[3b,10,11] measurements when the effects of solvent and temperature are considered. For example, K_{AD} for the complex of **1** and **3** in CH_2ClCH_2Cl at 33.5° from ^{1}H NMR[11] is 0.26 l. mol^{-1} compared to our 0.37 l. mol^{-1} at 28.5°. The magnitude of the association constants K_{AD} is **5** > **4** > **3** > **2** with trinitrobenzene, as expected on the basis of donor strength,[2b] and this series correlates directly with the HMO energies of the highest filled molecular orbitals.

The large differential chemical shifts Δ_0 obtained for a particular donor species suggests considerable sensitivity of ^{13}C NMR to the effect of charge transfer as well as diamagnetic anisotropy which, judging from the small variations in acceptor Δ_0 values obtained, is presumably the predominant effect in ^{1}H NMR.[2b] The negative shifts observed at C-2 of **4** and **5** are not well explained by the shielding arguments previously proposed,[2b] as these positions are well within the shielding cone of the acceptor molecule at the distances and geometries involved in complexation.[12,13,14] This phenomenon may be best ascribed to the predominance of the opposing charge-transfer effect at these positions and the apparent tendency to transfer charge more effectively from the extremities of the donor molecules.

The ability to completely describe the shielding parameters for 1,3,5-trinitrobenzene should allow for separation and quantitization of these two opposing effects.

Acknowledgment. We are pleased to acknowledge the assistance of Dr. Stefan Berger in writing the computer program, and for stimulating discussions regarding this work.

Registry No.—**1**, 99-35-4; **2**, 71-43-2; **3**, 108-67-8; **4**, 91-20-3; **5**, 120-12-7.

References and Notes

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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Chemical and Carbon-13 Proton Couplings in Some Esters and Ethers.[1]

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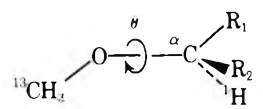
Carbon-13 chemical shifts and three- (or more) bond ^{13}C–proton couplings have been obtained for a variety of alkyl ethers and esters. The results have been interpreted on the basis of preferred rotational conformations.

The current availability of commercial spectrometers has made the measurement of carbon chemical shifts relatively routine. Thus, in unpublished work, we have compiled from the literature carbon chemical-shift data for nearly 2000 compounds on molecular fragments, and the current explosion of published ^{13}C data appears to make the task of continually updating this compilation quite impossible.

Despite the interest in carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy, the complete assignment of resonances remains one of the most difficult problems faced by the users of this method, and the application of carbon chemical-shift information to problems of structure elucidation and conformational analysis has, as a result, been relatively limited.

The measurement of relaxation times (T_1) for carbon nuclei is now becoming quite common, even for rather large molecules.[2] The unique information regarding molecular motions which can be derived from such measurements promises to give increasing importance to T_1 measurements in the future. Other techniques, notably the measurement of nuclear Overhauser enhancements,[3] will doubtless also provide much valuable information to organic chemists who seek to understand the structure and conformations of molecules.

In the present paper, we report some preliminary results regarding the measurement of geminal and vicinal carbon–proton couplings, and the application of such coupling data to problems in acyclic conformational analysis. A review[4] of the literature shows that a surprising number of measurements of these coupling constants have been made. Although their counterparts in proton–proton coupling commonly provide extensive and useful information about structure and conformation, few systematic investigations of vicinal and geminal carbon–proton couplings in other than aromatic systems[5] have appeared.[6] Frequently, these couplings are described as "long-range", thereby implying that they are small. In fact, their magnitudes are commonly comparable to those of the analogous proton–proton couplings and are easily measured with modern ^{13}C NMR spectrometers. In view of this, we have begun an extensive investigation of the measurement of carbon–proton couplings and report here some aspects of vicinal carbon–proton coupling, leaving the geminal cases for a later, more general, discussion. Our primary interest was the investigation of the earlier report[7] of a dihedral dependence of this coupling. More recently, the dihedral dependence of vicinal carbon–proton coupling has been verified in other laboratories, and the variation has been described as being similar in form to that of the analogous proton–proton coupling.[8] Our approach has been to study systems in which geminal coupling would be absent, thus facilitating the measurement of vicinal coupling. We therefore initiated our study with a survey of *O*-methyl ethers. Examination of **1** suggests that the dihedral angle θ should be, to at least



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some extent, dependent on the character and bulk of R_1 and R_2. By studying the vicinal coupling between the *O*-methyl carbon and the α proton as a function of R_1 and R_2, we sought to understand its dependence upon dihedral and substituent effects. During the course of this work it became clear that it was frequently possible to measure the vicinal coupling between the α carbon and the *O*-methyl protons, even though this situation was complicated by the presence of geminal and, in some cases, other vicinal couplings. This finding allowed the extension of this research to include a number of related compounds, including a selection of esters and cyclic ethers.

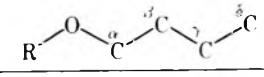
The measurement of splittings in proton-coupled spectra are rather more difficult than taking carbon spectra with full proton decoupling. For this reason, we have made some attempts to correlate carbon chemical-shift changes with conformational effects which influence the couplings. An earlier effort to correlate carbon chemical shifts of *O*-methyl ethers with conformation has been described for somewhat more complicated systems.[9]

Experimental Section

Carbon chemical shifts were measured in 1,4-dioxane or cyclohexane solutions under conditions of full proton decoupling with a digital frequency-sweep spectrometer described previously.[10] Chemical shifts were subsequently referred to external carbon disulfide on the basis of the chemical shifts of 1,4-dioxane and cyclohexane relative to that reference (126.2 and 166.2 ppm, respectively). They can be reasonably accurately converted to the Me_4Si scale by subtracting them from 192.8 ppm.

Proton-coupled carbon-13 spectra were measured with the same spectrometer, using neat solutions and internal proton lock. Several experiments using varied internal lock power had no effect on the spacings in the obtained spectra.

Table I
Carbon Chemical Shifts[a] of Selected Ethers and Esters



Registry no.		α	β	γ	δ		R
		A. *O*-Methyl Ethers					
							O-CH
115-10-6	Methyl[b]	133.5					133.5
540-67-0	Ethyl[b]	125.5	178.5				135.6
557-17-5	*n*-Propyl	126.5	171.2	184.1			136.5
628-28-4	*n*-Butyl	120.9	161.3	173.8	179.5		135.4
25154-53-4	1,2-Dimethoxyethane	121.5					135.4
625-44-5	Isobutyl	114.3	165.5	175.0			136.0
1118-00-9	Neopentyl	110.4	162.0	167.4			135.3
598-53-8	Isopropyl[b]	120.6	171.8				138.3
6795-87-5	*sec*-Butyl	115.8	165.1 (CH_2) 175.9 (CH_3)	184.9			137.7
1634-04-4	*tert*-Butyl[b]	121.1	166.3				144.6
		B. Formates					
							CHO
107-31-3	Methyl	143.7					31.9
109-94-4	Ethyl	134.0	79.8				32.4
110-74-7	*n*-Propyl	128.5	171.5	183.7			32.5
592-84-7	*n*-Butyl	130.3	162.7	174.4	180.2		32.7
542-55-2	Isobutyl	124.0	165.6	174.8			32.6
23361-67-3	Neopentyl	120.7	162.1	167.1			32.8
104-62-1	2-Phenylethyl[c]	129.2	158.5				32.3
625-55-8	Isopropyl	172.1	126.5				33.1
589-40-2	*sec*-Butyl	174.3	121.8	164.6	184.3		32.9
762-75-4	*tert*-Butyl	165.4	112.9				33.3
		C. Acetates					
						C=O	CH_3
79-20-9	Methyl	142.9				22.9	174.1
141-78-6	Ethyl	133.7	179.7			23.6	173.5
109-60-4	*n*-Propyl	128.2	171.2	183.5		23.8	173.2
123-86-4	*n*-Butyl	129.7	162.4	174.2	180.1	23.7	173.4
108-21-4	Isopropyl	172.0	126.5			24.3	173.0
540-88-5	*tert*-Butyl	165.6	114.3			24.4	171.7

[a] All chemical shifts measured in parts per million relative to external carbon disulfide. [b] Data from ref 13. [c] Shifts of aromatic carbons: C-1, 55.5; C-2, 3, 5, 6, 64.3, 64.7; C-4, 66.6 ppm.

Table II
Carbon Chemical Shifts[a] of Cyclic Ethers

Compd	C-2	C-3	C-4	C-5	Registry no.
Tetrahydrofuran	125.7	167.7			109-99-9
1,3-Dioxolane	98.5		129.0		505-22-6
1,4-Dioxane	126.2				123-91-1
1,3,5-Trioxane	93.1				111-88-3

[a] Chemical shifts measured in parts per million relative to external carbon disulfide.

Table III
Vicinal Carbon-Proton Coupling Constants of Some Methyl Ethers

Compd	$^3J_{C_YOC_XH}$[b]	$^3J_{C_XOC_YH}$[c]
Dimethyl ether[d]	+5.7	+5.7
Methyl *n*-propyl ether	5.2	3.2
Methyl *n*-butyl ether	5.25	3.1
Methyl isobutyl ether	5.2	3.05
Methyl neopentyl ether	5.3	2.65
Methyl isopropyl ether	5.0	3.85
Methyl *sec*-butyl ether	4.8	4.2
Methyl *tert*-butyl ether	4.0	
1,2-Dimethoxyethane	5.15	1.85
Diethyl ether[e]		3.1

[a] All coupling constants given in hertz. [b] ±0.1 Hz. [c] ±0.05 Hz. [d] Reference 30. [e] Registry no., 60-29-7.

Proton NMR spectra were measured with a Varian A-56/60A spectrometer. Computer programs, used to enhance resolution in NMR spectra, were adapted from programs described elsewhere.[11]

All compounds were of either commercial origin or were prepared by standard procedures and were distilled before use. Methyl ethers were prepared from the corresponding alcohol using dimehtyl sulfate and sodium hydride. Formates were generally prepared from the alcohol and formic acid. Tertiary esters were prepared by the method of Stevens and Van Es.[12]

Results

Carbon chemical-shift data used in subsequent discussion are presented in Tables I and II. All chemical shifts are considered accurate to at least ±0.1 ppm. Data for some of the more common methyl ethers were taken from the literature.[13] Because these published shifts were measured relative to internal carbon disulfide, we have adjusted these data by +0.7 ppm, an increment which has been found to bring data measured in these two ways into accord.

Carbon–proton spin–spin coupling constants are reported in Tables III–V. The convention used in the present paper to designate specific coupling constants is defined in

Table IV
Vicinal Carbon-Proton Coupling Constants[a] in Simple Esters

Ester	$^3J_{C_yOC_xH}$	$^3J_{C_xOC_yH}$
Methyl formate	4.27	4.00
Ethyl formate	4.14	3.32
n-Propyl formate		3.15
n-Butyl formate		3.15
Isobutyl formate		3.10
Neopentyl formate	4.20	2.80
Isopropyl formate	4.25	3.22
sec-Butyl formate		3.45
tert-Butyl formate	0.99	
Methyl acetate[b]		3.83, 3.95[c]
Ethyl acetate		3.20, 3.25[c]
Benzyl acetate[d]		3.40[c]
Neopentyl acetate[e]		2.70[c]
Isopropyl acetate		3.00, 2.90[c]
2,2,4,4-Tetramethyl-3-pentyl acetate[f]		4.60[c]

[a] All coupling constants are in hertz. Experimental uncertainty is approximately ±0.05 Hz. [b] The geminal coupling between the carbonyl carbon and the protons of the adjacent methyl group was approximately 6.9 Hz throughout the acetates. [c] Data taken from ref 35. [d] Registry no., 140-11-4. [e] Registry no., 926-41-0. [f] Registry no., 13432-79-6.

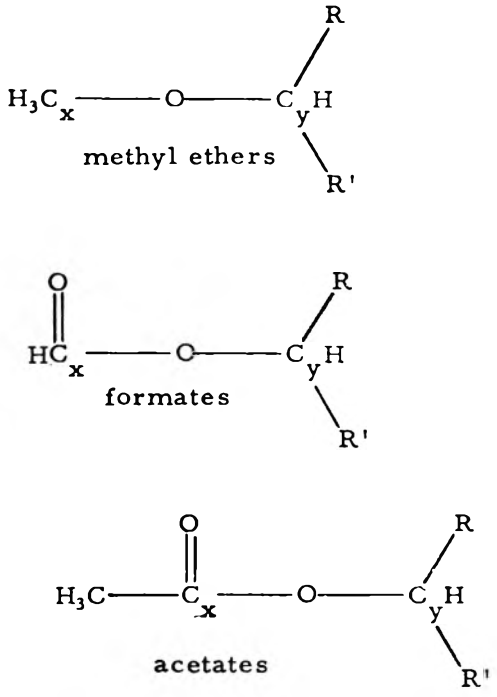


Figure 1. Labeling convention used in this paper in describing carbon-proton coupling. Thus, $J_{C_xOC_yH}$ will represent the coupling constant for the spin-spin interaction between C_x and the proton(s) attached to C_y.

Figure 1. Most of the data in Tables III–V were derived from simple first-order analyses of the proton-coupled ^{13}C NMR spectra. Because the spectrometer sweep and recorder were digitized,[9] side-band calibration was not necessary. The data reported for 1,4-dioxane and for carbons 4 and 5 of 1,3-dioxolane (Table V) were derived from computer analysis using LAOCOON III,[14] and, in some of these cases, it is possible to specify the sign of the coupling constants.

Four- and five-bond proton–proton coupling constants measured in this study are compared with published data in Table VI. It is seen that our values, obtained by resolution-enhancing line-shape and LAOCOON analyses, are in

Table V
Carbon-Proton Coupling Constants in Simple Cyclic Ethers

Compd	Type of coupling	Coupled nuclei ^{13}C	Coupled nuclei ^1H	J, Hz
1,3-Dioxolane	Geminal	4	5	+2.29
	Vicinal	4	2	+3.55
	Vicinal	2	4,5	3.25
1,4-Dioxane	Geminal	2	3	2.16
	Vicinal	2	6	4.23
1,3,5-Trioxane	Vicinal	2	4,6	5.65

Table VI
Long-Range Proton-Proton Coupling in Simple Formates[a]

Formate	Present study $^4J_{HH}$	Present study $^5J_{HH}$	Literature[b] $^4J_{HH}$	Literature[b] $^5J_{HH}$
Methyl	0.86		−0.82	
Ethyl	0.83	0.60	−0.83	0.63
n-Propyl	0.86	0.57	−0.82	0.54
n-Butyl	0.85	0.52	−0.86	0.54
2-Phenylethyl	0.83	0.51		
Isobutyl	0.89	0.42	−0.87	0.42
Neopentyl	0.84			
Isopropyl	1.02	0.51	−1.00	0.52
sec-Butyl	1.01	0.53 (CH_3)	−0.91	0.52 (CH_3)
		0.43 (CH_2)		0.48 (CH_2)
tert-Butyl		0.38		0.40[c]

[a] All coupling constants are reported in hertz. Experimental error is approximately ±0.03 Hz. [b] Unless indicated otherwise, all data are taken from ref 14. [c] Reference 15.

excellent agreement with the previously reported values.[15,16] The only ether which showed a measurable four-bond proton–proton coupling was 1,3-dioxolane, for which $J_{H_2H_4}$ was found to be 0.22 ± 0.04 Hz. For the acetates, we were only able to measure the five-bond boupling between the protons of the acetyl methyl and those on the α carbon for the methyl (J = 0.26 ± 0.03 Hz) and the ethyl (J = 0.20 ± 0.03 Hz) esters. This is again in accord with previously reported data.[17]

Discussion

The Ethers. The conformational behavior of acyclic ethers is generally assumed to be similar to that of the analogous alkanes.[18] Certainly the conformations of dimethyl ether[19] and propane[20] are qualitatively similar, as demonstrated by microwave spectroscopy. In the case of ethyl methyl ether, there exist two conformations, gauche and trans, the latter being more stable by approximately 1.35 kcal/mol.[18,21] Similarly, methyl isopropyl ether shows evidence of two rotamers in the liquid form, one of which, presumably that with two gauche interactions, is only slightly populated.[18] In the present study, then, we shall assume that the general, qualitative conformational characteristics of the acyclic ethers will parallel those of the acyclic alkanes.[22]

We will use here a convenient convention for describing carbon chemical-shift changes in biological molecules.[23] In the past,[24] it has become common to relate the chemical shift of a particular carbon, °C, to the number of substituents introduced at the α, β, γ, and δ positions (cf. Figure 2). Unfortunately, in both biological and organic chemistry, Greek letters are used to specify positions relative to functional groups and the dual usage of these symbols frequently becomes rather confusing. We therefore replace the

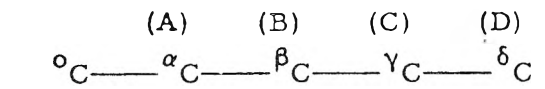


Figure 2. Definition of the conventions used in discussing carbon chemical-shift changes. The original[24] convention related the chemical shift of °C to the number of °C, ᵝC, ᵞC . . . . carbons, i.e., the number of carbons in those positions relative to °C. We replace the Greek letters with **A, B, C,** etc., as shown in parentheses, in referring to particular carbons.

Greek letters with the boldface capital letters **A, B, C** . . . (Figure 2).

This convention allows us to discuss conveniently the **B** effect shown by the α-carbon resonance (Table VII). The data in Table VII were obtained by comparing the spectra of the ethers with those of the analogous, unsubstituted alcohols.[25] The changes in chemical shift at the α carbon would therefore be attributed to the **B** effect. It appears to be amply demonstrated that the **B** effect is broadly independent of the **A** substituent past which it must be transmitted.[13,24-26] In the acyclic alkanes, the **B** effect is greatest (ca. −9.0 to −9.5 ppm) when °C is primary or secondary, somewhat reduced when °C is tertiary (−6.6 ppm), and severely attenuated when °C is quaternary (−2.3 ppm).[27] Reference to Table VII shows that the same characteristics are evident at the α carbon. Thus, when the α carbon is secondary, the **B** effect is approximately −10 ppm, while in cases where α/C is tertiary and quaternary, the **B** effects are ca. −9 and −4 ppm, respectively.

Continued comparisons show other interesting parallels between the chemical shifts of ethers and alkanes. Thus, the chemical-shift changes observed at the β carbon (Table VII) can be attributed to the **C** effect of the *O*-methyl group. This effect is known to be generally shielding in character,[24-27] and this accords with the data in Table VII. Moreover, this effect is seen to be attenuated in those cases where the β carbon is more heavily substituted, as is the case for the isobutyl and neopentyl ethers. This is again as observed in the alkanes.[27] In the latter group of compounds, however, the **C** effect becomes deshielding when °C is quaternary. For methyl neopentyl ether it is evident that the same situation does not obtain for the ethers. In addition, the **C** effects observed at this position for some of the ethers appear to be somewhat larger than observed for the alkanes. These differences may be due in part to the presence of carbon–oxygen bonds in the ethers. These bonds are shorter than the analogous carbon–carbon bonds,[18,19] a fact which could emphasize the steric effects to which the **C** effect is generally attributed.[28] Additionally, the presence of the carbon–oxygen bond dipole could lead to electric-field[29] or other effects.

Some insight into the origin of these **C** effects in the ethers can be drawn from comparisons of the *O*-methyl resonances of these ethers to that of dimethyl ether (Table VII, first column). The β carbons of these ethers are in the **C** position relative to the *O*-methyl group. Thus, in dimethyl ether, the *O*-methyl carbon has no **C** substituent, while the ethers of primary, secondary, and tertiary alcohols have one, two, and three **C** carbons, respectively. The data in Table VII shows that for all cases except that of methyl *tert*-butyl ether, which will be discussed separately, there is an average **C** effect of approximately +2.5 ppm for each **C** carbon. This value is very close to those observed for the alkanes.[24,27] Here again, we have the shorter intermediary carbon–oxygen bonds between °C and ᶜC, yet the steric effect is not enhanced. The most probable explanation for this phenomenon lies in the greater energy difference between the trans and gauche rotational conformations of the ethers[21] than in the alkanes.[22] Thus, in the ethers, the gauche form, the only conformation in which steric effects can become important, is less populated, and the expected enhancement of the steric effect due to the shorter carbon–oxygen bonds would be in part nullified.

Table VII
Chemical-Shift Changes Associated with Methylation for CH_3–O–C_α–C_β–C_γ–C[a]

Methyl ether	OCH_3[b]	α	β	γ	δ
Methyl	0	−10.7			
Ethyl	+2.1	−10.7	+2.9		
n-Propyl	+3.0	−3.1	+3.8	+0.9	
n-Butyl	+2.8	−10.1	+3.8	+0.5	+0.8
Isobutyl	+2.5	−10.0	+3.1	+0.7	
Neopentyl	+1.8	−10.2	+1.4	+0.5	
Isopropyl	+4.8	−9.2	+3.7		
sec-Butyl	+5.2	−8.7	+3.9 (CH_2)	+1.6	
			+5.3 (CH_3)		
tert-Butyl	+11.1	−3.7	+4.4		

[a] Chemical shifts in parts per million measured relative to the analogous carbon of the alcohol.[25] [b] This column represents the chemical shift of the *O*-methyl carbon relative to that of dimethyl ether.

Methyl *tert*-butyl ether is especially relevant to this explanation. In this molecule, the conformation is constrained to that shown in Figure 3d, in which the *O*-methyl carbon is forced into a gauche relationship to two methyls of the *tert*-butyl group. Here, the **C** effect observed at the *O*-methyl carbon is much larger than observed at carbon 4 of the analogous case of 2,2-dimethylbutane.[24] Thus, when gauche interactions are enforced, the shorter carbon–oxygen bond lengths appear to lead to intensified steric[28] effects.

Additional information regarding the populations of the various conformational states of these ethers is available from analysis of the vicinal coupling between the *O*-methyl carbon and the α proton ($J_{C_xOC_yH}$ in Table III). In the case of dimethyl ether, for which the conformation shown in Figure 3a has been determined,[19] the vicinal carbon–proton coupling has been measured to be +5.7 Hz.[30] One can suppose that this observed coupling is the average of one trans (J_t) and two gauche (J_g) couplings.[31]

$$J_{obsd} = \tfrac{1}{3}(J_t + 2J_g)$$

Assuming that J_g is approximately 2.7 Hz (vide infra), the trans coupling comes out as approximately 11.8 Hz.

For the methyl ethers of primary alcohols, we shall assume[18,21] that the conformational equilibria are as represented in Figure 3b, with the trans form being favored by 1–1.5 kcal/mol.[21] The population of the gauche form should then be only about 10% of that of the trans. Using $J_t \simeq$ 11.8 Hz and $J_g \simeq$ 2.7 Hz, one can estimate that the vicinal couplings should be about 3.4 Hz. This is in reasonable agreement with the observed values in Table III. These data also show that as R (Figure 3b) becomes bulkier, the observed coupling is reduced, reaching a minimum of 2.65 Hz when R is *tert*-butyl. It is from this datum that we approximate J_g on the assumption that the gauche rotamer of methyl neopentyl ether will be negligibly populated.

The $J_{C_xOC_yH}$ couplings in the methyl ethers of isopropyl and *sec*-butyl alcohols are significantly higher than the foregoing cases. For methyl isopropyl ether, one of the expected conformations, g_2 of Figure 3c, has been shown to be only very slightly populated.[18] If g and g′, the conformations involving only one gauche interaction, were the only contributing forms, the observed coupling should be equivalent to J_g, or ca. 2.65 Hz. Unless there is a substituent effect operating here (vide infra), the substantially larger

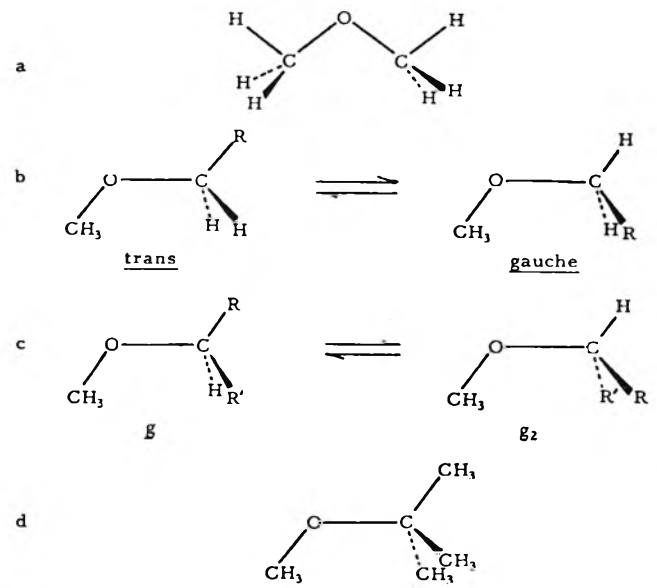


Figure 3. Some possible conformations of methyl ethers.

coupling observed may indicate a distortion of the conformation away from the perfectly staggered form to a situation wherein the α proton approaches the eclipsed disposition relative to the C-methyl carbon.

For 1,2-dimethoxyethane, $J_{C_xOC_yH}$ is significantly smaller (1.85 Hz) than the analogous coupling in the methyl ethers of primary alcohols. This is rather surprising in that one might have expected the dihedral angles around the oxygen–methylene carbon bonds to be rather similar in these compounds. It is possible that this difference in coupling is due to a substituent effect, though in view of other results this appears unlikely. Thus, for example, the coupling between the α carbon and the O-methyl protons ($J_{C_yOC_xH}$) in 1,2-dimethoxyethane is very similar to those of the methyl ethers of primary alcohols. In view of these results, it may be significant that the most stable conformation about the carbon–carbon bond of 1,2-dimethoxyethane is that in which the ether oxygens are gauche to one another.[32] It is possible that this phenomenon could lead to dipole–dipole interactions or other effects which would distort the dihedral angles of the adjoining carbon–oxygen bonds slightly from the staggered conformation.

The above analysis is based upon the assumption that dihedral angles are the only important effect determining the magnitude of vicinal carbon–proton coupling. Some of the $J_{C_yOC_xH}$ data (Table III), however, suggest that there may also be an important substituent effect. Thus, the coupling between the α carbon and the O-methyl protons is significantly larger for dimethyl ether than for all other cases. Also, there appear to be small differences in this coupling between the methyl ethers of primary ($J_{C_yOC_xH} \simeq$ 5.2–5.3 Hz) and secondary ($J_{C_yOC_xH} \leq 5$ Hz) alcohols. There is a further reduction in this coupling when the α carbon is quaternary, as in methyl *tert*-butyl ether. There are other indications, however, that this substituent effect may be negligible in those cases in which the extent of substitution on the coupled carbon is the same. Thus, the vicinal coupling in diethyl ether is not significantly different from the $J_{C_yOC_xH}$ values observed in methyl ethers of primary alcohols. At present, we believe that the greatest changes in the coupling constants in Table III are due to the effects of dihedral angles.

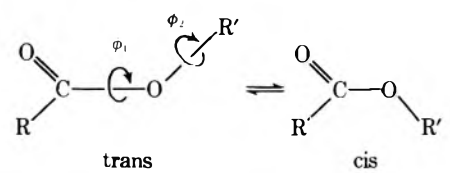
At this time, there are too few data for the cyclic ethers to allow extended discussion. There are, nevertheless, some interesting results tabulated in Table V. Thus, the values for the vicinal coupling between carbons 4 and 5 of 1,3-dioxolane and the protons on carbon 2 is positive, like the corresponding coupling in dimethyl ether.[30] It has been our presumption throughout the above discussion that all other vicinal coupling constants in this series are positive. Second, there are notable differences in some of the vicinal coupling constants which do not seem attributable to the effects of dihedral angles. Most probably the small differences between the vicinal couplings in 1,4-dioxane and 1,3,5-trioxane are due to the substitution effect of oxygen. If the substituent effect on vicinal carbon–proton coupling is dependent upon the electronegativity of the substituent, as in the analogous proton–proton coupling,[33] these results again suggest that carbon substitution is associated with rather small effects.

Table VIII
^{13}C Chemical-Shift Changes on Ester Formation[a]

Ester	α	β	γ	δ
Methyl formate	−0.5			
Ethyl formate	−2.2	+4.2		
n-Propyl formate	−1.1	+4.1	+0.5	
n-Butyl formate	−1.5	+4.5	+0.3	+0.6
Isobutyl formate	−0.3	+3.2	+0.5	
Neopentyl formate				
Isopropyl formate	−3.3	+4.0		
sec-Butyl formate	−2.7	+3.7		
		+3.2		
tert-Butyl formate	−11.9	+3.5		
Methyl acetate	−1.3			
Ethyl acetate	−2.5	+4.1		
n-Propyl acetate	−1.4	+3.8	+0.3	
n-Butyl acetate	−2.1	+4.2	+0.1	+0.5
Isobutyl acetate				
Neopentyl acetate				
Isopropyl acetate	−3.3	+3.9		
sec-Butyl acetate				
tert-Butyl acetate	−10.5	+3.7		

[a] The data tabulated represent the chemical shifts of the indicated carbons of the esters relative to the analogous carbon in the alcohol. All shifts are in parts per million.

The Esters. The conformational behavior of esters must be rather different from that of the alkanes because the resonance effect allows only two stable planar conformations about the acyl–oxygen bond, with ϕ_1 equal to 0° or 180°. The enforced planarity doubtless influences the rotational equilibria around the alkyl–oxygen bond which involves ϕ_2. Thus, we expect, and observe, rather different effects in the spectra of these compounds from those of the ethers (see Table VIII).



The carbon chemical shifts of esters show that the α-carbon resonance of a primary alcohol undergoes a small (generally ≤2 ppm) deshielding effect on formylation or acetylation. For secondary alcohols, this deshielding effect is slightly larger, averaging about −3 ppm. For the *tert*-butyl esters, however, this effect becomes much larger, and acetylation leads to shifts of at least −10 ppm at the α carbon. Thus, while the effect of acetylation at this position resembles that of methylation (Table VII) in that this nucleus is deshielded, the dependences of the magnitude of the effect upon substitution at the α carbon in the two types of compound are quite different.

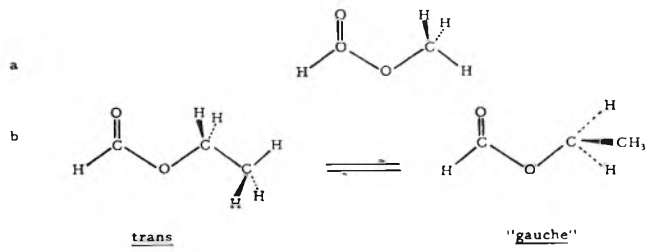


Figure 4. Conformations of methyl and ethyl formate, as deduced from microwave spectroscopy.[33,34]

Some aid to understanding these changes is available from the carbon–proton coupling data of Table IV. In the formates, the $^3J_{C_yOC_xH}$ coupling constant should be expected to reflect the dihedral angle about the acyl–oxygen bond. For methyl[34] and ethyl[35] formate, the cis conformation was found to be indetectable by microwave spectroscopy, and the trans form seems generally preferred energetically. Certainly, in most of the cases studied to date (Table IV), the $^3J_{C_yOC_xH}$ couplings appear to be independent of substitution at the α carbon. This suggests not only that the simple esters exist preferentially in the trans conformation but that there is only a small substituent effect. However, for *tert*-butyl formate, $^3J_{C_yOC_xH}$ is rather different from the other examples. This suggests that the cis conformation makes a much more important contribution to the conformational population than with the other examples.

This conclusion also accounts for the acylation shift changes discussed above. For amides and peptides, it has been found that carbon nuclei which are proximal to the carbonyl oxygen are subject to strong shielding effects.[23] In the amides, this effect had been previously recognized and attributed to an electric-field effect.[29] Such a mechanism might also be expected to operate in the esters, and in the trans conformation would be expected to counteract the deshielding **B** effect arising from the acyl group. If, however, the *tert*-butyl group forced the molecule into the cis rotational conformation, the α carbon would be much more remote from the carbonyl oxygen and should be much less affected by its electric field, and the **B** effect would become dominant.

At present, there seems to be no recognizable pattern in the effects of acylation on the β- and γ-carbon resonances. The constancy of the acylation shifts at the β carbon suggests that these changes are not dependent to any large degree on proximity effects.

We have already suggested that the properties of the acyl group may well be expected to have an effect on the conformation around the alkyl–oxygen bond. There is evidence derived from microwave spectroscopy that this is indeed true. Thus, although the conformation of methyl formate[34] was found to be perfectly staggered, one of the major contributors to the conformational equilibrium of ethyl formate[35] is not. (Cf. Figure 4.) In the "gauche" conformer of Figure **4b**, the dihedral angle between the acyl oxygen and $^{\alpha}C$–$^{\beta}CH_3$ bond is approximately 85°, not 120° as would be the case in the perfectly staggered form. Furthermore, the energy difference between these two conformers is less than 200 cal/mol, with the trans form being favored. The conformational situation of the esters is therefore rather different from that of the ethers.

In view of this, it is rather surprising that the $^3J_{C_xOC_yH}$ values in Table IV are so similar to the analogous couplings observed for the ethers (Table III). For derivatives of primary alcohols, these vicinal couplings in the two classes of compound are very similar. As observed for the analogous chemical-shift differences, these couplings seem broadly independent of whether the acyl group is acetate or formate. On the basis of these couplings one might easily be tempted to conclude that the conformations of the esters and ethers are very similar. However, for the methyl esters, $^3J_{C_xOC_yH}$ values are quite different from those of dimethyl ether.

Earlier workers[36] have used ^{13}C isotopic enrichment and proton nuclear magnetic resonance spectroscopy to analyze the conformation around the acyl–oxygen bond of acetates. By studying the variation of $^3J_{C_xOC_yH}$ with temperature, these investigators were able to make rough estimates of the values J_t and J_g. Unfortunately, these estimates were based on the assumption of perfectly staggered conformations which, in view of the more recent microwave study of ethyl formate,[35] may not be valid. From the fact that no temperature dependence for $^3J_{C_xOC_yH}$ would be detected for di-*tert*-butylcarbinyl acetate (2,2-4,4-tetramethyl-3-pentyl acetate), it was concluded[36] that this molecule was conformationally rigid and that the observed coupling constant (4.6 Hz) approximated that of cis coupling between vicinally disposed carbon and hydrogen.

At present, we do not feel that sufficient data exist to allow detailed analyses of these couplings in the esters. However, some interesting conclusions emerge from the data in Table IV. First, by comparing the $J_{C_xOC_yH}$ couplings in the formate and acetate esters of methyl, ethyl, neopentyl, and isopropyl alcohols, it can be concluded that the effect of carbon substitution on C_x is very small. The greatest difference is observed for the isopropyl cases, and in view of the other examples, it seems likely that this particular difference may reflect changes in the alkyl–oxygen dihedral angle.

Second, in the esters of primary alcohols, there is a trend for the magnitude of the $^3J_{C_xOC_yH}$ values to decrease as the bulk of the R group attached to the α carbon is increased. If we assume that the coupling in the "gauche" type of conformation (Figure 4b) is larger than that of the trans, this trend signals an increase in the energy difference between these two conformations, as was concluded for the ethers.

Third, there seems to be a tendency for the coupling in the formates of secondary alcohols to be slightly larger than for primary alcohols. Again, isopropyl acetate forms the only exception to this generalization. The striking difference between the $^3J_{C_xOC_yH}$ values of the formate esters of isopropyl and *sec*-butyl alcohols again suggests that the assumption of perfectly staggered conformations is likely to be an oversimplification. Because the same difference is observed for the *O*-methyl ethers of these alcohols, this caveat may apply to the ethers as well.

Finally, we shall consider the long-range proton–proton coupling constants presented in Table VI. The theoretical aspects of such couplings has been reviewed.[37] It is apparent that the trends observed in the vicinal $^3J_{C_xOC_yH}$ values are not reproduced in the $^4J_{HH}$ values of Table VI. Indeed, $^4J_{HH}$ appears to be insensitive to any but substituent effects, which may or may not be related to the influence of dihedral angles. The theoretical interpretation of $^4J_{HH}$ appears to be complicated and is influenced by many factors.[37] At present, these data appear to add little to our analysis of the conformations of these systems.

The $^5J_{HH}$ data in Table VI, however, can be interpreted in terms of our previous conclusions based on carbon chemical shifts and vicinal carbon–proton coupling. The theoretical model for this coupling suggests that five-bond proton–proton coupling to the formyl proton should be independent of the dihedral angle about the alkyl–oxygen bond.[37] Instead, this coupling should depend on the dihedral angles about the acyl–oxygen and the $^{\alpha}C$–$^{\beta}C$ bonds, being at a maximum when the bonds transmitting the coupling are

trans.[37] This situation is most likely for ethyl formate (cf. the trans conformer, Figure 4b) and, indeed, the largest $^5J_{HH}$ is observed for this compound. As substituents are added to the β carbon, the optimum conformation around the C_α–C_β bond becomes less likely, as it requires gauche interactions between the γ carbon(s) and the ester oxygen. This is as observed in Table VI. For isobutyl formate, where the optimum conformation requires two gauche interactions, $^5J_{HH}$ becomes particularly reduced. A similar effect is observed for *tert*-butyl formate, in which we have deduced a cis acyl–oxygen bond. Unfortunately, these speculations involve presumptions of perfectly staggered forms and are based on a theoretical model[37] derived for hydrocarbons.

Conclusion

It seems clear that measurement of vicinal carbon–proton couplings can be useful in the analysis of conformations. Furthermore, these couplings seems to be related to much more easily measured carbon chemical-shift changes.

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Benzoin Oximes in Sulfuric Acid. Cyclization and Fragmentation

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The kinetics of the reaction of benzoin, α-methylbenzoin, and α-phenylbenzoin oximes with sulfuric acid in acetic acid, resulting in concurrent cyclization to the corresponding 1-hydroxyindoles and fragmentation to benzonitrile and benzaldehyde, acetophenone, or benzophenone respectively, have been investigated at several temperatures in 60–100% sulfuric acid. Cyclization predominates at higher acidities. Mechanisms involving initial protonation on both oxime and carbinol followed by either direct fragmentation or dehydration and cyclization are proposed based on rate vs. acidity data, oxime basicity and the effects of perdeuteration and substitution of the benzoin oximes.

While benzoin oxime cyclizes to 1-hydroxy-2-phenylindole in concentrated sulfuric acid,[2] fragmentation to benzaldehyde and benzonitrile has been observed under other acidic conditions.[3] We have explored the concurrent cyclization and fragmentation reactions of benzoin oxime over a range of acidities produced from appropriate mixtures of sulfuric acid and acetic acid. As mechanistic interpretations frequently can be made from the relationship between reaction rate and solvent acidity,[4] we initially determined the H_0 values of anhydrous sulfuric acid in acetic acid for the concentration range used in this investigation (50–95%) at the temperatures used for the kinetic determinations. In addition to the detailed investigation of the reactions of benzoin oxime we obtained limited kinetic data for ring perdeuterated benzoin oxime, for α-methyl and α-phenyl benzoin oximes, and for benzoin oxime methylated on the α-hydroxyl position. All the oximes used in this investigation had the anti (or α) geometry.

The results of the H_0 determinations in the range 50–95% sulfuric acid are in Table I. The indicators used, with sulfuric acid concentration range and appropriate pK values at 30, 50, and 70°, obtained by interpolation from the data of Tickle, Briggs, and Wilson,[5] are as follows: 2,6-dinitroaniline, 50–60%, −5.35, −5.28, −5.21; 2-bromo-4,6-dinitroaniline, 55–70%, −6.43, −6.26, −6.10; 2,4,6-trinitro-*m*-toluidine, 70–85%, −8.03, −7.80, −7.68; picramide, 85–95%, −9.82, −9.62, −9.42. Figure 1 shows the relationship H_0 vs. % H_2SO_4 w/w for solutions in water,[6] acetic acid,[7]

Table I
$-H_0$ Values Derived from Log I Ratios

H_2SO_4, % w/w	30° Log I	30° $-H_0$	50° Log I	50° $-H_0$	70° Log I	70° $-H_0$
	2,6-Dinitroaniline (606-22-4)					
	(pK = −5.35)		(pK = −5.28)		(pK = −5.21)	
50	+0.66	6.01	+0.47	5.75	+0.29	5.50
55	+1.10	6.45	+0.97	6.25	+0.81	6.62
60	+1.51	6.86	+1.35	6.63	+1.26	6.47
	2-Bromo-4,6-dinitroaniline (1817-73-8)					
	(pK = −6.43)		(pK = −6.26)		(pK = −6.10)	
55	+0.05	6.48	−0.10	6.36	−0.08	6.02
60	+0.50	6.93	+0.37	6.63	+0.40	6.50
65	+0.85	7.28	+0.75	7.01	+0.65	6.75
70	+1.28	7.71	+1.14	7.40	+1.05	7.15
	2,4,6-Trinitro-*m*-toluidine (22603-58-3)					
	(pK = −8.03)		(pK = 7.80)		(pK = −7.68)	
70	−0.37	7.66	−0.47	7.33	−0.58	7.10
75	+0.17	8.20	+0.10	7.90	−0.14	7.54
80	+0.59	8.62	+0.47	8.27	+0.36	8.04
85	+1.01	9.04	+0.99	8.79	+0.86	8.54
	Picramide (489-98-5)					
	(pK = −9.82)		(pK = −9.62)		(pK = −9.42)	
85	−0.69	9.13	−0.79	8.83	−0.92	8.50
90	−0.29	9.53	−0.41	9.21	−0.64	8.78
95	+0.27	10.19	+0.30	9.92	+0.19	9.61

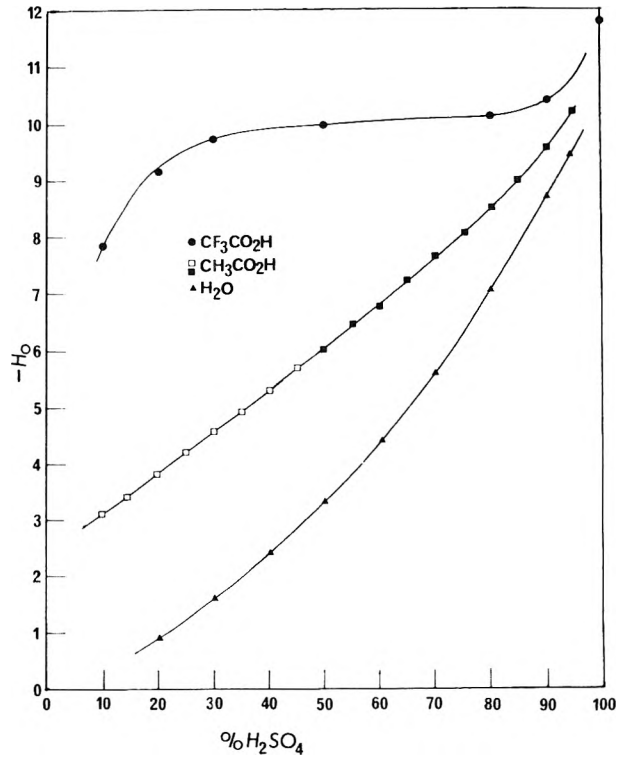


Figure 1. Acidity function, $-H_0$ vs. % H_2SO_4; ■, present work, □, ref 7; ▲, ref 6; ●, ref 8.

Table II
Kinetic Parameters for the Cyclization and Fragmentation of α-Benzoin Oxime

$-H_0$	30° k_c, sec^{-1}	30° k_f, sec^{-1}	50° k_c, sec^{-1}	50° k_f, sec^{-1}	70° k_c, sec^{-1}	70° k_f, sec^{-1}	% H_2SO_4
6.86	1.38×10^{-6}	1.77×10^{-6}					
6.63			4.36×10^{-6}	7.23×10^{-6}			60
6.45					2.25×10^{-5}	3.56×10^{-5}	
8.20	6.3×10^{-5}	2.82×10^{-5}					
7.90			1.76×10^{-4}	1.26×10^{-4}			75
7.54					4.67×10^{-4}	3.53×10^{-4}	
9.13	8.90×10^{-4}	2.81×10^{-4}					
8.83			2.81×10^{-3}	1.40×10^{-3}			85
8.50					7.16×10^{-3}	5.59×10^{-3}	
10.19	3.54×10^{-2}	3.53×10^{-3}					
9.92			1.10×10^{-1}	1.75×10^{-2}			95
9.62					2.96×10^{-1}	7.96×10^{-2}	
11.84	14.2	3.16×10^{-1}					100

and trifluoroacetic acid.[8] A check on our data stems from the observation that our curve smoothly intercepts that of Hall and Spengeman,[7] which terminates at approximately 50% sulfuric acid. The 100% sulfuric acid value is that determined by Vinnik.[9]

The rates of the cyclization and fragmentation reactions were determined at 30, 50, and 70°. The appearance of 1-hydroxy-2-phenylindole was cleanly first order to at least 4 half-lives. Infinity values were obtained at about 6 half-lives and where reproducible when the apparatus was swept with dry nitrogen throughout the reaction. In most cases a computer-generated infinity value was also determined, by finding the value of $A_{\infty e}$ which gave the best linear presentation of the first-order relationship log $A_{\infty e}/(A_{\infty e} - A_t)$ vs. t. In most instances the calculated and experimental value were in close accord. The values of rate constants for the fragmentation reactions were determined indirectly considering the cyclization and fragmentation to be two parallel first-order reactions with a common starting material.

The rates of cyclization and fragmentation (Table II) were obtained at 30, 50, and 70° over a wide range of acidities (55–95% sulfuric acid). The Hammett–Zucker plots of log k_c and log k_f against H_0 over this range of acidities and at all reaction temperatures were slightly curved with the slope increasing at higher acidities (Figures 2 and 3). The slopes at the different temperatures were almost parallel.

These curves gave slopes of about 1.3 for the plot of log k_c against $-H_0$ and about 1.0 for the plot of log k_f against $-H_0$, both at 30°. At other temperatures the results are very similar.

In addition to the extensive data obtained for benzoin oxime, a series of substituted benzoin oximes was investigated at $H_0 = -10.2$ and at 30°. Replacing the α hydrogen of the benzoin oxime by deuterium, methyl, or phenyl groups gave compounds which reacted analogously to benzoin oxime but at differing rates. In all cases the corresponding hydroxyindole was formed as well as the fragmentation products: benzonitrile, and benzaldehyde, acetophenone, or benzophenone, respectively. The rates of the fragmentations and cyclizations differed from that of benzoin oxime and are shown in Table III. Additionally benzoin methyl ether oxime was investigated. This compound gave mainly cyclization; much less fragmentation was ob-

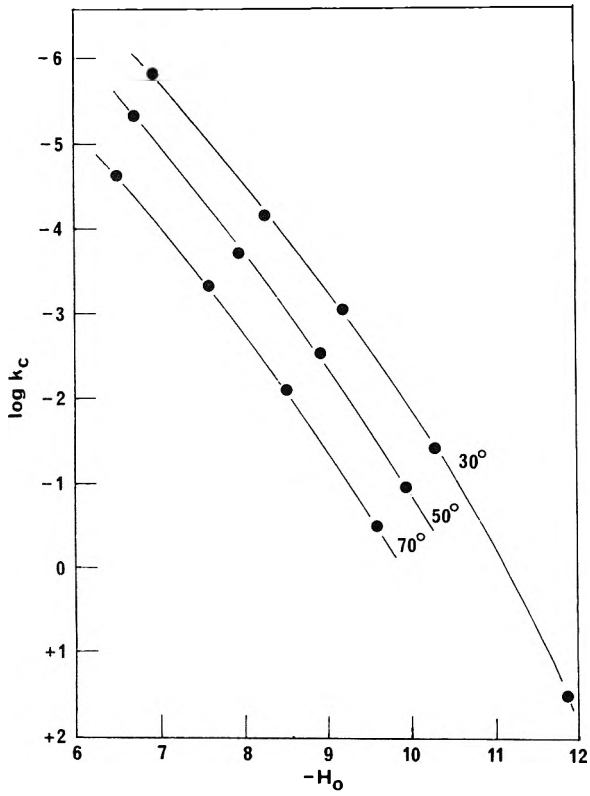


Figure 2. Hammett–Zucker plot for cyclization reactions.

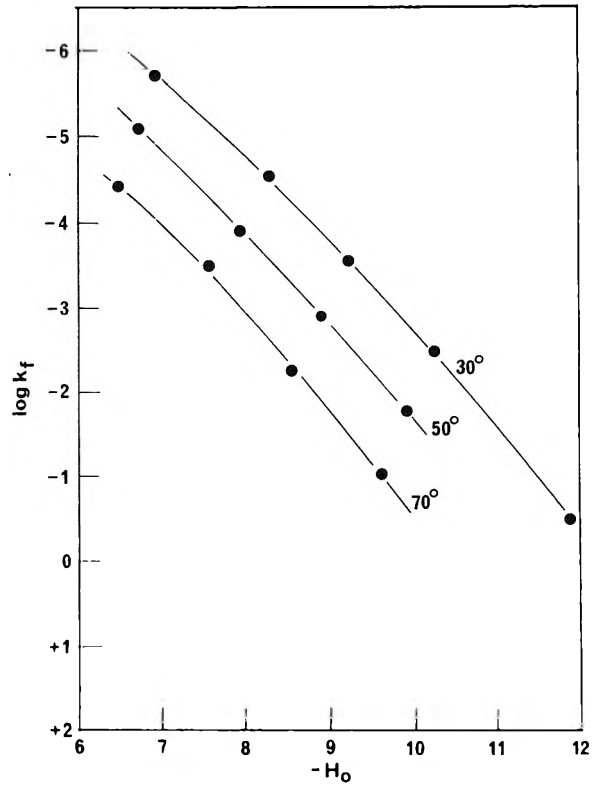


Figure 3. Hammett–Zucker plot for fragmentation reactions.

Table III
Effect of Substitution on Cyclization and Fragmentation at H_0 = −10.2 at 30°

Substitution (etc.)	k_c, sec^{-1}	k_f, sec^{-1}	Registry no.
α-H	3.54×10^{-2}	3.53×10^{-3}	441-38-3
α-Me	8.87×10^{-2}	5.89×10^{-3}	889-89-4
α-Ph	7.34×10^{-2}	1.47×10^{-2}	56830-59-2
α-OCH_3	3.27×10^{-2}	6.87×10^{-4}	56830-60-5
Perdeuterio	3.66×10^{-2}	3.68×10^{-3}	56830-61-6

Table IV
Kinetic Parameters in Trifluoroacetic Acid at 30°

H_2SO_4, M	$-H_0$	k_c, sec^{-1}	k_f, sec^{-1}
4.3	9.0	1.44×10^{-5}	6.30×10^{-5}
11.5	9.4	1.12×10^{-4}	1.58×10^{-4}
17.7	10.2	8.32×10^{-3}	3.37×10^{-3}

served. Finally we briefly examined the effect on reaction rate of substituting trifluoroacetic acid for acetic acid (Table IV). These reaction mixtures were prepared by interpolation from the data of Hyman and Garber.[8] The values obtained for k_c were considerably less in trifluoroacetic acid than in acetic acid at the same H_0. The k_f values were much less sensitive to solvent change. Substitution of acetic acid for water results in a significant increase in solution acidity at similar concentrations of sulfuric acid. Hall and Spengeman[7] observed a 3 H_0 unit separation between the parallel curves for acetic acid and water solutions to about 50% sulfuric acid. We have found that beyond this point the curves converge and extrapolate smoothly to the value for anhydrous sulfuric acid (H_0 = −11.94). Because of the limited number of points delineating the acidity function curve, the present data, while adequate for this study, do not claim the precision and accuracy of more definitive investigations. In particular we omitted the interesting range 95–100% sulfuric acid because we desired kinetic data over a wide range of sulfuric acid concentrations. Because of the high sulfuric acid concentrations used, the problem of ion-pair formation resulting from the low dielectric constant of acetic acid[10] can be minimized and the system should behave similarly to aqueous systems. Assuming an approximately linear variation of dielectric constant with mole fraction we can estimate that the minimal value of dielectric constant for the solutions will be about 46.

A number of factors are germane to the mechanism of fragmentation and cyclization of benzoin oxime in strong acid. Oximes are quite basic; for example, cyclohexanone oxime is claimed to be completely monoprotonated in 2.5×10^{-2} M sulfuric acid[11] and potentiometric titrations have shown values near zero for the pK_a's of several oximes.[12] Consequently, benzoin oximes are monoprotonated, even at the lowest acidities used in this investigation. In benzoin oximes sites for protonation are limited. Initial protonation will occur at the oxime on either oxygen or nitrogen, with the former site preferred from a comparison of the pK_a's of alcohols, imines, and oximes.[12] A second protonation can occur on the carbinol oxygen (alcohols have pK_a's in the range −2 to −5[12]) or much less easily again on the oxime or its adjacent carbon. If diprotonated structures are involved in the fragmentation or cyclization reactions, the former possibility is more plausible and indeed one would expect that appreciable carbinol protonation would occur at the higher acidities used in this investigation.

In a detailed study of the Beckmann rearrangement in strong acid,[11] Vinnik and Zarakhani have convincingly demonstrated that dehydration of the conjugate acid of the oxime to an iminium ion or ion pair intervenes and that this process only becomes important at reasonably high acidities, e.g., $-H_0 > 8$. If this is the case in the present study fragmentation and/or cyclization may also require this step. Fragmentation is the major reaction at the lower acidities while crossover to cyclization occurs near $H_0 = -7$ and this becomes the predominant reaction at the highest acidities. In the absence of solvent effects fragmentation and cyclization reactions must arise from two different in-

Table V
Activation Parameters for Benzoin Oxime Cyclization obtained at $H_0 = -9.5$ by Interpolation of Rate Data

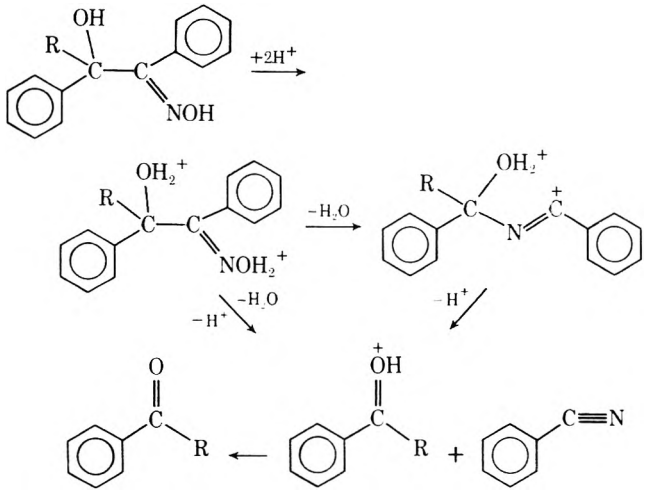
	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol deg
Cyclization	21.1	−2.8
Fragmentation	25.5	+9.9

termediates, because, although the Zucker–Hammett plots of log k_f and log k_c vs. $-H_0$ are reasonably linear curves over the range of H_0 values studied, the slopes are different (1.0 and 1.3, respectively) and the ratio of k_f to k_c is acidity dependent.

The use of Zucker–Hammett criteria as a mechanistic probe in the current investigation, rather than the more recent Bunnett parameters[13] w, w^*, ϕ is justified because these latter criteria are only strictly applicable to aqueous systems where the large body of experimental evidence allows valid mechanistic correlations to be made. This is not the case for nonaqueous systems, particularly sulfuric acid–acetic acid solutions where experimental results are very limited. The reasonable linearity and the slopes of the Zucker–Hammett plots for both fragmentation and cyclization suggests that proposed mechanisms for these reactions should be consistent with A-1 processes where equilibrium protonations precede an unimolecular rate-determining step which does not involve solvent.

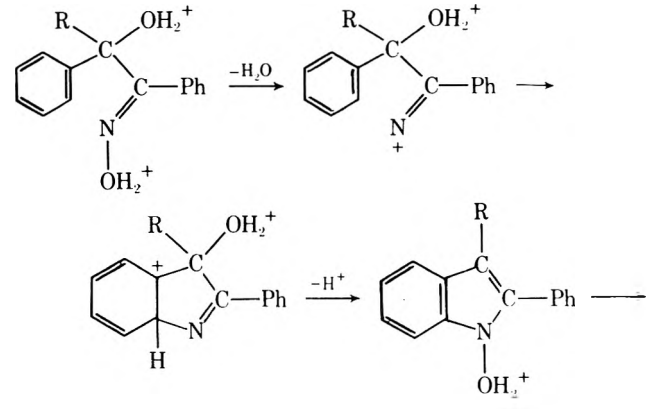
The above observations afford convenient rationalizations for the observed crossover in rates and their acidity dependence and allow several reasonable mechanistic possibilities to be proposed.

Because fragmentation predominates at lower acidities the following schemes, both involving protonation on the carbinol but occurring without intermediacy of iminium ions, are suggested: direct fragmentation or, by analogy with Grob's proposals for fragmentation of α-aminoketoximes,[14] via an intermediate nitrilium ion.

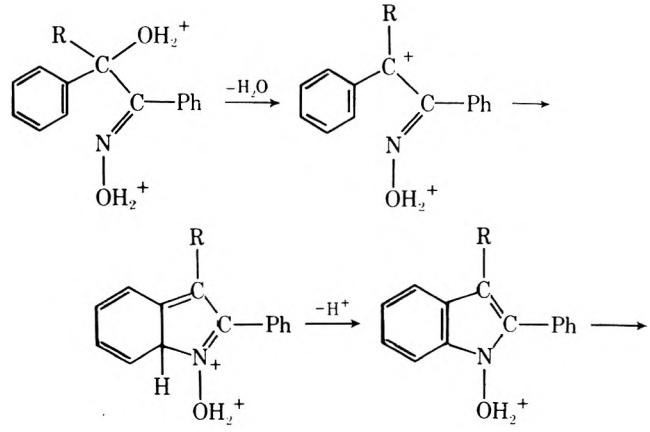


In any case the rate-determining step is probably the fission of the C–C or C–N bond to give the carbonyl compound and the nitrile. Subsequent hydrolysis of the nitrile to the amide and air oxidation of the carbonyl to the carboxylic acid may accompany this phase of the reaction or subsequent work-up as shown by the mass balance experiments.

The generation of the electrophilic iminium ion affords a species which can also easily lead to ring closure. The predominance of cyclization at the higher acidities suggests that acidity plays a further role in the cyclization and it is reasonable to suppose that this involves formation of the iminium ion. Cyclization shows only a small secondary deuterium isotope effect consistent with proton loss and aromatization not being the rate-determining step. Further, the rate of cyclization is not particularly sensitive to conjugative effects of substituents at the carbinol carbon and thus the formation of a carbonium ion at this site is also not involved in a rate-determining step. A tentative scheme can be constructed for the cyclization as follows.



Quenching of completed reactions in sulfuric acid with methanol or acetic acid fails to yield N-methoxy or N-acetoxy products which suggests that rapid transfer of water from position 3 to the nitrogen occurs and that an indolium ion does not intervene in the reaction. The timing of the dehydration of the oxime and the carbinol could conceivably be reversed so that rate-determining attack of the oxime nitrogen lone pair on the aromatic ring, activated by the adjacent carbonium ion, could occur; this sequence of steps maintains the integrity of the oxime oxygen in the final product.



Limited data obtained in trifluoroacetic acid instead of acetic acid suggest that the concentration of sulfuric acid as well as solution acidity is important. The lower rates of cyclization in the former solvent may be interpreted as a medium effect where the decreased dielectric constant resulting from the lower sulfuric acid concentrations retards the formation of the iminium or carbonium ions. Interestingly, however, at $H_0 = -10.2$, where the assumption that dielectric constant is proportional to mole fraction results in approximately equal values of dielectric constant for these solvent systems, the rate of cyclization is about fourfold slower.

The activation parameters for the reactions (Table V), which, because of the variation of H_0 with temperature, were obtained by interpolation at $H_0 = -9.5$, were unexceptional. The values of $\Delta H^{\ddagger}$ for cyclization and fragmentation lie between 20 and 25 kcal/mol and are very typical of

enthalpies of activation observed for a wide variety of oxime rearrangements and fragmentations in a variety of solvents.[11,15] Too much stress cannot be placed on the values of $\Delta S^{\ddagger}$ obtained, although the values of −2.8 and +9.8 cal/mol deg for cyclization and fragmentation, respectively, are reasonable for such processes. The complex nature of the equilibria intervening before and after the proposed rate-determining steps in each case reduce the significance of the entropy of activation in the absence of data for these intervening steps.

Experimental Section

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. NMR spectra were obtained on a Varian T-60 spectrometer in $CDCl_3$.

Sulfuric acid (100%) was obtained from reagent grade material and sufficient oleum. It had mp 10.3°.[16] Anhydrous acetic acid was obtained by distilling reagent grade acetic acid from phosphorus pentoxide, followed by fractional distillation. It had mp 16.5°.[17] The Hammett indicators were purified by column chromatography on neutral alumina followed by recrystallization from aqueous ethanol. 2,4,6-Trinitro-*m*-toluidine was prepared as described;[18] the others were commercial samples. After purification all had melting points and spectra which agreed with reported values.

Benzoin oxime,[19] α-methylbenzoin oxime,[20] α-phenylbenzoin oxime,[21] and benzoin methyl ether oxime[2] were prepared by published procedures.

Samples of the hydroxyindoles were prepared by dissolving the appropriate oximes in concentrated sulfuric acid and stirring the solution, under nitrogen, for about 12 hr at room temperature. Dilution with ice, filtration, and two recrystallizations from ethanol afforded the pure compounds.

1-Hydroxy-2-phenylindole: mp 168° (lit.[2] mp 175°); uv max (65% aqueous acetic acid containing 0.5 *M* sodium acetate) 302 nm (ε 17050).

1-Hydroxy-2-phenyl-3-methylindole: mp 158–160°; uv max (same solvent) 310 nm (ε 18340).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.54; H, 6.01; N, 6.48.

1-Hydroxy-2,3-diphenylindole: mp 195–197° dec; uv max (same solvent) 321 nm (ε 16960).

Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 83.97; H, 5.56; N, 4.93.

1,1′,2,2′,3,3′,4,4′,5,5′-Decadeuteriobenzoin. A slow stream of chlorine gas was passed into refluxing toluene-d_8 (10 g, 0.1 mol) with irradiation by a sun lamp until there was a weight increase of 7.4 g. The mixture was distilled at 96–100° (22 mm) and the distillate was refluxed under nitrogen with a mixture of calcium carbonate (8 g) and water (30 ml) for 4 hr. Additional water (150 ml) was added and the mixture distilled until the distillate was clear. The distillate was adjusted to pH 8 with sodium carbonate and extracted with methylene chloride (3 × 25 ml). The extract was dried ($MgSO_4$) and evaporated. The residue of benzaldehyde-d_6, without purification, was dissolved in ethanol (10 ml) and potassium cyanide (0.1 g) in water (1 ml) was added. The mixture was refluxed under nitrogen for 2 hr, cooled, and diluted with an equal volume of water. The slightly oily precipitate was filtered and crystallized from aqueous ethanol. Perdeuteriobenzoin was isolated as almost colorless crystals, mp 135–138°, 5.7 g (52% based on toluene-d_8).

The NMR spectra showed a doublet at δ 5.95 (~0.1 H relative to the –OH signal at δ 4.58) and a series of weak peaks at δ 7.4 and 7.9 due to aromatic protons. Integration relative to the OH signal showed that the rings were <1% protonated.

After three recrystallizations from aqueous methanol containing a few drops of 2 *N* NaOH the NMR peak at δ 5.95 gave 1 H.

The oxime was prepared in the usual way.

Acidity Functions. These were determined essentially as described by Tickle, Briggs, and Wilson,[5] and by Jorgenson and Hartter.[18] Aliquots of indicator stock solutions (in acetone or methylene chloride) were pipetted into volumetric flasks, the solvent was removed in vacuo, and the indicator was dissolved in appropriate sulfuric acid–acetic acid mixtures at 30, 50, or 70°. Spectra, with the same acid mixture as reference, were determined on a Beckman DB-GT spectrophotometer with a Beckman 10-in. recorder. Temperature control was obtained with a Haake Model E52 thermocirculator. Solutions were equilibrated in the spectrometer for about 10 min before spectra were determined.

The molar absorptivities, ϵ_{In} and ϵ_{HIn^+}, were obtained at appropriate wavelengths about 2 H_0 units below the pK_{In} of the indicator and in 100% sulfuric acid, respectively. Log I was determined as $\log (\epsilon_{In} - \epsilon_{obsd})/(\epsilon_{obsd} - \epsilon_{HIn^+})$ and thus

$$H_0 = pK_{HIn^+} - \log I$$

Rate Data. These were obtained as follows. The oxime was dissolved in a small amount of anhydrous acetic acid in one bulb of a two-bulb apparatus. Sulfuric acid–acetic acid mixture of such a concentration that addition of the acetic acid from the first bulb would give the required H_0 value was placed in the second bulb. The apparatus was purged continuously with dry nitrogen. After thermal equilibrium was established the solutions were mixed, aliquots were withdrawn with a calibrated pipet at noted time intervals and quenched in 65% aqueous acetic acid containing 0.5 *M* sodium acetate, and the spectra were determined immediately. 1-Hydroxy-2-phenylindole was determined spectrophotometrically at 302 nm; the 1-hydroxy-2-phenyl-3-methyl- and 1-hydroxy-2,3-diphenylindoles were determined at 310 and 321 nm, respectively.

The rate constants k_c and k_f were obtained by considering the cyclization and fragmentation to be the only reactions occurring to a significant extent[22] and as parallel first-order processes. A least-squares plot of $\log A_{\infty e}/(A_{\infty e} - A_t)$ vs. time yields $(k_c + k_f)$. If $A_{\infty c}$ is the calculated infinity absorbance, assuming only cyclization, obtained for pure 1-hydroxy-2-phenylindole, and $A_{\infty e}$ is the experimental infinity absorbance, then

$$k_c/k_f = A_e/(A_{\infty c} - A_{\infty e})$$

and k_c and k_f can be evaluated independently.

Because of the difficulty in some experiments in obtaining consistent values of $A_{\infty e}$, a simple incremental computer procedure was used such that a value of $A_{\infty e}$ was determined so that $\log [A_{\infty e}/(A_{\infty e} - A_t)]/t$ was constant at all experimentally determined values of A_t. The values of $A_{\infty e}$ thus obtained were usually close to and often identical with those measured at about 6 half-lives.

$\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were determined at $-H_0 = 9.5$ from values of log k_c and log k_f obtained by interpolation on the Hammett–Zucker plots.

Product Analyses and Mass Balance. In a typical experiment benzoin oxime (11.35 g, 0.05 mol) was dissolved, under nitrogen, in a mixture of anhydrous sulfuric acid (65 g) and anhydrous acetic acid (35 g) ($H_0 \simeq -7.2$). After about 6 hr on a steam bath and about 12 hr at room temperature the yellow solution was poured onto ice (500 g) and the mixture immediately extracted with methylene chloride (5 × 75 ml). The extract was washed thoroughly with 5% sodium bicarbonate to remove the benzoic and acetic acids and then shaken under nitrogen with 2 *N* sodium hydroxide (3 × 50 ml) to extract the hydroxyindole. The cooled sodium bicarbonate extract was acidified and extracted with methylene chloride which was washed with water and evaporated to yield benzoic acid (1.52 g, 0.0125 mol). The cooled sodium hydroxide extract was cautiously acidified with concentrated hydrochloric acid and filtered to yield crude 1-hydroxy-2-phenylindole (5.08, 48.4%, 0.024 mol) as yellow crystals, mp 164–168°. One recrystallization from ligroin–chloroform raised the melting point to 170–171° (lit.[2] 175°). The original methylene chloride solution was evaporated and the pale yellow oily residue was chromatographed on silica gel (500 g). Elution with petroleum naphtha (bp 60–80°) and increasing amounts of methylene chloride eluted in sequence benzaldehyde (1.03 g, 0.01 mol), benzonitrile (0.85 g, 0.008 mol), and benzamide (1.68 g, 0.014 mol). Assuming hydrolysis and air oxidation, this accounted for 0.0448 mol of starting material. Thus the mass balance was 94%.[22] Data obtained at other H_0 values were always near 95%. Similar data were obtained for α-methyl and α-phenyl benzoin oxime.

Registry No.—1-Hydroxy-2-phenylindole, 1859-39-8; 1-hydroxy-2-phenyl-3-methylindole, 56830-62-7; 1-hydroxy-2,3-diphenylindole, 56830-63-8; perdeuteriobenzoin, 56830-64-9.

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On Fragmentation of Aryl Sulfide Radical Anions during Aromatic SRN1 Reactions[1]

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The photostimulated reaction of ethanethiolate ion with iodobenzene in liquid ammonia produces not only ethyl phenyl sulfide but also thiophenoxide ion and diphenyl sulfide. This shows that the presumed intermediate in the SRN1 mechanism, the ethyl phenyl sulfide radical anion, fragments in part into ethyl radical and thiophenoxide ion. The reactions of *p*-iodoanisole with thiophenoxide ion and of iodobenzene with *p*-methoxythiophenoxide ion both produce phenyl *p*-methoxyphenyl sulfide in good yield without any detectable amount of symmetrical diaryl sulfide, indicating that the phenyl *p*-methoxyphenyl sulfide radical anion intermediate does not fragment appreciably in this system. Reactions of four unsymmetrical phenyl aryl sulfides with acetone enolate ion afford more *m*-methyl-, *p*-methyl-, *m*-methoxy-, or *p*-methoxyphenylacetone than phenylacetone.

Diaryl sulfides and alkyl aryl sulfides are cleaved cathodically or by alkali metals to form an arenethiolate ion and a hydrocarbon (eq 1), the necessary hydrogen atom being derived from the solvent.[2-7]

$$\mathrm{ArSR} \xrightarrow{2e} \mathrm{ArS^-} + \mathrm{RH} \qquad (1)$$

Both stoichiometry[6] and polarographic data[7] indicate a two-electron process. However, there is evidence that an alkyl[6] or aryl[8] radical is formed as a primary cleavage fragment, as well as the arenethiolate ion. It follows that the aryl sulfide radical anion is the entity which actually fragments (eq 2).

$$[\mathrm{ArSR}]\cdot^- \longrightarrow \mathrm{ArS^-} + \mathrm{R}\cdot \qquad (2)$$

In aromatic substitution by the SRN1 mechanism,[9] the radical anions of aryl sulfides sometimes appear as intermediates.[10-14] In Scheme I, this radical chain mechanism is

Scheme I

$$\mathrm{ArX} + \text{electron source} \longrightarrow [\mathrm{ArX}]\cdot^- + \text{residue} \qquad (3)$$

$$[\mathrm{ArX}]\cdot^- \longrightarrow \mathrm{Ar}\cdot + \mathrm{X^-} \qquad (4)$$

$$\mathrm{Ar}\cdot + \mathrm{Y^-} \longrightarrow [\mathrm{ArY}]\cdot^- \qquad (5)$$

$$[\mathrm{ArY}]\cdot^- + \mathrm{ArX} \longrightarrow \mathrm{ArY} + [\mathrm{ArX}]\cdot^- \qquad (6)$$

$$\text{termination steps} \qquad (7)$$

presented in generalized form.[15] When a diaryl sulfide is involved as substrate (ArX), the fragmentation of its radical anion, $[\mathrm{ArX}]\cdot^-$, occurs in step 4. When a thiolate ion is involved as nucleophile ($\mathrm{Y^-}$), the species $[\mathrm{ArY}]\cdot^-$ formed in step 5 is an aryl sulfide radical anion, and conceivably it might suffer fragmentation before transferring an electron to another substrate molecule in step 6.

In the present investigation, we address a number of questions suggested by this discussion. If an alkanethiolate ion is employed as nucleophile $\mathrm{Y^-}$, will radical anion $[\mathrm{ArY}]\cdot^-$ fragment before it loses its "extra" electron? If an arenethiolate nucleophile, $\mathrm{Ar'S^-}$, is employed, with an aryl group different from that in substrate ArX, will the radical anion $[\mathrm{ArSAr'}]\cdot^-$ formed in step 5 fragment to Ar'· and $\mathrm{ArS^-}$, leading eventually to products $\mathrm{Ar_2S}$ and/or $\mathrm{Ar'_2S}$ as well as ArSAr'? If an unsymmetrical diaryl sulfide, ArSAr', is used as substrate in photostimulated reaction with acetone enolate ion,[11] in what proportions will the two arylacetones $\mathrm{ArCH_2COCH_3}$ and $\mathrm{Ar'CH_2COCH_3}$ be formed? Inasmuch as each of these questions has required separate investigation, we shall present and discuss the results from each before moving on to the next.

I. Reaction of Iodobenzene with Ethanethiolate Ions. Although the photostimulated reaction of iodobenzene with excess thiophenoxide ion in ammonia is quite fast, giving a nearly quantitative yield of diphenyl sulfide in 70 min,[12] that of iodobenzene with ethanethiolate ion is much slower. Under similar conditions, only 60% of iodide ion was released in 90 min. The products from an extended (200 min) reaction included 30% of ethyl phenyl sulfide and 3% of diphenyl sulfide.

Formation of the latter product suggested the intermediacy of thiophenoxide ion. A further run was performed under the same conditions, the ammonia was allowed to evaporate, and ethyl iodide was added to convert any thiophenoxide ion to ethyl phenyl sulfide. The yield of the latter was thereby raised to 61%, supporting the hypothesis. In a further experiment of similar type, benzyl chloride was added to benzylate the thiophenoxide ion, and 44% of benzyl phenyl sulfide was formed.

The reaction of iodobenzene with ethanethiolate ion, in ammonia under irradiation, thus gives products as indicated in eq 8.

$$\underset{}{\mathrm{PhI}} + \mathrm{EtS^-} \xrightarrow[\mathrm{NH_3}]{h\nu} \underset{30\%}{\mathrm{PhSEt}} + \underset{44\%}{\mathrm{PhS^-}} + \underset{3\%}{\mathrm{Ph_2S}} \qquad (8)$$

This result is interpreted as follows. Combination of phenyl radical with EtS^- in step 5, Scheme I, forms the ethyl phenyl sulfide radical anion, $[PhSEt]\cdot^-$. In part this transfers an electron to an iodobenzene molecule (step 6), and emerges as ethyl phenyl sulfide. In part it expels ethyl radical, and the resulting thiophenoxide ion reacts partially with iodobenzene by the SRN1 mechanism to form diphenyl sulfide. Much of the thiophenoxide ion, which is generated amid an excess of ethanethiolate ion, does not react but can later be captured by reaction with ethyl iodide or benzyl chloride.

The fate of the expelled ethyl radical is unclear. Many modes of reaction are conceivable. Most of them lead eventually to termination of the radical chain, and therefore to depression of overall reactivity. In these terms one comprehends why ethanethiolate is less reactive than thiophenoxide ion with iodobenzene.

We call attention to some similarity between this ethanethiolate ion reaction and the photostimulated reaction of the cyanomethyl anion with bromobenzene.[17] The latter reaction is also slow, owing to fragmentation of the phenylacetonitrile radical anion to benzyl radical and cyanide ion. The benzyl radical engages in termination steps.

It is noteworthy that the SRN1 mechanism (Scheme I) provides a straightforward interpretation of the phenomenon represented in eq 8, one that is consistent with published information on the reductive cleavage of alkyl phenyl sulfides.[2-8] This constitutes a further instance in which this mechanistic hypothesis has accommodated observations never anticipated when it was formulated.

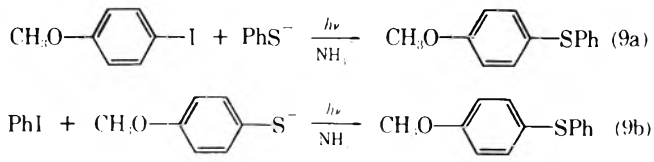
II. Reactions of Aryl Iodides with Arenethiolate Ions. According to the SRN1 mechanism, the same radical anion intermediate should be formed by reaction of ArI with PhS^- as by reaction of PhI with ArS^-, where Ar represents an aryl group other than phenyl. If the experiment is performed both ways, and if there is appreciable fragmentation of $[ArSPh]\cdot^-$, at least one of the symmetrical diaryl sulfides, Ar_2S and Ph_2S, should appear in one experiment or the other.

Let us consider starting with ArI and PhS^-. If $[ArSPh]\cdot^-$ does not fragment as fast as it transfers an electron in step 6, or if it fragments only in the sense of reverting to Ar· and PhS^-, only the unsymmetrical diaryl sulfide will be formed. On the other hand, if $[ArSPh]\cdot^-$ fragments into Ph· and ArS^- appreciably, the Ph· can combine with PhS^- to form $[Ph_2S]\cdot^-$ and ultimately Ph_2S, and the ArS^- can be attacked by Ar· (from ArI) to form $[Ar_2S]\cdot^-$ and ultimately Ar_2S. However, if PhS^- is present in excess over ArI, the latter behavior may be difficult to detect because of the statistical preference for combination of Ar· with the more abundant thiolate ion.

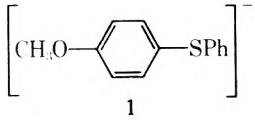
If only ArSPh is formed from ArI and PhS^- because, although $[ArSPh]\cdot^-$ fragments, it does so only to Ar· and PhS^-, some symmetrical diaryl sulfide(s) should, however, be obtained starting from PhI and ArS^-.

For the experiment to be meaningful, it must also be demonstrated that the symmetrical diaryl sulfides are formed from ArI + ArS^- and from PhI + PhS^-.

In conducting this experiment, we chose *p*-iodoanisole and *p*-methoxythiophenoxide ion as ArI and ArS^-. From their photostimulated reaction with each other we obtained bis(*p*-methoxyphenyl) sulfide in 73% yield. Iodobenzene and thiophenoxide are known to form diphenyl sulfide in 94% yield.[12] *p*-Iodoanisole and potassium thiophenoxide gave 76% of phenyl *p*-methoxyphenyl sulfide, but not a trace of either of the symmetrical diaryl sulfides (eq 9a). The same product was obtained from reaction of iodobenzene with *p*-methoxythiophenoxide ion (eq 9b), again without any symmetrical diaryl sulfide.



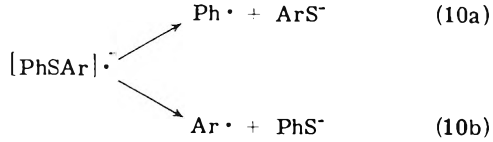
We conclude that in these reactions the intermediate radical anion, 1, transfers an electron to p-iodoanisole (eq



1

9a) or iodobenzene (eq 9b) in step 6 faster than it fragments.

Cleavage of phenyl *p*-methoxyphenyl sulfide by sodium in ammonia or lithium in methylamine is reported to furnish 100% of thiophenol but no *p*-methoxythiophenol.[4] The implication is that 1 does indeed fragment in the absence of an electron acceptor, such as an aryl iodide, and that it does so in the sense of eq 10b.



III. Reactions of Unsymmetrical Diaryl Sulfides with Acetone Enolate Ions. When an unsymmetrical diaryl sulfide undergoes photostimulated SRN1 reaction with acetone enolate ion, the radical anion of the sulfide is an intermediate and in principle it can split to give either of two pairs of aryl radical and arenethiolate ion (eq 10). The radicals are rapidly captured by acetone enolate ion with ultimate formation of arylacetones.[8] The relative yields of phenylacetone and the other arylacetone provide a measure of the relative tendencies of the radical anion to sunder in the two ways shown.

This experiment was performed with four different aryl phenyl sulfides. The results are summarized in Table I. An attempt also to perform it with 1-naphthyl phenyl sulfide was frustrated by the very low solubility of this substance in liquid ammonia.

In all cases the yield of phenylacetone is less than of the arylacetone derived from the other aryl moiety in the sulfide employed. This indicates that fragmentation in the sense of eq 10b is favored over that according to eq 10a when Ar is a *m*- or *p*-tolyl or *m*- or *p*-methoxyphenyl group.

On the presumption that transition state theory applies to this situation and that the transition state for fragmentation has some of the character of the products of fragmentation, the preference for route 10b over 10a might arise either from greater stability of Ar· over Ph· radical, or of lesser stability of ArS^- as compared to PhS^- anion. The latter factor might be invoked in three of the cases studied, for *m*- and *p*-CH_3 and *p*-OCH_3 increase the pK_a of thiophenol, but *m*-methoxythiophenol has a lower pK_a than thiophenol itself.[19] Perhaps substituent effects on aryl radical stability are the more important consideration.

Whatever determines the sense of cleavage of $[PhSAr]\cdot^-$, the preference for route 10b over 10a is not very great. The product yield ratio, $ArCH_2COCH_3/PhCH_2COCH_3$, varies from 1.2 to 3.1. If transition state theory applies, the difference in free energy between the two fragmentation transition states is at greatest 0.54 kcal/mol.

The cleavage of the four aryl phenyl sulfides of Table I with lithium in methylamine or sodium in ammonia was re-

Table I
Photostimulated Reactions of Unsymmetrical Diaryl Sulfides with Acetone Enolate Ion in Liquid Ammonia

Sulfide	Registry no.	Irradiation time, min	Products, % Phenylacetone (103-79-7)	Other arylacetone	Registry no.
m-$CH_3C_6H_4SC_6H_5$	13865-48-0	105	39	48[a]	18826-61-4
p-$CH_3C_6H_4SC_6H_5$	3699-01-2	105	28	38[b]	2096-86-8
m-$CH_3OC_6H_4SC_6H_5$	30723-54-7	75	28	49[c]	3027-13-2
p-$CH_3OC_6H_4SC_6H_5$	5633-57-8	90	16	50[d]	122-84-9

[a] m-Tolylacetone. [b] p-Tolylacetone. [c] m-Methoxyphenylacetone. [d] p-Methoxyphenylacetone.

ported by Truce, Tate, and Burdge.[4] For the most part the sense of fragmentation indicated by their studies is qualitatively in agreement with that shown by ours, but the indicated ratios of rupture by paths 10a and 10b differ in quantitative detail.

Ethyl phenyl sulfide was found not to react appreciably with acetone enolate ion under irradiation for 60 min; most of the sulfide remained unreacted. Benzyl phenyl sulfide for the most part survived exposure to acetone enolate ion during 50 min irradiation, and no products with the GLC behavior of phenylacetone or 4-phenyl-2-butanone could be found, though traces of some products did appear, one of them perhaps toluene.

Experimental Section

Reaction of Iodobenzene with Potassium Ethanethiolate. A solution of potassium *tert*-butoxide (*t*-BuOK) in 130 ml of liquid ammonia was prepared from 1.45 g of *tert*-butyl alcohol and 0.75 g of potassium metal with a trace of ferric nitrate. Ethanethiol (1.2 g) was added followed by 0.987 g of iodobenzene. The entire procedure was carried out under nitrogen. The mixture was irradiated under reflux and under a slow stream of nitrogen for 200 min in a Rayonet Model RPR-100 photochemical reactor equipped with 16 ca. 24-W fluorescent lamps emitting maximally at 350 nm. The ammonia was allowed to evaporate and the residue was taken up into diethyl ether and water. The organic phase was separated and dried over anhydrous Na_2SO_4, and the yields of phenyl ethyl sulfide and diphenyl sulfide were determined by GLC on a 1.22-m column of 10% SE-54 silicone rubber on Chromosorb P with diphenyl ether being used as internal standard. Samples of these two products were isolated by GLC and identified by comparison of infrared spectra and GLC retention times with those of authentic samples.

In a similar run, 25 ml of ethanol and 6 ml of ethyl iodide were added after evaporation of the ammonia, the mixture was heated at reflux for 1 hr, the ethanol was removed by evaporation, water and ether were added, and ethyl phenyl sulfide was determined by GLC as above; the yield was 61%.

In a third similar run, after evaporation of the ammonia, 25 ml of ethanol and 3.6 g of benzyl chloride were added, the mixture was heated at reflux for 1.5 hr, water and ether were added, and benzyl phenyl sulfide was determined by GLC to be present in 44% yield, the internal standard being 1-naphthyl phenyl sulfide.

Reactions of Aryl Iodides with Arenethiolate Ions. A solution of 1.02 g of *p*-iodoanisole, 1.55 g of thiophenol and 1.65 g of *t*-BuOK in ca. 125 ml of liquid ammonia, with the *p*-iodoanisole not entirely dissolved, was irradiated in the photochemical reactor (vide supra) for 30 min, during which time the *p*-iodoanisole dissolved. The residue from evaporation of the ammonia was taken up in ether and water, and the ether layer was dried over anhydrous Na_2SO_4 and the solvent removed by evaporation. GLC analysis of the residue on the above column at 200° revealed the presence of a small amount of anisole, about 10% of *p*-iodoanisole, and a major product of longer retention time, but no trace of diphenyl sulfide. Distillation of the residue at reduced pressure afforded 0.69 g (76%) of phenyl *p*-methoxyphenyl sulfide: ^{1}H NMR (60 MHz, CCl_4) δ 3.78 (s, CH_3), 6.90 (d, J = 9 Hz), 7.25 (pseudosinglet, C_6H_5), 7.48 (d, J = 9 Hz).

By a similar reaction of iodobenzene with ammonium *p*-methoxythiophenoxide with 120-min irradiation, a substance of identical infrared spectrum, bp 118–120° (0.05 Torr), was obtained in 71% yield; GLC analysis of the crude product indicated about 10% of unreacted iodobenzene and about 5% of a material with retention time similar to that of the main product, probably the ortho isomer thereof, but no trace of bis(*p*-methoxyphenyl) sulfide.

By a similar reaction of *p*-iodoanisole with potassium *p*-methoxythiophenoxide with 100-min irradiation, a crude product was obtained, GLC analysis of which indicated about 10% of anisole, a little unreacted *p*-iodoanisole, and a major product peak. By distillation at reduced pressure, 73% of bis(*p*-methoxyphenyl) sulfide was obtained. The ^{1}H NMR spectrum agreed with that reported by Fujisawa and Tsuchihashi.[20] The mass spectrum showed a predominant peak at *m/e* 246 (the main product) and substantial peaks at *m/e* 231 and 139, as well as a lesser but significant peak at *m/e* 278 (bis-*p*-methoxyphenyl disulfide).

Reactions Summarized in Table I. In a typical reaction, 2.20 g (0.0196 mol) of *t*-BuOK, 1.08 g (0.0186 mol) of acetone, and 0.990 g (0.0046 mol) of phenyl *m*-methoxyphenyl sulfide were dissolved in 150 ml of liquid ammonia, and the mixture was irradiated under reflux in the photochemical reactor described above for 75 min. After standard processing, the product mixture was analyzed by GLC on a 2.44-m column of 3% Carbowax plus 2% Apiezon L with naphthalene and biphenyl being used as internal standards for phenylacetone and *m*-methoxyphenylacetone, respectively.

For calibration of the GLC analysis, authentic samples of *m*-methyl-, *p*-methyl-, *m*-methoxy-, and *p*-methoxyphenylacetone were prepared by photostimulated reactions of the corresponding iodotoluenes or bromoanisoles with acetone enolate ion. *m*-Methylphenylacetone had NMR and ir spectra in agreement with those reported by Thigpen and Fuchs:[21] MS *m/e* 148 (M^+), 105, 91. *p*-Methylphenylacetone: NMR (CCl_4) δ 2.02 (s, 3 H), 2.45 (s, 3 H), 3.58 (s, 2 H), 7.19 (s, 4 H); ir (film) 1715 (s), 1226 and 1159 (m), 830 and 790 cm^{-1} (m); MS *m/e* 148 (M^+), 105, 91; the NMR and mass spectra agree with those recorded by Rossi,[22] who prepared an authentic sample by the reaction of *p*-methylbenzylcadmium chloride with acetyl chloride. *m*-Methoxyphenylacetone had an NMR spectrum in agreement with two reports in the literature:[23] ir (film) 1705 (s), 1255 (s), 1152 (m), 1055 (m), 781, and 701 cm^{-1} (m); MS *m/e* 164 (M^+), 121, 107, 91. *p*-Methoxyphenylacetone: NMR (CCl_4) δ 2.01 (s, 3 H), 3.51 (s, 2 H), 3.76 (s, 3 H), 6.7–7.3 (m, 4 H); ir (film) 1705 (s), 1248 (s), 1180 and 1159 (m), 1035 (m), 845 cm^{-1} (m); MS *m/e* 164 (M^+), 135, 121, 91; the NMR spectrum agrees with that recorded by Rossi,[22] who prepared an authentic sample by the method of Heinzelman.[24]

Acknowledgments. We thank Eric W. Bouldin for technical assistance, and Dr. R. P. Traber for advice.

Registry No.—Iodobenzene, 591-50-4; potassium ethanethiolate, 54669-43-1; phenyl ethyl sulfide, 622-38-8; diphenyl sulfide, 139-66-2; *p*-iodoanisole, 696-62-8; potassium thiophenolate, 3111-52-2; potassium *p*-methoxythiophenoxide, 56830-32-1; bis(*p*-methoxyphenyl) sulfide, 3393-77-9; bis(*p*-methoxyphenyl) disulfide, 5335-87-5.

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Addition of Singlet Oxygen to Arene Oxides[1,2]

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Singlet oxygen adds to benzene oxide to afford endo peroxide **2** that readily rearranges to *trans*-benzene trioxide (**3**), and reacts with triphenyl phosphite to afford *trans*-benzene dioxide (**5**). Endo peroxide **2** was also converted into **4**, **6**, and **7**. Indan 8,9-oxide reacts with singlet oxygen to afford endo peroxide **9** that undergoes similar reactions to give **10** and **11**.

Since the initial reports on the synthesis of *trans*-benzene trioxide (**3**) from rearrangement of the endo peroxide obtained by addition of singlet oxygen to oxepin–benzene oxide (**1**),[3,4] similar products have been prepared from addition of singlet oxygen to oxidoannules[5] and indene.[6] The synthesis and chemistry of *cis*-benzene trioxide have been reported.[5,7–13] *trans*-Benzene dioxide,[14] *cis*-benzene dioxide,[15] and *cis*-benzene dioxide derivatives[16,17] have also been studied. Of particular interest is the valence bond isomerism of *cis*-benzene trioxide and *cis*-benzene dioxides with the corresponding *cis,cis,cis*-1,4,7-trioxacyclononatriene and 1,4-dioxacins, respectively. A variety of substances related to the benzene oxides described above in which one or more oxygen atom is replaced by carbon, nitrogen, or sulfur have been prepared.[5,8,11,12,14,18]

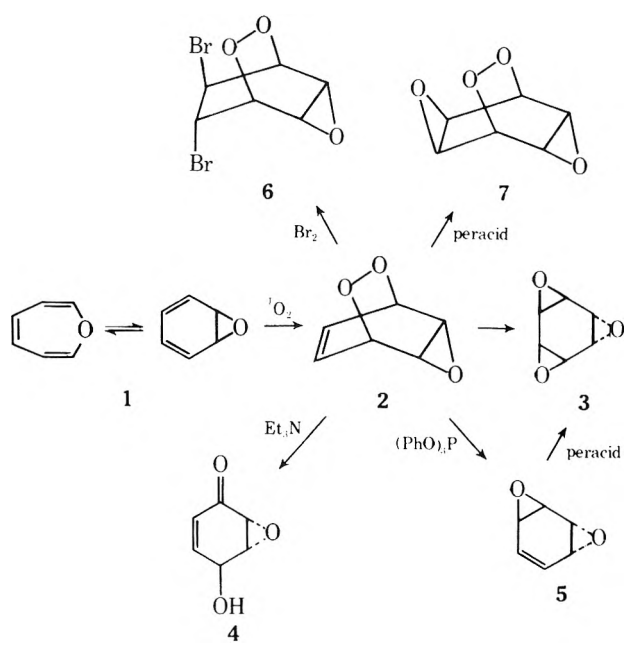
Reaction of oxepin–benzene oxide (**1**) with singlet oxygen generated from hypochlorite–hydrogen peroxide by the method of Foote[19] affords, in 37% yield, pure, crystalline endo peroxide **2**, which undergoes quantitative rearrangement to **3** on heating in chloroform at 45° (half-life ~14 hr) or on heating under reflux for 16 hr in ethyl acetate. (Scheme I). Photosensitized oxygenation of **1** with Methylene Blue or Rose Bengal as sensitizer gives mainly phenol.[20] Singlet oxygen generated from the adduct of ozone and triphenyl phosphite[21] also oxygenates **1**, but separation of **2** from triphenyl phosphate is difficult; sublimation of the product mixture affords **3** (17% yield).

The facile rearrangement of **2** to **3** is particularly interesting in view of previously reported rearrangements of 1,4-endo peroxides derived from 1,3-cyclohexadienes that require higher temperature and tend to yield mixtures including hydroxy ketone or epoxy ketone in addition to bisepoxide.[22–24] Photochemical rearrangement of **2**[25] affords **3** in only 27% yield. It is our belief that the thermal rearrangement of **2** to **3** is a concerted reaction, but ionic or radical pathways cannot be ruled out completely.

Endo peroxide **2** reacts with triethylamine to give ketol **4**, and with triphenyl phosphite to give *trans*-benzene dioxide (**5**).[26] The latter substance is a fairly volatile white solid that readily decomposes on standing. Catalytic hydrogenation (Pd/C) of **5** affords *trans*-1,2-cyclohexanediol.[27] Epoxidation of **5** affords **3**.

Reaction of **2** with bromine in chloroform gives dibromide **6** and with peroxytrifluoroacetic acid gives **7**. Both products are crystalline substances that undergo violent decomposition without melting at ~100°.

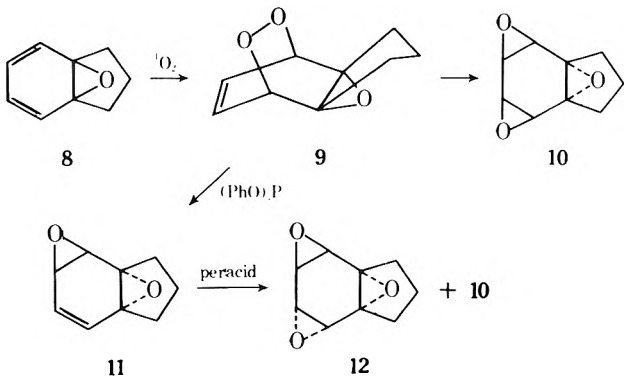
Scheme I



The addition of singlet oxygen to indan 8,9-oxide (**8**) is more facile than the photooxygenation of **1**. Thus, photosensitized addition of singlet oxygen to **8** gives **9** in quantitative yield (Scheme II). The more facile addition to **8** as compared to **1** may be due to the greater stability of **8** or the fact that **8** exists entirely in the arene oxide form[28] and is not subject to side reactions through the oxepin form. Rearrangement of **9** occurs in ~3 days at room temperature or overnight in refluxing chloroform to give **10** in essentially quantitative yield. The ease of conversion of **9** to **10** is similar to that for conversion of **2** to **3** and suggests that the stereochemistry of the endo peroxy and epoxy groups is the same in **9** and **2**. For establishment of the stereochemistry in **10**, see Experimental Section.

Reaction of **9** with triphenyl phosphite is exothermic and affords *trans*-indan dioxide (**11**). Epoxidation of **11** affords a 2.6:1 mixture of **12** and **10**, respectively.

Scheme II



Experimental Section

All melting points are corrected, boiling points uncorrected, and the former were taken using a Thomas-Hoover Uni-Melt apparatus or a Kofler hot stage. Infrared spectra were determined with a Perkin-Elmer Model 237B grating spectrophotometer. The proton NMR spectra were determined with either a Varian T-60 or HA-100, or Perkin-Elmer Model R-20-B spectrometer. Fourier transform ^1H NMR spectra were taken on the Perkin-Elmer Model R-20-B equipped with a Digilab FTS/NMR-3 data system.[29] Chemical shift data were reported in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D or Du Pont 21-491 mass spectrometer with an ionizing potential of 70 eV unless otherwise indicated. High-resolution mass spectra were determined on a CEC-21-110B spectrometer.[30] The GLC analyses were done on a Hewlett-Packard Model 5750 (thermal conductivity detector) chromatograph using 6–8 ft × 0.25 in. stainless steel columns packed with the specified liquid phase on 60–80 mesh Chromosorb P, or on a Varian Aerograph Series 2100 (flame ionization) chromatograph with 6 ft × 2 or 3.5 mm i.d. glass columns, glass injection port, and glass effluent splitter. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Anacon Associates, Chelmsford, Mass.

***endo*-3,8,9-Trioxatricyclo[3.2.2.0^{2,4}]non-6-ene (2).** Using the method of Foote[19] a solution of 1.9 g (20 mmol) of 1[28] in 125 ml of methanol was chilled to −5 to −15°, and 13.29 g (120 mmol) of H_2O_2[31] was added. To this solution was added dropwise 103 ml of 0.73 *M* NaOCl[31] with continual cooling and stirring. The reaction mixture was diluted with 125 ml of H_2O and extracted with six 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$), and the solvent was removed on a rotary evaporator to give a semicrystalline residue. Trituration with ether gave white crystals: mp 91–92°; ir ($CHCl_3$) 3015, 1405, 1372, 1285, 973, 920, 882, and 874 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (m, 2 H), 5.1 (m, 2 H), and 6.35 ppm (t, 2 H, J = 4 Hz); mass spectrum *m/e* (rel. intensity) 126 (10), 95 (8), 94 (100), 81 (7), 68 (11), 66 (42), 65 (7), 64 (metastable), 41 (6), 40 (6).

Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.00; H, 4.74.

Caution: In one preparation using 9.8 g of 1, an explosion occurred when the solvent was being evaporated from the crude product. Subsequent preparations were carried out on a smaller scale.

Oxygenation of 1 with Singlet Oxygen Generated from Triphenyl Phosphite–Ozone Adduct. In a procedure similar to that used by Murray and Kaplan,[21] triphenyl phosphite (MCB, 9.3 g) in 150 ml of CH_2Cl_2 was ozonized at −78°. When the blue color of excess ozone was observed, the ozone stream was disconnected and replaced by a stream of N_2. When all of the ozone had been purged, 1.8 g of 1 in 45 ml of CH_2Cl_2 (cold) was added, and the solution was allowed to warm to room temperature. The CH_2Cl_2 was removed on a rotary evaporator. The resulting yellow liquid gave an NMR spectrum which showed that 2 had been formed. However, attempted isolation of 2 by column chromatography (neutral alumina) failed and sublimation required heating to 60°, which caused partial rearrangement to 3 (spectral data described below). Thus the endo peroxide could not be isolated using this procedure, but when a $CHCl_3$ solution of the crude product was stirred at reflux overnight, then concentrated and sublimed at 50–60° (0.5 Torr), 3 was isolated in 17% yield.

***trans*-3,6,9-Trioxatetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane (*trans*-Benzene Trioxide, 3).** A solution of 100 mg of 2 in 2 ml of ethyl acetate was stirred at reflux for 16 hr. The solvent was then evaporated on a rotary evaporator to give 100 mg of white crystals: sublimed at 40° (0.4 Torr); mp 84–86°; ir ($CHCl_3$) 3020, 1450, 1239, 950, and 860 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (s, 4), 3.5 ppm (s, 2); NMR (C_6D_6) δ 2.4–2.7 (m, 4), 2.8 ppm (s, 2); mass spectrum *m/e* (rel intensity) 126 (5), 97 (26), 81 (21), 71 (52), 70 (6), 69 (75), 68 (61), 55 (16), 54 (8), 53 (17), 52 (6), 44 (5), 43 (22), 42 (21), 41 (100), 40 (15); ^{13}C NMR (acetone) 20.659, 17.477, 17.045, 0.000 ppm (CH_3 of acetone).

A solution of 2 (~20 mg) in ~0.5 ml of $CDCl_3$ was heated at 45° in an NMR tube. The NMR spectrum was observed at several times during the reaction and from the integration, the percentage conversion to 3 could be derived {time (hr), log [2]}: 2.1, 1.93; 3.8, 1.90; 7.6, 1.83; 20.8, 1.52; 24.8, 1.42; 32.9, 1.27. A first-order rate constant of $k = 1.4 \times 10^{-5}$ sec^{-1} ($t_{1/2}$ = 14 hr was obtained from a plot of time vs. log [2].

Photochemical Rearrangement of 2. Using a procedure similar to that described by Maheshwari, de Mayo, and Wiegand,[22] a solution of 77 mg of 2 in CH_3OH (25 ml) was degassed by N_2 purge (30 min). The solution was irradiated through Pyrex for 22 hr (3000 Å in a Rayonet reactor[32]). The solvent was removed on a rotary evaporator to give a yellow oil which was only partially soluble in $CHCl_3$. The soluble fraction (59 mg) gave an NMR spectrum with peaks assigned to 3 but also had peaks at δ 5.8–7.2 ppm. Purification by distillation (50–60°, 0.05 Torr) gave 21 mg (27% yield) of a brown oil which was shown by NMR to be mainly 3.

***trans*-4-Hydroxy-5-epoxycyclohex-2-enone (4).** To a solution of 2 (102 mg) in 1 ml of $CHCl_3$ was added 30 μl of $(C_2H_5)_3N$. After standing for 5 min at room temperature the resulting black solution was filtered through 1.0 g of alumina (acid washed) with 15 ml of EtOAc. The solvent was removed on a rotary evaporator to give 80 mg (80% yield) of a brown oil which was pure by NMR: NMR ($CDCl_3$) δ 6.6 (ddd, 1 H, J_1 = 10, J_2 = 5, J_3 = 3 Hz), 5.9 (d, 1 H, J = 10 Hz), 4.6 (m, 1 H), 3.8 (m, 1 H), 3.5 (m, 1 H), 2.6 ppm (d, 1 H, J = 8 Hz); when the absorption at δ 4.6 was irradiated the pattern at δ 6.6 ppm collapsed to a doublet (J = 10 Hz) and the doublet at 2.6 ppm collapsed to a singlet. Attempted purification of 4 by TLC on silica gel or alumina caused decomposition. Sublimation (40–50°, 0.05 Torr) or column chromatography on neutral alumina using ether for elution gave a poor yield (~10%) of 4 as white crystals: mp 49–50°; ir ($CHCl_3$) 3580, 3400, 2950, 1690, 1420, 1380, 1245, 1040, 855 cm^{-1}; NMR as described above; mass spectrum *m/e* (rel intensity) 126 (24), 98 (12), 97 (100), 82 (12), 81 (11), 80 (8), 71 (29), 69 (40), 68 (11), 55 (35).

Anal. Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 56.79; H, 4.85.

Purification of 4 was also accomplished by GLC on a glass column at 120° using an SE-30 liquid phase.

***trans*-5,8-Dioxatricyclo[5.1.0.0^{4,6}]oct-2-ene (*trans*-Benzene Dioxide, 5).** Endo peroxide 2 (250 mg, 2 mmol) was added neat to 620 mg of triphenyl phosphite (MCB, 2 mmol) at −50°. The mixture was allowed to warm and a very exothermic reaction took place. Sublimation of the reaction mixture (~20 Torr, 40°) gave white crystals (73% yield) which quickly turned yellow on isolation: ir (CCl_4) 3000, 1465, 1440, 1398, 1230, 1110, 1060, 975, 940, 828 cm^{-1}; NMR ($CDCl_3$) δ 6.05 (t, 2 H, J = 3 Hz), 3.7 (dd, 2 H, $J_1 \simeq 3$, $J_2 \simeq 1$ Hz), 3.1 ppm (m, 2 H); mass spectrum *m/e* (rel intensity) 111 (8), 110 (100), 94 (16), 92 (11), 82 (19), 81 (65), 66 (14), 65 (10), 64 (26), 63 (17). These data are in agreement with those reported by Vogel.[14]

Epoxidation of 5. *m*-Chloroperbenzoic acid (MCPBA, Aldrich, 40 mg) was added to a solution of 5 (20 mg) in CD_2Cl_2. After 1 hr the NMR spectrum of the reaction mixture indicated partial conversion to 3. After 16 hr the precipitate which had formed was filtered off. The NMR of the resulting solution indicated complete conversion to 3.

Hydrogenolysis of 5. A solution of 79 mg of 5 in 5 ml of EtOAc was hydrogenated over 10% Pd/C (8 mg) at atmospheric pressure. Filtration followed by evaporation of solvent gave 79 mg of white crystals. The product gave one peak on GLC (6 ft, 10% Carbowax 20M, 180°), with a retention time of 14 min. Retention times of known samples of *cis*-1,2-cyclohexanediol (Frinton) and *trans*-1,2-cyclohexanediol (Aldrich) were 12.8 and 14 min, respectively. The ir spectrum of the product was identical with that of *trans*-1,2-cyclohexanediol.

1β,4β-Epidioxy-2β,3α-dibromo-5α,6α-epoxyhexahydrobenzene (6). Br_2 (35.8 ml, 70 mmol) was added to a solution of 88 mg (70 mmol) of 2 in 2 ml of $CHCl_3$. The solvent was removed on a rotary evaporator to give 6 as a white solid (90% crude yield). Recrys-

tallization from $CHCl_3$–hexane at low temperature gave 85 mg (43% yield) of white crystals, which were sublimed at 40–50° (0.03 Torr). The product exploded at 100° without melting; ir (KBr) 2985, 1270, 1240, 1205, 1185, 1110, 1000, 955, 925, 860, 840, 810, 705 cm^{-1}; NMR (acetone-d_6) δ 4.9 (m, 2 H), 4.6 (d, 1 H, J = 4 Hz), 4.4 (d, 1 H, J = 4 Hz), 3.9 ppm (t, 2 H, J = 3 Hz); mass spectrum m/e (rel intensity) 288 (9), 286 (16), 209 (12), 207 (14), 206 (11), 191 (82), 189 (84), 135 (47), 127 (44), 125 (96).

High-resolution mass spectrum. Calcd for $C_6H_6O_3Br_2$: 283.86842. Found: 283.87090.

***trans*-3,7,9,11-Tetraoxatetracyclo[3.3.2.0^{2,4}.0^{6,8}]decane (7).** Peroxytrifluoroacetic acid was prepared from 123 μl of 90% H_2O_2 and 762 μl of trifluoroacetic anhydride in 500 μl of CH_2Cl_2 by the procedure of Emmons and Pagano.[33] The solution was added to a solution of 2 (177 mg, 1.4 mmol) in 4 ml of CH_2Cl_2. The solution was stirred for 3 hr at room temperature, 5 ml of CH_2Cl_2 was added, and the solution was washed with three 5-ml portions of H_2O and dried ($MgSO_4$). The CH_2Cl_2 was removed on a rotary evaporator to give 101 mg (57% yield) of white crystals which were sublimed at 55–65° (0.04 Torr) to give **7**, a white solid, which explodes at 110° without melting; ir ($CHCl_3$) 3000, 1390, 1330, 1250, 1200, 990, 950, 935, 900, 845, 830 cm^{-1}; NMR (CD_2Cl_2) δ 4.75 (m, 2 H), 3.8 (m, 2 H), 3.3 ppm (t, 2 H, J = 2 Hz); mass spectrum m/e (rel intensity) 142 (39), 126 (22), 100 (24), 99 (16), 97 (16), 96 (13), 85 (15), 84 (19), 73 (23), 71 (100).

High-resolution mass spectrum. Calcd for $C_6H_6O_4$: 142.02661. Found: 142.02789.

4β,7β-Epidioxy-3aα,7aα-epoxy-3a,4,7,7a-tetrahydroindan (9). An apparatus similar to that described by Foote[19] was used except that the solution, in a water-cooled round-bottom flask, was irradiated with two 300-W.G.E. floodlights. A solution of 5.0 g of 8[28] (37 mmol) and 30 mg of Rose Bengal in 300 ml of acetone was irradiated; oxygen uptake (850 cm^3, 35 mmol) stopped after 3 hr. To minimize the risk of explosion the solution was divided into four portions, and acetone was removed on a rotary evaporator to give a red solid (6.2 g, 100%). The product was pure by NMR but contained Rose Bengal that could be removed by sublimation (room temperature, 0.04 mm) or TLC (silica gel, ether) to give **9** as a white, crystalline solid: mp 76–77°; ir (CCl_4) 2955, 1435, 1425, 1410, 1360, 1275, 1245, 1055, 965, 940, 935, 915, 880, 860 cm^{-1}; NMR (CCl_4) δ 6.2 (t, 2 H, J = 3 Hz), 4.7 (t, 2 H, J = 3 Hz), 1.6–2.2 ppm (m, 6 H); mass spectrum m/e (rel intensity) 166 (2), 137 (13), 110 (14), 109 (20), 96 (12), 95 (16), 94 (17), 81 (100), 79 (52), 71 (23).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.04; H, 6.09.

Thermal rearrangement of **9** was so facile that all samples of **9** contained some **10**; the analytical sample may have been mostly **10** when analyzed.

4β,5β;6β,7β;3aα,7aα-Triepoxyhexahydroindan (10). A solution of 1.0 g of **9** in 20 ml of $CHCl_3$ was allowed to stir at reflux for 20 hr. The solvent was removed on a rotary evaporator to give 1.0 g of white solid which was pure by NMR but had a small carbonyl absorption in the ir spectrum. The product was further purified by sublimation (50°, 0.05 Torr) followed by GLC (6ft, 10% Silicone U. C. W., 160°) to give a white, crystalline solid: mp 102–103°; ir ($CHCl_3$) 2955, 1445, 1420, 1295, 1255, 1100, 1065, 1040, 1010, 940, 915, 875, 855 cm^{-1}; NMR ($CDCl_3$) δ 3.4 (s, 4 H), 2.2–1.4 ppm (m, 6 H); NMR (C_6D_6) δ 2.9 (m, 2 H), 2.7 (m, 2 H), 1.8–1.0 ppm (m, 6 H); mass spectrum m/e (rel intensity) 137 (11), 110 (10), 109 (17), 97 (11), 95 (17), 82 (17), 81 (100), 79 (54), 68 (34), 67 (44).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.20; H, 6.07.

The trisepoxide **10** was also prepared by allowing a solution of **9** in $CDCl_3$ to stand at room temperature for 3 days, after which the NMR spectrum showed complete conversion to **10**.

6β,7β;3aα,7aα-Diepoxy-3a,6,7,7a-tetrahydroindan (11). Triphenyl phosphite (1.24 g, 4 mmol) was added slowly to a stirred solution of 664 mg (4 mmol) of **9** in 4 ml of $CHCl_3$. Since the reaction is exothermic, care must be taken in order to keep the solution near room temperature. After the addition, the solution was stirred at room temperature for 30 min. The solvent was evaporated on a rotary evaporator and distillation (29–31°, 0.05 Torr) gave **11** as a colorless liquid (510 mg, 85% yield). Further purification by preparative TLC (alumina, ether) gave a colorless oil: ir (neat) 2950, 1460, 1430, 1400, 1300, 1250, 1185, 1060, 1025, 950, 910, 870, 830, 795, 720 cm^{-1}; NMR ($CDCl_3$) δ 6.0 (m, 2 H), 3.7 (d, 1 H, J = 4 Hz), 3.1 (m, 1 H), 2.2–1.2 ppm (m, 6 H), when the absorption at 6.0 ppm (H_4, H_5) was irradiated the multiplet at 3.1 (H_6) collapsed to a doublet (J = 4 Hz); mass spectrum m/e (rel intensity) 151 (10), 150 (100), 132 (30), 131 (22), 122 (39), 121 (44), 95 (95), 94 (52), 79 (69), 66 (91).

High-resolution mass spectrum. Calcd for $C_9H_{10}O_2$: 150.06808. Found: 150.06930.

Comparison of the proton NMR spectrum of **11** with that of **5** and *cis*-benzene dioxide[15] confirms the indicated stereochemistry in **11** and, consequently, in **9** and **10** (H's numbered according to formal name).

	δ	δ	δ
11	6.0 (H_4, H_5)	3.7 (H_7)	3.1 (H_6)
5	6.05 (H_2, H_3)	3.7 (H_6, H_7)	3.1 (H_1, H_8)
cis-Benzene oxide[15]	6.47 (H_2, H_3)	3.71 (H_6, H_7)	3.39 (H_1, H_4)

Epoxidation of 11. A solution of *m*-chloroperbenzoic acid (670 mg, 3.3 mmol) in 3 ml of CH_2Cl_2 was added to a solution of 450 mg of **11** in 1 ml of CH_2Cl_2. The solution was stirred at room temperature for 3 days. A precipitate which had formed was removed by filtration. The resulting solution was washed with a saturated aqueous sodium bisulfite solution, followed by a 5% aqueous NaOH solution. The CH_2Cl_2 solution was dried ($MgSO_4$). The CH_2Cl_2 was removed on a rotary evaporator to give a colorless oil which gave an NMR spectrum similar to that of trisepoxide **10**, but also had peaks at δ 6.8–8.2 ppm. Repeated washing with bisulfite and 5% NaOH solutions did not remove the impurities. Analysis by GLC (6 ft, 12% QF-1, glass column, 160°) showed two major peaks in a ratio of 1:2.6. The smaller peak was collected and identified as **10** by retention time, ir, and mass spectra. The larger peak was collected from GLC (reinjection showed only one peak) as a white solid, 4α,5α;6β,7β;3aα,7aα-triepoxyhexahydroindan (**12**): mp 88–90°; ir ($CHCl_3$) 2950, 1445, 1420, 1295, 1195, 1135, 1060, 1015, 915, 875, 835 cm^{-1}; Fourier transform NMR (C_6D_6) δ 2.82 (s, 2 H), 2.62 (s, 2 H), 1.78–0.68 ppm (m, 6 H); mass spectrum m/e 166 (3), 137 (41), 109 (38), 108 (26), 94 (26), 81 (100), 79 (70), 71 (42), 67 (79), 65 (29).

Registry No.—**1**, 291-70-3; **2**, 39597-90-5; **3**, 39078-13-2; **4**, 55164-61-9; **5**, 51153-58-3; **6**, 56411-66-6; **7**, 56411-67-7; **8**, 1488-21-7; **9**, 56411-68-8; **10**, 56411-69-9; **11**, 56411-70-2; **12**, 56452-86-9; singlet oxygen, 17778-80-2; NaOCl, 7681-52-9; triphenyl phosphite, 101-02-0; *m*-chloroperbenzoic acid, 937-14-4; peroxytrifluoroacetic acid, 359-48-8.

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The Nef-Type Transformation in Basic Solution

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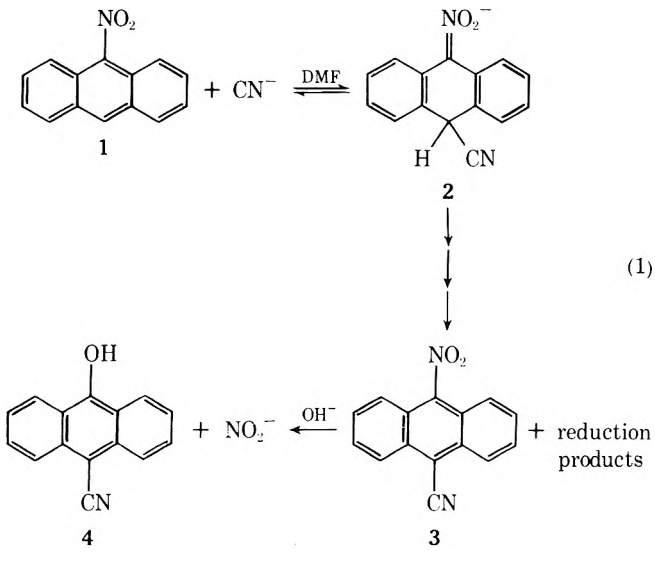
The replacement of the nitro group of *o*-nitrobenzonitrile, which takes place when the substance is converted to 2-hydroxyisophthalonitrile by the action of sodium cyanide in Me_2SO, occurs via a Nef-type process of the cyanide ion adduct of the nitronitrile. The normal second product of the Nef reaction, nitrous oxide, is produced in yield comparable to that of the hydroxyisophthalonitrile. The similar conversions of *p*-nitrobenzonitrile and *p*-nitrobenzophenone to hydroxynitriles also produce nitrous oxide and hence proceed via the Nef route, although a part of the product from the nitro ketone may also form by the more complex path in which the cyanide ion adduct undergoes oxidation–reduction reactions via the ion radical with final displacement of the nitro group by hydroxide ion. The reactions constitute new examples of the rare occurrence of the Nef-type process in basic medium. For preparative use the nitrocyano compound may be produced in situ by reaction of sodium cyanide with a nitrohalo compound, e.g. *o*-nitrofluorobenzene, and converted on to the hydroxynitrile by reaction with excess sodium cyanide in the solution. Both the hydroxyisophthalonitriles prepared are rapidly converted to the high-melting, highly insoluble trimers, e.g., 2,4,6-tri-3-cyano-2-hydroxyphenyl-*s*-triazine from 2-hydroxyisophthalonitrile, by heating, conveniently, for preparative purposes, in dimethylaniline solution.

The direct conversion of an aromatic nitro compound to a cyanophenol in which the hydroxyl group is located on the carbon atom originally bearing the nitro group, occurring when the nitro compound is treated with sodium cyanide in an aprotic solvent, has been explained[1,2] as the result of displacement by hydroxide ion of the nitro group of an intermediate aromatic nitrocyano compound. Thus, 10-cyano-9-anthranol (**4**) was considered to form from 9-nitroanthracene (**1**) as the result of electron exchange of the Meisenheimer-type adduct (**2**), disproportionation of the resulting radical with the formation of 10-cyano-9-nitroanthracene (**3**) and other products, and, finally, displacement of the nitro group of **3** by hydroxide ion. The hydroxide ion effecting the displacement was assumed to form from water adventitiously present in the solvent and/or reagent or produced in the oxidation–reduction reactions also occurring in the reaction solution.[1] A reduction product of **2**, 10-cyano-9-aminoanthracene, could be isolated in yields up to 20%, and the proposed intermediate **3**, an oxidation product of **2**, could be isolated in trace amounts.



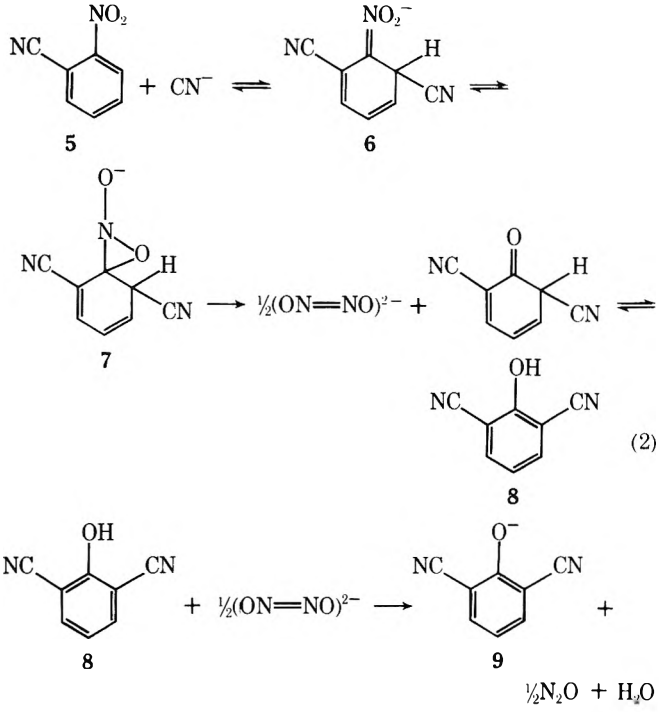
(1)

In a test of the substitution–displacement reaction on *o*-nitrobenzonitrile (**5**), carried out in Me_2SO with 2 equiv of sodium cyanide at 120° for 1 hr, the product mixture was much simpler than that from 9-nitroanthracene, and 2-hydroxyisophthalonitrile (**8**) could be isolated in 60% yield.[3] The absence of isolable amounts of reduction products suggested that the reaction occurred by a different course, perhaps one related to the Nef reaction. The Nef reaction itself has long been regarded as an exclusively acid-catalyzed transformation,[4,5] but recently the formation of levulinic acid from 4-nitrovalerate anion has been considered[6] an example of the Nef reaction occurring in basic medium; a gas presumed to be nitrous oxide, a normal product of the Nef reaction, was evolved.[6] The fact that the reaction also occurred with the anion of 4-nitro-3-methylvaleric acid but not with that of either 3-nitropropionic or of 6-nitrohexanoic acid led to the suggestion of a cyclic ester intermediate (carboxylate participation) in the formation of the levulinate anion.[6] No such intermediate could be involved in the transformation of the cyanide ad-

duct of a simple aromatic nitro compound, such as *o*-nitrobenzonitrile (**5**).

In a repetition of the o-nitrobenzonitrile reaction the gas evolved was swept by a stream of helium into a liquid nitrogen cooled trap, purified by vacuum distillation at −80°, and submitted to mass spectral examination. The gas proved to be nitrous oxide, the fragmentation patterns and the ratios of the peaks observed with the product and with an authentic sample being identical; it was isolated in 54% yield based on the nitronitrile employed (or approximately 90% based on the hydroxyisophthalonitrile isolated from the preparative test under the same conditions). A similar treatment of *p*-nitrobenzonitrile produced 4-hydroxyisophthalonitrile, along with a gas similarly shown to be nitrous oxide.

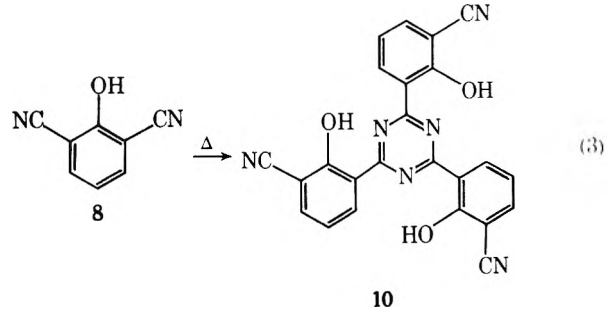
The key step in the reaction may be the ejection of hyponitrite ion from the Meisenheimer-type adduct (**6**) formed from *o*-nitrobenzonitrile (**5**) and cyanide ion, perhaps via the oxaziridine isomer (**7**), leading to the hydroxyisophthalonitrile (**8**) which can liberate nitrous oxide by protonating the hyponitrite anion. That nitrous oxide is formed as the reaction proceeds, rather than during the work-up, is shown by the experiment just cited, in which the gas formed during the heating period was collected. That the phenoxide anion **9** is present at the end of the reaction is indicated by the isolation of the methyl ether, in 30% yield, when a cooled reaction mixture was treated with methyl sulfate in the absence of any added base.



The identification of nitrous oxide as a principal product from the reaction of *o*- or *p*-nitrobenzonitrile makes it evident that the path differs from that of the reaction of 9-nitroanthracene. Further indication of different courses may be seen in the paramagnetic resonance spectra of the various reaction solutions. A solution of 9-nitroanthracene in DMF gave a strong EPR signal which diminished with time, interpreted as arising from radicals and ion radicals resulting from the participation of the adduct **2** in electron-transfer reactions.[1] Disproportionation of the radical corresponding to **2** leads to reduction products and to the intermediate **3**, in a process similar to a number of reactions which have been studied.[7] However, a solution of o-nitrobenzonitrile (**5**) and sodium cyanide gave no detectable EPR signal, suggesting that the adduct (**6**) is rapidly removed from the solution by another process (e.g., eq 2). Other simple benzene derivatives tested (*m*-nitrobenzonitrile, nitrobenzene, *o*- and *p*-nitrotoluenes, *p*-dinitrobenzene, and 1-nitronaphthalene) all gave strong signals, but they gave deeply colored reaction solutions from which no pure compounds could be isolated, probably because the radical process converted each of these substances into a large number of products. Nevertheless, the two reaction pathways are not necessarily mutually exclusive. Gorvin[2] found that *p*-nitrobenzophenone, which resembles the *p*-nitronitrile in having a stable electron-withdrawing group para to the nitro function, yields the expected cyanophenol along with colored by-products (considered to be azo and azoxy compounds, reduction products). He also found that when this reaction was conducted in Me_2SO containing methanol, some (10%) of the methyl ether, presumably formed by participation of methoxide ion in the displacement process (eq 1), could be isolated. In the present work the gas evolved in the *p*-nitrobenzophenone reaction was collected and found to be nitrous oxide. Thus, the cyanophenol from this nitro compound probably arises by both paths, with the Nef-type course predominating.

It should be possible to prepare the hydroxyisophthalonitriles from *o*- and *p*-nitrohalobenzenes in a single step by displacement of the halogen by cyanide ion and further reaction in situ of the nitrocyano compounds. When a reaction was run with equimolar amounts of *o*-nitrofluorobenzene and sodium cyanide the products isolated were 2-hydroxyisophthalonitrile (20%) and *o*-nitrobenzonitrile (14%), with 30% of the nitrofluoro compound being recovered. The figures indicate that the nitronitrile is consumed in the reactions of eq 2 at a rate somewhat faster than its rate of formation. The use of excess sodium cyanide resulted in the isolation of 2-hydroxyisophthalonitrile in 60% yield. *p*-Nitrofluorobenzene gave 4-hydroxyisophthalonitrile in somewhat lower yield (40%).

2-Hydroxyisophthalonitrile has been reported[8] to melt at a temperature above 350°, far above the melting point (98°) of salicylonitrile.[9] In our observations, the hydroxyisophthalonitrile (**8**) appeared to undergo a change at temperatures near 250°. Since salicylonitrile is known[9] to trimerize rapidly when heated to temperatures above 260°, it appears that 2-hydroxyisophthalonitrile may trimerize so rapidly at temperatures near its melting point that no phase change is apparent and that the very high-melting substance is the triazine **10**. Examination of the very stable, highly insoluble substance obtained confirmed the triazine structure (**10**). The triazine **10** was conveniently prepared in the analytically pure state by heating **8** in dimethylaniline. 4-Hydroxyisophthalonitrile also gave a trimer on heating, alone or in dimethylaniline. Although the monomer **8** is soluble in many common solvents and can be recrystallized from water, the trimer **10** proved to be completely insoluble in all the organic solvents tried except nitrobenzene and pyridine, and in these the solubility was slight. It did dissolve in cold concentrated sulfuric acid and in hot polyphosphoric acid, but not in dilute aqueous sodium hy-



droxide. Probably because of the extremely low solubility, attempts to convert the triazine **10** to an acetyl derivative by heating with acetic anhydride and to a methyl ether by heating with methyl sulfate were unsuccessful.

Experimental Section

The high-resolution mass spectrometer and data processing equipment employed in the present study were provided by NIH Grants CA 11388 and GM 16864, from the National Cancer Institute and the National Institute of General Medical Sciences, respectively. Either a Perkin-Elmer 521 or a Beckman IR-12 spectrophotometer was used for ir spectra which were run as KBr disks. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH5 spectrometer at 70 eV. Microanalyses were performed by Mr. J. Nemeth and associates. Products were identified by comparison of ir and NMR spectra unless otherwise noted. All starting materials were either commercially available reagent grade and were used as received or were prepared in the laboratory by well-known synthetic routes. Me_2SO was stored over Linde Type 4A molecular sieves for 2 weeks before use.

1. 2-Hydroxyisophthalonitrile (8). A mixture of *o*-nitrobenzonitrile (1.48 g, 0.01 mol) and sodium cyanide (1.0 g, 0.02 mol) in 50 ml of Me_2SO was heated at 120° for 1 hr. The cooled solution was poured into 250 ml of dilute hydrochloric acid. The resulting red solution was filtered and extracted five times with 60-ml portions of methylene chloride. The combined extracts were decolorized and extracted four times with 20-ml portions of 5% sodium hydroxide solution. Acidification of the combined cooled extract to pH 3 gave a tan solid (0.80 g) which was recrystallized from water to give white crystals: mp >350°; ir 3200, 2242, 2238, 1600, 1570, 1460, 1320, 1255, 1215, 795 cm^{-1}.

Anal. Calcd for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.43. Found: C, 66.41; H, 2.86; N, 19.56.

2. Isolation of Nitrous Oxide from the Reaction of *o*-Nitrobenzonitrile and Sodium Cyanide. A solution of *o*-nitrobenzonitrile (1.48 g, 0.01 mol) in 50 ml of Me_2SO in a three-necked flask equipped with a gas inlet dipping into the liquid, a condenser, and a thermometer was thoroughly flushed with helium. The system was connected, via the condenser, to two liquid nitrogen cooled traps which in turn were connected to a high-vacuum line. After the system was thoroughly flushed with helium, sodium cyanide (1.0 g, 0.02 mol) was added and the mixture was heated to 120° for 1 hr with the helium flow continuing. At the end of this time the reaction flask was isolated from the high-vacuum line, which was then evacuated to 10^{-4} mm. The material which had collected in the liquid nitrogen traps was distilled through a trap cooled to −80°, recondensed in a liquid nitrogen trap, and then measured in the gaseous state. The amount of gas produced corresponded to 2.70 mmol. The mass spectrum of the gas was compared to the spectra of samples of carbon dioxide and nitrous oxide also purified in the same way. The experimental sample gave the following peaks: *m/e* 44, 30, 28, 27, 16, 14. The known nitrous oxide sample gave the same peaks with identical peak ratios and fragmentation patterns, and the carbon dioxide sample gave peaks at *m/e* 44, 28, and 16.

3. 2-Methoxyisophthalonitrile from o-Nitrobenzonitrile, Sodium Cyanide, and Methyl Sulfate. After a reaction mixture identical with that of 1 had been cooled to room temperature, dimethyl sulfate (2.37 ml, 0.025 mol) was added and the resulting solution was allowed to stand at room temperature for 3 hr. After acidification the mixture was extracted with methylene chloride, as in 1, and the methylene chloride solution was extracted with dilute sodium hydroxide. Acidification of the alkaline extract gave 0.22 g of 2-hydroxyisophthalonitrile. The remaining methylene chloride solution was washed well with water, concentrated, and placed on a silica gel column. Elution with benzene gave 0.47 g of 2-methoxyisophthalonitrile, mp 87–88°.

Anal. Calcd for $C_9H_6N_2O$: C, 68.34; H, 3.82; N, 17.71. Found: C, 68.31; H, 3.52; N, 17.50.

4. 4-Hydroxyisophthalonitrile and the Identification of Nitrous Oxide as Coproduct. A reaction of 1.48 g (0.01 mol) of *p*-nitrobenzonitrile and 1.0 g (0.02 mol) of sodium cyanide was carried out as described in 2. The gas evolved was collected, measured (3.6 mmol), and shown to be nitrous oxide by mass spectral examination (fragmentation patterns and ratios of peaks identical with those of authentic N_2O). The reaction mixture was worked up as described in 1 to give 0.9 g of tan solid which after two recrystallizations from water gave white crystals that did not melt below 350°: ir 3150, 2252, 2238, 1602, 1503, 1420, 910, 830, 413 cm^{-1}.

Anal. Calcd for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.43; mol wt, 144. Found: C, 66.36; H, 2.78; N, 19.47; mol wt, 144 (mass spectrum).

5. 5-Benzoylsalicylonitrile and Nitrous Oxide as a Coproduct. In apparatus similar to that used in 2 a mixture of 4-nitrobenzophenone (4.54 g, 20 mmol) and sodium cyanide (2.0 g, 40 mmol) was heated at 120° for 1 hr, cooled, and poured into 500 ml of ice water which had been acidified with 5 ml of concentrated hydrochloric acid. The aqueous mixture was extracted with ether and the ether solution was extracted with 5% sodium hydroxide. The dark oil which separated crystallized from benzene–toluene (1:2) to give 1.34 g (30%) of 5-benzoylsalicylonitrile which after recrystallization from benzene melted at 184–185° (lit.[10] 185–186°), and was of analytical purity; ir, 3270, 2235, 1610, 1310, 1285 and 705 cm^{-1}; mol wt by mass spectrum, 223 (calcd, 223). The gas evolved in this reaction was measured (2.29 mmol, 23%); it gave a mass spectrum identical with that of an authentic sample. The identification was confirmed by a high-resolution exact mass measurement (calcd for N_2O: *m/e* 44.0011; found, *m/e* 44.0011).

6. Hydroxyisophthalonitriles from Fluoronitrobenzenes and Sodium Cyanide in Me_2SO. A. A mixture of *o*-fluoronitrobenzene (1.0 ml, 0.01 mol) and sodium cyanide (1.0 g, 0.02 mol) in 50 ml of Me_2SO was heated at 120° for 2 hr under nitrogen. Workup similar to that described in 1 (addition to dilute acid, filtration, methylene chloride extraction, alkaline extraction of the methylene chloride solution, acidification, recrystallization from water) gave 0.87 g (60%) of **2-hydroxyisophthalonitrile** identified by melting point, ir spectrum, and analysis.

B. A reaction mixture differing from the above only in containing 0.5 g (0.01 mol) of sodium cyanide was treated in the same way, yielding 0.28 g (20%) of **2-hydroxyisophthalonitrile,** identified by melting point and ir. Concentration of the methylene chloride solution from this reaction, addition to a silica gel column, and elution with benzene gave 0.21 g (14%) of *o*-nitrobenzonitrile.

C. A reaction of *p*-fluoronitrobenzene under the conditions of 6A gave **4-hydroxyisophthalonitrile,** identity confirmed by analysis, in 40% yield.

7. Trimerization of Hydroxyisophthalonitriles in Dimethylaniline. A. A solution of 0.5 g of 2-hydroxyisophthalonitrile in 2.5 ml of dimethylaniline was refluxed for 1 hr, at the end of which time an orange solid was present. After dilution with 100 ml of benzene, filtration, stirring with acetone, and filtration the yellow solid, **2,4,6-tri(3-cyano-2-hydroxyphenyl)-*s*-triazine,** was collected, dried, and analyzed: mp >350°; ir 2239, 1596, 1525, 1476, 1260, 791, 740 cm^{-1}.

Anal. Calcd for $C_{24}H_{12}N_6O_3$: C, 66.67; H, 2.80; N, 19.43; mol wt, 432. Found: C, 66.67; H, 2.81; N, 19.63; mol wt, 432 (mass spectrum).

B. The same procedure applied to 4-hydroxyisophthalonitrile produced **2,4,6-tri(5-cyano-2-hydroxyphenyl)-*s*-triazine:** mp >350°; ir 2232, 1580, 1440, 1300, 840 cm^{-1}.

Anal. Calcd for $C_{24}H_{12}N_6O_3$: C, 66.67; H, 2.80; N, 19.43. Found: C, 66.74; H, 2.79; N, 19.77.

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Registry No.—**5,** 612-24-8; **8,** 28177-80-2; sodium cyanide, 143-33-9; nitrous oxide, 10024-97-2; 2-methoxyisophthalonitrile, 22433-93-8; dimethyl sulfate, 77-78-1; 4-hydroxyisophthalonitrile, 34133-58-9; *p*-nitrobenzonitrile, 619-72-7; 5-benzoylsalicylonitrile, 34133-53-4; 4-nitrobenzophenone, 1144-74-7; o-fluoronitrobenzene, 1493-27-2; *p*-fluoronitrobenzene, 350-46-9; 2,4,6-tri(3-cyano-2-hydroxyphenyl)-*s*-triazine, 56829-87-9; 2,4,6-tri(5-cyano-2-hydroxyphenyl)-*s*-triazine, 56829-88-0.

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Reactivity of Primary and Secondary N-2-(1,1-Dichloroalkylidene)anilines. V[1,2]

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Treatment of primary N-2-(1,1-dichloroalkylidene)anilines with sodium methoxide in methanol under reflux leads to nucleophilic substitution and a new type of the Favorskii rearrangement, yielding respectively N-2-(1,1-dimethoxyalkylidene)anilines and cis N-aryl α,β-unsaturated imidates. The formation of the latter compounds is explained by a cyclopropylidene amine intermediate, which is formed stereospecifically by disrotative closure of a delocalized zwitterion. Secondary N-2-(1,1-dichloroalkylidene)anilines undergo three types of reaction, i.e., nucleophilic substitution, a nonstereospecific Favorskii-like rearrangement, and a solvolysis leading to N-2-(1,3-dimethoxyalkylidene)anilines. The influence of alkyl substitution, concentration of nucleophilic reagent, reaction medium, nitrogen substituent, and substitution of the aromatic nucleus are discussed.

The base-induced skeletal rearrangement of α-halogeno ketones to carboxylic acid derivatives is known as the Favorskii rearrangement,[4,5] which is most reasonably explained in terms of a cyclopropanone intermediate.[6,7] The semibenzilic mechanism has been found to be important for certain ketone substrates.[8] The direction of opening of the cyclopropanone intermediate is influenced to a limited extent by the base and by the carbanion stabilities[9] of the cleavage intermediates and/or steric factors.[10] The Favorskii rearrangement is often accompanied by solvolysis, which is promoted by introduction of alkyl groups.[11,12]

Recently[13,14] we described the Favorskii rearrangement of 1,1-dichloro-2-alkanones **1a** and **1b**. Treatment of primary dichloromethyl ketones **1a** with sodium methoxide in methanol at ambient temperature gave rise to cis acrylic esters **7a**, next to α-chloromethyl esters **6a** in increasing amount with increasing R_1 group (Scheme I).

The stereospecificity was complete for primary dichloromethyl ketones **1a**, while for secondary derivatives **1b** the ratio between cis and trans acrylic esters **7b** depended on the difference between both alkyl substituents. Introduction of an alkyl group at 3 position caused also solvolysis to occur, yielding varying amounts of 1-chloro-3-methoxy ketones **10b** (Scheme I). These reactions were in full agreement with the mechanisms proposed by Bordwell and coworkers.[11,12]

In order to compare the reactivity of these α,α-halo ketones with their nitrogen analogues, we investigated N-2-(1,1-dichloroalkylidene)anilines **11** and **12**. Starting compounds were prepared by chlorination of appropriate N-2-(alkylidene)anilines with N-chlorosuccinimide as reported in preceding papers.[1,15]

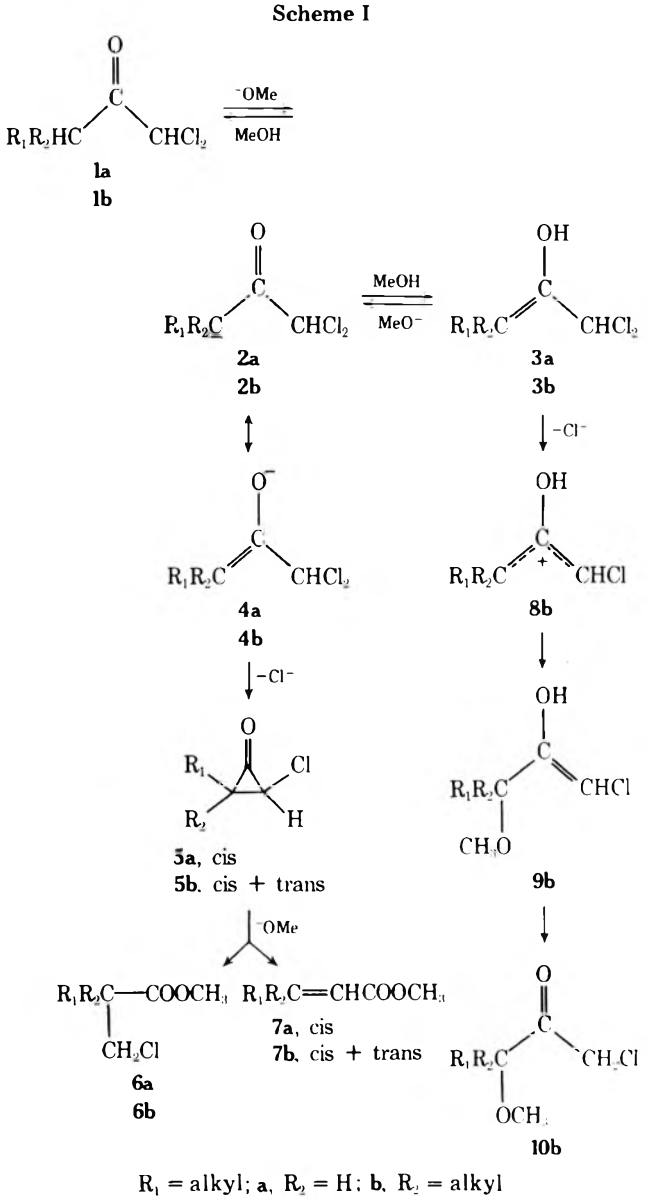
This paper deals with the reactivity of the first members of the new class of α,α-dihalogenated ketimines.

Results

As mentioned in the preliminary communication,[16] reactions of primary N-2-(1,1-dichloroalkylidene)anilines **11** with nucleophilic reagents such as sodium methoxide in methanol led to both nucleophilic substitution and to Favorskii-type rearrangement. Nucleophilic substitution afforded N-2-(1,1-dimethoxyalkylidene)anilines **13** while the new type of the Favorskii rearrangement proceeded stereospecifically with formation of exclusively cis N-aryl α,β-unsaturated imidates **15** (Table I).

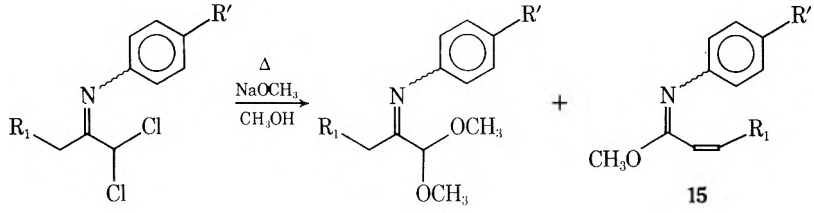
Secondary N-2-(1,1-dichloroalkylidene)anilines **12** underwent in addition to Favorskii rearrangement (**16** and **18**) and nucleophilic substitution (**14**), also solvolysis, yielding N-2-(1,3-dimethoxyalkylidene)anilines **17**. In some cases α,β-unsaturated imidates derived from secondary dichloromethylketimines **12** isomerized partly into β,γ-unsaturated compounds. All four α,β and β,γ cis and trans isomers were separated neatly by capillary column gas chromatography (150 m, OV_1). Besides the base and solvent mentioned, also less polar media (ether, diisopropyl ether) and stronger bases (sodium ethylate, potassium *tert*-butylate) were used. Results are compiled in Table II.

Scheme I



R_1 = alkyl; a, R_2 = H; b, R_2 = alkyl

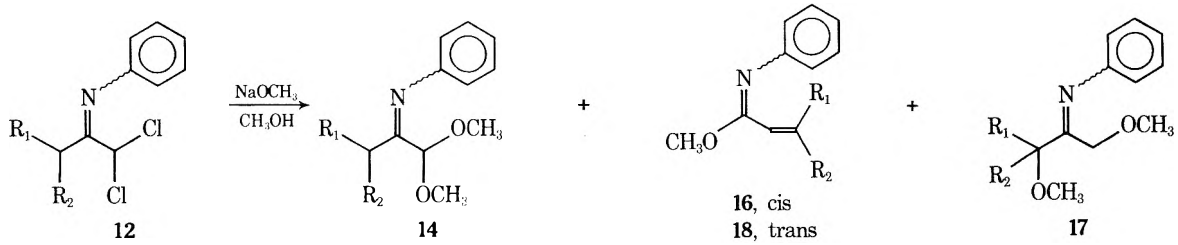
Table I[a]
Reactivity of Primary Dichloromethylketimines 11



	R_1	R'	Nucleophilic reagent	Concn *N* (equiv)	Reflux time, hr	Starting material, %	13, %	15, %
11a	*i*-Pr	H	$NaOCH_3$–CH_3OH	0.5 (2)	32	0	48	48
11a	*i*-Pr	H	$NaOCH_3$–CH_3OH	1 (2)	16	0	49	47
11a	*i*-Pr	H	$NaOCH_3$–CH_3OH	2.5 (2)	16	0	45	51
11a	*i*-Pr	H	$NaOCH_3$–Et_2O	(10)	40	20	0	74
11a	*i*-Pr	H	$NaOCH_3$–*i*-Pr_2O	(10)	32	0	0	92
11a	*i*-Pr	H	KO-*t*-Bu–*t*-BuOH	1 (2)	40	100	0	0
11a	*i*-Pr	H	NaOEt–EtOH	1 (3)	32	0	46[b]	28[b]
11b	*i*-Pr	CH_3	$NaOCH_3$–CH_3OH	1 (2)	8	0	42	50
11c	*i*-Pr	OCH_3	$NaOCH_3$–CH_3OH	0.5 (3)	40	2	49	47
11c	*i*-Pr	OCH_3	$NaOCH_3$–CH_3OH	1 (3)	40	0	49	46
11c	*i*-Pr	OCH_3	$NaOCH_3$–CH_3OH	2 (3)	24	1	47	46
11c	*i*-Pr	OCH_3	$NaOCH_3$–Et_2O	(10)	40	14	0	71
11d	Et	H	$NaOCH_3$–CH_3OH	1 (2)	24	0	55	20
11d	Et	H	$NaOCH_3$–CH_3OH	2.5 (2)	24	0	59	19
11e	*t*-Bu	H	$NaOCH_3$–CH_3OH	1 (2)	32	45	43	0
11f	*n*-Bu	H	$NaOCH_3$–CH_3OH	1 (2)	40	0	54	22
11g	*n*-Pe	H	$NaOCH_3$–CH_3OH	1 (2)	32	0	50	20
11g	*n*-Pe	H	$NaOCH_3$–CH_3OH	2.5 (2)	24	0	38	16

[a] Compounds were determined by NMR spectrometry and gas chromatography as imino compounds or, after acidic hydrolysis, as carbonyl compounds. [b] Corresponding ethoxy compounds.

Table II[a]
Reactivity of Secondary Dichloromethylketimines 12



	R_1	R_2	Nucleophilic reagent	Concn, *N* (equiv)	Reflux time, hr	Starting material, %	14, %	16 + 18, % cis	16 + 18, % trans	17, %
12a	CH_3	CH_3	$NaOCH_3$–CH_3OH	1 (4)	56	0	16	24		54
12a	CH_3	CH_3	$NaOCH_3$–CH_3OH	2 (4)	58	0	24	28		45
12a	CH_3	CH_3	$NaOCH_3$–Et_2O	(10)	96	65	0	12		0
12b	Et	CH_3	$NaOCH_3$–CH_3OH	2 (3)	96	6	16	35[b]		38
12c	*i*-Pr	CH_3	$NaOCH_3$–CH_3OH	1 (4)	210	29	9	10	25	25
12c	*i*-Pr	CH_3	$NaOCH_3$–CH_3OH	2 (4)	164	9	21	14	34	19
12c	*i*-Pr	CH_3	$NaOCH_3$–*i*-Pr_2O	(10)	60	100	0	0	0	0
12d	Cyclohexyl		$NaOCH_3$–CH_3OH	1 (4)	127	26	26	23		21
12d	Cyclohexyl		$NaOCH_3$–CH_3OH	2 (4)	103	0	50	28		20
12d	Cyclohexyl		$NaOCH_3$–Et_2O	(10)	24	100	0	0		0

[a] Compounds were determined by NMR spectrometry and gas chromatography as imino compounds or, after acidic hydrolysis, as carbonyl compounds. [b] Mixture of four isomers (cis and trans α,β and β,γ-unsaturated imino esters). [c] Mixture of α,β- and β,γ-unsaturated imidate.

α,β-Unsaturated imidates can be isolated by distillation in vacuo from the evaporated reaction mixture. Dimethoxyketimines could be determined only after hydrolysis to the corresponding ketones. The composition of the reaction mixture was measured by gas chromatography; corroborating results were obtained by analysis of the imino compounds, and, after acidic hydrolysis, of the carbonyl compounds. Stereochemistry was determined by NMR spectrometry (J_{AB}) of the reaction mixture, while distillation as well as gas chromatography caused isomerization to the trans compounds. In spite of the rapid isomerization of the cis α,β-unsaturated imino esters **15** (neutral medium), two pure cis derivatives (**15a, 15c**) were isolated by thin layer chromatography.

Varying the concentration of base (0.5, 1, and 2–2.5 *N*) and aromatic substituent (electron-donating groups) does not change the reaction appreciably. Less polar solvents cause the Favorskii product to increase at the expense of nucleophilic substitution, although reaction becomes excessively slow with secondary ketimines. Changing the aro-

matic N substituent into cyclohexyl afforded only nucleophilic substitution.[17]

Comparison with dichloromethyl ketones showed two main differences: (1) dichloromethyl ketones do not exhibit nucleophilic substitution; (2) from dichloromethylketimines only one Favorskii product is formed.

Discussion

From the theoretical point of view the mechanisms concerning the reactivity of 1,1-dichloro-2-alkanones and *N*-2-(1,1-dichloroalkylidene)anilines seem to be analogous. The base abstracts a proton from the 3 position in the dihalogenated ketimine, yielding a mesomeric anion, which then can lead to enamines **19**. This equilibrium is directly related to the equilibrium of a ketone with its enol and enolate.

Ketimines (**11, 12**) are less acidic then ketones (**1a, 1b**), while the anion is less stable owing to the lower electronegativity of nitrogen. The immediate consequence is the much longer reaction time of dichloromethylketimines (20–40 hr at reflux temperature for primary derivatives **11**) as compared to dichloromethyl ketones (<1 min at room temperature).

Secondary dichloromethylketimines **12** possess an even lower reactivity, while ketimines derived from aliphatic amines (X = *N*-cyclohexyl) show no reactivity at all for Favorskii rearrangement.[17] This phenomenon can be envisaged as a better stabilization of the negative charge on nitrogen in the case of *N*-aryl α,α-dichloroketimines. The stability of the ambident ions has a key position in the reactivity of the dichlorocarbonyl and dichloroimino compounds.

For the same reason along with Favorskii rearrangement, *nucleophilic substitution* in imino compounds occurs, which does not take place in dichloro ketones. Nucleophilic substitution (presumably bimolecular) could proceed via the tautomeric enamines, although their presence is not observable in the NMR spectrum. The reactivity of these enamine allylhalogenides and the corresponding ketimines toward methoxide is of comparable magnitude.[18]

On the other hand, in both secondary dichloromethyl ketones and secondary dichloromethylketimines 1-chloro-3-methoxy derivatives **10b** and **22** are yielded by *solvolysis* (Scheme II). The 1-chloro-3-methoxyimino compounds **22** are further converted to the 1,3-dimethoxyketimines by means of a nucleophilic substitution. The intermediacy of the *N*-2-(1-chloro-3-methoxyalkylidene)anilines **22** was proved by spectral evidence as they were detected in the reaction mixture after a short reaction time (approximately half the time required for completion of the reaction). Moreover, acidic hydrolysis of the reaction mixture revealed the presence of 1-chloro-3-methoxy-2-alkanones **10b** along with 1,3-dimethoxy-2-alkanones.

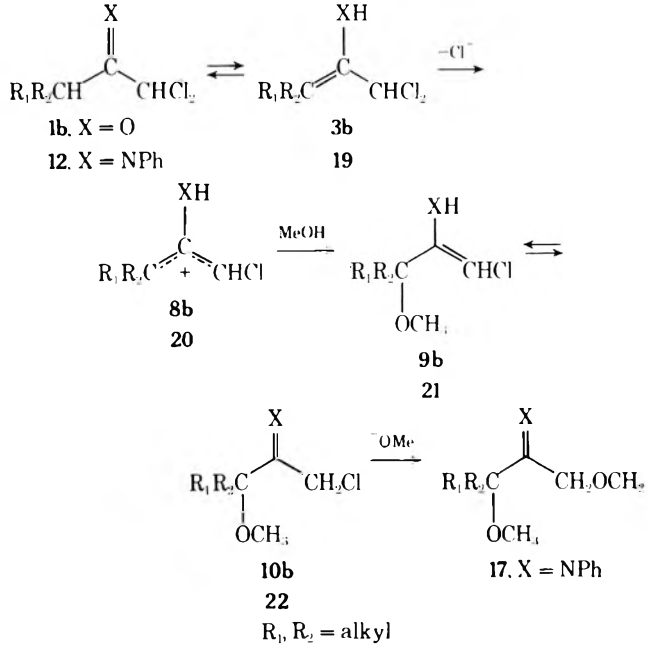
Solvolysis occurs in secondary derivatives only, owing to the enhanced stability of the delocalized carbonium ion (**8b, 20**) produced by loss of a chloride anion from respectively enol allylhalogenide **3b** and enamine allylhalogenide **19**.

It is known that alkyl substitution in either the α or γ position of allylhalogenides enhances the rate of solvolysis by a factor of hundreds or thousands.[19–21] A SN2′ mechanism is rejected while it has been found only in allylhalogenides having no substituents in the γ position.[19]

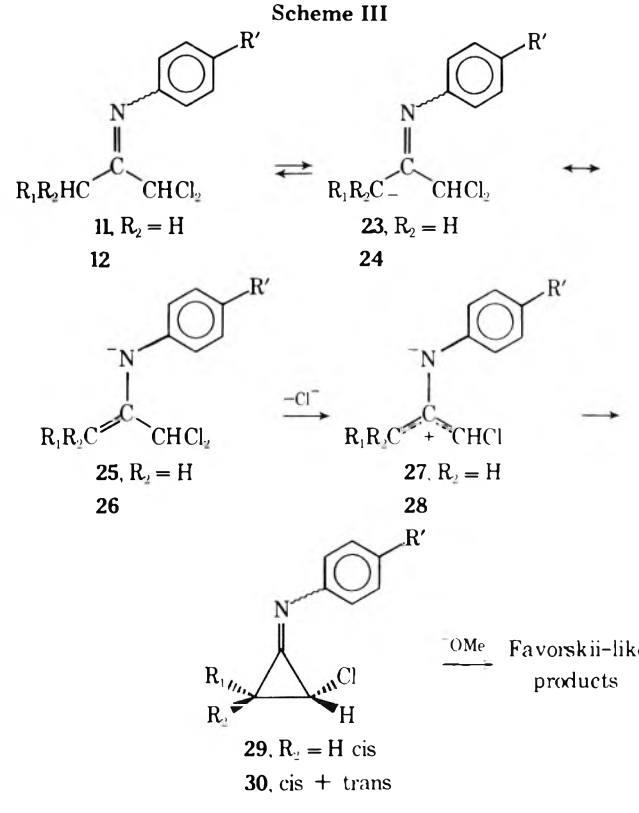
The main reaction in both dichlorinated ketimines and ketones is the *Favorskii rearrangement* (Scheme III). Anions (**2, 23,** and **24**) produced by proton abstraction lose slowly a chloride anion forming a zwitterion, which by a disrotative closure, according to the rules of conservation of orbital symmetry,[22,23] gives rise to a cyclopropanone **5** and cyclopropylidene amine (**29, 30**), respectively. Cyclopropane derivatives are opened by nucleophilic attack, but the opening in cyclopropanones occurs at both sides, while in cyclopropylidene imines only the classical opening (Scheme IV, path A) takes place, leading to a concerted expulsion of a chloride anion.

Thus[14] 1,1-dichloro-4-methyl-2-pentanone (**1a**, R_1 = *i*-Pr) yields via 2-chloro-3-isopropylcyclopropanone *cis*-methyl 4-methyl-2-pentenoate (67%), **7a** (R_1 = *i*-Pr), and methyl 2-chloromethyl-3-methylbutanoate (33%), **6a** (R_1 = *i*-Pr), while the corresponding ketimine *N*-2-(1,1-dichloro-4-methylpentylidene)aniline (**11a**) yields only *cis*-methyl *N*-phenyl 4-methyl-2-pentenoimidate (**15a**, ~50%) (along

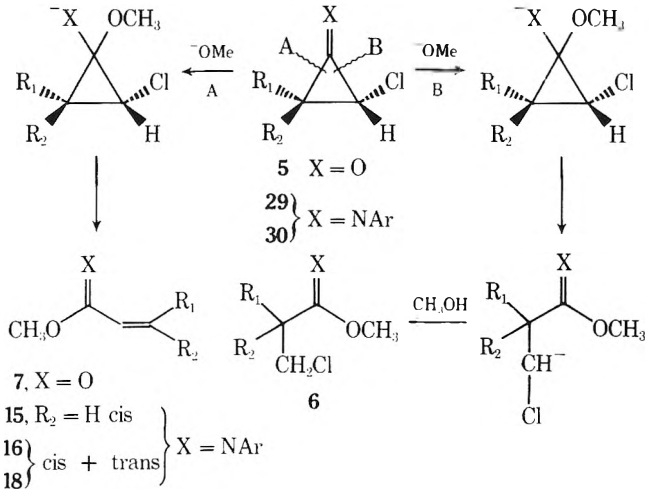
Scheme II



Scheme III



Scheme IV

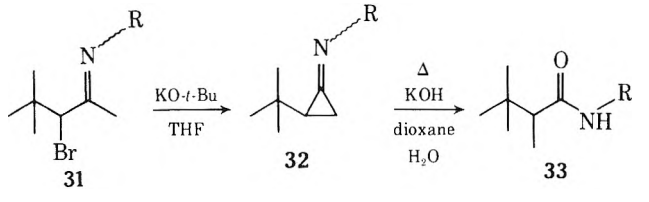


with substitution product **13a**, ~50%). Meanwhile the observation of opening at only one side of the intermediate three-membered ring is an open question.

In both series the classical products of primary derivatives (alkenoates, alkenoimidates) show complete stereospecificity, which is due to the stability of the intermediate zwitterion (**27**), formed by loss of a chloride anion from the least hindered anion **25**. In the case of secondary dichloromethylketimines **12** the formation of cis and trans *N*-phenyl α,β-unsaturated imidates **16** and **18** can be interpreted as derived from a chloride anion expulsion from both *E*/*Z* isomers of the anion **26**, whereby none of both isomers is extremely favored.

The intermediate cyclopropylideneamines are of recent interest and the synthesis has been described in only a few cases.[24-26] The first reported preparation[24] of such cyclopropylideneamines was executed under Favorskii rearrangement conditions, starting from *N*-2-(3-bromo-4,4-dimethylpentylidene)amines **31** and subsequent treatment with potassium *tert*-butoxide in tetrahydrofuran (Scheme V). When the *N*-1-(2-*tert*-butylcyclopropylidene)amine **32**

Scheme V



was refluxed with potassium hydroxide in dioxane–water, the amide **33** was isolated as the sole product, resulting from the expected opening of the three-membered ring (formation of the most stable anion[9]).

Cyclopropylideneamines, such as the proposed intermediates **29** and **30**, were predicted to exist in equilibrium with aziridines bearing an exocyclic double bond (methyleneaziridines) by means of a valence isomerization. The valence isomerization is similar to the one observed with cyclopropanones (and related alleneoxides),[23,27-29] methylenecyclopropanes[30] diaziridinones (and appropriate oxaziridineimines),[29,31] aziridinones (α-lactams and concordant imino oxiranes and methylene oxaziridines),[29,32] and α-lactones.[29,33] Though several reaction mechanisms have been interpreted to proceed via the already repeatedly postulated valence isomerization (see for instance ref 34 and 35), the occurrence was not adequately proved, until Quast and co-workers observed the phenomenon spectroscopically by NMR or indirectly by thermal decomposition of methylene aziridines.[25] Concerning the intermediacy of the cyclopropylideneamines **29** and **30** mentioned above, no trace of compounds derived from a valence isomerization could be observed. Attempts to trap the intermediate cyclopropylideneamines with furan under various conditions were unsuccessful, in spite of the successful trapping of their O analogues with furan derivatives.[23,36,37]

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were measured with Varian T-60 and Varian 300-MHz spectrometers. Mass spectra were recorded with a A. E. I. MS 30 mass spectrometer (70 eV), eventually coupled with a Varian 1200 gas chromatograph (150-m capillary column OV_1). Other GC–MS couplings were executed with a A. E. I. MS 20 mass spectrometer (70 eV) (SE-30 column, 1.5 m).

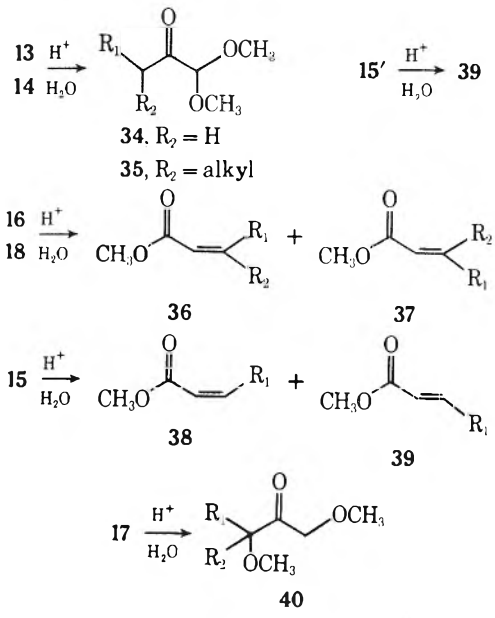
The analysis of the reaction mixtures was executed by gas chromatography using a Varian 1700 apparatus (3-m column, 12% SE-30, Chromosorb W, H_2 carrier gas). The composition was calculated from the area of the peaks, obtained by multiplying the peak height times the width at half-height. The results in the tables were given with respect to internal normalization. Preparative thin layer chromatography was performed with PSC Fertigplatten Merck Kieselgel F 254 (2 mm thickness) with isooctane–carbon tetrachloride–toluene (40:30:30) as eluent. Compounds were located by means of a Chromato-vue apparatus (short-wave uv light).

Preparation of Compounds. Methyl ketones were commercially available compounds or were prepared according to the literature: 2-heptanone,[38,39] methyl cyclohexyl ketone,[40] and 3,4-dimethyl-2-pentanone.[40,41] *N*-2-(1,1-Dichloroalkylidene)anilines **11** and **12** were prepared as described previously.[1,16]

Reaction of Primary *N*-2-(1,1-Dichloroalkylidene)anilines 11 with Sodium Methoxide in Methanol (or Sodium Ethoxide in Ethanol). For all *N*-2-(1,1-dichloroalkylidene)anilines the same general procedure was followed. In a typical experiment, a mixture of 19.52 g (0.080 mol) of freshly prepared[1] *N*-2-(1,1-dichloro-4-methylpentylidene)aniline (**11a**) and 160 ml of 1 *N* sodium methoxide in methanol (0.160 mol) was stirred under reflux (protection by a calcium chloride tube) for 16 hr. The *first half* of the reaction mixture was treated with dry ether in order to precipitate sodium chloride and eventually sodium methoxide. After evaporation of the solvent the residue was treated once more with dry ether and this procedure was repeated till no further precipitate was formed. *cis*-Methyl *N*-phenyl-4-methyl-2-pentenoimidate (**15a**) was isolated by thin layer chromatography. The band at R_f 0.4–0.5 was extracted with dry acetone. Subsequent evaporation at low temperature in vacuo gave pure **15a** as a light yellow oil. A second band contained *N*-2-(1,1-dimethoxy-4-methylpentylidene)aniline (**13a**), which could not be isolated since it decomposed on the slightest contact with air and moisture. During gas chromatographic analysis and distillation **15a** isomerized into *trans*-methyl *N*-phenyl-4-methyl-2-pentenoimidate (**15'a**). Gas chromatographic analysis showed that the residual oil contained 47% **15'a** and 48% **13a** along with minor compounds. Distillation in vacuo (short Vigreux column) gave 3.7 g (45%) of **15'a**, bp 88–90°C (0.4 mmHg), and 3.3 g (35%) of **13a**, bp 92–95°C (0.4 mmHg), which turned black rapidly.[42]

The *second half* of the reaction mixture was neutralized with 2 *N* HCl and 25 ml of 2 *N* HCl was added in excess. After stirring overnight at room temperature, the mixture was extracted four times with ether, and the combined extracts were washed and dried ($MgSO_4$). The dried ethereal extract was evaporated through a 20-cm Vigreux column. Gas chromatographic analysis of the residual mixture of carbonyl compounds[43] revealed the presence of 49% 1,1-dimethoxy-4-methyl-2-pentanone (**34a**), 24% *cis*-methyl 4-methyl-2-pentenoate (**38a**), and 23% *trans*-methyl 4-methyl-2-pentenoate (**39a**). In other batches the cis/trans ratio of both isomeric α,β-unsaturated esters varied between 1:1 and 3:1. All carbonyl compounds were isolated by preparative gas chromatography and were compared with authentic samples.[13,14,17] Distillation in vacuo afforded 2.1 g (42%) of methyl 4-methyl-2-pentenoate (cis + trans, **38a**, **39a**), bp 48–52°C (12 mmHg), and 2.4 g (37%) 1,1-dimethoxy-4-methyl-2-pentanone (**34a**), bp 59–62°C (12 mmHg). A black polymeric material remained in the distillation flask presumably due to decomposition of **34a** (see ref 17).

Reaction of *N*-2-(1,1-Dichloroalkylidene)anilines 11 with Sodium Methoxide in Diethyl Ether or Diisopropyl Ether. The following typical experiment illustrates the procedure which



was used. A mixture of 2.44 g (0.01 mol) of freshly prepared[1] N-2-(1,1-dichloro-4-methylpentylidene)aniline (**11a**) and 5.4 g (0.1 mol) of dry sodium methoxide in 25 ml of dry diisopropyl ether was stirred under reflux for 32 hr (protection with a calcium chloride tube). After completion of the reaction, the suspension was filtered and washed with dry ether. Removal of the solvent in vacuo left an oil, which was further purified by preparative TLC. Extraction of the band at R_f 0.4–0.5 with acetone provided 1.8 g (92%) of pure *cis*-methyl N-phenyl-4-methyl-2-pentenoimidate (**15a**).

***cis*-Methyl N-Phenyl-4-methyl-2-pentenoimidate (15a):** NMR (CCl_4) 0.96 [d, 6, J = 7 Hz, $(CH_3)_2$], 3.15 (m, s, CH_xMe_2), 3.83 (s, 3, OCH_3), 6.5–7.4 (m, 5, C_6H_5), 5.4–5.6 [2 H, ABX pattern unresolved at 60 MHz, but completely of first order at 300 MHz: 5.42 (d, 1, J_{ba} = 12, J_{bc} = 0 Hz, $=CH_bC=N$), 5.51 ppm (dd, 1, J_{ab} = 12, J_{ac} = 9.4 Hz, $=CH_aCHMe_2$)]; ir (NaCl) 2850 (OCH_3), 1622 (C=C), 1672 cm^{-1} (C=N). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.61; H, 8.32.

***trans*-Methyl N-Phenyl-4-methyl-2-pentenoimidate (15'a):** NMR (CCl_4) 0.95 [d, 6, J = 6.5 Hz, $(CH_3)_2$], 2.2 (m, 1, CH_xMe_2), 3.80 (s, 3, OCH_3), 6.5–7.3 (m, 5, C_6H_5), 5.59 [dd (AMX), 1, J_{ab} = 15, J_{ac} = 1 Hz, $=CH_aC=N$], 6.49 ppm (dd, 1, J_{ba} = 15, J_{bc} = 6 Hz, $CH=CHC=N$); ir (NaCl) 2850 (OCH_3), 1672 (C=N), 1622 cm^{-1} (C=C), 1600, 1582–1491 cm^{-1} (aromatic); mass spectrum *m/e* (rel intensity) 203 (M^+, 60), 202 (23), 188 (8), 172 (19), 160 (100), 156 (14), 130 (14), 119 (25), 104 (21), 93 (47), 77 (65), 69 (21), 51 (32). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.65; H, 8.34. Compounds **15a** and **15'a** (and also other imidates mentioned in this paper) did not show syn–anti isomerism, since only one isomer was visible in the NMR spectrum.[44]

N-2-(1,1-Dimethoxy-4-methylpentylidene)aniline (13a): ir (NaCl) (recorded immediately after preparative GLC isolation) 2839 (OCH_3), 1669 (C=N), 1635 cm^{-1} (C=C enaminic form?); mass spectrum[46] (GC–MS coupling, AEI MS 20) *m/e* (rel intensity) 235 (M^+, 4), 204 (2), 203 (2), 160 (100), 118 (6), 104 (21), 77 (17), 75 (23), 57 (8), 51 (6). No analytical data could be obtained owing to decomposition. Acidic hydrolysis yielded **34a**. The reaction of N-2-(1,1-dichloro-4-methylpentylidene)aniline (**11a**) with sodium ethoxide was performed in similar manner as described for methoxide–methanol.

***trans*-Ethyl N-Phenyl-4-methyl-2-pentenoimidate:** NMR (CCl_4) 0.96 [d, 6, J = 7 Hz, $(CH_3)_2$], 2.2 (m, 1, CH_xMe_2), 4.26 (q, 2, J = 7.5 Hz, OCH_2), 1.36 (t, 3, J = 7.5 Hz, $OCCH_3$), 5.64 (dd, 1, J_{bx} = 1, J_{ba} = 15.5 Hz, $=CH_bC=N$), 6.54 (dd, 1, J_{ab} = 15.5, J_{ax} = 7 Hz, CH_aCHMe_2), 6.5–7.5 ppm (m, 5, C_6H_5). Protons H_a, H_b, and H_x displayed a AMX pattern. Ir (NaCl) 1670 (C=N), 1623 (C=C), 1601, 1585, 1495 cm^{-1} (aromatic); mass spectrum *m/e* (rel intensity) 217 (M^+, 29), 216 (5), 202 (4), 189 (6), 188 (7), 174 (100), 172 (11), 158 (24), 146 (10), 133 (11), 132 (21), 130 (10), 120 (11), 119 (14), 118 (70), 104 (9), 97 (25), 93 (50), 81 (14), 77 (61), 51 (21). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.81. Found: C, 77.62; H, 8.96.

1,1-Diethoxy-4-methyl-2-pentanone: NMR (CCl_4) 0.89 [d, 6, J = 6 Hz, $(CH_3)_2$], ~2 (m, 1, $CHMe_2$), 2.35 (d degenerated, 2, CH_2CO), 1.21 [t, 6, J = 7 Hz, $(CH_3CO)_2$], 4.33 [s, 1, $CH(OEt)_2$], 3.2–3.8 ppm [ABX_3, 4, $(OCH_2)_2$]; ir (NaCl) 1733 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) no M^+, 143 (3), 105 (13), 104 (12), 103 (100), 97 (8), 85 (6), 75 (75), 73 (10), 57 (13), 47 (83). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.70. Found: C, 63.60; H, 10.61.

***cis*-Ethyl 4-Methyl-2-pentenoate:** NMR (CCl_4) 1.00 [d, 6, J = 6.5 Hz, $(CH_3)_2$], 3.7 (m, 1, CH_xMe_2), 1.26 (t, 3, J = 7 Hz, CH_3CO), 4.11 (q, 2, J = 7 Hz, CH_2O), 5.55 (dd, 1, J_{ab} = 11.5, J_{bx} = 1 Hz, $=CH_bC=O$), 5.98 ppm (dd, 1, J_{ab} = 11.5, J_{ax} = 9 Hz, $=CH_a-CHMe_2$); ir (NaCl) 1729 (C=O), 1650 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 142 (M^+, 40), 127 (2), 114 (64), 99 (39), 97 (100), 81 (22), 73 (14), 71 (17), 69 (87), 67 (34), 59 (73), 56 (35), 43 (62).

***trans*-Ethyl 4-Methyl-2-pentanoate:**[47] NMR (CCl_4) 1.06 [d, 6, J = 7 Hz, $(CH_3)_2$], 2.4 (m, 1, CH_xMe_2), 4.13 (q, 2, J = 7 Hz, OCH_2), 1.27 (t, 3, J = 7 Hz, CH_3CO), 5.70 (dd, 1, J_{ab} = 15.5, J_{bc} = 1 Hz, $=CH_bCO$), 6.88 ppm (dd, 1, J_{ab} = 15.5, J_{ac} = 7 Hz, $=CH_a-CHMe_2$); ir (NaCl) 1725 (C=O), 1660 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 142 (M^+, 45), 114 (37), 99 (20), 97 (74), 96 (20), 69 (100), 59 (25), 43 (20).

Reactions with N-2-(1,1-Dichloro-4-methylpentylidene)-*p*-toluidine (11b). *trans*-Methyl N-*p*-Tolyl-4-methyl-2-pentenoimidate (15'b): NMR (CCl_4) 0.97 [d, 6, J = 6 Hz, $(CH_3)_2$], 2.30 (s, 3, para CH_3), 2.3 (m, 1, CH_xMe_2), 3.80 (s, 3, OCH_3), 5.63 (dd, 1, J_{ab} = 15.5, J_{bx} = 1.0 Hz, $=CH_bC=N$), 6.52 (dd, 1, J_{ab} = 15.5, J_{ax} = 7 Hz, $CH_a=C-C=N$), 6.57 (d, 2, J = 8 Hz, $CH=CN$), 7.01 ppm (d, 2, J = 8 Hz, $CH=C-CN$); ir (NaCl) 2850 (OCH_3), 1672 (C=N), 1620 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 217 (M^+, 81), 216 (24), 202 (10), 186 (23), 184 (6), 174 (100), 170 (13), 144 (11), 133 (22), 106 (38), 105 (35), 91 (27), 77 (11), 69 (11), 65 (19), 51 (7).

***cis*-Methyl N-*p*-tolyl-4-methyl-2-pentenoimidate (15b)** had the unresolved AB part (NMR, CCl_4) of the ethylenic protons at δ 5.3–5.6 ppm (ABX).[48]

Reactions with N-2-(1,1-Dichloro-4-methylpentylidene)-*p*-anisidine (11c). *trans*-N-*p*-Methoxyphenyl-4-methyl-2-pentenoimidate (15'c): NMR (CCl_4) 0.97 [d, 6, J = 6.5 Hz, $(CH_3)_2$], 2.3 (m, 1, CH_xMe_2), 5.67 (dd, 1, J_{ba} = 15.5, J_{bx} = 1 Hz, $=CH_bC=N$), 6.51 (dd, 1, J_{ab} = 15.5, J_{ax} = 7 Hz, $=CH_aCHMe_2$), 3.79 (s, 3, $CH_3OC=N$), 3.76 (s, 3, para OCH_3), 6.61 (d, 2, J = 8 Hz, $CH=CN$), 6.73 ppm (d, 2, J = 8 Hz, $CH=C-CN$); ir (NaCl) 2840 (OCH_3), 1670 (C=N), 1620 (C=C), 1586, 1510 cm^{-1} (aromatic); mass spectrum *m/e* (rel intensity) 233 (M^+, 100), 232 (24), 218 (21), 202 (27), 190 (96), 160 (15), 149 (39), 148 (12), 134 (21), 123 (33), 122 (21), 108 (18), 77 (21), 69 (21), 53 (15), 51 (10). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20. Found: C, 71.92; H, 8.03.

***cis*-N-*p*-Methoxyphenyl-4-methyl-2-pentenoimidate (15c):** NMR (CCl_4) 0.93 [d, 6, J = 6.5 Hz, $(CH_3)_2$], 3.1 (m, 1, CH_xMe_2), 3.83 (s, 3, $CH_3OC=N$), 3.67 (s, 3, para OCH_3), 5.3–5.8 (ABX, 2, $CH=CH$), 6.71 ppm (s, 4, C_6H_4); ir (NaCl) 2840 (OCH_3), 1660 (C=N), 1611 (C=C), 1610–1509 cm^{-1} (aromatic). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20. Found: C, 71.89; H, 7.99.

Reactions with N-2-(1,1-Dichloropentylidene)aniline (11d). *trans*-Methyl N-Phenyl-2-pentenoimidate (15'd): NMR (CCl_4) 0.96 (t, 3, J = 6.5 Hz, $CH_3C-C=$), 2.07 [m, 2, $(CH_2)_xC=$], 3.83 (s, 3, OCH_3), 6.6–7.4 (m, 5, C_6H_5), 5.70 (dt, 1, J_{ba} = 15.5, J_{bx} = 0.8 Hz, $=CH_bC=N$), ~6.6 ppm (overlapping by aromatic multiplet, J_{ax} = 7, J_{ab} = 15.5 Hz); ir (NaCl) 2850 (OCH_3), 1675 (C=N), 1627 (C=C), 1602, 1586, 1497 cm^{-1} (aromatic); mass spectrum *m/e* (rel intensity) 189 (M^+, 50), 188 (23), 174 (11), 160 (100), 158 (28), 156 (11), 143 (17), 134 (9), 132 (15), 130 (13), 128 (10), 119 (23), 117 (17), 104 (20), 93 (30), 91 (19), 77 (50), 67 (9), 55 (21), 53 (10), 51 (21).

Reactions with N-2-(1,1-Dichloroheptylidene)aniline (11f). Both **13f** and **15f** were characterized by acidic hydrolysis, whereby **15f** yielded exclusively trans ester **39f**.

1,1-Dimethoxy-2-heptanone (34f): NMR (CCl_4) 0.89 (t, 3, CH_3), 1.0–1.6 [m, 6, $(CH_2)_3$], 2.43 (t, 2, J = 6.5 Hz, CH_2CO), 4.21 (s, 1, CHCO), 3.36 ppm [s, 6, $(OCH_3)_2$]; ir (NaCl) 2842 (OCH_3), 1737 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) no M^+, 143 (0.6), 99 (3.5), 75 (100), 71 (4), 59 (6), 55 (6).

***trans*-Methyl 2-Heptenoate (39f):** NMR (CCl_4) 0.93 (t, 3, CH_3), 1.1–1.7 [m, 4, $(CH_2)_2$], 2.2 [m, 2, $(CH_2)_xC=$], 3.67 (s, 3, OCH_3), 5.75 (dt, 1, J_{ba} = 15.5, J_{bx} = 1 Hz, $=CH_bCO$), 6.90 ppm (dt, 1, J_{ab} = 15.5, J_{ax} = 6 Hz, $=CH_aCH_2$); ir (NaCl) 2870 (OCH_3), 1735 (C=O), 1665 cm^{-1} (C=C).

Reactions with N-2-(1,1-Dichlorooctylidene)aniline (11g). *trans*-Methyl N-Phenyl-2-octenoimidate (15'g): NMR (CCl_4) 0.88 (t, 3, CH_3), 1.0–1.6 [m, 6, $(CH_2)_3$], 2.0 [m, 2, $(CH_2)_xC=$], 3.81 (s, 3, OCH_3), 5.67 (dd, 1, J_{ab} = 15, J_{bx} = 1 Hz, $=CH_bC=N$), $CH_a=C-C=N$ covered by the aromatic multiplet, 6.4–7.4 ppm (m,

5, C_6H_5); ir (NaCl) 2850 (OCH_3), 1675 (C=N), 1625 (C=C), 1602, 1585, 1508 cm^{-1} (aromatic).

***trans*-Methyl 2-Octenoate (39g):** NMR (CCl_4) 0.91 (t, 3, J = 7 Hz, CH_3), 1.1–1.6 [m, 6, $(CH_2)_3$], 2.15 [m, 2, $(CH_2)_xC$=|, 3.66 (s, 3, OCH_3), 5.72 (dt, 1, J_{ab} = 15, J_{bx} = 1 Hz, CH_bC=O), 6.80 ppm (dt, 1, J_{ab} = 15, J_{ac} = 7 Hz, =CH_aCH_2); uv max (CH_3OH) 217 nm. When the reaction of **11g** was performed in concentrated sodium methylate solution (2.5 N) a small amount of the α,β-unsaturated imidate underwent Michael addition of methylate, yielding the β-methoxy imidate which is characterized by its carbonyl compound (hydrolysis), i.e., methyl 3-methoxyoctanoate.

Methyl 3-Methoxyoctanoate: NMR (CCl_4) 0.90 (t, 3, CH_3), 1.1–1.8 [m, 8, $(CH_2)_4$], 2.35 (ABX, 1, J_{ab} = 12, J_{ac} = 6 Hz, CH_aCO), 2.48 (ABX, 1, J_{ab} = 12, J_{bx} = 6 Hz, CH_bCO), 3.6 (m, 1, CH_xOMe), 3.65 (s, 3, $COOCH_3$), 3.30 ppm (s, 3, OCH_3); ir (NaCl) 2835 (OCH_3), 1750 cm^{-1} (C=O); mass spectrum m/e (rel intensity) no M^+, 173 (13), 156 (7), 125 (12), 117 (50), 115 (24), 101 (12), 99 (12), 83 (25), 75 (100), 74 (15), 59 (25), 58 (17), 55 (35).

1,1-Dimethoxy-2-octanone (34g): NMR (CCl_4) 0.89 (t, 3, CH_3), 1.0–1.8 [m, s, $(CH_2)_4$], 2.44 (t, 2, J = 6.5 Hz, CH_2CO), 3.37 [s, 6, $(OCH_3)_2$], 4.22 ppm (s, 1, CHCO); ir (NaCl) 2840 (OCH_3), 1735 cm^{-1} (C=O); mass spectrum m/e (rel intensity) no M^+, 157 (2), 115 (3), 85 (5), 75 (100), 55 (11).

Reaction of Secondary *N*-2-(1,1-Dichloroalkylidene)anilines (12) with Sodium Methoxide in Methanol. A mixture of 2.30 g (0.01 mol) of freshly prepared *N*-2-(1,1-dichloro-3-methylbutylidene)aniline (**12a**) and 20 ml of sodium methoxide in methanol (2 N, 0.04 mol) was refluxed during 58 hr. Work-up as described above gave 2.1 g of an oil, which was analyzed by gas chromatography: 28% methyl *N*-phenyl-3-methyl-2-butenoimidate (**16a**, $R_1 = R_2 = CH_3$), 24% *N*-2-(1,1-dimethoxy-3-methylbutylidene)aniline (**14a**), and 45% *N*-2-(1,3-dimethoxy-3-methylbutylidene)aniline (**17a**). The composition of the carbonyl compounds obtained by acidic hydrolysis, as calculated from GLC, was identical with the composition of the imino compounds. Both *N*-2-(1,1-dimethoxyalkylidene)anilines (**13**) and *N*-2-(1,3-dimethoxyalkylidene)anilines (**17**) could not be isolated in pure form owing to rapid decomposition on contact with air. All other reaction mixtures, derived from secondary *N*-2-(1,1-dichloroalkylidene)anilines (**12**), were analyzed in similar manner.

Methyl *N*-Phenyl-3-methyl-2-butenoimidate (16a, $R_1 = R_2 = CH_3$): NMR (CCl_4)[49] 1.76 (d, 3, J = 1.2 Hz, trans CH_3), 1.95 (d, 3, J = 1.2 Hz, cis CH_3), 3.84 (s, 3, OCH_3), 5.44 (m, 1, =CHC=N), 6.5–7.4 ppm (m, 5, C_6H_5); ir (NaCl) 1668 (C=N), 1622 (C=C), 2850 (OCH_3), 1602, 1582, 1495 cm^{-1} (aromatic); mass spectrum m/e (rel intensity) 189 (M^+, 100), 188 (25), 174 (35), 158 (40), 157 (10), 144 (10), 143 (10), 131 (30), 130 (10), 129 (10), 119 (13), 117 (10), 107 (10), 104 (7), 93 (11), 91 (20), 83 (12), 77 (45), 55 (18), 51 (20). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.98. Found: C, 75.99; H, 7.89.

***N*-2-(1,1-Dimethoxy-3-methylbutylidene)aniline (14a):** NMR (CCl_4) 1.18 [d, 6, J = 6.5 Hz, $(CH_3)_2$], 3.0 (m, 1, $CHMe_2$), 3.23 [s, 6, $(OCH_3)_2$], 4.48 [s, 1, $CH(OMe)_2$], 6.4–7.5 ppm (m, 5, C_6H_5); mass spectrum m/e (rel intensity) 221 M^+, 6), 191 (8), 189 (25), 174 (12), 172 (6), 159 (7), 146 (100), 145 (12), 144 (58), 131 (11), 130 (11), 118 (8), 117 (7), 104 (75), 93 (67), 77 (60), 75 (54), 66 (27), 65 (17), 51 (33). Rapidly discoloring liquid.

1,1-Dimethoxy-3-methyl-2-butanone (35a): NMR (CCl_4) 1.02 [d, 6, J = 7.5 Hz, $(CH_3)_2$], 2.95 (septet, 1, J = 7.5 Hz, $CHMe_2$), 4.34 (s, 1, CHCO), 3.37 ppm [s, 6, $(OCH_3)_2$]; ir (NaCl) 2840 (OCH_3), 1730 cm^{-1} (C=O); mass spectrum m/e (rel intensity) no M^+, 115 (7), 87 (10), 75 (100), 71 (4), 55 (10), 43 (15). Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.60; H, 9.50.

1,3-Dimethoxy-3-methyl-2-butanone (40a): NMR (CCl_4) 1.26 [s, 6, $(CH_3)_2$], 3.21 (s, 3, Me_2COCH_3), 3.33 (s, 3, CH_2OCH_3), 4.25 (s, 2, CH_2CO); ir (NaCl) 2835 (OCH_3), 1740 cm^{-1} (C=O); mass spectrum m/e (rel intensity) 146 (M^+, 0.2), 115 (0.5), 73 (100), 69 (4), 55 (6), 45 (17). The most abundant ion m/e 73 is originated either from $(CH_3)_2C{=}O^+CH_3$ or $CH_3OCH_2C{\equiv}O^+$, as both fragment ions are derived from α-cleavage at the C_2–C_3 bond. Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.34; H, 9.49.

***N*-2-(1,3-Dimethoxy-3-methylbutylidene)aniline (17a).** This unstable compound was identified by its corresponding carbonyl compound **40a** (see above) and by its mass spectrum (GC–MS coupling with A. E. I. MS 20): m/e (rel intensity) 221 (M^+, 5) 191 (14), 189 (8), 148 (42), 144 (18), 119 (7), 118 (8), 104 (11), 77 (28), 73 (100), 51 (13), 45 (83).

1-Chloro-3-methoxy-3-methyl-2-butanone (10, $R_1 = R_2 = CH_3$). When *N*-2-(1,1-dichloro-3-methylbutylidene)aniline (**12a**) was refluxed with sodium methylate in methanol (1 N, 4 equiv) during 16 hr, subsequent acidic hydrolysis afforded, along with the normal products, 1-chloro-3-methoxy-3-methyl-2-butanone (**10**, $R_1 = R_2 = Me$), which is derived from the corresponding imino compound **22** ($R_1 = R_2 = CH_3$). It was compared with authentic material.[14]

Methyl 3-Methyl-2-butenoate (36a). Compound **36a** arose from **16a** and was a known compound.[52] Similar to the case mentioned above, α,β-unsaturated imidate **16a** was found to undergo (2 N NaOMe–MeOH) Michael addition (only a small amount) yielding a β-methoxy imidate, which was hydrolyzed to **methyl 3-methoxy-3-methylbutanoate** (see similarly 3-methoxyoctanoate): NMR (CCl_4) 1.25 [s, 6, $(CH_3)_2$], 2.41 (s, 2, CH_2), 3.19 (s, 3, OCH_3), 3.65 ppm (s, 3, $COOCH_3$); ir (NaCl) 1747 (C=O), 2838 cm^{-1} (OCH_3); mass spectrum m/e (rel intensity) no M^+, 131 (17), 116 (7), 115 (4), 99 (11), 89 (33), 83 (7), 75 (11), 73 (100), 71 (17), 59 (13), 48 (42), 55 (8).

Reaction of *N*-2-(1,1-Dichloro-3-methylbutylidene)aniline (12a) with Sodium Methoxide in Diethyl Ether. Preparation of Methyl *N*-Phenyl-3-methyl-2-butenoimidate (16a, $R_1 = R_2 = CH_3$). A mixture of 1.15 g (0.005 mol) of freshly prepared[1] *N*-2-(1,1-dichloro-3-methylbutylidene)aniline (**12a**) and 2.7 g (0.05 mol) of dry sodium methoxide in 15 ml of dry diethyl ether was stirred under reflux for 96 hr. The suspension was filtered and washed with dry diethyl ether and the solvent evaporated in vacuo. The residual oil was chromatographed by means of TLC (see experimental conditions above), affording 0.61 g (65%) of methyl *N*-phenyl-3-methyl-2-butenoimidate (**16a**, $R_1 = R_2 = CH_3$). Spectroscopic and analytical data were given above.

Reactions with *N*-2-(1,1-Dichloro-3-methylpentylidene)aniline (12b). The Favorskii rearrangement of compound **12b** afforded a mixture of α,β- and β,γ-unsaturated imino esters, each present as cis and trans isomers.[53] Some NMR data were given, obtained from the NMR spectrum of the mixture of isomers (bp 72–76° C, 0.03 mmHg).

***trans*-Methyl *N*-Phenyl-3-methyl-2-pentenoimidate (18b):** mass spectrum m/e (rel intensity) 203 (M^+, 100), 202 (16), 188 (18), 174 (20), 172 (26), 156 (8), 148 (1), 145 (15), 130 (9), 119 (13), 111 (30), 97 (20), 93 (20), 91 (20), 77 (53), 69 (13), 51 (27); NMR (CCl_4) 0.9 (t, 3, J = 7 Hz, CH_3), 1.90 (d, 3, J = 1.2 Hz, CH_3C=), 5.40 (m, 1, CH=), 3.81 (s, 3, OCH_3), 6.4–7.4 ppm (m, 5, C_6H_5), CH_2 covered.

***cis*-Methyl *N*-Phenyl-3-methyl-2-pentenoimidate (16b):** mass spectrum m/e (rel intensity) 203 (M^+, 100), 202 (21), 188 (33), 174 (8), 172 (17), 156 (8), 148 (3), 145 (12), 130 (8), 119 (21), 111 (92), 97 (17), 93 (25), 91 (29), 77 (67), 69 (25), 51 (33); NMR (CCl_4) 0.9 (t, 3, J = 7 Hz, CH_3), 1.72 (d, 3, J = 1.2 Hz, CH_3C=), 5.4 (m, 1, CH=), 3.81 (s, 3, OCH_3), 6.4–7.4 ppm (m, 5, C_6H_5), CH_2 covered.

***trans*-Methyl *N*-Phenyl-3-methyl-3-pentenoimidate (41):** NMR (CCl_4) 2.83 (s, broadened, 2, N=C–CH_2C=C), 3.75 (s, 3, OCH_3), 1.6 (CH_3C=), 5.1 ppm (m, 1, CH=); mass spectrum m/e (rel intensity) 203 (M^+, 47), 202 (44), 188 (71), 174 (3), 172 (5), 170 (3), 148 (11), 134 (41), 119 (100), 111 (21), 110 (21), 93 (9), 91 (27), 77 (27), 69 (22), 51 (18).

***cis*-Methyl *N*-Phenyl-3-methyl-3-pentenoimidate (42):** mass spectrum m/e (rel intensity) 203 (M^+, 42) 202 (43), 188 (63), 174 (3), 172 (4), 170 (3), 148 (1), 134 (46), 119 (100), 111 (25), 110 (25), 93 (12), 91 (29), 77 (33), 69 (25), 51 (21); NMR (CCl_4) 2.92 (s broadened, 2, N=CCH_2C=), 3.75 (s, 3, OCH_3), 1.55 (CH_3C=), 5.1 ppm (m, 1, CH=). Attempts to separate the isomeric compounds by thin layer chromatography were unsuccessful (R_f 0.3–0.4, silica gel F254 Merck, isooctane–CCl_4–toluene, 40:30:30).

***trans*-Methyl 3-methyl-2-pentenoate (36b) and *cis*-methyl 3-methyl-2-pentenoate (37b)** were previously described.[14]

***N*-2-(1,3-Dimethoxy-3-methylpentylidene)aniline (17b).** The unstable compound **17b** was identified by its mass spectrum (obtained from GC–MS coupling) and by hydrolysis to **40b**: mass spectrum of **17b** m/e (rel intensity) 235 (M^+, 2), 204 (10), 158 (9), 148 (20), 119 (8), 118 (6), 104 (9), 87 (100), 77 (22), 55 (24), 51 (11), 45 (9).

1,3-Dimethoxy-3-methyl-2-pentanone (40b): NMR (CCl_4) 0.77 (t, 3, J = 7.5 Hz, CH_3CCCO), 1.61 (m, 2, CH_2), 1.20 (s, 3, CH_3CCO), 4.23 (s, 2, CH_2O), 3.19 (s, 3, CH_3OCMe), 3.32 ppm (s, 3, OCH_3); ir (NaCl) 2835 (OCH_3), 1738 cm^{-1} (C=O); mass spectrum m/e (rel intensity) 160 (M^+, 1.2), 131 (1.5), 129 (2), 128 (3), 115 (4), 98 (4), 87 (100), 83 (20), 75 (20), 71 (5), 59 (7), 57 (7), 56 (7), 55 (75).

***N*-2-(1,1-Dimethoxy-3-methylpentylidene)aniline (14b):** bp

80–86°C (0.03 mmHg); rapidly decomposing liquid; mass spectrum *m/e* (rel intensity) 235 (M^+, 6), 160 (100), 130 (3), 104 (87), 77 (35), 75 (41), 57 (11), 51 (11). Acidic hydrolysis afforded **35b.**

1,1-Dimethoxy-3-methyl-2-pentanone (35b): NMR (CCl_4) 1.83 (t, 3, J = 7 Hz, CH_3CCCO), 1.6 (m, 2, CH_2), 2.8 (m, 1, CHMe), 1.02 (d, 3, J = 6 Hz, CH_3CCO), 4.30 [s, 1, $CH(OMe)_2$], 3.38 ppm [s, 6, $(OCH_3)_2$]; ir (NaCl) 2842 (OCH_3), 1730 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) no M^+, 129 (3), 114 (25), 101 (3), 96 (9), 85 (4), 75 (100), 71 (16), 69 (25), 68 (16), 67 (12), 57 (6), 55 (25).

Reactions with N-2-(1,1-Dichloro-3,4-dimethylpentylidene)aniline (12c). The Favorskii rearrangement of **12c** afforded a mixture of cis and trans α,β-unsaturated imidate **16c** and **18c.** Preparative gas chromatography transformed **16c** partially into the trans derivative **18c;** no trace of β,γ-unsaturated imino esters was found.

***trans*-Methyl N-Phenyl-3,4-dimethyl-2-pentenoimidate (18c):** NMR (CCl_4) 0.92 [d, 6, J = 6.5 Hz, $(CH_3)_2$], 2.20 (m, 1, $CHMe_2$), 1.84 (d, 3, J = 1.5 Hz, CH_3C=), 3.83 (s, 3, OCH_3), 5.45 (m, 1, =CHC=N), 6.5–7.3 ppm (m, 5, C_6H_5); ir (NaCl) 2845 (OCH_3), 1663 (C=N), 1620 (C=C), 1601, 1583, 1494 cm^{-1} (aromatic); mass spectrum *m/e* (rel intensity) 217 (M^+, 93), 216 (16), 202 (56), 186 (20), 174 (53), 171 (10), 170 (21), 159 (15), 144 (16), 143 (13), 142 (18), 134 (13), 131 (11), 130 (13), 125 (96), 124 (49), 119 (42), 117 (15), 111 (17), 110 (8), 109 (16), 104 (12), 93 (62), 91 (49), 81 (18), 77 (100), 73 (10), 67 (28), 66 (20), 65 (19), 55 (51), 53 (17), 51 (44).

***cis*-Methyl N-Phenyl-3,4-dimethyl-2-pentenoimidate (16c):** NMR (CCl_4) 0.90 [d, 6, J = 6 Hz, $(CH_3)_2$], 1.58 (d, 3, J = 1.5 Hz, CH_3C=), 5.4 (m, 1, CH=C), 3.79 (s, 3, OCH_3), 6.4–7.4 ppm (m, 5, C_6H_5); ir (NaCl) 2845 (OCH_3), 1663 (C=N), 1620 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity 217 (M^+, 54), 216 (15), 125 (100), 109 (20), 93 (20), 77 (42), 67 (13), 55 (20), 51 (20).

***cis*-Methyl 3,4-dimethyl-2-pentenoate (36c) and *trans*-methyl 3,4-dimethyl-2-pentenoate (37c)** were obtained by acidic hydrolysis of **16c** and **18c** and were described previously.[14]

N-2-(1,1-Dimethoxy-3,4-dimethylpentylidene)aniline (14c): mass spectrum *m/e* (rel intensity) 249 (M^+, 1), 217 (2), 207 (4), 174 (31), 172 (6), 104 (18), 93 (5), 87 (100), 77 (14), 75 (19), 71 (5), 69 (4), 55 (17), 51 (5), 43 (12) (GC–MS coupling). Acidic hydrolysis gave **35c.**

1,1-Dimethoxy-3,4-dimethyl-2-pentanone (35c); NMR (CCl_4) 0.90 [d, 6, J = 6 Hz, $(CH_3)_2$], 1.90 (m, 1, $CHMe_2$), 0.95 (d, 3, J = 7 Hz, CH_3CCO), 3.36 and 3.38 (2 s, 6, 2 OCH_3), 4.27 [s, 1, $CH(OMe)_2$], 2.77 ppm (quintet, 1, J = 7 Hz, CHCO); ir (NaCl) 2840 (OCH_3), 1730 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) no M^+, 143 (0.5), 100 (1), 87 (2), 83 (1), 75 (100), 71 (2), 55 (2).

N-2-(1,3-Dimethoxy-3,4-dimethylpentylidene)aniline (17c): mass spectrum *m/e* (rel intensity) 249 (M^+, 52), 217 (54), 202 (50), 174 (100), 117 (41), 104 (56), 101 (51), 99 (62), 93 (32), 77 (73), 75 (75), 69 (33), 51 (26). GC–MS coupling revealed the presence of a small amount of the intermediate **N-2-(1-chloro-3-methoxy-3,4-dimethylpentylidene)aniline (22c,** R_1 = *i*-Pr; R_2 = CH_3): mass spectrum *m/e* (rel intensity) 253/255 (M^+, 1), 210/212 (3), 152/154 (6), 117 (29), 101 (100), 77 (20), 69 (23), 51 (6). Compound **17c** was hydrolyzed to **10** (R_1 = *i*-Pr; R_2 = CH_3).[14]

1,3-Dimethoxy-3,4-dimethyl-2-pentanone (40c): NMR (CCl_4) 0.78 (d, 3, J = 7 Hz, CH_3CCCO), 0.91 (d, 3, J = 7 Hz, CH_3CCCO), 1.14 (s, 3, CH_3CCO), 3.19 (s, 3, CH_3OCMe), 3.34 (s, 3, OCH_3), 4.18 (s, 2, OCH_2), 2 ppm (m, 1, $CHMe_2$); ir (NaCl) 2830 (OCH_3), 1738 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 174 (M^+, 0.4), 131 (0.5), 129 (2), 101 (100), 69 (72), 59 (8), 55 (4), 43 (14).

Reactions with N-1-(2,2-Dichloro-1-cyclohexylethylidene)aniline (12d). The Favorskii-type rearrangement of **12d** (2 *N*/4 equiv NaOMe–MeOH) gave rise to 28% imidate, which consisted of 16% α,β- and 12% β,γ-unsaturated imidate, respectively methyl *N*-phenylcyclohexylideneacetoimidate (**16d**) and methyl *N*-phenyl-1′-cyclohexenylacetoimidate (VPC analysis). The structure was further proved by hydrolysis to methyl cyclohexylideneacetate (**36d**) and methyl 1′-cyclohexenylacetate, which were compared with authentic material.[14]

Methyl N-Phenylcyclohexylideneacetoimidate (16d): NMR (CCl_4) 1.2–2.5 [m, 10, $(CH_2)_5$], 5.3 (m, 1, =CHC=N), 6.3–7.4 (m, 5, C_6H_5), 3.76 ppm (s, 3, OCH_3); ir (NaCl) 2842 (OCH_3), 1671 (C=N), 1625 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 229 (M^+, 100), 228 (50), 214 (44), 200 (16), 199 (62), 198 (62), 197 (29), 196 (69), 195 (37), 187 (19), 186 (19), 184 (44), 182 (12), 181 (12), 180 (62), 170 (16), 156 (19), 134 (29), 119 (62), 118 (37), 104 (16), 93 (75), 91 (25), 81 (25), 79 (25), 77 (94), 66 (25), 65 (19), 51 (37).

Methyl N-Phenyl-1′-cyclohexenylacetoimidate: NMR (CCl_4) 1.2–2.5 [m, 8, $(CH_2)_4$], 5.3 (m, 1, CH=), 6.3–7.4 (m, 5, C_6H_5), 3.76 (s, 3, OCH_3), 2.75 ppm (s broadened, 2, CH_2C=N); mass spectrum *m/e* (rel intensity) 229 (M^+, 86), 228 (40), 214 (29), 134 (53), 119 (100), 77 (24).

N-2-(2,2-Dimethoxy-1-cyclohexylethylidene)aniline (14d) decomposed immediately after preparative GLC to a tarry material. Compound **14d** was identified by GC–MS coupling and by acidic hydrolysis to 1-cyclohexyl-2,2-dimethoxyethanone **(35d):** mass spectrum *m/e* (rel intensity) of **14d** 261 (M^+, 4), 186 (100), 104 (79), 83 (9), 77 (39), 75 (32), 55 (32), 51 (11).

1-Cyclohexyl-2,2-dimethoxyethanone (35d). This compound has been described in one of our previous papers.[17]

N-1-[1-(1′-Methoxy)cyclohexyl-2-methoxyethylidene]aniline (17d). The same remarks were valid as given for **14d:** mass spectrum *m/e* (rel intensity) 261 (M^+, 1.5), 229 (31), 214 (17), 184 (100), 158 (8), 113 (15), 104 (18), 81 (21), 77 (46), 55 (8), 53 (14), 51 (20). Acidic hydrolysis afforded **40d.**

1-(1′-Methoxy)cyclohexyl-2-methoxyethanone (40d): NMR (CCl_4) 1.2–1.8 [m, 10, $(CH_2)_5$], 3.16 (s, 3, OCH_3), 3.34 (s, 3, CH_2OCH_3), 4.21 ppm (s, 2, CH_2); ir (NaCl) 2835 (OCH_3), 1735 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) no M^+, 113 (100), 81 (58), 71 (10), 67 (5), 55 (10), 53 (5), 45 (52), 41 (13). GC–MS coupling revealed the presence of a small amount of 1-(1′-methoxy)cyclohexyl-2-chloroethanone, which was identified by comparison with authentic material.[14]

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Registry No.—**11a,** 54884-65-0; **11b,** 54884-66-1; **11c,** 56829-89-1; **11d,** 54913-00-7; **11e,** 54884-70-7; **11f,** 54884-68-3; **11g,** 54884-69-4; **12a,** 56829-90-4; **12b,** 56829-91-5; **12c,** 56829-92-6; **12d,** 56829-93-7; **13a,** 54884-71-8; **14a,** 56829-94-8; **14b,** 56829-95-9; **14c,** 56829-96-0; **14d,** 56829-97-1; **15a,** 54884-78-5; **15′a,** 56829-98-2; **15b,** 54884-79-6; **15′b,** 56830-26-3; **15c,** 54884-80-9; **15′c,** 56829-99-3; **15′d,** 56830-00-3; **15′g,** 56830-01-4; **16a,** 56830-02-5; **16b,** 56830-03-6; **16c,** 56830-04-7; **16d,** 56830-05-8; **17a,** 56830-06-9; **17b,** 56830-07-0; **17c,** 56830-08-1; **17d,** 56830-09-2; **18b,** 56830-10-5; **18c,** 56830-11-6; **22c,** 56830-12-7; **34f,** 6344-11-2; **34g,** 6956-55-4; **35a,** 56830-13-8; **35b,** 56830-14-9; **35c,** 56830-15-0; **39f,** 38693-91-3; **39g,** 7367-81-9; **40a,** 56830-16-1; **40b,** 56830-17-2; **40c,** 56830-18-3; **40d,** 56830-21-8; **41,** 56830-19-4; **42,** 56830-20-7; sodium methoxide, 124-41-4; sodium ethoxide, 141-52-6; *trans* ethyl *N*-phenyl-4-methyl-2-pentenoimidate, 56830-22-9; 1,1-diethoxy-4-methyl-2-pentanone, 56830-23-0; *cis* ethyl 4-methyl-2-pentenoate, 15790-85-9; *trans* ethyl 4-methyl-2-pentenoate, 15790-86-0; methyl 3-methoxyoctanoate, 56830-24-1; methyl 3-methoxy-3-methylbutanoate, 56830-25-2; methyl *N*-phenyl-1′-cyclohexenylacetoimidate, 56868-51-0.

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(42) The NMR spectrum of **13a** (obtained from preparative gas chromatography or distillation in vacuo) showed a complex pattern of methoxy peaks at δ 3.2–3.4 ppm, which immediately collapsed to a single peak on addition of a few drops of 2 *N* HCl; this trituration with acid resulted in the spectrum of the appropriate dimethoxymethyl ketone, i.e., 1,1-dimethoxy-4-methyl-2-pentanone (**34a**), in pure form.
(43) In general cis α,β-unsaturated imidates **15** were converted into a mixture of cis and trans α,β-unsaturated esters **38** and **39**, while trans imidates **15′** were transformed into exclusively trans α,β-unsaturated esters **39**. Contrary to the immediate hydrolysis of dimethoxymethylketimines, the α,β-unsaturated imidates were hydrolyzed in a slower way. In a typical standardized experiment, *trans*-methyl *N*-phenyl-4-methyl-2-pentenoimidate (**15′a**) was dissolved in CCl_4 and treated with excess 2 *N* HCl (in an undegassed and unsealed NMR tube). The emulsion was shaken regularly, followed by NMR measurement of the organic layer. Compound **15′a** showed a half-life period of 105 min at 35°C.
(44) The imidates were most probably existing in the *Z* form (i.e., the one with the aryl group cis with respect to the methoxy group) based on accepted concepts of steric considerations, although a recent paper, concerning *E*/*Z* isomerism (syn/anti) of saturated imidates, reported that steric influences as well as dipole interactions play a role in the determination of the equilibrium.[45]
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(48) All cis *N*-aryl α,β-unsaturated imidates **15** showed the unresolved AB part (NMR, 60 MHz, CCl_4) of the ethylenic protons at δ 5.3–5.6 ppm (**ABX** or $\mathbf{ABX_2}$). Since the structural assignment of **15a** and **15c** was fully established, the correspondance of spectral analysis, especially the typical AB line pattern, allowed us to determine the cis *N*-aryl α,β-unsaturated imidates **15** by analogy.
(49) The δ values of the β-methyl groups allowed us to distinguish cis and trans isomers **16** and **18**. Similar to α,β-unsaturated carbonyl compounds[50,51] the methyl group cis with respect to the carbon–nitrogen double bond in α,β-unsaturated imidates resonated at lower field than when trans, the cis methyl group being deshielded because of the anisotropy of the C=N function.
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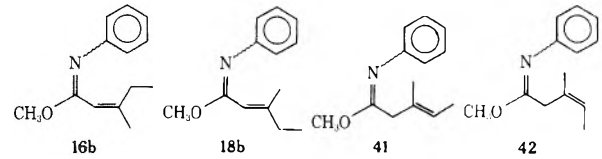
(53) These four isomeric compounds were characterized by their mass spectrum, obtained by GC–MS coupling (Varian 1200, AEI MS 30 OV_1 capillary column 150 m, temperature 80 → 160°C, 0.5°C/min). The observation that β,γ-unsaturated imino esters were more volatile than the α,β-unsaturated isomers and that cis isomers were more volatile than trans isomers allowed us to classify the imino esters as follows (increasing volatility with percent amount in parentheses): **18b** (45%) < **16b** (15%) < **41** (28%) < **42** (12%).



16b 18b 41 42

Solvolytic Rearrangement of Quadricyclyl-7-carbinol[1]

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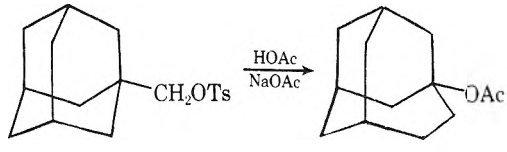
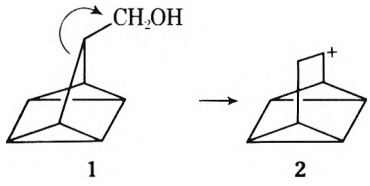
Quadricyclyl-7-carbinol was synthesized from 7-benzyloxymethylnorbornenone via 7-benzyloxynorbornadiene. The triflate ester of the carbinol upon solvolysis in buffered trifluoroethanol rearranged via a cyclopropylethyl carbonium ion pathway. This result indicates that the energy gained by rearrangement from a primary to a secondary carbonium ion to form a quadricyclooctyl system is insufficient to overcome the strain engendered in the new ring system.

Much work has been reported on the solvolysis of strained ring systems,[2] and the usual result has been the formation of less strained ring systems. A problem which has been less thoroughly investigated is the use of carbonium ion rearrangements to incorporate strain into the ring system. Considerable energy can be released when a less stable primary carbonium ion rearranges to the highly stabilized tertiary carbonium ion, and it should be possible to salvage some of this energy in the form of higher skeletal strain. One such case of such energy salvage is found in the solvolysis of 1-adamantylcarbinyl tosylate.[3] In this case, the stabilization energy gained in going to the tertiary carbonium ion outweighs the increased skeletal strain of the homoadamantyl ring system.



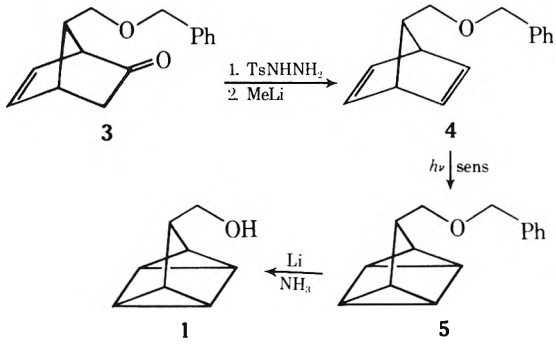
It is well known that an adjacent cyclopropyl ring can stabilize a carbonium ion,[4] but a less investigated problem is how early in the process of rearrangement does the assistance of a neighboring group take effect. A compound that

has the potential of providing answers to both the questions of introduction of strain by rearrangement and participation of stabilizing groups in the process of rearrangement is quadricyclyl-7-carbinol (1). Solvolysis of the sulfonate ester of 1 would give an ion theoretically capable of a myriad of rearrangements. Of special interest is the most obvious rearrangement, a 1,2-alkyl shift. In this rearrangement an intermediate with a highly stabilized cyclopropylcarbinyl structure would be formed from the unstabilized primary cation, but the rearranged structure 2 is very highly strained. The strain of 2 is evident both from molecular models and from the extreme thermal lability of compounds with the same skeleton.[5] A minimum of 8 kcal/mol would be gained by rearrangement from a primary to a secondary cation, and even more if the cyclopropyl ring can participate in the rearrangement step.[5] The question raised is whether the stabilization gained is sufficient to overcome the concomitant increase in ring strain introduced by the rearrangement to the quadricyclooctane skeleton.



Compound 1 was synthesized by the route shown in Scheme I. It was found that the *p*-toluenesulfonate ester

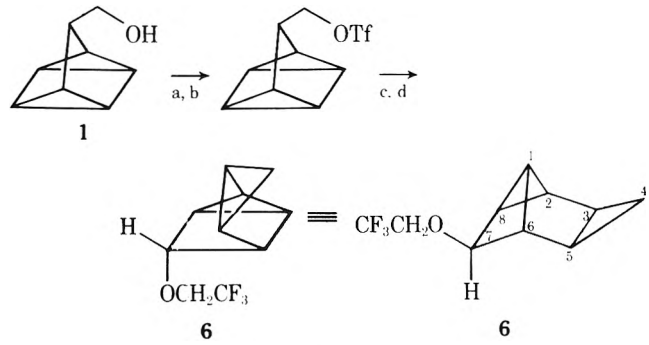
Scheme I



and the *p*-bromobenzenesulfonate ester of 1 upon acetolysis in sodium acetate buffered acetic acid at 60 and 100° gave an intractable mixture of ten or more products. This multitude of products formed in the acetolysis was apparently due to attack of the solvent on the strained quadricyclane system, itself.

A manageable solvolysis product mixture was obtained by solvolysis of the highly reactive trifluoromethanesulfonate ester[6] in the nonacidic, nonnucleophilic solvent trifluoroethanol.[7] The triflate of 1 was prepared by reaction of the lithium salt of 1, prepared with *n*-butyllithium in benzene, with triflic anhydride. Solvolysis of the triflate in trifluoroethanol with 1 equiv of triethylamine, to scavenge the acid produced in the reaction, led to a mixture of five products. One of these products comprised 80% of the product mixture, and it was obtained in a pure state by preparative gas chromatography; the other four products ranged from 1 to 7% of the mixture, and they could not be resolved into pure compound on preparative gas chromatography.

The major solvolysis product was assigned structure **6** on the basis of spectral evidence. The mass spectrum showed a parent ion at *m/e* 204, consistent with **6**; the infrared spectrum displayed no absorptions for olefinic bonds, suggesting a quadricyclic structure. The NMR spectrum also had no resonance bands higher than δ 5.0, a feature also indicating the absence of olefinic hydrogens. There were eight resolved signals in the NMR spectrum, as described in Table I. The two-proton quartet at δ 3.88 is characteristic



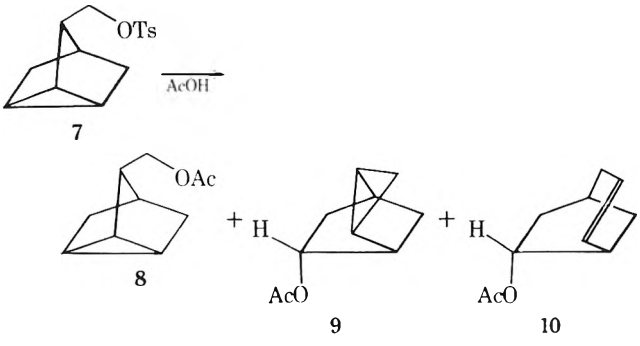
a, BuLi; b, $(CF_3SO_2)_2O$; c, Et_3N; d, CF_3CH_2OH

Table I
NMR Resonances of Compound 6

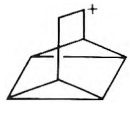
δ	Protons	Assignment	Coupled to protons
0.20	2	C-4	C-3, C-5; J = 2.8 Hz
0.92	1	C-5	C-3, C-4, C-6 (J = 1.0 Hz)
1.37	2	C-2, C-3	C-1, C-3, C-4, C-6, C-8
1.80	1	C-1	C-2, C-6, C-8
1.86	1	C-8	C-1, C-2, C-7
2.88	1	C-6	C-5 (J = 1.0 Hz), C-2 (J = 0.4 Hz), C-1, C-7
3.88	2	CH_2CF_3	Fluorine (J = 8.8 Hz)
4.03	1	C-7	C-6 (J = 3.4 Hz), C-8 (J = 1.8 Hz)

of the trifluoroethyl group. The two-proton multiplet at δ 0.2 is assigned to the two secondary cyclopropyl protons on C-4. The doublet of doublets integrating for one proton at δ 4.03 is assigned to the proton on the carbon bearing the trifluoroethyl group, and the doublet of multiplets at δ 2.88 is ascribed to the proton on the tertiary noncyclopropyl carbon, C-6. The remaining protons were assigned by extensive homonuclear decoupling, as summarized in Table I, except that carbons 2 and 3 could not be distinguished owing to overlapping of their signals. The stereochemistry of the cyclopropyl ring at C-3 and C-5 is assigned exo for two reasons. First, the most plausible mechanism suggests such an arrangement. Second, a coupling constant of 1 Hz between the protons on C-5 and C-6 is in line with a large dihedral angle relationship. Inspection of models of the exo and endo ring fused isomers show a dihedral angle of 55° for the exo and 15° for the endo; using the Karplus[8] equation these values suggest coupling constants of 2.5 and 7.5 Hz, respectively. An enlarged CCH angle at C-5, due to the cyclopropyl ring, could cause a reduction of the predicted coupling constants, but the magnitude is not known.[9] In view of the fact that the exo stereochemistry is mechanistically predicted, it is assumed that bond angle changes would not reduce the coupling constant sufficiently to indicate an endo stereochemistry. All other coupling constants are consistent with the assigned structure **6**.

The solvolysis of 1 involves a cyclopropylethyl carbonium ion, and a close analogy to it is to be found in the solvolysis of 7.[10] In the latter case, the major products were **8**, **9**, and **10**, and the primary difference in these two systems is that in the case of 7, the product **9** only comprises 35% of the reaction mixture whereas **6** makes up 80% of the products from 1. Consideration of other possible results of the Wagner–Meerwein rearrangement of 1, in analogy to 7, shows that all such detectable products should be olefinic. Not only should 2 continue to rearrange by one or more cyclopropylcarbinyl-homoallyl openings, but if trapped as 2,



the observed product should be a bicyclooctadiene in view of the known lability of the quadricyclooctyl system **2**.[5]



2

Olefinic materials account for less than 2% of the reaction mixture. The stabilization that is obtained by conversion of primary to a secondary carbonium thus is insufficient to overcome the increase in strain engendered in such a simple 1,2 shift. With such a shift ruled out, the more obscure cyclopropylethyl carbonium ion rearrangement becomes the main path of the rearrangement process.

Experimental Section

7-Benzyloxymethylnorbornadiene (4). A solution of 27.8 g (0.12 mol) of 7-benzyloxymethylnorbornenone (**3**)[11] and 22.7 g (0.12 mmol) of *p*-toluenesulfonylhydrazine in 100 ml of THF was heated under reflux for 12 hr. TLC with 25% ether–pentane on silica gel G indicated the absence of ketone (R_f 0.7) and the presence of tosylhydrazone (R_f 0.05). The solution was diluted with 400 ml of benzene, and the mixture distilled until the distillation temperature reached 80°. The residue was cooled to 0° and treated with 153 ml (5.49 g of methyllithium, 0.25 mol) of 5.07% methyllithium solution. The addition was done slowly with a syringe; foaming occurred during the first part of the addition. A Gilman test of the solution after the addition was complete was positive.

The orange solution was stirred under nitrogen at room temperature for 6 hr, 150 ml of water was added, and the organic layer separated. The extract was washed with water and saturated NaCl solution, filtered through $MgSO_4$, and concentrated at reduced pressure. The residue was Kugelrohr distilled to yield 10.62 g (41%) of **4**: NMR δ 2.74 (tr of m, 1), 3.24 (d, J = 8 Hz, 2), 3.35 (sextet, J = 2 Hz, 2), 4.30 (s, 2), 6.45 (tr, J = 2 Hz, 2), 6.70 (tr, J = 2 Hz, 2), 7.14 (s, 5); ir 3080, 2980, 2970, 2850, 1080 cm^{-1}; mass spectrum *m/e* 212, 145, 91.

Anal. Calcd for $C_{15}H_{16}O$ (212.29): C, 84.87; H, 7.60. Found: C, 84.66; H, 7.73.

7-Benzyloxymethylquadricyclane (5). A solution of 10.8 g (0.048 mol) of 7-benzyloxymethylnorbornadiene (**4**) and 250 mg of triphenylene in 840 ml of benzene was irradiated with Vycor-filtered light from a Hanovia 450-W lamp for 6 hr. The benzene was rotary evaporated, and the residue chromatographed on 500 g of silica gel. The triphenylene was eluted with twelve 200-ml fractions of 10% benzene–pentane and the 7-benzyloxymethylquadricyclane with three 200-ml fractions of 10% ether–pentane: yield 7.47 g (73%); NMR δ 1.2–1.6 (m, 6), 2.74 (tr of m, 1), 3.39 (d, 2), 4.40 (s, 2), 7.25 (s, 5); ir 3030, 2850, 1090 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}O$ (212.29): C, 84.87; H, 7.60. Found: C, 84.61; H, 7.37.

Quadricyclyl-7-carbinol (1). A solution of 7.25 g (34.2 mol) of 7-benzyloxymethylquadricyclane in 500 ml of ammonia (distilled from blue sodium–ammonia solution) and 500 ml of THF was stirred at −78° and 0.47 g (2 equiv) of lithium wire was added in 1-cm long pieces. The mixture was allowed to reflux for 90 min and an additional 50 mg of lithium added (blue color remained). To the solution was carefully added 200 ml of water and 200 ml of ether; the ammonia was allowed to evaporate. The residue was chromatographed on 800 g of silica gel with 10–30% ether–pentane. The most polar fraction was quadricyclyl-7-carbinol, crude yield 4.02 g (96%), and the material recrystallized from pentane: yield 1.92 g (47%); mp 42.0–43.5°; NMR δ 1.20–1.60 (m, 6), 2.65 (tr of m, J = 7 Hz, 1), 3.56 (d, J = 7 Hz, 2), 4.26 (s, 1, variable with concentration); ir 3330, 3075, 2920, 1230, 1030 cm^{-1}; mass spectrum *m/e* 122, 91.

Anal. Calcd for $C_8H_{10}O$ (122.17); C, 78.65; H, 8.25. Found: C, 78.66; H, 8.09.

Quadricyclyl-7-carbinyl Triflate. A solution of 221 mg of the carbinol in 10 ml of anhydrous benzene was cooled to 0° and allowed to react with 0.84 ml of a 2.27 *M* butyllithium solution. At 0°, 525 mg (1.8 mmol) of triflic anhydride was weighed into the solution, with swirling. A gelatinous precipitate of lithium triflate formed within 1 min and the precipitate was removed by centrifugation. The benzene was rotary evaporated to yield the crude triflate, which decomposed on attempted purification. The crude product had the following spectral properties: NMR δ 1.2–1.8 (m, 6), 2.95 (tr of m, 1), 4.45 (d, 2); ir 3080, 2940, 1740, 1410, 1240, 1140, 930 cm^{-1}; mass spectrum *m/e* 254, 105, 91.

Trifluoroethanolysis of 7-Quadricyclylcarbinyl Triflate. A solution of 450 mg of crude triflate and 250 mg of triethylamine in 10 ml of trifluoroethanol was allowed to stand at room temperature for 20 hr, at which time the NMR spectrum of an aliquot indicated the absence of triflate (doublet at δ 4.46). The solution was diluted with aqueous sodium bicarbonate solution and with pentane. The pentane layer was removed and the aqueous trifluoroethanol solution extracted three times with pentane. The combined extracts were washed with saturated NaCl solution, dried ($MgSO_4$ and $NaHCO_3$), and the solvent removed as samples studied. The mixture was analyzed by VPC (6 ft × 0.125 in., 10% Carbowax 600–10% KOH, 30°).

The major product (80%) was the only one of the six products which could be isolated. The NMR spectral data are given in the text; mass spectrum *m/e* 204, 139, 105, 91, 78, 77.

Registry No.—**1**, 56817-37-9; **3**, 56817-38-0; **4**, 56817-39-1; **5**, 56817-40-4; **6**, 56817-42-6; quadricyclyl-7-carbinyl triflate, 56817-41-5; triflic anhydride, 358-23-6.

References and Notes

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Chemistry of Heterocyclic Compounds. 18. Transition Metal Complexes of Selected 2-Pyridylacetylenes[1]

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The synthesis of several 2-pyridyl-, di(2-pyridyl)-, and di(6-methyl-2-pyridyl)acetylene platinum complexes is described. Selected platinacycles derived from di(2-pyridyl)acetylenes were subsequently converted into metallabicycles which possess both a platinum–acetylene and metal–pyridine bond. The crystal and molecular structure of **9** has been determined by single-crystal X-ray diffraction. Ligand exchange reactions of **4** were studied by ^1H NMR spectroscopy.

Since the preparation of $(Ar_3P)_2Pt$(arylacetylene) complexes,[2] a wide variety of substituted acetylene transition metal complexes have been characterized.[3] During the course of our studies associated with the synthesis of ion selective chelating ligands, several 2-pyridylacetylenes were prepared.[4] In view of the substantial attention given to platinum–acetylene complexes, we sought to explore the unique dual coordinating properties of these heterocyclic acetylenes.

The 2-pyridyl moiety, although structurally similar to benzene, displays enhanced electron-withdrawing properties relative to benzene, somewhat analogous to the *p*-nitrophenyl substituent. Since nitrophenylacetylene complexes are known[5] to form comparatively more stable complexes in the phosphine–platinum series, we had reason to expect that the 2-pyridylacetylene complexes could also be prepared. However, the more significant question which remained to be answered was: how will the dual functionality of the acetylene π bond and the nitrogen lone pair within the same molecule affect the mode of coordination? Platinum complexes with pyridine as one of the ligands are certainly profuse in the literature; however, no reports of platinacycles which possess the free 2-pyridyl function(s) are known to these authors.[1b] Accordingly, we presently describe the unique dual functionality of these di(2-pyridyl)acetylenes to form initially heterocyclic platinacycles, then metallabicycles which possess both a platinum–acetylene and metal–pyridine bond. We also report the results of an X-ray crystallographic determination of one such platinum–cobalt metallabicycle **9**.

Experimental Section[6]

Bis(triphenylphosphine)(diphenylacetylene)platinum was prepared according to the method of Greaves, Lock, and Maitlis,[7] mp 161–165° dec (lit.[7] mp 161–164°). Bis(diphenyl-4-tolylphosphine)(diphenylacetylene)platinum was similarly prepared: mp 161–165° dec; NMR ($CDCl_3$) δ 2.2 (ArCH_3, s, 6 H) and 6.8–7.3 (ArH, m, 38 H); ir (KBr) ν 1750 cm^{-1} (>C=C<).

Anal. Calcd for $C_{52}H_{44}P_2Pt$: C, 67.51; H, 4.79. Found: C, 67.41; H, 4.85.

Bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinum. Method A. A solution of 709 mg (1 mmol) of tetrakis(triphenylphosphine)platinum[8] in 20 ml of benzene was added to a benzene solution of di(2-pyridyl)acetylene[4] (mp 69–71°, 360 mg, 2.2 mmol) under nitrogen. The mixture was stirred for 2 hr at room temperature, then the solvent was removed under reduced pressure. The residual yellow semisolid was extracted with 20 ml of hot petroleum ether (bp 35–45°), affording a yellow product, which was recrystallized from benzene–petroleum ether, then from ethanol, giving 420 mg of **7**: mp 192–193° (sealed tube); ir (KBr) ν 1764 (>C=C<), 1583 cm^{-1} (Pyr); NMR ($CDCl_3$) δ 8.5 (6-Pyr-H, d, 2 H), 7–8 (Ar- and Pyr-H, m, 36 H).

Anal. Calcd for $C_{48}H_{40}N_2P_2Pt$: C, 64.07; H, 4.26; N, 3.11. Found: C, 64.17; H, 4.20; N, 3.07.

Method B. A suspension of *cis*-dichlorobis(triphenylphosphine)platinum[9] (760 mg, 1 mmol) in 15 ml of 95% ethanol was treated with a solution of 2 ml of hydrazine hydrate in 5 ml of ethanol. The reaction mixture was stirred for 10 min under nitrogen at 40°, during which time the white suspension gave way to a pale yellow solution. The solution was filtered into a flask containing di(2-pyridyl)acetylene (750 mg, 4.6 mmol) dissolved in 10 ml of 95% ethanol. The mixture was warmed to 45°, and water was added dropwise until slightly turbid. The mixture was stored at 0° for 5 days, during which time the pale yellow complex slowly crystallized: 270 mg; mp 192–193°. The spectral data were superimposable with those of product obtained via method A.

Anal. Calcd for $C_{48}H_{38}N_2P_2Pt$: C, 64.07; H, 4.26; N, 3.11. Found: C, 63.81; H, 4.28; N, 2.92.

Bis(triphenylphosphine)[di(6-methyl-2-pyridyl)acetylene]platinum. A benzene solution of di(6-methyl-2-pyridyl)acetylene[4] (mp 138–139°, 208 mg, 1 mmol) was added to a benzene solution of tetrakis(triphenylphosphine)platinum (1.2 g, 1 mmol). The solution was stirred for 15 min at room temperature under nitrogen, then the solvent was removed in vacuo. The residue was extracted with cyclohexane and filtered. The filtrate was allowed to evaporate slowly. The initially formed white, crystalline triphenylphosphine oxide (mp 151–153°) was discarded, and after approximately 4 days the desired orange crystalline complex was isolated: mp 189–195° (sealed tube); ir (KBr) ν 1760 cm^{-1} (>C=C<); NMR ($CDCl_3$) δ 2.16 (6-Pyr-CH_3, s, 6 H) and 6.95–7.39 (Ar- and Pyr-H, m, 36 H).

Anal. Calcd for $C_{50}H_{42}N_2P_2Pt$: C, 64.72; H, 4.56; N, 3.02. Found: C, 64.63; H, 4.54; N, 3.02.

Bis(triphenylphosphine)[phenyl(2-pyridyl)acetylene]platinum was prepared by method B from phenyl(2-pyridyl)acetylene[10] [bp 120–122° (0.3 mm)]. Upon cooling at 0° for 36 hr, the product crystallized from methanol as yellow needles: mp 170–175°; ir (KBr) ν 1747 (>C=C<), 1580 cm^{-1} (Pyr); NMR ($CDCl_3$) δ 8.5 (6-Pyr-H, d, 1 H), 7–8 (Ar- and Pyr-H, m, 37 H).

Anal. Calcd for $C_{49}H_{39}NP_2Pt$: C, 60.52; H, 4.88; N, 1.22. Found: C, 60.53; H, 4.55; N, 1.47.

Bis[diphenyl(4-tolyl)phosphine][di(2-pyridyl)acetylene]platinum was prepared by method B from di(2-pyridyl)acetylene and *cis*-dichlorobis[diphenyl(4-tolyl)phosphine]platinum (mp 288–292°). After 4 days at 0°, the complex crystallized from aqueous ethanol as yellow cubes: mp 112–115° (sealed tube, dec); ir (Nujol) ν 1748 (>C=C<), 1578 cm^{-1} (Pyr); NMR ($CDCl_3$) δ 2.2 (ArCH_3, s, 3 H), 8.5 (6-Pyr-H, d, 1 H), 6.9–7.2 (Ar- and Pyr-H, m, 38 H).

Anal. Calcd for $C_{50}H_{42}N_2P_2Pt$: C, 64.72; H, 4.56; N, 3.02. Found: C, 64.59; H, 4.38; N, 3.17.

Bis(tri-4-tolylphosphine)[phenyl(2-pyridyl)acetylene]platinum was prepared by method B from phenyl(2-pyridyl)acetylene and *cis*-dichlorobis(tri-4-tolylphosphine)platinum.[11] The complex was recrystallized from ethanol, affording yellow crystals: mp 209–211° (sealed tube, dec); ir (Nujol) ν 1780, 1750 (>C=C<), 1578 cm^{-1} (Pyr); NMR ($CDCl_3$) δ 2.2 (ArCH_3, s, 18 H), 8.4 (6-Pyr-H, d, 1 H), 6.9–7.2 (Ar- and Pyr-H, m, 32 H).

Anal. Calcd for $C_{55}H_{51}NP_2Pt$: C, 67.20; H, 5.23; N, 1.42. Found: C, 67.20; H, 5.20; N, 1.39.

Bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinum-dichlorocobalt(II). A benzene solution of 900 mg of bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinum was warmed to 40°

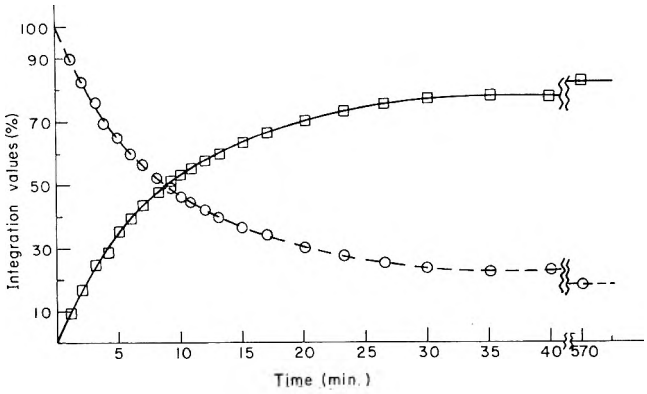

Figure 1. Plot of NMR integration values (±2%) of the 6-pyridylmethyl groups for **4** (- - -) vs. **12** (—) in benzene-d_6 at 37°.

and an ethanolic cobalt chloride solution (150 mg/20 ml) was added. The resulting green solution was evaporated in vacuo to dryness, and the residual solid was dissolved in benzene (ca. 70 ml). After filtration of undissolved solids, cyclohexane was added, and upon standing, the product formed as long, dark green needles: mp 270–280° (sealed tube, dec); ir (KBr) ν 1730 (>C=C<), 1597 (Pyr), 1120, 874, 770 cm^{-1}, uv–visible (EtOH) 610 nm (ϵ 246), 577 (182), 392 sh (3020).

Anal. Calcd for $C_{48}H_{38}N_2P_2Cl_2CoPt$: C, 59.09; H, 4.18; N, 2.55. Found: C, 59.13; H, 4.01; N, 2.49.

Bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinumdichloropalladium(II). A benzene solution of bis(benzonitrile)dichloropalladium (960 mg, 0.25 mmol) was added dropwise under nitrogen to a stirred benzene solution of bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinum at room temperature. Upon initial addition of a portion of palladium complex solution, a dark brown solid formed; then toward completion of this addition, a yellow solid precipitated, which was collected and copiously washed with cold benzene to remove benzonitrile: mp 250–260° (sealed tube, dec); ir (Nujol) ν 1707 (>C=C<), 1595 (Pyr), 1560 cm^{-1}.

Anal. Calcd for $C_{48}H_{38}N_2P_2Cl_2PdPt$: C, 53.47; H, 3.55; N, 2.60. Found: C, 53.56; H, 3.42; N, 2.51.

Attempted recrystallization of this solid from either dichloromethane–cyclohexane or ethanol–cyclohexane caused partial decomposition.

Attempted Preparation of Bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinumdichloromercury(II). An ethanolic solution of 90 mg of bis(triphenylphosphine)[di(2-pyridyl)-acetylene]platinum was stirred under nitrogen and an ethanolic mercuric chloride solution (28 mg/10 ml) was added. After cooling and filtering, the precipitate was dissolved in hot chloroform and filtered to remove the metallic mercury. Upon cooling and trituration with acetone or cyclohexane, $PtCl_2(PPh_3)_2$ was isolated: mp 305–308° (lit[9] mp 310–312°); ir (CsBr–Nujol) ν 319 and 295 cm^{-1}.

The ethanol filtrate was concentrated to dryness and the residue chromatographed [thick layer, Brinkmann silica gel PF, 2 mm, ethyl acetate–cyclohexane (1:1)] affording 17 mg (94%) of di(2-pyridyl)acetylene, mp 69–71°.

NMR Study of Acetylene Exchange. Bis(diphenyl-4-tolylphosphine)(diphenylacetylene)platinum with Di(6-methyl-2-pyridyl)acetylene. Bis(diphenyl-4-tolylphosphine)(diphenylacetylene)platinum (93 mg, 0.1 mmol) dissolved in dry benzene-d_6 (500 μl) was added to a NMR tube and thoroughly degassed with argon. At time zero, 21 mg (0.1 mmol) of di(6-methyl-2-pyridyl)-acetylene in degassed benzene-d_6 (500 μl) was added. The integration values for the free (δ 2.68) to complexed (δ 2.49) pyridylmethyl function vs. time (minutes) are plotted in Figure 1.

Crystal Data for Bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinumdichlorocobalt(II). Bis(triphenylphosphine)[di(2-pyridyl)acetylene]platinumdichlorocobalt(II), $C_{48}H_{38}N_2P_2Cl_2CoPt$, dark green needles, mol wt 1030 g mol^{-1}, a = 9.39 (1), b = 22.59 (2), c = 23.73 (2) Å, β = 101.4 (1)°, V = 4935 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.39 g cm^{-3}. The 3306 independent observed reflections were measured with Zr filtered Mo Kα radiation (λ = 0.7107 Å) by the $\theta/2\theta$ scan technique on an Enraf-Nonius PAD-3 diffractometer. All 56 nonhydrogen atoms were located by standard Patterson and Fourier techniques. Refinement is in progress, but the unweighted residual factor based on an isotropic, rigid group model stands at 0.125. No dispersion, absorption, or extinction corrections have yet been made, and all observed reflections have been included with unit weights.

Results and Discussion

Metallacycles. The platinum complexes of the pyridylacetylenes were prepared by the general methods previously described by Chatt et al.[2] or Maitlis et al.[6] Addition of the acetylene to the hydrazine reduction product of *cis*-dichlorobis(triarylphosphine)platinum is the method of choice in these heterocyclic systems. The resultant complexes possess considerable stability as reflected by their inertness to air oxidation, diverse solvents, and thermal dissociation. The nitrogen lone pair also appears to be essentially inert to Pt(0) reactants under the reaction conditions. This inactivity sharply contrasts to behavior of these heterocyclic acetylenes with ether metal substrates, e.g., $Pd(PhCN)_2Cl_2$ or $Rh_2Cl_2(CO)_4$, from which polymeric metal–pyridyl complexes immediately precipitate. The absences of the initial, as well as expected reduced, acetylenic stretching frequencies in the infrared spectrum are indicative of such polymeric complexes.

Synthesis and recrystallization of **7** in hydrocarbon solvents led to the formation of transparent bright yellow prisms of a complex which analyzed consistently for $Pt_2(Ph_3P)_4$(2-Pyr-C≡C-2-Pyr)$_3$. However, recrystallization

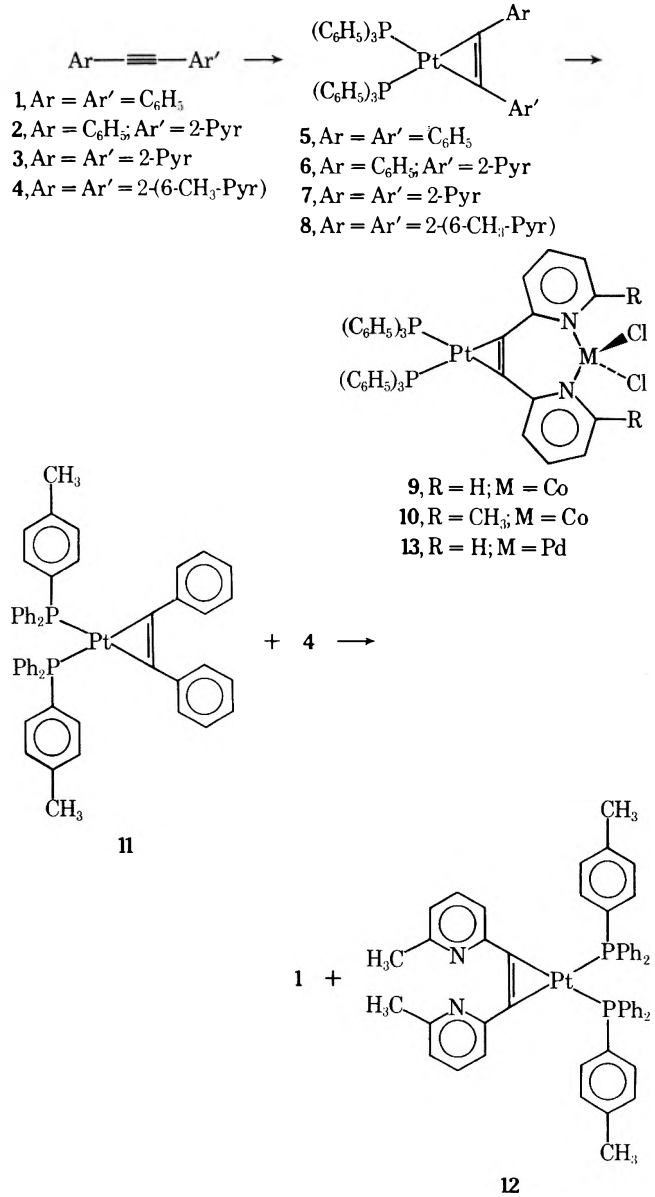

Table I
Selected Infrared Data

Ligand	ν_{max}, cm^{-1}	Platinacyclopropenes	ν_{max}	Metallabicycles	ν_{max}
1	2222[a]	5	1768, 1740[b]		
2	2227	6	1747		
3	2220[a]	7	1764	9	1730
				13	1707
4	2215[a]	8	1760	10	

[a] Raman data. [b] From ref 7.

of this material from ethanol afforded the desired 1:1 complex. Since occlusion of the extra acetylene per two platinum 1:1 complexes is completely inhibited by recrystallization from donor solvents, the extra heterocyclic acetylene was probably loosely coordinated axially to the platinum complex plane.

The infrared spectra of these heterocyclic platinum complexes (6–8) display an observed reduced acetylene stretching frequency (ca. 450 cm^{-1}; Table I), which is indicative of a strong acetylene to metal bonding and increased deviation of the acetylenic bond from linearity. This strikingly similar reduced acetylene stretching frequency of 6–8 to the metallabicycle 9, as well as 5,[13] is suggestive of an approximate deviation of 40° from linearity.

Metallabicycles. Preparation of the metallabicycles exploits the cis orientation of the 2-pyridyl groups in 7. Addition of anhydrous cobalt chloride in ethanol to a benzene solution of 7 immediately produced a green solution, from which 9 can be isolated as green needles. The infrared spectrum of 9 shows a further lowering of the acetylenic stretching frequency (1730 cm^{-1}), and the visible absorption spectrum is similar to such tetrahedral cobalt complexes as $Co(EtOH)_2Cl_2$[14] and o-di(2-pyridyl)benzene·$CoCl_2$.[15]

The cobalt bicycle, 9, is stable indefinitely in the solid state, but slowly dissociates in protic solvents. The half-life in ethanol is approximately 6 days at the initial concentration of 5×10^{-4} *M*. Although in complex 9 the cobalt is bound loosely in solution, the addition of a 6-methyl substituent on the pyridine rings prevents isolation of a stable crystalline complex (10); however, there is physical evidence that complexation does occur, albeit weakly. Slow dissociation of 9 may be, in part, the rationale for its unusually strong inhibitory properties in the electron transport chain of beef heart mitochondria. Preliminary studies[16] indicated that 9 shows strong inhibition (89%) specifically for succinate-coenzyme Q reductase (complex II) at 10^{-6} *M*, whereas 7 showed little, if any, inhibition in these systems at 10^{-6} *M*.

Limited success has been realized in attempts to incorporate alternate transition metals into 7. Addition of a benzene solution of $PdCl_2(PhCN)_2$ to 7 instantaneously gave an initial brown precipitate, which redissolved and gradually afforded a new semicrystalline solid. The infrared spectrum of this product included a bond attributable to the reduced acetylenic stretch (1707 cm^{-1}). This further reduction of ca. 50 cm^{-1} over platinacycle 7 is consistent with the preparation of the palladium-containing bicycle 13. Dissolution of 13 in protic or "wet" solvents caused rapid decomposition; the resultant decomposition products were not investigated. All other attempts to add transition metal halides in ethanol to 7 failed to yield any fully characterizable products. The products isolated from attempted incorporations of $FeCl_2$, $CuCl_2$, $NiCl_2$, $PdCl_2$, $ZnCl_2$, and $RhCl_3$ gave infrared spectra which showed no reduced acetylenic stretching frequency (1600–1800 cm^{-1}) region.

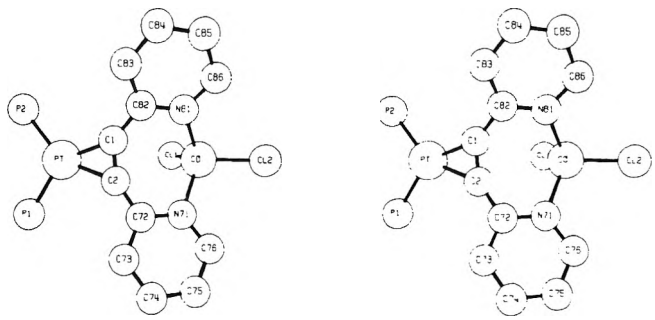

Figure 2. Stereopair diagram of the metallabicycle 9. Phenyl rings and hydrogen atoms have been omitted for clarity.

When 7 was subjected to ethanolic $HgCl_2$, an immediate reaction occurred from which *cis*-dichlorobis(triphenylphosphine)platinum(II) and metallic mercury were isolated from the precipitate. The filtrate yielded a quantitative recovery of the starting acetylene 3. This spontaneous oxidation–reduction reaction can best be envisioned as two-electron oxidation of the ethylene dianion portion of the metallacycle 7 to 3 with simultaneous reduction of Hg^{II} to Hg^0. The other platinacycles undergo a similar reaction with ethanolic $HgCl_2$ with an observable rapidity with increased electron-withdrawing acetylene substituents.

$$\underset{7}{(Ph_3P)_2Pt(2\text{-}Pyr\text{-}C{\equiv}C\text{-}2\text{-}Pyr)} + HgCl_2 \longrightarrow cis\text{-}(Ph_3P)_2PtCl_2 + Hg^\circ + 3$$

X-Ray Crystal Structure of Metallabicycle 9. Figure 2 is a stereopair diagram of the molecule with phenyl rings and hydrogen atoms omitted for clarity. The platinum(II) ion is bonded to two phosphorus atoms and the di(2-pyridyl)acetylene moiety in essentially planar coordination, though the C_1–C_2 axis is inclined at an angle of 5.8° to the mean platinum coordination plane. Upon coordination to the platinum, there occurs an effective reduction of the acetylene to an ethylene dianion, thus forming a platinacyclopropene ring. Rehybridization of the acetylenic carbon atoms causes the pyridine rings to bend back from the C_1–C_2 axis by 40°, identical with the angle found in bis(triphenylphosphine)diphenylacetyleneplatinum.[13] The C_1–C_2 bond also apparently increases in length, from 1.20 Å in acetylene[17] to 1.28 (8) Å. According to Pauling's formula,[18] this is equivalent to a bond order of approximately 2.2. A similar lengthening, to 1.32 Å, was observed in bis(triphenylphosphine)diphenylacetyleneplatinum.[13]

Although there is a slight (15°) torsion of the pyridine rings about the C_1–C_2 axis, the ethylenic π-nodal plane is essentially coplanar with the platinum coordination plane. However, the pyridine rings are rotated out of the platinum coordination plane by 36°, which orientation must drastically reduce conjugation between the pyridine π system and the platinacyclopropene π system. Pyridine ring rotation allows the two nitrogen atoms to bond to the $CoCl_2$ moiety, thereby completing the tetrahedral coordination polyhedron about the cobalt(II) ion to give the molecule a puckered appearance. Indeed, the cobalt lies 1.88 Å below the platinum coordination plane, which plane makes a dihedral angle of 101° with the N–Co–N plane. The N–Co–N and Cl–Co–Cl planes are almost exactly perpendicular to one another. The awkward orientation of the two coordination polyhedra, and the Pt–Co distance of 4.614 (7) Å, precludes any direct metal–metal interaction.

Some further average molecular dimensions are as follows: Pt–P = 2.239 (9) Å, Pt–C = 2.03 (4) Å, P–phenyl C =

1.81 (1) Å, ethylenic C–pyridyl C = 1.40 (4) Å, Co–N = 2.05 (2) Å, Co–Cl = 2.19 (1) Å, P–Pt–P = 103.5 (5)°, N–Co–N = 106.1 (8)°, Cl–Co–Cl = 114.0 (7)°, Cl_1–Co–N = 112.1 (6)°, Cl_2–Co–N = 106.1 (6)°. All interatomic distances are consistent with previously reported[19] values, though the Co–Cl distances may be slightly shorter than normal.

Ligand Exchange Reaction. Chatt originally noted[2a] the ligand displacement reactions in complexes of the type $Pt(Ar_3P)_2(Un)$, where Un represents either an olefin or acetylene. In general, acetylenic ligands bearing more electron-withdrawing substituents tend to displace from the complex the acetylene bearing less strongly electron-withdrawing substituents. Cook et al.[20] further explored the displacement reaction with respect to complexes of variously substituted phenylacetylenes and interpreted their results strictly in terms of a dissociative mechanism. Later Cook et al.[5b] reported that an associative mechanism could also account for the observed kinetics. From a recent investigation, Halpern concluded that both mechanisms are involved and that the predominance of either is a function of the concentration of the exchanging ligands.[21]

The ligand substitution rates in these heterocyclic platinum complexes can be ascertained from ^1H NMR spectral data of the complexed vs. free acetylene ligands. Specifically, the chemical shifts of the methyl groups in **4** and **8** (δ 2.68 and 2.49, respectively) are separated sufficiently to permit accurate integration. One further convenience is to utilize diphenyl-4-tolylphosphine (δ 2.34 in the platinum complex) as an internal standard. Reaction of bis(diphenyl-4-tolylphosphine)(diphenylacetylene)platinum (**11**) with **4** was conducted in benzene-d_6 at 37°. The plot of integrated ^1H NMR signal intensities vs. time (Figure 1) indicated that **4** was 82% coordinated at equilibrium, and the reaction was 50% complete after 8.7 min. The initial rate of formation of complex **12** was 8.3×10^{-2} mol/l. min^{-1}. Although we are not pursuing the kinetic aspects of this problem, the initial experiments indicate the electronic similarity between the 2-pyridyl and 4-nitrophenyl substituents in these acetylenic systems. The equilibrium constant (K_{eq} = 21) favors the displacement of diphenylacetylene from **11** to form the more stable heterocyclic complex. A comparable equilibrium constant was found for 4-nitrophenylacetylene and phenylacetylene complexes.[5b]

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Registry No.—**2**, 13141-42-9; **3**, 28790-65-0; **4**, 42296-34-4; **5**, 15308-61-9; **6**, 51455-90-4; **7**, 51455-89-1; **8**, 51455-91-5; **9**, 56783-88-1; **11**, 56783-89-2; **12**, 56783-90-5; **13**, 56783-91-6; tetrakis(triphenylphosphine)platinum, 14221-02-4; *cis*-dichlorobis(triphenylphosphine)platinum, 15604-36-1; bis[diphenyl(4-tolyl)phosphine][di(2-pyridyl)acetylene]platinum, 56783-92-7; *cis*-dichlorobis[diphenyl(4-tolyl)phosphine]platinum, 56783-93-8; bis(tri-4-tolylphosphine)[phenyl(2-pyridyl)acetylene]platinum, 56783-94-9; *cis*-dichlorobis(tri-4-tolylphosphine)platinum, 31173-67-8; bis(benzonitrile)dichloropalladium, 14220-64-5.

References and Notes

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(6) All melting points were taken in capillary tubes with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 621 spectrophotometer, and nuclear magnetic resonance (NMR) spectra were recorded using either a Varian Associates HA-100 or H-60A spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si as an internal standard. X-ray data were measured with Zr filtered Mo Kα radiation (λ = 0.7107 Å) by the $\theta/2\theta$ scan technique on an Eraf-Nonius PAD-3 diffractometer. Elemental analyses were performed by Mr. R. Seab in these laboratories or by Galbriath Laboratories, Knoxville, Tenn.
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Carbon–Phosphorus Heterocycles. A Study of the Mechanism of Cyclization of Alkenyl-Substituted Phosphonium Salts by 115% Polyphosphoric Acid via Stereochemical and Phosphorus-31 Nuclear Magnetic Resonance Analyses

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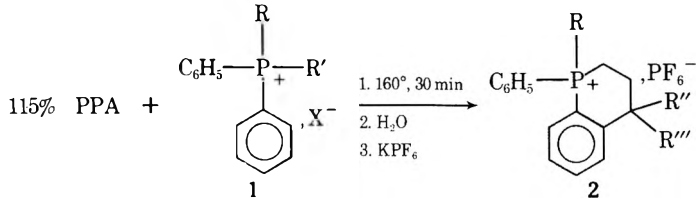
Evidence is presented that intramolecular cyclization of alkenyl-substituted phosphonium salts $(C_6H_5)_2(R)[R'CH{=}CH(CH_2)_n]P^+$, X^- or $(C_6H_5)_2(C_6H_5CH_2)(CH_2{=}CHCH_2)P^+$, PF_6^-, via reaction with polyphosphoric acid (PPA) at 150°, proceeds through a mechanism reminiscent of a cation-alkylation process to give phosphinolinium systems and an isophosphinolinium salt, respectively. Stereochemical analysis of the products and ^{31}P NMR monitoring of the cyclization support a mechanism of marked resemblance to a cation alkylation of an arene, i.e., an electrophilic substitution process. An intermediate with strong ^{31}P NMR signal was observed in the reaction of 2-butenyltriphenylphosphonium bromide (**1j**) with PPA to give **2d** but such a signal was absent when allylbenzyldiphenylphosphonium bromide (**7**) was converted to 1,2,3,4-tetrahydro-4-methyl-2,2-diphenylisophosphinolinium hexafluorophosphate (**8**). The latter observation was rationalized on the basis of a rapidly formed intermediate of a classic type in electrophilic aromatic substitution. Fast loss of a proton to re-form the aromatic ring to yield **8** ensues and no intermediate detectable by ^{31}P NMR accumulates.

The recent discovery that alkenyl-substituted arylphosphonium salts undergo cyclization in the presence of commercial 115% polyphosphoric acid (PPA) to yield tetrahydrophosphinolines and tetrahydroisophosphinolines has not heretofore been investigated from a mechanistic standpoint.[1] We wish to report that a careful study of selected salts (Table I contains data on the open salts) indicates that the ring closure shown in Chart I follows a course predictable, in part, from current carbonium ion theory.

When the 4-pentenyl compound **1g** was subjected to the same conditions, the six-membered ring analogue **2g** formed as evidenced by ^1H NMR, ^{31}P NMR, ir, mass spectral, and elemental analysis.[2] This shows that the six-membered ring is formed in preference to the seven-membered ring which would have resulted from initial protonation at the terminal carbon atom to generate a secondary cation. The observation suggests that either hydride transfer and cyclization to **2g** together are faster than cyclization to the seven-membered ring or all three species equilibrate. The latter is a separate problem under study. The stability of the phosphorinane ring both singly and as a part of a fused system is well known.[3] As noted previously, it was observed

Chart I



Compd*	R	R′	X⁻	Compd	R	R″	R‴
1a	C_6H_5	$CH_2CH{=}C(CH_3)_2$	Cl	2a	C_6H_5	CH_3	CH_3
1b	CH_3	$CH_2CH{=}C(CH_3)_2$	Cl	2b	CH_3	CH_3	CH_3
1c	C_2H_5	$CH_2CH{=}C(CH_3)_2$	Cl	2c	C_2H_5	CH_3	CH_3
1d	C_6H_5	$CH_2CH_2CH{=}CH_2$	Br	2d	C_6H_5	H	CH_3
1e	CH_3	$CH_2CH_2CH{=}CH_2$	PF_6	2e	CH_3	H	CH_3
1f	C_2H_5	$CH_2CH_2CH{=}CH_2$	PF_6	2f	C_2H_5	H	CH_3
1g	C_6H_5	$CH_2(CH_2)_2CH{=}CH_2$	Br	2g	C_6H_5	H	C_2H_5
1h	CH_3	$CH_2(CH_2)_2CH{=}CH_2$	PF_6	2h	CH_3	H	C_2H_5
1i	C_2H_5	$CH_2(CH_2)_2CH{=}CH_2$	PF_6	2i	C_2H_5	H	C_2H_5
1j	C_6H_5	$CH_2CH{=}CHCH_3$	Br	2d	C_6H_5	H	CH_3

When R′ = $(CH_3)_2C{=}CHCH_2^-$, the cyclization proceeded smoothly for R = CH_3, C_2H_5, or C_6H_5 in high yields (86, 89, and 88%) as shown in Chart I (Table II contains data on the phosphinolinium salts). The loss of HBr was instantaneous with the mixing of reagents at 160°. Thus, any intermediate involved is *not* likely dependent to an influential degree upon R as a *stabilizing group* under the conditions illustrated. The open-chain 3-butenyl analogue **1d** closed to give **2d** which was the identical product obtained previously[1] from the 2-butenyl precursor **1j**. Consequently, the same transitory secondary cation **4** is likely to be involved in both cases. Similarly, **2e** and **2f** were prepared and have ^1H NMR spectra very nearly superimposable on that of **2d**, except for the signals arising from R.

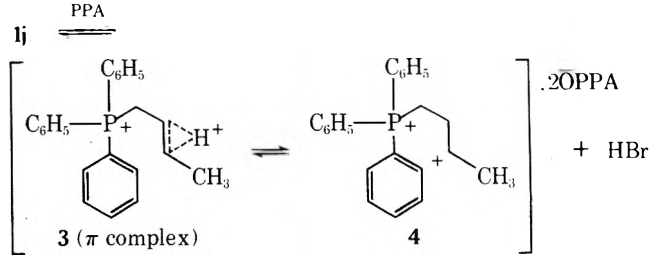
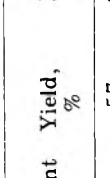


Table I



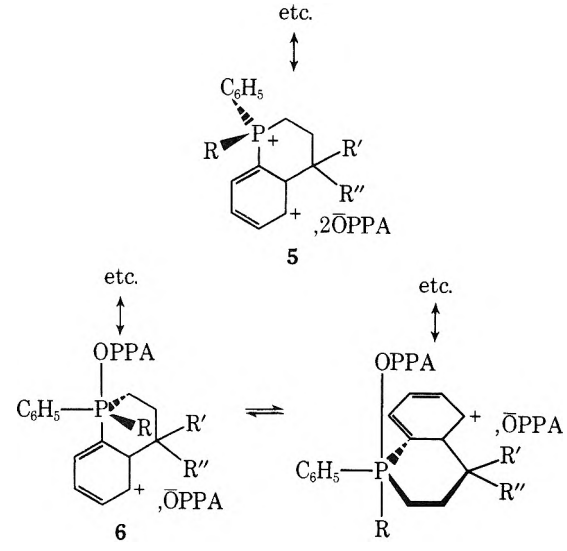
Compd	R	R′	X⁻	Mp, °C	Quaternizing solvent (reaction time, hr)	Equivalent halide	Yield, %	Molecular formula	Anal., % (P)
1a	C_6H_5	$CH_2CH{=}(CH_3)_2$	Cl	253–254.5	Toluene (24)	0.88	57	$C_{23}H_{24}ClP$	Calcd: 8.44 Found: 8.24
1b	CH_3	$CH_2CH{=}C(CH_3)_2$	Cl	189.5–191.5	Benzene (24)	0.88	69	$C_{18}H_{22}ClP$	Calcd: 10.16 Found: 9.96
1c	C_2H_5	$CH_2CH{=}C(CH_3)_2$	Cl	163–165	Toluene (48)	1.43	73	$C_{19}H_{24}ClP$	Calcd: 9.71 Found: 9.51
1d	C_6H_5	$CH_2CH_2CH{=}CH_2$	Br	224–226[a]	Xylene (50)	0.73	71	$C_{22}H_{22}BrP$	Calcd: 15.47
1e	CH_3	$CH_2CH_2CH{=}CH_2$	PF_6	117.5–119	Benzene (60)	1.50	69	$C_{17}H_{20}F_6P_2$	Found: 15.07
1f	C_2H_5	$CH_2CH_2CH{=}CH_2$	PF_6	129–131	Benzene (48)	1.50	52	$C_{18}H_{22}F_6P_2$	Calcd: 14.95 Found: 15.00
1g	C_6H_5	$CH_2(CH_2)_2CH{=}CH_2$	Br	189–191[b]	Xylene (50)	0.73	76	$C_{23}H_{24}BrP$	Calcd: 7.53 Found: 7.64
1h	CH_3	$CH_2(CH_2)_2CH{=}CH_2$	PF_6	89.5–91.5	Benzene (60)	1.50	77	$C_{18}H_{22}F_6P_2$	Calcd: 14.95 Found: 14.69
1i	C_2H_5	$CH_2(CH_2)_2CH{=}CH_2$	PF_6	108–110	Benzene (48)	1.43	50	$C_{19}H_{24}F_6P_2$	Calcd: 14.46 Found: 14.44
1j	C_6H_5	$CH_2CH{=}CHCH_3$	Br	241–242[c]	Xylene (24)	1.36	90	$C_{22}H_{22}BrP$	

[a] Lit. mp 288° [E. Schweizer, J. Thompson, and T. Ulrich, *J. Org. Chem.*, 33, 3082 (1968)]. [b] Lit. mp 134–140° [C. Hauser, T. Brooks M. Miles, M. Raymond, and G. B. Butler, *J. Org. Chem.*, 28, 372 (1963)]. [c] Reported previously in ref 1.

that the phosphorinane system **2d** formed in preference to a phosphindoline system when 2-butenyltriphenylphosphonium bromide (**1j**) was the starting material. Again, this hints at ring stability and intermediate cation stability as governing factors in controlling the ring closure.

Attempts to cyclize **1h** and **1i** appeared successful but mixtures of isomers were obtained in both cases as suggested by a melting range for products and ^1H NMR analysis. All efforts to separate these isomers have not been fruitful in view of the nearly identical solubility properties of the components in the mixtures.

Assuming **5** or **6** as tentative candidates for cyclic intermediates in the reaction, a ^{31}P NMR study of the cyclization was conducted on **1j** in an NMR tube at 150°. At this temperature, the rate of reaction permitted reasonable monitoring ease, and the viscosity of the medium was such that fine structure of the ^{31}P NMR signals was clearly visible.



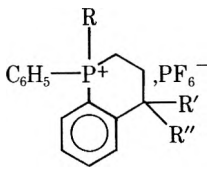
Within 5 min (t_0 + 5) after mixing **1j** with 115% PPA at 150° and inserting the tube into the probe (heated 150°), broad signals appeared at −8.7, −19.4, and −22.5 ppm (1.2:1.2:1) relative to external 85% H_3PO_4. Signals at −0.03, +15.3, and +31.6 ppm (1:10.2:9.6) were discernible for PPA in all samples examined and were continuously monitored in all experiments.

At t_0 + 45, only two signals at −8.7 and −22.5 ppm (5.2:1) were detected. Addition of one-half of an equivalent weight of **2d** (or **2d** as the Br^- salt) caused the ratio of the two peaks to change to 13.7:1. Thus, the signal at −8.7 ppm was for product. Moreover, after hydrolysis of the reaction mixture in the NMR tube, solid **2d** was isolated in high yield. A separate ^{31}P NMR analysis of the water solution also gave a strong signal at −8.7 ppm.[4] The signal at −22.5 ppm disappeared, however.

Freshly prepared 115% PPA (84% by weight of P_2O_5 in 85% H_3PO_4) or commercial 105% PPA gave identical results but the rate of reaction was much slower. In fact, in 105% PPA only one signal at −19.3 ppm was observed at t_0 + 5. Only at t_0 + 20 did three peaks appear in the spectrum of the reaction with 105% PPA as seen previously when 115% PPA was used. In the latter, the signal at −19.4 ppm[5] vanished after t_0 + 45 at 150°. Thus, the signal at −19.4 ppm must be for **1j**.

Related experiments with **1d** and commercial 115% PPA at 150° showed three peaks at −9.5, −20.0, and −23.1 ppm. The addition of **1d** and **2d** showed reinforcement of the signals at −20.0 and −9.5 ppm, respectively. Persistence of the signal at −23.1 ppm for the intermediate was very rem-

Table II

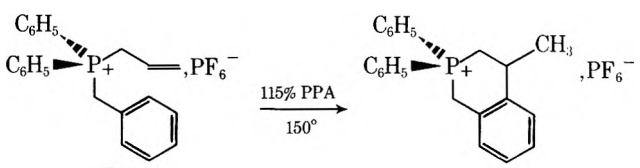


Compd	R	R′	R″	Mp, °C	Yield, %	Molecular formula	Anal., % P
2a	C_6H_5	CH_3	CH_3	209–211	89	$C_{23}H_{24}F_6P_2$	Calcd: 13.00 Found: 12.94
2b	CH_3	CH_3	CH_3	211–213.5	86	$C_{18}H_{22}F_6P_2$	Calcd: 14.95 Found: 15.04
2c	C_2H_5	CH_3	CH_3	144–146	89	$C_{19}H_{24}F_6P_2$	Calcd: 14.46 Found: 14.49
2d	C_6H_5	H	CH_3	203.5–205[a]	95	$C_{22}H_{22}F_6P_2$	
2e	CH_3	H	CH_3	177.5–179	73	$C_{17}H_{20}F_6P_2$	Calcd: 15.47 Found: 15.09
2f	C_2H_5	H	CH_3	145.5–147	45	$C_{18}H_{22}F_6P_2$	Calcd: 14.95 Found: 14.90
2g	C_6H_5	H	C_2H_5	159–161	60	$C_{23}H_{24}F_6P_2$	Calcd: 13.00 Found: 13.30

[a] Reported previously; see ref 1.

iniscent of the signal at −22.5 ppm found in the reaction with **1j**. Since **2d** was formed in the reaction of **1d**, the intermediates must be identical.

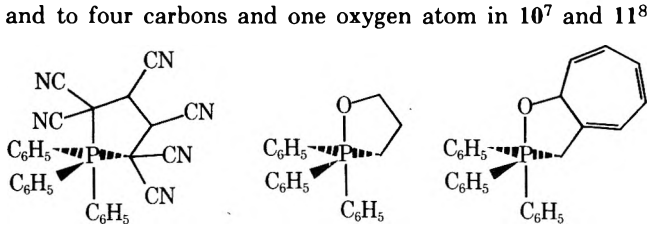
When the phosphorus atom was moved one position in the ring system as in allyldiphenylbenzylphosphonium hexafluorophosphate (**7**), a somewhat similar pattern was observed in the conversion to 8 with but one exception. Sig-



7 8

nals for ^{31}P at −16.1 and −21.9 ppm (3:6:1) were strong at t_0 + 15 but *only* the signal at −21.9 ppm was noted at t_0 + 5. The ratios of **8**:**7** changed to 4.6:1 (t_0 + 125), 4.9:1 (t_0 + 134), and 10.2:1 (t_0 + 180). Addition of an authentic sample of **8** at t_0 + 30 in a separate experiment resulted in a large increase in the signal at −16.1 ppm, thus confirming it to be assigned to **8**. Hydrolysis of the reaction mixture in the NMR tube revealed that **8** had formed in high yield (>90%) and was identical with the reported compound.[1] Similarly, addition of authentic **7** caused the signal at −21.9 ppm to increase, substantiating its assignment. In no experiment studied up to t_0 + 180 did another signal appear in **7** → **8**.

A search of the literature did not reveal a similar system with sulfur or arsenic involved. Likewise, no data could be uncovered for molecular structures (or intermediates) in which a pentavalent phosphorus as part of a *six-membered ring* system was bound to four carbons and one oxygen atom in a trigonal bipyramid or tetragonal pyramid. However, the phosphorus is bound to five carbon atoms in **9**[6] and to four carbons and one oxygen atom in **10**[7] and **11**[8]



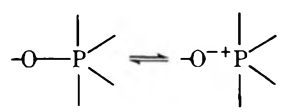
9 10 11

(−22.0 ppm, dioxane) (+49.5 ppm, H_2CCl_2) (+66.9 ppm, $DCCl_3$)

$R(R')(R'')(R''')P^+,X^-$

12

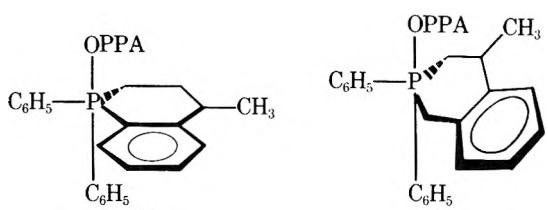
but the ring system is five membered. Moreover, a dipolar ion (A) may exist in solution as suggested by a long P–O



A

distance of 2.14 Å in **11**.[8] The dependence of ^{31}P shifts upon the nature of substituents is well known,[9,10] and there are several other pentavalent P-containing systems reported to have *negative shifts*.[11] Most simple phosphonium salts like **12** have negative ^{31}P values commonly ranging from −10 to −40 ppm.[9]

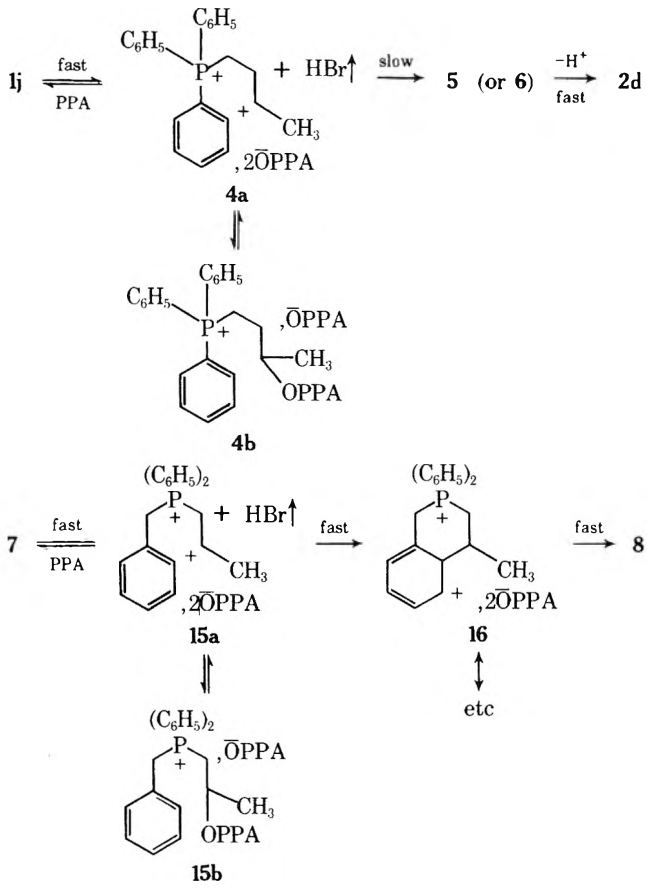
Intuitively, one would estimate the inherent stability of **5** or **6** to be low under the reaction conditions since the stabilization energy gained via aromatization would be significant. The same should be true for a similar intermediate formed in the conversion **7** → **8**. In **1j** → **2d**, the ^{31}P NMR signal at −22.5 ppm is not much different from the signal for **1j** at −19.4 ppm. Initially, it is tempting to consider candidates like **13** (or rotamer thereof) since **2d** accumu-



13 14

lates as the intermediate at −22.5 ppm decreases (as evidenced by the change in ^{31}P NMR signals after t_0 + 45). However, in **7** → **8** a third ^{31}P NMR signal did *not* appear, and the other peaks were confirmed as for **7** and **8**. Thus, there is no intuitively obvious reason why **13** or **14** should not be stable candidates as intermediates in **7** → **8** as well. Consequently, an intermediate does not form or is very reactive and does *not* accumulate.

Several other observations in the cyclization are relevant. The intermediate (at −22.5 ppm) in **1j** → **2d** is relatively stable since the signal persisted to t_0 + 90 min and the ^{31}P NMR signal is close in field position to that of **1j** (−19.4 ppm). Thus, an intermediate with an environment around phosphorus similar to that of **1j** would seem defensible.



One reasonable compromise could involve equilibria such as with **4a** (or **4b**) and **15a** (or **15b**). In **1j** → **2d**, a conversion of **4a** (or **4b**) to **5** (or **6**) would be expectedly slow since the process should have a high energy barrier. Thus **4a** or **4b** could accumulate in the high acid media and could account for the ^{31}P signal at −22.5 ppm indicating a similar environment for P as in **1j** (−19.4 ppm). Rapid loss of a proton from **5** (or **6**) should follow since it is known that $>P^+<$ has an electron-withdrawing effect on electrophilic substitution processes[12] and regeneration of the aromatic nucleus would be energetically favorable. This is also in accord with the observation that the intermediates accumulate at the expense of **1j** and decreases with time as **2d** amasses.

In contrast, conversion of **7** to **15a** (or **15b**) would be fast followed by a rapid intramolecular cyclization to **1b**. An insulating methylene group prevents direct electronic interaction between $>P^+<$ and the ring under attack. Thus, a rather classic intermediate **16** in a classic electrophilic substitution rapidly loses a proton to yield **8**. Consequently, **15a** (or **15b**) and **16** do not persist significantly at 150° to produce a ^{31}P NMR signal.

PPA is known to attack conjugate double bonds in unsaturated phosphine oxides.[13] In fact, a postulate was made that Ō–PPA adds to the sp^2 carbon.[13] To be sure, attack on salts **1j** or **7** should be more difficult but at 150° the problem is circumvented. The evidence available does not support the pentavalent intermediates **13** or **14**, and we interpret the data with the more classical type intermediate, i.e., **5**.

Experimental Section

General Data. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. ^{31}P NMR data were obtained on a XL-100(15) Varian spectrometer operating at 40.5 MHz and with 85% H_3PO_4 as an external standard with the total scan area examined being −123 to +184 ppm without ^1H decoupling. Of course, the ratios of ^{31}P signals is only roughly qualitative because of probable differential NOE effects.[9] Ir, mass spectral, and ^1H NMR data were collected on a Beckman IR-5A unit (as KBr pellets), a CEC Model 21 HR unit, and an XL-100(15) spectrometer, respectively, and are available upon request. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

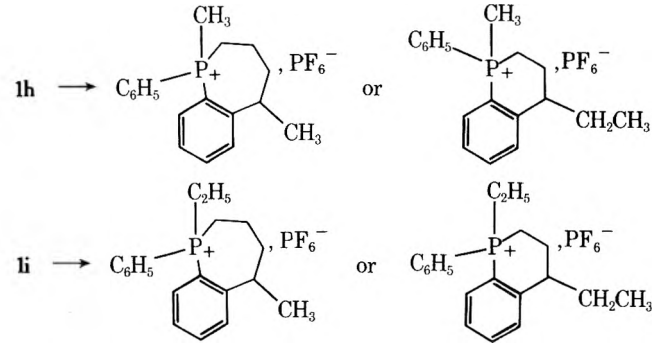
Starting Materials. The phosphine $(C_6H_5)_2PR$ (R = CH_3, C_2H_5, or C_6H_5) required to prepare the open-chain salts in Table I were synthesized as described previously.[1] Allylbenzyldiphenylphosphonium hexafluorophosphate (**7**) was prepared by a metathetic exchange from the corresponding bromide[1] in water when treated with a saturated aqueous solution; mp of 7 was 118–119.5°.

Anal. Calcd for $C_{22}H_{22}F_6P_2$: C, 57.12; H, 4.76; P, 13.41. Found: C, 57.18; H, 4.52; P, 13.18.

Commercial 115% and 105% PPA was obtained from FMC Corp., Inorganic Division, via Mr. J. P. Cassidy.

Quaternization and Cyclization Techniques. Both of these techniques have been outlined in detail previously.[1] All salts of families **1** and **2** as well as **7** and **8** were prepared in a similar fashion. The work-up was modified slightly from that reported.[1] The tube was removed from the probe and allowed to cool to about 80–90°. The various contents were added to 25 ml of distilled H_2O, and the resulting mixture was allowed to stand overnight. A solution resulted and was analyzed at 80° via ^{31}P NMR analysis to confirm the signal for product **2d**. In the case of **8**, the PF_6^- salt precipitated at once when the contents of the tube were discharged into the H_2O. In the work-up for **2d**, the solution of 80° was allowed to cool to room temperature, and a saturated solution of KPF_6 was added. The corresponding salt precipitated and was purified and identified as described.[1]

In the reactions of **1h** and **1i** with 115% PPA, solids were isolated by the standard procedure. However, the melting ranges were



long for the products from both open-chain compounds. ^1H NMR analysis revealed a very complex spectrum in each case. Absent were simple doublets for methyl protons at high field if a seven-membered ring had formed. Neither did the spectrum show a triplet at high field for the terminal methyl group if a six-membered ring had formed. Of course, two sets of geometrical isomers are possible in each example and may be present. All attempts to separate the isomeric mixture have been unsuccessful to date.

Acknowledgment. We gratefully acknowledge support of this work by the USPHS National Cancer Institute, Grant CA 11967.

Registry No.—**1a**, 52750-95-5; **1b**, 56771-23-4; **1c**, 56771-24-5; **1d**, 16958-42-2; **1e**, 56771-26-7; **1f**, 56771-28-9; **1g**, 56771-29-0; **1h**, 56771-31-4; **1i**, 56771-33-6; **1j**, 28975-45-3; **2a**, 56771-35-8; **2b**, 56771-37-0; **2c**, 56771-39-2; **2d**, 54230-12-5; **2e**, 54293-29-7; **2f**, 54230-14-7; **2g**, 56771-41-6; **7**, 56771-43-8.

References and Notes

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(2) All new compounds gave satisfactory elemental (±0.3% P or C, H, and P) analysis as well as the expected ^1H NMR, ^{31}P NMR, ir, and mass spectral data.
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Oxymercuration–Demercuration and Hydroboration–Oxidation of *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene. Stereospecific Oxymercuration Leading to the 4-*exo*-Hydroxy Derivative

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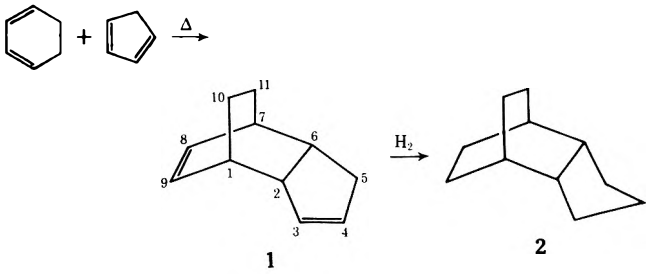
Oxymercuration–sodium borohydride reduction of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) was found to proceed highly regioselectively and stereospecifically, giving 4-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**3**). Saturation of the 8,9 ethylenic bond in **1** resulted in a great reduction in the reactivity as well as the stereoselectivity. In contrast to this, hydroboration of **1** proceeded stereospecifically but not regiospecifically, to give three *exo*-hydroxytricycloundecene isomers. The result suggests a trans addition mechanism for the oxymercuration of **1** with the attack of mercuric ion from the endo side of the diene, the transition state being stabilized with the coordination of the 8,9 ethylenic bond to the mercuric ion.

In a series of the studies on biological activities of substituted polycycloalkanes,[1] we have been interested in the plant-hormonal properties of hydroxypolycycloalkanes. After some hydroxynorbornanes and -adamantanes as well as 3-[2] and other hydroxy derivatives of 4-homoisotwistane (tricyclo[5.3.1.0^{3,8}]undecane) had been tested,[3] examination of the activity of tricyclo[5.2.2.0^{2,6}]undecane (**2**) with hydroxy substituents was planned. The hydrocarbon **2** was prepared for the first time by us[4-6] through hydrogenation of the Diels–Alder adduct (**1**)[7] of cyclohexa-1,3-diene and cyclopentadiene. Although adamantane rearrangement of **2** under the catalysis of Lewis[4,5] and Bronsted[5,6,8] acids was studied, no functionalization reaction has been attempted to date. In this paper, oxymercuration–demercuration and hydroboration–oxidation of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) giving a variety of hydroxy compounds related to **2** are described.

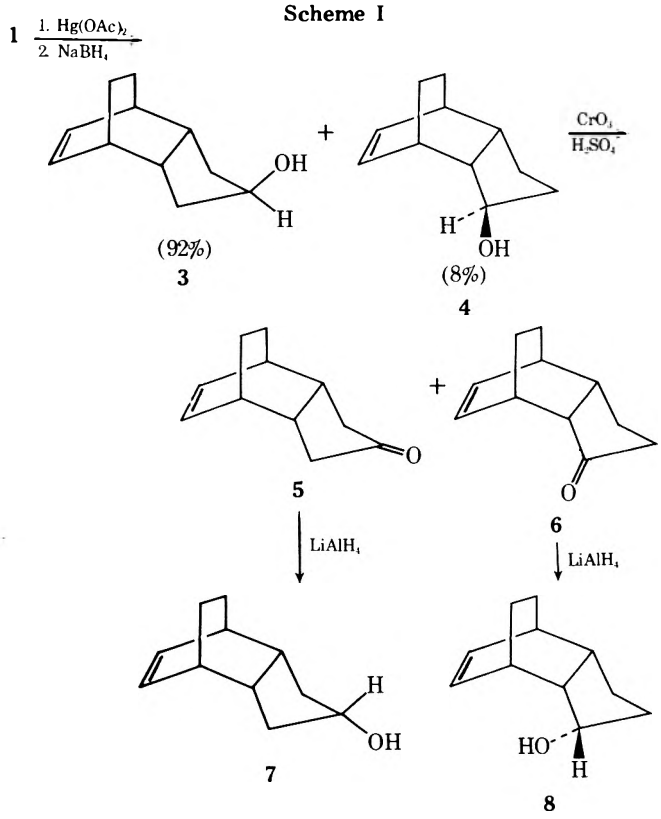


Results

Oxymercuration–sodium borohydride reduction[9,10] of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) in aqueous tetrahydrofuran at ambient temperature for 1 hr gave in 96% yield a mixture of 92% 4-*exo*-hydroxy (**3**) and 8% 3-*exo*-hydroxy (**4**) derivatives of *endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**13**) (Scheme I). The ratio of the two isomeric alcohols in the product was determined on a Golay GC–MS, since conventional VPC could not separate them. However, a pure sample of **3** could be isolated by repeated recrystallizations.

The structure of the alcohol **3** was established as follows.

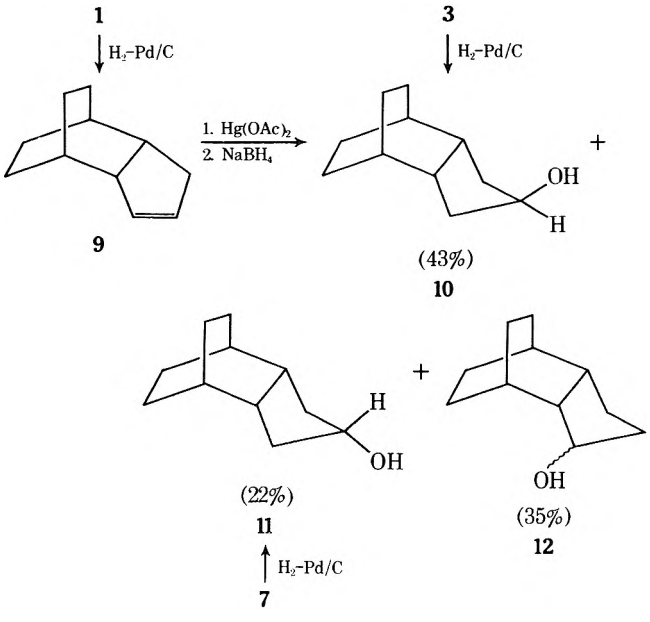
Scheme I



The ^{13}C NMR spectrum indicated that the molecule had a C_s symmetry, showing a correct chemical shift,[11] fine structure, and relative intensity of the signal for the hydroxy-substituted 4-carbon atom. The structure assignment was supported by the ^{1}H NMR spectrum, which had a olefinic proton signal corresponding to that of bicyclo[2.2.2]oct-2-ene,[12] and in which no resonance similar to that of the olefinic protons of 2,4-dimethylcyclopentene[13] was observed.

Jones oxidation[14] of the above oxymercuration–demercuration product from **1** gave a mixture of *endo*-tricy-

Scheme II



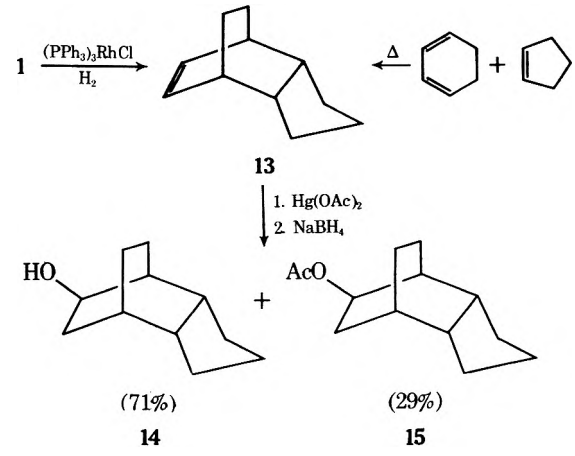
clo[5.2.2.0^{2,6}]undec-8-en-4-one (**5**) and -3-one (**6**) (Scheme I), which could be separated on preparative VPC. The ketone **5** gave endo[15-17] alcohols **7** on lithium aluminum hydride reduction (Scheme I), which was found different from the original alcohol **3**. The exo configuration of the 4-hydroxy group of **3** was thus established.

^{1}H NMR of the ketone **6** showed the presence of intact 8,9-ethylenic bond in the molecule. Since the endo alcohol **8** obtained on lithium aluminum hydride reduction of **6** (Scheme I) was different from **4**, the original alcohol **4** should have an exo configuration.

Tricyclo[5.2.2.0^{2,6}]undec-3-ene (**9**), prepared by partial hydrogenation of the diene **1** over palladium catalyst (Scheme II) was found to react quite sluggishly with mercuric acetate at ambient temperature. The decrease in the reactant **9** was only 33% at the end of 1 week, as monitored by VPC. Golay GC–MS showed that the product consisted of 43% 4-*exo*-hydroxy (**10**), 22% 4-*endo*-hydroxy (**11**), and 35% 3-hydroxy (**12**) derivatives of *endo*-tricyclo[5.2.2.0^{2,6}]undecane (**2**) (Scheme II). The configurations of the 4-hydroxy groups in **10** and **11** were determined unequivocally by comparison of the VPC retention time and mass spectrum with those of authentic specimens prepared by the hydrogenation of the corresponding unsaturated alcohols, **3**, and **7**, obtained above (cf. Scheme II). The structure of **12**[18] was proven by Jones oxidation of the mixture of **10**, **11**, and **12** obtained above, whereby **12** was converted to tricyclo[5.2.2.0^{2,6}]undecan-3-one (**22**) which was identical with the specimens prepared by hydroboration–sodium dichromate oxidation of **9** (Scheme IV) as well as by hydrogenation of **6**.

Oxymercuration of *endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**13**), prepared either by partial hydrogenation of the diene **1** in the presence of Wilkinson complex [$(PPh_3)_3RhCl$][19] (Scheme III) or by Diels–Alder addition of cyclohexa-1,3-diene and cyclopentene, proceeded also fairly slowly, 33% of the reactant **13** having disappeared in 24 hr at ambient temperature. The products were 71% 8-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**14**) and 29% of its acetate (**15**) (Scheme III). The structures of **14** and **15** were unambiguously established by comparison of VPC retention time and mass spectrum with those of authentic specimens prepared by hydroboration–oxidation of the olefin **13** and subsequent acetylation, as described below (Scheme IV).

Scheme III



Hydroboration–hydrogen peroxide oxidation[20] of the diene **1** gave three hydroxytricycloundecenes, **3**, **4**, and a compound of unknown structure, in the ratio of 30, 67, and 3%, respectively. The alcohols **3** and **4** obtained in this reaction were in complete agreement on examination by Golay GC–MS with the **3** and **4** formed in the oxymercuration–demercuration of the diene **1** (Scheme I). The third component in the product mixture was identified as 8-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-3-ene (**16**)[21] by the following reactions (Scheme IV). Jones oxidation of the above hydroboration product gave a mixture of ketones, **5**, **6**, and *endo*-tricyclo[5.2.2.0^{2,6}]undec-3-en-8-one (**17**),[21] from which **17** could be separated on preparative VPC. The ketone **17** gave on reduction with lithium aluminum hydride followed by hydrogenation over palladium catalyst 8-*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**19**) which was identical with the specimen prepared from **13** through hydroboration, Jones oxidation, and lithium aluminum hydride reduction (Scheme IV).

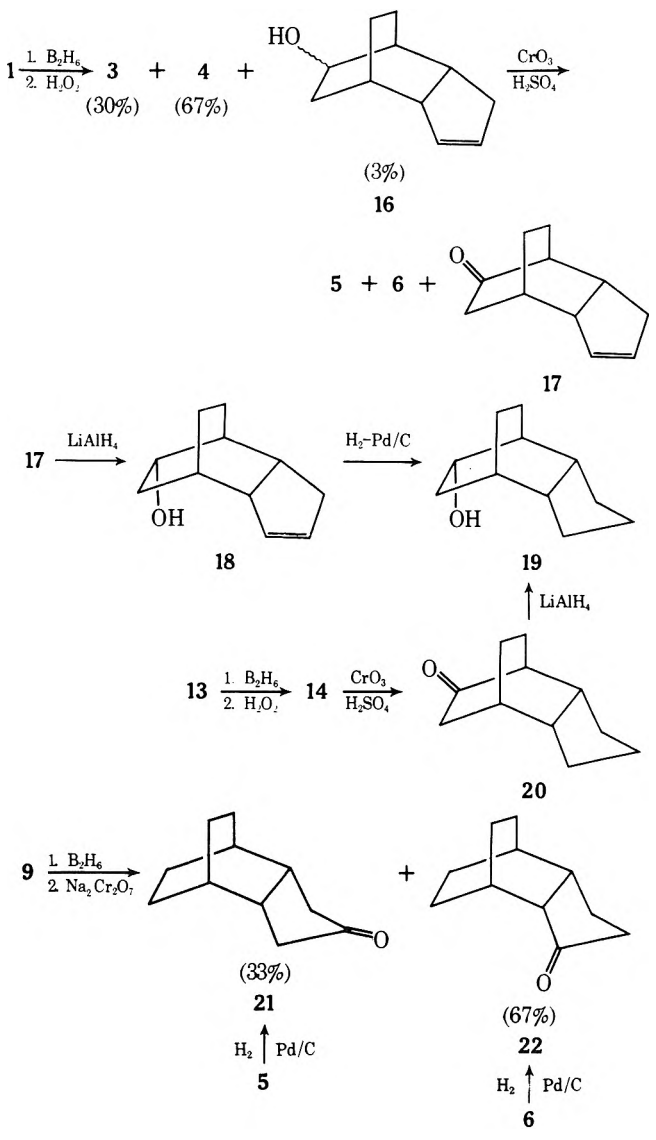
Hydroboration–sodium dichromate oxidation[20] of tricyclo[5.2.2.0^{2,6}]undec-3-ene (**9**) gave two ketones, tricyclo[5.2.2.0^{2,6}]undecan-4-one (**21**) and -3-one (**22**), in 33:67 ratio (Scheme IV), that was almost the same as that of **3** to **4** (30:67) in the hydroboration of the diene **1**. The 4-one **21** separated on preparative VPC exhibited a correct ^{13C} NMR spectrum corresponding to the structure. Structures of the ketones **21** and **22** were unambiguously established by comparison with authentic specimens prepared by hydrogenation of unsaturated ketones **5** and **6**, respectively.

Discussion

Oxymercuration of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) was found to proceed highly regioselectively (92%) and stereospecifically (practically 100%). The high stereospecificity as well as the high reactivity of **1**, as compared to those of tricyclo[5.2.2.0^{2,6}]undec-3-ene (**9**) and -8-ene (**13**), could be interpreted most reasonably in terms of trans addition of mercuric ion and nucleophile with the attack of the mercuric ion from the more hindered, endo side of the diene molecule. Although this assumption might apparently be inconsistent with the established cis addition on the exo side in bicyclic olefins,[15,22-25] no better alternative seems to be at hand, as will be discussed below, for the explanation of the whole experimental results presented here.

Oxymercuration of the monoolefin **9** progressed quite slowly (33% completion in a week) with a loss in regio- and stereoselectivity (Scheme II).[26] It would be rational, in accordance with the preferential exo attack of mercuric ion in oxymercuration of bi- and polycyclic olefins,[15,22-25,27] to presume also the exo attack for the monoolefin **9**. If this is

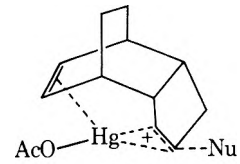
Scheme IV



the case, predominant formation of **10** (Scheme II) would be explained, based on the above exo attack of mercuric ion, by cis addition, and that of **11** by trans addition, of the reagents. The slow formation of **10** then could be attributed to a high activation energy associated with cis addition,[28] while an unusually low trans addition rate for the formation of **11** might be a result of steric hindrance to the approach of the nucleophile from endo side. An exo cis addition mechanism also in the oxymercuration of **13** (Scheme III) is indicated by its low reactivity (33% completion in 24 hr) and exclusive formation of the exo products (**14** and **15**), especially that of the exo acetate[23,24] **15.**

Contrary to the monoolefins **9** and **13,** the diene **1** shows high reactivity and selectivity in oxymercuration. It would be apparent that this cannot be explained by a mechanism involving exo attack of mercuric ion. If exo attack occurred, the high reactivity and selectivity of the diene **1,** as compared to the monoolefin **9,** has to be attributed to the presence of the 8,9-ethylenic bond in the former compound. However, it is quite improbable that the 8,9-unsaturated bond exerts such a large influence on the reactivity and selectivity of the remote 3,4 bond. Furthermore, exo attack of mercuric ion on **1** should give a 8- (and/or 9-) substituted derivative(s), since the 8,9-ethylenic bond would be more reactive than the 3,4 bond, as is shown in the reactivity difference between the model compound **9** and **13.** This is also contrary to the experimental results.

On the other hand, a supposition of the transition state **23,** that corresponds to a trans addition mechanism involv-



23

ing endo attack of mercuric ion with some stabilization by coordination of the 8,9-ethylenic bond to the mercury atom (chelate effect), seems to best explain the whole experimental results. A high rate of reaction for **1** would be a characteristic of the trans addition, while the high stereospecificity is a result of an exclusive approach of nucleophile from the exo side.

No definite explanation can be given to the orientation of nucleophile to the 3,4-, rather than the 8,9-, ethylenic bond to give **23.** The orientation of nucleophile should be interpreted in terms of the relative reactivity for trans oxymercuration of the two ethylenic bonds in **1.** However, it seems difficult to estimate this because no appropriate model is available at present.[29] Steric hindrance might be a predominating factor to control the orientation of the nucleophile, which attacks the less hindered 3,4 bond. Selection between the 3 and the 4 position (8 and 92%, respectively) within the bond by the nucleophile seems to be determined, as in ordinary Markownikoff additions, mainly by the charge distribution on the mercury-bridged 3,4 bond.[30]

Stabilization of the transition state of oxymercuration reaction by coordination of a p orbital to the mercury atom has some precedents.[31-33] Thus coordination of hydroxyl,[31] cyano,[31] carboxyl,[32] and carbamate[33] groups determined the regio- and stereoselectivity of the reaction in these examples. It would be probable, therefore, to assume a similar role of the 8,9-ethylenic bond in the oxymercuration of **1** which leads to a more or less stabilization of the transition state **23.** This stabilization would also contribute to a counterbalance to nonbonded repulsions between endo hydrogens and the mercury atom.[34]

The oxymercuration of the diene **1** can be contrasted to that of *endo*-dicyclopentadiene, a lower homolog of **1.** *endo*-Dicyclopentadiene gave a mixture of 8- and 9-*exo*-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]dec-3-ene as sole products.[22,26,27] The result is in complete agreement with what is expected from the oxymercuration reaction of norbornene.[25,28] Norbornene has been shown to undergo oxymercuration quite rapidly, yet with exo cis addition mechanism. This exceptional reactivity was ascribed to a high strain of the molecule with steric congestion on the endo side.[28] The 8,9-ethylenic bond of **1** is not so strained as the corresponding bonds in *endo*-dicyclopentadiene and norbornene.[35] Therefore, the same, exo cis addition mechanism must be unfavorable for the reaction of the 8,9 bond of **1,** and the activation energy for the transition state **23** is possibly smaller than that for the exo cis attack to the 8,9 bond.

In contrast to oxymercuration, hydroboration of the diene **1** proceeded with a loss in regiospecificity (Scheme IV). However, stereospecificity of the reaction was high, giving predominantly exo alcohols (**3** and **4**). Prevalent formation of **3** and **4,** in turn, may indicate a smaller steric congestion around the 3,4 bond as compared to that around the 8,9 bond. This result, coupled with those for the monoolefins **9** and **13,** confirmed the preference to exo attack by diborane that had been demonstrated in many other bi- and polycyclic systems.[16,17,19,36,37] The loss of regioselectiv-

ity in hydroboration was observed also for *endo*-dicyclopentadiene,[22,27] in spite of the large difference in the reactivities between the two ethylenic bonds in the molecule.

Experimental Section

All melting and boiling points are uncorrected. Ir spectra were obtained for neat samples on a Hitachi 215 spectrophotcmeter. ^{1}H NMR spectra were obtained on a Varian T-60 instrument, and ^{13}C NMR spectra were measured at 15.03 MHz on a Jeol JNM FX-60 spectrometer, both using deuteriochloroform as solvent. Chemical shifts are reported in δ for protons and in parts per million downfield from the internal Me_4Si standard for ^{13}C nuclei. Golay column GC–MS measurements were done with a combination of a Jeol JGC-20-KP gas chromatograph and a JMS-D-100 mass spectrometer. Capillary columns used were of the dimension of 0.01 in. × 150 ft, packed with Apiezon L or silicone SE-30, and the VPC was run at 60–70°. A Varian Aerograph 700 instrument was used for the preparative VPC. Preparation of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) is described in the previous work.[5,7]

Tricyclo[5.2.2.0^{2,6}]undec-3-ene (9). A mixture of 29.2 g (0.2 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**), 300 ml of ethyl ether, and 1.5 g of palladium on charcoal catalyst (containing 5% metal) was placed in a 500-ml autoclave. After being flushed thoroughly with hydrogen, the vessel was charged with 10 kg/cm^2 of hydrogen. Hydrogenation was done at room temperature with efficient stirring until about 0.2 mol of hydrogen had been absorbed. The catalyst was filtered off, and the filtrate was concentrated to give 23.8 g of a mixture consisting of 48% tricyclo[5.2.2.0^{2,6}]undec-3-ene (**9**) and 52% tricyclo[5.2.2.0^{2,6}]undecane (**2**). Purification on a preparative VPC gave a pure sample of **9**: ir 3040 cm^{-1}; ^{1}H NMR δ 1.0–3.0 (m, 14), 5.63 (s, 2); mass spectrum *m/e* (rel intensity) 148 (51, M$^+$), 120 (46), 105 (41), 92 (46), 91 (78), 81 (49), 80 (90), 79 (88), 67 (65), 66 (100).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.03; H, 10.59.

***endo*-Tricyclo[5.2.2.0^{2,6}]undec-8-ene (13). A. Partial Hydrogenation of *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (2) in the Presence of Wilkinson Complex.** A mixture of 43.8 g (0.3 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**), 20 ml of benzene, and 0.2 g of tris(triphenylphosphine)chlororhodium(I) in a 500-ml autoclave was hydrogenated with efficient stirring at 50° under 50 kg/cm^2 of hydrogen, until the calculated amount (0.3 mol) of hydrogen had been absorbed. The reaction mixture was concentrated to remove benzene, and the residue was chromatographed with *n*-hexane through a column packed with alumina containing 10% silver nitrate, whereby any unreacted **1** and the catalyst were separated. The eluent was concentrated to give 39.4 g of a mixture consisting of 52% **13** and 48% **2**. Separation on a preparative VPC gave a pure sample of **13**: ir 3060 cm^{-1}; ^{1}H NMR δ 0.7–2.75 (m, 14), 6.13 (t, 2); mass spectrum *m/e* (rel intensity) 148 (7, M$^+$), 120 (4), 92 (6), 91 (12), 81 (9), 80 (100), 79 (20), 78 (6), 77 (8), 67 (4), 51 (5), 41 (8), 39 (9).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.86; H, 10.87.

B. Diels–Alder Addition of Cyclohexa-1,3-diene and Cyclopentene. Diels–Alder reaction of cyclohexa-1,3-diene and cyclopentene, similar to cyclopentadiene and cyclopentene,[38] was found to undergo endo addition to give *endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**13**). In a 500-ml autoclave were placed 20 g (0.25 mol) of cyclohexa-1,3-diene, 79.3 g (1.17 mol) of cyclopentene, and 50 mg of hydroquinone. After being flushed thoroughly with nitrogen, the vessel was closed and heated to 200° for 6 hr with efficient stirring. The reaction mixture was filtered to separate undissolved hydroquinone, and the filtrate was fractionated in vacuo through a 1-ft Vigreux column to give 5.2 g (14% yield) of **13**. Ir, ^{1}H NMR, and mass spectra of a VPC-purified sample of the **13** thus obtained agreed completely with those of the sample described in the preceding paragraph.

Oxymercuration–Sodium Borohydride Reduction of *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (1). To a yellow solution of 127.4 g (0.4 mol) of mercuric acetate in 200 ml of water and 200 ml of tetrahydrofuran was added with efficient stirring at ambient temperature 58.4 g (0.4 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) in 20 min. The yellow color of the solution disappeared in a few minutes after the completion of the addition of **1**. The reaction solution was then stirred for an additional 1 hr. The reaction mixture was cooled down to −10°, to which was added 400 ml of 3 *N* sodium hydroxide solution followed by a solution of 7.56 g (0.2 mol) of sodium borohydride in 400 ml of 3 *N* sodium hydroxide solution. After precipitated mercury was filtered off, the organic layer was separated from the filtrate, and the aqueous layer was extracted once with ether. The combined organic layer and ether extract were dried over anhydrous magnesium sulfate and concentrated. The solidified residue amounted to 62.9 g (96% yield), which was found on Golay GC–MS to consist of 92% 4-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**3**) and 8% 3-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**4**). Three recrystallizations of a sample of the crude product from *n*-hexane gave a pure sample of **3**: mp 98–99°; ir 3290, 3050, 2920, 2860, 1610, 1460, 1370, 1330, 1280, 1210, 1170, 1020, 940, 860, 720 cm^{-1}; ^{1}H NMR δ 1.0–2.6 (m, 12), 2.02 (s, 1, OH), 4.18 (m, 1, CHOH), 6.12 (t, 2, CH=CH); ^{13}C NMR (multiplicity, rel intensity) 25.3 (t, 2), 34.4 (d, 2), 40.8 (t, 2), 42.5 (d, 2), 73.6 (d, 1), 133.7 ppm (d, 2); mass spectrum *m/e* (rel intensity) 164 (50, M$^+$), 121 (18), 108 (17), 92 (13), 91 (19), 83 (55), 82 (31), 80 (100), 79 (43), 77 (13).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.15; H, 9.93.

The mass spectrum of **4** was taken on the Golay GC–MS: *m/e* (rel intensity) 164 (26, M$^+$), 92 (14), 91 (20), 83 (64), 82 (27), 80 (100), 79 (49), 77 (15), 41 (14), 39 (17).

***endo*-Tricyclo[5.2.2.0^{2,6}]undec-8-en-4-one (5) and *endo*-Tricyclo[5.2.2.0^{2,6}]undec-8-en-3-one (6).** The crude product of the oxymercuration–demercuration of **1** was converted to a mixture of *endo*-tricyclo[5.2.2.0^{2,6}]undec-8-en-4-one (**5**) and -3-one (**6**) by Jones oxidation. A solution of 32.8 g (0.2 mol) of the crude product obtained above in 200 ml of acetone was kept at 0–5°, while an oxidizing agent prepared from 14 g (0.14 mol) of chromium trioxide, 20 ml of 95% sulfuric acid, and 60 ml of water was added with efficient stirring in a period of 5 hr. The reaction mixture was stirred for an additional 4 hr at ambient temperature. Any excess chromium trioxide in the reaction mixture was destroyed by the addition of a sodium bisulfite solution, and the mixture was extracted with two 100-ml portions of ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether left a solid, crude product which contained **5** and **6** in 93:7 ratio.

Three recrystallizations of the above crude product mixture from *n*-hexane gave a pure sample of **5**: mp 38–39°; ir 3040, 2950, 2910, 2870, 1730 cm^{-1}; ^{1}H NMR δ 1.0–2.8 (m, 12), 6.30 (t, 2, CH=CH); mass spectrum *m/e* (rel intensity) 162 (8, M$^+$), 92 (7), 91 (9), 81 (8), 80 (100), 79 (20), 77 (7), 39 (10), 27 (9), 18 (19).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.18; H, 8.75.

Fractionation of the above crude product mixture on preparative VPC gave a pure sample of **6**: ir 3050, 2950, 2870, 1740 cm^{-1}; ^{1}H NMR δ 1.0–3.2 (m, 12), 6.22 (t, 2, CH=CH); mass spectrum *m/e* (rel intensity) 162 (13, M$^+$), 92 (20), 91 (16), 83 (22), 80 (100), 79 (28), 78 (21).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.53; H, 8.90.

4-*endo*-Hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (7) and 3-*endo*-Hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (8). To a suspension of 1.0 g (0.026 mol) of lithium aluminum hydride in 50 ml of dry ether was added dropwise under gentle reflux with efficient stirring a solution of 5.8 g (0.036 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undec-8-en-4-one (**5**) in 30 ml of ether. The reaction was then refluxed for an additional 2 hr and worked up in the usual manner to give 5.4 g (92% yield) of solid crude **7**. Purification on preparative VPC gave a pure material: mp 101–102°; ir 3280, 3040, 2920, 2860, 1610, 1460, 1440, 1370, 1350, 1290, 1080, 1020, 840, 710 cm^{-1}; ^{1}H NMR δ 0.8–2.8 (m, 13), 3.8 (m, 1, CHOH), 6.17 (t, 2, CH=CH); mass spectrum *m/e* (rel intensity) 164 (3, M$^+$), 92 (5), 91 (6), 81 (8), 80 (100), 79 (15), 77 (5), 67 (3), 44 (3).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.23; H, 9.90.

A sample (2.9 g, 0.018 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undec-8-en-3-one (**6**) was reduced in ether with 0.5 g (0.013 mol) of lithium aluminum hydride with the same procedure as above. Crude **8** obtained (2.6 g, 88% yield) was purified on preparative VPC to give a pure sample: ir 3400, 3050, 2930, 2870, 1620, 1460, 1440, 1370, 1090, 1050, 1020, 960, 900, 870, 850, 820, 710 cm^{-1}; mass spectrum *m/e* (rel intensity) 164 (5, M$^+$), 92 (14) 91 (11), 80 (100), 79 (27), 68 (24), 67 (10).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.68; H, 9.79.

4-*exo*-Hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (10) and 4-*endo*-Hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (11). Authentic specimens of 4-*exo*- and -*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**10** and **11**) were prepared by catalytic hydro-

genation of 4-*exo* and -*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]-undec-8-ene (**3** and **7**), respectively. A mixture of 10 g (0.061 mol) of **3**, 50 ml of ethanol, and 0.5 g of the palladium on charcoal catalyst was stirred at room temperature in a 100-ml autoclave with repeatedly charged hydrogen (pressure below 10 kg/cm^2), until pressure drop was no longer observed (30 min). The catalyst was filtered off, and the filtrate was concentrated. Recrystallization of the residue from *n*-hexane gave 8.6 g (85% yield) of pure **10**: mp 98–99°; mmp with **3** 65–68°; ir 3250, 1060, 1020 cm^{-1}; ^{1}H NMR δ 1.0–2.5 (m, 16), 2.17 (s, 1, OH), 4.4 (m, 1, CHOH); mass spectrum *m/e* (rel intensity) 166 (3, M$^+$), 148 (71), 120 (35), 119 (27), 107 (33), 94 (54), 93 (30), 81 (41), 80 (100), 79 (50), 67 (38).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.26; H, 10.98.

Hydrogenation in the same procedure of 1.7 g (0.01 mol) of the crude **7** obtained above gave 1.3 g (75% yield) of the crude crystals of **11**. Purification on preparative VPC gave a pure sample: mp 87–88°; ir 3250, 1090, 1060, 1040 cm^{-1}; ^{1}H NMR δ 1.0–2.6 (m, 16), 2.63 (s, 1, OH), 4.13 (m, 1, CHOH); mass spectrum *m/e* (rel intensity) 166 (1, M$^+$), 148 (32), 107 (29), 81 (33), 80 (100), 79 (47), 67 (40), 66 (35), 41 (35).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.88; H, 10.73.

Oxymercuration–Sodium Borohydride Reduction of Tricyclo[5.2.2.0^{2,6}]undec-3-ene (9). A sample (1.48 g, 0.01 mol) of tricyclo[5.2.2.0^{2,6}]undec-3-ene (**9**) was stirred at ambient temperature with a solution of 3.19 g (0.01 mol) of mercuric acetate in 20 ml of 50% aqueous tetrahydrofuran. After 1 week, the reaction mixture was treated at −10° with 10 ml of 3 *N* sodium hydroxide solution and then with 0.19 g (0.005 mol) of sodium borohydride in 10 ml of 3 *N* sodium hydroxide solution. After being saturated with sodium chloride the mixture was extracted with three 10-ml portions of ether. The combined ether extracts were dried over sodium sulfate and concentrated to give 0.9 g of residue. The residue was found by Golay GC–MS to consist of 67% unreacted **9**, 14% 4-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**10**), 7% 4-*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**11**), and 12% a tricycloundecanol of undetermined structure. This compound was identified as 3-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**12**)[18] since Jones oxidation of the above oxymercuration–demercuration product gave a mixture comprising 65% unreacted **9**, 22% tricyclo[5.2.2.0^{2,6}]undecan-4-one (**21**), and 13% tricyclo[5.2.2.0^{2,6}]undecan-3-one (**22**). Identification of **10**, **11**, **21**, and **22** was made by comparison on Golay GC–MS with authentic materials.

Oxymercuration–Sodium Borohydride Reduction of *endo*-Tricyclo[5.2.2.0^{2,6}]undec-8-ene (13). *endo*-Tricyclo[5.2.2.0^{2,6}]undec-8-ene (**13**, 1.48 g, 0.01 mol) was treated with 3.19 g (0.01 mol) of mercuric acetate in 20 ml of 50% aqueous tetrahydrofuran for 24 hr at ambient temperature. The reaction mixture was reduced with 0.19 g (0.005 mol) of sodium borohydride in sodium hydroxide solution. The reaction product consisted of 67% unreacted **13**, 23% 8-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**14**), and 10% 8-*exo*-acetoxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**15**). Identification of **14** and **15** was made on Golay GC–MS by comparison with the authentic specimens prepared in the following paragraph.

8-*exo*-Hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (14) and Its Acetate (15). Tricyclo[5.2.2.0^{2,6}]undec-8-ene (**13**) gave 8-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**14**) on hydroboration–hydrogen peroxide oxidation. To a suspension of 4.44 g (0.03 mol) of **13** and 0.57 g (0.015 mol) of sodium borohydride in 15 ml of tetrahydrofuran was dropped under nitrogen stream at ambient temperature with efficient stirring a solution of 2.84 g (0.02 mol) of boron trifluoride etherate in 5 ml of tetrahydrofuran in a period of 45 min. The reaction mixture was then stirred overnight, allowed to react with hydrogen peroxide, and worked up in the usual way to give 4.55 g (91% yield) of crude **14**. Purification on preparative VPC gave a pure sample: mp 66–67°; ir 3300, 2930, 2870, 1470, 1360, 1310, 1090, 1070, 1020, 980, 910, 810, 720 cm^{-1}; ^{1}H NMR δ 1.0–2.4 (m, 16), 2.13 (s, 1, OH), 4.07 (m, 1, CHOH); mass spectrum *m/e* (rel intensity) 166 (12, M$^+$), 148 (67), 122 (44), 93 (44), 81 (55), 80 (100), 79 (88), 78 (53), 67 (61).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.18; H, 11.07.

Acetylation of **14** with acetic anhydride in pyridine at reflux gave 8-*exo*-acetoxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**15**). Purification on preparative VPC gave a pure sample: ir 1730 cm^{-1}; mass spectrum *m/e* (rel intensity) 148 (56), 120 (58), 119 (47), 91 (37), 80 (100), 79 (55), 77 (20), 67 (36), 43 (77), 41 (38).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.10; H, 9.89.

***endo*-Tricyclo[5.2.2.0^{2,6}]undecan-8-one (20).** Jones oxidation of 1.66 g (0.01 mol) of 8-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**14**) with 0.7 g (0.007 mol) of chromium trioxide in 1 ml of 95% sulfuric acid and 3 ml of water gave 1.31 g (81% yield) a crude *endo*-tricyclo[5.2.2.0^{2,6}]undecan-8-one (**20**). Purification on preparative VPC gave a pure sample: ir 1720 cm^{-1}; ^{1}H NMR δ 1.0–2.6 (m); mass spectrum *m/e* (rel intensity) 164 (30, M$^+$), 120 (46), 106 (100), 95 (30), 80 (30), 79 (41), 67 (46), 41 (44), 39 (39).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.19; H, 9.90.

8-*endo*-Hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (19). Reduction of 0.66 g (0.004 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undecan-8-one (**20**) with 0.15 g (0.004 mol) of lithium aluminum hydride in 7 ml of ether gave 0.6 g (92% yield) of crude 8-*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**19**), which was purified on preparative VPC to afford a pure sample: mp 92–93°; ir 3250 cm^{-1}; ^{1}H NMR δ 1.0–2.3 (m, 16), 2.15 (s, 1, OH), 3.89 (t, 1, CHOH); mass spectrum *m/e* (rel intensity) 148 (38), 93 (24), 81 (54), 80 (100), 79 (46), 67 (50), 66 (29), 41 (36), 39 (24).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.66; H, 10.91.

Hydroboration–Hydrogen Peroxide Oxidation of *endo*-Tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (1). A suspension of 14.6 g (0.1 mol) of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-3,8-diene (**1**) and 1.17 g (0.03 mol) of sodium borohydride in 50 ml of dry tetrahydrofuran kept at 25–30° was treated under nitrogen stream with 5.68 g (0.04 mol) of boron trifluoride etherate in 10 ml of tetrahydrofuran. After being stirred for 3 hr at ambient temperature, the reaction mixture was oxidized with hydrogen peroxide and worked up in the usual manner. The crude product (16 g, 96% yield) was found by Golay GC–MS to consist of 30% 4-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**3**), 67% 3-*exo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-8-ene (**4**), and 3% 8-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-3-ene (**16**).[21] Jones oxidation of the above reaction product gave a mixture of ketones, from which *endo*-tricyclo[5.2.2.0^{2,6}]undec-3-en-8-one (**17**)[21] was separated on preparative VPC. The ketone **17** was reduced with lithium aluminum hydride to 8-*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undec-3-ene (**18**).[21] Hydrogenation of **18** over the palladium on charcoal catalyst gave 8-*endo*-hydroxy-*endo*-tricyclo[5.2.2.0^{2,6}]undecane (**19**), which was identical by comparison on Golay GC–MS with an authentic specimen prepared in the preceding paragraph.

Hydroboration–Sodium Dichromate Oxidation of Tricyclo[5.2.2.0^{2,6}]undec-3-ene (9). A sample (1.48 g, 0.01 mol) of tricyclo[5.2.2.0^{2,6}]undec-3-ene (**9**) and 0.19 g (0.005 mol) of sodium borohydride in 5 ml of tetrahydrofuran was allowed to react with 0.95 g (0.007 mol) of boron trifluoride etherate in 2 ml of tetrahydrofuran for 2 hr. The reaction mixture was oxidized with 2.4 g (0.008 mol) of sodium dichormate dihydrate in 1.8 ml of 95% sulfuric acid and 8 ml of water at 20–25° and worked up in the usual manner to give 1.5 g (92% yield) of crude product. Golay GC–MS showed the presence of two ketones in a ratio of 33:67. They were separable on preparative VPC. The less abundant component was, as determined by ^{13}C NMR spectroscopy, tricyclo[5.2.2.0^{2,6}]undecan-4-one (**21**): mp 81–82°; ir 1740 cm^{-1}; ^{1}H NMR δ 1.2–3.0 (m); ^{13}C NMR (multiplicity, rel intensity) 19.9 (t, 2), 26.5 (t, 2), 29.1 (d, 2), 36.2 (d, 2), 41.8 (t, 2), 220.6 ppm (s, 1); mass spectrum *m/e* (rel intensity) 164 (100, M$^+$), 93 (46), 81 (41), 80 (75), 79 (81), 67 (57), 41 (65), 39 (57).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.53; H, 9.65.

The more abundant component, tricyclo[5.2.2.0^{2,6}]undecan-3-one (**22**): ir 1730 cm^{-1}; ^{1}H NMR δ 1.0–3.1 (m); mass spectrum *m/e* (rel intensity) 164 (17, M$^+$), 83 (100), 80 (30), 79 (27), 67 (17).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.21; H, 10.02.

The spectra of **21** and **22** were in complete agreement with those of authentic specimens prepared by palladium-catalyzed hydrogenation of tricyclo[5.2.2.0^{2,6}]undec-8-en-4-one (**5**) and tricyclo[5.2.2.0^{2,6}]undec-8-en-3-one (**6**), respectively.

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Registry No.—**1**, 54483-01-1; **3**, 56804-77-4; **4**, 56804-78-5; **5**, 56804-79-6; **6**, 56846-30-1; **7**, 56846-31-2; **8**, 56846-32-3; **9**, 56804-80-9; **10**, 56804-81-0; **11**, 56846-33-4; **13**, 56804-82-1; **14**, 56804-83-2; **15**, 56804-84-3; **19**, 56846-34-5; **20**, 56804-85-4; **21**, 56804-86-5; **22**, 56804-87-6; cyclohexa-1,3-diene, 592-57-4; cyclopentene, 142-29-0.

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The 4-Homoadamantyl Cation. II.[1] Mechanistic Studies on Lewis Acid Catalyzed Conversion of Homoadamantene to 2-Methyladamantane by Carbon-13 Labeling Techniques. Convenient Synthesis of 4-Homoadamantanone-*5*-^{13}C and Homoadamantene-*4*-^{13}C

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The Lewis acid catalyzed conversion of homoadamantene-*4*-^{13}C in CS_2 yielded 20% of 2-methyladamantane with the majority of the label equally distributed between the α position and the methyl group, indicating that only the olefinic carbons were involved in this rearrangement. The mechanism probably involves protonation of the olefinic bond by $AlX_3{\cdot}H_2O$ to form the classical 4-homoadamantyl cation. This cation appears to rearrange rapidly to an unsymmetrically bridged 2-adamantylcarbinyl cation which yields 2-methyladamantane by hydride abstraction. The degenerate homoadamantyl rearrangement is retarded in such a low polar solvent as CS_2 presumably by intimate ion pairing. 4-Homoadamantanone-*5*-^{13}C was prepared in 46% overall yield by addition of $(CH_3)_3Si^{13}CN$ to adamantanone followed by $LiAlH_4$ reduction of the α-trimethylsilyloxy nitrile and Demjanow–Tiffeneau ring enlargement of the resulting α-aminomethyl alcohol [$(CH_3)_3Si^{13}CN$ was obtained in 88% yield from $(CH_3)_3SiCl$ and $Ag^{13}CN$]. This synthetic procedure appears to be a convenient general method for the preparation of ^{13}C-labeled ketones and their derivatives.

Lewis acid catalyzed rearrangements of polycyclic hydrocarbons are extremely useful methods for the preparation of adamantane and other diamonoid molecules.[4,5] The catalyst reacts with a promoter present in the reaction mixture to form carbonium ions which initiate intermolecular hydride transfers involving the hydrocarbon.[4a,f] The resulting carbonium ions then undergo a series of hydride transfers and 1,2-alkyl shifts leading to the thermodynamically most stable products, diamonoid hydrocarbons.[4a,f]

Although these processes have been known[4] for some time to involve carbonium ion intermediates, the first studies of these intermediates appeared in the literature only recently. Whitlock and Siefken constructed a rearrangement graph for tricyclodecane isomers showing the interrelationships among the isomers.[6] There are at least 2897 pathways between tetrahydrodicyclopentadiene and adamantane but no studies have yet succeeded in isolation and identification of intermediates during this isomerization.[4f] Most of the studies up to 1970 have only provided suggestive mechanistic information.[4,5a,6,7] Schleyer and co-workers[8] recently proposed a plausible pathway for the rearrangement of tetrahydrodicyclopentadiene to adamantane

on the basis of molecular mechanics calculations. The last part of this pathway was demonstrated experimentally. Thus, *exo*-1,2-trimethylenenorbornane was shown to rearrange to adamantane in the presence of AlX_3 through 2,6-trimethylenenorbornane and protoadamantane as it had been predicted.[8] Protoadamantane-*4*-^{13}C, under similar conditions, gave exclusively adamantane-*1*-^{13}C.[9] ^{14}C-Labeling techniques were used in mechanistic studies of the Lewis acid catalyzed isomerization of 1- and 2-methyladamantanes.[10a] 2-Methyladamantane-*2*-^{14}C yielded exclusively 1-methyladamantane-*1*-^{14}C. The methyl group thus remained attached to the same ring carbon throughout the isomerization indicating a skeletal rearrangement involving 2-adamantyl and 4-protoadamantyl cationic intermediates. An analogous mechanism was suggested for the degenerate isomerization of adamantane itself.[10b]

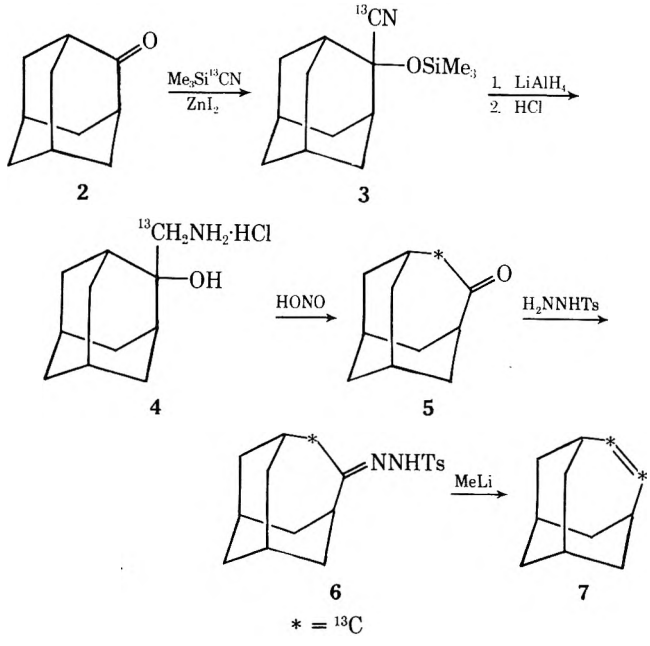
Recently we reported[11] the Lewis acid catalyzed conversion of homoadamantene to 2-methyladamantane. Homoadamantane, under similar conditions, yielded a 2:1 mixture of 2- and 1-methyladamantane.[11] Since no 1-methyladamantane was formed from homoadamantene, 1- and 2-methyladamantane presumably arise through different intermediates which interconvert very slowly, if at all. We now report mechanistic studies on the Lewis acid catalyzed conversion of homoadamantene to 2-methyladamantane using ^{13}C labeling techniques and homoadamantene-*4*-^{13}C as the starting material.

Synthesis of 4-Homoadamantanone-*5*-^{13}C (5) and Homoadamantene-*4*-^{13}C (7). Homoadamantene can be obtained readily by the reaction of an alkyllithium with the tosylhydrazone of 4-homoadamantanone.[11] However, the reported procedures for the preparation of 4-homoadamantanone[12-14] are not convenient for the introduction of ^{13}C isotope into the homoadamantane nucleus.

The key step in our synthesis of 4-homoadamantanone-*5*-^{13}C (5) and homoadamantene-*4*-^{13}C (7) was a modification of Evans–Sundermeyer's reaction. Evans[15] and Sundermeyer[16] found recently that ketones and aldehydes react readily with trimethylsilyl cyanide in the presence of a Lewis acid catalyst to give α-trimethylsilyloxy nitriles which can be reduced readily to the corresponding α-aminomethyl alcohols. No excess of either reactant was necessary. However, the reported preparation of trimethylsilyl cyanide required stirring of AgCN with a large excess of trimethylsilyl chloride followed by fractional distillation of the resulting mixture of trimethylsilyl cyanide and trimethylsilyl chloride.[15,17] This procedure is inconvenient for small-scale preparations of expensive trimethylsilyl cyanide-^{13}C (1). We found, however, that the separation of trimethylsilyl cyanide and trimethylsilyl chloride was unnecessary; the crude mixture can be used just as well. The complete synthetic sequence is outlined in Scheme I. The reaction of adamantanone (2) with an equimolar amount of trimethylsilyl cyanide-^{13}C (1), in trimethylsilyl chloride at 25° in the presence of zinc iodide as catalyst, gave 2-cyano-^{13}C-2-trimethylsilyloxyadamantane (3) smoothly in 98% yield. Reduction of 3 by $LiAlH_4$ followed by introduction of gaseous HCl yielded 2-aminomethyl-^{13}C-2-hydroxyadamantane hydrochloride (4). 4-Homoadamantanone-*5*-^{13}C (5) was obtained by Demjanow–Tiffeneau ring enlargement[13b] of 4 in 46% yield based on 1. The ketone 5 was converted to the corresponding tosylhydrazone which gave homoadamantene-*4*-^{13}C (7) upon treatment[11] with an excess of methyllithium in an overall yield of 56%. The described synthesis of 4-homoadamantanone-*5*-^{13}C and homoadamantene-*4*-^{13}C should be a convenient general method for the preparation of ^{13}C-labeled ketones and olefins.

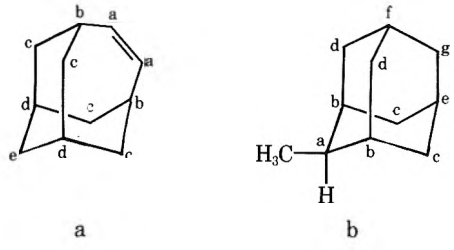
The proton-decoupled ^{13}C NMR spectrum of homoadamantene shows signals at 138.1 (d), 37.2 (t), 34.1 (t), 32.5

Scheme I



(d), and 30.0 ppm (d) (the multiplicity, indicated in parentheses, was determined by proton off-resonance decoupling). The CH_2 signals at 37.2 and 34.1 ppm were assigned on the basis of their relative line intensities to carbons e and c, respectively (Chart I, a). The assignment of the CH

Chart I



signals (32.5 and 30.0 ppm) was based on selective ^1H-decoupling experiments. The lower field signal (32.5 ppm) was assigned to carbons b which are coupled with the lower field protons. The chemical shift of olefinic carbons a is in good agreement with the value (135.8 ppm) of the chemical shift of the olefinic carbons in cycloheptene when corrected for substituents.[18]

Comparison of the ^{13}C NMR spectra of labeled and unlabeled homoadamantene, recorded under identical operating conditions, shows that no label scrambling occurred during the synthesis. The label was located exclusively at the olefinic carbons. Mass spectrometric analysis indicated the ^{13}C enrichment as 10 ± 1%.

Results and Discussion

Homoadamantene-*4*-^{13}C (7) was stirred with an excess of $AlBr_3$ in carbon disulfide for 5 min at room temperature. Substantial amounts of tar (almost insoluble in CS_2) were formed during the reaction. The carbon disulfide solution was decanted from the tar, the solvent was evaporated, and the residue was sublimed to yield 20% of a crude product which was analyzed by GLC. The major product (80–85%) was isolated by preparative GLC and identified as 2-methyladamantane (8) by ^{13}C NMR, ^1H NMR, ir, and mass spectra, and GLC comparison with an authentic sample. Less than 0.5% of 1-methyladamantane was present.[19] The

Table I
^{13}C NMR Signal Intensities of Unlabeled 2-Methyladamantane (8a) and 2-Methyladamantane-^{13}C (8b) Obtained from Homoadamantene-4-^{13}C (7)

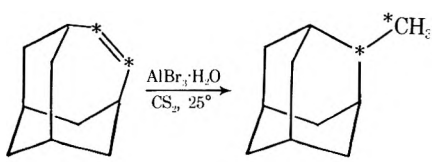
Carbon[a]	Chemical shift[b]	T_1, sec[c]	Relative signal intensities[d] 8a[e]	8b[f]
a	39.2	19.5	1.10 ± 0.05	5.27 ± 0.05
b	34.0	17.5	2.19 ± 0.01	2.62 ± 0.05
c	39.6	10.5	2.38 ± 0.04	2.72 ± 0.16
d	31.5	9.5	2.25 ± 0.02	2.67 ± 0.07
e	28.7	16.5	1.08 ± 0.02	1.08 ± 0.05
f	28.4	16.5	1.06 ± 0.01	1.07 ± 0.04
g	38.8	11.5	1.11 ± 0.03	1.15 ± 0.12
CH_3	19.0	10.0	0.92 ± 0.06	5.52 ± 0.06

[a] See Chart I, b. [b] Relative to Me_4Si; solvent $CDCl_3$. [c] Measured in undegassed solutions. [d] Uncertainties are standard deviations. [e] The sum of the signal intensities was taken as 12.1 (the number of carbons multiplied by the natural abundance of ^{13}C); mean value of five measurements. [f] The sum of the signal intensities was taken as 22.1 ± 1 (12.1 + 10, the percentage of the ^{13}C enrichment); mean value of three measurements.

proton-decoupled ^{13}C NMR spectrum of 2-methyladamantane shows eight signals which were assigned according to Maciel et al.[20] (see Table I and Chart I, b). The assignment of carbons e and f remains tentative.

The signal intensities in routine ^{13}C NMR spectra are generally not proportional to the number of equivalent carbons owing to the saturation effect, different nuclear Overhauser effect (NOE) enhancement for different carbons, the dependence of the digital spectrum signal intensities on their positions, and systematic errors of the spectrometer. To eliminate the influence of the saturation effect a waiting time between successive pulses five times as long as the longest relaxation time was used. Dependence of signal intensities on their positions in the digital spectrum was avoided by using the narrowest possible sweep width (1250 Hz) and a mathematical filtering[21] which enhanced the signal to noise ratio and increased the signal width. By this procedure more than ten data points per signal were available. The NOE enhancements were not eliminated, since the sample amounts were limited. The spectra of the labeled and the unlabeled compounds were taken under precisely the same operating conditions. Comparison of the corresponding relative signal intensities gave intensity enhancements proportional to the amounts of the label at the particular positions. The results are shown in Table I.

The relative signal intensities of all corresponding carbons except for a and CH_3 in labeled and unlabeled 2-methyladamantane are almost the same. There is a small increase in the signal intensities of carbon atoms b, c, and d in 2-methyladamantane obtained from homoadamantene-4-^{13}C. However, the signal intensities of carbons a and CH_3 are significantly and equally enhanced. In other words, the majority of the label (~90%) in 2-methyladamantane obtained by $AlBr_3$ catalyzed conversion of homoadamantene-4-^{13}C is equally distributed between positions a and CH_3.

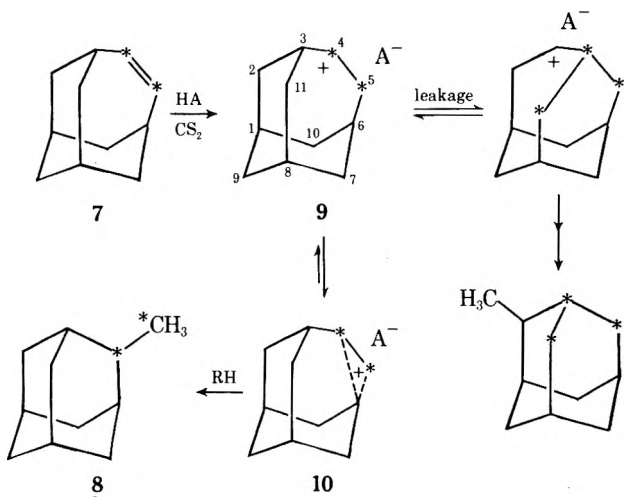


7 8

* = ^{13}C

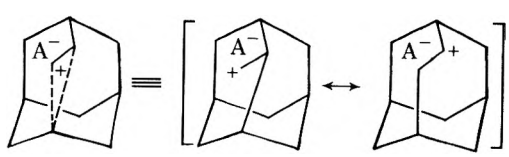
The mechanism of this reaction almost certainly involves protonation of the olefinic bond in the initial step to form a carbonium ion. An analogous mechanism has been suggested and is generally accepted for the Lewis acid catalyzed alkylations of alkenes by alkanes.[22] Lewis acids readily react with moisture (e.g., from air) to form a strongly acidic complex.[23,24] Such an acid can easily protonate olefinic bonds. Protonation of homoadamantene (7) presumably leads first to the classical 4-homoadamantyl cation (9) (Scheme II). Homoadamantene does not have the required

Scheme II



7 9 8 10

geometry for a concerted one-step transformation to a bridged ion, since the olefinic and two adjacent bridgehead carbons lie in the same plane and, therefore, the incipient empty p orbital at carbon C_4 is perpendicular to the C_5–C_6 bond. However, the classical cation 9 cannot give 2-methyladamantane (8) directly and probably rearranges rapidly to another intermediate which yields 8 by hydride abstraction. The classical primary 2-adamantylcarbinyl cation may be ruled out as the intermediate because such carbonium ions appear to be energetically inaccessible under normal reaction conditions.[26] Since the majority of the label in 2-methyladamantane-^{13}C (8b) is equally distributed between carbons a and CH_3, only the olefinic carbons of homoadamantene-4-^{13}C (7) are involved in the rearrangement. Any rearrangement involving other carbons would lead to extensive label scrambling. The unsymmetrically bridged 2-adamantylcarbinyl (4-homoadamantyl) cation[27] (10) appears to be the most plausible intermediate to account for the experimental results. This structure is a hybrid between the primary 2-adamantylcarbinyl cation (10a) and the more strained but secondary 4-homoadamantyl cation (10b).



10 10a 10b

Protonation of homoadamantene in a nonpolar solvent like carbon disulfide presumably leads to intimate ion pairs. Stability differences between secondary and primary intimate ion pairs should be significantly reduced relative to those between the corresponding free ions. In addition, the adamantane skeleton is about 10 kcal/mol less strained than the homoadamantane skeleton.[29] Consequently, the contribution of structure 10a should be predominant and hydride abstraction by the "primary" center leading to 2-methyladamantane (8) is highly favored.

The small amount of label scrambling over carbons b, c,

and d indicates a limited extent of the degenerate homoadamantyl rearrangement (Scheme II). This leakage provides additional evidence for the intermediacy of the 4-homoadamantyl cation. Since degeneracy is generally limited by ion pairing,[13a,30] the small extent of degenerate homoadamantyl rearrangement observed in CS_2 is consistent with the formation of intimate ion pairs in this nonpolar solvent. In other media the degenerate homoadamantyl rearrangement is well known to occur to a large extent. For example, the 4-homoadamantyl cation formed in acetolysis and formolysis of the specifically deuterated 4-homoadamantyl tosylate was reported to undergo extensive label scrambling and degenerate rearrangement.[12a,13a] In concentrated sulfuric acid the degenerate rearrangement of the 4-homoadamantyl cation is essentially complete.[31]

Experimental Section

The labeled $K^{13}CN$ was purchased from Merck Sharp and Dohme, Canada Ltd. and contained 90% of ^{13}C. $AlBr_3$ (Fluka) was kept in a tightly closed flask; no special protection from air moisture was used during its handling. Other chemicals were analytical grade. All melting points were taken on a Kofler hot stage and are uncorrected. The ^{13}C NMR spectra were taken at 22.628 MHz on a Bruker-Spectrospin HFX-90 spectrometer equipped with a B-SC-FFT-12 Fourier transform unit. Samples (40–50 mg) in deuteriochloroform solutions (ca. 160 μl) were measured using a 5-mm cylindrical microcell. The deuterium signal of the solvent was used as the internal lock. The free induction decay signals were accumulated in 8192 data points. Chemical shifts are given in parts per million relative to internal Me_4Si. The ^1H NMR spectra were recorded on a Varian A-60A spectrometer using $CDCl_3$ as solvent, ir spectra were taken on a Perkin-Elmer M-257 spectrophotometer, and mass spectra on a Varian CH-7 mass spectrometer. GLC analyses were carried out on a Varian Aerograph M-1800 gas chromatograph with a M-480 integrator. All new compounds gave satisfactory elemental analyses.

Silver cyanide-^{13}C was obtained in quantitative yield by mixing aqueous solutions of $K^{13}CN$ ($K^{13}CN/KCN$ = 1:9) and $AgNO_3$ in equimolar amounts. The product was collected by filtration, washed with water, alcohol, and ether, and dried in vacuo.

Trimethylsilyl Cyanide-^{13}C (1). A modification of the reported[15,17] procedures was used. A suspension of dry $Ag^{13}CN$ (7.5 g, 56 mmol) in trimethylsilyl chloride (18.5 g, 170.5 mmol) was stirred vigorously for 3 days at room temperature in a tightly closed flask protected from light. The volatile liquid was then carefully filtered from AgCl and unreacted $Ag^{13}CN$. A fresh amount of trimethylsilyl chloride (21.0 g, 193.5 mmol) was added to the mixture of silver salts, the suspension was stirred for 3 more days, and the liquid was filtered off. The combined filtrates (37.5 g), which contained 13% of **1** and 87% of trimethylsilyl chloride, were used directly in the following reaction step. The content of **1** was determined by GLC (SE-30, 55°) or by integration of the methyl signals in the ^1H NMR spectrum [δ 1 0.73 ppm, $(CH_3)_3SiCl$: 0.85 ppm]. The overall yield of **1** was 88% (based on $Ag^{13}CN$).

2-Cyano-^{13}C-2-trimethylsilyloxyadamantane (3) was prepared by a modification of Evans–Sundermeyer's synthesis[15,16] for trimethylsilyl cyanohydrin ethers. To a mixture of 5.0 g (33.3 mmol) of adamantanone (**2**) and a catalytic amount of dry ZnI_2, stirred in a flask closed with a rubber serum cap, 34.2 mmol of **1** (26.0 g of a 13% solution of **1** in trimethylsilyl chloride) was added via syringe. The flask was previously flushed with dry nitrogen. The reaction is exothermic, but external cooling is unnecessary for small scale preparations. The resulting clear solution was stirred for 2 hr at room temperature and filtered. The flask and the filter were rinsed with dry ether and combined filtrates were evaporated in vacuo without heating to give 8.15 g (98%) of **3**: mp 92–95°; ir (KBr) 2900 s, 2850 w, 2230 w, 1450 s, 1250 s, 1115 s, 1080 s, 887 s, 835 s, 755 cm^{-1} s; ^1H NMR δ 0.22 (9 H, s), 1.3–2.7 (14 H, m, maximums at 2.0 and 1.7 ppm); mass spectrum *m/e* (rel intensity) 249 (M^+, 2.13), 234 (100), 207 (11.7).

2-Aminomethyl-^{13}C-2-hydroxyadamantane Hydrochloride (4). A solution of 8.1 g (32.3 mmol) of crude **3** in 10 ml of dry ether was added dropwise within 20 min to a stirred mixture of 1.4 g (37.0 mmol) of $LiAlH_4$ in 30 ml of dry ether. The reaction mixture was stirred under gentle reflux for an additional 2 hr, cooled to room temperature, and diluted with 30 ml of ether. Water (20 ml) and 15% NaOH (2 ml) were added dropwise, followed by more water until two layers separated. The aqueous layer was extracted five times with 50 ml of ether. (2-Methylamino-2-hydroxyadamantane[32] is only moderately soluble in ether). The combined ether extracts were dried overnight and filtered. Dry gaseous HCl was introduced until no more solid precipitated (2–3 hr). The product was collected by filtration and air dried to yield 4.6 g (65%) of **4**, mp 287–290° dec (lit.[13b] mp 288–290° dec.).

4-Homoadamantanone-5-^{13}C (5) was prepared in 71% yield starting from 4.5 g (20.7 mmol) of **4** following Schlatmann's procedure,[13b] except that the precipitate formed in the reaction was not collected by filtration but extracted five times with 20-ml portions of ether. The combined extracts were washed three times with saturated $NaHCO_3$ solution, dried, and evaporated. The crude product was sublimed to give 2.4 g (71%) of **5** (~95% pure by GLC). If necessary, **5** can be purified by column chromatography on Al_2O_3 (neutral, activity II) using ether as the eluent.

4-Homoadamantanone-5-^{13}C Tosylhydrazone (6). To a solution of 2.7 g (14.5 mmol) of *p*-toluenesulfonylhydrazide in 7 ml of warm methanol was added 2.3 g (14 mmol) of **5** in small portions. The reaction mixture was allowed to stand overnight in a refrigerator and the crystallized product (4.1 g) was collected. Additional 0.3 g of the product was obtained from the mother liquor. The overall yield was 4.4 g (95%), mp 169–172°.

Homoadamantene-4-^{13}C (7). Methyllithium (20 ml of a 2 *M* solution in ether) was added dropwise over 30 min to a suspension of 3 g (9.0 mmol) of **6** in 15 ml of dry ether stirred at 0° in a nitrogen atmosphere. The stirring was continued for 2–3 hr at 0° and overnight at room temperature. The reaction mixture was diluted with 10 ml of ether and water was added dropwise until two layers separated. (The color of the reaction mixture changed gradually during the addition of water from brown-red through yellow to white.) The reaction mixture was neutralized with dilute HCl and the aqueous layer was extracted four times with ether. The combined extracts were dried, the solvent was removed through a Vigreux column, and the residue was sublimed in vacuo to give 0.8 g (60%) of **7** (99% pure by GLC), mp 236–238°.

Reaction of Homoadamantene-4-^{13}C (7) with $AlBr_3$. A solution of 250 mg (1.7 mmol) of **7** and 750 mg (2.8 mmol) of $AlBr_3$ in 5 ml of CS_2 was stirred for 5 min at room temperature. A substantial amount of tar was formed during the reaction. The reaction mixture was diluted with 5 ml of CS_2 and 100 ml of ice–water was added. The layers were separated, and the carbon disulfide solution was washed with water and dried. The solvent was carefully removed through a Vigreux column to give 51.4 mg (20.3%) of crude product. GLC analysis (SE-30, 80°) indicated a single major product and four minor products (15–20% in total) with considerably longer retention times. The major product was isolated by preparative GLC (30% SE-30, 120°) and identified as 2-methyladamantane by ^{13}C NMR, ^1H NMR, ir, and mass spectra and GLC comparison with an authentic sample.

A partly reacted sample of **7** was isolated from the reaction mixture as described for the product. The ^{13}C NMR spectrum indicated no label scrambling.

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(32) Mp 100–105°; ir (KBr) 3355 m, 3110 m, 2890 s, 2850 m, 1570 m, 1450 m, 1285 m, 970 s, 900 m cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.83 (2 H, s), 1.3–2.4 (17 H, m, maximums at 1.72 and 1.87 ppm).

Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Kinetic Studies on the Reactions between Ethers and Thioethers of 2,4-Dinitrophenol and Nucleophiles

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Steric retardation, observed in nucleophilic aromatic substitution, has been attributed in part to interaction between hindered nucleophile and leaving group during the transition state;[1] however, this has been the subject of dispute, since there are circumstances[2] reported in which no predictable fall in reactivity occurs with increasing size of displaced groups. Moreover, our recent studies[3] on halogen displacement by action of ortho-hindered phenoxides on 2,6-dimethyl-4-nitrohalogenobenzenes showed that the expected effect of leaving group size can be obscured by the influence of its electronic effect. In fact, recalculation of experimental data, corrected for contribution of electronic effects, established the expected correlation between size of leaving groups and retardation in reactivity. In the present studies we attempt to evaluate the influence of hindered leaving groups in nucleophilic aromatic substitution. For this purpose we performed kinetic studies on the reactions between 2,4-dinitrodiphenyl ethers with methoxide and thiomethoxide ions and thioethers with methoxide ion at 25°C in methanol. The electronic contribution of displaced groups to reactivity was also investigated.

Results

The second-order rate constants of all reaction series are listed in Table I. When possible, the data were calculated by means of two independent kinetic procedures (see Experimental Section). All reactions of diphenyl ethers with thiomethoxide ion were performed in the presence of high concentrations of free methyl mercaptan. These experimental conditions were necessary, because the acid–base interaction of MeS^- with MeOH yields free methoxide which could compete for phenoxy displacement. In spite of higher reactivity of MeS^-, a considerable amount (~10%) of methoxy substitution was detected in reaction products in the absence of free CH_3SH. Concentrations above 1×10^{-1} *M* were required to minimize this competitive reaction. No influence on rate by CH_3SH was observed when its free concentration ranged between 1×10^{-1} and 1 *M*. Very likely, owing to the small difference in pK_a values between ethanethiol and methanol, the addition of relatively small amounts of the former species does not influence proticity of the medium.

Discussion

As expected the reactivity increases when the displaced group becomes more electron withdrawing. There is an excellent correlation between experimental data of meta- and para-substituted leaving groups from each series and σ^0 values;[4] ρ values, standard errors (s),[5] and correlation coefficients (r) are listed at the bottom of Table I. The use of σ^0 scale appears to be appropriate, since in this system no direct conjugative transmission from Z substituent to reaction center can be operative, owing to an insulating effect of oxygen or sulfur bridges. This conclusion is strengthened by comparing the present results with those reported by Bunnett[6] on nucleophilic displacement on the same compounds by action of piperidine or OH^-; in that case, the "primary" σ values[7] are used; thus the 4-methoxyphenyl ether does not quite fit the $\rho\sigma$ relationship in contrast with the other compounds. This is a consequence of the fact that the "primary" σ scale was calculated from systems in which conjugative effects are involved for strong electron-releasing groups.[8] The ρ value for reaction of thioethers with methoxide ion is somewhat higher than that for ethers with the same nucleophile. This difference can be attributed to a more efficient transmission of polar effects by sulfur atom. Our results are in good agreement with those reported by Kajimoto[9] et al. for very similar systems on ionization equilibrium constants of ring-substituted cis-β-phenoxy and thiophenoxy acrilic acids.

Table I
Nucleophilic Displacement of Z-C_6H_5-X Groups: Experimental Rate Constants of Reactions between Ethers and Thioethers of 2,4-Dinitrophenol and Nucleophiles (N)

	k_2, sec^{-1} mol^{-1} l.		
	X = O	X = S	X = O
Z	N = CH_3O^-	N = CH_3O^-	N = CH_3S^-
o-OCH_3	1.3×10^{-3}	4.6×10^{-5}	4×10^{-1}
p-OCH_3	3.3×10^{-3}	6.8×10^{-5}	6.9×10^{-1}
p-CH_3	4.5×10^{-3}	8.7×10^{-5}	8.5×10^{-1}
H	5.0×10^{-3}	1.1×10^{-4}	1.1
m-Cl	1.5×10^{-2}	4.0×10^{-4}	2.8
m-NO_2	4.8×10^{-2}	1.5×10^{-3}	7.9
p-NO_2	7.7×10^{-2}	2.6×10^{-3}	1.1×10^{-1}
o-NO_2	1.2×10^{-2}	3.5×10^{-3}	2.9
ρ	1.3	1.6	1.2
s	0.07	0.05	0.04
r	0.999	0.999	0.999

In sharp contrast with ideas that the leaving group size cannot be involved in steric effects, the ortho-substituted diphenyl ethers show a high steric retardation. In fact, if compared to the para derivative, the *o*-nitro compound with methoxide ion is sevenfold less reactive, while the *o*-methoxydiphenyl ether shows a smaller effect according to the E_s[10] value scale.

These steric effects cannot be observed in the corresponding reactions of thioethers, where reactivity is actually larger for ortho as compared to para derivative. These findings can be interpreted on the basis of length differences[11] between C–O (1.28 Å) and C–S (1.75 Å) linkages in diphenyl ethers and thioethers, respectively, such that in the latter circumstance the site of hindered group is further away from the reaction center. The higher flexibility of sulfur bridge can also help, minimizing steric compression. Similar conclusions were reached previously when we examined the steric effect of hindered nucleophiles. In those

Table II
$k_{o\text{-obs}}/k_{o\text{-exd}}$[a] and $k_{o\text{-obs}}/k_{p\text{-exd}}$ Values for Reactions of 2,4-Dinitrophenyl Ethers with MeO^- and MeS^-

	MeO^-		MeS^-	
Substituent	A	B	A	B
NO_2	0.12	0.16	0.18	0.26
OCH_3	0.58	0.39	0.77	0.58

[a] $k_{o\text{-exd}}$ was calculated from ρ and σ° ortho values.

studies,[12] based upon reactions between halogenobenzothiazoles and thioalkoxy ions, high steric retardation occurred only with α-branched nucleophiles; in contrast, when the bulky group was moved further away in β position, there was an increase of reactivity owing to increasing basicity. In addition, substituting[13] oxygen for sulfur in these hindered nucleophiles caused a higher steric effect.

Since geometry at the reaction center closely approximates tetrahedral structure and free rotation exists around the linkage between the reaction carbon center and leaving group in the transition state, the distance between the displaced group on one side and both the entering group and the benzenoid substrate ring on the other side must be approximately the same. This mitigates against assigning the observed effects exclusively to steric compression during the transition state either between leaving group and entering group or between leaving group and hydrogen and carbon atoms of the substrate.

Nevertheless, the observed lessening of steric phenomena, when the nucleophile is thiomethoxide ion, strongly suggests that in this case the interaction with benzenoid substrate ring is less important.

Finally, assuming complete lack of steric effects for thioethers, σ^0 ortho values of o-nitro (+0.93) and o-methoxy groups (−0.26) can be calculated.[14]

Thus we can estimate the actual steric retardation as expressed by $k_{o\text{-obs}}/k_{o\text{-exd}}$ ratio, where $k_{o\text{-exd}}$ represents the expected rate constant in the absence of steric phenomena and $k_{o\text{-obs}}$ is the experimental one. In Table II these ratio values are compared with $k_{o\text{-obs}}/k_{p\text{-obs}}$ values, which would represent a more immediate, but an approximate valuation of steric effects. $k_{o\text{-obs}}/k_{o\text{-exd}}$ ratios are somewhat higher for the nitro group and somewhat less for the methoxy group. This can be taken as additional evidence that contribution of electronic effect should be accounted for in order to evaluate steric effects with a high degree of accuracy.

Experimental Section

Materials. Methanol (reagent grade) was purified by distillation over magnesium. 2,4-Dinitrophenyl ethers were prepared by refluxing a mixture, prepared from 0.2 mol of the appropriate phenol and 0.1 mol of NaOH in 50 ml of methanol, with 0.1 mol of 2,4-dinitrochlorobenzene in 50 ml of methanol. The mixture was diluted with a large amount of alkaline water and then quickly filtered. The precipitated product was washed and crystallized from ethanol. Thioethers were prepared by the same procedure from 0.1 mol of the appropriate thiophenol and 0.1 mol of 2,4-dinitrochlorobenzene by performing the reaction at room temperature.

Rate Measurements. Reactions of Diphenyl Ethers with MeO^-. For all derivatives kinetic experiments were performed by following the appearance of phenoxide ions. The same titrimetric procedure as described by Ogata[17] was used. When possible, a spectrophotometric procedure was also applied. This was for example the case of Z'-nitro substituted compounds. These reactions (performed under pseudo-first-order conditions) were run in the thermostatic cells of a Gilford automatic spectrophotometric apparatus, by following the appearance of the developed nitrophenoxide ion at the appropriate wavelength.

Reactions of Diphenyl Thioethers with MeO^-. Kinetic experiments were performed by following the appearance of thiophenoxide ions by the iodimetric method.[18]

In the case of nitro-substituted compounds an additional spectrophotometric procedure, as above described, was also applied.

Reactions of Diphenyl Thioethers with MeS^-. A spectrophotometric procedure was used for all kinetic experiments, by following the appearance of reaction products (2,4-dinitrophenyl methyl thioether) except in the case of nitro derivatives, in which the appearance of nitrophenoxide ions was again followed. For this very fast system the Durrum-Gibson stopped-flow apparatus was used.

In all cases, in which two different kinetic procedures were applied, a good agreement of calculated second-order rate constants was obtained.

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Registry No.—1-(2-Methoxyphenoxy)-2,4-dinitrobenzene, 2363-29-3; 1-(4-methoxyphenoxy)-2,4-dinitrobenzene, 2363-27-1; 2,4-dinitrophenyl p-tolyl ether, 2363-25-9; 2,4-dinitrophenyl phenyl ether, 2486-07-9; m-chlorophenyl 2,4-dinitrophenyl ether, 2363-38-4; 2,4-dinitrophenyl m-nitrophenyl ether, 2548-97-2; 2,4-dinitrophenyl p-nitrophenyl ether, 2363-36-2; 2,4-dinitrophenyl o-nitrophenyl ether, 2363-39-5; 1-[(2-methoxyphenyl)thio]-2,4-dinitrobenzene, 42178-88-1; 1-[(4-methoxyphenyl)thio]-2,4-dinitrobenzene, 1871-44-9; 2,4-dinitrophenyl p-tolyl sulfide, 20114-05-0; 2,4-dinitrophenyl phenyl sulfide, 2486-09-1; m-chlorophenyl 2,4-dinitrophenyl sulfide, 56679-05-1; 2,4-dinitrophenyl m-nitrophenyl sulfide, 1657-86-9; 2,4-dinitrophenyl p-nitrophenyl sulfide, 20834-66-6; 2,4-dinitrophenyl o-nitrophenyl sulfide, 20834-65-5; CH_3O^-, 3315-60-4; CH_3S^-, 17302-63-5.

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Nucleophilic Displacements on Halogen Atoms. VI.[1] Determination of σ^- Values for the Carboxyl, Carbethoxy, and Methylsulfonyl Groups.

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Recently, we[2] have shown that the reaction of triphenylphosphine (TPP) with α-halobenzyl phenyl sulfones in

aqueous dimethylformamide (DMF) leads to the reduced sulfone 2 and triphenylphosphine oxide in quantitative yield (e.g., eq 1). The rates of these reactions show excel-

$$ArCHBrSO_2Ph + Ph_3P \longrightarrow [ArCHSO_2Ph]\,Br\overset{+}{P}Ph_3 \xrightarrow[DMF]{H_2O}$$

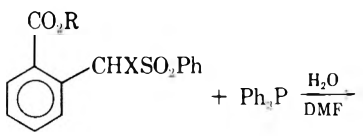
1a, Ar = *p*-$HOOCC_6H_4$
b, Ar = *p*-$C_2H_5OOCC_6H_4$
c, Ar = *p*-$CH_3SO_2C_6H_4$

$$ArCH_2SO_2Ph + Ph_3P{=}O + HBr \quad (1)$$

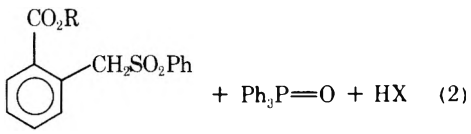
2a, Ar = *p*-$HOOCC_6H_4$
b, Ar = *p*-$C_2H_5OOCC_6H_4$
c, Ar = *p*-$CH_3SO_2C_6H_4$

lent correlations with σ^- values (determined from the acidity of phenols)[3] and yield large positive values of ρ. An interesting feature of this reaction is that carbanions are generated under neutral and even acidic conditions which then allows the determination of certain quantities which could not be measured under basic conditions. We have utilized this characteristic to determine a σ^- value for the carboxyl group which would not remain un-ionized under basic condition, thus precluding a determination of this value from the ionization of phenols.

The standard reaction used (eq 1) was the reaction of α-bromobenzyl phenyl sulfones with TPP in 90% aqueous DMF at 25° which was shown to give a ρ value of 5.97 (r = 0.998).[2] Three new σ^- values were determined from this reaction: (COOH) σ^- = 0.61 (σ_a^- = 0.73);[4] ($COOC_2H_5$) σ^- = 0.65 (σ_a^- = 0.68);[4] (CH_3SO_2) σ^- = 0.82 (σ_a^- = 1.13[5] and 1.14[6]; σ_p^- = 0.98[5]). The σ^- value for the carbethoxy group is close to that reported earlier,[3a] but (COOH) σ^- is significantly lower than the σ_a^- value.[3a] In fact, for reaction 1, we find the carbethoxy group to be a stronger electron-withdrawing group than is the carboxyl group, a result which is at variance with a number of previous studies.[7] The α-bromo-*p*-carbethoxybenzyl phenyl sulfone (**1b**) reacts ca. twice as fast as the acid **1a** with TPP at 25° (Table II). This result is not unique in this system. In the reaction of TPP with the ortho isomers **3a** and **3b** (eq 2), the ester also is



3a, R = H; X = Br
b, R = C_2H_5; X = Br
4a, R = H; X = I
b, R = C_2H_5; X = I



(2)

more reactive than the acid. However, for the corresponding iodides **4**, the reverse holds, i.e., the acid **4a** reacts slightly faster than the ester **4b** (Table III). However, the reactivities of the acids and esters are so similar that subtle differences in solvation could easily account for their behavior.

The σ^- value for the *p*-methylsulfonyl group is significantly lower than the σ^- values determined either from the acidity of phenols or anilinium ions. Somewhat surprisingly, our value agrees with the σ^- value determined from the ionization of thiophenols (σ^- = 0.82).[9] The relative magnitude of the σ^- value(s) of a substituent often is taken as a measure of the resonance interaction between the substituent and the reaction center.[10] The σ^- values reported for these substituents are significantly higher than the normal σ values,[7] which indicates a strong resonance interaction between the reaction site (a carbanion)[11] and the substituent. The σ^- values tend to have some degree of spread depending upon the reaction system,[3,7,10] and this appears to be particularly true of the *p*-methylsulfonyl group. We find that for reaction 1, a plot of log k/k_0 vs. σ^- gives an excellent correlation with the σ^- values determined from the ionization of phenols for NO_2, CN, CH_3CO, and $COOC_2H_5$, but for *p*-COOH and *p*-CH_3SO_2, the σ^- values reported earlier give a rather poor fit with our rate data (Tables I and II).

Table I
Rate Constants for the Reaction of α-Bromobenzyl Phenyl Sulfones 1 with TPP in 90% Aqueous DMF

Compd	Temp, °C (±0.05°)	k, M^{-1} sec^{-1}
1a	20.00	2.25×10^{-3}
	30.00	5.05×10^{-3}
	40.00	9.19×10^{-3}
1b	10.00	2.40×10^{-3}
	20.00	5.33×10^{-3}
	30.00	1.15×10^{-2}
1c	25.00	8.29×10^{-2}

Table II
Rate Constants and Activation Parameters for the Reaction of α-Bromobenzyl Phenyl Sulfones 1a and 1b with TPP in 90% Aqueous DMF at 25°

Compd	k, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
1a	3.38×10^{-3}	12.1 ± 0.7	−32 ± 2
1b	7.89×10^{-3}	12.8 ± 0.8	−25 ± 2

Table III
Rate Constants for the Reactions of α-Bromo- and α-Iodo-o-carboxylbenzyl Phenyl Sulfones (3a and 4a) and α-Bromo- and α-Iodo-o-carbethoxybenzyl Phenyl Sulfones (3b and 4b) with TPP in 90% Aqueous DMF at 60.0°

Compd	k, M^{-1} sec^{-1}
3a	3.46×10^{-3}
3b	8.09×10^{-3}
4a	1.18×10^{-3}
4b	7.03×10^{-4}

Experimental Section

Melting points reported in this section were taken on Fisher-Johns and Mel-Temp apparatus and are not corrected. The NMR spectra were recorded on a Varian Associates A-60D and Varian Associates EM 360 NMR spectrometer operating at ambient temperature. All spectra were taken in carbon tetrachloride or deuteriochloroform with tetramethylsilane (δ 0.00) as an internal standard. The ir spectra were taken on a Perkin-Elmer 337 or Beckman IR-8 infrared spectrometer. The ir spectra of analytically pure samples were taken in carbon tetrachloride or as KBr pellets. Polystyrene absorptions at 1028.0 and 1601.4 cm^{-1} were used for calibration of ir spectra. Elemental analyses were performed by Dr. Franz Kasler of the University of Maryland.

***p*-Carbethoxybenzyl Phenyl Sulfone (2b).** To a dry 100-ml round-bottom flask, equipped with a reflux condenser and a drying tube, containing 10 g (65 mmol) of *p*-toluoyl chloride was added 25 ml of sulfuryl chloride. Two sun lamps (G. E. 250 W) were placed 0.5 in. from the flask. The course of the reaction was followed by NMR spectroscopy. The reaction was complete after 10 hr of irradiation, and the excess sulfuryl chloride was removed in vacuo. To the remaining oil was added 20 ml of absolute ethanol. In a separate flask, thiophenol (7.1 g, 64.5 mmol) was added dropwise to a solution of 4.00 g (71.5 mmol) of potassium hydrox-

ide in 50 ml of 95% ethanol. The thiophenoxide solution was added dropwise to the chloride solution with stirring. After 4 hr, the solution was poured into 400 ml of water. The solution was extracted twice with 150-ml portions of ether. The ether layer was washed twice each with 100 ml of dilute potassium hydroxide solution and 100 ml of water and dried ($MgSO_4$), and the ether was removed in vacuo. The residual oil was dissolved in 100 ml of glacial acetic acid, and the solution was chilled in an ice–water bath. To this solution was added dropwise 20 ml of 30% hydrogen peroxide. After standing overnight at room temperature, the solution was poured into 500 ml of water and extracted twice with 150-ml portions of ether. The ether extracts were combined and washed once with 200 ml of water and twice with 150 ml of saturated sodium bicarbonate solution followed once by 200 ml of water. The ether was dried with anhydrous magnesium sulfate and removed in vacuo. Crystallization from dichloromethane–Skellysolve B gave 8.93 g (45%) of **2b**: mp 112°; ir (KBr) 1700 (C=O), 1310 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) 1.42 (t, J = 7 Hz, 3 H), 4.35 (s, 2 H), 4.40 (q, J = 7 Hz, 2 H), and 7.0–8.0 ppm (m, 9 H).

Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.16; H, 5.26. Found: C, 62.88; H, 5.33.

α-Bromo-*p*-Carbethoxybenzyl Phenyl Sulfone (1b). One gram (3.0 mmol) of **2b** was dissolved in 15 ml of dry DMF in a dry 50-ml three-necked flask under a dry nitrogen atmosphere. To the solution was added 200 mg (4.15 mmol) of 50% sodium hydride in oil dispersion. The solution turned dark yellow in color and was heated to 60° for 10 min. The solution was cooled to room temperature and transferred via syringe into a solution containing 400 mg (3.78 mmol) of cyanogen bromide in 25 ml of dry DMF. A reddish brown color appeared. After 15 min, the solution was poured into 200 ml of water and extracted twice with 50-ml portions of dichloromethane. The dichloromethane solution was washed twice with sodium thiosulfate solution followed by water and dried ($MgSO_4$), and the solvent was removed in vacuo. Crystallization from methylene chloride–Skellysolve B gave 460 mg (37%) of **1b**: mp 112°; ir (KBr) 1710 (C=O), 1325 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) 1.42 (t, J = 7 Hz, 3 H), 4.40 (q, J = 7 Hz, 2 H), 5.81 (s, 1 H) and 7.2–8.1 ppm (m, 9 H).

Anal. Calcd for $C_{16}H_{15}BrO_4S$: C, 50.13; H, 3.95. Found: C, 50.25; H, 4.12.

α-Bromo-*p*-carboxylbenzyl Phenyl Sulfone (1a). To a solution of 500 mg (1.49 mmol) of **1b** in 50 ml of 75% ethanol was added 50 ml of 4% potassium hydroxide in 75% ethanol. After 4 hr, hydrochloric acid was added until the solution was acidic. From this solution precipitated 330 mg (100%) of **1a**: mp 252°; ir (KBr) 3200–2400 (OH), 1690 (C=O), 1300 and 1150 cm^{-1} (SO_2); NMR (Me_2SO-d_6) 4.3–5 (1 H), 6.94 (s, 1 H), and 7.4–8 ppm (m, 9 H).

Anal. Calcd for $C_{14}H_{11}BrO_4S$: C, 47.34; H, 3.12. Found: C, 47.22; H, 2.97.

***p*-Methylsulfonylbenzyl Phenyl Sulfone (2c).** In a two-neck 300-ml flask, 3.4 g (0.020 mol) of *p*-methylsulfonyltoluene (Aldrich) was dissolved in 50 ml of dry carbon tetrachloride. The solution was brought to reflux and a bromine solution of 3.5 g (0.022 mol) in 20 ml of carbon tetrachloride was added dropwise (ca. 30 min) while the flask was illuminated with a 275-W sun lamp. After 1 hr, an NMR spectrum showed a mixture of starting material (5%), α-bromo-*p*-methylsulfonyltoluene, (75%) and α,α-dibromo-*p*-methylsulfonyltoluene (20%). The solvent was removed by rotary evaporation and 20 ml of hexane added. The resulting precipitate (2.7 g) was collected and shown by NMR spectroscopy to be a mixture of α-bromo-*p*-methylsulfonyltoluene (60%) ($-CH_2Br$, δ 4.47) and α,α-dibromo-*p*-methylsulfonyltoluene (40%) ($CHBr_2$, δ 6.69). The mother liquor gave 0.9 g of the monobromide, mp 93–94° (lit.[12] 94–96°).

The mixture of 2.7 g of the monobromide and dibromide (vide supra) and 6.0 g of sodium benzenesulfinate in 70 ml of dry dimethyl sulfoxide was heated at 90–100° for 30 min. The progress of the reaction can be followed conveniently by TLC (dichloromethane, silica gel). The mixture was poured into 600 ml of water, and the precipitate was collected and recrystallized from acetonitrile to give 1.9 g (50% based on 2.7 g of the mixture of bromides) of **2c**: mp 261–262°; NMR ($CDCl_3$) 3.04 (s, 3 H), 4.40 (s, 2 H), and 7.1–7.7 ppm (m, 9 H).

Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.17; H, 4.54. Found: C, 54.25; H, 4.50.

α-Bromo-*p*-methylsulfonylbenzyl Phenyl Sulfone (1c). Compound **1c** was prepared from **2c** following the same procedure used to convert **2b** to 1b. One gram of **2c** gave 0.63 g (50%) of **1c**: mp 178–179° (acetonitrile); NMR ($CDCl_3$) 3.04 (s, 3 H), 5.78 (s, 1 H), and 7.2–7.9 ppm (m, 9 H).

Anal. Calcd for $C_{14}H_{13}BrO_4S_2$: C, 43.19; H, 3.37. Found: C, 43.31; H, 3.32.

The syntheses of **3a, 3b, 4a** and **4b** were reported earlier.[2]

Kinetic Procedure. The rates for compounds **1a, 1b, 3a, 3b, 4a,** and **4b** were determined by the conductance method.[2] The rate of reaction of **1c** was determined by the spectrophotometric technique.[2] All runs were made in at least duplicate. The precision in the rate constants reported in Tables I–III is ±5%. The σ^- values reported were determined from $\log k_X = \sigma^-$ (5.97) + (−5.970) where X = *p*-COOH, *p*-$COOC_2H_5$, and *p*-CH_3SO_2, k_X are the rate constants at 25° reported in Tables I and II, and −5.970 is $\log k_H$[2] at 25°. The σ^- values reported have a precision of ±0.02 units.

Acknowledgment. Support from the University of Maryland Computer Science Center is gratefully acknowledged.

Registry No.—**1a**, 56571-76-7; **1b**, 56571-77-8; **1c**, 56571-78-9; **2b**, 56571-79-0; **2c**, 56571-80-3; **3a**, 41037-90-5; **3b**, 51229-69-7; **4a**, 41037-91-6; **4b**, 51229-70-0; TPP, 603-35-0; *p*-toluoyl chloride, 874-60-2; sulfuryl chloride, 7791-25-5; thiophenol, 108-98-5; cyanogen bromide, 506-68-3; *p*-methylsulfonyltoluene, 3185-99-7; α-bromo-*p*-methylsulfonyltoluene, 53606-06-7; α,α-dibromo-*p*-methylsulfonyltoluene, 33460-70-7; sodium benzensulfinate, 873-55-2.

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[α,α-$^2H_2$]Dibenzyl Sulfoxide. Synthesis, Reactions, and Chiroptic Properties

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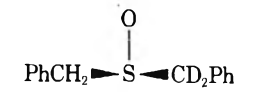
We wish to report on the synthesis, some reactions, and the chiroptic properties of (*R*)- and (*S*)-[α,α-$^2H_2$]dibenzyl sulfoxide (**1**), dissymmetric by substitution of deuterium for hydrogen, two bonds from the asymmetric sulfur atom.



(*R*)-**1**

Optical activity in molecules whose dissymmetry arises from isotopic differences is well known and has been observed in compounds containing the isotope pairs ^1H–^2H, ^{16}O–^{18}O, and ^{12}C–^{13}C. Chiroptic properties of these com-

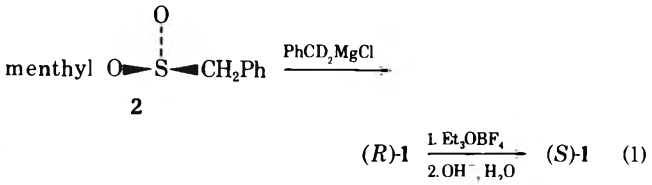
pounds have often been difficult to obtain because of their low rotation, combined, in many cases, with a highly absorbing chromophore such as an aromatic ring. Nevertheless, the first extrema of Cotton effects were observed in the ORD spectra of (*R*)-[1-^{2}H]-1-butyl acetate,[2] (*R*)- and (*S*)-[1-^{2}H]succinic acid,[3] and several imines of the general structure RR'CNCHDR".[4] Both extrema were observed for (*R*)-[1-^{2}H]-*N*-(isopropylidene)neopentylamine, which unlike the other imines studied, does not have R or R' equal to phenyl. The CD spectra of (1*R*)-[1-^{2}H]-α-fenchocamphoronequinone[5] and (*S*)-[4-^{2}H][2.2]paracyclophane[6] have recently been reported.

The CD spectrum of (1*R*)-[2-^{18}O]-α-fenchocamphoronequinone has been recorded and is the only example of chiroptical measurements on an ^{16}O–^{18}O dissymmetric molecule.[7] The other optically active ^{16}O–^{18}O compounds, all aryl sulfones,[8] have unfavorable rotation to absorption ratios which precluded CD or ORD measurements of Cotton effects.

Cotton effect measurements on (*R*)- and (*S*)-[α-^{13}C]dibenzyl sulfoxides, the only examples of ^{12}C–^{13}C dissymmetric molecules for which optical activity has been detected, were similarly thwarted.[9]

The ^{1}H–^{2}H compounds cited above, except for the quinone and the paracyclophane, all contain a monodeuterium substituted methylene group as the center of chirality which asymmetrically perturbs a symmetric chromophore, but in sulfoxide **1**, the deuterium atoms are two bonds away from the asymmetric center.

Sulfoxide (*R*)-**1** was synthesized by treating (R_S)-menthyl phenylmethanesulfinate (**2**) with the Grignard reagent prepared from [α,α-^{2}H$_2$]benzyl chloride,[10] and converted to its enantiomer by ethylation followed by alkaline hydrolysis (eq 1).



(1)

The enantiomeric purity of (*R*)-**1** was calculated to be 96% based on the highest rotation reported for **2** and assuming that the transformation of **2** to (*R*)-**1** proceeded with complete inversion. The conversion of (*R*)-**1** to (*S*)-**1** proceeded with 89% inversion based on their rotations at 300 nm.

The ORD and CD spectral data for (*R*)-**1** and the ORD data for (*S*)-**1**, measured from 300 to 250 nm in 95% ethanol and in chloroform, are given in Table I together with uv spectral data obtained on racemic **1**. The chiroptic spectra for **1** are depicted in Figure 1. Since the ORD curve for (*S*)-**1** was simply a mirror image of that for (*R*)-**1**, although diminished in magnitude by about 0.8, it is not shown.

Several small Cotton effects superimposed on a positive background, apparent in both the ORD and CD spectra (EtOH) and shown in Figure 1, occur in the $^1L_b \leftarrow {}^1A$ region of uv absorption.

The shape of the ORD curve of (*R*)-**1** was the same in chloroform as it was in ethanol. Sign changes, ascribed to conformational differences, have been observed for some alkyl benzyl sulfoxides[11] when the solvent was changed from ethanol to chloroform.

Since ^{1}H and ^{2}H have almost the same electronic and steric properties, it is unlikely that the chiroptic behavior of our compound is due to electronic or steric perturbations of the chromophore. It is more likely that $PhCH_2$ vibronic interactions differ significantly from $PhCD_2$ vibronic interactions and, consequently, lead to an appreciable rotatory strength. Specifically, it appears as if there is a coupling of aromatic molecular vibrations with electron motions which shows up in an electronic transition of the $^1L_b \leftarrow {}^1A$ type. Recently, other workers have presented theoretical arguments and experimental evidence to account for rotatory

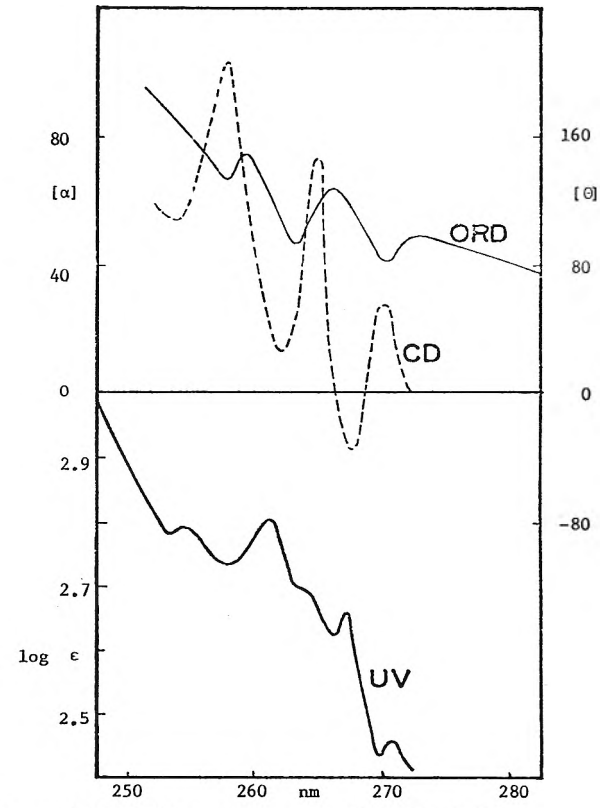


Figure 1. ORD, CD, and uv spectra of **1** in 95% EtOH.

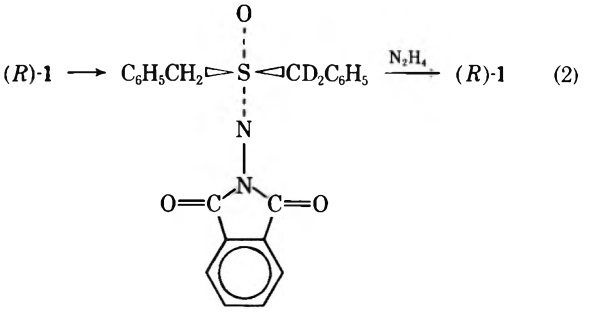
Table I
Optical Rotatory Dispersion, Circular Dichroism, and Ultraviolet Spectra of $PhCH_2SOCD_2Ph$

Compd	Spectral values[e]
(*R*)-**1**[a]	23 (300), 30 (290), 40 (280), 47 (275), 49 (272.5 P), 41 (270 T), 65 (266 P), 45 (263 T), 75 (259 P), 66 (258 T), 80 (255), 102 (250)
(*S*)-**1**[a]	−18 (300), −23 (290), −31 (280), −42 (275), −45 (272.5 T), −32 (270 P), −58 (266 T), −37 (263 P), −37 (263 P), −62 (259 T), −59 (258 P), −66 (255), −91 (250)
(*R*)-**1**[b]	0 (272), 56 (270 Mx), −38 (267.5 Mi), 147 (265 Mx), 23 (262 Mi), 205 (258 Mx), 103 (254 Mi), 119 (252)
(*R*)-**1**[c]	0.69 (300), 0.82 (290), 0.99 (280), 1.68 (275), 2.46 (271 Mx), 2.43 (270 Mi), 2.66 (267 Mx), 2.62 (266 Mi), 2.66 (265 If), 2.70 (263 If), 2.81 (261 Mx), 2.77 (2.59 If), 2.73 (257.5 Mi), 2.79 (254 Mx), 2.78 (253 Mi), 2.81 (252), 2.99 (247.5), 3.13 (245), 3.32 (242.5)
(*R*)-**1**[d]	34 (300), 40 (290), 57 (280), 92 (274 P), 70 (271 T), 116 (267 P), 64 (264 T), 123 (261 P), 115 (258 T), 182 (250)

[a] ORD in 95% ethanol, specific rotation (nm), *c* 8.3–0.69 mg/ml. [b] CD in 95% ethanol, molecular ellipticity (nm), c 0.83 mg/ml. [c] Uv in 95% ethanol, log ε (nm), 8.3–0.17 mg/ml. [d] ORD in chloroform, specific rotation (nm), 0.73–0.29 mg/ml. [e] P = peak, T = trough; Mx = maximum, Mi = minimum, If = inflection.

strength in (−)-(*S*)-[4-^{2}H][2.2]paracyclophane via a similar vibronic coupling mechanism.[6,12]

Sulfoxide (*R*)-1 was converted to (*R*)-sulfoximine **3** which, upon hydrazinolysis, gave back partially racemized (*R*)-1 with 75% retention of configuration (eq 2).[13]



3

While this showed **3** to be nonracemic, **3** was not a detectably optically active compound. It formed strongly absorbing, yellow solutions which precluded chiroptic measurements in the region of interest; in fact, no rotation was observed at any wavelength. The cause for the partial racemization is not known, but **1** was observed to undergo partial racemization in chloroform solution. Thus, the process depicted in eq 2 may be completely stereospecific with the loss of optical activity resulting from the racemization of **1** in processes not involving the formation or hydrazinolysis of **3**.

Experimental Section

The ORD–CD spectra were recorded using a Cary 60 spectropolarimeter, the uv spectra using a Cary 14 spectrophotometer, the NMR using a Varian XL-100 spectrometer, and the mass spectra using an RMU Hitachi 6D spectrometer.

(*R*)-[α,α-^{2}H$_2$]Dibenzyl Sulfoxide (1). (R_S)-Menthyl phenylmethanesulfinate (2, 3.09 g, 10.5 mmol), $[\alpha]_D$ +105° ($CHCl_3$), in ether (15 ml) was added at −40° to a solution of the Grignard reagent prepared from [α,α-^{2}H$_2$]benzyl chloride (1.6 g, 12.4 mmol) and magnesium (0.26 g, 0.011 g-atom) in ether (50 ml). The mixture was stirred at −40° for 2 hr, kept at room temperature overnight, and then heated at reflux for 1 hr. The usual work-up afforded, after column chromatography (silica, ethyl ether) (*R*)-1 (1.59 g, 6.82 mmol) in 65% yield: mp 127–128° (lit. mp 131–134°); mass spectrum *m/e* (rel intensity) 230 (3), 231 (2), 232 (93), 234 (2); NMR ($CDCl_3$) δ 3.86 (q, 2.06, *J* = 12.5 Hz, CH_2), 7.33 (m, 10.0, C_6H_5).

(*S*)-[α,α-^{2}H$_2$]Dibenzyl sulfoxide (1) was synthesized from (*R*)-1, $[\alpha]_{300}$ +23° (EtOH) (41 mg, 0.18 mmol), by ethylation with triethyloxonium tetrafluoroborate (53 mg, 0.28 mmol) in methylene chloride (6 ml) followed by hydrolysis in rapidly stirred 1% sodium hydroxide solution; 98% yield, 40.2 mg, $[\alpha]_{300}$ −18° (EtOH).[14]

(*R*)-*N*-Phthalimido[α,α-^{2}H$_2$]-*S,S*-dibenzyl sulfoximide (3) was synthesized from (*R*)-1 with a reaction time of 2 hr in 65% yield (ethanol), mp 150° dec.[13] Isotopically normal sulfoximide **3** was similarly obtained in 74% yield, mp 152° dec.

Anal. Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.64; N, 7.17. Found: C, 67.50; H, 4.56; N, 7.16.

Hydrazinolysis of Sulfoximide 3.[13] Hydrazine hydrate (98%, 1.5 ml) was added to a stirred suspension of sulfoximide **3** (0.13 g) in ethanol (5 ml) at room temperature. After 30 min, ether (100 ml) was added. The organic layer was dried over sodium sulfate and concentrated, and the residue was chromatographed (silica, ether) to give (*R*)-1 (75 mg, 0.32 mmol) in 97% yield, mp 128°.

Acknowledgment. Support by the National Science Foundation, Grant GP23637, to K.K.A. and by CNR (Rome) to M.C. and S.C. is gratefully acknowledged, as are helpful comments by Professor G. G. Lyle.

Registry No.—(*R*)-1, 54976-21-5; (*S*)-1, 56804-68-3; **2**, 21204-21-7; **3** isomer A, 56804-69-4; **3** isomer B, 33296-98-9; [α,α-^{2}H$_2$]benzyl chloride, 33712-34-4, hydrazine, 302-01-2.

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Reactions of Undecyl Radicals with Substituted Toluenes

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Since we underscored the importance of establishing the slopes of Hammett correlations in hydrogen abstractions from substituted toluenes by alkyl radicals,[2] several reports have appeared which indicate that ρ is positive for benzyl hydrogen abstractions by *tert*-butyl,[3] undecyl,[4,5] and 3-heptyl[6] radicals. All of these determinations but one[5] were based on measurements of the amount of alkane produced; it was concluded that formation of alkane occurs only by abstraction of benzylic hydrogens and not also by addition to the aromatic nucleus and subsequent reactions of the alkyl radicals with products derived thereby,[7] or by disproportionation of the alkyl radicals themselves. The one determination based on measurements of reactant disappearance (NMR of methyls of the toluenes) was also the only one to include *p*-methoxytoluene among the substrates.[5]

We wish to make available some of our measurements that are relevant to this topic. We have determined the relative reactivities of substituted toluenes toward undecyl radicals in benzene solvent by measuring the disappearance of the aromatics by gas–liquid chromatography in the usual way.[2] We have measured also the reactivities of some substituted benzenes, by the same procedure. The results are given in Table I. The "total" reactivity values for the toluenes cannot be apportioned quantitatively between addition to the ring and abstraction from the side chain by comparison with the similarly substituted benzenes, because the effect of the methyl on ring addition cannot be taken into account quantitatively on the basis of existing knowledge. However, qualitative comparisons can be made; e.g., in comparing the methoxytoluenes to anisole, clearly the reactivity of anisole includes ring addition and hydrogen abstraction from the methoxy group, if any.

Our results show that the reactivity of *p*-cyanotoluene is

Table I
Relative Reactivities of Aromatics toward Undecyl Radicals at 81°

Registry no.	Compd	Relative reactivity[a]
104-85-8	*p*-Cyanotoluene	2.03 ± 0.02
100-47-0	Benzonitrile	1.78 ± 0.02
620-22-4	*m*-Cyanotoluene	1.66 ± 0.02
108-41-8	*m*-Chlorotoluene	1.24 ± 0.03
104-93-8	*p*-Methoxytolutne	1.24 ± 0.01
352-70-5	*m*-Fluorotoluene	1.16 ± 0.03
100-84-5	*m*-Methoxytoluene	1.12 ± 0.01
106-43-4	*p*-Cholorotoluene	1.09 ± 0.01
352-32-9	*p*-Fluorotoluene	1.04 ± 0.03
108-88-3	Toluene	1.00[b]
108-38-3	*m*-Xylene	0.97 ± 0.01[c]
106-42-3	*p*-Xylene	0.89 ± 0.02[c]
108-90-7	Chlorobenzene	0.72 ± 0.01
100-66-3	Anisole	0.45 ± 0.04

[a] Against toluene; each entry represents the results of at least two runs, each analyzed in triplicate. [b] Assigned. [c] Normalized.

only 14% greater than that of benzonitrile, an indication of preponderance of addition over benzyl hydrogen abstraction for this toluene. *p*-Chlorotoluene is 50% more reactive than chlorobenzene, indicating that addition and benzyl hydrogen abstraction are roughly comparable in this case. *p*-Methoxytoluene is 270% more reactive than anisole, indicating that benzyl hydrogen abstraction is predominant for this toluene.

A study of all the data in Table I supports the inferences that (1) electron-withdrawing groups on the aromatic nucleus increase the rate of addition by undecyl radicals, and (2) electron-donating groups increase the rate of benzyl hydrogen abstraction. The first inference is in agreement with the conclusions of Shelton and Uzelmeir on additions of secondary alkyl radicals to substituted benzenes,[8] and the second with our predictions regarding abstractions by alkyl radicals.[2]

Our analyses indicate that the amount of undecane obtained exceeds the combined amounts of toluenes reacted, in all cases, often by as much as 25%. The stoichiometry of alkane formation following addition is not clear enough to warrant any additional quantitative conclusions. However, it is well known that methane-*d* is one of the products of the reaction of methyl radicals with ring-deuterated toluene.[9]

A serious discrepancy exists between the value of relative reactivity for *p*-methoxytoluene determined by us (1.24 by GLC) and that of Pryor et al.[5] (0.69 by NMR of the benzylic CH_3).

If the data for *p*-methoxytoluene and for the benzenes are disregarded (Table I), a Hammett plot of *total* reactivity for the remaining toluenes gives $\rho = 0.4$, with tolerable scatter. This is near the value of 0.47 reported by Henderson and Ward,[4] and 0.50 by Pryor and Davis;[5] both groups have described their Hammett plots as reflecting benzylic hydrogen abstraction exclusively.[10]

It must be pointed out that our results can support only tentative interpretations at this point. Kinetic studies, such as this and similar ones,[3-6] without fairly complete mass balance, should be interpreted with care.[11]

Experimental Section

Relative reactivities were determined by direct competition against toluene. Each toluene or substituted benzene was made approximately 0.67 *M* in benzene and brought to a gentle reflux; a solution of lauroyl peroxide in benzene was added over a 15-min period to a final concentration of 0.47 *M*. Reflux was continued for 36 hr. A blank (no peroxide) was treated in the same way. Each experiment was performed at least twice. Analyses were performed by GLC in triplicate; *p*-dichlorobenzene was added at the completion of the reaction as an internal standard.

Registry No.—Undecyl radical, 55101-35-4.

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Reaction of Ketene Bis(trimethylsilyl) Acetals with *m*-Chloroperbenzoic Acid. Synthesis of α-Hydroxycarboxylic Acids

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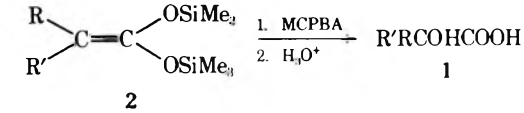
Available methods for the preparation of α-hydroxycarboxylic acids, **1**, include the aeration of lithiated carboxylic acids,[1] the hydrolysis of α-acyloxycarboxylic acids,[2] and the Favorski reaction.[3] Recently, also syntheses of **1** via trihalomethylcarbinols[4] and by use of the Pummerer reaction[5] have been noted.

We should like to report here that the oxidation of ketene bis(trimethylsilyl) acetals, **2**, with *m*-chloroperbenzoic acid (MCPBA), followed by mild acid hydrolysis, affords an extremely general, high-yield method for the preparation of **1** (Scheme I). The data included in Table I indicate the utility of the method.

Scheme I



2 **1**

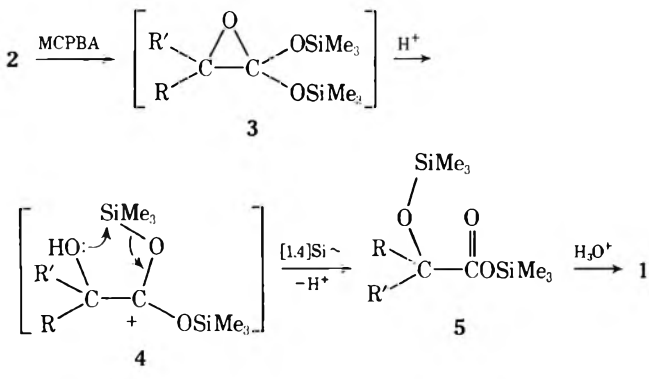
The mode of reaction of **2** with MCPBA may be envisioned as shown in Scheme II. This mechanistic route follows closely the scheme proposed for the reaction of trimethylsilyl enol ethers with MCPBA.[6] The presence of **5b** in the reaction mixture obtained from treating **2b** with MCPBA, prior to hydrolysis, was ascertained by direct distillation of the crude reaction mixture. Despite a great deal of decomposition, a 32% yield of **5b** was obtained. The structure of **5b** was verified by NMR and mass spectral comparison with authentic **5b**. The low yield of **5b** obtained by this procedure makes mechanistic considerations somewhat tenuous, but, based on analogy,[6] a [1,4]silatropic shift accounting for the production of **5b** seems to best fit the data.[6,7] No evidence for the presence of **3** was noted, but, in

Table I
Preparation of α-Hydroxycarboxylic Acids 1

2[a]	1[a]	% yield of 1[b]	Mp (lit. mp), °C
$Ph_2C{=}C(OSiMe_3)_2$ (2a)	Ph_2COHCO_2H (1a)	81	149–150.5 (148–150[c])
$PhCH{=}C(OSiMe_3)_2$ (2b)	$PhCHOHCO_2H$ (1b)	82	119–120.5 (118–120[c])
p-OMe—$PhCH{=}C(OSiMe_3)_2$ (2c)	p-OMe—$PhCHOHCO_2H$ (1c)	83	101–103 (98–102[c])
t-$BuCH{=}C(OSiMe_3)_2$ (2d)	t-$BuCHOHCO_2H$ (1d)	50	84–86 (91[d])
$C_5H_{10}C{=}C(OSiMe_3)_2$ (2e)	$C_5H_{10}COHCO_2H$ (1e)	80	106–107 (106–107[e])

[a] All compounds show ir, NMR, and mass spectral data consistent with the proposed structure. [b] Yields based on isolated, pure 1; average of at least two runs. [c] Values taken from ref 1. [d] Authentic 1d prepared by the method of M. Charpentier-Morize, *Bull. Soc. Chim. Fr.*, 920 (1962), gave a melting point of 84–86°, and showed no melting point depression upon admixture with 1d prepared by the present method. [e] J. Rouzoud, G. Cauquil, and L. Giral, *ibid.*, 2908 (1964).

Scheme II



the case of the oxidation of trimethylsilyl enol ethers, an analogous epoxide has been isolated,[6b] making **3** a likely intermediate in the oxidation of **2**.

Experimental Section

Preparation of Ketene Bis(trimethylsilyl) Acetals, 2. The method of Ainsworth and Kuo[8] afforded the ketene bis(trimethylsilyl) acetals, **2a–e**, in yields of ca. 80%. Physical properties of **2a, 2b, 2d,** and **2e** were in accord with the literature values. Compound **2c**: bp 113–114° (0.5 mm); $n^{26.5}$D 1.5868; ir ($CHCl_3$) 1655 cm^{-1}; NMR (CCl_4–Me_4Si) δ 0.18 (9 H, s), 0.22 (9 H, s), 3.65 (3 H, s), 4.41 (1 H, s), 6.50–7.30 (4 H, m); MS M^+ *m/e* (rel abundance) 310 (31), 295 (3), 148 (95), 147 (40), 120 (17), 75 (20), 73 (100).

Anal. Calcd for $C_{15}H_{26}O_3Si_2$: C, 58.02; H, 8.44. Found: C, 58.30; H, 8.37.

Preparation of α-Hydroxycarboxylic Acids, 1. General Procedure. A precooled (ice–methanol bath), stirred solution of 1.8 mmol of MCPBA in 10 ml of dry hexane under 1 atm of N_2 was treated with a solution containing 1.8 mmol of **2** in 10 ml of dry hexane (ca. 5 min addition time). After the addition was complete, the resulting slurry was stirred at room temperature for 30 min. After filtration of the mixture to remove the bulk of *m*-chlorobenzoic acid formed in the reaction, the crude filtrate was partitioned between 20 ml of ether and 20 ml of 1.5 *N* hydrochloric acid. After brief shaking, the layers were separated and the aqueous layer was extracted with 3 × 20 ml of ether. The combined ethereal portion was dried with anhydrous magnesium sulfate. Filtration, followed by solvent removal in vacuo, afforded crude **1** which was purified by a combination of sublimation and crystallization from chloroform–hexane mixtures.

Preparation of Trimethylsilyl-α-(trimethylsiloxy) Phenylacetate (5a). To a solution containing 20 mmol of dry triethylamine, 40 mmol of chlorotrimethylsilane, and 120 ml of dry THF was added, with stirring, under N_2, a solution containing 10 mmol of *dl*-mandelic acid (**1b**) in 30 ml of dry THF (ca. 5 min addition time). The resulting mixture was then stirred overnight at room temperature. The slurry was then filtered and the solvent removed in vacuo. The residue was then diluted with 60 ml of dry ether and the resulting mixture filtered once again. Removal of solvent in vacuo, followed by distillation at reduced pressure, afforded a 91% yield of pure trimethylsilyl-α-(trimethylsiloxy) phenylacetate (**5b**): bp 78–79° (0.65 mm); n^{22}D 1.5688; ir (CCl_4) 1740 cm^{-1}; NMR (CCl_4–CH_2Cl_2) δ 0.18 (9 H, s), 0.22 (9 H, s), 5.10 (1 H, s), 7.2–7.5 (5 H, m); M^+ *m/e* (rel abundance) 296 (1), 281 (4), 179 (100), 147 (26), 75 (9), 73 (65).

Anal. Calcd for $C_{14}H_{24}O_3Si_2$: C, 56.71; H, 8.16. Found: C, 56.65; H, 7.89.

Acid hydrolysis of **5b** (see above) afforded a quantitative yield of **1b**, mp 118.5–119.5°.

Acknowledgments. The authors gratefully acknowledge the Economic Development Administration of the Commonwealth of Puerto Rico (R.M.) and the Research Council of the University of Idaho (G.M.R.) for support of this work.

Registry No.—**1a**, 76-93-7; **1b**, 611-72-3; **1c**, 10502-44-0; **1d**, 4026-20-4; **1e**, 1123-28-0; **2a**, 31469-27-9; **2b**, 31491-21-1; **2c**, 56817-43-7; **2d**, 31469-23-5; **2e**, 40348-04-7; **5a**, 2078-19-5; *m*-chloroperbenzoic acid, 937-14-4.

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Transformation of 1-Azirines to 1*H*-Indoles with Benzyne. Evidence for the Intermediacy of the 3*H*-Indole System

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The synthetic capabilities of *o*-benzyne have been examined and utilized effectively in recent years.[1] It appears to possess a symmetric singlet ground state,[2] behaves as a highly reactive ethylenic component, and participates in cycloadditions with olefins and dienes in a [2 + 2], [2 + 4], or "ene" fashion.[1-10] Although the reaction of benzyne with enamines has been studied,[5,16] little is known about the reactivity of benzyne toward C=N bonds. We wish to report on the reaction of benzyne with the reactive C=N bond of the 1-azirine ring system.

Results and Discussion

2,3-Diphenyl-1-azirine (**1**) reacts with excess *o*-benzyne, generated by the thermal decomposition of benzenediazonium 2-carboxylate,[11] to give two products. The major product, a 1:1 adduct produced in 50% yield, was identified as

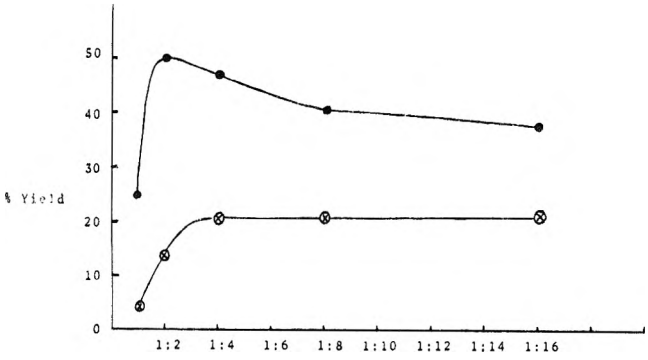
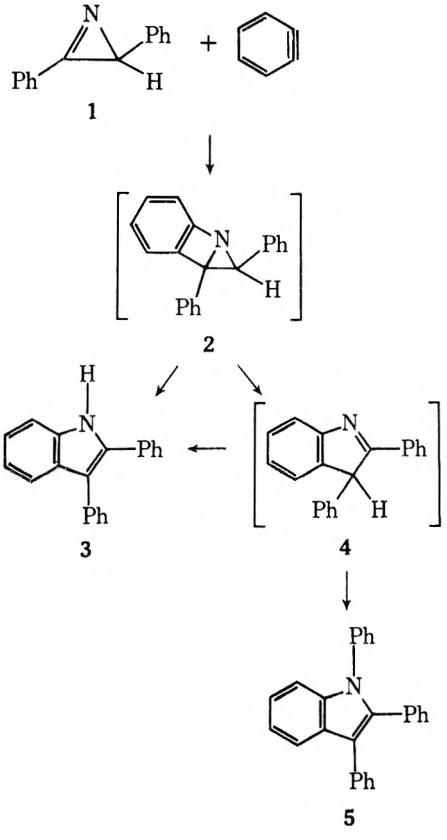
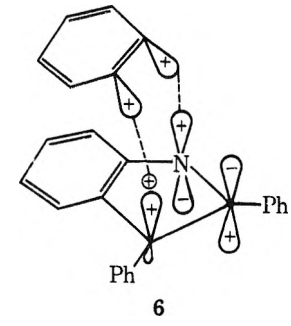


Figure 1. Millimolar ratio of azirine (1) to benzyne: ⊕, indole 5; •, indole 3.

2,3-diphenylindole[12] (3). A 1:2 adduct of azirine and benzyne, identified as 1,2,3-triphenylindole (5),[13] was isolated in 14% yield. Increase in the concentration of benzyne was accompanied by an increase in the yield of 5 as shown in Figure 1. Under the same conditions 2,3-diphenylindole was found to be relatively inert to benzyne, and no triphenylindole (5) could be isolated even after extended reaction times.

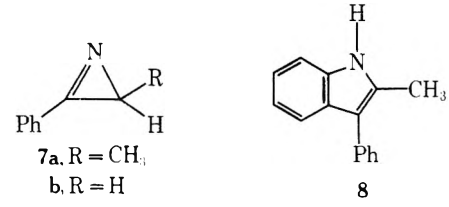
The mechanism of formation of 2,3-diphenylindole (3) may require initial formation of 2, the result of 1,2 addition on the azirine ring system. Initial 1,3 addition may be ruled out by the isolation of 2-methyl-3-phenylindole (8) from the reaction of azirine 7a and benzyne, although it is possible that more than one mechanism is operating depending on the substituent of carbon 3 of the azirine. It is known that the [2 + 2] cycloaddition between benzyne and simple olefins occurs in a nonconcerted fashion.[3,8-10] It can be presumed then that following the stepwise [2 + 2] cycloaddition of benzyne to the 1-azirine and the formation of intermediate 2, two reaction pathways for partitioning of this intermediate are available. A 1,2-hydrogen shift to the nitrogen would give the stable aromatic indole 3. A 1,2 shift to carbon would give the 3*H*-indole system 4, which can be trapped by benzyne to give the 1,2,3-triphenylindole (5). The conversion of indolenine (4) to the indole 3 is a symmetry-forbidden process and it appears likely that in the presence of a large excess of benzyne, partitioning of 4 to 3, a symmetry-forbidden process, is less favorable than the alternate symmetry-allowed "ene" reaction (see 6) to give 5.[6,10,15] That this may indeed be the case is borne out by the observation illustrated in Figure 1. The yield of 5 reaches a steady maximum value when large excesses of benzyne are used implying efficient trapping of 4. Some natural partitioning of 4 to 3 cannot still be ruled out. Interestingly, no "ene" product from 1 and benzyne was isolated.





6

When 3-methyl-2-phenyl-1-azirine (7a) was treated with excess benzyne, the only isolable product was 2-methyl-3-phenylindole (8). Under the same conditions, 2-phenyl-1-azirine (7b) gave only polymeric products.



7a, R = CH_3
b, R = H

8

Experimental Section

Benzenediazonium 2-carboxylate was prepared by the method of Friedman.[11]

Reaction of 2,3-Diphenyl-1-azirine (1) with Benzyne. To a solution of 0.386 g (2 mmol) of 2,3-diphenyl-1-azirine (1) in 20 ml of dichloroethane was added 0.592 g (4 mmol) of benzene-wet benzenediazonium 2-carboxylate, and the reaction mixture was heated under reflux for 5 hr. The solvent was then carefully removed in vacuo and the residual material was chromatographed on silica gel PF_{254} plates with 30% ether–pentane as the developing solvent. The top band (R_f 0.85) was cut out and eluted with ether to give, after solvent removal and drying, white crystals (0.097 g, 14%): mp 185–186° (lit.[13] mp 186°); ^1H NMR δ_{Me_4Si} ($CDCl_3$) 7.07 (s, 5 H), 7.16–7.85 (m, 14 H); ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 110.6, 116.7, 119.6, 120.9, 122.8, 125.9, 127.1, 127.4, 127.6, 127.9, 128.3, 129.1, 130.2, 131.2, 131.6, 134.9, 137.1, 137.9, 138.1; mass spectrum (70 eV) *m/e* 345 (M^+).

The middle band (R_f 0.55) was cut out and eluted with ether to give 0.289 g of pale yellow oil after solvent removal. The oil crystallized from ether–pentane as colorless, rectangular crystals (0.267 g, 50%): mp 122–123° (lit.[12] mp 123–124°); ^1H NMR δ_{Me_4Si} ($CDCl_3$) 7.21–7.72 (m, 14 H), 7.95 (s, br, 1 H); ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 110.9, 115.0, 119.7, 120.4, 122.6, 126.2, 127.7, 128.2, 128.5, 128.7, 130.2, 132.6, 134.1, 135.1, 135.9; mass spectrum (70 eV) *m/e* 269 (M^+).

Attempted Reaction of 2,3-Diphenylindole (3) and Benzyne. To a solution of 0.538 g (2 mmol) of 2,3-diphenylindole (3) in 10 ml of dichloroethane was added approximately 0.60 g (4 mmol) of benzenediazonium 2-carboxylate and the reaction mixture was heated under reflux for 5 hr. Solvent removal and chromatographic separation gave 0.489 g (91% recovery) of 3. No 1,2,3-triphenylindole was isolated. Some decomposition of 3 does occur in the presence of benzyne (see Figure 1).

Reaction of 3-Methyl-2-phenyl-1-azirine (7a) with Benzyne. The azirine 7a (0.393 g, 3 mmol) in 20 ml of dichloroethane was treated with 0.90 g (6 mmol) of benzenediazonium 2-carboxyl-

ate, and the reaction mixture was heated under reflux for 4 hr. Solvent removal and chromatographic separation gave 0.198 g (32%) of 2-methyl-3-phenylindole (8): mp 58° (lit.[14] mp 59–60°); ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.28 (s, 3 H), 7.05–7.76 (m, 10 H); mass spectrum (70 eV) *m/e* 207 (M^+).

Registry No.—**1**, 16483-98-0; **3**, 3469-20-3; **5**, 54879-94-6; **7a**, 16205-14-4; **8**, 4757-69-1; benzyne, 462-80-6.

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Photolysis of 4,4-Dimethylcholesta-1,5-dien-3-one

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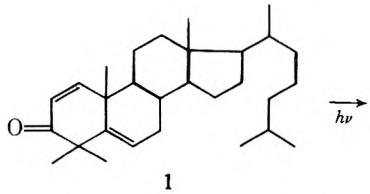
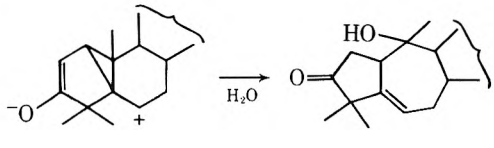
The photolysis of 4,4-dimethylcholesta-1,5-dien-3-one (1) has been examined in the hope that the AB portion of the steroid nucleus would rearrange to a hydroazulene system of the type found in the grayanotoxins.[1-5] A plausible

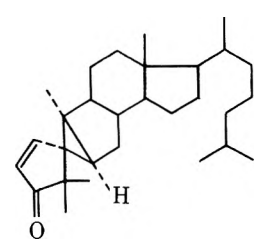


1

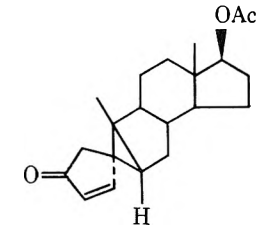


mechanism can be written for this transformation and the change from a decalin system to a hydroazulene skeleton is frequently encountered in the photochemical reactions of dienones. Nonetheless this type of transformation was not encountered. Photolysis of 1 in either 95% ethanol or dioxane in the 250-nm region produced at least eight new compounds. However, photolysis at 300 nm in aqueous dioxane gave predominantly one new compound which is assigned structure **2**.

The formation of **2** is entirely expected from the elegant and extensive studies of Jeger, Schaffner, and their collaborators, who examined the photolysis of 3-oxo-17β-acetoxy-$\Delta^{1,5}$-androstadiene which presents the same hexalone system only lacking the two methyl groups at C-4.[7] The photolysis of 3-oxo-17β-acetoxy-$\Delta^{1,5}$-androstadiene afforded the photoisomer **3** accompanied by three of its stereoisomers.



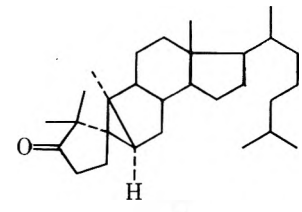
2



3

The structure of **2** follows from a comparison of its spectroscopic properties with those of **3**. The ultraviolet spectrum of **2** showed λ_{max} 263 nm (ϵ 8800) whereas **3** exhibited λ_{max} 267 nm (ϵ 9750). The vinyl protons of **2** appeared as an AB quartet (δ 5.98 and 7.03, J = 6 Hz) similar to that found for **3** (δ 6.07 and 7.25, J = 6 Hz). The infrared spectrum of **2** had absorption maxima at 1707 and 1681 cm^{-1} in good agreement with those found for **3**.

Photolysis of dienone 1 at 350 nm in dioxane–acetic acid gave **2** along with two new photoisomers, **4** and **5**. Photoisomer **4** is clearly a stereoisomer of **2**. Moreover, photolysis of **2** leads to the formation of **4**. The third photoisomer is assigned structure **5** based on its spectroscopic properties which are very similar to those found for compound **6** obtained from the photolysis of 3-oxo-17β-acetoxy-$\Delta^{1,5}$-androstadiene.



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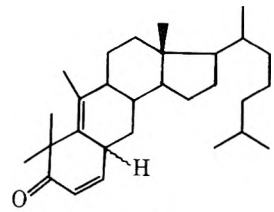

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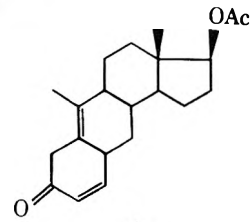
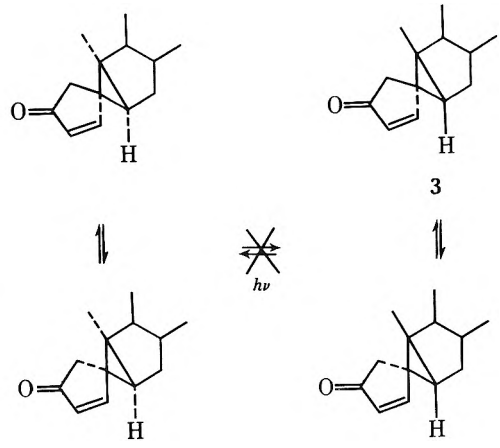


6

The infrared spectrum of **5** showed carbonyl absorption at 1667 cm^{-1} and double bond absorption at 1640 cm^{-1}. The ^{1}H NMR spectrum showed an AB quartet (δ 5.79 and 6.45, J = 10 Hz) whereas the ultraviolet spectrum showed a maximum at 227 nm. These spectroscopic characteristics are in good agreement with those found for **6**.

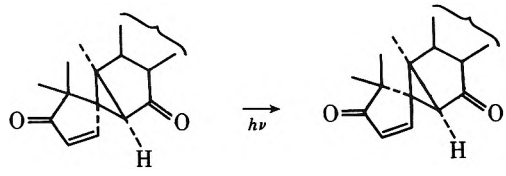
The remaining structural problem is the stereochemistry of the spiro photoisomers. It was shown previously in the studies of **3** and its stereoisomers that the four stereoisomers formed two pairs. Members of one pair reached a photostationary state but did not give rise to either member of the other pair. Extensive degradations and circular dichroism measurements indicated that members of a pair were related to one another by change in the stereochemistry of the spiro carbon.

Moreover, members of a pair showed enantiomeric circular dichroism curves. However, in the case at hand, both of the stereoisomers we obtain had positive circular dichroism curves. Although we did not establish that the spiro photoisomers **2** and **4** achieve a photostationary state, it was established that photolysis of **2** gives rise to **4** and following



3

the progress of the photolysis of dienone **1**, photoisomer **4** appeared only after substantial quantities of **2** had been produced. The situation may be similar to that observed in the photolysis of the closely related dienone, 3,7-dioxo-4,4-dimethyl-17β-acetoxy-$\Delta^{1,5}$-androstadiene. In that case, photolysis produced the two photoisomers shown below and it was established that photoisomer **7** was the precursor to **8** and that the isomerization of **7** to **8** is irreversible.[8]

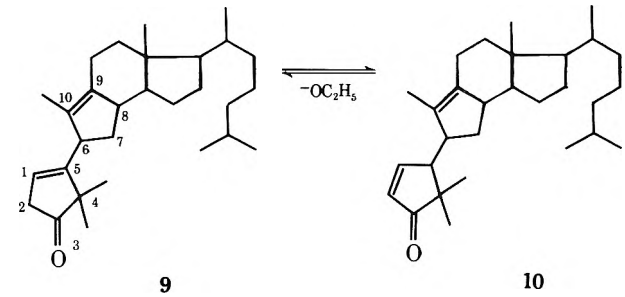


7 8

In any event, the cyclopropane ring juncture was not changed in any of the previous photochemical studies. Hence, we make the assumption that the spiro photoisomers in the present study have the same stereochemistry at the cyclopropane ring juncture. The ^{1}H NMR spectra and the circular dichroism measurements are consistent with the stereochemistry indicated for photoisomer **4**. Thus **4** showed an intense positive Cotton effect and the vinyl proton at C-1 were found at δ 7.72 which compares favorably with the properties of the relevant photoisomer from the photolysis of 3-oxo-17β-acetoxy-$\Delta^{1,5}$-androstadiene (an intense positive Cotton effect; δ 7.92 for the C-1 proton). The stereochemistry of **2** is thus as shown in structural formula **2**, differing from **4** only in the configuration of the spiro carbon. Moreover, subsequent chemical transformations indicate that **2** and **4** have the same configuration at C-6, which is consistent with the stereochemical proposals. Both spiro photoisomers were subjected to the action of hot acetic acid. A single compound was produced in high yield in both instances. The chemical transformations and spectroscopic properties of this material indicate structure **9**.

The infrared spectrum of **9** showed carbonyl absorption at 1750 cm^{-1} ascribed to a cyclopentanone moiety along with absorption at 1637 cm^{-1} indicating a carbon–carbon double bond. The ultraviolet spectrum did not show absorption characteristic of conjugated double bonds. The ^{1}H NMR spectrum showed a two-proton doublet (J = 2 Hz) at δ 2.78 ascribed to the C-2 protons coupled to the vinyl proton at C-1 which appears as a triplet at δ 5.40. Treatment of **9** with deuterium oxide and acid in tetrahydrofuran resulted in the incorporation of two deuteriums and the ^{1}H NMR spectrum showed the expected changes, namely, the loss of the signal at δ 2.78 and the collapse of the triplet at δ 5.40 to a singlet.

Treatment of **9** with 0.1 N sodium hydroxide in aqueous ethanol gave a mixture of materials from which **9** was isolated (68%) and an isomerization product (16%) which is



9 10

assigned structure **10**. The infrared spectrum of **10** shows absorptions at 1716 and 1591 cm^{-1} ascribed to the cyclopentenone moiety whereas the ultraviolet spectrum showed a maximum at 213 nm (ϵ 12700). The ultraviolet absorption maximum is at somewhat shorter wavelength with a greater extinction coefficient than the corresponding values for cyclopentenone. However, the shape of the curve, the position of the maximum, and the extinction coefficient are very well approximated by adding the ultraviolet absorption spectra for cyclopentenone and 1,2-dimethylcyclohexene. The ^{1}H NMR spectrum of **10** revealed two complex one-proton multiplets at δ 6.08 and 7.14 ascribed to the vinyl protons at C-2 and C-1, respectively. Decoupling experiments yielded the coupling constants between the protons at C-1, -2, and -5 (see Experimental Section). The base peak of the mass spectrum appears at m/e 310, suggesting that the most prominent fragmentation is the loss of the entire A ring by cleavage of the doubly allylic single bond joining the A ring to the remainder of the molecule.

That the conversion of **9** to **10** is a simple base-catalyzed double bond isomerization is indicated by an experiment in which pure **10** gave rise to **9** under the equilibrating conditions. Equilibration of **9** in deuterated solvent afforded doubly deuterated **10** in 15% yield. The ^{1}H NMR spectrum of this material showed a singlet at δ 6.08 and 2.69, ascribed to the protons as at C-2 and C-5, respectively, were missing. The same experiment afforded doubly deuterated **9** which exhibited the same ^{1}H NMR spectrum as the material produced by acid-catalyzed exchange.

These data would seem to secure the structures of the photochemical products and the material produced by acid-catalyzed rearrangement of the spiro photoisomers except for some stereochemical questions.

Experimental Section[9]

Photolysis of 4,4-Dimethylcholesta-1,5-dien-3-one in Acetic Acid–Dioxane. A sample of 4,4-dimethylcholesta-1,5-dien-3-one[6] (1.6 g) was dissolved in 120 ml of dioxane-containing 6% acetic acid. The solution was placed in a 30 × 404 mm Pyrex tube and nitrogen was bubbled through for 30 min. The solution was photolyzed at 6° for 30 min. Removal of the solvent gave a light yellow gum.

A. 4,4-Dimethyl-1(10→6ξ)-*abeo*-cholesta-1,5(10)-dien-3-one (5). The crude photolysis product obtained above was chromatographed on silica gel (50 g). Elution with 2 l. of 20% benzene in hexane gave a mixture (600 mg) of starting dienone and **5**. further elution afforded 200 mg (ca. 20% based on unrecovered starting material) of **5**: mp 83–85.5° from ethanol; ir (CCl_4) 1667 (C=O), 1640 (C=C), and 1570 cm^{-1} (C=C); ^{1}H NMR (CCl_4) δ 0.74 (s, CH_3-18), 0.85, 0.91, 0.95 (m, CH_3-21, -26, and -27), 1.30 (s, CH_3-4), 1.44 (s, CH_3-4), 1.19 (br s, CH_3-19), 3.29 (complex m, CH-6), 5.79 (d, J = 10 Hz, CH-2), 6.45 (d, J = 10 Hz, CH-1); uv λ_{max} (EtOH) 227 nm (ϵ 9200); and the mass spectrum had a molecular ion (m/e) peak of 410 (calcd mol wt 410.17).

Anal. Calcd for $C_{29}H_{46}O$: C, 84.88; H, 11.22. Found: C, 84.98; H, 11.42.

B. 6β,10-Cyclo-(5*R*)-1(10→5)-*abeo*-4,4-dimethylcholest-1-en-3-one (4). Further elution with 2.5 l. of 25% benzene in hexanes gave 360 mg (36%) of photoisomer **4**: mp 107–108° from ethanol; ir (CCl_4) 1712 (C=O), 1670 (C=C), and 1575 cm^{-1} (C=C); ^{1}H NMR (CCl_4) δ 0.73 (s, CH_3-18), 0.88 (d, J = 7 Hz, CH_3-26, -27), 0.94 (d, J

= 5 Hz, CH_3-21), 0.96 (s, CH_3-4), 1.10 (s, CH_3-4), 1.34 (s, CH_3-19), 6.06 (d, J = 6 Hz, CH-2), 7.72 (d, J = 6 Hz, CH-1); near ir (CCl_4) 1.65 μ; uv λ_{max} (EtOH) 263 nm (ϵ 9400); mass spectrum m/e (rel intensity) 410 (40), 395 (26), 297 (70), 275 (100); CD (c 4.6 × 10^{-4}, cyclohexane) $[\theta]_{370}$ +6800, $[\theta]_{352}$ +13500, $[\theta]_{338}$ +14100, $[\theta]_{325}$ +10300.

Anal. Calcd for $C_{29}H_{46}O$: C, 84.88; H, 11.22. Found: C, 84.80; H, 11.49.

C. 6β,10-Cyclo-(5*S*)-1(10→5)-*abeo*-4,4-dimethylcholest-1-en-3-one (2). Elution with 2.5 l. of 30% benzene in hexane gave 370 mg (37%) of photoisomer **2**: mp 72–72.5° from ethanol; $[\alpha]_{578}^{25}$ −10.80° (c 0.148); ir (CCl_4) 1711 (C=O), 1681 (C=C), and 1591 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.72 (s, CH_3-18), 0.89 (d, J = 7 Hz, CH_3-26, -27), 0.94 (d, J = 6 Hz, CH_3-21), 1.06 (s, CH_3-4), 1.17 (s, CH_3-4), 1.37 (s, CH_3-19), 5.98 (d, J = 6 Hz, CH-2), 7.03 (d, J = 6 Hz, CH-1); uv λ_{max} (EtOH) 263 nm (ϵ 8800); mass spectrum m/e (rel intensity) 410 (25), 395 (15), 297 (70), and 275 (100); CD (c 4.7 × 10^{-4}, cyclohexane) $[\theta]_{355}$ +520, $[\theta]_{342}$ +1040, $[\theta]_{322}$ +1080, $[\theta]_{310}$ +765.

Anal. Calcd for $C_{29}H_{46}O$: C, 84.88; H, 11.22. Found: C, 84.31; H, 11.25.

Photolysis of Dienone 1 at 300 nm in Dioxane–Water. Dienone **1** (1.08 g) was dissolved in 100 ml of pure dioxane and 5 ml of water. The solution was deoxygenated with nitrogen and photolyzed for 20 hr in a Pyrex tube using the 300-nm source. Isolation and separation as previously described afforded 700 mg of starting material, 200 mg of photoisomer **2** and a trace of unidentified material.

Photolysis of Photoisomer 2. A solution of **2** (41 mg, 0.10 mmol) in 1,4-dioxane (15.0 ml) and glacial acetic acid (0.90 ml) was placed in a 25 × 200 mm Pyrex test tube and degassed by purging with nitrogen for 30 min. The solution was then irradiated at 3500 Å and 6°C under nitrogen. The progress of the reaction was followed by TLC. After 4 hr TLC showed that approximately half the starting material had been consumed. The mixture was evaporated under reduced pressure to approximately 20% of its original volume, taken up in 30 ml of toluene, and evaporated to a yellow gum. A ^1H NMR spectrum of this material showed only enone protons of **2** and **4**.

This material was separated by preparative thin layer chromatography (silica gel GF, 50:50:4.5 benzene–heptane–2-propanol). Two bands were observed and photoisomer **4** (6 mg) was obtained from the more mobile band and identified by ^1H NMR and infrared spectroscopy. Photoisomer **2** (7 mg) was recovered from the less mobile band.

4,4-Dimethyl-1(10→5)-*abeo*-10(5→6α*H*)-*abeo*-cholesta-1(5),9-dien-3-one (9). Photoisomer **2** (100 mg) was taken up in 15 ml of glacial acetic acid and refluxed under nitrogen for 1.5 hr. Over this time, a new compound (**9**) was observed by TLC. Build-up of an impurity caused the solution to turn red and eventually dark. The acetic acid was removed with toluene on the rotatory evaporator and the 100 mg of gum was chromatographed on 3 g of silica gel. Elution with 300 ml of 10% benzene in hexane gave 94 mg (94%) of **9**: mp 61.5–62.5° from ethanol; ir (CCl_4) 1750 (C=O) and 1637 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.76 (s, CH_3-18), 0.89 (d, J = 7 Hz, CH_3-26, -27), 0.95 (d, J = 6 Hz, CH_3-21), 1.07 (s, *gem*-CH_3-4), 1.52 (br s, CH_3-19), 2.04–3.00 (unstructured, miscellaneous peaks), 2.78 AX_2 pattern (d, J = 2 Hz, $-CH_2C{=}O$), 5.40 (t, J = 2 Hz, $=CHCH_2C{=}O$); uv showed only end absorption; mass spectrum m/e (rel intensity) 410 (100), 395 (44), 382 (16), 367 (15), 353 (2), 340 (15), 325 (28), 297 (38).

Anal. Calcd for $C_{29}H_{46}O$: C, 84.88; H, 11.22. Found: C, 84.53; H, 11.39.

Deuterium Exchange of Ketone 9. A sample of **9** (100 mg) was taken up in dry THF (2 ml) and 0.3 ml of D_2O was added. After the addition of two drops of acetyl chloride, the mixture was refluxed under nitrogen for 5.5 min. The solvent was removed on the rotatory evaporator, and the residue was taken up in 10 ml of ether and washed with deuterium oxide. The 100 mg of yellow gum resulting from evaporation of the ether was chromatographed on silica gel (2 g). Elution with 200 ml of hexane gave 80 mg of an oil whose ^1H NMR spectrum indicated the incorporation of deuterium at the α-methylene position: ^1H NMR (CCl_4) δ 0.76 (s, CH_3-18), 0.85, 0.91, 0.98 (m, CH_3-26, -27, -21), 1.06 (s, *gem*-CH_3-4), 1.50 (s, CH_3-19), 5.40 (s, CH-1).

4,4-Dimethyl-1(10→5)-*abeo*-10(5→6α*H*)-*abeo*-cholesta-1,9-dien-3-one (10). To a solution of **9** (147 mg) in 3 ml of 95% ethanol under nitrogen was added 1.1 ml of 0.4 *N* aqueous sodium hydroxide. This mixture was stirred at reflux for 14 hr, cooled, poured into ether, washed with water until neutral, and dried over magnesium sulfate. Removal of the solvent gave 125 mg of a red gum. Chromatography of 5 g of silica gel gave 100 mg of starting material and 23 mg of **10**: mp 100–101.5°; ir (CCl_4) 1716 (C=O), 1591 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.72 (s, CH_3-18), 0.88 (d, J = 7 Hz, CH_3-26, -27), 0.93 (d, J = 6 Hz, CH_3-21), 0.99 (s, CH_3-4), 1.04 (s, CH_3-4), 1.67 (br s, CH_3-19), 1.72 (complex m, $-CHC{=}$), 2.69 (complex m, CH-5), 6.08 (dd, CH-2), 7.14 (dd, CH-1); decoupling experiments of the sample in CCl_4–Me_4Si gave $J_{1,2}$ = 6 and $J_{2,5}$ = 2 Hz; uv showed only end absorption; mass spectrum m/e (rel intensity) 410 (20), 395 (18), 316 (13), 301 (100).

Anal. Calcd for $C_{29}H_{46}O$: C, 84.88; H, 11.22. Found: C, 84.54; H, 11.45.

Deuteration of 10. Sodium deuterioxide was prepared by treating 150 mg of freshly cut sodium with 8 ml of ethanol-*O*-*d* containing 1 ml of deuterium oxide. To this solution was added 100 mg of **9** in 1 ml of ethanol-*O*-*d*. The solution under nitrogen was refluxed for 3 hr, taken up in 8 ml of ether, and washed to neutrality with 3 ml of D_2O in three portions. The excess D_2O was removed on the rotatory evaporator using dioxane and the resulting yellow oil chromatographed on 6 g of silica gel. Elution with 200 ml of 30% benzene–hexane gave 15 mg of **10**, isolated as an oil: ir (CCl_4) 1712 (C=O) and 1569 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.72 (s, CH_3-18), 0.84, 0.90 (complex m, CH_3-21, -26, -27), 0.98 (s, CH_3-4), 1.02 (s, CH_3-4), 1.67 (br s, CH_3-19), 7.13 (s, CH-1); mass spectrum m/e (rel intensity) 412 (16), 411 (8), 410 (6), 397 (8), 318 (5), 310 (100). Recovered **9** showed incorporation of two deuterium atoms: ^1H NMR (CCl_4) δ 0.76 (s, CH_3-18), 0.85, 0.91, 0.98 (complex m, CH_3-21, -26, -27), 1.50 (br s, CH_3-19), 5.40 (s, CH-1).

Registry No.—**1**, 6384-44-7; **2**, 56761-43-4; **4**, 56782-71-9; **5** 56761-44-5; **9**, 56761-45-6; **9** dideuterio, 56782-72-0; **10**, 56761-46-7; **10** dideuterio, 56761-47-8.

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(9) Melting points (measured in open capillaries) are corrected. Infrared spectra were recorded with Beckman IR-7 and IR-5 spectrophotometers. Proton magnetic resonance spectra were measured with a Varian HA-100 spectrophotometer. Chemical shifts are reported in parts per million, δ values, relative to the internal standard tetramethylsilane. The following notations are employed in the presentation of ^1H NMR spectra: s = singlet, d = doublet, t = triplet, br s = broad singlet, complex m = complex multiplet. A Perkin-Elmer Model 141 polarimeter having a sample cell path length of 1 dm was used in measuring the molecular rotations. Circular dichroism spectra were taken on a Cary Model 6001 recording spectropolarimeter. Ultraviolet spectra were measured in 95% ethanol solution on a Cary Model 15 recording spectrometer. A Consolidated Electrodynamics Corp. Model 21-110 mass spectrometer at 70 eV was used to obtain mass spectra. Carbon and hydrogen microanalyses were completed by Chemanalytics, Inc., Tempe, Ariz., and by the University of Oregon. Anhydrous magnesium sulfate was utilized in drying samples. Column chromatography employed J. T. Baker silica gel powder, 60–200 mesh. TLC spots on 5 × 20 cm Baker-flex qualitative plates were visualized with uv light and by spraying the dried plates with 3% ceric sulfate in 10% sulfuric acid and subsequent heating. All ultraviolet irradiations were carried out in a Rayonet photochemical reactor from the Southern New England Ultraviolet Co.

Preparation of *trans*-1,2-Bis(tri-*n*-butylstannyl)ethylene

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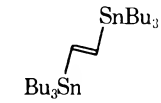
Received August 12, 1975

Recently we have described the use of *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene (**1**) as a reagent for the synthesis

of acetylenes including some types which are not otherwise accessible.[1] A number of other applications of this valuable reagent are presently being investigated in these laboratories, especially in connection with total synthesis of natural products. Because of the potentially broad range of utility of **1** a convenient, large-scale preparation was desirable. Although **1** is prepared by simply heating a neat mixture of 1 equiv of tri-*n*-butyltin hydride with 1 equiv of tri-*n*-butylethynylstannane (**2**),[1-3] the preparation of **2** in quantity by current procedures is complicated and cumbersome.



1

$Bu_3SnC{\equiv}CH$

2

$Bu_3SnC{\equiv}CSnBu_3$

3

$Bu_3SnC{\equiv}CCl$

4

Reaction of tri-*n*-butyltin halides with ethynylmagnesium halides[4] or with sodium acetylide in ether[5] results in only a very low yield of **2**, the major side product being bis(tri-*n*-butylstannyl)acetylene (**3**).[6] A modification of the latter process has been described[7] in which 1 equiv of tri-*n*-butyltin chloride in ether is added to a solution of sodium acetylide prepared in liquid ammonia. Although this procedure results in a higher yield of **2**, the reaction in our hands was found to be very capricious and usually resulted in large amounts of the side product **3**.

A new method has been developed for the synthesis of **1** which possesses the advantages of (1) high yield, (2) applicability on a large scale, (3) avoidance of low temperatures or the use of liquid ammonia, and (4) elimination of further reaction of **2** and specifically the by-product **3**. Tri-*n*-butyltin chloride was added to the readily prepared anion, lithium chloroacetylide,[8] and the product, tri-*n*-butylchloroethynylstannane (**4**), was isolated in 83% yield by distillation. Treatment of **4** with 2 equiv of tri-*n*-butyltin hydride afforded tri-*n*-butyltin chloride (99%) and *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene (**1**, 86%) by direct distillation of the reaction mixture. The readily separated tri-*n*-butyltin chloride was very pure and could be recycled for the preparation of more **1**.

Experimental Section

***trans*-1,2-Bis(tri-*n*-butylstannyl)ethylene (1).** To a cooled (0°) solution of 50.0 ml (82.4 mmol) of 1.65 *M* methyllithium in ether under an argon atmosphere was added dropwise a solution of 3.2 ml (42 mmol) of *trans*-1,2-dichloroethylene in 15 ml of ether during 1 hr (gas evolution). The mixture was warmed to room temperature, stirred for 90 min, then recooled (0°), and 11.1 ml (41.2 mmol) of tri-*n*-butyltin chloride was added. After stirring for 1 hr at room temperature, 1 ml of methyl iodide was added and stirring was continued for 30 min. The mixture was filtered (quickly in the air) through a pad of Celite and concentrated in vacuo. Distillation at bp 100–105° (0.01 mm) afforded 12.0 g (83%) of pure chloroacetylene **4**, ir (neat) 4.72 μ. This material could be used in the next step; redistillation did not change the spectra.

A neat mixture of 17.8 g (50.9 mmol) of tri-*n*-butylchloroethynylstannane, 29.7 g (102 mmol) of tri-*n*-butyltin hydride, and 0.18 g of azobisisobutyronitrile were heated at 90° for 4 hr. Distillation afforded 16.4 g (99%) of tri-*n*-butyltin chloride, bp 102–105° (0.1 mm), and 26.4 g (86%) of *trans*-bis(tri-*n*-butylstannyl)ethylene (**1**)[1]: bp 175–195° (0.07 mm); ir (neat, partial) 6.83 and 10.4 μ; NMR (CCl_4) δ 0.50–1.90 (br m, 54 H) and 6.85 (s, 2 H, $J_{^{117}Sn-H}$ = 106, $J_{^{119}Sn-H}$ = 110 Hz). The NMR, ir, and near ir spectra of **1** were identical with those of material prepared as previously described.[1,9]

Registry No.—**1**, 14275-61-7; *trans*-1,2-dichloroethylene, 156-60-5; tri-*n*-butyltin chloride, 1461-22-9.

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The Structure of Hallol[1]

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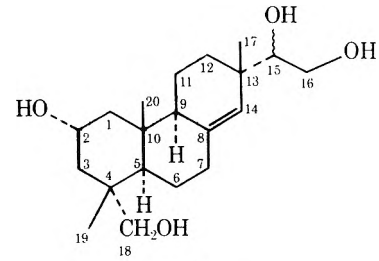
A study of the heartwood constituents of the New Zealand podocarp *Podocarpus hallii* Kirk has revealed the presence of the terpenic substances sugiol, podocarpic acid, totarol, its 19-hydroxy and 19-oxo derivatives,[2] sellowin A,[3] and a compound (B, mp 204°) of unknown constitution.[2] The following discussion shows the latter, herewith named hallol, to be 8(14)-sandaracopimaren-2α,15ξ,16,18-tetrol (**1**).



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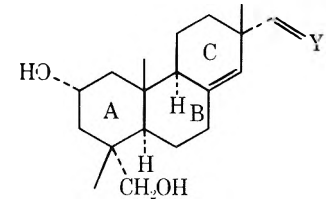
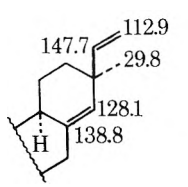


2a, Y = O
b, Y = CH_2

Both elemental and mass spectral analyses indicate the compound to possess a $C_{20}H_{34}O_4$ molecular framework, while the mass spectrum of a sample exposed to deuterium oxide reveals the incorporation of four deuteriums and hence the presence of a hydrogen on each of the oxygens. The ^1H NMR spectrum of a deuteriomethanol solution contains three methyl singlets at 0.82, 0.87, and 0.97 ppm, a six-hydrogen multiplet at 2.9–4.0 ppm corresponding to two oxymethylenes and two oxymethines, and an olefinic hydrogen multiplet at 5.32 ppm. These facts are accommo-

dated most readily, albeit not exclusively, by tricarbocyclic, monoolefinic, diterpenic structures reminiscent of pimarenic and related triols and tetrols containing 15,16-dihydroxy units.[4] As a consequence, hallol was oxidized with periodic acid, yielding a noraldehyde (**2a**), whose reaction with methylenetriphenylphosphorane led to a dienediol (**2b**). If the relationship of hallol to the earlier pimarenic natural products were well founded, the two-step procedure would have furnished a pimaradiene derivative, a substance ideally suited for ^{13}C NMR analysis in view of the previous accumulation of ^{13}C NMR data in this field.[5]

Comparison of the olefinic carbon shifts of the dienic degradation product **2b** with those of pimaradienic (**3**), sandaracopimaradienic (**4**), and isopimaradienic (**5**) systems[5] shows the compound to be of the sandaracopimaradiene type and comparison of the oxymethylene shift of 18-hydroxy (**6**) and 19-hydroxy (**7**) diterpenic substances[6] with that of **2b** classifies the degradation product, and hence the natural product, as an 18-hydroxy diterpene.



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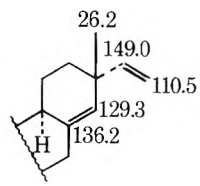

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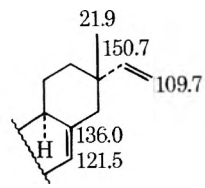

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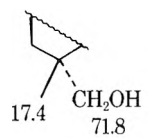

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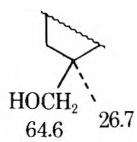

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These facts are confirmed by the three methyl shifts of **2b.**[5] The virtual identity of the δ values of the ring B and C methylenes and methines of **2b** with those of analogous carbon centers of ring B of pimarol and ring C of sandaracopimaric acid[5] limits the secondary hydroxy group of **2b** to ring A and a 2α configuration. Alternative hydroxyl locations at 1α, 1β, 2β, 3α, and 3β sites are precluded by the absence of shift perturbations at C(9) and C(10), at C(10), C(11), and C(20), at C(19) and C(20), at C(4), C(5), and C(18), and at C(4), C(18), and C(19), respectively.[6,7]

The ^{13}C NMR data for diene **2b** readily permits shift assignment for aldehyde **2a.** Since the natural tetrol (**1**) is not soluble in deuteriochloroform, the common ^{13}C NMR spectral solvent, its spectrum, and, for sake of comparison, that of diene **2b** were obtained in deuteriopyridine solution. Shift differences only in the vicinity of C(13) and the replacement of the resonances of the vinyl group of **2b** by those of an oxymethylene and oxymethine show hallol to be a 15,16-dihydroxy compound and to possess the relative configuration depicted in formula **1**. The carbon shifts of compounds **1** and **2** are listed in Table I.

The ^1H NMR signals of the hydrogens of the vinyl group and nuclear double bond of the pimaradienes **3, 4,** and **5** are distinct,[8,9] making the olefinic hydrogens of diene **2b** readily recognizable as those of the sandaracopimaradiene system (**4**). Similarly, the ^1H NMR signals of both the methyl and hydroxymethyl groups occupy different field positions in structures **6** and **7**,[9,10] permitting the identification of the C(4) stereochemistry of **2b** as that illustrated in partial structure **6**.

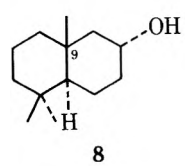
Table I of ^{13}C NMR data reveals an unusually strong attenuation of the γ-anti-periplanar heteroatom effect.[11] While equatorial hydroxy groups shield the γ carbons in cyclohexane compounds by ca. 3 ppm, the 2α-hydroxy

Table I
Carbon Chemical Shifts[g]

	1[a]	2b[a]	2b[b]	2a[b]
C(1)	48.7	48.7	48.1	48.0
C(2)	63.6	63.7	65.1	65.0
C(3)	45.2	45.3	44.7	44.6
C(4)	39.1[c]	39.1	39.4[e]	39.4[f]
C(5)	46.6	46.7	47.0	46.7
C(6)	21.8	21.8	22.1	21.9
C(7)	35.5	35.4	35.5	35.4
C(8)	136.5	[d]	136.2	141.0
C(9)	50.6	50.3	50.4	50.4
C(10)	38.9[c]	39.1	39.6[e]	39.7[f]
C(11)	18.4	18.9	18.9	18.1
C(12)	30.2	34.2	34.4	28.3
C(13)	37.8	37.1	36.9	47.3
C(14)	128.1	128.6	129.3	121.7
C(15)	79.1	[d]	148.7	192.6
C(16)	62.7	109.8	110.0	
C(17)	22.5	25.4	25.9	20.5
C(18)	70.6	70.8	71.5	71.4
C(19)	18.7	18.9	18.9	18.8
C(20)	16.0	16.1	16.5	16.8

[a] In pyridine-d_5 solution; $\delta(Me_4Si) = \delta$(pyridine-d_5 C-4) + 134.6 ppm. [b] In $CDCl_3$ solution; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [c,e,f] Signals in any vertical column may be reversed. [d] Signal under solvent signal. [g] The δ valves are in parts per million downfield from Me_4Si.

function of **2a** and **2b** deshields C(4) and C(10) by ca. 1 ppm. This deshielding seems to affect especially quaternary γ carbons in rigid ring systems, as shown also by the $\Delta\delta$ value of ca. 1 ppm for C(9) of the decalol **8**[1] and C(14) of the lupane derivative **9**.[12]



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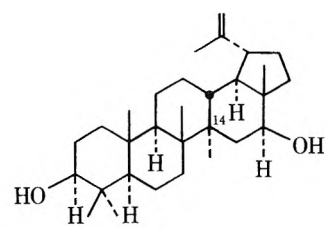

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Experimental Section[13]

Hallol (1):[2] mp 204°; $[\alpha]^{20}D$ +18.7° (*c* 0.14, EtOH); ir (KBr) OH 3300–3620 cm^{-1} (m); ^1H NMR (methanol-d_4) δ 0.82, 0.87, 0.97 (s, 3 each, methyls), 3.02, 3.33 (AB pair of d, 1 each, J = 9.0 Hz, OCH_2), 3.67 (t, 1, J = 7.0 Hz, OCH), 5.32 (broad s, 1, olefinic H); MS *m/e* 338 (rel intensity) (M^+, 4), 277 (base), 276 (28), 259 (80), 241 (30), 229 (38), 121 (80).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.87; H, 10.08.

Aldehyde 2a. A mixture of 50 mg of hallol (**1**) and 35 mg of finely powdered periodic acid (H_5IO_6) in 5 ml of 95% ethanol was stirred at room temperature for 4 hr. Saturated sodium bicarbonate solution (1 ml) was added, the mixture was filtered, and the residue was washed with ethanol. The combined washings and original solution were evaporated to dryness and the solid residue washed exhaustively with water and extracted with chloroform. The extract was dried over magnesium sulfate and evaporated, leaving 41 mg of aldehyde **2a** as a colorless powder: mp 130.5–132.5°; ir ($CHCl_3$) OH 3690 (m), 3620 (m), 3460 (m), C=O 1720 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 0.85, 0.87, 1.10 (s, 3 each, methyls), 3.06, 3.39 (AB pair of d, 1 each, J = 11.0 Hz, OCH_2), 3.74 (t, 1, J = 8.0 Hz, OCH), 5.28 (s, 1, olefinic H), 9.20 (s, 1, aldehydic H); MS *m/e* (rel intensity) 306 (M^+, 2), 288 (2), 276 (12), 258 (10), 21 (base). Anal. *m/e* 306.2207 (calcd for $C_{19}H_{30}O_3$, 306.2194).

Diene 2b. A 2.0 *M* solution of *n*-butyllithium (0.60 ml) in hexane was added over a 10-min period with stirring to a mixture of 429 mg of methyltriphenylphosphonium bromide [dried at 70° (0.1 Torr) for 2 hr and then over phosphorous pentoxide at 25 ° (0.2 Torr) for 2 hr] in 6.5 ml of tetrahydrofuran (distilled from lithium aluminum hydride onto 4A molecular sieves) under nitrogen at room temperature. After the mixture had been stirred for an extra

15 min a solution of 57 mg of crude aldehyde **2a** in 5.5 ml of dry tetrahydrofuran was added quickly. Upon further stirring at room temperature for 30 min the mixture was refluxed for 4 hr, then diluted with 75 ml of ether and filtered through Celite. The filtrate was evaporated under vacuum and the residue rinsed thoroughly with water and extracted with ether. The extract was dried over magnesium sulfate and evaporated. The solid residue was purified by two successive preparative TLC operations on silica gel (one by elution with chloroform and the second with ether). Crystallization of the colorless solid, 45 mg, from ether yielded colorless needles of diene **2b**: mp 192–193.5°; $[\alpha]^{24}D$ +10.3° (c 1.6, EtOH); ir ($CHCl_3$) OH 3670 (w), 3615 (m), 3450 (m), C=C 1631 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 0.84, 0.88, 1.04 (s, 3 each, methyls), 3.12, 3.39 (AB pair of d, 1 each, J = 11.0 Hz, OCH_2), 4.65, 4.69, 4.71, 4.74, 4.87, 4.90, 4.95, 4.98, 5.49, 5.64, 5.78, 5.93 (ABX lines, 3, vinyl H's), 5.18 (broad s, 1, nuclear olefinic H); MS *m/e* (rel intensity) 304 (M^+, 9), 286 (40), 256 (33), 187 (100). Anal. *m/e* 304.2399 (calcd for $C_{20}H_{32}O_2$, 304.2401).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.75; H, 10.46.

Registry No.—**1**, 56816-57-0; **2a**, 56783-50-7; **2b**, 56783-51-8.

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(12) E. Wenkert, G. V. Baddeley, and I. R. Burfitt, unpublished observation.
(13) Proton-decoupled and single-frequency off-resonance decoupled ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.20 MHz in the Fourier transform mode. The δ values portrayed on formulas **3–7** are from the literature in parts per million downfield from Me_4Si.

Preparation of Mono- and Diiodocyclopropene

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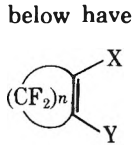
A variety of methods used for the preparation of mono- and diiodoperfluorocycloalkenes possessing the general structure shown below have been previously reported.[1-3]



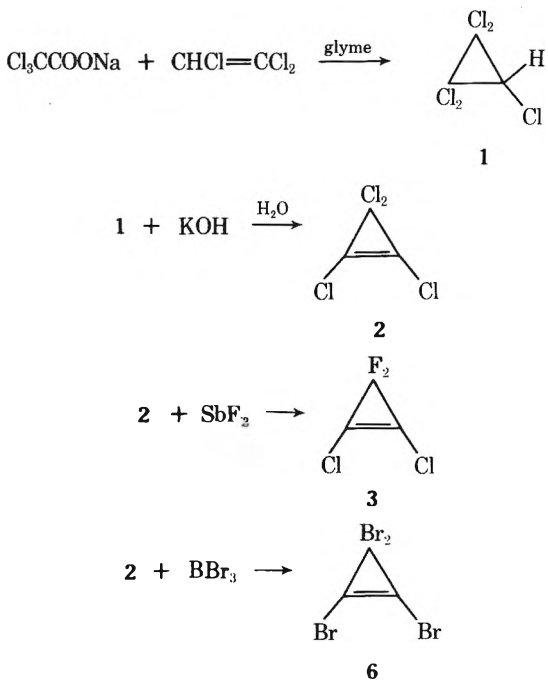
X = Cl or I
Y = I
n = 2, 3, 4,

These perfluorovinyl iodides have shown unique synthetic utility in copper coupling reactions[4,5] and in the preparation of various organometallic derivatives.[6,7]

Previous attempts to prepare the iodo derivatives of the highly strained cyclopropene system (where n = 1) have been unsuccessful.[8] Although many perhalocyclopropenes have been prepared, including tetrabromocyclopropene,[9] a recent report indicated that iodocyclopropenes are expected to be very unstable.[10]

We wish now to report on a facile synthesis of 1-chloro-2-iodo-3,3-difluorocyclopropene (**5**) and 1,2-diiodo-3,3-difluorocyclopropene (**4**). These compounds are readily distilled under vacuum and darken slowly on standing and exposure to sunlight. Studies on the reactions of **4** and **5** with copper powder and various nucleophiles are being investigated and will be reported in another paper.

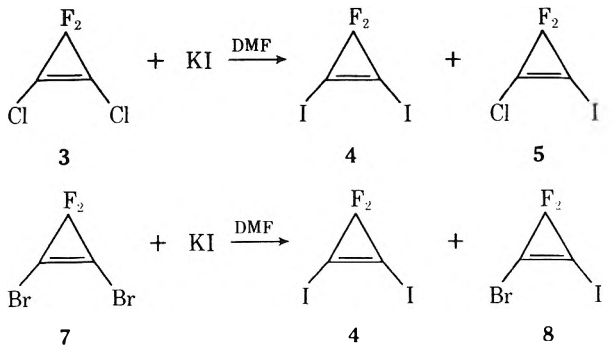
The method of Tobey and West[9] was used to prepare 1,2-dichloro-3,3-difluorocyclopropene (**3**). We have introduced several changes in this procedure which have increased the overall yield of **3** eightfold. The principal changes occur in the first and third step below.



The yield of pentachlorocyclopropane (**1**) was doubled by employing approximately half the quantity of glyme previously suggested. This change causes the decomposition of sodium trichloroacetate to proceed more slowly; however, there are fewer by-products arising from the reaction of glyme with the generated dichlorocarbene.

A significant improvement in the reaction of tetrachlorocyclopropene (**2**) with SbF_3 has been obtained by using freshly sublimed SbF_3. The reaction initiates at a much lower temperature and the distillate contains nearly pure **3** in 76% yield. Sublimed SbF_3 permits only trace amounts of the monofluoro product (3-fluoro-1,2,3-trichlorocyclopropene) to be formed even when **2** is used in excess. This would tend to give further support to a proposed intermediate involving both allylic chlorine atoms of **2** and three fluorine atoms in a tight coordination sphere around a pentacoordinated antimony.[9]

Previous studies on the reaction of anhydrous KI with 1,2-dichloroperfluorocycloalkenes in DMF indicated that the degree of substitution, yields, and reaction rates were largely determined by ring size or strain energies of the perfluorocycloalkene.[1] It was not surprising to observe that **3** reacted with KI in DMF at room temperature.



The monoiodide **5** was obtained in a 57% yield by allowing **3** and KI (1:1.2 molar ratio) in DMF to react overnight at room temperature. By contrast, the corresponding cyclopentene and cyclohexene with KI (1:2 molar ratio) gave only 45 and 9% of the monoiodides after 19 and 134 hr reflux, respectively. Cyclobutene gave 36% mono- and 26% diiodides after 5 hr reflux under similar conditions.[1]

When the molar ratio of **3** to KI was changed to 1:5 only the diiodide **4** was isolated in a 60% yield. A similar reaction using 1,2-dibromo-3,3-difluorocyclopropene (**7**) and KI in a 1:5 ratio gave the diiodide **4** in an 87% yield. Using a 1:1.5 ratio of the dibromide **7** and KI gave a 60% yield of 1-bromo-2-iodo-3,3-difluorocyclopropene (**8**) and a small quantity of the diiodide **4**. These compounds could not be separated by simple distillation and required preparative VPC to isolate a pure sample of **8**.

The ir spectra of the 1,2-dihalo-3,3-difluorocyclopropenes are quite similar, showing only five principal absorptions. The carbon–carbon double bond stretch appeared as a weak band from 1729 cm^{-1} for **5** down to 1656 cm^{-1} for **4**. This band is absent in 1,2-dichloro-3,3-difluorocyclopropene; however, it is found at the highest recorded value in perfluorocyclopropene (1945 cm^{-1}).[11]

The other principal bands of 1,2-dihalo-3,3-difluorocyclopropenes appeared at 1310 ± 30, 1090 ± 25, 835 ± 15, and 725 ± 30 cm^{-1}. These bands form a smooth linear relationship when the position of their absorption is plotted against the sum of the square root of the molecular weight of the halogen atoms in the 1 and 2 position of cyclopropene.

The mass spectra of **4**, **5**, and **8** are similar to the spectra reported previously for bromo- and chlorotrifluorocyclopropene.[10] The base peaks appear as the trihalopropenium ion produced through the preferential loss of bromine or iodine from a vinylic position and not through loss of fluorine from the allylic position.

The ^{19}F NMR spectra for **4**, **5**, and **8** showed only a sharp singlet arising from the geminal fluorine atoms in the allylic position. Their values are shifted slightly from those reported earlier for 1,2-dichloro-3,3-difluorocyclopropene.[10]

Experimental Section

Commerically available trichloroethylene, dimethylformamide, and glyme (1,2-dimethoxyethane) were dried and purified according to known procedures.[12] Antimony trifluoride (PCR, Inc.) was freshly sublimed (220°, 0.03 mm) prior to each reaction. All temperatures are uncorrected. Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo. Fluorine NMR were obtained on a Varian 56/60 using F-11 as an internal standard. The mass spectra were obtained on a Du Pont 21-491 instrument and the ir spectra were obtained on a Beckman IR-8 and calibrated at 1601.0 cm^{-1}.

Pentachlorocyclopropane (1). A slurry of sodium trichloroacetate (350 g, 1.89 mol) in 1300 ml of trichloroethylene was mechanically stirred and heated to gentle reflux for 3 hr. During this time approximately 0.1 ml of H_2O was collected in a Dean-Stark trap. The water trap was removed and 200 ml of glyme was added. The mixture was heated to gentle reflux (92–94°) for 5 days. Evolution of CO_2 was slow and uniform during this period. The reaction mixture was washed repeatedly with water, dilute HCl, and finally water and then dried over $CaCl_2$. The excess trichloroethylene was removed by fractional distillation and the higher boiling residue distilled under vacuum. The fractions boiling between 80 and 85° (31 mm) gave 189 g (47%) of **1**, $n^{34.0}D$ 1.5110 [lit.[9] bp 57° (7 mm), $n^{27.5}D$ 1.5170].

Tetrachlorocyclopropene (2). To a solution of 35.5 g of 95% KOH in 40 ml of water was added 50.0 g (0.233 mol) of **1**. The two-phase mixture was stirred slowly and heated to 75° where a spontaneous reaction initiated. The heat was removed and the temperature rose to 88° where it was maintained by occasional ice cooling. After 25 min the mixture was cooled to 50° and 50 ml of ice water and then 25 ml of cold concentrated HCl were added. The organic layer was taken up in CH_2Cl_2, washed with water, and dried ($CaCl_2$). Fractionation of the CH_2Cl_2 extracts gave 32.0 g (77%) of **2**, bp 71–72° (98 mm). $n^{21.0}D$ 1.5054 [lit.[9] bp 130–131° (745 mm), $n^{25.0}D$ 1.5065].

1,2-Dichloro-3,3-difluorocyclopropene (3). Antimony trifluoride (20.0 g, 0.112 mol) and 15.0 g (0.084 mol) of **2** were placed into a 25-ml flask fitted with a 150-mm Vigreux column and distillation head. The reaction mixture was heated to 110–115° over a 40-min period during which time 9.3 g (76%) of a colorless liquid (bp 58–61°) collected in an ice-cooled receiver. Chilled water was circulated through the distillation head condenser. Analysis by VPC of the distilled product indicated that it was essentially pure **3**, $n^{26.0}D$ 1.4045 [lit.[9] bp 60° (733 mm), $n^{25.0}D$ 1.4032].

1,2-Diiodo-3,3-difluorocyclopropene (4). A solution of 28.6 g (0.172 mol) of KI in 78 ml of DMF was cooled to 19° and 5.0 g (0.034 mol) of **3** was added dropwise. After stirring at room temperature for 1.5 hr the mixture was heated to 70° for 5 hr and then left overnight at room temperature. The darkened mixture was diluted with water and then steam distilled and the distillate extracted with CH_2Cl_2. The combined extracts were dried ($CaCl_2$) and fractionated, yielding 6.8 g (60%) of **4**: bp 82–85° (35 mm); $n^{25}D$ 1.5920; ir (neat film) 1656 w, 1280 s, 1065 s, 819 s, and 694 cm^{-1} s; MS *m/e* 328 (M^+), 309, 278, 201 (base peak), and 74. The ^{19}F NMR spectrum gave a singlet at 100.5 ppm upfield from F-11 (Cl_3CF).

Anal. Calcd for $C_3F_2I_2$: C, 10.98; F, 11.59; I, 77.41. Found: C, 11.19; F, 11.90; I, 76.85.

1-Chloro-2-iodo-3,3-difluorocyclopropene (5). Compound **3** (12.0 g, 0.0828 mol) was added to a solution of 16.49 g (0.0994 mol) of KI in 50 ml of DMF at 18° and then allowed to warm to room temperature overnight. The mixture was steam distilled and the distillate extracted with CH_2Cl_2. The $CaCl_2$-dried extracts were fractionally distilled, yielding 11.1 g (57%) of **5**: bp 64–65° (133 mm); $n^{24.0}D$ 1.4993; ir (neat film) 1729 m, 1300 s, 1080 s, 1080 s, 830 s, and 730 cm^{-1} s; MS *m/e* 238, 236 (M^+) 219, 217, 188, 186, 111, 109 (base peak), and 74. The ^{19}F NMR spectrum gave a singlet at 100.6 ppm upfield from F-11 (Cl_3CF).

Anal. Calcd for C_3F_2ClI: C, 15.24; F, 16.07; Cl, 14.99; I, 53.68. Found: C, 14.97; F, 16.07; Cl, 15.22; I. 53.27.

The small amount of undistilled liquid was principally **4**.

Tetrabromocyclopropene (6). The procedure of Tobey and West[9] was used to prepare **6**, bp 61–64° (1.1 mm), $n^{26.0}D$ 1.6348 [lit.[9] bp 70–95° (0.1–0.4 mm), $n^{25.1}D$ 1.6344].

1,2-Dibromo-3,3-difluorocyclopropene (7). Freshly sublimed SbF_3 (18.9 g, 0.105 mol) and 23.7 g (0.066 mol) of **6** were placed into a 25-ml flask and attached to a short-path distillation head. The mixture was heated to 118° for 30 min, during which time 12.6 g (81%) of almost pure **7** distilled over at 104°. A second distillation gave **7**, bp 104–105°, $n^{26.0}D$ 1.4752 [lit.[9] bp 105° (742 mm), $n^{25.0}D$ 1.4757].

Reaction of 7 with KI in DMF (1:5 Ratio). Compound **7** (5.00 g, 0.21 mol) was added to a solution of 17.7 g (0.106 mol) of KI in 50 ml of DMF at room temperature, causing the immediate appearance of a fine precipitate. The mixture was stirred at room temperature for 1.5 hr and then heated to 70° for 3 hr. Work-up of the reaction mixture was similar to that described for **4**. Distillation of the CH_2Cl_2 extracts gave 6.1 g (87%) of product, bp 82–83° (35 mm), whose ir spectrum was identical with that of **4**.

Reaction of 7 with KI in DMF (1:1.5 Ratio). Compound **7** (4.00 g, 0.0171 mol) was added to a solution of 4.25 g (0.0256 mol) of KI in 20 ml of DMF at 18° and then allowed to warm to room temperature. Total reaction time was 4.5 hr. Work-up in a manner similar to that described for **4** gave 3.5 g of a crude product (bp 76–100°, 79 mm) which was a mixture of **4** and 1-bromo-2-iodo-3,3-difluorocyclopropene (**8**). A second distillation of the mixture gave 2.9 g (60%) of nearly pure **8** which again contained small

amounts of 4. A VPC-purified sample (25 ft × 0.25 in. column containing 20% SF-1265 on Chromosorb W) gave pure 8: $n^{27.0}$D 1.5326; ir (neat film) 1708 w, 1290 s, 1070 s, 820 m, and 708 cm^{-1} m; MS *m/e* 282, 280 (M^+), 263, 261, 232, 230, 201 (base peak), 155, 153, 127, and 74. The ^{19}F NMR spectrum gave a singlet at 100.5 ppm upfield from F-11 (Cl_3CF).

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Registry No.—1, 6262-51-7; 2, 6262-42-6; 3, 6262-45-9; 4, 56830-73-0; 5, 56830-74-1; 6, 6262-43-7; 7, 6262-46-0; 8, 56840-75-2; sodium trichloroacetate, 2923-18-4; trichloroethylene, 79-01-6; antimony trifluoride, 7783-56-4; potassium iodide, 7681-11-0.

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Reaction of Xenon Difluoride with Polycyclic Aromatic Hydrocarbons. Fluorination of Pyrene

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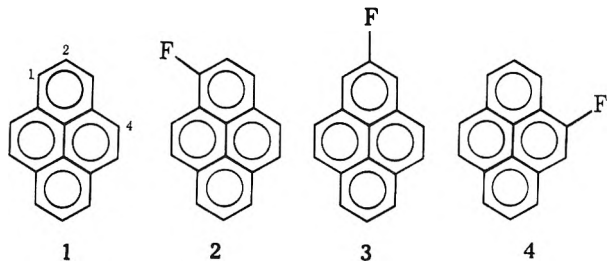
Fluorine-substituted condensed polycyclic aromatic hydrocarbons and heterocyclics are of interest in experimental carcinogenesis.[3–5] Heretofore, their syntheses were based mostly on the following two general methods. (a) A "tailor-made" sequence analogous to the one applied in a well-established synthesis of the corresponding polycyclic hydrocarbon, but with a fluorine-substituted starting material (e.g., 3-fluorophthalic anhydride,[6] 4-fluoro-1-bromonaphthalene[7]). (b) A direct electrophilic substitution of the polycyclic aromatic hydrocarbon followed by appropriate transformations of the substituent to fluorine[8] (e.g., ArH → $ArNO_2$ → $ArNH_2$ → $ArN_2^+BF_4^-$ → ArF and ArH → $ArSO_3H$ → ArOH → ArOCOF → ArF). In the latter method, the fluorine is usually introduced at the most reactive sites of the hydrocarbon. Neither method is very satisfactory. Direct methods for the introduction of a fluorine atom into polycyclic aromatics are still in their infancy. Recently, xenon difluoride has been shown to act as an efficient and selective fluorinating agent for simple aromatic compounds, both in solution and in the vapor phase.[9–14] The reaction is catalyzed by HF and does not proceed without it.[11,15] We report the application of this direct fluorination route in the aromatic polycyclic series. Pyrene (1) was selected as a model substrate for examining the mode of the reaction of xenon difluoride with polycyclic aromatic hydrocarbons. The convenience of pyrene stemmed from its high symmetry (point group D_{2h}), its tetracyclic structure, and the presence of three characteristic substitution sites (1, 2, and 4) which lend themselves readily to identification by ^{19}F NMR spectra (vide infra).



1 2 3 4

The reaction of xenon difluoride and pyrene was carried out in a vacuum line system as well as in an open system. Both experiments were performed under anhydrous conditions. The products were separated from the crude reaction mixture by column chromatography on silica gel.

The major monomeric products of the reaction (apart from the starting material 1), were 1-fluoropyrene (2, 16–22% yield) and 2-fluoropyrene (3, 11–14% yield). Fluorination at the 4 position apparently also occurred, albeit in very low yields. The *patterns* of the ^{19}F NMR absorptions served as a probe for identifying the site of the fluorination. The 1 isomer (2) showed a quartet (at 43.2 ppm, J_1 = 10.0, J_2 = 5.4 Hz) while the 2 isomer (3) showed a triplet (at 38.9 ppm, J = 9.2 Hz). Fluorination at the 4 position was indicated by a ^{19}F NMR doublet (at 42.1 ppm, J = 10.8 Hz). However, this product could not be purified and analyzed adequately and its structure [perhaps 4-fluoropyrene (4)] has not been established. The melting point of 2 was practically identical with that reported in the literature.[16] The melting point of 3 (147–148°) was very similar to that reported by Jensen and Berg (151–152°).[17] The structures of 2 and 3 were supported also by the elemental analyses and the appropriate molecular ions in the mass spectra. The 1 isomer (2) has previously been prepared by the conventional Balz–Schieman method.[16] Very low yields of 2 (as a picrate) were obtained also by a direct fluorination of pyrene with *p*-tolyl iododifluoride.[16] The 2 isomer (3) has previously been prepared by the use of cine substitution via a 1,2-dehydropyrene intermediate: 1-bromopyrene was converted to a mixture of 1- and 2-aminopyrene, the amines were separated, and 2-aminopyrene was transformed by the Balz–Schieman method to 3.[17,18] The fluorination of pyrene with xenon difluoride yielded also appreciable amounts (ca. 25%) of "dimeric" products [$(C_{16}H_9)_2$, $C_{16}H_8F)_2$, $C_{16}H_8F$–$C_{16}H_9$ (?), prominent mass spectral signals at *m/e* 438, 420, and 402] which were not further characterized. It should be noted that comparable results were obtained in an open system and in a vacuum line system. Furthermore, the XeF_2/pyrene ratio did not affect the yields of the various substitution products of the reaction.

The mass spectra of some fractions obtained from the chromatography, including the impure 4-fluorination product, indicated the formation of difluoropyrene isomers, but these could not be separated and characterized. It has recently been reported that xenon difluoride adds fluorine to the phenanthrene system to form vicinal difluorides.[19]

The relative yields of 2 and 3 are exceptional, in view of the overwhelming preference of position 1 as the initial site of electrophilic substitutions of pyrene.[18,20–21] It may reflect the lower degree of selectivity of the attacking species.

The direct fluorination of pyrene with xenon difluoride widens the scope and generality of this fluoroaromatic syn-

thesis: it illustrates the applicability of this straightforward route to the synthesis of fluorine-substituted polycyclic aromatic hydrocarbons. The versatility of the reaction is manifested by the feasibility of directing the reaction to conventional as well as unconventional sites of substitution, thus leading to novel fluoropolycyclic aromatic compounds.

Experimental Section

Melting points were taken on a Tottoli Buchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer in KBr disks. Ultraviolet spectra were recorded on a Unicam Model SP800A spectrophotometer. The ^1H and ^{19}F NMR spectra were taken on a Varian HA-100 spectrometer at 100 and 94.1 MHz, respectively. ^1H chemical shifts are reported in parts per million downfield from Me_4Si (internal standard). ^{19}F chemical shifts are reported in parts per million downfield from C_6F_6 (internal standard). Mass spectra were measured on a Varian MAT-311 instrument operating at 70 eV, employing the direct insertion technique. The mass spectra of the compounds reported below contained the appropriate signals representing the molecular ions. Analytical TLC separations were carried out at 24° on precoated plastic sheets (layer thickness 0.2 mm), Polygram Sil N-HR/UV$_{254}$ and Polygram Alox N/UV$_{254}$ (Machery-Nagel and Co.). Materials were detected with uv light. Pyrene (1) was obtained from Fluka AG (Buchs, Switzerland) and was further purified by recrystallization [dichloromethane–petroleum ether (bp 40–60°)]. Xenon difluoride was prepared by thermal means from xenon and fluorine, according to the procedure of Schreiner et al.[22] No special precautions were taken to purify the XeF_2 completely from HF.

Fluorination of Pyrene with Xenon Difluoride. Method A. Reaction in a Vacuum Line System. Xenon difluoride (0.90 g, 5.3 mmol) was transferred to a Kel-F tube. A solution of pyrene (1, 2.18 g, 10.7 mmol) in 10 ml of dry dichloromethane was introduced into a second Kel-F tube. Both tubes were connected via a flexible Kel-F line. The tube containing the organic solution was degassed by the freeze–thaw technique until a pressure change after freezing to −125° was $<10^{-4}$ mm. The tube containing the XeF_2 was cooled to −78° and evacuated to 10^{-4} mm. The organic solution was then poured under vacuum into the Kel-F tube containing the XeF_2 at −195°. Upon warming to −125° no reaction was observed. Upon warming to −78°, the colorless reaction mixture turned dark blue, and xenon evolution was indicated. The reaction tube was occasionally shaken until the evolution of xenon ceased. After 8 hr the reaction appeared to be completed. The mixture was diluted with dichloromethane (50 ml), washed successively with aqueous sodium bicarbonate (5%, 20 ml) and water, and dried (Na_2SO_4), and the solvent was evaporated to dryness under vacuum. The remaining oily crude product was chromatographed on a column of silica gel, petroleum ether (bp 40–60°) serving as an eluent. The following compounds were isolated.

1-Fluoropyrene (2): mp 135–136° (from petroleum ether) (lit.[16] mp 136–137°); yield 16%; R_f (silica gel, petroleum ether) 0.72. Anal. Calcd. for $C_{16}H_9F$: C, 87.27; H, 4.09; F, 8.63. Found: C, 86.81; H, 4.32; F, 8.55. Uv max (cyclohexane) 233 nm (log ϵ 4.58), 242 (4.78), 264 (4.34), 274 (4.53), 297 s (3.48), 308 (3.87), 322 (4.19), 338 (4.34), 358 (3.11), 361 s (3.06) 369 (2.72), 378 (3.01), and 382 (3.00); ir max (KBr) 2930, 1602, 1498, 1460, 1438, 1250, 831, and 707 cm^{-1}; ^{19}F NMR δ ($CDCl_3$)[23] 43.2 ppm (q, $J_1 = 10.0$, $J_2 = 5.4$ Hz).

2-Fluoropyrene (3): mp 147–148° (from ethanol) (lit.[17] mp 151–152°); yield 11%; R_f (silica gel, petroleum ether) 0.76. Anal. Found: C, 87.00; H, 4.05; F, 8.55. Uv max (cyclohexane) 233 nm (log ϵ 4.62), 242 (4.86), 252 s (4.38), 338 (4.45), 358 (3.21), 370 (2.78), 378 (3.22), and 382 (3.02); ir max (KBr) 2927, 1598, 1490, 1452, 1435, 1248, 830, and 703 cm^{-1}; ^{19}F NMR δ ($CDCl_3$) 38.8 ppm (t, $J = 9.2$ Hz).

4-Fluorination Product: mp 142–144° (from petroleum ether); yield 0.7%; R_f (silica gel, petroleum ether) 0.78; uv max (cyclohexane) 234 nm (log ϵ 4.03), 243 (4.23), 262 (3.75), 273 (3.97), 296 (3.08), 308 (3.40), 322 (3.76), 337 (3.96), 343 s (2.42), 361 s (2.63), 366 (2.79), 380 (2.70), and 386 (2.92); ir max (KBr) 2920, 1600, 1500, 1452, 1438, 1283, 1250, 1070, 832, and 702 cm^{-1}; ^{19}F NMR δ ($CDCl_3$) 42.1 ppm (d, $J = 10.8$ Hz).

Pyrene–Fluoropyrene Dimers. These were eluted from the column with petroleum ether–ether mixtures, mp ca. 268°, yield ca. 25%.

Fluorination of Pyrene with Xenon Difluoride. Method B. Reaction in an Open System. A solution of pyrene (1, 2.446 g, 14.1 mmol) in dry dichloromethane (16 ml) was added, at −75°C under anhydrous conditions, to xenon difluoride (2.38 g, 14.1 mmol) in a Kel-F tube. The raction mixture, which immediately turned dark blue, was occasionally shaken, and xenon evolution was observed. After 6 hr, the reaction seemed to be completed. The reaction complex was diluted with dichloromethane (50 ml) and decomposed with aqueous sodium bicarbonate (5%). The organic layer was washed with water and dried (Na_2SO_4) and the solvent was removed under vacuum. The remaining oily crude product was chromatographed as described above (method A). Yields: 2, 22%; 3, 14%; 4-fluorination product, 0.9%; "dimers", ca. 25%.

Registry No.—1, 129-00-0; 2, 1691-65-2; 3, 1714-25-6; 4, 56744-05-9; xenon difluoride, 13709-36-9.

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Fluorination with Xenon Difluoride. The Reactivity of Phenanthrene

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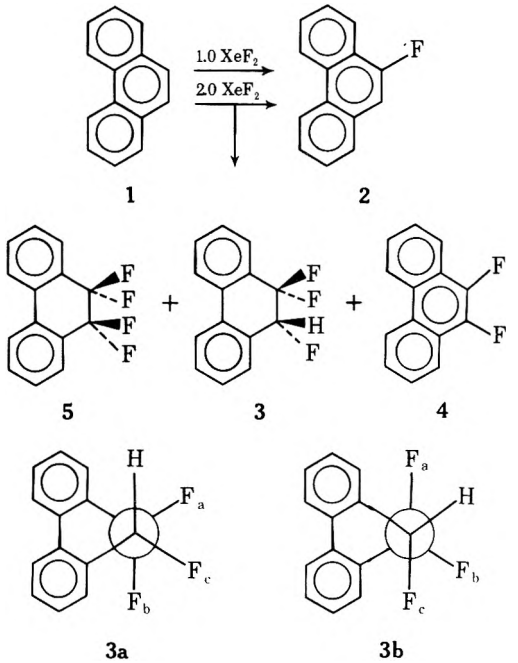
Recently, we have found that xenon difluoride readily adds fluorine to 1,1-diphenylethylenes[1] and stilbene[2] in hydrogen fluoride catalyzed reactions to form the corresponding vicinal difluorides in high yield. Although the fluorination of benzene[3,4] and its substituted derivatives[5,6] has been investigated, there has been, up to now, no report of a similar fluorination of a polynuclear aromatic system with this reagent. Phenanthrene is well known to undergo addition across the 9,10 positions accompanying substitution in chlorination[7] and bromination.[8] It seemed to us, therefore, of interest to explore whether the addition of fluorine will compete with the substitution in the fluorination of this ar-

omatic system with xenon difluoride. We now report the results of such a study.

A 3-hr reaction of phenanthrene (1) with 1.0 molar equiv of XeF_2 and anhydrous HF as catalyst in methylene chloride at 25°C gave a reaction mixture from which two pure products could be separated by preparative GLC. One of them, obtained in 30% yield, was identified with unreacted 1 and the second one with 9-fluorophenanthrene[9] in 60% yield.

A 24-hr reaction of 1 with 2.0 molar equiv of XeF_2 gave an oily reaction mixture. Its mass spectrum showed prominent peaks at *m/e* 196, 214, and 234 and a low intensity at *m/e* 252 indicating the presence of mono-, di-, tri-, and tetrafluoro compounds. Preparative GLC afforded four pure products. One of them was identified with **2** (in 46% yield) and the second one with 9,9,10,10-tetrafluoro-9,10-dihydrophenanthrene[10] (**5**). The third, oily product, obtainable in only 3% yield, was assigned the structure of 9,10-difluorophenanthrene (**4**) on the basis of its spectral data. The structure assignment of the fourth reaction product, i.e., 9,10,10-trifluoro-9,10-dihydrophenanthrene (**3**), a colorless oil (20% yield), was made on the basis of its ^1H and ^{19}F NMR and mass spectrum. As presented in Table I, the 9 proton is coupled to one geminal and two unequivalent vicinal fluorine nuclei. Following the Karplus equation[11] for $^3J(H\text{-}F_{vic})$ dependence of dihedral angle, $J_{HF_b} \neq J_{HF_a}$ should be observed for the conformation **3a** and $J_{HF_b} = J_{HF_a}$ for **3b**. The obtained values, i.e., 12.0 and 5.2 Hz, therefore strongly support the preferred conformation **3a** for **3** in CCl_4 solution at room temperature.



The mass spectra of **3** and **5** are also of interest, the loss of a CF_2X· (X = H, F) radical being most notable (25 and 17% relative abundance for X = H and X = F, respectively) at 70 eV. A rationalization, similar to that proposed for CH_3 radical loss from 9,10-dihydrophenanthrene[12] via a fluorene intermediate (**6**), might be proposed.

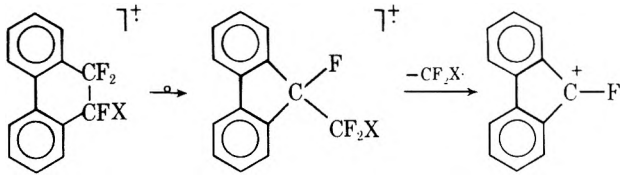


Table I
NMR Data for Compound 3[a]

∂H 5.32 (ddd, 1 H)	$J_{F_aH} = 5.2$ Hz
∂F_a −121.5 (ddd, 1 F)	$J_{F_bH} = 12.0$ Hz
∂F_b −132.0 (ddd, 1 F)	$J_{F_aF_c} = J_{F_bF_c} = 16.5$ Hz
∂F_c −215.8 (dt, 1 F)	$J_{F_cH} = 50$ Hz $J_{F_aF_b} = 276$ Hz

[a] 94.1 MHz (CCl_4), Me_4Si or CCl_3F as internal standard.

The fluorination of 9-fluorophenanthrene (**2**) with 1.0 or 2.0 molar equiv of XeF_2 under the same reaction conditions gave **3** and **5** in higher yields, but the amount of **4** did not exceed 5%.

All our efforts to detect the primary addition product, i.e., 9,10-difluoro-9,10-dihydrophenanthrene, were unsuccessful. This addition product was either not formed at all or decomposed so rapidly during the reaction or isolation that it had escaped our method of analysis. However, the formation of **3** and **5** clearly showed that addition of fluorine took place with **2** and **4**. The rather high reactivity of **4** for the further addition of fluorine is probably the reason for its low presence in the reaction mixtures. This phenomenon we also observed in the fluorination of phenylacetylenes with XeF_2,[13] as we could not detect the primary adducts, i.e., the corresponding fluoro olefins thus appeared also to be more reactive toward the addition of fluorine than the parent phenylacetylenes. The possibility of the formation of **4** by the elimination of hydrogen fluoride from **3** was also ruled out, because under the reaction and the isolation conditions an authentic sample of trifluoro compound **3** did not give a detectable amount of **4**.

Although the addition of fluorine to the phenanthrene system and the accompanying substitution were clearly evidenced, work is in progress to elucidate the mechanism of fluorination with xenon difluoride, which appears to be more complex in comparison to chlorination[7] and bromination[8] of this aromatic system.

Experimental Section

Ir spectra were recorded by using a Perkin-Elmer 257 spectrometer, ^1H and ^{19}F NMR spectra by a Jeol JNM-PS-100 from CCl_4 solution with Me_4Si as internal standard, and mass spectra were recorded on a CEC 21-110C spectrometer. Melting points were determined on a Kofler apparatus and are uncorrected. Gas–liquid partition chromatography was carried out on Varian Aerograph Model 1800.

Materials. The phenanthrene was obtained from commercial sources and purified to conform with published physical and spectral data. Xenon difluoride was prepared by the photosynthetic method[14] and its purity was better than 99.5%. Methylene chloride was purified by literature methods[15] and stored over molecular sieves. Hydrogen fluoride of Fluka Purum quality was used.

9-Fluorophenanthrene (2). To a solution of **1** (0.178 g, 1.0 mmol) in methylene chloride (6 ml), XeF_2 (0.169 g, 1 mmol) was added at 25°C and under stirring anhydrous HF (0.02 g, 1 mmol) was introduced intc the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was slowly evolved. After 3 hr gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 ml), washed (10 ml of 5% aqueous $NaHCO_3$), and dried (Na_2SO_4) and solvent was evaporated in vacuo. The crude product was separated by preparative GLC (10% Carbowax 20M on Varaport 30, 210°C). Unreacted phenanthrene was isolated in 30% yield and 9-fluorophenanthrene (**2**) in 60% yield (0.1176 g): mp 51–52°C; ^{19}F NMR (94.1 MHz, CCl_4) δ −138.0 (dd, J_{HF} = 12.8 and 2.3 Hz), high-resolution mass spectrum *m/e* 177.0693 $(M - F)^+$ (calcd for $C_{14}H_9$, 177.0704).

9-Fluorophenanthrene (2), 9,9,10,10-Tetrafluoro-9,10-dihydrophenanthrene (5), 9,10-Difluorophenanthrene (4), and 9,10,10-Trifluoro-9,10-dihydrophenanthrene (3). To a solution of 1 (0.356 g, 2 mmol) in methylene chloride (15 ml), XeF_2 (0.677 g, 4 mmol) was added at 25°C and under stirring HF (0.080 g, 4 mmol) was introduced into the reaction mixture. After a few sec-

onds the colorless solution turned dark blue and xenon gas was slowly evolved. After 24 hr gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (30 ml), washed (20 ml of 5% aqueous $NaHCO_3$), and dried (Na_2SO_4) and solvent was evaporated in vacuo. The crude product was separated by preparative GLC (10% Carbowax 20M on Varaport 30, 210°C) and afforded as pure products the following.

9-Fluorophenanthrene (**2**) in 46% yield (0.180 g).

9,9,10,10-Tetrafluoro-9,10-dihydrophenanthrene (**5**) in 10% yield (0.050 g): mp 95–96°C; ^{19}F NMR (94.1 MHz, CCl_4) δ −134.2 (s); high-resolution mass spectrum *m/e* 176.0582 $(M - 4F)^+$ (calcd for $C_{14}H_8$, 176.0626).

9,10-Difluorophenanthrene (**4**), oily product in 3% yield (0.0128 g): ^{19}F NMR (CCl_4) δ −169.5 (s); mass spectrum *m/e* 214 (100%), 107 (9), 98 (11); high-resolution mass spectrum *m/e* 214.0574 (M^+) (calcd for $C_{14}H_8F_2$, 214.0603).

9,10,10-Trifluoro-9,10-dihydrophenanthrene (**3**), colorless oil in 20% yield (0.0936 g): mass spectrum *m/e* 234 (100%), 183 (25), 165 (6), 107 (6); high-resolution mass spectrum *m/e* 234.0631 (M^+) (calcd for $C_{14}H_9F_3$, 234.0669); NMR data are stated in Table I.

Acknowledgment. We thank Professor J. Slivnik for the XeF_2 and Professor J. Marsel for facilities. The financial assistance of the Boris Kidrič Foundation is acknowledged.

Registry No.—**1**, 85-01-8; **2**, 440-21-1; **3**, 56830-33-2; **4**, 56830-34-3; **5**, 14205-64-2; XeF_2, 13709-36-9.

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Direct Fluorination of Polycyclic Hydrocarbons with Xenon Difluoride

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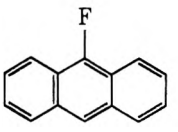
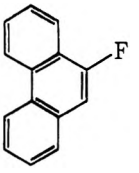
In previous papers[5] we described the usefulness of xenon difluoride for the introduction of fluorine into the aromatic nucleus. Recently, we reported[6] that aryl oxygen compounds undergo rapid nuclear fluorination with XeF_2, even in the absence of initiation by hydrogen fluoride.

We now report that this reaction has been extended to polynuclear aromatics, including naphthalene, anthracene, and phenanthrene. These compounds are converted with facility to monofluoro analogues which are not readily accessible by other means.[7] Although initiation is not required, the addition of a trace of HF leads to an immediate and vigorous reaction.

The fluoro isomers obtained in these reactions were identified by comparison of their gas chromatograms and mass spectra (interfaced) with those of authentic samples. Thus, naphthalene, in methylene chloride solution, was converted to a mixture of 1-fluoronaphthalene (50% yield) and 2-fluoronaphthalene (11%). Similarly, anthracene in chloroform reacted with XeF_2 to give a mixture of three isomers. Column chromatography on neutral alumina of the reaction mixture derived from 10 mmol of anthracene gave 9-fluoroanthracene (1,[8] 26%), 1-fluoroanthracene (45%),[9] and 2-fluoroanthracene (9%).[8] In analogous fashion and without addition of external HF, crystalline 9-fluorophenanthrene (**2**)[10] was isolated in 40% yield. In addition, a



1



2

higher melting yellow substance, decomposing at 181–182°, was obtained. Although this material has not yet been characterized, its mass spectrum suggests a difluorophenanthrene.

In a separate experiment, a small amount of anhydrous HF was added to a mixture of phenanthrene and XeF_2 in methylene chloride. Although no products could be isolated, mass spectral analysis indicated the formation of difluoro, trifluoro, and tetrafluoro addition products. Similar results have been reported by Zupan and Pollak.[11] Although these reactions were carried out in a vacuum line system,[5b] we have conducted several reactions with other substrates in an open system, with similar results. This adaptation markedly increases the attractiveness of this method.

As recently proposed,[6] we believe that the reaction proceeds via cation radicals which are readily generated, owing to the facile one-electron transfer from the aromatic to the strongly oxidizing $[XeF]^+$ species.

These observations, together with the recent findings on the fluorination of pyrene with XeF_2,[12] further extend the scope and potential of this unusual one-step fluorination of aromatic molecules.

Experimental Section

Materials. Xenon difluoride was prepared photosynthetically according to a procedure described previously.[6] Purified solvents and reagents of AR grades were used and handled under a dry nitrogen atmosphere. Melting points were determined on a Fisher-Johns block and are uncorrected. All gas chromatographic data were recorded on a Perkin-Elmer Model 900 instrument equipped with a flame ionization detector. Mass spectra were recorded on a Bendix time-of-flight instrument and some GC–MS data were obtained on a Finnegan Model 3000 instrument. All reactions were carried out in Kel-F tubes of about 30 ml capacity fitted with 0.25-in. brass valves[5] and under reduced pressure (10^{-5}–10^{-6} Torr). A small portion of the reaction mixture, when removed for GC or MS analysis, was always treated with sodium fluoride pellets to remove hydrogen fluoride produced during the course of the reaction. The remainder of the reaction mixture was dried under reduced pressure at room temperature to remove the solvents as well as HF.

Naphthalene and XeF_2. A solution of 1.47 g (11.5 mmol) of naphthalene in 15 ml of methylene chloride was degassed up to 5×10^{-6} Torr and poured into 0.63 g (ca. 3.7 mmol) of XeF_2 contained in an evacuated Kel-F tube (10^{-6} Torr) at −196°. The reaction mixture was warmed gradually from −196° to −78° to 0° and finally to room temperature during a period of 2 hr. A deep green coloration and the evolution of gas bubbles were observed while

the reaction mixture was allowed to warm to room temperature. The xenon which evolved was collected in a storage can and the resulting solution was distilled at 25° under vacuum into another Kel-F tube at −196°. Comparison of GC retention times of the distillate on a 12 ft × 0.125 in. column packed with 2.5% Apiezon L on Chromosorb W at 150° with those of authentic samples showed the formation of 1-fluoronaphthalene (50%) and 2-fluoronaphthalene (11%). Further analysis of the redistilled reaction mixture on a GC–MS instrument, using the same GC column, indicated that each peak consisted of a single component and had the correct parent ion mass and fragmentation pattern expected for the particular monofluoro substituted naphthalene. No attempt was made to separate the isomers physically from the reaction mixture. Some unreacted naphthalene was also found.

Reaction of Anthracene with XeF_2. A degassed solution of 1.78 g (10 mmol) of anthracene in 15 ml of chloroform up to 10^{-5} Torr was introduced into an evacuated (5×10^{-6} Torr) Kel-F tube containing 0.67 g (ca. 4.0 mmol) of XeF_2 at −196°. After the gradual increase of the temperature to −12°, a light yellow solution formed which intensified into a deep green by increasing the temperature to 12° during a period of 4 hr. The reaction products were filtered through a glass wool plug into another Kel-F tube under vacuum. The course of reaction as followed by GC, using an 11 ft × 0.125 in. column packed with 2.5% Carbowax 20 mesh on Chromosorb G at 225° indicated no unreacted anthracene and comparison of the data with those of authentic samples showed the formation of 1-fluoroanthracene, 2-fluoroanthracene, and 9-fluoroanthracene in the relative ratio of 5:1:3, based on their relative retention times. The mass spectra (interfaced with GC) were used to identify the three components and analysis of the fragmentation patterns and maximum mass peaks of each component allowed assignment of three of the peaks to monofluoroanthracenes. The distillate was concentrated almost to dryness under reduced pressure and chromatographed on an 18 × 1.5 in. column packed with neutral alumina. By eluting the column with *n*-hexane, 9-fluoroanthracene, mp 102° (lit.[8] 103°), was obtained as light lemon-colored crystals, which sublimed under vacuum at 78° (yield 26%), followed by pale yellow crystals of 1-fluoroanthracene, mp 108° (lit.[9] 108°), which sublimed in vacuo at 80° (yield 45%). Further elution with *n*-hexane–chloroform (3:1) gave yellow, crystalline 2-fluoroanthracene, mp 212° (lit.[8] 212°), which was crystallized from ethanol to give sublimable yellow crystals (yield 9%). An unidentifiable dark brown solid was obtained by eluting the column with *n*-hexane–$CHCl_3$ (1:1), while another deep pink material, which did not dissolve even in tetrahydrofuran and methanol, remained behind.

Reaction of Phenanthrene with XeF_2. XeF_2 (0.43 g) contained in a Kel-F tube was allowed to react with a degassed solution of 1.1 g (ca. 6 mmol) of phenanthrene in 10 ml of methylene chloride at 10^{-5} Torr at −196°. The solution was gradually warmed from −196° to room temperature during a period of 2 hr by means of a series of baths to give a brown-green reaction mixture which was further warmed in a water bath at 60° to ensure complete reaction. The course of reaction, followed by GC, using the same column described for the anthracene reaction mixture, indicated the presence of one fluoro derivative in addition to some unreacted phenanthrene.

The reaction mixture was freed from the solvent as well as HF under reduced pressure and the deep green solid was chromatographed on an 18 × 1.5 in. column packed with Florisil. Elution with *n*-hexane gave a 40% yield of a colorless, crystalline compound, 9-fluorophenanthrene, which was crystallized from petroleum ether (bp 30–60°) to give colorless needles, mp 50° (lit.[10] 51–52°). The rest of the material, on further elution with *n*-hexane–CH_2Cl_2 (10:3), gave a bright yellow substance which was crystallized from petroleum ether–$CHCl_3$ (1:1) to give a yellow compound which decomposed at 181–182° to a brown mass and presumably is a difluorophenanthrene as inferred from the highest mass fragment obtained in its MS, *m/e* 214 (100%), $C_{14}H_8F_2$.

In another experiment, 0.51 g (2.8 mmol) of phenanthrene and 8 ml of CH_2Cl_2 were allowed to react with 0.5 g (ca. 3 mmol) of XeF_2 under similar conditions in the presence of 0.05 mmol of anhydrous HF. On warming the reaction mixture to 0°, an intense green color developed, with brisk evolution of xenon gas. At room temperature, the mixture turned to dark magenta after 15 min. The course of reaction as followed by GC indicated the absence of any phenanthrene and no formation of any monofluoro species as found in the previous experiment. The MS interfaced with GC indicated the formation of difluoro, trifluoro, and tetrafluoro addition products of phenanthrene. However, no polyfluoro compounds could be isolated either by column chromatography or crystallization. A separate analysis of the fragmentation patterns and maximum mass peaks of each component permitted identification of the di-, tri-, and tetrafluoro compounds.

Acknowledgments. We wish to thank Drs. M. Studier and L. Kaplan for assistance with the mass spectra and gas chromatography, respectively. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support (to R.F.) of this research.

Registry No.—1, 529-85-1; 2, 440-21-1; naphthalene, 91-20-3; XeF_2, 13709-36-9; 1-fluoronaphthalene, 321-38-0; 2-fluoronaphthalene, 323-09-1; anthracene, 120-12-7; 1-fluoroanthracene, 7651-80-1; 2-fluoroanthracene, 21454-60-4; phenanthrene, 85-01-8.

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(2) Illinois Institute of Technology.
(3) 1972 Honors Research Program Participant.
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Reduction of Bromohydrins to Olefins with Low Valent Titanium

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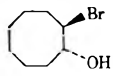
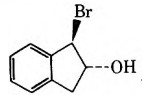
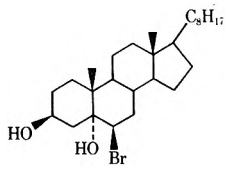
Although the reduction of bromohydrins to olefins is of some importance in synthesis, few direct methods have been devised to effect the reaction. To our knowledge, only the well-known zinc–acetic acid method has been used to any extent,[1] although chromous ion has been shown to be effective[2] and has been studied in some detail. Low valent tungsten halides also appear to work, but details are not available.[3]

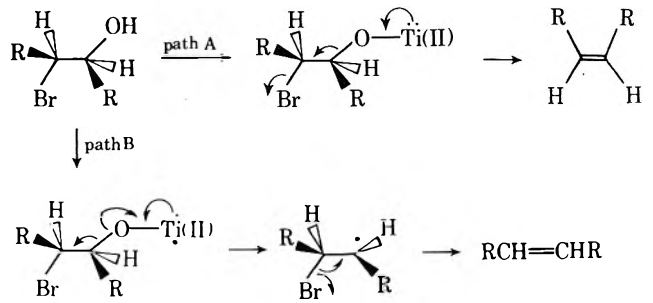
We have been involved recently in a study of low valent titanium reagents for use as reducing agents in organic synthesis,[4] and among the substrates we have examined have been some representative bromohydrins. We have found that a reagent prepared by mixing 1 molar equiv of $LiAlH_4$ with 0.25 molar equiv of $TiCl_3$ in tetrahydrofuran is extremely effective in reducing bromohydrins to olefins. Some of our results are given in Table I.

From a synthetic point of view, several comments should be made. The first is that all substrates studied reduced in high yields indicating the generality of the reaction. Second is the fact that the reaction conditions are nonacidic, making the method compatible with the presence of acid-sensitive functional groups and quite different from the other methods. Finally, we note from the reductions carried out on *erythro*- and *threo*-5-decene bromohydrins, that these reactions proceed with little stereoselectivity. In this respect, the results are similar to those obtained both with zinc[5] and with chromous ion.[2]

Table I
Reduction of Bromohydrins to Olefins with $TiCl_3$–$LiAlH_4$

	Yield, %
 → Cyclooctene	96
 → Indene	93
 → Cholesterol	79
2-Bromo-1-decanol → 1-Decene	74
2-Bromo-1-dodecanol → 1-Dodecene	91
erythro-5-Bromo-6-decanol → 5-Decene (4:1 trans/cis)	91
threo-5-Bromo-6-decanol → 5-Decene (2.3:1 trans/cis)	82

It had been our hope in initiating this study that titanium(II) might function as a two-electron reducing agent in the manner shown (path A). Should this occur, one would expect preferential trans elimination leading to specific olefin geometry (threo → cis; erythro → trans). Since this desired retention of geometry is not observed, however, we favor a mechanistic pathway involving one-electron transfer and the intermediacy of radicals, similar to that proposed for chromous ion[2] (path B).



Experimental Section

General Reaction Procedure. The reactive titanium(II) species was made in either of two ways.

Method A. $LiAlH_4$ (0.142 g, 3.75 mmol) was added to a stirred slurry of $TiCl_3$ (2.3 g, 15 mmol) in 70 ml of dry tetrahydrofuran (THF) under a nitrogen atmosphere. Hydrogen evolution was immediate, and the resulting black titanium(II) suspension was stirred for 10 min at room temperature before use.

Method B. Alternatively, a 4:1 premix of $TiCl_3$ and $LiAlH_4$[6] (effective mol wt 164, 2.46 g, 15.0 mmol) was added cautiously with stirring to 70 ml of dry THF at room temperature under a nitrogen atmosphere. The black titanium(II) suspension was stirred for 10 min before use.

The substrate bromohydrin (5.0 mmol) in 5 ml of THF was added to the Ti(II) suspension, and the reaction mixture was refluxed for 16 hr. After cooling, the reaction was quenched by addition of 60 ml of water, and then diluted with pentane. The organic layer was drawn off, washed with brine, dried ($MgSO_4$), and concentrated by distillation. Product yields were then determined by GLC using appropriate internal standards. Product identities were determined in all cases by comparison with authentic samples. In this manner, the following reactions were run.

***trans*-2-Bromocyclooctanol** gave **cyclooctene,** 96% as determined by GLC using indene as internal standard.

***trans*-1-Bromo-2-hydroxyindan** gave **indene,** 93% as determined by GLC using cyclooctene as internal standard.

6β-Bromo-3β,5α-dihydroxycholestane gave **cholesterol,** 79% isolated yield, mp 148° (lit. 148.5°).

2-Bromo-1-decanol gave **1-decene,** 74% as determined by GLC using 1-dodecene as internal standard.

2-Bromo-1-dodecanol gave **1-dodecene,** 91% as determined by GLC using 1-decene as internal standard.

***erythro*-5-Bromo-6-decanol** gave **5-decene,** 91% as determined by GLC using 1-decene as internal standard. The product 5-decene was analyzed for cis/trans composition by the following method (the cis and trans 5-decenes were inseparable by GLC under all conditions tried). Epoxidation of the olefin mixture with *m*-chloroperbenzoic acid ($CHCl_3$, room temperature) gave a mixture of isomeric epoxides which could be analyzed either by NMR integration [*cis*-5-decene epoxide, NMR (CCl_4) δ 2.91 (–CHO–, broad singlet); *trans*-5-decene epoxide, NMR (CCl_4) δ 2.67 (–CHO–, broad singlet)] or by GLC (12 ft × 0.25 in. 5% Carbowax 20M on Chromosorb P). A control experiment on a known cis/trans mixture established the validity of the analysis.

The 5-decene thus analyzed contained 80% trans olefin and 20% cis olefin.

***threo*-5-Bromo-6-decanol** gave **5-decene,** 82% as determined by GLC using 1-decene as internal standard. The product was 70 trans, 30% cis.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

Registry No.—*trans*-2-Bromocyclooctanol, 1502-14-3; *trans*-1-bromo-2-hydroxyindan, 56804-70-7; 6β-bromo-3β,5α-dihydroxycholestane, 1857-83-6; 2-bromo-1-decanol, 39579-74-3; 2-bromo-1-dodecanol, 56804-71-8; *erythro*-5-bromo-6-decanol, 56804-72-9; *threo*-5-bromo-6-decanol, 56804-73-0; cyclooctene, 931-88-4; indene, 95-13-6; cholesterol, 57-88-5; 1-decene, 872-05-9; 1-dodecene, 112-41-4; *trans*-5-decene, 7433-56-9; *cis*-5-decene, 7433-78-5.

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Stereochemistry of Hydride Reductions. Participation by Heteroatoms

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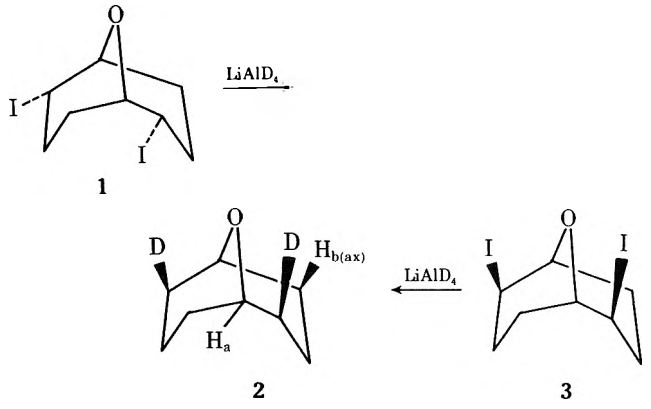
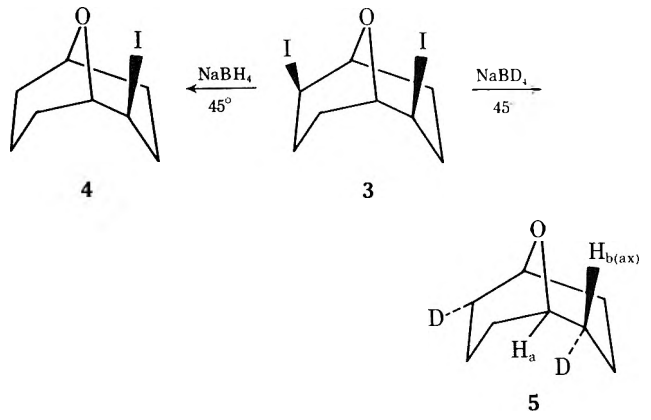
The reduction of alkyl halides with hydride ion is generally believed to occur by an SN2 mechanism leading to inversion of configuration. Studies using $LiAlD_4$, $NaBD_4$ in HMPA, and $LiEt_3BD$ have shown exclusive inversion in the absence of any secondary factors.[1,2] However, a recent example of nitrogen participation through complexing with the hydride reagent has resulted in retention of configuration.[3]

We have studied the $LiAlD_4$ reduction of the isomeric *endo,endo-* and *exo,exo*-2,6-diiodo-9-oxabicyclo[3.3.1]nonanes[4,5] (structures 1 and 3). In each case reduction led to an identical product identified as *exo,exo*-2,6-dideuterio-9-oxabicyclo[3.3.1]nonane (2) by NMR, ir, and mass spectroscopy. In particular, the infrared spectrum showed C–D absorptions at 2140 and 2160 cm^{-1} which correspond to values reported for axial C–D stretch in 1,3-dioxanes.[6] The NMR was studied in detail by use of $Eu(thd)_3$. The 9-oxabicyclononanes have been found to form strong shift com-



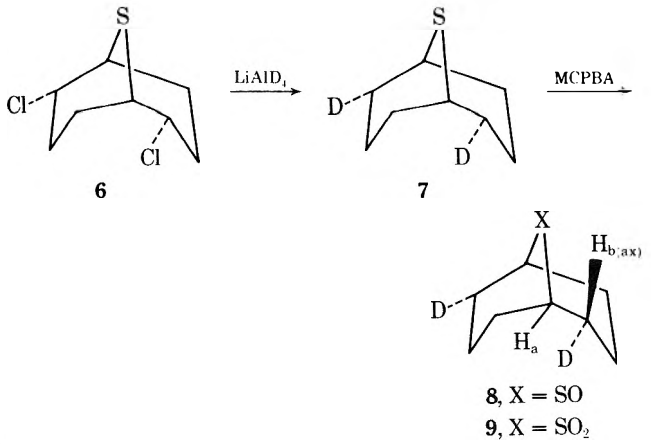
plexes ($\Delta Eu = 37$)[4] and it was possible to obtain individual peaks for all the protons of **2**. Thus integration of the shifted spectrum $H_a/H_{b(axial)}$ (2:2) provided clear evidence that the deuteriums were in the axial (exo) positions (Figure 1).

Reduction of the exo,exo diiodide **3** with $NaBH_4$ (1:1) in HMPA at 45° gives the monoiodide **4** while reduction with excess hydride gives 9-oxabicyclo[3.3.1]nonane. Use of $NaBD_4$ gives 2,6-dideuterio-9-oxabicyclo[3.3.1]nonane (**5**)



(mass spectrum and NMR). Analysis of the NMR with $Eu(thd)_3$ showed an $H_a/H_{b(axial)}$ ratio of 2:4 indicating that the deuteriums are in the equatorial (endo) positions. The results of the analysis for the location of the deuteriums become readily apparent when the shifted NMR spectra of the endo,endo diiodide **1**, *endo,endo*-dideuterio-**5**, and *exo,exo*-dideuterio-**2** are directly compared.

A similar reduction of *endo,endo*-2,6-dichloro-9-thiabicyclo[3.3.1]nonane (**6**) with $LiAlD_4$ was found to give exclusively *endo,endo*-2,6-dideuterio-9-thiabicyclo[3.3.1]nonane (**7**). For analysis **7** was converted into both the sulfoxide (**8**)



and the sulfone (**9**). Mass spectral data of the parent peak and major cleavage peaks (sulfone, P − SO_2; sulfoxide, P − O, P − SO) indicated the presence of two deuteriums while analysis of the NMR spectrum with $Eu(thd)_3$ showed the deuteriums to be in the equatorial (endo) positions. The sulfone **9** showed no change in the integrated ratio of the H_a to $H_{b(axial)}$ protons. The sulfoxide **8** spectrum was more complex because of the unsymmetrical nature of the structure and of its europium complex **10**.[8] Thus, the protons H_b

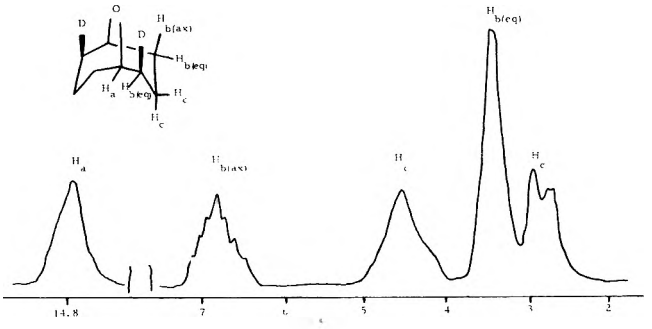
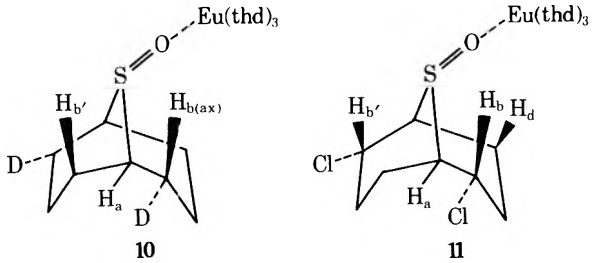
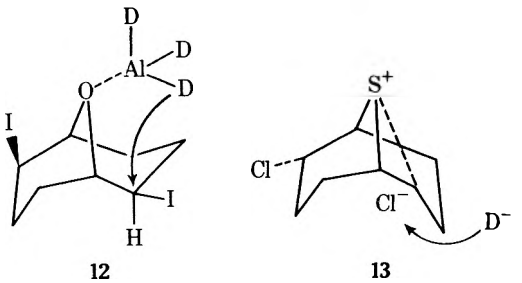


Figure 1. Europium-shifted spectrum of exo,exo-2,6-dideuterio-9-oxabicyclo[3.3.1]nonane.



axial are different from $H_{b'(ax)}$ and have a higher ΔEu value (8.0) than the H_a proton ($\Delta Eu = 5.0$). Integration of these protons showed an H_a/H_b ratio of 2:2 indicating that the deuteriums are not in the axial (exo) position (no change in this integration between deuterated and nondeuterated **10**). To further check these assignments, the europium-shifted spectrum of *endo,endo*-2,6-dichloro-9-thiabicyclo-[3.3.1]nonane 9-oxide (**11**) was studied.[7] The ΔEu values obtained follow: $H_a = 6.7$, $H_b = 11.7$, $H_d = 10.0$, $H_{b'} = 1.4$. Interestingly, proton H_d moves through both H_a and H_b with added amounts of $Eu(thd)_3$ and gives the correct proton ratios of H_d/H_b (1:1) and H_d/H_a (1:2). This behavior parallels that for the deuterated product (**10**) and supports the analysis.

The above results indicate that, in the presence of heteroatoms, hydride reduction can proceed with retention of configuration. The reduction of **3** requires a complex, whose exact nature is unclear, between the reagent and the bridging oxygen. A possible change in conformation of the ring to a pseudoboat conformation **12** with donation of deu-



teride from this intermediate, in which iodine is equatorial, could result in formation of **2**. Evidence for oxygen participation in hydride reactions has been found in the reduction of bonds in 7-*tert*-butoxynorbornadiene and similar compounds,[9] in 2-methoxy-1,3-dioxanes,[6] and in allylic ace-

tals.[10] The reduction of the endo,endo isomer 1 proceeds with inversion as expected, but it could also involve a prior oxygen complex. The $NaBD_4$ reduction in HMPA also proceeds with inversion with the exo,exo diiodide (3) and would not involve any complexation. These contrasting stereochemical results between $NaBD_4$ and $LiAlD_4$ thus support an oxygen–aluminum complex as an intermediate in the $LiAlD_4$ reductions.

All reported SN2 reactions of 6 proceed with retention of configuration through an episulfonium ion as an intermediate.[7] Thus a similar intermediate 13 could account for the observed retention in the hydride reduction of 6. The lack of rearrangement to the 9-thiabicyclo[4.2.1]nonane could be due to the stability of the episulfonium ion as well as the known thermodynamic stability of the bicyclo[3.3.1]nonane over the bicyclo[4.2.1]nonane.[4,11] In contrast to the oxa and thia cases, the aza analog, *endo,endo*-2,6-dichloro-*N*-methyl-9-azabicyclo[3.3.1]nonane, suffers 30% rearrangement to the [4.2.1] system.[12] The stereochemistry of this reduction is presently being investigated.

Experimental Section

Materials and Reactions. Ether was distilled from $LiAlH_4$ before use. The diiodides, 1 and 3, and the dichloride 6 were prepared from 1,5-cyclooctadiene as previously described and purified by recrystallization to the reported melting points.[4,5,7] The sulfone was prepared using acetic acid and hydrogen peroxide as reported[7] while the sulfoxide was prepared using *m*-chloroperbenzoic acid. The recrystallized products had the reported melting points.[7] The $LiAlD_4$ was purchased from Research Organic/Inorganic Corp., and the $NaBD_4$ from Ventron Corp. The analyses were done on a Varian EM-600 mass spectrometer, a Varian T-60 NMR spectrometer, and a Varian 1200 gas chromatograph. The reduction reactions were carried out on a 1-g scale with excess deuteride and worked up by standard procedures to give exclusively the products indicated. The 9-oxabicyclo[3.3.1]nonane was shown to be pure by GLC analysis at 105° on 10% CW-20M column.

Spectral Analysis. *exo,exo*-2,6-dideuterio-9-oxabicyclo[3.3.1]nonane (2): NMR δ 4.0 (2), 1–2.0 (10); MS *m/e* 128 (P); infrared 2140, 2160, 1490, 1030 cm^{-1}. *endo,endo*-2,6-Dideuterio-9-oxabicyclo[3.3.1]nonane (5): NMR δ 4.0 (2), 1–2.0 (10); MS *m/e* 128 (P). *exo*-2-Iodo-9-oxabicyclo[3.3.1]nonane (4): NMR δ 4.4 (1) ($W_{1/2}$ = 8, endo $W_{1/2}$ = 16 Hz), 4.0 (2), 2.8–1.0 (10); infrared 1490, 1028 cm^{-1}. *endo,endo*-2,6-Dideuterio-9-thiabicyclo[3.3.1]nonane 9-dioxide (9): NMR δ 1.4–3.05; MS *m/e* 176 (P), 112 (P − SO_2); infrared 2920 w, 1280, 1120 (sulfone), 1090 cm^{-1}. Sulfoxide 8: NMR δ 1.4–3.2; MS *m/e* 160 (P), 144 (P − 0), 112 (P − SO); infrared 2160, 2130, 1050 cm^{-1}.

Acknowledgment. We wish to thank Frank Kerdesky and Ralph Gatrone for laboratory assistance and the Wilkes College Research Fund for financial assistance.

Registry No.—**2**, 56830-27-4; **4**, 25662-60-6; **5**, 56830-28-5; **8**, 56830-29-6; **9**, 56830-30-9.

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An Attempt to Observe Neighboring-Group Participation in Hydrogen Abstraction from β-(Substituted Phenyl)-Ethyl Bromides[1]

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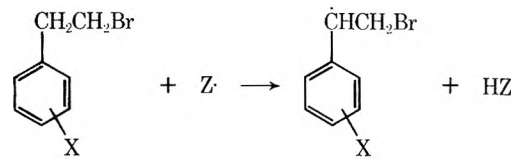
Some recent applications of the Hammett equations have been concerned with nonlinearity. Streitwieser and his co-workers, for example, have shown that the data for acetolysis of substituted benzyl tosylates define two intersecting straight lines. This has been interpreted in terms of a change in the expected SN1 mechanism to an SN2 pathway when carbonium ion destabilizing groups are present.[2] Similarly Gassman and Fentiman have determined that a nonlinear behavior for the Hammett correlation of the data for dissociations of *syn*-7-aryl-*anti*-7-norbornenyl *p*-nitrobenzoates is indicative of variable nonclassical participation by the olefinic double bond.[3]

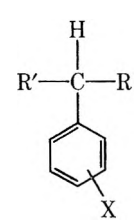
It was felt that a similar approach might be fruitfully applied to a problem in radical chemistry. Participation by neighboring bromine atoms in the course of hydrogen abstraction was first observed by Thaler in the bromination of 1-bromobutane.[4] Although there have been several attempts at refutation, this type of participation has been observed in many related systems. A vast body of evidence may be cited in support of the original findings.[5,6] One system which has not been investigated, however, is the formation of 1-aryl-2-bromoethyl radical (1) from β-(substituted phenyl)-ethyl bromides (2) via hydrogen abstraction.



2 1

Normally a radical such as 1 would attain extensive stabilization by benzylic delocalization. Bromine participation would be unnecessary in such an event. As electron-withdrawing groups are introduced into the system, however, the destabilized radical might now make use of any additional mode of stabilization available. This should not only be true of 1, but also of the transition state leading to 1 in an endothermic reaction.[7]

As an additional point of reference, it was felt that a ρ value for hydrogen abstraction from 2 by the trichloromethyl radical could be theoretically evaluated in advance. Several series of α-substituted toluenes (3) have undergone



3

hydrogen abstraction with the radical generated from bromotrichloromethane. The corresponding ρ values are functions of the electronic and steric parameters of the groups directly attached to the reaction site. An empirical relationship has been developed which successfully correlated the available data (eq 1).[8]

$$\rho = -0.606(\sum\sigma_p^+) + 0.195(\sum E_s) - 1.063 \quad (1)$$

Application of this equation predicts a ρ value for **2** at 70°C in the range −0.84 to −0.90 in the absence of neighboring group participation.[9]

The reaction of **2** with bromotrichloromethane is straightforward. Hydrogen abstraction occurs exclusively at the benzylic position. The products are the expected dibromides. All kinetic determinations are based on direct competition with mesitylene. They were run in replicate under nitrogen. Conversion to product varied from 10 to 85%. Analyses of reaction mixtures was by GLC. Table I summarizes the relative data obtained corrected to the parent compound.

Table I
Relative Rates of Secondary Benzylic Hydrogen Abstraction from β-(Substituted Phenyl)-Ethyl Bromides

Substituent	Registry no.	σ^+ [b]	k_{subst}/k_H	No. of runs
p-CH_3O	14425-64-0	−0.778	4.23 ± 0.21	5
p-CH_3 [a]	6529-51-7	−0.311	1.87 ± 0.26	6
p-*t*-Bu	56829-61-9	−0.295	1.81 ± 0.16	7
p-*F*	332-42-3	−0.073	1.08 ± 0.03	6
H	103-63-9	0.000	1.00 ± 0.10	7
p-Cl	6529-53-9	0.114	0.86 ± 0.04	5
m-Cl	16799-05-6	0.399	0.49 ± 0.03	10
m-CF_3	1997-80-4	0.520	0.33 ± 0.04	7

[a] Corrected for reaction at both benzylic positions. Hydrogen abstraction at the secondary site accounts for 66% of total reactivity. [b] Reference 10.

Optimum correlation was with σ^+ parameters. An experimental ρ value of −0.83 ± 0.02 was obtained. The correlation coefficient was −0.997. No systematic deviation from linearity was observed. This is graphically represented in Figure 1.

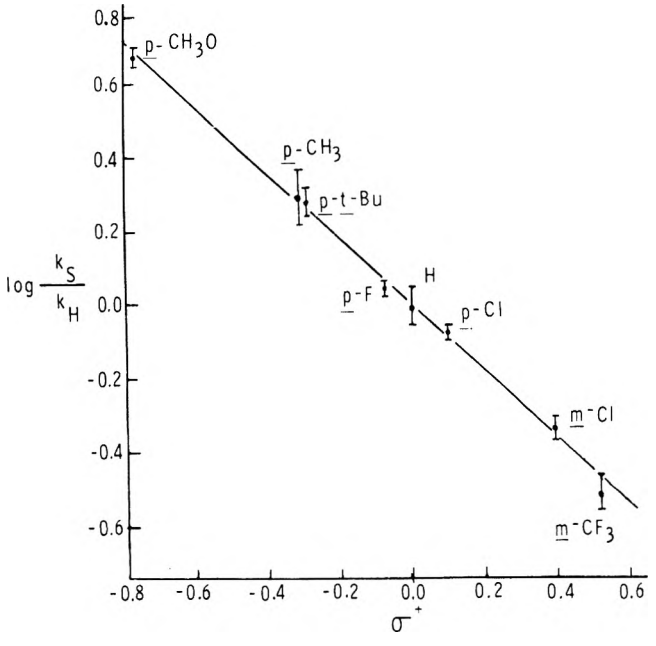


Figure 1. Logarithms of the relative rates of reaction of β-(substituted phenyl)-ethyl bromides vs. σ^+ parameters.

It is apparent that no evidence for participation is found. Unlike aliphatic radicals, radicals such as **1**, even with electron-withdrawing groups present, must achieve sufficient stabilization so as to make bromine participation unnecessary under the reaction conditions employed.

Experimental Section

Materials. With the exception of the parent compound, all the β-(substituted phenyl)-ethyl bromides were prepared from the corresponding alcohols by reaction with phosphorous tribromide. All compounds showed physical properties (boiling points and indices of refraction) in agreement with literature values. The NMR spectra of all compounds were as expected and GLC indicated purities in excess of 98%. Bromotrichloromethane, mesitylene, and bromobenzene were purified by distillation prior to use. Purity was again in excess of 98%.

Kinetic Determinations. Solutions of substituted phenethyl bromides, mesitylene or (2-bromoethyl)benzene, bromobenzene, and bromotrichloromethane were prepared in the approximate molar ratios of 1:1:0.5:10. Approximately 0.75 ml of the solution was placed in each of several ampules.

The ampules were cooled to dry ice–isopropyl alcohol temperature until the solutions solidified. The ampules were evacuated at 2.0–3.0 mm and flushed several times with nitrogen with intermediate thawing. The ampules were sealed under vacuum and one was reserved for the analysis of the unreacted starting materials. The remainder were placed horizontally just below the surface of mineral oil constant-temperature bath maintained at 70.0 ± 0.5°C. The solutions were irradiated with uv light provided by a Sylvania 275-W sun lamp placed 20 cm above the surface of the oil. Reaction times varied from 1 to 3 hr, by which time up to 85% of substituted phenethyl bromides and mesitylene had reacted. The ampules were then cooled and opened. Analysis of the mixtures, both before and after the reaction, was via GLC on a 5% SE-30 on Chromosorb W column.

Conversion of raw data to relative rates involved the use of standard formulas.[11]

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Reactions Which Relate to the Environmental Mobility of Arsenic and Antimony. I. Quaternization of Trimethylarsine and Trimethylstibine

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Several papers have appeared which discuss the environmental distribution of arsenic[2-8] and antimony.[6-9] However, little attention has been given to the chemical changes which facilitate the movement of these elements from one subsystem of the biosphere to another. One of the more important processes in arsenic mobilization has been shown to be the reduction and methylation of inorganic arsenic compounds by microorganisms to produce trimethyl- and dimethylarsine.[10-12] At this time, it has not been demonstrated that methylstibines are metabolites of microorga-

Table I
Quaternization of Tertiary Stibines and Arsines in Methanol and Acetonitrile at 29.5 ± 1° C
$R_3E + R'X \rightarrow (R_3ER')^+X^-$

Solvent[a]	R_3E[b]	$R'X$[a,b]	Rate constant, M^{-1} sec^{-1}[c]	N[d]	%[e]	Days[f]
Methanol	$(CH_3)_3Sb$[k]	CH_3I[j,m]	$(3.85 \pm 0.06) \times 10^{-4}$	17	99+	1/3
Methanol	$(CH_3)_3Sb$[k]	CD_3I[j,n]	$(3.80 \pm 0.18) \times 10^{-4}$	13	90	1/3
Methanol	$(CH_3)_3Sb$[k]	CH_3CH_2I[o]	$(9.36 \pm 0.53) \times 10^{-7}$	6	45	7
Methanol	$(CH_3)_3Sb$[k]	CH_3CH_2Br[p]	$(1.98 \pm 0.60) \times 10^{-7}$	6	19	6
Methanol	$(CH_3)_3Sb$[k]	$CH_3CH_2CH_2I$[q]	$(4.41 \pm 0.76) \times 10^{-7}$	6	50	15
Acetonitrile	$(CH_3)_3Sb$[k]	CH_3I[j]	$(1.14 \pm 0.06) \times 10^{-3}$	7	99+	1/24
Acetonitrile	$(CH_3)_3Sb$[k]	CH_3CH_2I[j]	$(4.25 \pm 0.27) \times 10^{-6}$	8	76	4
Acetonitrile	$(CH_3)_3Sb$[k]	CH_3CH_2Br	$(1.44 \pm 0.74) \times 10^{-6}$[i] $(3.18 \pm 2.10) \times 10^{-7}$[i]	3 4	0–13 6–21	0–1 1–7
Acetonitrile	$(CH_3)_3Sb$[k]	$CH_3CH_2CH_2I$	$(2.52 \pm 0.19) \times 10^{-6}$	9	58	4
Methanol	$(CH_3)_3As$[l]	CH_3I[j]	$(1.35 \pm 0.04) \times 10^{-3}$	6	99	1/24
Methanol	$(CH_3)_3As$[l]	CH_3CH_2I	$(1.26 \pm 0.09) \times 10^{-5}$	8	93	2
Methanol	$(CH_3)_3As$[l]	$CH_3CH_2CH_2I$	$(7.34 \pm 0.39) \times 10^{-6}$	8	88	4
Methanol	Pyridine[g]	CH_3CH_2I	1.94×10^{-6}			
Acetone	Pyridine[g]	CH_3CH_2I	1.0×10^{-5}			
Acetone	$C_6H_5As(CH_2CH_3)_2$[h]	CH_3I	1.11×10^{-3}			

[a] Solvents were reagent grade containing only trace amounts of water (<0.1%). They were manipulated only in the inert atmosphere box. Alkyl halides were reagent grade. [b] Typical initial concentrations of R_3E and $R'X$ were 0.5 and 1.0 M, respectively. [c] Standard error in rate is indicated from statistical least-squares fit of rate data. [d] Number of data points. [e] Percent reaction observed. [f] Days reaction observed. [g] From National Bureau of Standards Circular 510 (1951), Table 652.477; reactions at 25°C. [h] From ref 18; reaction at 35°C. [i] Reaction seems to drift at long reaction times. This is possibly the result of experimental difficulties, but similar phenomena observed in ref 18 were attributed to approach to equilibrium. [j] Product $(R_3ER')^+X^-$ precipitates during latter part of reaction. [k] Registry no., 594-10-5. [l] Registry no., 593-88-4. [m] Registry no., 74-88-4. [n] Registry no., 865-50-9. [o] Registry no., 75-03-6. [p] Registry no., 74-96-4. [q] Registry no., 107-08-4.

nisms acting on inorganic antimony compounds, but the extensive similarity of the chemistry of arsenic and antimony gives reason to believe that antimony can be biologically methylated. Methylarsines and -stibines are subject to a number of reactions such as oxidation, quaternization, and complex formation which could facilitate or inhibit their dispersal in the environment. It has recently been reported that environmentally important concentrations of halocarbons (CH_3I, CH_3Br, and CH_3Cl) are produced naturally and accumulate in the oceans and atmosphere.[13] In this paper we report quantitative measurements of the rate of quaternization of trimethylstibine and trimethylarsine by alkyl halides in polar solvents.[14-18] Methanol (a protic solvent) and acetonitrile (an aprotic dipolar solvent) were chosen as reaction media because trimethylstibine and trimethylarsine are not soluble enough in water to allow study by the available techniques. It should be possible to extrapolate the results to water by use of appropriate solvent parameters. A typical kinetic run is shown in Figure 1 and the measured rate constants are summarized in Table I.

Several factors can be noted which indicate that the reaction is a bimolecular nucleophilic displacement of halogen from carbon by antimony or arsenic (SN2). The reactions are all first order in alkyl halide and first order in stibine or arsine, i.e., second order overall. The orders of reactivity of the alkyl halides, $CH_3I \gg CH_3CH_2I \gtrsim CH_3CH_2CH_2I$ and $CH_3CH_2I > CH_3CH_2Br$, are typical of SN2 type reactions. Also, as expected for an SN2 reaction, there is no appreciable α-secondary isotope effect in the reaction of CH_3I or CD_3I with trimethylstibine.[19] It should be noted that when CD_3I was treated with trimethylstibine, no CH_3I was observed in the sample. This result confirms the idea that there is no low-energy intermediate which would allow exchange of methyl groups between methyl iodide and trimethylstibine. The data in Table I, including reactions of pyridine taken from other sources, indicate a qualitative nucleophilic reactivity of trimethylarsine and trimethylstibine in the order $(CH_3)_3As >$ pyridine $\gtrsim (CH_3)_3Sb$.

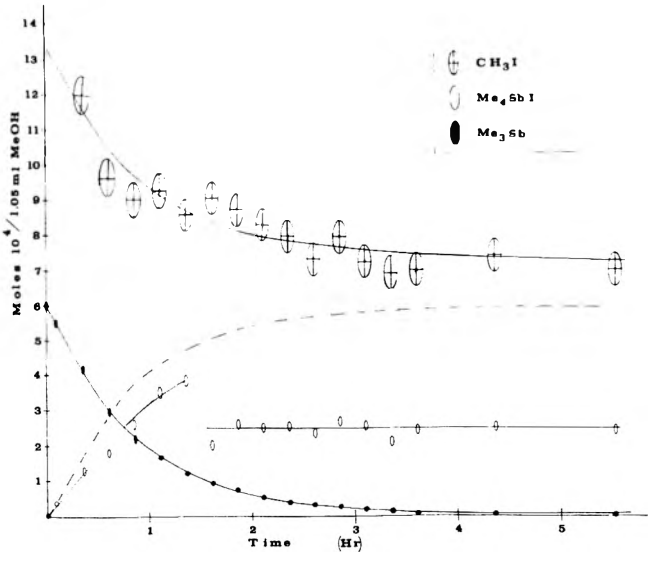

Figure 1. Plot of moles of trimethylstibine (●), methyl iodide (⊕), and tetramethylstibonium iodide (○) contained in 1.05 ml of methanol solution as a function of time. The dashed line represents the concentration of tetramethylstibonium iodide expected if no precipitation occurred. Note that tetramethylstibonium iodide supersaturates before reaching equilibrium concentration (0.24 M). The error in each measurement of trimethylstibine or tetramethylstibonium iodide is approximately 3%. Error bars representing approximately 6% error are used for methyl iodide because its signal is interfered with by a ^{13}C–^1H satellite of the methanol solvent.

Concerning the solvent effect on the reaction of trimethylstibine with methyl iodide, note that the reaction is very slow, requiring weeks to reach completion,[14] in diethyl ether. The more polar solvents greatly increase the rate of quaternization. In addition, Kosower[20] has suggested that there are specific interactions between nitrile solvents and halogen leaving groups which account for the enhanced rate of quaternization in acetonitrile relative to methanol

even though the solvents have similar dielectric constants. The reactions of primary environmental interest occur in water. There are a number of solvent parameters (Y, Ω, Z, S, E_T, δ)[21] which could be used to correlate reaction rates in various solvents. Kosower[22] has used Z to correlate the rates of SN2 reactions in a series of protic solvents. We can write $\log k_2 = AZ + C$, where $A \simeq 0.025$ in protic solvents and C is a constant which depends only on the nucleophile and substrate. Using our results for trimethylstibine and trimethylarsine reacting with methyl iodide in methanol (Z value 83.6), the C's for the reactions are −5.5 and −5.0, respectively. The Z value of water is 94.6. Thus, the rate constant for reaction of $(CH_3)_3Sb$ and $(CH_3)_3As$ with CH_3I in water can be estimated to be 7×10^{-4} and 3×10^{-3} M^{-1} sec^{-1}, respectively. A similar approach can be applied to the other reactions in Table I. The result is that the reactions are expected to be about twice as fast in water as in methanol.

Experimental Section

Trimethylantimony dibromide was prepared by the method described by Doak et al.[23] It was recrystallized from acetone. Solutions of trimethylstibine for kinetic studies were prepared in a recirculating inert atmosphere (N_2) box by refluxing $(CH_3)_3SbBr_2$ with a twofold excess of 30-mesh zinc in the solvent of choice (methanol or acetonitrile) for 1 hr, followed by vacuum distillation of the solution. The solutions were standardized by adding an excess of methyl iodide to a weighed sample of each solution and weighing the tetramethylstibonium iodide isolated after removal of solvent.

Trimethylarsine was obtained from a commercial source. Solutions of trimethylarsine for kinetic studies were prepared by weight using conventional vacuum line techniques.

The reactions of trimethylstibine and trimethylarsine with alkyl halides were observed by an NMR technique using a commercial 60-MHz instrument. In an inert atmosphere box, approximately 1 ml of the typically 0.5 M stibine or arsine solution was transferred into a tared thin-wall NMR tube which was then stoppered with a rubber septum. The exact quantity of solution was determined by weight. After allowing the sample to equilibrate thermally in the NMR probe, about 0.15 ml of a mixture of the desired alkyl halide and hexamethyldisilane (prepared and stored under nitrogen; typical mole ratio 10:1) was injected through the septum to initiate the reaction. The exact amount of RX-$(CH_3)_6Si_2$ solution added was determined by weight at the completion of the reaction. In most kinetic runs, only the signals for the stibine or arsine and the standard, $(CH_3)_6Si_2$, were observed using 50-Hz sweep width and changing the offset as necessary to put both signals in the scan. The areas of the two signals were measured (±3%) with a planimeter and related to the moles of reactant and standard. Concentrations were calculated by relating the liquid level in the sample tube to the volume of the reacting solution. For the slow reactions which required days to reach a reasonable extent of reaction, the sample tubes were stored in a bath regulated to the probe temperature, 29.5 ± 1°C. The concentration vs. time data was fitted by computer to a second-order rate equation by the method of least squares.

In the course of this study the chemical shifts of trimethylstibine (δ 0.73), trimethylarsine (δ 0.91), and tetramethylstibonium iodide (δ 1.58 low concentration, δ 1.66 saturated) were determined in methanol relative to internal hexamethyldisilane (δ 0.04).[24] The signal for tetramethylstibonium iodide is quite broad ($W_{1/2} \simeq 4.5$ Hz) owing to unresolved Sb–C–H coupling. The signal for trimethylstibine is not detectably broadened ($W_{1/2} \simeq 0.7$ Hz) because in an asymmetric electric field the antimony quadrupole successfully relaxes the Sb–C–H coupling. In addition, it was noted that the maximum solubility of $(CH_3)_4SbI$ in methanol is 0.24 M and the maximum solubility of $CH_3CH_2Sb(CH_3)_3I$ in acetonitrile is about 0.2 M.

Acknowledgment. The assistance of Mr. Richard Thompson in recording the NMR spectra is appreciated.

Registry No.—Tetramethylstibonium iodide, 2185-78-6; tetra(methyl-d_3)stibonium iodide, 56929-85-2; ethyltrimethylstibonium iodide, 56929-86-3; ethyltrimethylstibonium bromide, 56929-87-4; trimethylpropylstibonium iodide, 56929-88-5; tetramethylarsonium iodide, 5814-20-0; ethyltrimethylarsonium iodide, 56929-89-6; trimethylpropylarsonium iodide, 56929-90-9; trimethylantimony dibromide, 5835-64-3.

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Applications of Surfactants to Synthetic Organic Chemistry

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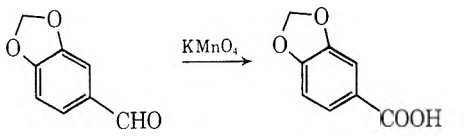
Synthetic chemists are frequently faced with the problem of reacting a water-insoluble organic compound with a water-soluble reagent (hydroxide, permanganate, formate, periodate, hypohalite, hydrogen peroxide, hydrobromic acid, hydrazine, etc.)[2]. Several methods are available for countering this difficulty. The organic phase can be stirred rapidly with the aqueous phase; agitation promotes interfacial contact between the two reactants. An alternative procedure utilizes a cosolvent such as dioxane or ethanol in the water. Although a water–cosolvent mixture does not usually dissolve all the organic reactant, the hope is that at least a small portion of the reactant will enter the watery solvent. As the compound is consumed, more of it is supplied from the organic layer. Dipolar aprotic solvents,[3] crown ethers,[4] and phase transfer catalysts[5] are also commonly used in synthesis; they function by dissolving or solubilizing ionic reagents in organic phases. In the present article we assess the value of surfactants in several two-phase reactions. Surfactants disperse organic liquids in water; this could conceivably generate higher yields and shorter reaction times. Surfactants also form micelles which are capable of catalyzing organic reactions.[6] Yet neither "emulsion catalysis" nor micellar catalysis by surfactants has been exploited to any degree in synthetic organic chemistry.[7]

Table I
Percent Yields of Piperonylic Acid Produced from the Oxidation of Piperonal at 55° by $KMnO_4$

Reaction mode	Reaction time, min		
	70	100	150
Magnetic stirring	37	33, 36	37
Mechanical stirring	39	37	38
Magnetic stirring (0.01 *M* surfactant)[a]	66, 74[b]	64	65
Magnetic stirring (20% dioxane)	43		

[a] The initial concentration of surfactant (cetyltrimethylammonium bromide) was 0.01 *M*. When aqueous $KMnO_4$ was added to the reaction mixture, the surfactant was diluted about twofold. [b] In this one run only the $KMnO_4$ solution contained 0.01 *M* surfactant so that the surfactant concentration in the reaction vessel was maintained at 0.01 *M* throughout the addition of $KMnO_4$.

We first investigated the heterogeneous oxidation of piperonal to piperonylic acid (eq 1). Reactions were carried



(1)

out by stirring 1.0 g of aldehyde with 60 ml of aqueous $KMnO_4$ in the presence or absence of a small quantity (0.11 g) of cetyltrimethylammonium bromide, a cationic surfactant. Yields of piperonylic acid are listed in Table I. A single person performed all the reactions, and no attempt was made to maximize yields by varying the conditions other than those shown in the table.[8] Although changing the mode of stirring had no effect, the presence of surfactant invariably elevated the yields from about 37% to about 65%. Even a 20% dioxane cosolvent did not improve the yield as much as 0.01 *M* surfactant.

Table II lists the yields of benzoic acid formed when 4.1 g of neat α,α,α-trichlorotoluene was hydrolyzed with 30 ml of 20% NaOH at 80°. The reaction times were easily assessed from the disappearance of the organic phase. Hydrolysis of α,α,α-trichlorotoluene in the presence of 0.01 *M* cetyltrimethylammonium bromide required 1.5 hr. By contrast, the reaction without surfactant took 60 hr. No product was isolated if the reaction without surfactant was allowed to proceed only for 1.5 hr. Brij 35 (a neutral surfactant, $C_{12}H_{25}(OCH_2CH_2)_{23}OH$) accelerated the hydrolysis but to a lesser extent than did the quaternary ammonium salt. The facility of the surfactant-induced hydrolyses may stem either from an "emulsion catalysis" or from a micellar catalysis.[6] Since micelles of cationic but not neutral surfactants are known catalysts for basic hydrolyses,[9] we suspect that cetyltrimethylammonium bromide operates by both emulsification and micellization whereas Brij 35 serves as a dispersing agent only.

Phase transfer catalysis is an alternative explanation for the data in Table II. Cetyltrimethylammonium ion might dissolve in the organic phase, dragging hydroxide counterions with it.[10] Hydroxide ion consumed by reaction in the organic phase would be replenished continuously by hydroxide in the water. Three considerations argue against phase transfer catalysis. (1) Cetyltrimethylammonium bromide and Brij 35 aid the hydrolysis of α,α,α-trichlorotoluene far more effectively than does tetrabutylammonium bromide (Table II). This is true despite the fact that tetrabutylammonium ion is a 35-fold better phase transfer catalyst than our cationic surfactant in the reaction of thiophenoxide and 1-bromooctane.[11] Tetrabutylammonium ion

Table II
Hydrolysis Yields of α,α,α-Trichlorotoluene to Benzoic Acid in 20% NaOH at 80°

Additive	Reaction time, hr	% yield
0.01 *M* $C_{16}H_{33}N(CH_3)_3^+Br^-$	1.5[a]	98
None	1.5	0
None	60[a]	97
0.006 *M* Brij 35[b]	11[a]	97
0.02 *M* n-Bu_4N^+ Br^-	15[a]	98
20% dioxane[c]	1.5	0

[a] This is roughly minimum time required for completion of the reaction. [b] $C_{12}H_{25}(OCH_2CH_2)_{23}OH$. [c] Two phases.

and other short-chain quaternary salts are known to mediate several phase transfer reactions involving hydroxide ion.[5,12,13] (2) The concentration of surfactant used in our work (0.01 *M*) is much smaller than the concentration of quaternary salt generally used in phase transfer processes.[14] (3) Diluting the α,α,α-trichlorotoluene with 10 ml of benzene *increases* the reaction time for the cationic surfactant-containing system by a factor of 11. These data suggest, but do not prove, the presence of an emulsion or micellar catalysis. Obviously Brij-35 *must* operate by one of these mechanisms.

Cetyltrimethylammonium bromide does not benefit the heterogeneous nitric acid oxidation of *o*-xylene to *o*-toluic acid.[15] However, the reaction time for hydrolysis of ethyl naphthoate in 5% NaOH at 80° decreases fourfold in the presence of 0.005 *M* cationic surfactant. Brij 35 also catalyzes the hydrolysis. Finally, we tested the effect of cetyltrimethylammonium bromide on a recently reported conversion of amides to acids using sodium peroxide.[16] It is stated that "only extremely water-insoluble amides failed to react and, although ethanol can be substituted as solvent for some of the reactions, it was of no value in these cases".[16] We treated *N,N*-diethylbenzamide, one of the water-insoluble amides which gave no product, with sodium peroxide at 90° in the presence and absence of 0.005 *M* surfactant. After a long reaction time (30 hr) we isolated 57 and 32% benzoic acid, respectively.

In summary, we have shown that cationic and neutral surfactants can in certain cases lead to higher yields and shorter reaction times. If the work-up of the product includes an extraction step, then the time saved by using a surfactant may not justify possible problems caused by emulsions.[17] On the other hand, emulsion–micellar catalysis may find utility in large-scale reactions or in reactions of sensitive water-insoluble liquids that require a minimum exposure to an aqueous solution.

Experimental Section

Oxidation of Piperonal. Piperonal (1.00 g, 6.7 mmol) and 25 ml of water were placed into each of three 100-ml round-bottom flasks. After cetyltrimethylammonium bromide (0.11 g, 0.30 mmol) was added to one of the flasks, all of them were immersed in oil baths preheated to 55°. Magnetic stirring was initiated in two vessels including the one containing the surfactant (every effort being made to equalize the stirring rates). The third flask was stirred with a motor-driven shaft and propeller. Solutions of 1.50 g (9.5 mmol) of $KMnO_4$ in 35 ml of water were added dropwise over a period of 30 min, and heating was continued for 70–150 min. Briefly stated, the work-up consisted of adding KOH, removing the MnO_2 by filtration, combining the filtrate and MnO_2 wash, removing the unreacted material with an ether extraction, acidifying the water, and filtering, washing, and drying the resulting piperonylic acid. When surfactant was present, 2 hr were allowed for phase separation during the ether extraction step. The product was a colorless powder melting at 227–228° (lit.[8] mp 227–228°). Product from reactions containing surfactant had a slightly sharper melting point than product from reactions without surfactant.

Hydrolysis of α,α,α-Trichlorotoluene. α,α,α-Trichlorotoluene (4.1 g, 21 mmol) was stirred magnetically with 30 ml of 20% aqueous NaOH at 80°. Runs catalyzed by surfactant contained either 0.11 g (0.30 mmol) of cetyltrimethylammonium bromide or 0.20 g (0.17 mmol) of Brij 35. All organic reagents were purchased from Aldrich. The work-up of product consisted of acidifying with HCl, cooling in ice, filtering, washing the collected solid with cold water, and drying the solid. The unpurified benzoic acid melted at 119–121°.

Acknowledgment. This work was supported by grants from the National Science Foundation (GP-42919X) and from the National Institutes of Health (GM-20336 and GM-21457).

Registry No.—Piperonal, 120-57-0; piperonylic acid, 94-53-1; α,α,α-trichlorotoluene, 98-07-7; benzoic acid, 65-85-0; cetyltrimethylammonium bromide, 57-09-0; Brij 35, 9002-92-0; tetrabutylammonium bromide, 1643-19-2.

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Anodic Acetoxylation of Dimethoxybenzenes

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Many of the electrochemical oxidations of aromatic compounds are considered to proceed via cation radical intermediates.[1] Dimethoxybenzenes produce the quinone diketals in methanolic potassium hydroxide[2] and form methoxybenzonitriles in acetonitrile solution of tetraethylammonium cyanide[3] or in methanol containing sodium cyanide.[4] These products arise from the attack of nucleophiles on the highest positive center of cation radical, a carbon atom bearing a methoxy substituent. When a bulky nucleophile such as pyridine or substrate itself is used, the attacking point changes; the anodic pyridination[5] and the anodic coupling[6] of *o*-dimethoxybenzene[10] occur on the carbon atom with an aromatic hydrogen.

On the other hand, the electron transfer reaction of dimethoxybenzenes by lead tetraacetate in acetic acid produces dimethoxyphenyl acetates.[11] In this case, the acetoxylated position is the carbon atom with an aromatic hydrogen. Data on anodic acetoxylation are indispensable to clarify which is the cause of an apparent contradiction of attacking points, the different oxidant or the nature of nucleophile. Anodic acetoxylation of dimethoxybenzenes has been described only in the case of the para isomer. The reported product is 2,5-dimethoxyphenyl acetate; however, details are not clear.[12]

Results

Methoxybenzenes were electrolyzed in a one-compartment cell under a nitrogen atmosphere using platinum foil anode in glacial acetic acid containing sodium acetate with a constant current of 0.1 A. The results of these studies are summarized in Table I.

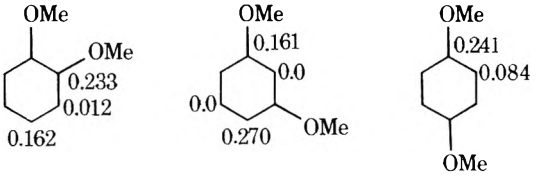
Anodic oxidation of *p*-dimethoxybenzene produced a 68% yield of 2,5-dimethoxyphenyl acetate as the sole organic product, except for a very small amount of a brownish substance.

The electrochemical oxidation of *m*-dimethoxybenzene gave a 2.5% yield of a 16:1 mixture of 2,4- and 2,6-dimethoxyphenyl acetate, respectively, together with a considerable amount of tarry product.

Under identical conditions, *o*-dimethoxybenzene produced a 8.9% yield of a mixture of 2,3- and 3,4-dimethoxyphenyl acetate in the proportions 1:90, along with a significant amount of tarry residue.

Discussion

The primary step of anodic acetoxylation is attributed to a direct discharge of the aromatic at the anode to a cation radical intermediate.[1,13] The second stage is the combination reaction of the cation radical intermediate with nucleophile. Observed orientations in the aromatic cyanation of methoxybenzenes are in accord with the spin density distributions calculated from ESR spectra of the cation radicals.[3,14,15] In each case, the methoxyl displacement by



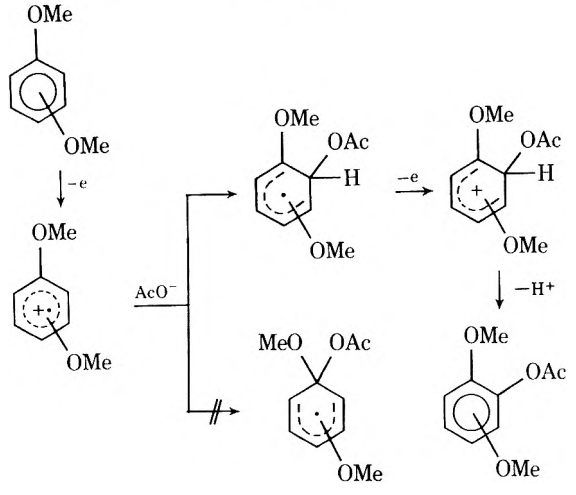
cyanide ion occurs at the position of highest spin density. This can also account for the position of attack by methoxide ion.[2] In contrast, the acetoxylation by a metal ion oxidant[11] and the present electrode process does not occur at these positions. This would be ascribable to the instability of an acylal type intermediate, because acetate ion is a better leaving group than methoxide ion.[20] Bonding between the oxygen atom of the cation radical and acetate ion, followed by rearrangement,[21] is also improbable, because *o*-dimethoxybenzene does not produce 2,3-dimethoxyphenyl acetate predominantly (see Table I). The mechanism shown in Scheme I would, therefore, be reasonable to account for the anodic acetoxylation of dimethoxybenzenes.

Table I
Anodic and Lead Tetraacetate Oxidation of Dimethoxybenzenes

Reactant[d]	Faradays	Conversion, %	Product[e]	Yield,[b] %	Product distribution: Anodic	Product distribution: Lead tetraacetate
p-Dimethoxybenzene	0.183	93.1	2,5-Dimethoxyphenyl acetate	68.0	100	100
m-Dimethoxybenzene[a]	0.072	34.5	2,4-Dimethoxyphenyl acetate	2.3	94	95
			2,6-Dimethoxyphenyl acetate	0.2	6	5
o-Dimethoxybenzene[a]	0.074	13.8	2,3-Dimethoxyphenyl acetate	0.1	1	1
			3,4-Dimethoxyphenyl acetate	8.8	99	99

[a] Considerable amounts of tarry substance were produced. [b] Based on dimethoxybenzene consumed. [c] Data from ref 11. [d] Registry no. are, respectively, 150-78-7, 151-10-0, 91-16-7. [e] Registry no. are, respectively, 27257-06-3, 27257-07-4, 944-99-0, 27257-08-5, 7203-46-5.

Scheme I



Isomer distributions from anodic acetoxylation are also shown in Table I, together with the corresponding data from lead tetraacetate oxidation. A comparison between anodic and lead tetraacetate oxidations demonstrates the fundamental similarity between these two reactions; the cation radical intermediates produced from the different sources show the analogous preference for aromatic acetoxylation.

An alternative mechanism for aromatic substitution involves an aromatic proton release,[22,23] followed by further anodic oxidation and attack by acetate ion (or solvent acetic acid), thus leading to the aromatic acetoxylation products. However, this mechanism cannot elucidate the isomer distribution observed.

Experimental Section

The spectroscopic instrumentation was as previously described.[17]

Materials. Analytical grade acetic acid and sodium acetate were used directly. *o*- and *m*-dimethoxybenzene were shaked with aqueous sodium hydroxide and purified by distillation. *p*-Dimethoxybenzene was recrystallized from ethanol.

The following reference materials were prepared according to the literature: o-, *m*-, and *p*-methoxyphenyl acetate,[11] 2,3-,[11,24] 2,4-,[25] 2,5-,[26] 2,6-,[24] 3,4-,[27] and 3,5-dimethoxyphenyl acetate,[26,28] and *o*-methoxyphenoxymethyl acetate.[26]

Electrolysis. The preparative experiments were run according to the following standard procedure. The electrolyte was made up of 0.09 mol of the organic compound, 0.15 mol of anhydrous sodium acetate, and 150 ml of glacial acetic acid. The electrolysis was conducted at the terminal voltage of about 20 V to maintain the current of 0.1 A in an undivided cell under a nitrogen atmosphere. Platinum foils having an area of 8 cm^2 were used as electrodes. During the electrolysis, the solution was stirred magnetically and cooled externally with water. The electrolyzed solution was poured into a vigorously stirred slurry of sodium bicarbonate in water. The ether extract was washed with sodium bicarbonate, dried over sodium sulfate, filtered, and stripped on a rotary evaporator. A crude product was then analyzed by GLC using AGL and PEG 6000 columns. Each product was separated in pure form by preparative VPC and characterized by ir and NMR spectra.

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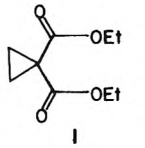
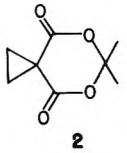
A Spiroactivated Vinylcyclopropane

Summary: The spiroactivated vinylcyclopropane, 6,6-dimethyl-2-vinyl-5,7-dioxaspiro[2.5]octane-4.8-dione is readily available. It reacts with nucleophiles cleanly at carbon 2. A much faster rate of racemization is observed in the optically active compound than was observed for the optically active dimethyl 2-vinylcyclopropane-1,1-dicarboxylate.

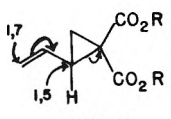
Sir: Recently we described the preparation of the spiroacylal **2** and its reactions with nucleophiles.[1] The enormous facility of the ring-opening reactions of compound **2** relative to its diester analog, **1**, is presumably a consequence of the enhanced stabilization provided by the conformationally constrained cyclic acylal system for the anionic leaving group. We have, for some time, been interested in the multiple electrophilic capabilities of activated vinylcyclopropanes.[2,3] For instance, compound **3** is susceptible to nucleophilic attack in both the 1,5 and 1,7 modes. The former pathway is the predominant one, in the most obviously nucleophilic cases.[4-6] However, the two pathways are somewhat competitive under the relatively vigorous reaction conditions required to rupture the cyclopropane ring. This behavior sharply compromises the utility of system **3** for synthetic purposes.



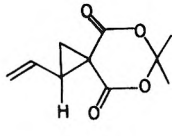
1



2



3 R = Et
4* R = Me (optically active)
5 R = H (**5*** optically active)

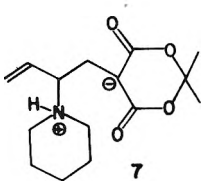


6

Accordingly, the behavior of the spiroactivated vinylcyclopropane, **6**, was investigated. This compound, mp 51–53°,[7a,b] was prepared in 60% yield by the reaction of diacid **5** with isopropenyl acetate under the influence of concentrated sulfuric acid. Below it is shown that compound **6** reacts with nucleophiles exclusively in the 1,5 sense under very mild conditions, and in high yield. Furthermore the effects of spiroactivation on the thermal fragmentation of the three-membered ring has also been demonstrated by the remarkably facile racemization of optically active **6*** relative to optically active **4***.

Compound **6** reacts with piperidine (room temperature, 4 hr) in benzene to give a 95% yield of **7**,[7a,b] mp 168–170°. It will be noted that the analogous reaction with **3**[3,4] is achieved only by heating at 105°.

Compound **6** reacts with dimethyl sodiomalonate in dimethoxyethane at room temperature, whereas the analogous reaction with compound **3** requires temperatures of 75–85°.[3,5] Moreover, while the reaction in the case of **3** occurs via competitive 1,5 and 1,7 addition (5:1),[3,5] in the case of compound **6** only 1,5 addition occurs, leading to compound **8**,[7a,b] mp 109–111°, in 83% yield. Compound **6** reacts with sodium thiophenoxide in DME at room temperature to give **9**,[7a,b] mp 72–74°. The corresponding reaction in the case of **3**, produces ~20% 1,7 product.[3,5] As in the case of **2**,[1] hydrogenolysis of the cyclopropane in **6** is achieved under relatively mild conditions. Thus, compound **6** reacts with 2 mol of hydrogen (5% Pd/C–EtOAc, atmospheric pressure, room temperature, 3 hr) to give *n*-butyl Meldrum's acid, **10**.[7b]



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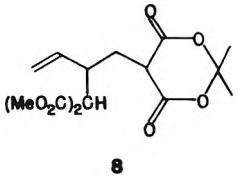

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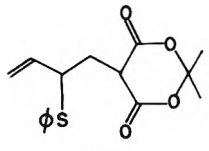

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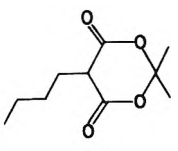
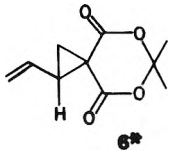


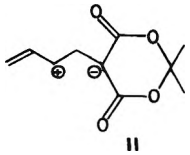
10

Previously we had prepared[8] optically active **4*** by esterification of the resolved (brucine salt), of diacid **5***. It was of interest to compare the relative rates of racemization of **4*** and **6***, thereby assessing the effects of spiroactivation on unimolecular ionization. Optically active **6***, $[\alpha]D$ (benzene) −18.80°, was prepared from resolved **5**[8a,b] by reaction with isopropenyl acetate in the usual fashion.

At 80° in benzene, the racemization of **6*** is cleanly first order with $t_{1/2} = 1.2 \times 10^2$ min. At 100°, $t_{1/2rac}$, in toluene, is 9 min. We have repeated, for comparison, the racemization of **4***. At 140°, $t_{1/2}$ (xylene) for the racemization of **4*** is 2.7×10^3 min. It would appear that the massive[9] accelerating effect of the spiroacylal system on the racemization rate involves stabilization of the transition state leading to the presumed intermediate, **11**.[10] This must reflect stabilization of intermediate **11** itself[11] (cf. enhanced acidity of Meldrum's acid[12] relative to acylic malonic esters).



6*



11

The effect of spiroactivation, in promoting 1,5 addition to the exclusion of the 1,7 mode, may be a consequence of specific structural features of the system. Alternatively, it may arise from the mild reaction conditions which suffice for **6**. These serve to obscure other processes[3,8] (free-radical reactions, rearrangements, etc.) which compete with the purely nucleophilic reactions of **3**. In any case, the phenomenon of clean 1,5 attack, exhibited by **6**, will increase the value of activated vinylcyclopropanes in synthesis. The use of **6** as a synthetic equivalent of $CH_2{=}CHCH^+\text{-}CH_2CH(CO_2R)_2$, which reacts predictably at the secondary center, will be demonstrated shortly.

Acknowledgments. This research was supported by PHS Grant CA-12107-11. NMR spectra were obtained on facilities supported by PHS Grant RR-00292-04.

Supplementary Material Available. Experimental procedures for these reactions will appear following these pages in the microfilm edition of this volume of this journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3807.

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(9) Unfortunately we are unable to measure the rates for **4*** and **6*** at the same temperature. While the temperature dependence of k_{rac} has not been measured, the minimum ratio would appear to be 10^4.
(10) Cf. A. B. Chmurny and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 4237 (1973), and papers cited therein.
(11) The possibility that this type spiroactivation arises from additional strain imposed on the three-membered ring seems to us unlikely but has not been disproven.
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(13) An Andrew Mellon Fellow.

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Selective Fluorination of Hydroxy Amines and Hydroxy Amino Acids with Sulfur Tetrafluoride in Liquid Hydrogen Fluoride

Summary: At −78° and atmospheric pressure sulfur tetrafluoride in liquid hydrogen fluoride selectively replaces alcoholic hydroxyl groups in hydroxy amines and hydroxy amino acids by fluorine.

Sir: Sulfur tetrafluoride, SF_4, is the most frequently employed reagent for transforming organic compounds containing certain oxygen functionalities into the corresponding organofluorine compounds. It is regarded as the standard reagent for converting aldehydes, ketones, and carboxylic acids into difluoro and trifluoro compounds, respectively.[1,2] However, fluorination of alcohols by SF_4 was found to be restricted to those containing "acidified" hydroxyl groups.[3] Owing to its low reactivity, SF_4 is employed in high pressure apparatus, generally at temperatures of 50–200°.

We have found that the reactivity of SF_4 toward a variety of alcohols is dramatically and selectively increased when employing liquid hydrogen fluoride (HF) as solvent. Surprisingly, the reactivity of SF_4 with carbonyl compounds and carboxylic acids is not concomitantly increased and thus the SF_4–HF solution becomes a selective fluorinating system toward alcohols.[4] Moreover, the protection of amino groups against electrophilic reagent by use of liquid HF solvent, observed in the C-chlorination[5] and C-fluorination[6] of amines and amino acids, also obtains in this system. (In the absence of this protection amino groups react with SF_4 to form imino sulfur difluorides.[7])

Sulfur tetrafluoride, taken as a gas from a cylinder and measured as a liquid in a graduated trap at −78° (dry ice–acetone bath, ≃2.5 ml, 0.042 mol) was bubbled into 40 ml of liquid HF, kept at −78°. (The HF was taken as a gas from a cylinder, liquefied directly by passing into the cooled reactor, made of polyethylene or KEL-F®.[5]) Threo-β-phenylserine monohydrate (1.99 g, 0.01 mol) was added. (Throughout slight positive pressure of N_2 was maintained.) After a 45-min reaction period at −78°, the solvent was blown off by a stream of N_2, concentrated HCl was added, and the solution was evaporated to dryness in vacuo to give the HCl salt of β-fluorophenylalanine. The free amino acid was liberated in water–pyridine (mp 173–74° dec, yield 65%). Spinco amino acid analysis showed a single symmetrical peak.[8] Also, by a similar procedure, L-threonine was transformed into L-2-amino-3-fluorobutyric acid. The results on free amino acids indicated that there was no protection needed for –COOH groups.[9,10]

The mechanism of the SF_4–ROH reaction has been extensively discussed and it is commonly felt that an alkoxysulfur trifluoride, $ROSF_3$, is the key intermediate and that this intermediate collapses to product via an SNi or SN2 pathway.[1] However in the liquid HF–SF_4 system a carbonium ion mechanism is suggested by the following: (1) The product from the most stable carbonium ion seems to be obtained [the quantitative rearrangement of 3-hydroxypiperidine to 4-fluoropiperidine was observed (indicating a shift of the carbonium ion away from the positive $-NH_2^+-$)]; (2) 2-methylserine affords in addition to a 23% yield of the expected 2-fluoromethylalanine, a 40% yield of 1-aminocyclopropane carboxylic acid (this type of insertion into a C–H bond has been well documented in the literature of carbonium ions[11,12]); (3) in the case of simple alcohols (*n*-hexanol), the products are complex (branched chain fluorides, olefins, and dimers). Since fluorination is not observed in the absence of HF (choline chloride afforded no 2-fluoroethyl trimethyl ammonium product when it was reacted with SF_4 in diglyme at −5°), it is important to consider the role of this acid. It is proposed that HF not only induces the well-known dissociation of SF_4 to the much more electrophilic SF_3^+ (eq 1)[13] but also plays an important role in the ionization of the alkoxysulfur trifluoride (eq 3) by providing a solvent of high dielectric constant and possibly engendering an ionization analogous to the one in eq 1. The latter would provide a better leaving group (eq 4).

$$SF_4 + HF \rightleftharpoons SF_3^+ + HF_2^- \quad (1)$$

$$ROH + SF_3^+ \rightarrow ROSF_3 + H^+ \quad (2)$$

$$ROSF_3 \rightarrow R^+ + SOF_2 + F^- \rightarrow RF \quad (3)$$

$$ROSF_3 + HF \rightarrow ROSF_2^+ + HF_2^- \rightarrow R^+ + SOF_2 \rightarrow \text{etc} \quad (4)$$

This method for the C–OH → C–F transformation[14] (formally "fluorodehydroxylation") is considered a promising tool of antimetabolite synthesis. The physicochemical similarity of the C–OH and C–F bonds has been recognized

Table I
Products from Reaction of SF_4–HF with Various Hydroxy Amino Compounds at −78°

Product[a]	Mp, °C	Yield, %[b]
3-Fluoro-D-alanine[c]	168 dec	51
3-Fluoro-L-2-aminobutyric acid hydrochloride		85
β-Fluoro-DL-phenylalanine	173–174 dec	65
2-*tert*-butylaminoethyl fluoride hydrochloride	214–215	38
2-Fluoroethyltrimethylammonium chloride[c]	255–257	75[d]
4-Fluoropiperidine hydrochloride	163–164	64
4-Fluoropiperidine hydrochloride[e]	163–164	46
2-Fluoromethylimidazole hydrochloride		32
4-Methyl-5-(2-fluoroethyl)thiazole hydrochloride	116–117	29

[a] Elemental (C, H, N, F) analyses and NMR spectra were in accord with product structures. The substrates were the hydroxy congeners except where otherwise noted. [b] Yields are those of pure isolated products unless otherwise noted; NMR analysis of reaction mixtures indicated much higher yields (75–100%). [c] Known compounds. [d] NMR yield. [e] The substrate was 3-hydroxypiperidine.

in regard to bond length, electronegativity, and crystal lattice geometry.[15]

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(3) Reference 1, pp 12–20.
(4) Benzaldehyde, α-aminoacetophenone, and glycine are recovered unchanged after treatment with SF_4 in liquid HF at −78°. Cf. also ref 9.
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(8) For an attempted synthesis, see E. D. Bergmann and A. M. Cohen, *Israel J. Chem.*, **8**, 925 (1970).
(9) Catalysis of the

$$-COOH \xrightarrow{SF_4} -CF_3$$

reaction by HF was recognized [D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962)]. This catalysis apparently is not operative with amino acids at −78°. Note, however, that in HF–SF_4 at 120° common α-amino acids have been transformed to the corresponding $-CF_3$ derivatives [M. S. Raasch, *Ibid.*, **27** 1406 (1962)]. The modest yields (averaging 11.6% of theory) imply a rather ineffective degree of protection of $-NH_2$ groups by HF at 120°.
(10) Recently we noticed an abstract (R. S. Loy and M. Hudlicky, Abstracts of Papers, 170th National Meeting of the American Chemical Society, Chicago, Ill., 8/24–29, 1975, FLUO 12) describing the synthesis of a mixture of *threo*- and erythro-L-2-amino-3-fluorobutyric acids via hydrolysis of the ethyl esters which in turn were obtained from ethyl L-threoninate in HF–SF_4 at 60°.
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Additions and Corrections

Vol. 39, 1974

Leonard H. Schwartz,* Richard V. Flor, and Vincent P. Gullo: A Reinvestigation of the Direction of Acid-Catalyzed Ring Opening of Substituted Spirocyclopropylcyclohexadienones.

Page 222. Column 2, line 15. "See ref 3 and 5" should be See ref 3 and 4. Line 16. "Within ref 3" should be within ref 4.

Gabor Fodor,* Shiow-yueh Abidi, and Thornton C. Carpenter: *N*-Cyanoammonium Salts as Intermediates in the von Braun Cyanogen Bromide Reaction.

Page 1516. Column 1. The correct acknowledgment should read as follows. This work was supported by the National Science Foundation under Grant GP-26558. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research since 1972.

Charles R. Flynn and Josef Michl*: Ethylene Iminocarbonate.

Page 3442. In our report on preparation of ethylene iminocarbonate, its spontaneous trimerization to 2,4,6-tris(β-hydroxyethoxy)-1,3,5-triazine, mp 117–120° (sintering), was noted. A reference [J. R. Dudley, J. T. Thurston, F. C. Schaefer, C. J. Hull, D. Holm-Hansen, and P. Adams, *J. Am. Chem. Soc.*, **73**, 2999 (1951)] to the latter compound, giving mp 130–132°, was overlooked. We have repeated our work and wish to report that repeated crystallization from dioxane raised the melting point of our sample to 132–134°. We are grateful to Dr. G. R. Newkome (Louisiana State University, Baton Rouge) for calling the reference to our attention. Our reinvestigation was carried out by Dr. R. P. Steiner.

Clifford A. Bunton,* Albert A. Kamego, and Patricia Ng: Micellar Effects upon the Decomposition of 3-Bromo-3-phenylpropionic Acid Effect of Changes in Surfactant Structure.

Page 3471. Column 2, References and Notes. Reference 8 is C. A. Bunton and L. G. Ionescu, *J. Am. Chem. Soc.*, **95**, 2912 (1973).

Bruce Ganem* and Vernon R. Small, Jr.: Ferric Chloride in Acetic Anhydride. A Mild and Versatile Reagent for the Cleavage of Ethers.

Pages 3728–3730. This publication should have been presented as having issued from the Department of Chemistry, Stanford University, Stanford, California 94305, as well as from Cornell University. The experimental part of the work was performed at the former laboratories while both authors were in residence at Stanford. Thanks are due to the National Institutes of Health and the National Science Foundation for grants (to William S. Johnson at Stanford University) in support of this work. B.G. was also recipient of an NIH Postdoctoral Fellowship at Stanford during a portion of the period he was engaged in this project.

Vol. 40, 1975

James A. Profitt, David S. Watt,* and E. J. Corey: A Reagent for the α,β Reduction of Conjugated Nitriles.

Page 127. The manuscript was received on July 9, 1974. Ed.

Paul A. Grieco* and Yukio Masaki: Synthesis of the *Valeriana Waalichi* Hydrocarbon Sesquifenchene. A Route to Specifically Functionalized 7,7-Disubstituted Bicyclo[2.2.1]heptane Derivatives.

Page 150. Column 2, line 2. "δ 1.28" should read δ 1.48.

Stan S. Hall* and Frank J. McEnroe: Alkylation–Reduction of Carbonyl Systems. IV. The Convenient and Selective Synthesis of Simple and Complex Aromatic Hydrocarbons by Phenylation–Reduction of Aldehydes and Ketones.

Pages 271 and 273. See correction published in *J. Org. Chem.*, **40**, 972 (1975).

Stuart S. Kulp,* Ronald W. Schmoyer, David E. Freeze, and Jerome Buzas: Synthesis and Enol Determinations of 2,2-Disubstituted 6-Cyanocyclohexanones.

Page 455. Line 46 of column 1. Ozbal reports that the cyano group of 2-cyanocyclohexanones adopts the eclipsed (equatorial) conformation preferentially 3:1. He determined the conformational free energy of CN as −0.66 kcal/mol by NMR analysis of the 2 proton. He attributes these results to strong electrostatic attractive forces. [References: personal communication; H. Ozbal, *Bogazici Univ. J.*, **2**, 95 (1975); H. Ozbal, Ph.D. Thesis, Villanova University, 1971.]

Wai Lee Tan, Carl Djerassi,* José Fayos, and Jon Clardy: Terpenoids. LXX. The Structure of the Sea Cucumber Sapogenin Holotoxinogenin.

Page 469. Table III. The last entry (z) in line 4 should be 0.0965.

Theodore Cohen,* Glen Herman, J. R. Falck, and Albert J. Mura, Jr.: Copper(I)-Promoted Thiophenoxide Ionization in Solution. A Simple Synthesis of Vinyl Phenyl Sulfides.

Page 812. In eq 3 (above Table I), the C^+ just before the arrow should read Cu^+; the formula just after the arrow should read RR′C=C(SPh)R″ and should be designated as compound **1**.

G. A. Dilbeck, Don L. Morris, and K. Darrell Berlin*: Carbon–Phosphorus Heterocycles. A New Route to Tetrahydrophosphinolines, Tetrahydroisophosphinolines, and Related Systems via Cyclization of Alkenyl-Substituted Phosphonium Salts with 115% Polyphosphoric Acid.

Page 1152. In Scheme III, **6a** should be $(C_6H_5)_3P^+CH_2CH{=}CHCH_3Br^-$.

Page 1156. Structure **14** is incorrect: one of the phenyl groups on the phosphorus should be an ethyl group.

James Z. Ginos: Precursors to Apomorphine and Morphinan Analogs. Studies on Catalytic Reduction of Quinoline and Isoquinoline.

Page 1193. Column 1, paragraph 2 of Conclusions, line 2. "**10**" should be **12**.

Masahiro Minabe and Kazuo Suzuki*: Stable Rotamers of 9,9′:9′,9″-Terfluorenyls at Room Temperature.

Page 1299. Column 2. In Figure 2, the names of the first and third structures have been transposed: the first structure is s-cis,s-cis (A); the third structure is s-trans,s-trans.

Rudolph A. Abramovitch,* Stanley R. Challand, and Yorinobu Yamada: Addition of Aryl Nitrenes to Olefins.

Page 1546. Column 2. Add the following before Registry No. paragraph.

Acknowledgment. This work was carried out with the support of a National Science Foundation grant for which we are grateful.

Werner Herz* and Ram P. Sharma: Complete Stereochemistry of Tenulin. Carbon-13 Nuclear Magnetic Resonance Spectra of Tenulin Derivatives.

Page 2559. Column 2. The following acknowledgment was inadvertently omitted. This work was supported in part by U.S. Public Health Service Grant CA-13121 through the National Cancer Institute.

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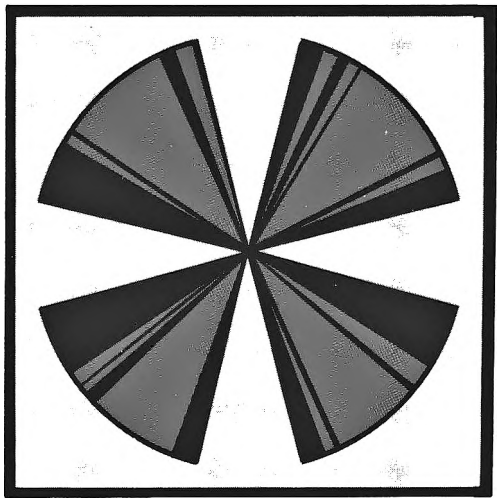

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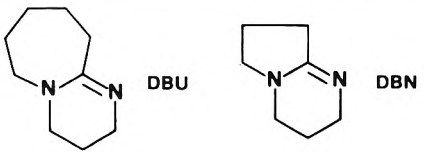
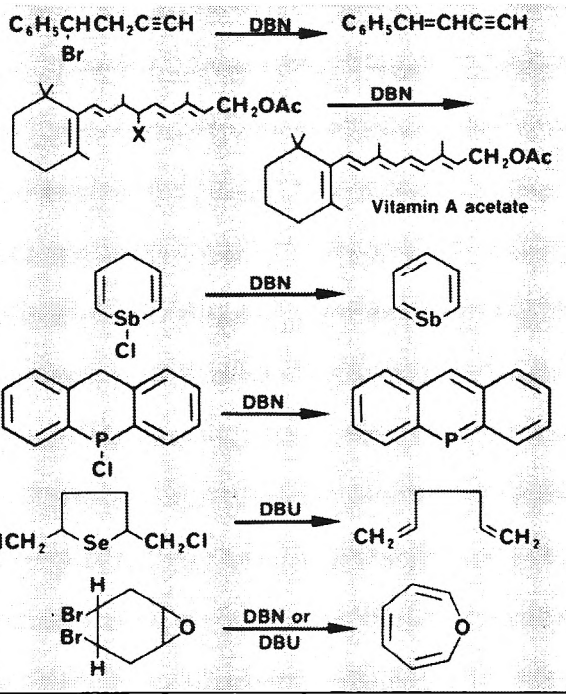
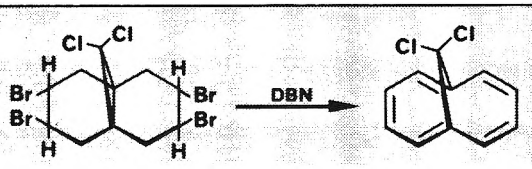
DBU and DBN: Reagents of choice for dehydrohalogenation



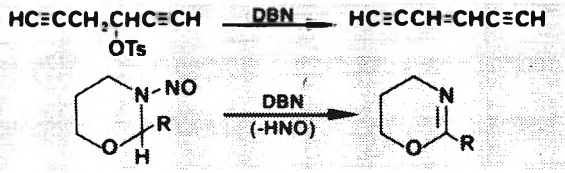
1,5-Diazabicyclo[5.4.0]undec-5-ene (DBU) and **1,5-diazabicyclo[4.3.0]non-5-ene (DBN)** are of particular interest as reagents in synthetic organic chemistry[1-3] since they have been shown to be extremely versatile dehydrohalogenating agents,[4-7] being more reactive than the amines generally used. As a result, much milder reaction conditions can be employed and even generally unstable compounds such as α,β-unsaturated terminal acetylenes can be prepared. **DBN** has been used in the preparation of Vitamin A acetate,[6] where other tertiary amines such as pyridine, *N*-methylmorpholine and *N,N*-dimethylaniline have failed. A large number of examples of dehydrohalogenation for the introduction of single or multiple double bonds have been reviewed.[3] Some interesting examples are highlighted below:



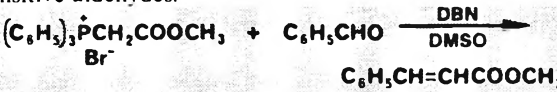


A comparison of the relative dehydrohalogenation activities of **DBU** and **DBN** using 4- and 2-bromoheptanes showed that **DBU** gave higher yields of the heptenes.[7]

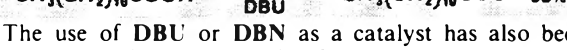
The use of **DBU** and **DBN** has been extended to the elimination of sulfonic acid and hyponitrous acid.[3]



DBN has also been used in Wittig reactions with alkali-sensitive aldehydes.[6]



An interesting application of **DBU** as a catalyst in the preparation of acid chlorides has been patented.[8]



The use of **DBU** or **DBN** as a catalyst has also been demonstrated in the synthesis of macromolecules such as polyurethanes and polyaryl ethers.[9]

References:

1) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, New York, N.Y., 1967, 1969 and 1974.
2) K. Yamakawa, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 429 (1971).
3) H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 591 (1972).
4) E. Truscheit and K. Eiter, *Ann. Chem.*, **658**, 65 (1962).
5) K. Eiter and H. Oediger, *ibid.*, **682**, 62 (1965).
6) H. Oediger *et al.*, *Chem. Ber.*, **99**, 2012 (1966).
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8) C.F. Hansen, German Patent 1,931,074 (1970) [*Chem. Abstr.*, **72**, 78472 (1970)].
9) H. Weiden and U. Bahr, German Patent 595,609; British Patent 1,134,613 [*Chem. Abstr.*, **70**, 29589 (1969)].

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