VOLUME 39 JANUARY 11, 1974 NUMBER 1 JOCEAH

THE JOURNAL OF Organic Chemistry

Notice to Authors and Readers, page 8A

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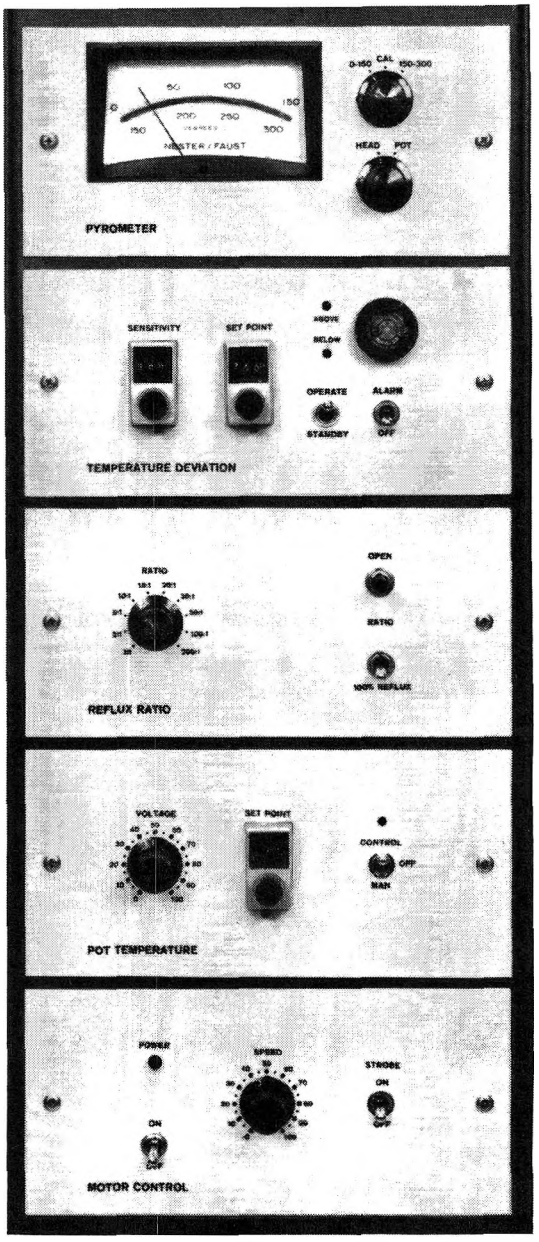

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AUTHOR INDEX

Notice to Authors and Readers

Rising costs confront all of us everywhere. In an effort to find ways to keep costs down or, at the least, to minimize the rate of increases in subscription prices and/or page charges, this journal, as part of a program of the American Chemical Society, is seeking evaluation of several publication experiments. One of these is "miniprinting," in which an author's typescript pages are reproduced directly in reduced size, nine manuscript pages to a single journal page. For many readers this degree of reduction will require magnification. This issue of the journal contains three articles, the Experimental Sections of which appear in "miniprint" (see pages 1-20).

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Frederick D. Greene, Editor

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VOLUME 39, NUMBER 1

JANUARY 11, 1974

Resin Acids. XXIV. Intramolecular Functionalizations of 11-Oxygenated Abietanes and Podocarpanes[1]

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Received July 24, 1973

The transformation of dehydroabietonitrile and podocarpic acid to 11-hydroxy- and 11-ketoabietanes and podocarpanes is described. Key reactions were metal–amine reductions of 12-methoxydehydroabietic acid, *O*-methylpodocarpic acid, 12-acetoxy-9(11)-abietenes, and 12-acetoxy-9(11)-podocarpenes. Hypoiodite reaction and oxidative cyclization of the C-11 alcohols and photochemical isomerizations of the C-11 ketones followed by oxidative cleavage resulted in functionalization at C-1 and C-18 of the resin acid skeleton. Differences in product distribution and ease of ether cleavage between this work and observations in the steroid series are attributed to the absence of an axial substituent on C-13. Chiroptical properties of two new isomers of methyl levopimarate are discussed in terms of the helicity rule.

Our previous studies on the partial synthesis of more complex diterpenoids from readily available resin acids were directed mainly at the introduction of modifications which permitted construction of tetracyclic and pentacyclic ring systems. Since many diterpenes of interest can be construed as being derived from 1-hydroxylated intermediates or are actually functionalized on ring A or on the C-10 methyl group, whereas most resin acids are not, it was desirable to test whether functionalization reactions developed in the steroid series[2-4] were also applicable to 11-oxygenated resin acid derivatives.

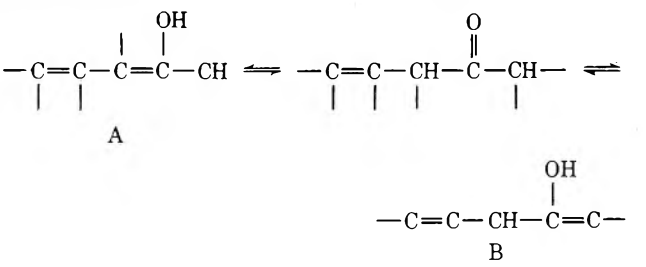
The synthesis of some 11-oxygenated abietanes was reported earlier,[5] but the low yields precluded further study of the products. In the present communication we describe the synthesis of 11-oxygenated abietanes and podocarpanes by a different route and report results of functionalization reactions which differ to some extent from observations in the steroid series.

Results and Discussion

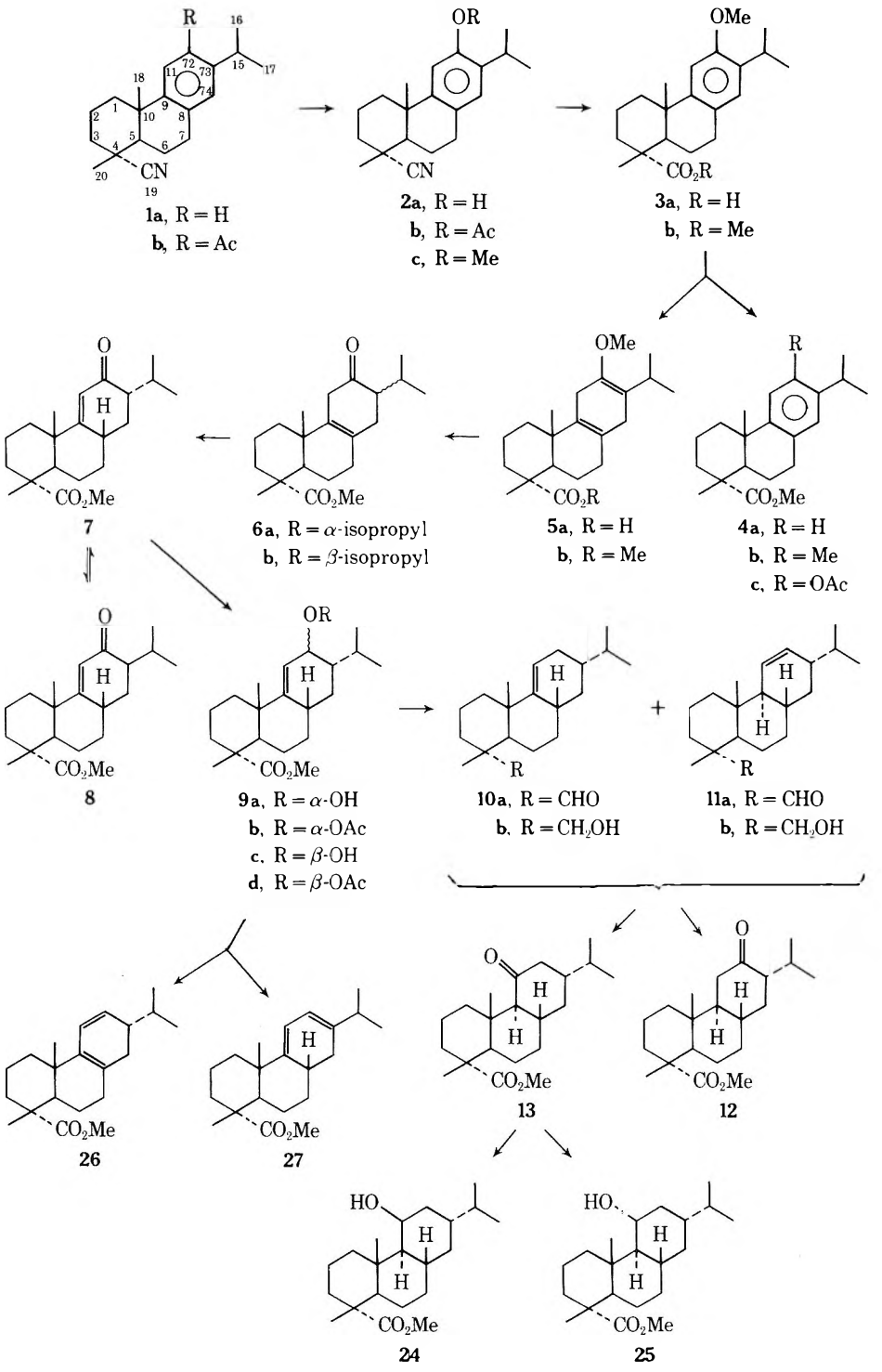
Synthesis of 11-Oxygenated Abietanes. Our first target was the α,β-unsaturated ketone **7** (Scheme I) which should result from dissolving metal reduction of 12-methoxydehydroabietic acid (**3a**). Since the previously described[6] route to **3a** proceeded only in poor overall yield, the following reaction sequence to **3a** was adopted. Dehydroabietonitrile (**1a**) underwent Friedel–Crafts acylation in 92% yield to **1b**[7] which gave a 76% yield of **2b** on treatment with 40% peracetic acid in chloroform. Hydrolysis to **2a** (quantitative yield, 1% HCl–MeOH, room temperature), methylation to **2c** (80% yield, *t*-BuOH, K^+t-OBu^-, CH_3I) and, finally, hydrolysis (NaOH, diethylene glycol–water, 170°) gave an 88% yield of **3a**.

Considerable effort was devoted to a study of the Birch reduction of **3a** with lithium, ethylamine, and *tert*-amyl alcohol (high-speed stirring).[8] This was followed by acidification and ether extraction of the product mixture, methylation of the acidic extract, treatment with 0.5% hydrochloric acid in methanol under carefully defined conditions (*vide infra*) to induce hydrolysis of **5b** and isomerization of **6** without equilibrating[9] **7** and **8**, and finally acetylation of the crude product to permit subsequent separation of the by-product **4b** from **7** and **8** in the form of **4c**. Chromatography of the product mixture gave **4a** (10%), **3b** (14%), **4c** (18%), **7** and **8** (4:1 ratio, 60% combined yield). The properties of **7** and **8** corresponded to those reported in our earlier publications.[9]

Hydrolysis and rearrangement of **5b** with 0.5% HCl could be followed closely by tlc. A new compound, presumably **6**, was formed rapidly and rearranged gradually to form a mixture of **7** and **8**. When the reaction mixture was worked up immediately after disappearance of **6** (2 hr), the ratio of **7** to **8** was 4:1; when the acid concentration was increased or the mixture was exposed to acid for a longer period, the ratio of **7** to **8** approached the equilibrium ratio (1:1).[9] Now acid-catalyzed enolization of β,γ-unsaturated ketones to conjugated enols of type A, which may be followed by rearrangement to α,β-unsaturated ketones, proceeds much faster than enolization to unconjugated enols of type B;[10] hence rearrangement of the double bond of **6** should proceed faster than epimerization of the isopropyl group. Consequently the 4:1 ratio of **7** to **8**



Scheme I



reflects the ratio of the initially obtained C-13 epimers of **6**, since **6** is the product of kinetically controlled protonation at the α carbon and favors axial addition of the proton to the least hindered side of the enol ether.[11a] Dreiding models (Figure 1) reveal that that conformation of **5b** which would yield **6a** by protonation from the β side is preferred over the conformation which would yield **6b** by protonation from the α side because 1,3 interactions between the two hydrogens at C-11 and the C-18 methyl and the C-1 methylene group are minimized. The observed preference for the formation of **6a**, and therefore **7**, was fortunate, since in a trans-anti-trans-fused perhydrophenanthrene a β-oriented isopropyl group could compete with the C-10 methyl group for functionalization from the C-11 position and thus negate the proposed reaction sequence.

With the α,β-unsaturated ketone **7** in hand, its further transformation to the desired alcohols **24** and **25** (Scheme I) could be studied. $NaBH_4$ reduction of **7** gave a mixture of alcohols, one of which (**9c**) could be isolated in crystalline form. The configuration of the hydroxyl function was

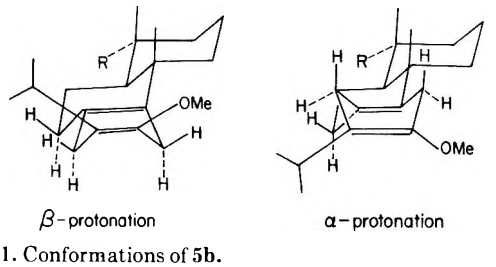
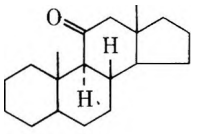


Figure 1. Conformations of **5b**.

apparent from the half-height width of the H-11 resonance at 5.32 ppm (5 Hz) and the shape of the H-12 resonance at 4.08 ppm (d br, $J_{12,13}$ = 9 Hz), which indicated that the H-11–H-12 dihedral angle was near 90°. By contrast the H-12 signal of the epimer **9a** was a broad peak ($W_{1/2}$ = 22 Hz). Reduction of the mixture of allylic acetates **9b** and **9d** with lithium in ethylamine gave a mixture of isomeric aldehydes **10a** and **11a** and alcohols **10b** and **11b**, in 87% yield (ratio of $\Delta^{9(11)}$ to Δ^{11} olefins was 5:1). Hydroboration–oxidation of this mixture followed by oxidation with Jones reagent and methylation afforded the known ketone **12** of established stereochemistry[9] (8% yield), and a new ketone **13** (64% yield) whose stereochemical assignment is based on the following observations. The chemical shift of the C-10 methyl signal (1.08 ppm) is almost the same as that of **14** (Scheme II, 1.09 ppm)[5] and is in consonance with Zürcher's rules[12] which are based on the observed influence of substituents on the chemical shift of angular methyl groups in steroids. A broadened absorption at 2.16 ppm ($W_{1/2}$ = 9 Hz) was assigned to the two C-12 protons and a broadened doublet at 2.48 ppm (J = 12 Hz) to the β proton at C-11 which is strongly shielded by the 11-ketone. Similar resonances in the region 2.1–2.6 ppm are displayed by **14** and by **15**,[13] the resonance due to the C-1β proton having been identified by deuterium exchange.



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The CD curve of ketone **13** displayed a negative Cotton effect ($[\theta]_{294}$ = −1050). Ketone **14** also exhibited a negative Cotton effect, although 11-keto steroids with trans B/C ring junctions display weak positive/Cotton effects.[14] The reasons for this apparent discrepancy have been discussed previously.[5] Finally, the mass spectral fragmentation of **13** was similar to that reported for **15**,[15] if allowance is made for the presence of substitution at C-4, the presence of the isopropyl group, and the absence of ring D. Ketone **15** undergoes a McLafferty rearrangement followed by three fragmentations, one of which is responsible for the base peak. An analogous process can explain the formation from **13** of three major peaks at m/e 139, 153, and 165.

We observed previously[5] that attack of diborane on **16** occurred preponderantly from the β side (Scheme II) and that oxidation of the resulting alcohol mixture yielded cis ketone **20** in 80% yield. Ketone **20** was epimerized by base to the more stable trans ketone **14**. In the present work no cis ketone **23** was isolated when **10** was subjected to a similar reaction sequence. Examination of Dreiding models (see Figure 2) suggests that attack of diborane on **10** and on **16** should occur predominantly from the β side, but that α attack on **10** is less obstructed than α-attack on **16**. β Attack on **10** would yield alcohol **22**, which, if rings B and C were in chair conformations, should orient the isopropyl group axially, thus resulting in a strong interaction with the C-7 methylene group. Flipping the B and/or C ring into a boat conformation would not significantly reduce the interaction, nor would oxidation to the cis ketone **23** reduce the strain. Thus alcohol **22** and ketone **23** are expected to be of higher energy than **18** and **20**, respectively. On the other hand, formation from **23** of a $\Delta^{9(11)}$-enol or enolate would relieve more strain than formation of a similar compound from **20**; thus steric acceleration should cause **23** to enolize faster, with eventual conversion to the thermodynamically favored trans ketone **13**, than

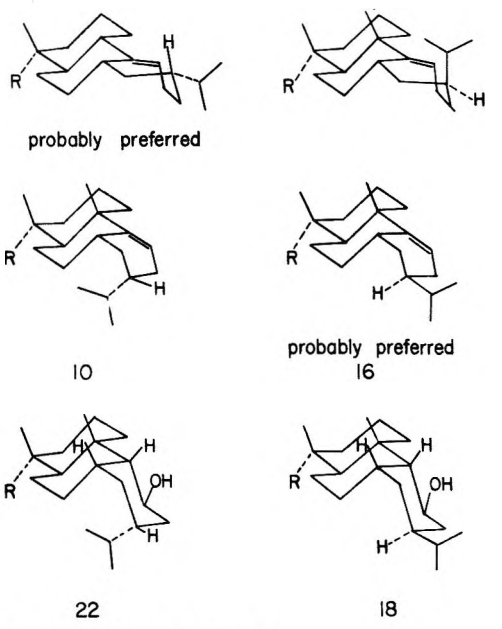
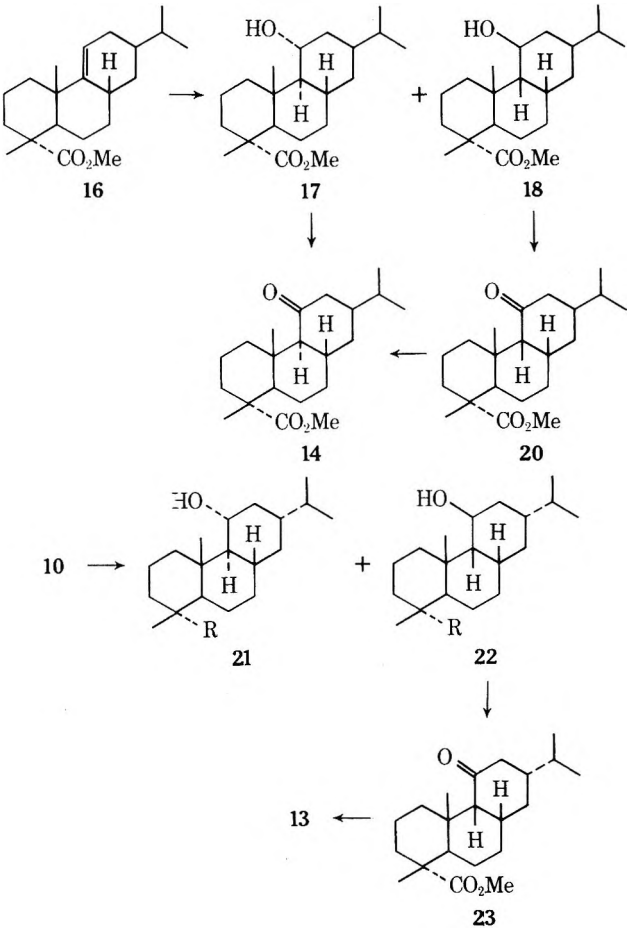


Figure 2. Hydroboration of **10** and **16**.

20. It is therefore not surprising that any cis ketone **23** obtained by oxidation of the alcohol mixture formed from olefin **10** is isomerized to the more stable ketone **13** more rapidly than **20** is isomerized to **14**.

Scheme II



Although the hindered ketone group of **13** was not affected by $NaBH_4$ in methanol at room temperature, reduction with $NaBH_4$ in THF and aqueous NaOH furnished the desired two epimeric alcohols **24** and **25** (85%, 11:9 ratio). The C-10 methyl resonance of the major alco-

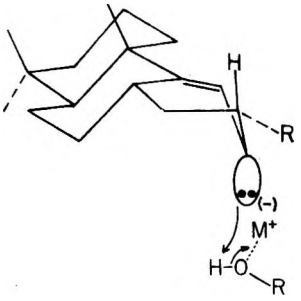


Figure 3. Anions from hydrogenolysis of **9b**, **9d**, and **32b**.

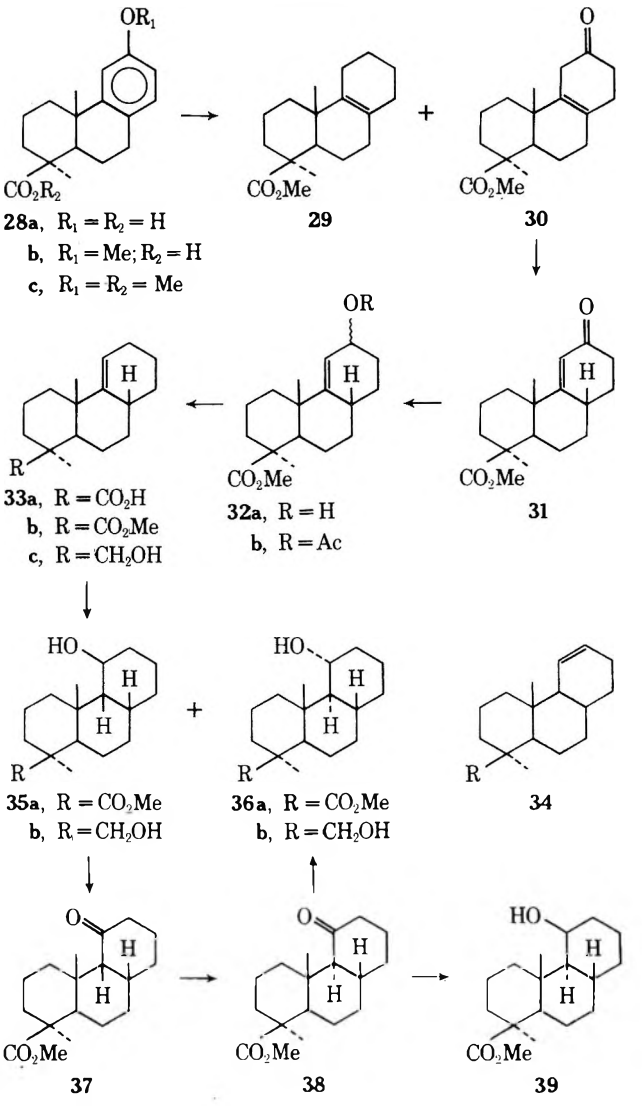
hol **24** (Scheme I) exhibited a chemical shift (1.16 ppm) near the value (1.14 ppm) previously[5] observed for the C-13 epimer and $W_{1/2}$ (11 Hz) of the H-11 signal at 4.31 ppm was characteristic of an equatorial proton coupled to two axial protons (H-9α, H-12α) and one equatorial proton (H-12β). The C-10 methyl resonance of the minor alcohol **25** at 1.03 ppm was near the value reported[5] for its C-13 epimer. The H-11 resonance at 3.64 ppm, under the three-proton singlet of the methyl ester function, was made visible by use of the Eu(fod)$_3$ shift reagent; $W_{1/2}$ (20 Hz) was characteristic of an axial proton coupled to two axial protons (H-9α and H-12α) and one equatorial proton (H-12β). Further evidence for the assigned stereochemistry was a broadened doublet at 2.39 ppm (J = 12 Hz) attributed to H-1β which is deshielded by the α-oriented hydroxyl group.

Synthesis of 11-Oxygenated Podocarpanes. The proposed reaction sequence for the synthesis of these compounds (Scheme III) was identical with that adopted in the abietic acid series. *O*-Methylpodocarpic acid (**28b**) was reduced with lithium in liquid NH_3–THF with *tert*-amyl alcohol as the proton source. Methylation of the crude product with diazomethane, rearrangement with 5% HCl in methanol, and chromatography afforded **29** (26%),[16] methyl *O*-methylpodocarpate **28c** (3%) and the two ketones **30** and **31** (52%). The less polar unconjugated ketone **30** could be isomerized to the more polar ketone **31**, which had the expected spectral properties.[17,18] $NaBH_4$ reduction of **31** gave a single allylic alcohol **32a** (or a mixture of epimeric allylic alcohols which could not be separated).[19] Conversion to the acetate **32b** followed by hydrogenolysis with lithium in ethylamine gave a mixture of **33a** (21%), characterized as **33b**, and **33c** (46%). The nmr spectra of these compounds in the vinyl region were similar to the nmr spectra of **10a** and **10b**, an observation which indicated that little if any Δ^{11} isomer **34** was present. An explanation of this result is the following.

In the hydrogenolysis leading to the podocarpenes **33a** and **33c**, approach of the bulky proton source (*tert*-amyl alcohol) to the most stable conformation of the planar allylic carbanion (Figure 3) from the α side is relatively unhindered and the $\Delta^{9(11)}$ olefin should be formed in high yield as actually observed. In the carbanion leading to the abietenes **10** and **11**, on the other hand, the α-oriented isopropyl group partially obstructs α approach of the bulky proton source and should therefore reduce the preference for formation of the more stable $\Delta^{9(11)}$ olefin.

Hydroboration–oxidation of the mixture of **33b** and **33c** followed by oxidation with chromic acid–acetic acid and subsequent methylation with diazomethane gave two keto esters which were difficult to separate. The less polar substance (20% yield) was assigned structure **37** with a cis B/C ring junction because it was isomerized by acid; the second more polar keto ester **38** was obtained in 55% yield. The characteristically deshielded resonances of H-12 and H-1β (*vide supra*) were masked by signals of other protons deshielded by the axial carbomethoxy

Scheme III



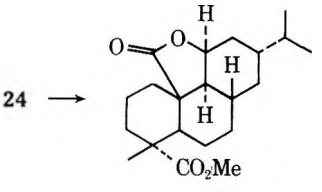
group, but the CD curve (Θ_{295} = −4360) was in harmony with the proposed stereochemistry. The groups of **38** which provide negative contributions are similar to those of keto ester **13**. However, there are two important differences. The positive contribution of the isopropyl group is no longer present and the axial carbomethoxy group located in the upper right rear octant probably provides an additional negative contribution. The Cotton effect of **38** should therefore be somewhat more negative than that of **13**, as was actually observed. Moreover, three major peaks in the mass spectrum of **13** at m/e 97, 110, and 123 correspond to the fragmentations observed in the mass spectra of **13** and **15**.

As described in the previous section, the main direction of diborane attack on **33** should be from the β side. The cis B/C alcohol **35** and cis ketone **37** obtained from it should be of lower energy than the corresponding abietanes **22** and **23** because of the absence of an axially oriented isopropyl group. Enolization of **37** (and its isomerization to **38**) would therefore result in relief of less strain and should therefore be slower than enolization (and isomerization) of the corresponding cis ketone **22** of the abietane series. On the other hand, cis ketone **37** should enolize and isomerize faster to the more stable trans ketone **38** than cis ketone **18** enolizes and isomerizes to trans ketone **14**, for **14** has an axial isopropyl group and should be of higher energy than **38**. However, the actual isomer ratios obtained after hydroboration–oxidation in the podo-

carpane series are not strictly comparable to the isomer ratios in the abietane series because of the need for a more strongly acidic medium to achieve oxidation of the axial carbinol function in the podocarpanes **35a** and **36a**. Hence oxidation of the crude alcohols of the podocarpane series may have been accompanied by partial epimerization.

$NaBH_4$ reduction of **38** in refluxing THF containing NaOH yielded alcohols **36a** and **39**, which were very difficult to separate, in approximately equal amounts. Structures were assigned by nmr spectroscopy, the C-10 methyl resonance of **39** being more deshielded (0.92 ppm) than that of **36** (0.82 ppm) and $W_{1/2}$ of H-11 in **39** (8 Hz) being considerably smaller than $W_{1/2}$ of H-11 in **36** (20 Hz).[20]

Functionalization Reactions. A. The Lead Tetraacetate–Iodine Reagent. Reaction of lead tetraacetate–iodine with **24** in cyclohexane gave a mixture (tlc) which on oxidation with Jones reagent afforded a complex mixture (tlc). Preparative tlc resulted in isolation of a lactone **40** (49%), obviously produced by oxidation of the corresponding hemiketal, whose infrared (carbonyl bands at 1760 and 1722 cm^{-1}) and nmr spectra (lack of the C-10 methyl signal, broadened one-proton resonance of H-11 at 4.77 ppm, $W_{1/2}$ = 7 Hz) were consonant with the proposed structure. The downfield shift of the H-11 signal indicated esterification; its half-height width showed that it had remained α and equatorial. Moreover, the model indicated that the C-4 methyl group was located within the deshielding influence of the lactone function, thus accounting for the downfield shift of the C-4 methyl resonance to 1.54 ppm. A similar lactone **41** was isolated in 40% yield after oxidation of the crude product obtained by lead tetraacetate–iodine oxidation of **39**. Disappearance of the C-10 methyl signal, downfield shift of the H-11 resonance, and a new infrared frequency at 1762 cm^{-1} (γ-lactone) supported the structure proposal.



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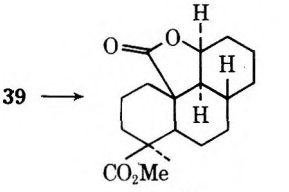
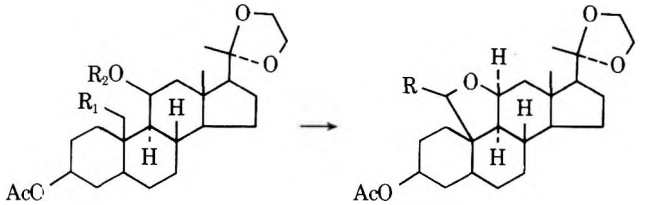


41

These results are slightly at variance with previously reported results in the steroid series, but can be easily rationalized in terms of the mechanism proposed for the hypoiodite reaction[2-4] and in fact serve to buttress it. Oxidation of the 11β-hydroxypregnane derivative **42a** afforded[21]

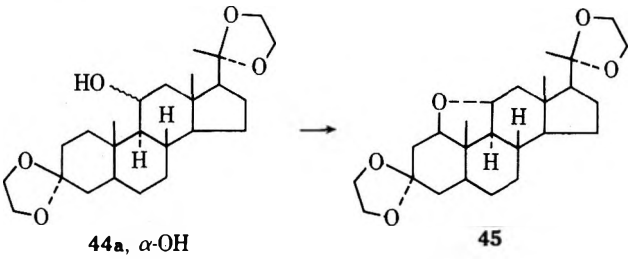


42a, $R_1 = R_2 = H$
b, $R_1 = I; R_2 = H$
c, $R_1 = R_2 = I$

43a, R = H
b, R = OH
c, R = I

ether **43a**, hemiketal **43b**, and C-18 functionalized products, although formation of an ether normally requires colinearity of iodine, carbon, and oxygen in the first intermediate, an iodohydrin, of the general reaction scheme and this condition is not fulfilled in the case of **42b** and the corresponding iodohydrins from **24** and **39**. In the case of **42a**, the formation of **43a** has been ascribed to steric factors which interfere with formation of hypoiodite **42c**, the precursor of **43c** and thence of **43b**, a situation which opens the way to a competing ring closure of **42b** to **43a**, "probably by an ionic mechanism."[3] In the case of **24** and **39**, the absence of an axial C-13 methyl group removes the obstacle to formation of the second hypoiodite corresponding to **42c** and allows the reaction to take a normal course, although the presence of a small amount of ether **49** (*vide infra*) corresponding to **43a** in the steroid series in the crude reaction product cannot be excluded. Similarly, if products are present which are the result of a "billiard-ball" reaction[22] on the axially oriented C-4 methyl group of **24**, they could not be isolated.

Subjection of **25** to the hypoiodite reaction yielded a complex mixture, none of whose components could be isolated or characterized. In the steroid series, hypoiodite reaction of the 11α-hydroxypregnane derivative **44a** resulted in functionalization at C-1 and formation of ether **45**.[23] The complexity of products in the case of **25** may

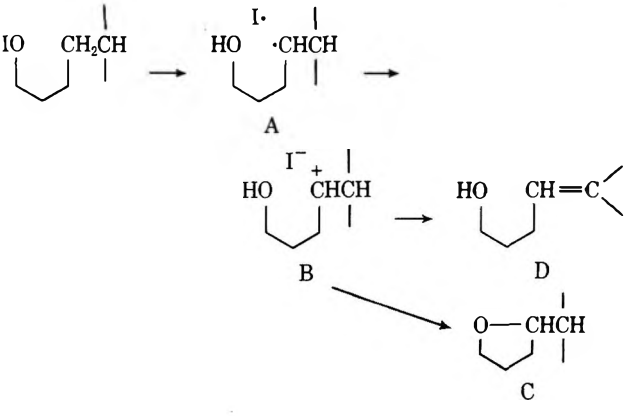


44a, α-OH
b, β-OH

45

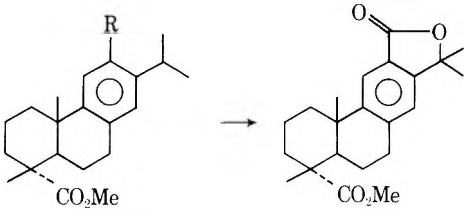
conceivably be rationalized in terms of the reaction sequence proposed for substitution on secondary and tertiary carbon.[3,4] If combination of the initially formed radical A (Scheme IV) with iodine is hindered, as in the radical resulting from decomposition of the hypoiodite of **25** and subsequent hydrogen transfer, electron transfer may lead to an ion pair B which can form an ether C by an ionic mechanism or stabilize itself by elimination of a proton to D. In the case of the resin acids, elimination of a proton from C-1 might be favored because a 1,2 double bond forces ring A into a quasi-boat conformation which relieves the strong 1,3 interaction between the C-10 methyl group and the axial substituent on C-1. Further possible complicating transformations of such olefinic alcohols under the influence of lead tetraacetate–iodine have been discussed.[3,4]

Scheme IV



Because of the disappointing results with **25**, no attempt was made to carry out a similar reaction on the analogous podocarpane derivative **36a**. However, the outcome of another hypoiodite reaction not directly related to the work so far described in this section merits brief discussion.

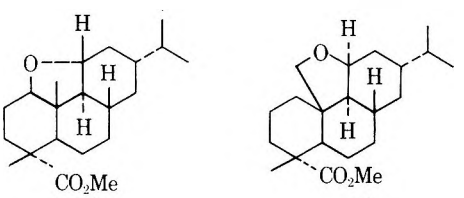
Cambie and Franich[24] have reported the successful functionalization of the isopropyl group of a dehydroabietic acid derivative by conversion of **46a** to **47** on treatment with lead acetate in benzene. The availability of **46b** and its facile conversion to a mixture of epimeric alcohols **46c**[25] suggested that hypoiodite oxidation of **46c** might provide another entry to C-15 functionalized resin acids. However, the product of this reaction was quite unexpectedly the lactone **47** (55% yield). This is obviously the result of a fragmentation of the originally formed O radical which is followed by oxidation of the fragmentation product **46d** to **46a** and subsequent functionalization at C-15 as observed previously.[24] The activation energy for intramolecular hydrogen abstraction reaches a minimum in rigid systems with a C–O distance of 2.5–2.7 Å.[4] In **46c**, however, the C–O distance (measured from Dreiding models) is 2.25 Å. The closeness of the reacting centers reduces their ability to orient properly for hydrogen abstractions and greatly increases the chance for the competing fragmentation to **46d**.



46a, R = CO_2H
b, R = Ac
c, R = $CHCH_3$ (OH)
d, R = CHO

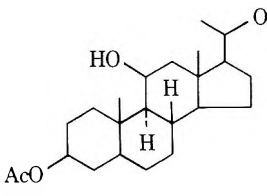
47

B. Oxidative Cyclization with Lead Tetraacetate. Because the hypoiodite reaction failed to yield the desired 1,11 ethers, attention was turned to oxidative cyclization with lead tetraacetate, for in rigid, hindered systems this reaction is believed to produce ethers without generation of carbonium ions.[2,4,26] Indeed, treatment of **25** with $Pb(OAc)_4$ in cyclohexane afforded two ethers. The more polar substance (33% yield) was assigned structure **48** in view of its nmr spectrum, which retained the three-proton singlets of the C-10 methyl (0.84 ppm), the C-4 methyl (1.28 ppm), and the carbomethoxyl group (3.65 ppm). A two-proton resonance hidden under the latter was made visible by the $Eu(fod)_3$ shift reagent and resolved into a doublet of doublets (H-1α) which was coupled to H-2β (J = 8.5 Hz) and H-2α (J = 5.5 Hz), and a doublets (H-11β) which was coupled to H-9α (J = H-12α (J = 10 Hz), and H-12β (J = 5 Hz). The less product (40% yield) was formulated as **49**, presumably the result of a reversible fragmentation leading to epimerization of starting material during $Pb(OAc)_4$ treatment,[3] because the nmr spectrum displayed only two methyl singlets at 0.95 (C-4 methyl) and 3.66 ppm (carbomethoxyl), a one-proton resonance characteristic of an equatorial H-11 proton (4.24 ppm, $W_{1/2}$ = 7 Hz) similar to H-11 of **24**, and an AB quartet centered at 3.80 ppm characteristic of the two hydrogens on C-20.



48

49



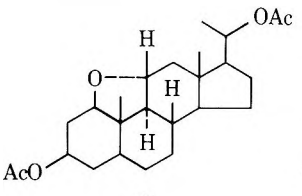
50

The products from **25** indicate that partial isomerization of an equatorial alcohol (**25**) to an axial alcohol (**24**) has taken place. By contrast, lead tetraacetate treatment of the equatorial alcohol **44a** furnished only the 1β,11α ether **45**[27a] without epimerization, whereas the axial 11β-hydroxy steroid **50** gave, in addition to 11β,18 and 11β,19 ethers, the 1β,11α ether **51**[28] by partial epimerization of an axial to an equatorial alcohol.

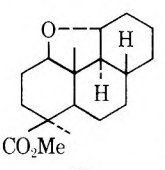
These differences can be rationalized by comparing the steric interactions experienced by α- and β-oriented hydroxyl functions in steroids **44a** and **44b** (or **50**) with those in the abietanes **24** and **25**. The equatorial 11α-hydroxyl group in both steroids and abietanes is rigidly positioned near the C-1 methylene group such that the C–O distance is 2.5 Å (measured on Dreiding models). The interaction between the 11α-hydroxyl group and the C-1 methylene of **44a** and **25** should therefore be approximately equal to the 1,3-diaxial interaction between the axial 11β-hydroxyl and the C-10 angular methyl group of **44b** or **50** and **24**, for in these substances the C–O distance is also 2.5 Å. In the case of steroid **44b** (or **50**), the axial hydroxyl experiences an additional 1,3-diaxial interaction with C-19; hence the axial alcohol is of higher energy than the equatorial alcohol to which it might be expected to epimerize.

Abietane **24**, on the other hand, should be of approximately the same energy as **25**. Both alcohols might, therefore, be expected to produce a mixture of epimers when exposed to oxidative cyclization with lead tetraacetate. This was observed experimentally; treatment of **24** with lead tetraacetate gave a mixture of **48** (13%) and **49** (54%).[29]

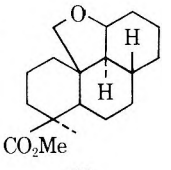
In analogy with the results in the abietane series, podocarpane **36a** furnished 1β,11α ether **52** in 33% yield and 11β,19 ether **53** in 38% yield. Treatment of podocarpane **35a** with lead tetraacetate–cyclohexane also gave **52** (40%) and **53** (30%).



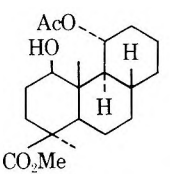
51



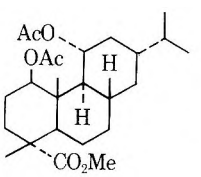
52



53



54



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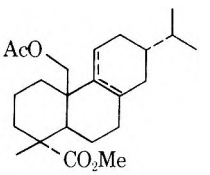


56a, 8,9 db
b, 9,11 db

Oxidation of ethers **49** and **53** (CrO_3–HOAc–Ac_2O) resulted in disappointingly poor yields of lactones **40** and **41**, presumably because of the obstruction presented to the oxidizing agent by the axial group at C-4. Cleavage of **52**

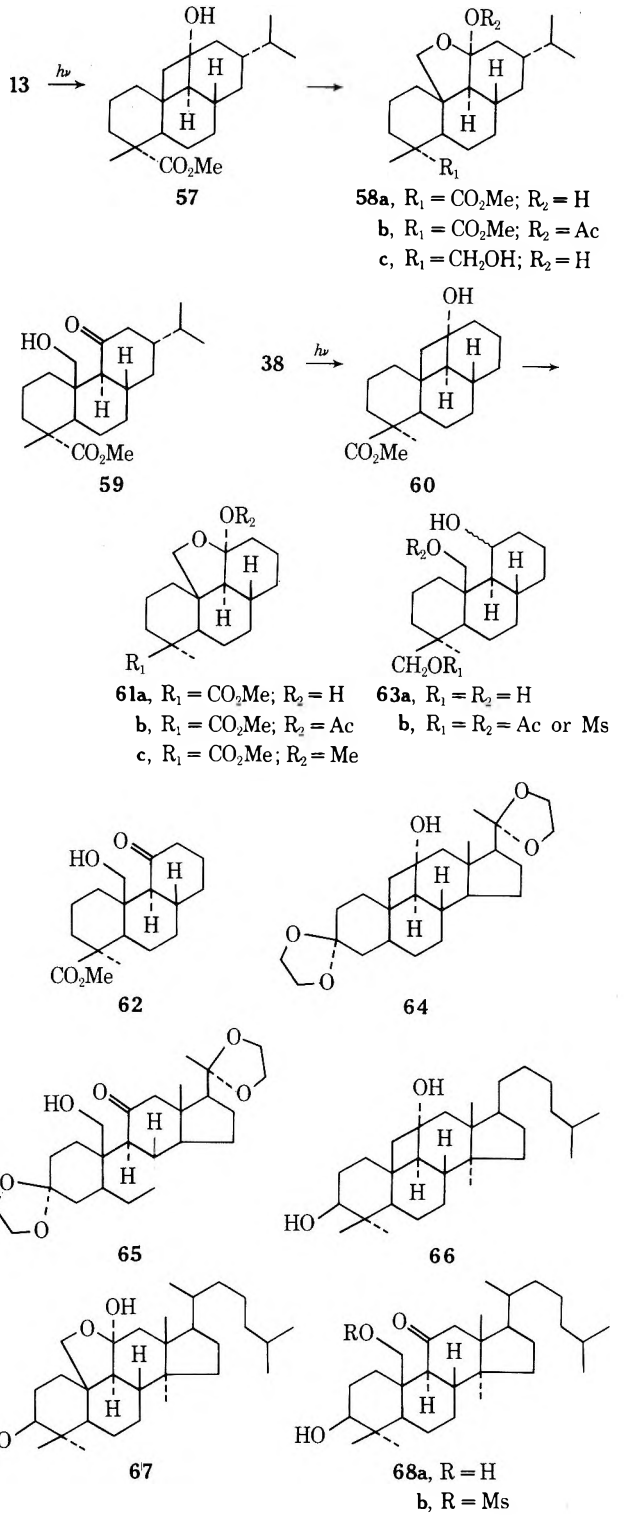
with acetic anhydride–boron trifluoride etherate[30] furnished a complex mixture from which **54** was isolated in 34% yield. Structure assignment was based on the observation that the one-proton resonance at lowest field (5.00 ppm, $W_{1/2}$ = 18 Hz) corresponded to that of H-11 in **36a** and that the chemical shift and coupling constant of a second signal (triplet at 3.56 ppm, J = 8 Hz), made visible with the shift reagent Eu(fod)$_3$, were characteristic of H-1α.[31] An analogous cleavage reaction of **48** gave **55** in 38% yield. BF_3 cleavage of **49** gave a mixture of **56a** and **56b.**

The preceding results indicate that while oxidative cyclization of 11-hydroxyabietanes and podocarpanes with lead tetraacetate proceeds quite efficiently, the reaction is not as selective as in the steroid series, since the direction of functionalization is not dependent on the original configuration of the 11-hydroxyl group.

C. Photoisomerization of 11-Ketones. Irradiation of **13** (quartz apparatus, Corex filter[33]) resulted in quantitative conversion to the cyclobutanol **57,** as indicated by disappearance of the ketone frequency from the ir spectrum, the appearance of OH absorption, and the disappearance of the C-10 methyl signal from the nmr spectrum. Cleavage of **57** with Pb(OAc)$_4$[34] did not furnish the expected hydroxy ketone **59,** but the hemiketal acetate **58b,** which could be hydrolyzed to **58a** and reduced (LiAlH$_4$–ether) to **58c.** Similarly, photoisomerization of **38** provided **60,** which was cleaved to **61b.** The latter was hydrolyzed to **61a,** which was stable in the hemiketal form. **58a** and **60a** were resistant toward oxidation attempts; reduction of **61a** (LiAlH$_4$–THF) furnished the triol **63a,** which could not be converted to derivatives in which the primary hydroxyl groups were protected selectively.

Hemiketal acetates have been isolated as products of the lead tetraacetate cleavage of certain strained tertiary alcohols,[35] but not from steroidal or triterpenoid cyclobutanols corresponding to **57** and **60.** The product formed by lead tetraacetate cleavage of **64** exists entirely in the hydroxy ketone form **65.**[34] Lead tetraacetate treatment of cyclobutanol **66** from 11-oxolanostanol, on the other hand, yields a hemiketal **67** which can be opened with base to the keto mesylate **68b.**[36] Attempts to duplicate this reaction with **61a** resulted only in recovery of starting material or formation of **61c.**

These differences in the hemiketal–hydroxy ketone equilibrium of the diterpenoids **58a** and **61a,** the steroid **65,** and the triterpenoid **67** can be rationalized as follows. (1) Formation of a hemiketal will reduce the interaction between an axial substituent at C-4 and the substituted C-10 methyl group by incorporating the hydroxyl group in a ring, thus favoring the hemiketal over the hydroxy ketone form. (2) Formation of a hemiketal introduces a new interaction between an axial substituent on C-13 and the axial substituent on C-11, thus favoring the hydroxy ketone over the hemiketal form. In steroid **65,** the absence of an axial substituent on C-4 and the presence of an axial substituent on C-13 both favor the hydroxy ketone form. In triterpenoid **67** the presence of an axial C-4 substituent shifts the equilibrium toward the hemiketal, but the presence of an axial substituent on C-13 permits displacement of the equilibrium toward **68a** under appropriate circumstances. In diterpenoids **58a** and **61a,** the presence of an axial C-4 substituent and the absence of an axial C-13 substituent conspire to favor the hemiketal forms over the hydroxy ketone forms **59** and **62** to such an extent that formation of derivatives of the latter is difficult, if not impossible. This result has so far interfered with utilization of the present route to C-10 methyl functionalized diterpenoids, although the photoisomerization reactions proceeded in high yield.



New Isomers of Levopimaric Acid. The availability of the acetates **9** from the synthesis of the 11-oxygenated abietanes suggested the possibility of conversion to the methyl levopimarate isomer **27** (Scheme I), which is of interest because of its chiroptical properties. This substance lacks the interactions which are probably responsible[37] for the "folded" conformation of levopimaric acid, originally invoked[38] to account for its deviation from what is now known as the cisoid helicity rule;[39] moreover, it is conceivable that **27** may be a component of the complex mixture which constitutes pine oleoresin.

In fact, pyrolysis of **9b** and **9d** by the method of Girotra and Zalkow[40] afforded a mixture of dienes **26** and **27** which was extremely difficult to separate. Very small amounts of pure samples were eventually obtained by re-

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Experimental Section[41]

(41) For details concerning methods, see footnote 32 of Ref. 1.

12-Acetyldehydroabietonitrile (1b)[7].--To a solution of 26.8 g of dehydroabietonitrile (Hercules Inc.) in 200 ml of tetrachloroethane cooled to 0° (dry atmosphere) was added 10 ml of acetyl chloride and 26.5 g of aluminum chloride. The mixture was stirred at 0° for 24 hr, poured into water and extracted with $CHCl_3$. The washed and dried extract was evaporated; the residue was recrystallized from methanol-water, yield 27.5 g of 1b, mp 157.5-158°, $[\alpha]_D^{25}$ + 97.0° (c, 0.320; 95% ethanol), ir bands at 2247 (nitrile) and 1692 cm^{-1}; nmr signals at 1.18 (C-10 methyl), 1.26d (J=6.5 Hz, isopropyl), 1.40 (C-4 methyl), 2.50 (methyl ketone), 7.00 and 7.26 ppm (aromatic protons).

Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.61; H, 9.19; N, 4.54.

12-Acetoxydehydroabietonitrile (2b).--A mixture of 10 g of 1b in 30 ml of $CHCl_3$ and 90 ml of 50% peracetic acid was stirred for 48 hr in the dark, poured into water and extracted with ether. The washed and dried ether extract was evaporated and the residue was recrystallized from ethanol-water, yield of 2b 8 g, mp 137.5-139°, ir bands 2250 (nitrile) and 1770 cm^{-1} (ester); nmr signals at 1.18d (J=6.5, isopropyl), 1.19 (C-10 methyl), 1.42 (C-4 methyl) 2.30 (acetate), 6.86 and 7.05 ppm (aromatic protons).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, r.13. Found: C, 77.83; H, 8.69; N, 4.17.

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12-Hydroxydehydroabietonitrile (2a).--A solution of 0.5 g of 2b in 20 ml of CH_3OH and 2.7 ml of conc. HCl was allowed to stand for 24 hr at room temperature, diluted with water and extracted with ether. The washed and dried ether extract was evaporated; the residue (quantitative yield of 2a) was recrystallized from methanol-water, mp of 2a 205.5-207°, $[\alpha]_D^{25}$ + 34.4° (c, 0.329, 95% ethanol), ir bands 3430 (-OH) and 2248 (-CN), nmr signals at 1.16 (C-10 methyl), 1.21d (J=6.5 Hz, isopropyl), 1.39 (C-4 methyl) 6.54 and 6.82 ppm (aromatic protons).

Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.58; H, 9.35; N, 4.80.

12-Methoxydehydroabietonitrile (2c).--To a solution of potassium t-butoxide, prepared from 1 g of potassium, and 100 ml of t-butyl alcohol (nitrogen atmosphere) was added 3 g of 2a. When solution was complete, 10 ml of CH_3I was added slowly with stirring for 3 hr. The solvent was removed at reduced pressure, and the residue was taken up in ether. The washed and dried ether extract was evaporated and the residue was recrystallized from ethanol-water, yield of 2c 2.53 g, mp 95-96°, $[\alpha]_D^{25}$ + 115° (c, 0.494, 95% ethanol), ir bands 2247 cm^{-1} (nitrile), nmr signals at 1.22d (J=6.5 Hz, isopropyl), 1.23 (C-10 methyl), 1.43 (C-4 methyl), 3.86 (methoxyl), 6.82 and 7.04 ppm (aromatic protons).

Anal. Calcd for $C_{21}H_{29}NO$: C, 80.98; H, 9.38; N, 4.50 Found: C, 81.05; H, 9.25; N, 4.49.

12-Methoxydehydroabietic Acid (3a).--A mixture of 2 g of 2c, 20 ml of diethylene glycol, 0.5 ml of H_2O and 1 g of NaOH was heated with stirring (nitrogen atmosphere) for 16 hr at 170°. The condenser

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was temporarily removed to drive off water and replaced. The mixture was refluxed at 200° for 6 hr, cooled, poured into H_2O and extracted with ether. The aqueous layer was acidified and extracted with ether. The washed and dried ether extract was evaporated and the residue recrystallized from ethanol-water, yield 1.82 g of 3a, mp 205-205°, $[\alpha]_D^{25}$ + 29.0° (C, 0.517, 95% ethanol), ir bands 3400 br (-OH) and 1640 cm^{-1} (carboxyl), nmr signals at 1.20d (J=6.5 Hz, isopropyl), 1.25 (C-10 methyl) 1.28 (C-4 methyl), 3.80 (methoxyl), 6.80 and 6.92 ppm (aromatic protons).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; O, 14.52. Found: C, 76.70; H, 9.28; O, 14.59.

Birch reduction of 3a.--A)[42] To a solution of 0.3 g of 3a

(42) A. W. Burgstahler and L. R. Worden, J. Am. Chem. Soc., 86, 96 (1964).

in 3.78 ml of dry t-butylalcohol was added 300 ml of ethylamine, dried and condensed by having been passed through a U-tube containing glass wool and KOH and a dry ice-isopropyl alcohol condenser. 0.48 g of Li wire was added in two portions with stirring; this was followed by 4.4 ml of t-butyl alcohol. The reaction mixture was stirred at reflux until the lithium was consumed and ethylamine was driven off with the aid of a stream of nitrogen. The residue was dissolved in water, acidified with NH_4Cl followed by 10% HCl and extracted with ether. The washed and dried ether layer was evaporated and methylated with diazomethane. Tlc showed the presence of 7 spots. Preparative tlc permitted the isolation of two pure

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compounds; 1) Methyl vinyl ether 5b (44% yield), gum, ir bands 1720 cm^{-1} (ester), nmr signals at 0.97d (J= 7 Hz, isopropyl), 1.07 (C-10 methyl), 1.25 (C-4 methyl), 3.58 (ester methoxyl), 3.72 ppm (ether methoxyl); 2) Methyl 12-hydroxydehydroabietate 4b (13% yield), mp 157-158°, nmr signals at 1.20 (C-10 methyl), 1.25d (J=6Hz, isopropyl, 1.30 (C-4 methyl), 3.64 (methoxyl), 6.60 and 6.81 ppm, (aromatic protons), identical with material obtained by hydrolysis of 2a in the manner described above for 2c followed by methylation.

B) In a 1 l. 3-necked, round-bottom creased flask fitted with a dry ice-isopropyl alcohol condenser and a high speed (6000 rpm) stirrer was placed 1g of 3a in 200 ml of dry ethylamine. Addition of 35 ml of dry t-amyl alcohol was followed by addition of 1.84 g (43 fold excess) of Li wire with high speed stirring. To prevent appearance of a dark blue color, an additional 35 ml of t-amyl alcohol was added. After consumption of lithium, ethylamine was removed as before, water was added to the residue and the solution acidified with 10% HCl. The aqueous mixture was immediately extracted with ether, the washed and dried ether extracts were evaporated and the residue was methylated with diazomethane. The methyl ester was taken up in 20 ml of MeOH containing 0.27 ml of conc. HCl, allowed to stand at room temperature for 2 hr (tlc control to monitor disappearance of 5b), poured into water and extracted with ether. The washed and dried ether extracts were evaporated and the residue was dissolved in a 1:1 mixture of acetic anhydride-pyridine. After standing overnight at room temperature, the mixture was poured into water, neutralized with solid $NaHCO_3$

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and extracted with ether. The washed and dried ether extracts were evaporated and the residual mixture was separated by preparative tlc. The following substances were isolated in increasing order of polarity: 1) Methyl dehydroabietate, 6a (10% yield), mp 62-63°, $[\alpha]_D^{25}$ (c, 0.314, 95% ethanol), identical with an authentic sample: 2) Methyl 12-methoxydehydroabietate, 3b (14%), physical properties identical with those of an authentic sample; 3) Methyl 12-acetoxydehydroabietate, 4c (18% yield), physical properties identical with those of an authentic sample; 4) Methyl 12-oxo-abiet-9(11)-en-18-oate, 7 (48% yield), mp 104-105°, $[\alpha]_D^{25}$ + 47° (c, 0.250, $CHCl_3$), ir and nmr spectra superimposable on those of material obtained previously[9]; 5) Methyl 12-oxo-13β-abiet-9(11)-en-18-oate, 8 (12% yield), mp 94-95°, $[\alpha]_D$ + 163° (c, 0.30, $CHCl_3$), ir and nmr spectra superimposable on those of material obtained previously[9].

Methyl 11α- and 11β-abiet-9(11)-en-18-oate (9a and 9c).--A solution of 0.403 g of 7 in 10 ml of methanol was reduced with 0.48 g of $NaBH_4$ and worked up in the usual manner. Recrystallization of the crude alcohol mixture, yield 0.40 g, from hexane afforded 9c, $[\alpha]_D^{25}$ -54.0° (c, 0.368, 95% ethanol); ir bands at 3340 and 1720 cm^{-1}; nmr signals at 0.80d and 0.94d (J=6 Hz, isopropyl), 1.06 (C-10 methyl), 1.16 (C-4 methyl), 3.64 (methoxyl), 4.02d (J=9 Hz, H-12α), 5.32 ($w_{\frac{1}{2}}$=5 Hz, H-11).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.32; H, 10.33; O, 14.27.

The presence of 9a in the alcohol mixture was revealed by the observation in the nmr spectrum of a broad resonance at 4.08 ($w_{\frac{1}{2}}$=22 Hz, H-12β).

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Acetylation of the crude alcohol mixture with acetic anhydride-pyridine followed by the usual work-up gave a mixture from which 9d was isolated by recrystallization from hexane, mp 106-107°, $[\alpha]_D^{25}$ -82.8° (c, 0.389, 95% ethanol); ir band at 1727 cm^{-1} (double intensity); nmr signals at 0.79d and 0.91d (J=7Hz, isopropyl), 1.07 (C-10 methyl), 1.18 (C-4 methyl), 2.05 (acetate, 3.62 (methoxyl), 5.15 ($w_{\frac{1}{2}}$ = 5 Hz, H-11), 5.27d (J=9 Hz, H-12α).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64; O, 17.00. Found: C, 73.30; H, 9.65; H, 16.90.

Methyl 11-Oxo- and 12-Oxoabietan-18-oate (13 and 12).--To 10 ml of purified dry ethylamine in a flask fitted with a dry ice-isopropyl alcohol condenser was added 0.550 g of Li wire followed immediately by 0.456 g of the mixture of 9b and 9d dissolved in the minimum amount of THF. The dark blue mixture was stirred for 1.5 hr; this was followed by addition of 20 ml of dry t-amyl alcohol to destroy the excess metal. The usual work-up described in part A of the Birch reduction of 3a gave a residue which could be separated by preparative tlc into two fractions. The less polar material (21% yield) was a mixture of 10 and 11a in a 5:1 ratio, which had nmr signals at 0.80d (J=5.5, isopropyl), 1.08 (6 H, C-4 and C-10 methyls), 5.37 C and 5.62 br ($w_{\frac{1}{2}}$ = 11 and 3 Hz, H-11 and H-12), 9.20 ppm (-CHO). The more polar fraction (66%) was a mixture of 10b and 11b in a 5:1 ratio, nmr signals at 0.80 (C-4 methyl), 0.86d (J=7 Hz, isopropyl), 1.04 (C-10 methyl), 3.25 (2 H, center of AB quartet of H-18), 5.40 c and 5.65 br ($w_{\frac{1}{2}}$ = 10 and 3 Hz, H-11 and H-12). To a solution of 0.176 g of the mixture of alcohols and aldehydes in 4 ml of ether was added (nitrogen atmosphere) 0.74 g of BF_3-etherate

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followed by 0.16 g of $LiAlH_4$ in 10 ml of ether. After addition of 10 ml of ether and one hr of stirring, a satd. solution of Na_2SO_4 was added dropwise until a granular white precipitate had formed. Solid anh. Na_2SO_4 was added to absorb excess water, the mixture was stirred for one hr and filtered, the precipitate being washed thoroughly with hot THF. The combined filtrate and washings were evaporated; the residue was dissolved in 40 ml of ethanol containing 0.20 g of NaOH and oxidized with 2 ml of 30% H_2O_2. After 10 min at room temperature and 5 min on the steam bath, the mixture was poured into water and extracted with ether. The washed and dried ether extract was evaporated and the residue was oxidized with Jones' reagent, methylated with diazomethane and separated by preparative tlc into two fractions.

Methyl 12-oxoabietan-18-oate (12), mp 98-99°, was isolated in 8% yield; its properties were identical with properties reported previously[6, 43, 44].

(43) W. G. Dauben and R. Coates, J. Org. Chem., 28, 1698 (1963).
(44) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, J. Org. Chem., 30, 3190 (1965).

Methyl 11-oxoabietan-18-oate (13) was obtained in 64% yield, mp. 105.5-106.5°, $[\alpha]_D^{25}$ -24.6° (C, 0.480, 95% ethanol); ir bands at 1720 and 1706 cm^{-1}; nmr signals at 0.84d (J=6 Hz, isopropyl), 1.08 (C-10 methyl), 1.15 (C-4 methyl), 2.16 2p, ($w_{\frac{1}{2}}$ = 9 Hz, H-12), 2.48d (J=12 Hz, H-18), 3.62 ppm (methoxyl); uv ε_{max} 292 nm (ε 43); CD curve θ_{294} -1050 (C, 0.00609 g/l, CH_3OH).

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Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.19; H, 10.33; O, 14.50.

Methyl 11α- and 11β-Hydroxyabietan-18-oate (25 and 24).--To 0.050 g of 13 in 10 ml of THF containing 0.86 ml of 5% NaOH solution was added 0.186 g of $NaBH_4$. The mixture was refluxed for 9 hr, poured into water and worked up in the usual way. The crude product was separated by preparative tlc into two fractions. The less polar material (42% yield) was 24, mp 101-102°, $[\alpha]_D^{25}$ -10.9° (C, 0.331, 95% ethanol); ir bands at 3500 and 1720 cm^{-1}; nmr signals at 0.84d (J=6 Hz, isopropyl), 1.16 (C-10 methyl), 1.20 (C-4 methyl), 3.64 (methoxyl), 4.31 ($w_{\frac{1}{2}}$ = 10 Hz, H-11α).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; O, 14.26. Found: C, 75.05; H, 10.86; O, 14.19.

The more polar material (34% yield) was 25, mp 88-89°, $[\alpha]_D^{25}$ +8.1° (C, 0.510, 95% ethanol); ir bands at 3400 and 1718 cm^{-1}; nmr signals at 0.86d (J=6 Hz, isopropyl), 1.02 (C-10 methyl), 1.20 (C-4 methyl), 2.39d (J=12 Hz, H-18), 3.64 (methoxyl), 3.64 ($w_{\frac{1}{2}}$ = 20 Hz, made visible by using $Eu(fod)_3$, H-11β).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78; O, 14.26. Found: C, 75.10; H, 10.85; O, 13.97.

Pyrolysis of Acetates 9b and 9d.--A solution of the mixture of allylic acetates, wt. 0.483 g, in 5 ml of benzene was added dropwise to a column filled with glass helices and kept at 300°, while a nitrogen stream was passed upward through the column. When addition was complete the nitrogen stream was stopped. After 30 min, the column was allowed to cool and washed with ether. Removal of solvent and chromatography furnished 0.091 g of starting

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material and 0.206 g (84%) of a diene mixture which proved difficult to separate. Chromatogrphay over silica gel impregnated with silver nitrate yielded methyl dehydroabietate due to disproportionation. Eventually, repeated continuous solvent flow preparative tlc permitted separation of the dienes 26 and 27 (1:5 ratio). The less polar substance, methyl 8,11-abietadien-18-oate (26) was noncrystalline and had $[\alpha]_D^{25}$ +65.5° (C, 0.578, 95% ethanol); nmr signals at 0.96d (J=6.5 Hz, isopropyl), 1.08 (C-10 methyl), 1.27 (C-4 methyl), 3.72 (methoxyl), 5.88 (2p, center of AB quartet of H-11 and H-12, J=10 Hz); uv λ_{max}246, 253, 267sh nm (ε 3230, 3170, 2620), λ_{min} 250 nm (ε 3160), Ord curve (C, 7.8 x 10^{-5} g/ml) Φ_{310} +2630, Φ_{285} +5780, Φ_{260} 0, Φ_{245} -3800.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.90; H, 10.19; O, 10.11. Found: C, 79.94; H, 10.13; O, 9.68.

The more polar methyl 9(11),12-abietadien-18-oate (27) was also non-crystalline and had $[\alpha]_D^{25}$ -25.8° (C, 0.538, 95% ethanol), nmr signals at 1.02d (J=7 Hz, isopropyl), 1.08 (C-10 methyl), 1.22 (C-4 methyl), 3.62 (methoxyl), 5.60 br (2H, $w_{\frac{1}{2}}$ = 2 Hz, almost coinciding center lines of AB system, H-11 and H-12); uv λ_{max} 260sh, 268, 280, 287.5 sh nm (ε 3300, 3840, 3580, 1950), λ_{min} 273.5 (ε 3500); Ord curve (C, 1.04 x 10^{-4} g/ml), Φ_{310} -1220, Φ_{296} - 2600, Φ_{282} 0, Φ_{275} +3050, Φ_{250} 0, Φ_{222} -1010.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.11. Found: C, 79.84; H, 10.07; O, 9.29.

Birch Reduction of O-Methylpodocarpic Acid[18].--To 600 ml of purified ammonia was added a solution of 10 g of 28b (prepared by methylation of the sodium salt of 28a with a limited amount of dimethylsulfate and separation of 28c in the usual manner) in

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120 ml of THF followed by 125 ml of t-amyl alcohol and then 5 g of Li wire. The mixture was stirred until the Li was consumed, 100 ml of MeOH was added and the ammonia was allowed to evaporate on a water bath. The remaining material was diluted with water, acidified with 10% HCl and extracted with ether. Evaporation of the washed and dried ether extracts gave a gum which was methylated with diazomethane, stirred overnight with 5% HCl in methanol to hydrolyze the vinyl ether and to rearrange the β,γ-unsaturated ketone, poured into water and extracted with ether. The washed and dried ether extracts were evaporated; chromatography gave the following fractions: 1) Methyl podocarp-8(9)-en-19-oate 29 (26% yield), mp 82-83°; $[\alpha]_D^{25}$ +190° (C, 0.400; 95% ethanol; ir band 1710 cm^{-1}; nmr signals at 0.78 (C-10 methyl), 1.19 (C-4 methyl) and 3.60 ppm (methoxyl). A similar substance, desoxytetrahydropodocarpinol, has been isolated as a minor product from the Li-NH_3-t-butyl alcohol reduction of O-methylpodocarpinol[16].

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.31; H, 10.21; O, 11.58. Found: C, 78.91; H, 10.42; O, 11.75.

2) Methyl O-methylpodocarpate 28c (3% yield), mp 128-129°, $[\alpha]_D^{25}$ +132° (C, 0.511, 95% ethanol), identical with an authentic sample.

3) Methyl 12-oxopodocarp-8(9)-en-19-oate, 30 (1.3%), a gum, ir band at 1710 cm^{-1}, nmr signals at 0.78 (C-10 methyl), 1.21 (C-4 methyl) and 3.62 ppm (methoxyl). Treatment with 5% HCl in methanol caused rearrangement to 31.

4) Methyl 12-oxopodocarp-9(11)-en-19-oate 31 (52% yield), mp 107-108°, $[\alpha]_D^{25}$ -12.4° (C, 0.500, 95% ethanol), ir bands 1710 and 1664 cm^{-1}, nmr signals at 0.97 (C-10 methyl), 1.20 (C-4 methyl), 3.66 (methoxyl) and 5.86d (J=2.5 Hz, H-11), uv λ_{max} 238 nm (ε 17000). The mp of this compound prepared by a more circuitous route, is reported as 116-118°[16].

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03; O, 16.53. Found: C, 74.36; H, 8.98; O, 16.90.

Methyl 12-Hydroxynodocarp-9(11)-en-19-oate (32a).--$NaBH_4$ reduction of 1 g of 31 in the manner described for 7 gave a gummy alcohol, possibly a mixture of epimers, which was homogeneous on tlc. It had ir bands at 3380, 1720 and 1650 cm^{-1}, nmr signals at 0.87 (C-10 methyl), 1.15 (C-4 methyl), 3.63 (methoxyl), 4.16 ($w_{\frac{1}{2}}$ = 18 Hz, H-12) and 5.42 br ($w_{\frac{1}{2}}$ = 5 Hz, H-11).

Acetylation with acetic anhydride-pyridine gave a gummy product 32b which was homogeneous on tlc, ir bands at 1735 (double strength) and 1650 cm^{-1}; nmr signals at 0.89 (C-10 methyl), 1.15 (C-4 methyl), 2.01 (acetate), 3.63 (methoxyl), 5.24 c (H-12) and 5.34 br (H-12).

Hydrogenolysis of 32b.--Reductive cleavage of 0.622 g of 32b in 200 ml of ethylamine and a little THF with 0.730 g of Li wire in the manner described for the mixture of 9b and 9d followed by preparative tlc of the crude product gave podocarp-9(11)-an-19-oic acid 33a (21% yield) by partial hydrolysis of the initially-formed 33b under Birch conditions; which was remethylated to gummy 33b. The latter had an ir band at 1720 cm^{-1} and nmr signals at 0.83 (C-10 methyl), 1.14 (C-4 methyl) and 3.62 ppm (methoxyl). The major product was podocarp-9(11)-en-19-ol 33c, mp 97-99°, $[\alpha]_D^{25}$-35.5° (C, 0.395, 95% ethanol), ir band at 3370 cm^{-1}, nmr signals at 0.93 (C-10 methyl), 1.00 (C-4 methyl), 3.60 (2p, center of AB quartet of H-19, J=10 Hz), and 5.36 ppm ($w_{\frac{1}{2}}$ = 9 Hz, H-11).

Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36; O, 6.44. Found: C, 82.22; H, 11.63; O, 6.30.

Methyl 11-Oxopodocarpan-19-oate (38) and Methyl 9β-11-Oxopodocarpan-19-oate (37).--Hydroboration-oxidation of 0.315 g of a mixture of 33b and 33c with 0.961 g of BF_3-etherate and 0.190 g of $LiAlH_4$, as described in the abietane series, followed by oxidation of the crude alcohol mixture with 5 ml of a solution of 5 g of CrO_3 in 10 ml of H_2O and 90 ml of acetic acid for 9 hr, methylation of the ketoacid mixture with CH_2N_2 and preparative tlc gave, in the less polar fraction, gummy ketone 38 (20% yield) which could be isomerized to 37 on treatment with a 5% solution of NaOH in CH_3OH, ir band at 1720 cm^{-1}, nmr signals at 0.80 (C-10 methyl), 1.16 (C-4 methyl) and 3.63 ppm (methoxyl). The more polar ketone 37 (55% yield) had mp 104-105°, $[\alpha]_D^{25}$ +22.2° (C, 0.577, 95% ethanol) ir bands at 1720 and 1705 cm^{-1}, nmr signals at 0.95 (C-10 methyl), 1.16 (C-4 methyl) and 3.63 ppm (methoxyl); uv λ_{max} 295 nm (ε 31.6); CD curve (C 0.00585 g/ml, CH_3OH), $[\theta]_{295}$ +4360.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 79.93; H, 9.65; O, 16.41. Found: C, 73.88; H, 9.74; O, 16.32.

Methyl 11α- Hydroxy- and 11β-Hydroxypodocarpan-19-oate (36a and 39).--Reduction of 0.3 g of 37 with sodium borohydride gave a 1:1 mixture of C-11 epimeric alcohols which was difficult to separate. Partial separation was achieved by continuous solvent flow preparative tlc using benzene as solvent. The alcohol band

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which broadened as it moved upward, was divided into 4 parts. Pure alcohols were obtained from the first and fourth part. The less polar α-hydroxy isomer 36a had mp 103-104°, $[\alpha]_D^{25}$ +7.0° (C, 0.343, 95% ethanol), ir bands at 3470 and 1710 cm^{-1}, nmr signals at 0.82 (C-10 methyl), 1.17 (C-4 methyl), 3.62 (methoxyl), and 3.62c ($w_{\frac{1}{2}}$ = 20 Hz, revealed by conversion to the acetate, H-11β).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27; O, 16.30. Found: C, 73.25; H, 10.48; O, 16.18.

The more polar β-hydroxy isomer 39 had mp 77-78°, $[\alpha]_D^{25}$ +40.3 (C, 0.201; 95% ethanol); ir bands at 3500 and 1710 cm^{-1}; nmr signals at 0.92 (C-10 methyl), 1.17 (C-4 methyl), 3.64 (methoxyl), and 4.89 ppm ($w_{\frac{1}{2}}$=8 Hz, H-11α).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27; O, 16.30. Found: C, 73.23; H, 10.44; O, 15.92.

Hypoiodite Reactions on 24.--A solution of 0.088 g of 24 in 130 ml of cyclohexane containing 0.53 g of $Pb(OAc)_4$, 0.360 g of $CaCO_3$ and 0.0725 g of I_2 was irradiated with a 70 watt incandescent lamp and refluxed (due to the heat of the lamp) for 90 min with stirring. After cooling, the mixture was filtered and the residue washed thoroughly with hexane. The combined organic layers were washed with 5% sodium thiosulfate, the wash solution was extracted with ether and the extract combined with the organic layers which were then washed with H_2O, dried and evaporated. The residue was oxidized with Jones' reagent and worked up in the usual manner. Preparative tlc of the crude product furnished lactone 40 (49% yield) which had mp 127-128°, $[\alpha]_D^{25}$ -15.5° (c 0.554, 95% ethanol), ir bands at 1760 and 1722 cm^{-1}, nmr signals at 0.86d (J=5.5, isopropyl), 1.54 (deshielded C-4 methyl), 3.66 (methoxyl), and 4.77 ppm br ($w_{\frac{1}{2}}$ = 7 Hz, H-11α).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.10; H, 9.26; O, 18.60.

Oxidation of 0.020 g of 25 in the same manner followed by a similar oxidative work up gave a complex mixture from which no pure compounds could be isolated.

Hypoiodite reaction on 39.--Irradiation of 0.126 g of 39 in 126 ml of cyclohexane with 0.770 g of $Pb(OAc)_4$ and 0.103 of iodine followed by oxidation and work-up as described for 24 gave a complex mixture. Preparative tlc of the crude product yielded lactone 41 (40% yield) which had mp 143.5-144.5°, $[\alpha]_D^{25}$ +46.2° (c 0.511, 95% ethanol); ir bands at 1762 and 1720 cm^{-1}; nmr signals at 1.22 (C-4 methyl), 3.70 (methoxyl) and 4.73 ppm ($w_{\frac{1}{2}}$ = 8 Hz, H-11α).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55; O, 20.89. Found: C, 70.42; H, 8.66; O, 20.85.

Hypoiodite oxidation of 46c.--Reduction[25] of 3 g of methyl 12-acetyldehydroabietate in 100 ml of methanol with 0.5 g of $NaBH_4$ gave a 1:1 mixture of the epimeric alcohols 46c which could be separated by preparative tlc. The less polar alcohol, mp 120-121°, $[\alpha]_D^{25}$ +92.6 (c 0.102, 95% ethanol) had nmr signals at 1.08d and 1.12d (J=7 Hz, isopropyl), 1.11 (C-10 methyl), 1.15 (C-4 methyl), 1.36d (J=6.5 Hz, C-22 methyl), 2.30 (AB quartet of H-7), 3.12 sept (J=7, H-15), 3.58 (methoxyl), 5.169 (J=6.5 Hz, H-21), 6.90 and 7.41 ppm (aromatic protons). The more polar alcohol, mp 133.5-134.5°, $[\alpha]_D^{25}$ +44.6° (c 0.102, 95% ethanol), had nmr signals at 1.11d (6 H, isopropyl), 1.11 (C-10 methyl), 1.17 (C-4 methyl), 1.36d (J=6.5, C-22 methyl), 2.30 (AB quartet of H-7), 3.12 sept (J=7, H-15), 3.58 (methoxyl), 5.179 (J=6.5 Hz, H-21), 6.90 and 7.40 ppm (aromatic protons).

A solution of 0.1 g of the mixture of epimers in 100 ml of cyclohexane was irradiated in the presence of $Pb(OAc)_4$-I_2 and worked up as usual without the chromic acid oxidation step. Preparative tlc of the crude product gave lactone 47^{24}, mp 198-199°, $[\alpha]_D^{25}$ +83.0° (c 0.636, 95% ethanol); ir bands at 1751 and 1721; nmr signals at 1.21 (C-10 methyl), 1.30 (C-4 methyl), 1.61 (C-16 and C-17-methyls), 3.67 (methoxyl), 7.10 and 7.78 ppm (aromatic protons).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.18; H, 7.81; O, 17.95. Found: C, 73.82; H, 7.81; O, 17.86.

Lead Tetraacetate Treatment of 24 and 25.--A mixture of 0.098 g of 25, 0.510 g of $CaCO_3$, 0.595 g of dry $Pb(OAc)_4$ and 150 ml of cyclohexane was refluxed for 5 hr, cooled, filtered and the residue washed with hexane. The combined filtrate and washings were washed with 5% sodium thiosulfate solution, the thiosulfate solution was extracted with ether and the combined organic layers were washed with H_2O and dried. Removal of solvent gave a mixture of two compounds which was separated by preparative tlc. The more polar product 48 (33% yield) was a gum, $[\alpha]_D^{25}$ -45.0° (c 0.450, 95% ethanol), ir band at 1720 cm^{-1}, nmr signals at 0.84 (C-10 methyl), 0.89d (J=7 Hz, isopropyl), 1.28 (C-4 methyl), 3.65 (methoxyl), 3.65m (resolved with shift reagent to show a doublet of doublets, J=8.5 and 5.5 Hz, H-1α, and a doublet of triplets,

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J=5, 10 and 10 Hz, H-11β).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.40; H, 10.21; O, 14.51.

The less polar product 49 (40% yield) had mp 127-128°, $[\alpha]_D^{25}$ +17.6° (c 0.975, 95% ethanol); ir band at 1728 cm^{-1}; nmr signals at 0.86d (J=6 Hz, isopropyl), 0.95 (C-4 methyl), 3.66 (methoxyl), 3.80 (2H, AB quartet of H-20, J=9 Hz), and 4.24 ppm ($w_{\frac{1}{2}}$ = 7 Hz, H-11α).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.38; H, 10.39; O, 14.26.

A solution of 0.035 g of 49 in 2 ml of acetic anhydride was oxidized with 6 ml of 5% CrO_3 acetic acid solution by heating on a steam bath for 12 hr. The solution was poured into H_2O, neutralized with $NaHCO_3$ and extracted with ether. The washed and dried ether extract was evaporated; the residue, a complex mixture, furnished lactone 40 after preparative tlc.

Lead tetraacetate treatment of 24 gave, after preparative tlc, ether 48 in 13% and ether 49 in 54% yield.

Lead Tetraacetate Treatment of 36a and 39.--$Pb(OAc)_4$ oxidation of 0.103 g of 36a in the usual manner gave, after preparative tlc of the crude product, the less polar ether 53 (38% yield) which had mp 71.5-72.5°, ir band at 1720 cm^{-1}, nmr signals at 1.13 (C-4 methyl), 3.60 (methoxyl), 3.61 (AB quartet of H-18, J=9 Hz), and 4.19 ppm ($w_{\frac{1}{2}}$ = 7 Hz, H-11α).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.41. Found: C, 74.02; H, 9.71; O, 16.03.

The more polar product (33% yield) was 52, mp 76.5-77.5°, ir band at 1724 cm^{-1}; nmr signals at 0.88 (C-10 methyl), 1.18 (C-4 methyl), 3.66 (methoxyl), 3.66m (resolved with Eu(fod)$_3$ into a doublet of doublets, J=11 and 5 Hz, H-1α, and a doublet of triplets, J=10, 10 and 4 Hz, H-11β).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.41. Found: C, 74.46; H, 9.76; O, 15.83.

Oxidation of 0.030 g of 53 in the manner described for 49 gave a complex mixture from which lactone 41 was isolated in 24% yield.

Lead tetraacetate oxidation of 0.050 g of 39 furnished, after preparative tlc, ether 52 in 30 % and ether 53 in 40% yield.

BF_3-Cleavage of 48 and 52.--To an ice-cold solution of 0.025 g of 48 in 5 ml of acetic anhydride was added 5 drops of BF_3-etherate. The mixture was immediately removed from the ice bath, allowed to stand for 5 min, poured into water, neutralized with solid $NaHCO_3$, care being taken to keep the system at or below room temperature, and extracted with ether. The washed and dried ether extract was evaporated; the residue was purified by preparative tlc and furnished non-crystalline methyl 18, 11α-diacetoxyabietan-18-oate 55 in 38% yield, $[\alpha]_D^{25}$ -24.7° (c 0.425, 95% ethanol); ir band 1728 cm^{-1} (triple intensity); nmr signals at 0.84d (J=6 Hz, isopropyl), 0.87 (C-10 methyl), 1.20 (C-4 methyl), 2.06 (2 acetates), 3.66 (methoxyl), 4.72 (2H, $w_{\frac{1}{2}}$ = 27 Hz, H-1α and H-11β.

Anal. Calcd for $C_{25}H_{40}O_6$: mol wt 436.2824. Found (MS) 436.2824.

Cleavage of 0.045 g of 52 with BF_3-etherate was carried out in the same manner; however, after the reaction was complete and the mixture had been diluted with water, it was warmed on the steam bath to drive off the ether. Preparative tlc of the crude product afforded a 34% yield of gummy 54 which had ir bands at 3450, 1740 and 1730 cm^{-1}; nmr signals at 1.08 (C-10 methyl), 1.25 (C-4 methyl), 2.04 (acetate), 3.56 (methoxyl), 3.56t (J=8 Hz, resolved by Eu(fod)$_3$, H-1α), and 5.00 ppm ($w_{\frac{1}{2}}$=18 Hz, H-11β).

BF_3-Cleavage of 49.--Treatment of an ice-cold solution of 0.030 g of 49 in 5 ml of acetic anhydride with 5 drops of BF_3-etherate and work-up as described for 48 gave, after chromatography, a 60% yield of a 1:1 mixture of 56a and 56b. Continuous solvent flow preparative tlc produced partial separation of the mixture into fractions which contained predominantly 56a or 56b. The less polar olefin acetate 56b had nmr signals at 0.87d (isopropyl), 1.19 (C-4 methyl), 1.95 (acetate), 3.64 (methoxyl), 4.35 (2H, center of AB quartet, H-20), and 5.44 ppm ($w_{\frac{1}{2}}$ = 9 Hz, H-11). The more polar olefin acetate 56a had nmr signals at 0.87d (J=6 Hz, isopropyl), 1.22 (C-4 methyl), 2.02 (acetate), 3.66 (methoxyl), and 4.27 ppm (2H, center of AB quartet, J=11 Hz, H-20). The olefin acetate mixture was analyzed.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64; O, 17.00. Found: C, 73.61; H, 9.63; O, 16.84.

Photoisomerization of 13.--A solution of 0.255 g of 13 and 45 ml of 95% ethanol in a quartz apparatus was purged of oxygen by means of a nitrogen stream and subsequently irradiated with uv light from a 450 watt Hanovia mercury vapor lamp passed through a Corex 9700 filter. Removal of solvent gave a quantitative yield of cyclobutanol 57, mp 182-184°, $[\alpha]_D^{25}$ +73.0 (c 0.305, 95% ethanol); ir bands at 3500 and 1720 cm^{-1}; nmr signals at 0.92d and 0.93d

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(J=5 Hz, isopropyl), 1.00 (C-4 methyl), 3.64 (methoxyl); no uv or CD absorption characteristic of a ketone.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.38; H, 10.30; O, 14.56.

Cleavage of 57.-- A solution of 0.104 g of 57 in 50 ml of dry benzene containing 0.430 g of $CaCO_3$ and 0.635 g of dry $Pb(OAc)_4$ was refluxed for 16 hr, allowed to cool and worked up as described for the oxidative cyclization of 25. Preparative tlc of the crude product gave 58b (50% yield), mp 88.5-89°, band 1721 cm^{-1}, nmr signals at 0.90d (J=6 Hz, isopropyl), 1.09 (C-4 methyl), 2.07 (acetate), 3.66 (methoxyl); no uv or CD maximum characteristic of a ketone.

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24; O, 20.38. Found: C, 70.46; H, 9.34; O, 20.27.

A solution of 0.020 g of 58b in 20 ml of MeOH containing 1 g of NaOH was stirred at room temperature for 25 hr, poured into H_2O and extracted with ether. The washed and dried ether extracts were evaporated; the residue which was recrystallized from hexane gave a quantitative yield of 58a, mp 179.5-180.5°, $[\alpha]_D^{25}$ +26.6° (c 0.478, 95% ethanol); ir bands 3380 and 1720 cm^{-1}; nmr signals at 0.89d and 0.93d (J=6 Hz, isopropyl), 1.08 (C-4 methyl) and 3.64 ppm (methoxyl); no uv or CD absorption characteristic of a ketone. The substance was not affected by CrO_3-acetic acid solution.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71.72; H, 9.98; O, 18.07.

Reduction of 0.041 g of 58b with $LiAlH_4$ in ether and work up

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in the usual way gave, after chromatography, 0.043 g of 58c which had mp 117-119°, $[\alpha]_D^{25}$ +75.6° (c 0.210, 95% ethanol); ir band at 3490 cm^{-1}; nmr signals at 0.70 (C-4 methyl), 0.89d and 0.90d (J=6 Hz, isopropyl), and 3.27 ppm (2H, AB quartet of H-9, J=11 Hz).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.99; H, 10.63; O, 14.88. Found: C, 74.18; H, 10.82; O, 15.01.

Photoisomerization of 38.--Irradiation of 0.1 g of 38 as described for 13 gave a quantitative yield of the non-crystalline cyclobutanol 60 which had $[\alpha]_D^{25}$ +149° (c 0.255, 95% ethanol); ir bands at 3400 and 1715 cm^{-1}; nmr signals at 1.14 (C-4 methyl) and 3.64 ppm (methoxyl); no uv or CD maximum characteristic of a ketone.

Anal. Calcd for $C_{18}H_{28}O_3$: mol wt 292. Found (MS): 292.

Cleavage of 60.--A solution of 0.050 g of 60 in 26 ml of dry benzene was refluxed with 0.218 g of $CaCO_3$ and 0.323 g of dry $Pb(OAc)_4$ for 12 hr and worked up as described for oxidative cyclization of 25. Preparative tlc gave 0.040 g of non-crystalline 61b which had $[\alpha]_D^{25}$ +231° (c 0.118, 95% ethanol); ir bands at 1735 and 1725 cm^{-1}; nmr signals at 1.19 (C-4 methyl), 2.02 (acetate) and 3.68 ppm (methoxyl).

Anal. Calcd for $C_{20}H_{30}O_5$: mol wt 350. Found (MS): 350.

Hydrolysis of 0.022 g of 61b in the manner described for 58b gave, after recrystallization from hexane, a quantitative yield of 61a which had mp 153-154°, ir bands at 3400 and 1730 cm^{-1}; nmr signals at 1.21 (C-4 methyl) and 3.68 ppm (methoxyl); no uv absorption characteristic of a ketone.

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15; O, 20.75. Found: C, 70.33; H, 9.83; O, 21.03.

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Attempted mesylations of 61a were unsuccessful. In an attempt to prepare a ditosylate, 0.100 g of NaH was added to 0.051 g of 61a in 50 ml of cyclohexane (nitrogen atmosphere). After gas evolution had ceased, 0.100 g of tosyl chloride was added. The mixture was stirred at room temperature for 19 hr, decomposed with 1 ml of methanol, diluted with water, acidified and extracted with ether. The washed and dried ether extracts were evaporated. Tlc of the residue yielded 0.026 g of starting material and 0.024 g of 61c, mp 65-66°, ir bands at 1724 cm^{-1}; nmr signals at 1.19 (C-4 methyl), 3.20 (methyl ether), and 3.66 ppm (methoxyl); no uv absorption characteristic of a ketone.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 70.77; H, 9.38; O, 19.85. Found: C, 70.49; H, 9.48; O, 19.23.

$LiAlH_4$ reduction of 0.024 g of 61a in refluxing THF gave the non-crystalline triol 63a which had ir bands at 3380 cm^{-1} (strong); nmr signals (d_5-pyridine) at 1.07 (C-4 methyl), 3.82 (4H, AB quartets of H-18 and H-19, J=11 Hz) and 4.39 ppm (W_h = 16 Hz, H-11).

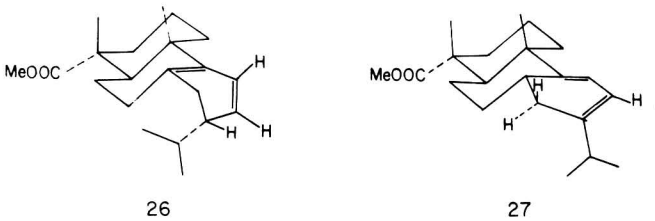
Anal. Calcd for $C_{17}H_{30}O_3$: mol wt 282. Found (MS): 282.

Mesylation of this substance resulted in complex mixtures which decomposed during attempts at chromatography.

peated continuous solvent flow thin layer chromatography; their spectroscopic properties (see Experimental Section) support the structure assignment.

The helicity rule for skewed dienes states that a strong positive Cotton effect associated with the lowest frequency cisoid diene π–π^* absorption band near 260–280 nm indicates that the diene is twisted in the form of a right-handed helix. Conversely, a strong negative Cotton effect is indicative of a left-handed twist.[39]

Diene **26** exhibited a positive Cotton effect, $[\Phi]_{285}$ 5780. Hence ring C must be in a quasi-boat conformation with the isopropyl group quasi-axial. Examination of Dreiding models (Figure 4) indicates that this conformation avoids an eclipsing interaction between the isopropyl group and H-12 and should be preferred over the half-chair form.



26 27

Figure 4. Conformations of **26** and **27**.

Diene **27** displayed a somewhat weaker *negative* Cotton effect, $[\Phi]_{296}$ −2600. In the Dreiding model of **27** the diene system of ring C is nearly planar, but flexible. The preference for a conformation at room temperature which contains a left-handed helix (Figure 4) could result from a reduction in the eclipsing interaction between the isopropyl group and the H-14 protons.

Registry No. 1a, 31148-95-5; **1b,** 5335-58-0; **2a,** 42400-87-3; **2b,** 42400-88-4; **2c,** 42400-89-5; **3a,** 42400-90-8; **4b,** 13742-23-9; **5b,** 42400-91-9; **7,** 20104-31-8; **9a,** 42400-93-1; **9b,** 42400-94-2; **9c,** 42400-95-3; **9d,** 42400-96-4; **10a,** 42400-97-5; **10b,** 42400-98-6; **11a,** 42400-99-7; **11b,** 42401-00-3; **13,** 42401-01-4; **24,** 42401-02-5; **25,** 42401-03-6; **26,** 42401-04-7; **27,** 42401-05-8; **28b,** 10037-26-0; **29,** 42401-07-0; **30,** 24402-18-4; **31,** 24402-17-3; **32a** (α-hydroxy), 42401-10-5; **32a** (β-hydroxy), 42401-11-6; **32b** (α-acetoxy), 42401-12-7; **32b** (β-acetoxy), 42401-13-8; **33b,** 42401-14-9; **33c,** 42401-15-0; **36a,** 42401-16-1; **37,** 42401-17-2; **38,** 42401-18-3; **39,** 42401-19-4; **40,** 42401-20-7; **41,** 42401-21-8; **46c** (*R* epimer), 20149-13-7; **46c** (*S* epimer), 20149-11-5; **47,** 30906-02-6; **48,** 42401-25-2; **49,** 42401-26-3; **52,** 42401-27-4; **53,** 42401-28-5; **54,** 42401-29-6; **55,** 42401-30-9; **56a,** 42401-31-0; **56b,** 42401-32-1; **57,** 42401-33-2; **58a,** 42401-34-3; **58b,** 42401-35-4; **58c,** 42401-36-5; **60,** 42401-37-6; **61a,** 42401-38-7; **61b,** 42401-39-8; **61c,** 42401-40-1; **63a,** 42401-41-2.

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(7) We wish to thank Professor R. L. Settine, University of Alabama at Birmingham, for making available to us his unpublished directions for this preparation.
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(30) C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc. C*, 1893 (1970).
(31) The path leading to **54** involves initial formation of an oxonium ion followed by cleavage of a C–O bond. If one of the carbon atoms bonded to oxygen can be easily attacked by acetate in an SN2 displacement reaction, a diacetate is formed with inversion at the carbon atom attacked and retention at the other carbon. Ethers which are hindered toward attack by acetate cleave by the SN1 mechanism to yield epimeric acetates or olefins.[32]

In the case of **52**, SN2 displacement on C-1 and C-11 to which oxygen is bonded equatorially is impossible. Hence the ether linkage must open to give a carbonium ion and attack by the nucleophile at either of the two possible sites from the least hindered direction would furnish an equatorial diacetate. Hydrolysis of the C-1 acetate may have occurred during the work-up (see Experimental Section) due to assistance by the axial carbomethoxy group. On the other hand, it has been suggested by a reviewer that the C-1 oxygen being complexed to BF_3 might never have been acetylated and that the BF_3 complex was hydrolyzed during work-up.
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Resin Acids. XXV. Chromic Acid Oxidation of $\Delta^{8(9)}$-Pimaranes and Isopimaranes. Long Range Deshielding in 8,9-Epoxides[1]

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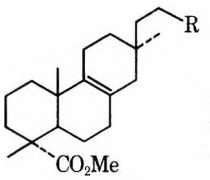
The substances formed by chromic acid oxidation of methyl pimar-8(9)-en-18-oates and isopimar-8(9)-en-18-oates have been identified as 8,9-epoxy 7-ketones. Long-range shielding effects in 8,9-epoxides of abietanes, pimaranes, and isopimaranes are discussed.

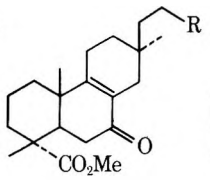
In the course of work on the synthesis of (−)-hibaene, it was noted[2] that chromium trioxide–glacial acetic acid oxidation of the pimaric acid derivatives **1a** and **1b** did not yield the hoped-for α,β-unsaturated ketones **2a** and **2b**, but gave products which contained an extra oxygen atom and did not exhibit unsaturation. These were tentatively formulated as the diketones **4**, possibly as the result of retroaldol reaction of **3** formed from **2**, or as **5**. We now report that these oxidation products actually possess the epoxy ketone structures **6a** and **6b**.

In connection with other studies, we undertook the chromic acid oxidation of methyl isopimar-8(9)-en-18-oate (**7a**). Three of the products were assigned structures **8**, **9**, and **10** on the basis of their spectroscopic properties (see Experimental Section) and corresponded to a similar set of ketones obtained by *tert*-butyl chromate oxidation of the abietane analog **7b**.[3] A fourth substance X seemed abnormal and bore a close resemblance to the "diketones" from **1a** and **1b**. However, further treatment of **10** and a still extant small sample of **2b** with acid under conditions approximating the reaction conditions under which the presumed diketones were formed resulted in recovery of starting material. Hence the theory of a retroaldol cleavage leading to **4** and **11** was abandoned. Since attempts to induce substance X and the "diketone" from **1a** to undergo an aldol condensation were also fruitless, formulas **5** and **12** seemed similarly doubtful.

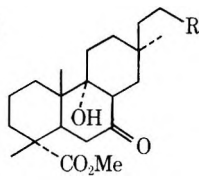
To resolve the doubt, synthesis of authentic **5a**, **12a**, and the corresponding compound **12b** of the abietane series was undertaken. Osmylation of **1a**, **7a**, and **7b** afforded in each case only one ditertiary glycol **13** in high yield, presumably the result of preferred α-attack.[4] Subsequent cleavage of the diols with lead tetraacetate or periodic acid produced the three authentic diketones **5a**, **12a**, and **12b**, two of which, **5a** and **12a**, were markedly different from the substances obtained by chromic acid oxidation of **1a** and **7a**.



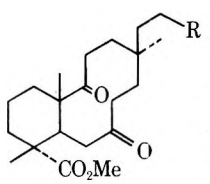
1a, R = H
b, R = OAc



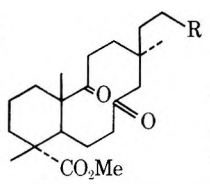
2a, R = H
b, R = OAc



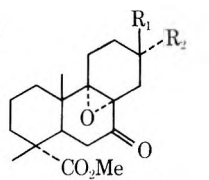
3a, R = H
b, R = OAc



4a, R = H
b, R = OAc



5a, R = H
b, R = OAc



6a, R_1 = Et; R_2 = Me
b, R_1 = CH_2CH_2OAc; R_2 = Me
c, R_1 = Me; R_2 = Et
d, R_1 = *i*-Pr; R_2 = H

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Experimental Section[8]

(8) For details concerning methods, see footnote 32 of Ref. 3.

Dihydropimaric acid was isolated from Staybelite resin kindly supplied by Mr. T. F. Sanderson, Hercules Powder Co., and converted to 1 a by the method of Edwards and Howe[9] followed

(9) O. E. Edwards and R. Howe, Can. J. Chem., 37, 760 (1959).

by methylation with diazomethane. Isopimaric acid was isolated fr WW gum rosin, kindly supplied by Mr. R. V. Lawrence and Dr. Glen W. Hedrick, Naval Stores Laboratory, Olustee, Florida, by the procedure of Baldwin, Loeblich and Lawrence[10] and converted to

(10) O. E. Baldwin, V. M. Loeblich and R. V. Lawrence, J. Org. Che 23, 25 (1958).

7 a by the method of Edwards and Howe[9].

Oxidation of 7 a. --To a solution of 10.44g of 7 a in 150 ml of acetic acid was added with stirring a solution of 11g of CrO_3 in 100 ml of acetic acid and 15 ml of H_2O. Stirring was continued for 2.5 hr, 100 ml of ether was added and the acid partially neutralized with 50% KOH solution. Complete neutralization was accomplished by adding solid $NaHCO_3$, small quantities of ether being added to reduce foaming. The two phase system was separated and the aqueous layer thoroughly extracted with ether. The combined washed and dried ether extracts were evaporated; the residue was taken up in methanol and yielded 1.24g of crystalline 6 c. The material from the mother liquor was quickly chromatographed over Florisil (seven fractions). The first fraction was nearly pure 8. The remaining fractions were further separated by preparative tlc (20 x 40 cm plates, ca. 0.8g per plate). The following substances were isolated:

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1) Methyl 11-oxo-8(9)-isopimaren-18-oate 8 (0.92g from the initial chromatography, the remainder from tlc). Recrystallization from methanol-water raised the mp to 107-108°; ir bands 1718, 1686 and 1650 cm^{-1}; nmr signals at 0.95 (C-13 methyl), 1.15 and 1.19 (C-4 and C-10 methyls) and 3.63 (methoxyl).

Anal. Calcd. for $C_{21}H_{32}O_3$: mol. wt. 332.2351. Found: mol. wt. (MS) 332.2344.

2) Methyl 7, 11-dioxo-8(9)-isopimaren-18-oate 9 (1.6g), recrystallized from methanol-water, mp 93.5-94.5°, $[\alpha]_D$ +18°(c 2.40, $CHCl_3$), ir bands 1722 and 1672 cm^{-1}; nmr signals at 0.87 (C-13 methyl), 1.29 and 1.36 (C-4 and C-10 methyls), and 3.70 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{30}O_4$: C,72.80; H, 8.73; O, 18.47. Found: C, 72.84; H, 8.57; O, 18.63.

3) Methyl 7-Oxo- 8α, 9α-oxidoisopimaran-18-oate 6 c (2.44 g), recrystallized from methanol-water, mp 91-92.5°, $[\alpha]_D$-67° (c 1.95, $CHCl_3$); ir bands at 1720 and 1698 cm^{-1}; nmr signals in Table I.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.57; H, 9.25; O, 18.48.

This substance was also prepared from 10 in low yield as follows. A mixture of 0.28 g of 10, 0.5 ml of H_2O_2, 0.04 g of NaOH and 40 ml of methanol was stirred for 8 hr, diluted with H_2O and extracted with ether. The aqueous layer was acidified and again extracted with ether. The acid extracts were washed, dried and evaporated, remethylated with diazomethane since hydrolysis of the ester function had taken place and combined with the product from the basic extraction. Preparative tlc (ether-hexane 4:6) separated the mixture into two compounds,

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0.09 g of starting material and 0.035 g of 6 c.

4) Methyl 7-oxo-8(9)-isopimaren-18-oate 10 (1.2 g), gum which could not be purified satisfactorily for analysis, ir bands 1724, 1661 and 1612 cm^{-1}; nmr signals at 0.82 (C-13 methyl), 1.12 (C-10 methyl), 1.26 (C-4 methyl and 3.61 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{32}O_3$: mol. wt. 332.2351. Found: (MS): 332.2344.

Methyl 7-Oxo-8α, 9α-oxidopimaran-18-oate (6 a).--Oxidation of 2.5 g of methyl pimar-8(9)-en-18-oate (1 a) with CrO_3-acetic acid-water in the manner described in the previous section and trituration of the crude product with methanol afforded 1.6 g of 6 a which was recrystallized from methanol-water and had mp 130-130.5°, ir bands at 1721 cm^{-1}, nmr signals in Table I.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9:26; O, 18.36. Found: C, 72.61; H, 9.21; O, 18.40.

Methyl 8α, 9α-Dihydroxypimaran-18-oate (13 a)--To a solution of 1.4 g of 1 a in 25 ml of dry ether was added 1. g of OsO_4 in 25 ml of dry ether. The flask was stoppered and stirred for 2 weeks. The mixture was diluted with 75 ml of CH_3OH and H_2S gas was passed through for 2 hr. The mixture was stirred overnight, again treated with H_2S for 1 hr, filtered through Celite and evaporated. Chromatography of the residue (wt. 1.3g) over 70g of alumina yielded initially 0.25g of starting material in the ether-hexane (1:9) fractions. Ether-hexane (7:13) eluted 0.81g of solid 13 a which was recrystallized from methanol-water and melted at 114-114.5°, ir band, 3455 (sharp evidence of intramolecular bonding) and 1704 cm^{-1}, nmr signals at 1.13 and 1.14 (C-10 and C-13 methyls), 1.22 (C-4 methyl) and 3.66 ppm (methyl).

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30; O,18.15. Found: C, 71.61; H, 10.09; O, 18.21.

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Methyl 8α, 9α-Dihydroxyisopimaran-18-oate (13 b).--Osmylation of 0.95 g of 7 a with 0.7g OsO_4 in the manner described in the previous paragraph and chromatography of the crude product over alumina gave 0.10 g of starting material and 0.81g of diol 13 b. Recrystallization from methanol afforded crystals, mp 139.5-141°; $[\alpha]_D$ +12° (c 1.36, $CHCl_3$); ir 3476 (sharp, evidence of intramolecular hydrogen bonding) and 1700 cm^{-1}; nmr signal at 0.83 (C-13 methyl), 1.20 (C-10 methyl), 1.23 (C-4 methyl) and 3.65 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30; O, 18.15. Found: C, 71.62; H, 10.11; O, 18.56.

Methyl 8α, 9α-Dihydroxyabietan-18-oate (13 c).--Osmylation of 1.36g of 7 b with 1g of OsO_4 in the usual manner and chromatography of the crude product over Florisil gave 0.551g of a mixture of starting material, methyl dehydroabietate and methyl tetrahydroabietate (by disproportionation of dehydration product?). Subsequent fractions (hexane-ether 4:1) yielded 0.78g of slightly impure diol. Rechromatography over silica gel furnished 0.693g of non-crystalline 13 c, ir bands at 3510, 1735 and 1720 cm^{-1} (bonded and non-bonded carbonyls), nmr signals at 0.85 d (J = $6H_2$, isopropyl), 1.12 (C-10 methyl), 1.17 (C-4 methyl) and 3.63 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{36}O_4$: mol. wt. 352.2613. Found (MS): 352.2623.

Cleavage of the Diols.-A)--To a solution of 0.50g of 13 a in 7 ml of dry benzene was added 0.70g of $Pb(OAc)_4$ slurried in 11 ml of dry benzene with stirring. Stirring was continued overnight. The mixture was washed with a saturated solution of $NaHCO_3$, and water. The dried benzene solution was evaporated; the residue

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(wt. 0.56g) solidified on trituration with methanol. Recrystallization from methanol furnished 12 a, mp 124-125°, $[\alpha]_D$ (c 2.88, $CHCl_3$) ; ir bands at 1724 and 1700 cm^{-1}; nmr signals at 1.00 (C-13 methyl), 1.22 and 1.23 (C-4 and C-10 methyls) and 3.80 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.78. Found: C, 72.21; H, 9.82; O, 18.32.

B) To 0.220g of diol 13 b in ether was added 15.5 ml of a satd. solution of periodic acid (0.248g). The mixture was stirred for 2 hr, and 2 drops of glycerol was added to decompose excess reagents. The solution was washed, dried and evaporated; the residue, wt. 0.15g, was taken up in methanol and recrystallized to give 5 a, mp 83.5-84.5°; ir bands at 1724 and 1697 cm^{-1}; nmr signals at 0.82 and 1.00 (C-10 and C-13 methyls), 1.20 (C-4 methyl) and 3.72 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78, O, 18.26. Found: C, 72.30; H, 9.84; O, 18.12.

C) 0.63g of 13 c was treated with 0.85g of $Pb(OAc)_4$ in the manner described for 13 a. Evaporation of the solvent furnished 0.58g of solid 12 b which was recrystallized from methanol and had mp 97.5-98.5°, $[\alpha]_D$ +17° (c 2.66, $CHCl_3$), ir bands at 1727, 1698, 1690, cm^{-1}; nmr signals at 0.88d (J = $6H_2$ isopropyl), 1.15 (C-10 methyl), 1.23 (C-4 methyl) and 370 ppm (methoxyl).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.99; H, 9.78; O, 16.26. Found: C, 71.77; H, 9.94; O, 18.30.

Treatment of 12 b with methanolic KOH gave a gum whose infrared spectrum indicated the presence of α, β-unsaturated ketones, presumably 21 and isomers.[11] The formation of such

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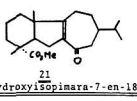
(11) A. Tahara and T. Ohsawa, Tetrahedron Letters, 2469 (1969); Chem. Pharm. Bull., 21 483 (1973).

products accounts for the failure of runs designed to produce 5 a, 12 a and 12 b by one-step reactions (OsO_4-HIO_4, RuO_4-HIO_4, RuO_4) from 1 a, 7 a and 7 b and an occasional failure with the periodic reagent, since the infrared spectra of the mixtures obtained from such runs indicated that aldol reactions had taken place.



21

Methyl 9α-Hydroxyisopimara-7-en-18-oate (16a)--To 1.5g of 6 c in 30 ml of methanol was added a solution of 3 ml of 85% hydrazine hydrate in 12 ml of methanol followed by 1 ml of acetic acid in 9 ml methanol. The mixture was heated at reflux for 0.5 hr (nitrogen atmosphere) until nitrogen evolution had ceased, evaporated and diluted with ether. The washed and dried ether layer was evaporated and the residue chromatographed over 140g of Florisil. The allylic alcohol 16a could not be induced to crystallize, yield 0.786g, ir bands at 3460, 1724 and 1682 cm^{-1}, nmr signals at 0.71, 1.00, 1.28 (C-13, C-10 and C-4 methyls), 3.58 (methoxyl) and 5.3 c (H-7).

Anal. Calcd. for $C_{21}H_{34}O_3$: mol. wt., 334.2508. Found: (MS): 334.2516.

Methyl Isopimara-7, 9 (11)-dien-18-oate (17 b).--A) A solution of 0.15g of 16a in 15 ml of acetic acid was subjected to solvent evaporation in a rotary evaporator at about 60°. The process was repeated with another 15 ml portion of acetic acid; the residue, essentially pure 17 b, was purified by preparative tlc. It could not be induced to crystallize, ir bands at 1729

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cm^{-1}; nmr signals at 0.78, 0.97, 1.22 (C-13, C-10 and C-4 methyls), 3.57 (methoxyl) and 5.25 c (2H, H-7 and H-11); uv λ_{max} 241 nm (ε 8200). An attempt to prepare 17 b by heating 16 with acetic acid and the steam bath gave a complex mixture.

B) A mixture of 0.19g of 18 a, 15 ml of freshly distilled collidine and 1.5g of LiI was refluxed for 18 hr (nitrogen atmosphere), cooled, diluted with ether and thoroughly extracted with 6 HCl. After the usual work-up[6], the product 17 a which could not be induced to crystallize was converted to the 2-amino-2-methyl-1-propanol salt. Recrystallization of the precipitate from ethanol gave the salt, mp 182-184.5° (dec.), $[\alpha]$-57° (c 2.18, CH_3OH), ir bands at 3400, (-OH) 2610 and 217 (NH_3^+), 1679 (carboxylate) and 1512 (NH_3^+).

Anal. Calcd. for $C_{24}H_{41}NO_3$: C, 73.61; H, 10.55; N, 3.58; O, 12.26. Found: C, 73.30; H, 10.68; N, 3.69; O, 12.33.

The acid was regenerated by adding 10% HCl to a suspension of the salt in a water-ether mixture. Pure 17 a had nmr signals at 0.80, 0.98, 1.25 (C-13, C-10 and C-4 methyls), 5.37 c (2H, H-7 and H-11) and 10.33 ppm (carboxyl -OH). Methylation with diazomethane furnished material identical with 17 b prepared by dehydration of 16a.

Methyl 8α, 9α and 8β, 9β-Oxidoisopimaran-18-oate. (18 a and 19 a).--A mixture of 3.1 g of 7 a, 50 ml of $CHCl_3$ and 2.0 g of m-chloroperbenzoic acid was stirred for 1.5 hr, shaken with a solution of KI to destroy excess reagent and then with sodium thiosulfate to remove I_2, extracted with 1 N NaOH solution, washed and dried. Evaporation of solvent furnished 3.3 g of residue which was chromatographed over Florisil. The less polar component 19 a did not crystallize, yield 1.02 g, ir band at 1726 cm^{-1}, nmr signals in Table I.

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Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.58; H, 10.28; O, 14.28.

The more polar component 18 a was recrystallized from methanol, yield 1.83 g, mp 86-87°; $[\alpha]_D$ 0° (c 2.04, $CHCl_3$), ir bands at 1717 cm^{-1}, nmr signals in Table I.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.23; H, 10.16; O, 14.20.

19-Acetoxy-8α, 9α- oxido- and 19-Acetoxy-8β, 9β-oxidoisopimarane (18 c and 19 c).--To a slurry of 2 g of $LiAlH_4$ in 450 ml of dry THF was added dropwise with stirring a solution of 11 g of 7 a in 50 ml of THF. After 48 hr, the mixture was decomposed with 20 ml of 1 N NaOH, filtered and the precipitate extracted twice with hot THF. The combined filtrate and washings were evaporated, yield of crude 19-hydroxy-isopimar-8(9)-ene (20 a) ca 10.5 g. A small fraction was chromatographed over Florisil but the product could not be induced to crystallize. It had ir bands at 3335 and 1660 cm^{-1}, nmr signals at 0.81 (6H, C-10 and C-13 methyls), 1.00 (c-4 methyl) and 3.31 ppm (2H, center of AB quartet of H-19).

Anal. Calcd. for $C_{20}H_{34}O$: mol. wt. 290.2610. Found: (MS): 290.2617.

Acetylation of 10 g of the preceding alcohol with acetic anhydride-pyridine in the usual fashion gave gummy 19-acetoxy-isopimar-8(9)-ene (20 b) which could not be induced to crystallize even after chromatography over alumina, ir bands at 1742 cm^{-1}, nmr signals at 0.82, 0.88 and 1.01 (C-13, C-10 and C-4 methyls), 2.06 (acetate) and 3.82 ppm (2H, center of AB quartet, H-19).

Anal. Calcd. for $C_{22}H_{36}O_2$: Mol. wt., 332.2715. Found: (MS): 332.2711.

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Epoxidation of 8.0 g of the foregoing ester with 5.5 g of m-chloroperbenzoic acid for 40 min and work-up in the manner described for 18 a and 19 a gave a gum which was chromatographed over Florisil. Elution with hexane gave 0.32 g of 19 c which did not crystallize, ir bands at 1740 cm^{-1}, nmr signals in Table I.

Anal. Calcd. for $C_{22}H_{36}O_3$: Mol. wt. 348.2664. Found: (MS): 348.2667.

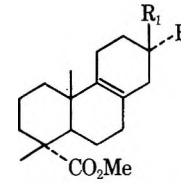
Elution with ether-hexane (1:9) gave 6.25 g of 18 c which did not crystallize, ir band at 1742 cm^{-1}; nmr signals in Table I.

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41; O, 13.77. Found: C, 75.99; H, 10.46; O, 13.88.

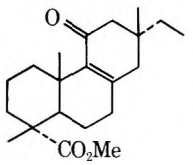
Deuteration of 6 c.--A solution of 0.30 g of 6 c in 2.5 ml of CH_3OD and 10 drops of a NaOD solution, prepared from 4 g of Na and 10 ml of D_2O, was refluxed overnight at which time 0.6 ml of a 38% solution of DCl in D_2O was added. The mixture was extracted with ether; the dried ether extract was mixed with excess diazomethane (a "dry" run with undeuterated reagent indicated that partial hydrolysis of the carboxyl functions had taken place) and allowed to stand. The solvent was removed and the residue was triturated to give crystalline 6 c - d_2, identical with starting material. The nmr spectrum given in Table I integrated for two less protons than 6 c.

Table I
Nmr Spectra of 8,9-Epoxides

Compd	H-5 (*J*, Hz)	C-4 Me	C-10 Me	OMe	C-13 Me	Isopropyl (*J*)
6a	2.90 (10.9, 8.1)	1.20	0.99	3.66	0.83	
6b	2.83 (11.3, 3.6)	1.21	1.01	3.67	0.93	
6c	2.84 (10.3, 7.5)	1.18	0.99	3.57	0.73	
6c-d_2	2.82	1.18	1.00	3.57	0.73	
15	2.84 (10.5, 8.0)	1.18	0.92	3.67		0.88 (6.1)
18a	2.48 (12.2, 3.6)	1.17	1.12	3.62	0.78	
18b	2.42 (12.2, 3.2)	1.28	1.17	3.66		0.96 (5)
18c	Not observed	0.84	1.13		0.79	
19a	Not observed	1.14	1.05	3.65	0.74	
19b	Not observed	1.14	1.05	3.67		0.81 (6.9)
19c	Not observed	0.80	1.06		0.74	



7a, R_1 = Me; R_2 = Et
b, R_1 = *i*-Pr; R_2 = H



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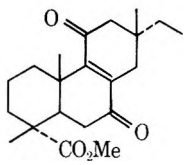

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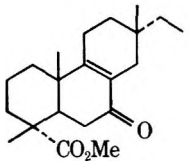

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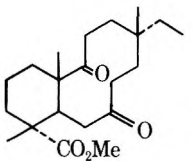

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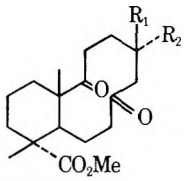
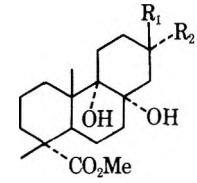
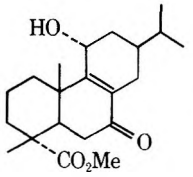


12a, R_1 = Me; R_2 = Et
b, R_1 = *i*-Pr; R_2 = H



13a, R_1 = Et; R_2 = Me
b, R_1 = Me; R_2 = Et
c, R_1 = *i*-Pr; R_2 = H



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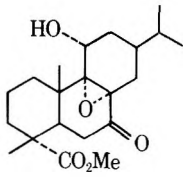

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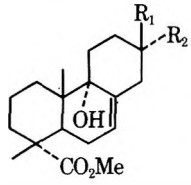
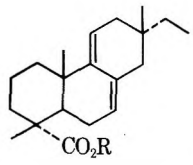
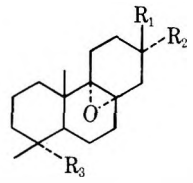


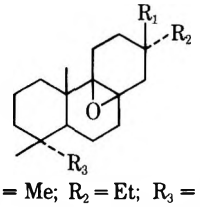
16a, R_1 = Me; R_2 = Et
b, R_1 = *i*-Pr; R_2 = H



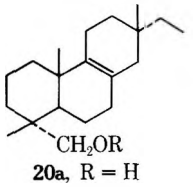
17a, R = H
b, R = Me



18a, R_1 = Me; R_2 = Et; R_2 = CO_2Me
b, R_1 = *i*-Pr; R_2 = H; R_2 = CO_2Me
c, R_1 = Me; R_2 = Et; R_3 = CH_2OAc



19a, R_1 = Me; R_2 = Et; R_3 = CO_2Me
b, R_1 = *i*-Pr; R_2 = Et; R_3 = CO_2Me
c, R_1 = Me; R_2 = Et; R_2 = CH_2OAc



20a, R = H
b, R = Ac

Although *tert*-butyl chromate oxidation[3] of **7b** had not furnished a substance comparable to the unknowns from **1a**, **1b**, and **7a**, two minor products were **14** and **15**, the latter an oxidation product of the former. This finding eventually suggested that the unknowns were actually the epoxy ketones **6a**, **6b**, and **6c**. Indeed, alkaline hydrogen peroxide oxidation of **10** furnished a small amount of substance X, although, since **10** was noncrystalline and often admixed with small amounts of X owing to the difficulty of chromatographic separation, this result was not considered as providing incontrovertible evidence for the identity of X with **6c**.

However, further transformations of X conclusively established this fact. Treatment of X with 85% hydrazine[5] produced the allylic alcohol **16a** which had properties similar to those of the abietane analog **16b**[6] and could be transformed to the trans diene **17b** by treatment with acetic acid at 60°. This substance was prepared independently as follows.

Epoxidation of **7a** afforded a 90% yield of two epoxides in a 9:5 ratio. In accordance with the principle of preferential attack from the α side, the major product, mp 86–87°, was assigned formula **18a**, the minor noncrystalline isomer structure **19a**. This was supported by the presence in the nmr spectra of the major product of a doublet of doublets at 2.48 ppm (*vide infra*) and the similarities to α[6] and β epoxides[3] of the abietane series. Finally, treatment of **18a** with the LiI–collidine[6] reagent resulted in the hoped-for conversion to **17a**, which was methylated to **17b**. This established unequivocally the structure of X as **6c** and, by inference, the structures of the presumed "diketones" from **1a** and **1b** as **6a** and **6b**.

Long Range Deshielding in 8,9-Epoxides. The nmr spectrum of **15** contains a doublet of doublets whose origin was previously ascribed[3,7] to conformational changes which cause deshielding of 14β H by the carbonyl group at C-7. Examination of the compounds described in this report showed that **6a**, **6b**, and **6c** also display the same characteristic signal (Table I). However, it is also found in the spectra of the nonketonic substances **18a** and **18b** at somewhat higher field. If the doublet of doublets owes its origin to the same proton in all six compounds, as seemed more than likely, a new explanation was needed.

Examination of Dreiding models of the compounds in question revealed that in all six cases H-5 was above the plane of the epoxide ring and near the oxygen atom. Previous studies have shown that shielding above and below the plane of an epoxide ring can be expected except when the proton is close to the oxygen atom, in which case deshielding results. Hence the signal in question could arise from H-5. Partial proof for the validity of this assignment was found in the spectra of **19a** and **19b**, which revealed no trace of the doublet of doublets. Definite confirmation was obtained by examining the nmr spectrum of **6c-6,6-d_2** (Table I). Collapse of the doublet of doublets to a slightly broadened singlet of one-proton intensity necessitates that it be identified with the resonance of H-5.

Analysis of the line shape shows two basic shapes for the H-5 signal. In the presence of a C-7 ketone group $J_{5,6\alpha}$

and $J_{5,6\beta}$ are approximately 10.5 and 8 Hz, respectively. In the absence of the ketone group, the J values are 12.2 and 3.4 Hz. Thus, the presence of a 7-ketone group is manifest in two ways: (1) it deshields H-5 by about 0.4 ppm by a field effect or by potentiating the local field already produced by the epoxide function; (2) the introduction of an sp^2-hybridized carbon atom into ring B alters the conformation such that changes in vicinal coupling constants are induced.

To determine whether the paramagnetic shift of H-5 was entirely due to the α-epoxide ring, compounds **18c** and **19c** were synthesized and examined. Table I demonstrates that neither substance exhibited the doublet of doublets; hence the downfield shift of the H-5 resonance is the result of cooperative deshielding effects on H-5 by the α-epoxide ring and the equatorial carbomethoxy group. Although the magnitude of the two components of the shift is difficult to estimate with any degree of precision, comparison of **18a** and **18c** indicates that the carboxyl group contributes at least 0.5 ppm, since the most deshielded line in the H-5 signal moved from above 2.1 (in **18c**) to 2.6 ppm (in **18a**).

Registry No. **1a**, 3582-25-0; **5a**, 7643-40-5; **6a**, 42855-23-2; **6c**, 42855-24-3; **7a**, 33952-78-2; **7b**, 33892-15-8; **8**, 42855-28-7; **9**, 42855-29-8; **10**, 42855-30-1; **12a**, 42855-31-2; **12b**, 42855-27-6; **13a**, 42855-32-3; **13b**, 42855-33-4; **13c**, 42855-34-5; **16a**, 42855-35-6; **17a** 2-amino-2-methyl-1-propanol salt, 42855-36-7; **17b**, 42855-37-8; **18a**, 42855-38-9; **18c**, 42855-39-0; **19a**, 42855-40-3; **19c**, 42855-41-4; **20a**, 42855-42-5; **20b**, 42855-43-6.

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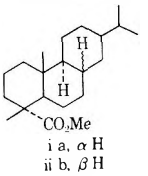
References and Notes

(1) Supported in part by a grant from the National Science Foundation (GP-12582). Previous paper: W. Herz and D. H. White, *J. Org. Chem.*, **39**, 1 (1974).
(2) W. Herz, A. R. Pinder, and R. N. Mirrington, *J. Org. Chem.*, **31**, 2257 (1966).
(3) W. Herz and J. J. Schmid, *J. Org. Chem.*, **34**, 3464 (1969).
(4) Peracid oxidation is not nearly as selective (*vide infra*), presumably because of the higher steric requirements of the osmate ester.
(5) P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).
(6) W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).
(7) Our argument for assuming a conformational change in **15** was based on a comparison of the observed $\delta_{C\text{-}10Me}$ (0.92 ppm) with that calculated on the assumption that $\Delta\delta_{C\text{-}10Me}$ (18a − i) = 1.17 − 0.85 ppm or 0.32 ppm was the incremental value for an 8α,9α-epoxide. A more nearly correct standard for calculating the effect of an α-8,9-epoxide is ii ($\delta_{C\text{-}10Me}$ 1.08), thus $\Delta\delta_{C\text{-}10Me}$ (18a − ii) =



i a, α H
ii b, β H

1.17 − 1.08 = 0.09 ppm; *i.e.*, an 8α,9α-epoxide produces an apparent shift of less than 0.1 ppm in the methyl signal. Even on this basis, however, $\delta_{C\text{-}10Me}$ of **15** seems anomalously small compared with that of the epoxy ketones **6a**, **6b**, and **6c** (Table I).

Resin Acids. XXVI. Biogenetic-Type Rearrangements of the Homoallylic Cation from Methyl 15(*R*)-Hydroxypimar-8(14)-en-18-oate[1]

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A modification of the solvomercuration–demercuration reaction is described which prevents the formation of cyclic ethers from dienes. Application of the procedure to methyl pimarate permitted the stereospecific synthesis of the title compound (**5a**) and a study of the homoallylic cation derived from it. Treatment of **5a** with toluenesulfonyl chloride–pyridine resulted in rearrangement to a new cyclopropane resin acid derivative **10** and a strobane derivative **11**. Similar treatment of methyl 15(*R*)- and 15(*S*)-hydroxy-$\Delta^{8(14)}$isopimarate (**18a** and **19b**) did not result in rearrangement. The results are ascribed to differences in the geometries of the homoallylic cations produced from **5a**, **18a**, and **19a**. Generation of the homoallylic cation from **5a** and the amine analog **6a** under different conditions resulted in conversion to methyl dehydroabietate. The rearrangements can be viewed as *in vitro* analogs of biological processes.

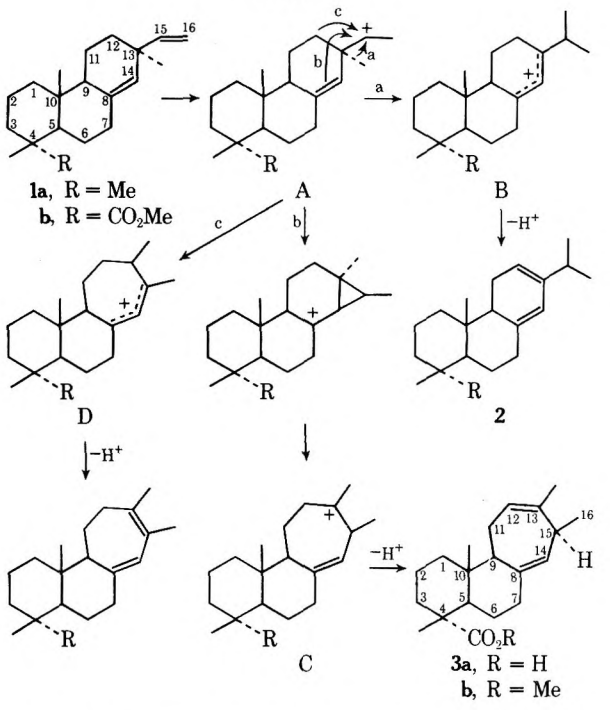
Methyl migration in cation A derived from a pimaradiene (**1a**, Scheme I, stereochemistry at C-13 as pictured) or isopimaradiene (stereochemistry at C-13 inverted) has been postulated as the crucial step (path a, Scheme I) in the biogenesis of the abietane (**2**) skeleton.[2] Our interest in the *in vitro* genesis of cation A under mild conditions was whetted by the recent discovery[4] of yet another resin acid type, exemplified by strobic acid (**3a**)[5] and its congeners, which is formally derivable from A by an alternate cationic rearrangement (path b, Scheme I). The realization of both rearrangement paths from suitable progenitors of cation A is reported herewith.[8]

Our approach was based on the introduction of a functional group at C-15 of the pimarane skeleton which could be subjected to methods customarily employed for generating transitory carbonium ions. Unfortunately, application of the original solvomercuration–demercuration procedure to methyl primarate (**1b**) had, in the hands of previous workers,[10] furnished ether **4**[11] rather than the hoped-for alcohol **5a** owing to participation by the 8(14) double bond; our use of modified procedures[9,12] applicable to dienes did not alter this result. Consequently, our initial efforts were directed toward the synthesis of the amine **6a**.

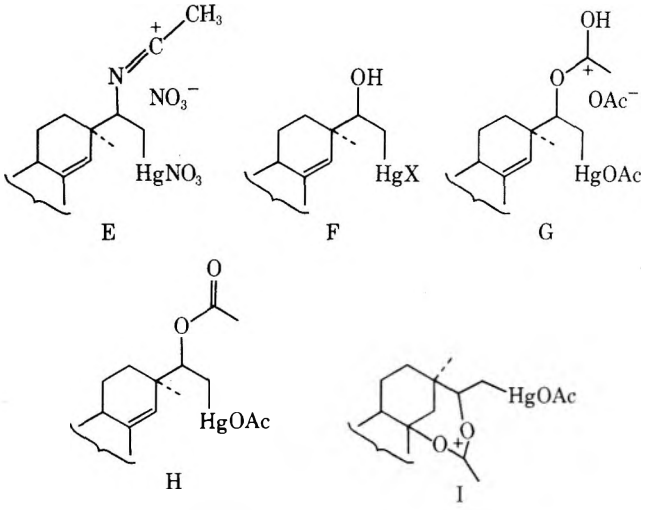
Solvomercuration–demercuration of **1b** in the presence of acetonitrile[13] afforded in nearly quantitative yield an amide **6b**.[14] Conversion of **6b** to the imino ether **7** by treatment with triethyloxonium fluoroborate[15] followed by hydrolysis with dilute acetic acid furnished **6a** in high yield.

The mechanism[13] by which **6b** is produced involves an intermediate such as E where, in contrast to the situation

Scheme I

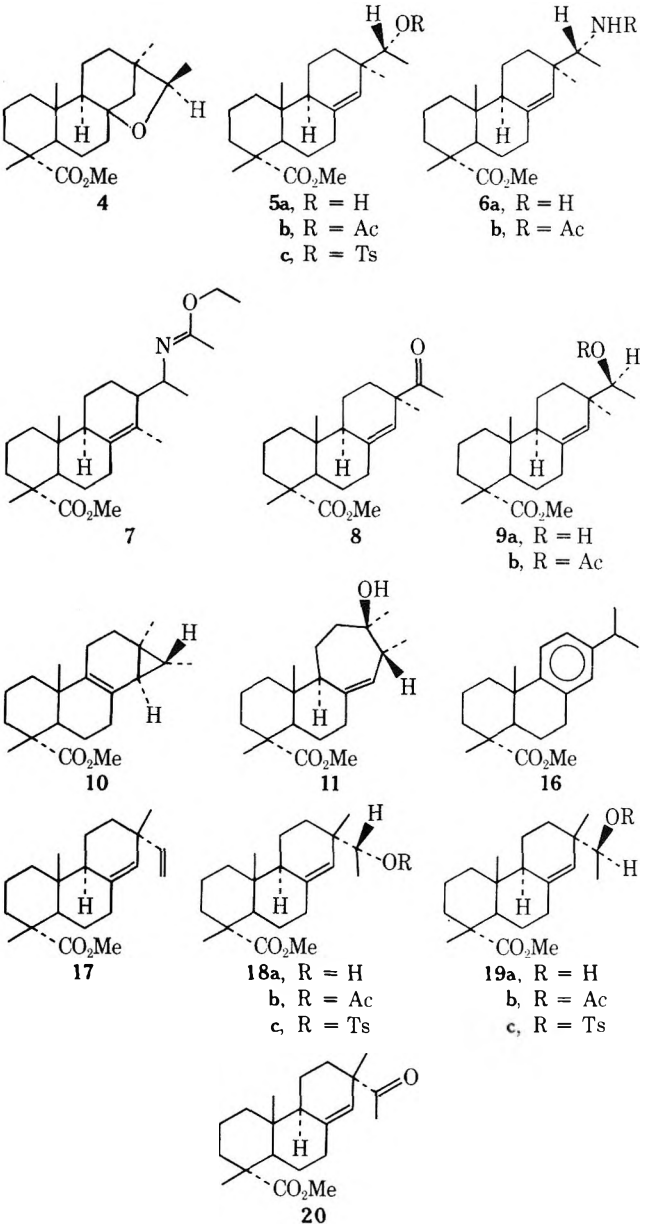


prevailing in intermediate F of the oxymercuration reaction, the nitrogen is not sufficiently nucleophilic to add to the 8,14 double bond. Accordingly, substitution of acetic acid for acetonitrile in the oxymercuration step should, it was reasoned, lead to an intermediate G which by proton transfer would furnish H. Subsequent intramolecular cyclization of H to I would not be expected to occur, since the oxygen is now deactivated. However, since the envisioned use of acetic acid as a solvent for the initial step would interfere with the second, reductive demercuration step, it would be necessary to remove it completely and conveniently. The solution to the second problem was azeotropic distillation with benzene at reduced pressure.



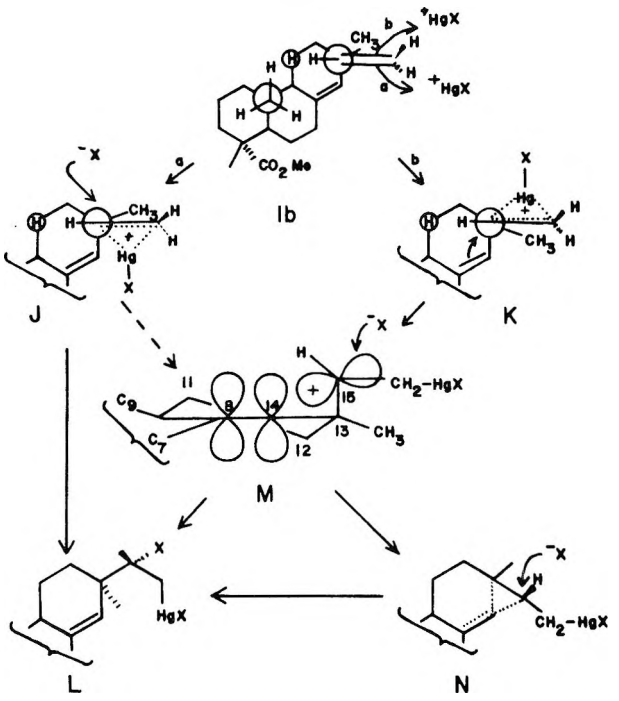
In the event, addition of 1 equiv of anhydrous $Hg(NO_3)_2$ to **1b** in acetic acid followed by addition of benzene, evaporation at reduced pressure and temperatures below 50°, and reduction with $NaBH_4$ furnished the crystalline acetate **5b** in 90% yield. This modification of the solvomercuration–demercuration reaction for the preparation of esters which can be hydrolyzed subsequently should therefore be useful whenever ether formation is a problem.

Hydrolysis of **5b** furnished crystalline **5a.** Oxidation of the latter gave 8; $NaBH_4$ reduction of 8 produced a mixture of **5a** and the C-15 epimer **9a** which resisted separation attempts, as did the mixture of acetates **5b** and **9b.** The absolute configuration of **5a** at the new asymmetric center C-15 was determined as *R* by application of Horeau's method[16] (24% optical yield). Further solvomercuration–demercuration of **5a** gave ether **4**, thus establishing the stereochemistry of the latter.



That only one acetate **5b** (and only one amide **6b**) was formed in the solvomercuration reaction is of considerable interest. Models show that mercuration of the 15,16 double bond is most probable in that conformation of **1b** in which the vinyl group is oriented away from ring C (Scheme II) if steric interactions are to be minimized. If the mercuric reagent approaches **1b** from a direction syn to the 8,14 double bond (Scheme II, path a), subsequent attack by nucleophile on the mercurium ion J should give rise to L with C-15 stereochemistry corresponding to that of **5b.** If, on the other hand, the mercuric ion approaches **1b** from a direction anti to the 8,14 double bond (path b), a stabilized ion, either a homoallylic or a cyclopropyl carbinyl ion, could be formed. Since the developing p orbital on C-15 lies parallel to the plane of ring C (as in M), $2p\sigma$ overlap of one lobe with the upper portion of the π-electron system of C-8 and C-14 is almost inevitable owing to the close approach of C-14 and C-15. M might be a step-

Scheme II



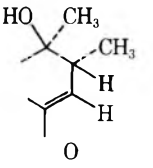
ping stone to the symmetrical homoallylic (cyclopropylcarbinyl) ion N, although intermediacy of N is doubtful since products derived from attack on C-8 or C-13 of N were not found.

In either M or N rotation about the 15,16 bond is possible such that the mercury atom is prevented from interfering sterically with approach of the nucleophile from the direction of original mercuric ion attack. This rotation, followed by subsequent nucleophilic attack, results in the same C-15 stereochemistry as that produced by path a.[17]

Attention could now be turned to preparation of a derivative of **5a** suitable for solvolysis studies. Prolonged treatment of **5a** with mesyl or tosyl chloride under carefully defined conditions (see Experimental Section) did not, however, result in the formation of the desired esters. Instead, two rearrangement products were isolated in 22 and 20% yield.

The nmr spectrum of the less polar substance, $C_{21}H_{32}O_2$, indicated the presence of the usual carbomethoxy group and the absence of vinyl protons, and exhibited four methyl singlets and a one-proton doublet at 0.30 ppm (J = 3.6 Hz). Three of the methyl singlets were easily accounted for by the C-4, C-10, and C-13 methyl groups; the remaining two signals of interest were interpretable in terms of formula **10** where the doublet at 0.30 ppm represents H-14. The fourth methyl resonance is that of C-16 whose appearance as a singlet instead of a doublet is due to a second-order nmr phenomenon; *i.e.*, the difference in chemical shift between the methyl signal and that of the proton to which it is coupled is of the same order as J. As regards stereochemistry, participation by the double bond in the loss of the oxygen function requires α orientation of the C-16 methyl group, a conclusion which is supported by the observed splitting (3.6 Hz, typical of trans coupling[18]) of H-14 which must be α.

The second substance, $C_{21}H_{34}O_3$, was a tertiary alcohol whose nmr spectrum exhibited three methyl singlets, one methyl doublet, and a vinyl resonance whose chemical shift and appearance (broadened doublet at 4.89 ppm) differed from that of H-14 in 8(14)-pimarenes. Double resonance experiments showed that the vinyl proton was spin coupled, hence adjacent, to the same (allylic) proton at 2.78 ppm which caused the methyl resonance at 0.98 ppm to appear as a doublet. Furthermore, irradiation at the frequency of the vinyl proton collapsed the complex multiplet of the allylic proton to a slightly broadened quartet, the broadening being presumably due to some homoallylic coupling to H-7α, H-7β, or H-9. It was therefore reasonable to assume that the proton at 2.78 ppm was adjacent to a quaternary center and that its chemical shift (in the low-field range for tertiary allylic protons) was due to deshielding by the hydroxyl group. Hence the two methyl groups should be cis and, on the basis of mechanistic considerations, α. Partial structure O indicated by the nmr spectrum could therefore be expanded to **11**, which possesses all the features of the strobane skeleton. Further support for this formulation was found in the observation of a mass spectrometric peak at m/e 221 ($C_{14}H_{21}O_2$ from the high-resolution mass spectrum) which appears to be characteristic of the methyl strobate system.[4-6,19,20]



O

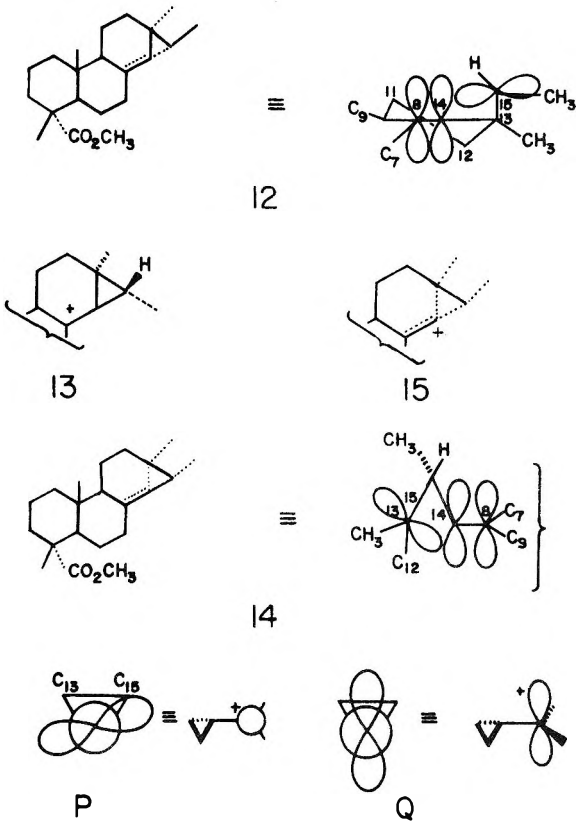
Thus, exposure of **5a** to toluenesulfonyl chloride–pyridine *resulted in operation of rearrangement path b of Scheme I,* although the enforced choice of starting material **5a** imposed a C-15 stereochemistry on the ring-expanded product **11** which is opposite to that of the strobanes so far found in nature. Moreover, *in vitro* realization of the rearrangement does not, of course, exclude the possibility that the strobanes are formed *in vivo* by direct cyclization of a labdane derivative rather than through the intermediacy of a pimarane.

Pertinent to the mechanistic aspects of the rearrangement are the following observations. Unbuffered acetolysis of **5a, 10,** or **11** produced in each instance acetate **5b** in 95% yield. Treatment of **5b** and **10** with aqueous acid yielded only **5a.** Hence the homoallylic isomer **5** appears to represent the thermodynamically favored component of the homoallylic–cyclopropylcarbinyl–homoallylic system **5, 10,** and **11** while **10** and **11** are products of kinetically controlled processes. Conversion of **5a** (and **10** or **11**) to **5b** with 100% retention of configuration at C-15 and genesis of **5b** by diazotization of **6a** with $NaNO_2$–acetic acid seems to implicate the unsymmetrical homoallylic ion **12** (analogous to ion M of Scheme II) as the result of 2pσ overlap between one lobe of the empty p orbital of cation A and the β face of the π-electron system at C-8 and C-14. Cyclopropyl derivative **10** could then be formed by kinetically controlled proton abstraction from the α face of **12**, a process which discharges the carbonium ion and renders the product immune to further reaction under the conditions of attempted tosylation.

Conversely, protonation of **10** in the usual manner from the α side leads to cation **13,** whose geometry resembles that of the skewed bisected cyclopropylcarbinyl ion P rather than that of the perpendicular bisected cyclopropylcarbinyl ion Q. As illustrated, such skewing favors overlap between the β lobe of the C-8 p orbital and the 14,15 bond rather than overlap between the α lobe and the 13,14 bond. Hence orbital control disposes ion **13** toward preferential cleavage of the 14,15 bond (*i.e.*, toward its representation as **12**), thus leading by subsequent reaction with an appropriate nucleophile to a product with the C-15 stereochemistry of **5,** as actually observed in the acetolysis of **10.**

One representation of the initial cationic species from the acetolysis of **11** is the second asymmetrical homoallylic ion **14,** which is the result of 2pσ overlap between one

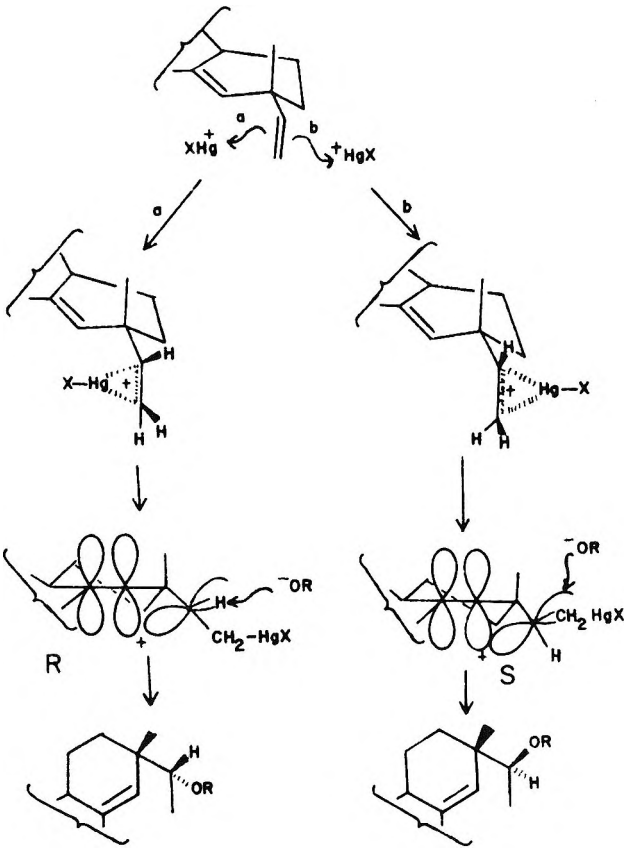
lobe of the empty p orbital of cation C (Scheme I) and the α face of the π-electron system at C-8 and C-14 and could also be described as stemming from preferential weakening of the 13,14 bond of P. It is interesting that the tertiary carbonium ion (or **14**) is completely converted to A, which must have substantial localization of charge at the secondary carbon atom C-15. In the absence of further information we would prefer not to speculate at this time on detailed aspects of the conversion of **5a** to **11**,[21] on the possible intermediacy of the symmetrical homoallylic (nonclassical cyclopropylcarbinyl) ion **15**,[22] and on the relative importance of **12**, **14**, and **15**[23] in the transformations we have observed. In any event, the required inversion at C-13 *en route* to the ring-expanded product, whether in **12** or **15**, leads to the stereochemistry (hydroxyl group β) depicted in formula **11**.



An additional series of experiments shed further light on the possible fate of cation A. Treatment of **5b** and **10** with anhydrous perchloric acid (0.12 *N*) in dioxane–acetic acid produced methyl dehydroabietate (**16**) in 58 and 28% yield, respectively, *thus resulting in realization of path a of Scheme I*.[24] Similarly, diazotization of **6a** in a nonnucleophilic solvent gave low yields of **1b** and **16**. Hence under more strongly acid conditions, irreversible rearrangement of homoallylic cation A, whatever its detailed aspect, to the allylic ion B takes place.

The observations recorded so far, which depend on the steric relationship of an axially oriented C-15 cation to the 8,14 double bond in the pimaric acid series, made it of interest to extend the study to sandaracopimaric acid. ApSimon and Krehm[10] had previously carried out the oxymercuration–demercuration of methyl sandaracopimarate (**17**) and obtained an inseparable 1:1 mixture of epimeric C-15 alcohols **18a** and **19a**. In the present work separation into a crystalline alcohol **18a** and a noncrystalline epimer **9a** could be achieved by combination of thin layer chromatography and fractional crystallization. Absolute configurations were again determined by the Horeau method.

Scheme III



The formation of two epimeric alcohols in the solvomercuration–demercuration of methyl sandaracopimarate contrasts with our observations in the pimarate series but is easily rationalized as follows. The spatial disposition of the vinyl group of **17** permits attack of mercuric ion from either side (Scheme III). Two different mercurium ions may therefore be formed, each of which gives rise by trans addition of the nucleophile water to a distinctive epimer. If, however, the mercurium ions are not immediately attacked by a nucleophile, but if the 8,14 double bond participates, a pair of homoallylic ions is produced as shown in Scheme III. This set of ions R and S is quite different from ion M of the pimarate series (Scheme II), since overlap between the C-15 carbonium ion and the 8,14 double bond will have to occur on the α face of the molecule. While ions R and S are more symmetrical about the nodal plane (*i.e.*, there is a greater amount of $2p\pi$ overlap than in M) nucleophilic attack would still be expected to proceed stereoselectively. Inclusion of further ions in the reaction scheme is not necessary since the yields of **18a** and **19a** were very high and no products corresponding to attack on C-8 and C-13 were found.

Treatment of **18a** and **19a** with toluenesulfonyl chloride under conditions identical with those of the attempted tosylation of **5a** gave excellent yields of the noncrystalline tosylates **18c** and **19c** in further evidence for the much poorer overlap between an equatorially oriented ion at C-15 and the 8,14 double bond than in the pimarate series. Preliminary attempts to investigate the solvolysis of 18c and 19c led to complex mixtures whose nmr spectra indicated the absence of ring-expanded substances corresponding to **11**. However, acetolysis of **18a** and **19a** occurred with retention of configuration; each alcohol gave in excellent yield a single but different acetate identical with the acetates **18b** or **19b** prepared from the respective alcohols by treatment with acetic anhydride–pyridine. This indicates that solvolysis leads to a pair of asymmetrical homoallylic ion

Experimental Section[25]

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(25) For experimental details, see W. Herz and J. J. Schmid, J. Org. Chem., 34, 3464 (1969).

Methyl 15(R)-Acetamino-8(14)-pimaren-18-oate (6b).--To a mixture of 10 g of dry mercuric nitrate and 22 ml of acetonitrile was added 10 g of methyl pimarate 1b in small portions with stirring during 15 min. Stirring was continued for 2.5 hr; this was followed by addition of 30 ml of 3N NaOH solution and, 5 min subsequently, by addition of 0.35 g of $NaBH_4$ in 30 ml of 3N NaOH solution followed by 1.5 hr of stirring. A chloroform-ether mixture was added followed by solid sodium chloride and 10 ml of 10% HCl solution. The organic layer was separated; the aqueous layer was acidified and again

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extracted with chloroform-ether. The combined organic layers were washed, dried and evaporated. Extraction of the residue with ether-hexane (1:1) furnished 3.42 g of methyl pimarate. Recrystallization of the remaining material from chloroform-hexane afforded two crops (7.13 g) of amide 6b. Column chromatography of the mother liquors resulted in recovery of an additional 0.45 g of 1b (hexane-ether 9:1) and isolation of an additional 0.67 g of 6b (hexane-ether 1:1). The product had mp 229.5-231°; $[\alpha]_D^{25}$-16 (c 1.10, $CHCl_3$); ir bands at 3270, 3080 (-NH), 1728 (ester) and 1643 cm^{-1} (amide), nmr signals at 0.85 (6p, C-10 and C-13 methyls), 1.08d (J = 7, C-16 methyl), 1.20 (C-4 methyl), 1.98 (acetyl), 3.67 (methoxyl), 4.1 m (H-15), 5.18 br (H-14).

Anal. Calcd for $C_{23}H_{37}NO_3$: C, 73.56; H, 9.93; N, 3.73; O, 12.78. Found: C, 73.60; H, 9.79; N, 3.83; O, 12.78.

An attempt to effect hydrolysis of the amide with 20% methanolic potassium hydroxide resulted only in partial hydrolysis of the ester function. Remethylation with diazomethane resulted in recovery of starting material. Treatment of 0.21 g of 6b with 7 ml of 50% H_2SO_4 for 30 min at 150° resulted in recovery of 0.097 g of starting material and a mixture of several unidentified products whose spectral properties indicated partial ester hydrolysis, but no amide hydrolysis.

Methyl 15(R)-Amino-8(14)-pimaren-18-oate (6a).--A mixture of 2 g of 6b in 50 ml of dry CH_2Cl_2 and 2.5 g of freshly prepared triethyloxonium tetrafluoroborate was stirred for 2 hr (nitrogen atmosphere), mixed with an additional 0.5 g of Meerwein's reagent, stirred overnight, mixed with one more g of the reagent, stirred

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the basicity of the medium. Recrystallization from methanol yielded pure 5b which melted at 109.5-110.5°, $[\alpha]_D^{25}$ +7 (c 1.42, $CHCl_3$); ir bands at 1725 cm^{-1} (double intensity); nmr signals at 0.80, and 0.89 (C-10 and C-13 methyls), 1.16 (C-4 methyl), 1.12d (J = 8.3 Hz, C-15 methyl), 2.02 (acetate), 3.63 (methoxyl), 4.94 g (J = 8.3 Hz, H-15), and 5.12 br (H-14).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64; O, 17.00. Found: C, 73.22; H, 9.86; O, 16.97.

Perchloric Acid Treatment of 5b.--A) A solution of 0.265 g of 5b in 4 ml of dioxane and 1 ml of 0.13 N aqueous perchloric acid was refluxed for 12 hr, cooled and extracted with ether. Preparative tlc of the crude product gave a small amount of methyl pimarate, 0.1 g of starting material and 0.12 g of 5a (vide infra).

B) A solution of 0.275 g of 5b, 4 ml of dry dioxane and 1 ml of 0.6 N perchloric acid in acetic acid containing sufficient acetic anhydride to remove all water was refluxed for 28 hr (nitrogen atmosphere), cooled and stirred for 2 days at room temperature. The dark brown solution was poured on ice and extracted with ether. The material from the washed and dried ether layer was subjected to preparative tlc; this resulted in isolation of 52 mg of somewhat impure methyl dehydroabietate and 87 mg of a complex mixture. Acidification of the base washings of the ether extract followed by the usual work-up and methylation with diazomethane furnished an additional 98 mg of crude methyl dehydroabietate, total yield 150 mg (>80% pure) = 58%. When refluxing was continued for only 2.75 hr, the yield of methyl dehydroabietate was 34%.

TABLE 1

Mass Spectra of Resin Acid Derivatives

Compd	M^+(%)	Major Ions(%)						Base Peak (100%)
1b	316(12)	257(10)	181(16)	180(22)	148(11)	133(10)		121
5a	334(2)	289(55)	229(32)	181(21)	107(30)			121
5b	376(1)	289(83)	229(35)	181(25)	107(28)	95(26)		121
6b	376(1)	289(63)	288(56)	229(42)	181(26)			121
8	332(1)	289(64)	229(33)	181(27)	107(24)			121
10*	316(95)	288(30)	159(31)	149(43)	135(66)	121(92)	119(48)	241
11	334(7)	316(18)	276(26)	181(25)	135(27)	109(23)	107(23)	121
17	316(13)	301(12)	257(13)	181(11)	180(10)	133(12)	107(14)	121
18a	334(1)	290(31)	289(58)	229(34)	181(23)	95(29)		121
19a	334(1)	290(25)	289(44)	229(31)	181(21)	95(25)		121
20	332(1)	289(34)	229(23)	181(12)	107(18)			121

*Run with probe temperature at 100° rather than usual 200°

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for 2 hr, concentrated at reduced pressure, and taken up in $CHCl_3$. The washed and dried extract was evaporated and the remaining gum extracted with ether-hexane. From the residue was recovered approx. 0.2 g of 6b. The ether-hexane extract furnished 1.68 g of gummy imino ether 7 which was homogeneous on tlc and had nmr signals at 0.83 (C-10 methyl), 0.93 (C-13 methyl), 0.94d (J = 7 Hz, C-16 methyl), 1.22 (C-4 methyl), 1.83 (imino methyl), 3.68 (methoxyl), 3.23q (J = 7 Hz, H-15), 4.08 q (2p, J = 7.5 Hz, ether methylene), and 5.31 br (H-14).

A mixture of 0.5 g of 7, 11 ml of acetic acid, 300 ml of water and 300 ml of $CHCl_3$ was refluxed for 2 days, made basic and separated. The amine was separated from neutral material by the usual methods; this furnished 3.87 g of non-crystalline 6a which was homogeneous on tlc and nmr signals at 0.82 (C-10 and C-13 methyl), 1.21 (C-4 methyl), 1.03d (J = 6.6 Hz, C-16 methyl), 3.74 (methoxyl) and 5.31 br (H-14). The substance was characterized by reacetylation to 6b.

Diazotization of 6a.--A) A mixture of 0.84 g of 6a, 15 ml of dry diglyme and 1 ml of isoamyl nitrite was refluxed for 4 hr (nitrogen atmosphere), an additional 1 g of nitrite being added after the first hour. The mixture was cooled, diluted with ether and extracted thoroughly with water. The washed and dried organic layer was evaporated and the residue separated by preparative tlc (developed with ether-hexane 3:2). This gave three bands. The top band (wt. 0.11 g) consisted of methyl pimarate (50%) and methyl dehydroabietate (20%), the other two bands were multicomponent mixtures. B) A solution of 0.127 g of 6a, 10 ml of

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Methyl 15(R)-Hydroxy-8(14)-pimaren-18-oate (5a).--A solution of 6.13 g of 5b in 150 ml of methanol containing 15 g of KOH was refluxed until starting material had been consumed (monitoring by tlc), diluted with ether, brought to pH 1 with 10% hydrochloric acid and separated. Evaporation of the washed and dried ether layer and trituration with hexane furnished 2.35 g of crystalline material which was a mixture of 5a and the corresponding acid. The solid and the material from the hexane mother liquor was therefore taken up in ether and methylated with diazomethane, yield of crude methyl ester 5.1 g. Recrystallization from methanol-water afforded 5a which melted at 194-196°, $[\alpha]_D^{25}$ -1.6° (c 1.23, $CHCl_3$); ir bands 3440 and 1700 cm^{-1}; nmr signals at 0.80 and 0.85 (C-10 and C-13 methyls), 1.13d (J = 7 Hz, C-15 methyl), 1.18 (C-4 methyl), 3.64 (methoxyl), 3.66 q (J = 7 Hz, H-15) and 5.13 br (H-14).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35; mol. wt.: 334.2508. Found: C, 75.25; H, 10.39; O, 14.21; mol. wt. (MS): 334.2533.

5b (73 mg, 2.18 x 10^{-4} mol) was esterified with 346 mg (1.11 x 10^{-3} mol) of (±) α-phenylbutyric anhydride in 3 ml of pyridine for 3 days. The usual work-up[26] produced a quantitative

(26) W. Herz and H. B. Kagan, J. Org. Chem., 32, 216 (1967).

yield of ester (purity checked by nmr spectroscopy) and 306 mg of α-phenylbutyric acid (purity checked by nmr spectroscopy) which had $[\alpha]_D^{25}$ +2.45 (c 6.12, benzene). A fully stereospecific esterification should have given $[\alpha]_D^{25}$ +10.4°. Therefore the optical

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acetic acid and 0.75 g of sodium nitrite was heated on the steam bath. Addition of portions of 0.25 g and then 0.2 g of $NaNO_2$ were added at half-hour intervals. After two hours, the reaction was stopped; the usual work up yielded 0.118 g of product mixture which was subjected to tlc (development with ether-hexane 1:1). The only substance which could be identified was the acetate 5b (vide infra).

Methyl 15(R)-Acetoxy-8(14)-pimaren-18-oate (5b).--To a solution of 5g of 1b in 13 ml of acetic acid was added 6 g of dry mercuric acetate in small portions during 10 min. Vigorous stirring was continued for 2.5 hr. The mixture was diluted with 200 ml of dry benzene and concentrated at reduced pressure (temperature <50°); this process was repeated twice more to remove all of the acetic acid. The residue was taken up in 70 ml of dry ether, placed in a 3 neck flask, and mixed with 10 ml of 10% NaOH solution which caused the mixture to turn orange. This was followed by addition with stirring of 10 ml of 10% NaOH solution containing 0.7 g of $NaBH_4$ which caused separation of elemental mercury and liberation of considerable heat. Stirring was continued for 1 hr, the two phases were separated, the aqueous layer was extracted with ether, the combined ether extract were washed, dried and evaporated and the residue was taken up in hot methanol. Cooling and addition of small amounts of water furnished two crops, 4.24 and 0.67 g, of crystalline 5b; the mother liquors, wt. 0.5 g, were at least 80% pure 5b (nmr analysis), hence the total yield was above 90%. The yields were quite variable until it was discovered that the efficiency of the reductive step depended on

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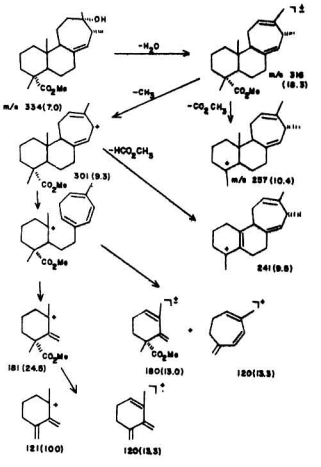
yield was 24%.

Perchloric Acid Treatment of 5a.--A solution of 0.115 g of 5b, 4 ml of dioxane and 1 ml of 0.13 N perchloric acid was stirred overnight and worked up in the usual fashion. Starting material was recovered in nearly quantitative yield.

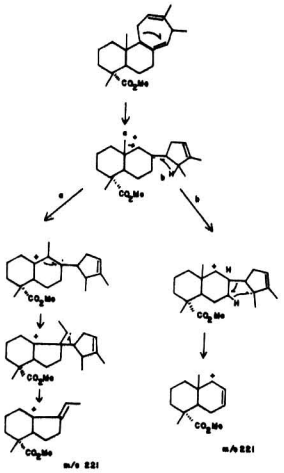
Acetolysis of 5b.--A solution of 0.1 g of 5b in 10 ml of acetic acid was refluxed (nitrogen atmosphere) for 3 days. Removal of solvent at reduced pressure resulted in isolation of crystalline 5a in quantitative yield.

Conversion of 5a to Ether 4.--A solution of 0.5 g of 5a in 15 ml of THF was gradually added with stirring to 0.6 g of mercuric nitrate in 10 ml of anhydrous THF. Addition of 10 ml of 10% NaOH solution after 35 min and subsequent addition of 0.13 g of $NaBH_4$ in 10 ml of 10% NaOH solution was followed by the usual work-up. This resulted in 0.5 g of 4, mp 129-131° (lit.[10] mp 130-132°), nmr signals at 0.84 (C-10 methyl), 1.01 (C-15 methyl), 1.16d (J = 6.3 Hz, C-15 methyl), 1.21 (C-4 methyl), 3.63 (methoxyl), and 3.74 q (J = 6.3 Hz, H-15).

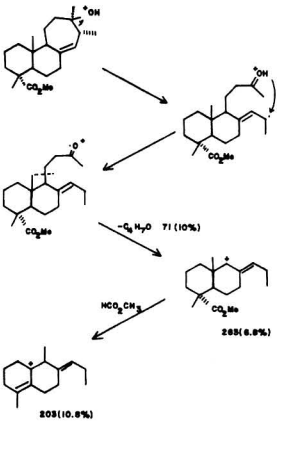
Methyl 15-Oxo-8(14)-pimaren-18-oate (8).--Oxidation of 0.5 g of 5a in 20 ml of acetone at ice bath temperature with Jones reagent, decomposition of excess reagent with methanol, dilution with water, extraction with ether and evaporation of the washed and dried ether extract furnished 0.5 g of ketone 8 which solidified on standing, was recrystallized from methanol and had mp 69.5-70°, $[\alpha]_D^{25}$ -32° (c 0.62, $CHCl_3$); ir bands 1724 and 1711 cm^{-1}; nmr signals at 0.67 (C-10 methyl), 1.09 (C-13 methyl), 1.18 (C-4 methyl), 2.12 (acetyl), 3.67 (methoxyl) and 5.45 br (H-14).



SCHEME IV



SCHEME V



SCHEME VI

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Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.49; H, 9.93; O, 14.73.

$NaBH_4$ reduction of 0.419 g of 8 in the usual manner yielded 0.406 g of a gummy mixture of alcohol 5a and its 15-epimer 9a (6:11 ratio based on integration of the H-14 signals) which could not be separated. Subtraction of the nmr spectrum of 5a from the spectrum of the mixture gave the following signals for the epimer: 0.83 and 0.88 (C-10 and C-13 methyls), 1.11d (J = 6.8 Hz, C-15 methyl), 1.20 (C-4 methyl), 3.67 (methoxyl), 3.69 g (J = 6.8 Hz, H-15) and 5.33 br (H-14). Acetylation of the alcohol mixture (acetic anhydride-pyridine) gave a mixture of acetates.

Rearrangement of 5a to 10 and 11.--A solution of 0.996 g of 5a in 10 ml of pyridine containing 0.898 g of p-toluenesulfonyl chloride was kept in a freezer at -15° with occasional swirling for 28 days[27]. The formation of crystals was noted after 5 days. Work-up in the usual way by pouring over ice, extraction with ether, washing, drying and evaporation of the extract yielded 0.64 g of gum which was subjected to preparative tlc. Development with ether-hexane (7:13) produced seven bands containing 16, 384, 79, 57, 22, 17 and 16 mg of material, respectively. Nmr analysis indicated that bands 1, 3, 5, 6 and 7 were complex mixtures, that band 2 contained 10 and 11 in the ratio 64/36 together with 10% of an impurity and that band 4 was pure 11. Further chromatography separated the components of band 2, total yield of 10, 0.210 g (22%), total yield of 11, 0.195 g (20%). Extraction of the aqueous layers gave a mixture of p-toluene sulfonic acid and starting material.

Recrystallization of 10 from methanol raised the mp to 76°, $[\alpha]_D^{25}$ -13° (c 1.50, $CHCl_3$), ir bands 1717 cm^{-1}, nmr signals at 0.31d (J = 3.8 Hz, H-14), 0.92, 1.08 (C-13 and C-10 methyl), 1.01 (C-15 methyl), 1.17 (C-4 methyl), and 3.63 ppm (methoxyl).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.90; H, 10.19; O, 10.11. Found: C, 79.64; H, 10.27; O, 10.40.

Alcohol 11 was recrystallized from ether-hexane and had mp 114-115°, $[\alpha]_D^{25}$ -29° (c 1.02, $CHCl_3$); ir bands at 3450 and 1727 cm^{-1}; nmr signals at 0.96, 1.06 (C-10 and C-13 methyls), 0.98d (J = 7 Hz, C-15 methyl), 1.17 (C-4 methyl), 2.78 m (H-15), 3.64 (methoxyl), and 4.89 dbr (J = 5 Hz, H-4).

Anal. Calcd for $C_{21}H_{34}O_3$: mol. wt.: 334.2507. Found (MS): 334.2509.

Reactions of 10.--A) A sample of 10 was kept at steam bath temperature for 3 hr and allowed to cool. Tlc and nmr analysis of the product indicated that 10 had undergone no change.

B) The cyclopropyl derivative was recovered unchanged after stirring overnight with silica gel in ether, and with silica gel, ether and a solution of 0.5 ml of 10% HCl in 5 ml of pyridine. Stirring of 10 overnight with silica gel and 5 drops of 10% hydrochloric acid resulted in quantitative transformation to 5a.

C) Acetolysis of 0.05 g of the cyclopropyl derivative by refluxing with 3 ml of acetic acid for 3 hr resulted in quantitative transformation to 5b.

D) A solution of 0.083 g of 10 in 4 ml of dioxane and 1 ml of 0.6 N perchloric acid in acetic acid containing sufficient acetic anhydride to remove all water was refluxed for 2.75 hr (nitrogen atmosphere), poured onto ice and worked up in the usual way. Preparative tlc resulted in isolation of 23 mg (28%) of pure methyl dehydroabietate.

Reactions of 11.--A) Acetolysis of 0.034 g of the tertiary alcohol by refluxing with 1 ml of acetic acid overnight (nitrogen atmosphere), cooling, dilution with toluene and removal of the solvents in vacuo resulted in isolation of 0.030 g of pure 5b.

B) An attempt to dehydrate 0.046 g of 11 with $POCl_3$-pyridine, work-up in the usual manner and preparative tlc of the gummy product resulted in isolation of 5 mg of starting material; transformation products could not be isolated.

Oxymercuration-Demercuration of Methyl Sandaracopimarate.--The sandaracopimaric acid utilized in this experiment was isolated from gum sandarac resin by the procedure of Edwards and coworkers[29]

(27) Under the conditions of the standard method for tosylation[28] the desired tosylate was apparently unstable; as a result a complex mixture containing considerable amounts of starting material was produced. Temperature and reaction time used in the present work were chosen to optimize the yield of 10 and 11, two components of the mixture.

(28) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1., John Wiley and Sons, Inc., New York, N.Y., 1967, p. 1179.

(29) O. E. Edwards, A. Nicolson, and M.N. Rodgers, Can. J. Chem., 38, 663 (1960).

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and methylated with diazomethane. To a solution of 1 g of methyl ester 17 in 20 ml of THF-water (1:1) was added 1.0 g of mercuric acetate. After 10 min, 20 ml of 10% NaOH solution was added followed by an additional 10 ml of 10% NaOH solution containing 0.1 g of $NaBH_4$. This phase of the reaction was ended after 15 min and was followed by the usual work-up. The alcohol mixture, wt. 0.9 g, was separated partially by careful column chromatography. Starting material and traces of methyl callitrisate were eluted with ether-hexane (1:9). Ether-hexane (1:3) produced crystalline alcohol 18a at the leading edge of the band containing the epimeric mixture and gummy alcohol 19a at the trailing edge. Slow crystallization of the fractions rich in crystalline isomer yielded additional quantities of 18a. Recombination of mother liquors and rechromatography eventually permitted nearly complete separation of the mixture; the two isomers were obtained in pure form, as judged by nmr and tlc criteria.

Solid isomer 18a (methyl 15(R)-hydroxy-8(14)-isopimaren-18-oate), was recrystallized from methanol and had mp 125-127°, $[\alpha]_D^{25}$ +28° (c 1.16, $CHCl_3$); ir bands at 3240 and 1725 cm^{-1}; nmr signals at 0.83 (C-10 methyl), 0.97 (C-13 methyl), 1.14 d (J = 7.1 Hz, C-15 methyl), 1.23 (C-4 methyl), 3.44 q (J = 7 Hz), 3.74 (methoxyl), and 5.48 br (H-14).

Anal. Calcd for $C_{21}H_{34}O_3$: 334.2507. Found (MS): 334.2498.

A solution of 0.092 mg of 18a and 0.643 g of α-phenylbutyric anhydride in 5 ml of pyridine yielded 0.139 g of pure ester and 0.572 g of α-phenylbutyric acid (purity checked by nmr spectrometry), $[\alpha]_D^{25}$ +0.52° (c 28.6, benzene); theoretical [α] for fully stereospecific

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esterification 6.9°. Hence the optical yield was 7.5 %.

Acetylation of 0.025 g of 18a with pyridine-acetic anhydride in the usual fashion gave a quantitative yield of non-crystalline 18b which exhibited nmr signals at 0.81, 0.96 (C-10 and C-13 methyls), 1.08 d (J = 6.5 Hz, C-15 methyl), 1.20 (C-4 methyl), 2.03 (acetate), 3.65 (methoxyl), 4.62 q (J = 6.5 Hz, H-15), and 5.18 br (H-14). Tosylation of 0.969 g of 18b gave 1.360 g of non-crystalline tosylate 18c which was pure by tlc standards and exhibited nmr signals at 0.75, 0.91 (C-10 and C-13 methyls), 1.19 (C-4 methyl), 1.22 d (J = 6.5 Hz, C-15 methyl), 2.43 (aromatic methyl), 3.67 (methoxyl), 4.33 q (J = 6.5 Hz, H-15), 5.02 br (H-14), 7.30 d and 7.78 d (2p each, J = 8 Hz, aromatic hydrogens).

Non-crystalline alcohol 19a had ir bands at 3470 and 1727 cm^{-1}; nmr signals at 0.83 (C-10 methyl), 0.94 (C-13 methyl), 1.12 d (J = 6.6 Hz, C-15 methyl), 1.23 (C-4 methyl), 3.48 q (J = 6.6 Hz, H-15), 3.74 (methoxyl) and 5.33 br (H-14).

Anal. Calcd for $C_{21}H_{34}O_3$: mol. wt. 334.2507. Found (MS): 334.2508.

A solution of 0.089 g of 19a and 0.440 g of α-phenylbutyric anhydride in 5 ml of pyridine yielded 0.125 g of pure ester and 0.466 g of α-phenylbutyric anhydride (purity checked by nmr spectroscopy), $[\alpha]_D^{25}$ -0.60°, (c 23.3, benzene), theoretical $[\alpha]_D$ for fully stereospecific reaction -10.0°; optical yield 6%.

The gummy acetate 19b was prepared from 19a in quantitative yield and had nmr signals at 0.80, 0.94 (C-10 and C-13 methyls), 1.11 d (J = 6.5 Hz, C-15 methyl), 1.20 (C-4 methyl), 1.99 (acetate), 3.65 (methoxyl), 4.90 q (J = 6.5 Hz, H-15) and 5.22 br (H-14).

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The non-crystalline tosylate 19c (1.30 g from 1.015 g of 19a) had nmr signals at 0.78, 0.90 (C-10 and C-13 methyls), 1.12 d (J = 7.2 Hz, C-15 methyl), 1.19 (C-4 methyl), 2.43 (aromatic methyl), 3.67 (methoxyl), 4.36 q (J = 7.2 Hz, H-15), 5.00 br (H-14), 7.35 dbr and 7.78 d (2 p each, aromatic hydrogens).

Acetolysis of 18a and 19a.--A) A solution of 0.115 g of 19a in 5 ml of acetic acid was refluxed overnight (nitrogen atmosphere). Removal of acetic acid by codistillation with toluene gave 0.138 g of gummy acetate identical in all respects with 18b produced by pyridine-acetic anhydride treatment of 18a.

B) Repetition of this experiment with 0.107 g of 19a yielded 0.119 g of 19b identical in all respects with the acetate produced by pyridine-acetic anhydride treatment of 19a.

Methyl 15-Oxo-8(14)-isopimaren-18-oate (20).--Oxidation of 0.3 g of the mixture of crude 18a and 19a from the oxymercuration reaction in 10 ml of acetone at ice bath temperature with Jones reagent and standard work-up gave 0.295 g of crude product which was recrystallized from methanol and then melted at 72-74° (lit[18] mp. 73-75°); nmr signals at 0.84 (C-10 methyl), 1.17 (C-13 methyl), 1.23 (C-4 methyl), 2.15 (acetyl), 3.74 (methoxyl) and 5.61 br (H-14).

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Appendix

Mass Spectral Studies Related to Substance 12.--Mass spectra of strobic acid derivatives have been reported[4,6,19]. These spectra and the spectra obtained in the course of the present work (Table I) contain most of the patterns found in the mass spectra of other tricyclic resin acids[19,30-34], particularly those which are minimally influenced by changes in the C-ring. Presumably fragments such as m/e 301, 257, 241, 181, and 121 in the mass spectra of methyl strobate and its derivatives arise by the same or similar pathways (Scheme IV) suggested earlier for other tricyclic resin acids.

Examination of the various spectra disclosed, however, that a peak at m/e 221, previously reported for methyl strobate and methyl dihydrostrobate (21) was also characteristic of 10 and 11.

(30) H. E. Audier, S. Bory, M. Fetizon, and N. T. Anh., Bull. Soc. Chim. France, 4002 (1966).

(31) H. H. Bruun, R. Ryhage, and E. Stenhagen, Acta Chem. Scand., 12, 789 (1958).

(32) L. A. Genge, Anal. Chem., 31, 1750 (1959).

(33) C. R. Enzell, R. A. Appleton, and I. Wahlberg in "Biochemical Applications of Mass Spectrometry", G. R. Waller, ed., John Wiley and Sons, Inc., New York, N.Y., 1972, Chapt. 13.

(34) T. L. Chang, T. E. Mead, and D. F. Zinkel, J. Amer. Oil Chem. Soc., 48, 455 (1971).

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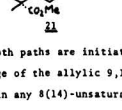
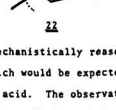
High resolution mass spectrometry revealed that this fragment had the elemental composition $C_{14}H_{21}O_2$; inclusion of the oxygen atoms requires that it be derived from rings A and B with loss of most of the ring C carbon atoms. Two possible paths leading to this fragment are detailed in Scheme V.



21



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Both paths are initiated by a mechanistically reasonable cleavage of the allylic 9,11-bond which would be expected to occur in any 8(14)-unsaturated resin acid. The observation of a unique pattern in resin acid derivatives of the methyl strobate type is rationalized by invoking a rearrangement-cum-cyclization step to form a five-membered ring. The same pathway, if followed by $\Delta^{8,11}$-resin acids with the "normal" six carbon C-ring, would generate an energetically unfavorable four-membered ring. The mass spectrum of methyl levopimarate (2, R = CO_2Me), the closest possible analog to 3b, gives no indication that this pathway is operational.

Evidence for the mechanism postulated to account for the appearance of the m/e 221 fragment is the difference in relative intensities for 3b (25%), 21 (2%), and 12 (5%). In 3b, the 9,11-double bond is doubly allylic; cleavage of this bond produces a structure in which both electron-deficient carbon atoms are allylically stabilized. In substances 11 and 21 which contain only the 8,14-double bond, only an electron deficiency at C-9 can be stabilized. Therefore reduced intensity of m/e 221 is to be expected. Appearance of the m/e 221 fragment in the mass spectrum of 10 (relative intensity 3%) may be due to thermolysis or fragmentation to a structure closely related to 3b or 11.

Burlingame and coworkers[35] have described the fragmentation of widdrol (22) which bears a strong structural resemblance to rings B and C of 11. When the scheme postulated by them to account for the base peak in the widdrol system is applied to 11, the fragmentation shown in Scheme VI results which can account for several observed peaks.

Most significantly, however, the mass spectrum of widdrol exhibits an ion equivalent to m/e 221 at m/e 123 (~25%). Since in widdrol the position equivalent to C-7 of 3b is blocked by two methyl groups, the last proton abstraction step, comparable to path b of Scheme V for 3b, is not possible in the widdrol case. Therefore path a of Scheme V is preferred as an explanation for the formation of the ion m/e 221.

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(35) A. L. Burlingame, C. Fenselau and W. J. Richter, J. Am. Chem. Soc., 89, 3232 (1967).

R′ and S′ similar to R and S of Scheme III (with CH_3 replacing CH_2HgX) and that crossover between them must be small.

Failure of **18a** and **19a** to yield ring-expanded products from substitution at C-13 is not surprising. When the charge of homoallylic ions R′ and S′ is localized at C-8 by conversion to a cyclopropylcarbinyl cation, the vacant p orbital at C-8 is aligned almost exactly with the 14,15 bond of the cyclopropane ring, while the 13,14 bond is very close to the nodal plane of the carbonium ion, making overlap most difficult. This means that conversion of homoallylic ions R′ and S′ to homoallylic ions analogous to **14** is an extremely unfavorable process, more so than in the pimarate series (see ion Q).

Registry No. 1b, 3582-26-1; **4,** 24267-82-1; **5a,** 42401-43-4; **5b,** 42401-44-5; **6a,** 42401-45-6; **6b,** 42401-46-7; **7,** 42401-47-8; **8,** 42401-48-9; **9a,** 42401-49-0; **10,** 42401-50-3; **11,** 42401-51-4; **17,** 19907-21-2; **18a,** 42401-52-5; **18b,** 42401-53-6; **18c,** 43025-21-4; **19a,** 42401-55-8; **19b,** 42401-56-9; **19c,** 42573-18-2; **20,** 24267-84-3.

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References and Notes

(1) Supported in part by a grant from the National Science Foundation (GP-12582). Previous paper: W. Herz and A. L. Hall, *J. Org. Chem.*, **39,** 11 (1974).

(2) The plausibility of the hypothesis has been successfully demonstrated,[3] but the conditions, which involved exposure of pimaric (**1**, R = CO_2H) and isopimaric acids to concentrated sulfuric acid can scarcely be classified as closely approximating those prevailing *in vivo*.

(3) E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.*, **81,** 688 (1959).

(4) (a) D. F. Zinkel and B. F. Spalding, *Tetrahedron Lett.*, 2459 (1971); (b) D. F. Zinkel and B. P. Spalding, *Tetrahedron*, **29,** 1441 (1973); (c) D. F. Zinkel and B. B. Evans, *Phytochemistry*, **11,** 3387 (1972).

(5) In the original report[4a] the stereochemistry of strobic acid at C-15 was unspecified. More recent results[4b] which appeared after the work described in the present communication was completed led to the assignment detailed in formula **3a**.[6]

(6) Numbering in formula **3a** is based on the systematic name abeopimaradienoic acid[7] originally used by the discoverers for strobic acid. In their recent paper[4b] Zinkel and Spalding have corrected the systematic name of strobic acid to that of a cyclolabdane[7] [(14S)-17-cyclolabda-8(17),12-dien-18-oic acid]. Thus; carbon atoms 14, 15, and 16 of formula **3a** become carbon atoms 17, 14, and 15, respectively.

(7) Numbering and nomenclature used in this paper follow the proposals of a committee chaired by J. W. Rowe, "The Common and Systematic Nomenclature of Cyclic Diterpenes," Forest Products Laboratory, U. S. Department of Agriculture, Madison, Wis., 1968 (with Addenda and Corrigenda 1969).

(8) Scheme I illustrates a third possible rearrangement route (path c) of the homoallylic ion A. Paths a and c involve simple alkyl migrations leading to allylic ions, one of which (D) could generate double-bond isomers of strobic acid; path b involves a homoallylic–cyclopropylcarbinyl–homoallylic rearrangement.

(9) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89,** 1522 (1967).

(10) J. W. ApSimon and H. Krehm, *Can. J. Chem.*, **47,** 2865 (1969).

(11) The Canadian workers did not specify the stereochemistry at C-15. As well will be evident from the sequel, the methyl group is β as shown in the formula.

(12) H. C. Brown, P. J. Geoghegan, Jr., G. J. Lynch, and J. T. Kurek, *J. Org. Chem.*, **37,** 1941 (1972).

(13) H. C. Brown and J. T. Kurek, *J. Amer. Chem. Soc.*, **91,** 5647 (1969).

(14) The assignment of stereochemistry to C-15 is based on the stereochemistry subsequently established for the acetate **5b,** which was prepared by an analogous procedure (*vide infra*).

(15) S. Hanessian, *Tetrahedron Lett.*, 1549 (1967).

(16) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962).

(17) It is also possible that π complex J rearranges to the same ions M or N as are necessarily produced by path b. This would eliminate the need to propose nucleophilic attack on two separate ions, J and M or N.

(18) L. M. Jackman and S. Sternheli, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 286.

(19) D. F. Zinkel, L. C. Zank, and M. W. Wesolowski, "Diterpene Resin Acids, a Compilation of Infrared, Mass, Nuclear Magnetic Resonance, Ultraviolet Spectra and Gas Chromatographic Retention Data," U. S. Department of Agriculture, Forest Service, Forest Products Laboratory, Madison, Wis., 1971.

(20) The significance of this peak and other pertinent mass spectrometric information is discussed in an appendix following the Experimental Section.

(21) A possible candidate is an intimate ion pair corresponding to **13,** with the tosylate situated on the β face of the molecule.

(22) For definition, see K. Wiberg, B. Andes Hess, Jr., and A. J. Ashe, III, in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., p 1297. It appears to us that the discussion of relative degree of overlap in P implies that **15** is either unsymmetrical (*i.e.*, that the partial bonds to C-13 and C-15 are of unequal strength) or possesses a geometry which rules out a role in the acetolysis of **10**.

(23) For leading references, see P. R. Story and B. C. Clark, Jr., in ref 22, p 1007.

(24) Aromatization of the expected methyl levopimarate (**2**, R = CO_2Me) to **16** is probably the result of disproportionation, a phenomenon frequently observed in resin acid chemistry. The lower yield of **16** from **10** may be due to partial protonation at C-9, which would be expected to lead to backbone rearrangements.

Preparation of N-Substituted Maleimides by Direct Coupling of Alkyl or Aralkyl Halides with Heavy Metal Salts of Maleimide[1]

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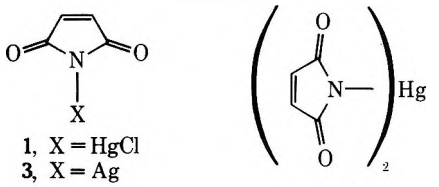
A new procedure for the preparation of some *N*-alkyl- and *N*-aralkylmaleimides has been developed. This procedure uses the reaction of a heavy metal salt of maleimide with alkyl and aralkyl halides in an inert solvent. Silver maleimide (**3**) was found to be far more reactive than mercuric maleimide (**2**). Compound **3** was prepared by treatment of maleimide with silver nitrate and sodium hydroxide in a mixture of ethanol and dimethyl sulfoxide. Compound **2** was prepared by treatment of maleimide with mercuric chloride and sodium hydroxide in ethanol–water. The latter reacted with trityl chloride in refluxing toluene to give a 60% yield of *N*-tritylmaleimide (**4**). The reaction of **3** with trityl chloride in benzene at room temperature increased the yield to 95%. Compound **3** was treated with benzhydryl bromide, benzyl bromide, α-bromo-*p*-xylene, and 9-bromofluorene in benzene under reflux to yield *N*-benzhydrylmaleimide (**5**, 57%), *N*-benzylmaleimide (**6**, 38%), α-*N*-maleimidyl-*p*-xylene (**7**, 17%), and *N*-(9-fluorenyl)maleimide (**8**, 55%), respectively. *N*-(1-Adamantyl)maleimide (**9**) was prepared in refluxing toluene in a 51% yield. When this last reaction was run at room temperature, *O*-(1-adamantyl)maleimide (**10**) was obtained in nearly quantitative yield. This compound represents the first synthesis of an *O*-alkylmaleimide and it can easily be distinguished from **9** and other N-substituted maleimides by nmr, ir, and uv spectroscopy, and by tlc. Compound **10** was converted to **9** in a 55% yield by heating the compound in toluene in the presence of silver bromide.

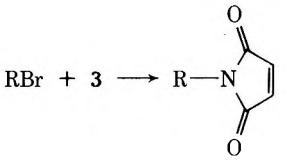
N-Alkyl- or *N*-arylmaleimides have been prepared by reaction of amines with maleic anhydride to give maleamic acids, which, after isolation, are then cyclized in such mixtures as refluxing acetic anhydride–sodium acetate or hot phosphoric acid.[2] A careful survey of the literature revealed that some amines did not afford good yields of maleimides after condensation with maleic anhydride because the cyclization of the maleamic acids proceeded poorly.[3,4] We, therefore, decided to attempt the preparation of a heavy metal salt of maleimide and to condense this with simple alkyl or aralkyl halides, a method that has been of use in the synthesis of nucleosides.[5] What we wish to report is the first synthesis of N-substituted maleimides by direct coupling of heavy metal salts of maleimide with organic halides in an inert solvent.

Attempted preparation of chloromercurimaleimide (**1**, Chart I) always led to the formation of mercuric maleimide (**2**), regardless of the relative molar quantities of maleimide, sodium hydroxide, and mercuric chloride used. Compound **2** was coupled with trityl chloride in hot toluene to afford a 60% yield of *N*-tritylmaleimide (**4**). However, this procedure was not useful for the synthesis of other N-substituted maleimides. A better reagent for this purpose was silver maleimide (**3**), easily prepared by treatment of maleimide with silver nitrate and sodium hydroxide.

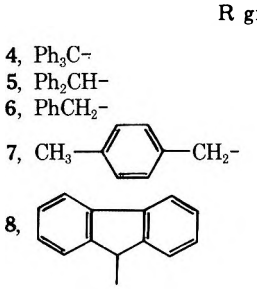
Chart I

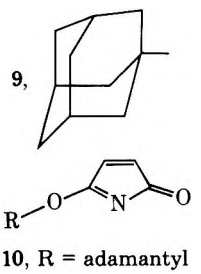


2



R group





10, R = adamantyl

Silver maleimide was treated with a number of organic halides in hot benzene or toluene. In general, benzene was the most satisfactory solvent. When silver maleimide was placed in warm polar solvents, such as dimethylformamide or acetonitrile, it rapidly decomposed. An advantage of this procedure is best demonstrated by the synthesis of *N*-(9-fluorenyl)maleimide (**8**) in 55% yield, whereas the older reaction sequence starting from 9-aminofluorene gave **8** in an overall yield of only 8%.[4] This procedure is particularly advantageous in cases where the amine is not readily available, such as in the synthesis of α-*N*-maleimidyl-*p*-xylene (**7**). Starting from α-bromo-*p*-xylene, the yield of **7** was only 17%. However, this direct single-step coupling precluded the necessity of preparing the amine. Reaction of **3** with benzyl bromide in toluene at reflux gave **6** in a significantly lower yield (11%) and maleimide and α-phenylxylenes were identified in the mixture. Such compounds were not detected when the same reaction was performed in benzene.

When silver maleimide was treated with 1-bromoadamantane in benzene at room temperature, a nearly quantitative yield of *O*-(1-adamantyl)maleimide (**10**) was obtained as a solid, representing the first reported synthesis of an O-substituted maleimide. The structure of **10** was clearly differentiated from *N*-(1-adamantyl)maleimide (**9**) and other N-substituted maleimides by nmr and ir spectroscopy. The nmr spectra of all of the N-substituted maleimides studied in this investigation had a sharp singlet between τ 3.19 and 3.45, which was expected because of the symmetrical environment of the two olefinic protons. This was also true of maleimide itself and for the two heavy metal salts, **2** and **3**, which was an important proof of structure for the latter. On the other hand, the nmr spectrum of **10** revealed two doublets for the same protons in the form of a nearly classical AB pattern at τ

Table I
Ultraviolet Spectra of Some Maleimide Derivatives

Compd	λ, nm (ε)[a] Maxima	Minima
N-Ethylmaleimide	297 (637)	243 (55)
N-(1-Adamantyl)maleimide (**9**)	301 (643)	251 (121)
O-(1-Adamantyl)maleimide (**10**)	310 (678)	276 (432)

[a] Spectra determined in 1,2-dichloroethane.

3.21 and 3.59 (J = 5.2 Hz). This indicated that the bond between the adamantane and maleimide was linked through one of the oxygen atoms of maleimide. The downfield shift of one of the peaks relative to that obtained for **9** at τ 3.43 may be due to an induced ring current, resulting in a deshielding effect. A fully conjugated planar structure such as **10** would be expected to produce such a ring current. The results of this conjugated planar geometry is also evident in the observed differences in the uv spectra of **10**, **9**, and *N*-ethylmaleimide (Table I).

Infrared spectra were also of important diagnostic value in studying the maleimides. Usually, the carbonyl peak near 1700 cm^{-1} has been utilized for structural purposes. However, an out-of-plane deformation at 678 cm^{-1} for maleimide was reported[6] which appears near 690 cm^{-1} in N-substituted maleimides. The phenyl C-H in phenyl-substituted maleimides is fully resolved at slightly higher wave numbers. Freedom from contamination with maleimide was verified by the absence of a peak at 678 cm^{-1} in addition to tlc data. Another strong band which was characteristic of the maleimides studied appeared between 820 and 850 cm^{-1} and has not yet been assigned to a bond. Compound **10** exhibited a strong infrared band at 1042 cm^{-1}, which was not present in **9** or the other maleimides, and which is due to an ether linkage. The conjugated C=C and C=N bands were also evident at 1600 and 1530 cm^{-1} and the C-H bending vibration at 694 cm^{-1} was shifted to 720 cm^{-1}. All of this evidence clearly identified **10** as *O*-(1-adamantyl)maleimide.

An examination of O → N isomerization was now undertaken with **10**, using mercuric bromide, a reagent often used to effect such transformations in pyrimidines[7] and other diazines.[8] When **10** was treated with mercuric bromide in boiling benzene, **9** was isolated in 34% yield. It was probable that in the coupling reaction **10** was the product first formed and that silver bromide, the by-product, catalyzed the O → N isomerization *in situ*. Treatment of **10** with an "activated" silver bromide[9] (prepared from *tert*-butyl bromide and silver succinimide) in hot toluene afforded a 55% yield of **9**. Compound **10** would not rearrange to **9** when heated under reflux without the heavy metal salts. A study of the course of the coupling reaction by tlc revealed that after 1 hr the only new product was **10** and that all of the 1-bromoadamantane had been consumed by silver maleimide. After an additional 3 hr, **10** and **9** were both observed and after 30 hr the only product was **9**. Presumably, the other coupling reactions proceeded by a similar pathway. A reinvestigation by tlc and ir spectroscopy of earlier periods in some of the reactions reported above or reactions at lower temperatures gave good evidence that this was the case, except in the synthesis of *N*-tritylmaleimide (**4**).

It is interesting to note that during attempts to purify **10** by sublimation above 90°, a small quantity of **9** was detected in the sublimate only. Since the residue did not contain any **9**, it was concluded that the rearrangement proceeded by a free-radical process in the vapor phase.[10] It was mentioned above that a mixture of α-phenylxylenes and maleimide appeared to be the major products during a synthesis of *N*-benzylmaleimide (**6**) in boiling toluene. It now seemed quite probable that these products arose *via* a free-radical process propagated by homolytic dissociation of *O*-benzylmaleimide, resulting in benzyl and maleimidyl free radicals. Earlier we had thought that such a reaction was initiated by homolytic decomposition of **3**, but, when **3** was suspended alone in boiling toluene, no decomposition took place.

Experimental Section[11]

Mercuric Maleimide (2). A solution of maleimide (15.0 g, 0.154 mol) in 100 ml of water was mixed with a solution containing 21.0 g (0.077 mol) of mercuric chloride in 80 ml of ethanol and to this stirring mixture was added 385 ml of 0.4 *N* sodium hydroxide solution, dropwise. Compound **2** (23.9 g, 80%) was isolated as a slightly off-white solid by filtration, washing with water, ethanol, and acetone in succession, and drying in a vacuum desiccator ($CaCl_2$, 20 mm): ir 3050, 1650 (br), 1345, 1175, 1165, 1080, 1008, 827, 770, 694, and 665 cm^{-1}; nmr τ 3.15 (sharp singlet). An analytical sample was prepared by recrystallization from dimethyl sulfoxide.

Anal. Calcd for $C_8H_4HgN_2O_4$: C, 24.47; H, 1.02; Hg, 51.07; N, 7.13. Found: C, 24.36; H, 1.13; Hg, 50.94; N, 6.97.

Silver Maleimide (3). A solution of silver nitrate (24.8 g, 0.146 mol) in 100 ml of DMSO was added to a solution of maleimide (14.2 g, 0.146 mol) in 600 ml of absolute ethanol and to this mixture was added, dropwise, 365 ml of 0.4 *N* ethanolic sodium hydroxide solution over a period of 2 hr while the mixture was vigorously stirred. The off-white solid was isolated by suction on filter paper[12] and thoroughly washed with absolute ethanol. The precipitate was suspended in water, stirred vigorously for several minutes, filtered, and washed again with ethanol. This process was repeated in acetone and the solid was dried in a vacuum desiccator (20 mm) for 48 hr, yielding 27 g (91%) of **3**: ir 3080, 1727, 1610, 1560, 1370, 1310, 1080, 990, 831, 710, 703 (sh), and 660 cm^{-1}; nmr (DMSO-d_6) τ 3.45 (sharp singlet); nmr (pyridine-d_5) τ 4.06 (sharp singlet).

Anal. Calcd for $C_4H_2AgNO_2$: C, 23.56; H, 0.99; Ag, 52.90; N, 6.87. Found: C, 23.62; H, 1.13; Ag, 53.04; N, 6.85.

Prior to the utilization of **5** it was further dried at 0.05 mm over P_2O_5 at room temperature for at least 24 hr. During the preparation and handling of **3**, precautions were taken to exclude light.

***N*-Tritylmaleimide (4). Method A. From Mercuric Maleimide (2).** From a mixture containing 0.57 g (1.5 mmol) of **2**, 0.3 g of Celite-545, and 28 ml of toluene, 12 ml of toluene was removed by distillation. Trityl chloride (0.40 g, 1.4 mmol) was added to it and the mixture was stirred at reflux for 4 hr. The precipitated solids were removed by filtration and washed with several portions of hot chloroform. The solvents were removed by evaporation and the residue was dissolved in 30 ml of ethyl acetate, washed with 30% aqueous potassium iodide (4 × 20 ml), and dried. Evaporation of the solvent left 0.72 g of a moist yellow solid which upon trituration with ethyl ether afforded 0.28 g (60%) of **4** as a white powder, mp 225–227°. Crystallization from a mixture of hexane and benzene produced the analytical sample: mp 225–228°; ir 3000, 1706, 1340, 1323, 836, 694, and 690 cm^{-1}; nmr τ 2.78 (m, 15 aromatic H), 3.44 (sharp singlet, 2 olefinic H).

Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.29; H, 5.06; N, 4.08.

Method B. From Silver Maleimide (3). Trityl chloride (0.72 g, 2.6 mmol) was dissolved in 22 ml of benzene and treated with 0.55 g (2.7 mmol) of **3** at 25°. After 4 hr, the mixture was filtered and the filtrate was evaporated to a white powder (0.81 g, 95%), mp 226–229°. The product was identical to that obtained by method A, as determined by ir spectroscopy and tlc.

***N*-Benzyhydrylmaleimide (5).** Benzhydryl bromide (4.4 g, 0.018 mol) and **3** (4.0 g, 0.020 mol) were stirred in 240 ml of dry benzene at reflux for 1.7 hr. The silver salts were removed by filtration and washed with methylene chloride. Evaporation of the solvent afforded a light-tan solid which was crystallized from 100 ml of ethanol, giving 2.7 g (57%) of **5**: mp 147–151°; ir 3050, 1698, 1357, 831, 698, 690 cm^{-1}; nmr τ 2.66 (sharp singlet, 10 aromatic H), 3.31 (sharp singlet, 2 olefinic H), 3.46 (s, benzylic H). Recrystallization from ethanol afforded the analytical sample.

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.83; H, 5.07; N, 5.27.

***N*-Benzylmaleimide (6). Method A.** Compound **3** (10.0 g, 49 mmol) was added in five equal portions at 0.5-hr intervals to a stirring solution of 7.8 g (45 mmol) of benzyl bromide in 145 ml of benzene maintained at 60°. The mixture was then heated to re-

flux for 15.5 hr, and the silver salts were removed by filtration and washed thoroughly with benzene. Evaporation of the benzene gave an amber-colored residue which was dissolved in 150 ml of carbon tetrachloride and washed with water (3 × 200 ml). The organic layer was dried and the solvent was evaporated, leaving 3.2 g (38%) of a liquid which almost completely solidified upon standing. Crystallization from ethanol and sublimation gave white crystals of **6**: mp 69–72° (lit.[13] mp 70–72°); ir 3060, 1701, 840, 697 (sh), 690 cm^{-1}; nmr τ 2.67 (sharp singlet, 5 aromatic H), 3.34 (sharp singlet, 2 olefinic H), 5.33 (sharp singlet, 2 benzylic H).

Method B. A repeat of the above reaction in toluene under reflux gave an oil which was separated by preparative tlc in benzene on 20 × 20 cm silica gel F-254 plates of 2-mm thickness (E. Merck, Darmstadt). The product having R_f 0.15 was identified as **6** (mp 67–68°) and the spectra of the faster moving substance (R_f 0.58) indicated that it could be a mixture of α-phenylxylenes: ir (film) 3000, 2900, 1602, 1515, 1495, 1455, 742, 722, 696 cm^{-1}; nmr τ 2.80 (m, 9 aromatic H), 6.00 and 6.05 (two singlets for two positional isomers, 2 methylene H), and 7.80 and 7.87 (2 singlets for two positional isomers, 3 methyl H).

***α*-*N*-Maleimidyl-*p*-xylene (7).** A mixture consisting of α-bromo-*p*-xylene (12.0 g, 0.065 mol), **3** (13.3 g, 0.066 mol) and 500 ml of dry benzene was refluxed for 16 hr. The silver salts were removed by filtration. Evaporation of the solvent left a tacky, amber-colored residue which was vigorously stirred in 200 ml of ether for 3 hr. After filtration, the solvent was evaporated, leaving a light-tan semisolid which was sublimed at 110° (0.02 mm). A small amount of an oily contaminant was removed from the sublimate (**7**) by sandwiching it between porous plates. Additional **7** was obtained by treatment of the residue as above. The combined solids were dissolved in 80 ml of benzene and washed with water (4 × 75 ml) to remove maleimide. The benzene solution was dried and evaporated to afford a white, crystalline solid. Sublimation (0.02 mm, 104°) produced 2.2 g (17%) of an analytically pure material: mp 101–104°; ir 3080, 3010, 2910, 1706, 1342, 1335, 825, 692 cm^{-1}; nmr τ 2.76 and 2.79 (two singlets, 4 aromatic H), 3.27 (sharp singlet, 2 olefinic H), 5.34 (sharp singlet, 2 methylene H), 7.67 (sharp singlet, 3 methyl H).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.78; H, 5.66; N, 6.72.

***N*-(9-Fluorenyl)maleimide (8).** To a suspension of **3** (6.1 g, 0.030 mol) in 50 ml of benzene was added, with stirring, a solution of 7.1 g (0.029 mol) of 9-bromofluorene in 200 ml of benzene and the mixture was refluxed for 2.5 hr. Solids were removed by filtration, and the solvent was evaporated, leaving a yellow solid. This material was stirred for 3 hr in 25 ml of ether and a white powder was isolated by filtration and washed with 10 ml of ice-cold ether. The solid was dissolved in 250 ml of benzene and washed with water (4 × 200 ml). Drying of the benzene layer and evaporation of the solvent left a white solid which was crystallized from heptane–benzene to give 4.2 g (55%) of white needles of **8**, mp 176–179°. Further purification was effected by sublimation (0.02 mm, 140–145°): mp 174–177° (lit.[4] mp 174–175°); ir 3080, 2880, 1355, 1350, 1704, 1686, 827, 738, 692 cm^{-1}; nmr τ 2.07–2.81 (m, 8 aromatic H), 3.28 (sharp singlet, 2 olefinic H), 3.83 (s, 1 aliphatic H).

***N*-(1-Adamantyl)maleimide (9).** A mixture of **3** (1.37 g, 6.7 mmol), 1-bromoadamantane (1.12 g, 5.2 mmol), and toluene (24 ml) was heated at reflux for 4 hr. Filtration and evaporation of the solvent left 0.83 g of a light-orange, waxy solid. Sublimation (0.3 mm, 110°) afforded 0.62 g (51%) of a white, crystalline material which was homogeneous by tlc, mp 120° (with sublimation). An analytical sample was prepared by recrystallization from petroleum ether (bp 30–60°): mp 118–121°; ir 3040, 2880, 1709, 1689, 1351, 828, 694, and 678 cm^{-1}; nmr (CCl_4, internal TMS) τ 3.57 (sharp singlet, 2 olefinic H), 7.67 (s, 6 methylene H), 7.88 (m, 3 bridgehead H), 8.28 (s, 6 methylene H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.75; H, 7.38; N, 5.99.

O-(1-Adamantyl)maleimide (10). A mixture of 1-bromoadamantane (3.2 g, 1.5 mmol), **3** (3.2 g, 1.6 mmol), and benzene (80 ml) was stirred at room temperature for 18 hr. The silver bromide was filtered off and the filtrate was evaporated to dryness to yield 3.4 g (98%) of **10**: mp 132–140° dec; ir 3080, 2900, 1745, 1732, 1600, 1530, 1383, 1378, 1355, 1042, 887, 822, 728, 720, and 662 cm^{-1}; nmr τ 3.21 and 3.59 (AB quartet, 2 olefinic H, J = 5.2 Hz), 7.67 (s, 6 methylene H), 7.83 (s, 3 bridgehead H), 8.29 (s, 6 methylene H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.52; H, 7.33; N, 5.74.

Rearrangement of 10 to 9. To a solution of *tert*-butyl bromide (0.24 g, 1.8 mmol) in 17 ml of toluene was added 0.33 g (1.6 mmol) of silver succinimide[14] and the mixture was stirred for 20 min. The silver bromide which precipitated was washed by decantation with nine 15-ml portions of toluene. At this point the toluene wash no longer gave a positive alcoholic silver nitrate test. The silver bromide was suspended in 15 ml of fresh toluene and a solution of **10** (0.31 g, 1.4 mmol) in 15 ml of toluene was added. The mixture was stirred at reflux for 4.5 hr and the salt was removed by filtration. After evaporation of the solvent, carbon tetrachloride was added and evaporated three times. Sublimation of the residue *in vacuo* (0.02 mm, 40–100°) produced 0.17 g (55%) of **9** which was shown to be identical with previous preparations by melting point and tlc and by ir and nmr spectroscopy.

Registry No. **2**, 42867-29-8; **3**, 42867-30-1; **4**, 42867-31-2; **5**, 32620-66-9; **6**, 1631-26-1; **7**, 42867-34-5; **8**, 7702-44-5; **9**, 42867-36-7; **10**, 42867-37-8; maleimide, 541-59-3; trityl chloride, 76-83-5; benzhydryl bromide, 776-74-9; benzyl bromide, 100-39-0; α-bromo-*p*-xylene, 104-81-4; 9-bromofluorene, 1940-57-4; 1-bromoadamantane, 768-90-1.

References and Notes

(1) (a) This work was supported by Grant No. CA 12205 from the National Cancer Institute, National Institutes of Health. (b) A communication of some of these results was reported by the above authors at the 165th National Meeting of the American Chemical Society, Dallas, Tex., April 1973, ORGN 115.

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(9) Silver bromide, prepared from silver nitrate and potassium bromide in water, gave greatly lowered yields in this reaction.

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(11) Melting points were determined on a Kofler micro hot stage and are corrected values. Infrared spectra were obtained from KBr pellets on a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra were recorded on a Beckman DK-2 spectrophotometer in 1.0-cm silica cuvettes. Nmr spectra of N- and O-substituted maleimides were recorded as $CDCl_3$ solutions (99.8%, internal TMS) and heavy metal salts of maleimide as DMSO-d_6 solutions (99.5%, internal TMS) on a Varian A-60 spectrophotometer. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn., or the Spang Microanalytical Laboratory, Ann Arbor, Mich. Solvent evaporations were carried out on a rotary evaporator under reduced pressure and at a bath temperature under 50°. Moist organic solutions were dried over anhydrous magnesium sulfate. Thin layer chromatography (tlc) was performed on silica gel F-254 precoated plates (E. Merck, Darmstadt) of 0.25 mm thickness. Spots were visualized with an ultraviolet lamp or in an iodine chamber.

(12) The use of a sintered-glass funnel causes the salt to turn dark at the salt-glass interface.

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Preparation and Synthetic Utility of Some Organotin Derivatives of Nucleosides

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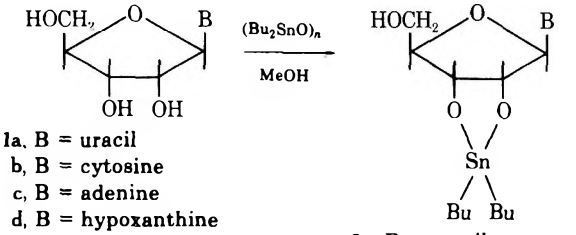
The reaction of ribo nucleosides with dibutyltin oxide in hot methanol gives rise to 2′,3′-*O*-(dibutylstannylene)nucleosides (**2**) that can be isolated in high yield and crystalline form. The dibutylstannylene function serves, not as a protecting group, but rather as an activating group for the 2′- and 3′-oxygen functions. Thus, the reactions of **2** prepared *in situ* in methanol with acyl chlorides or anhydrides leads to the selective formation of 2′(3′)-*O*-acyl nucleosides from which the pure 3′-*O*-acyl derivatives can be isolated in good yield by crystallization. In a similar way the reaction of methanolic solutions of **2** with *p*-toluenesulfonyl chloride leads quite selectively to the formation and isolation of 2′-*O*-*p*-toluenesulfonyl nucleosides. The related reaction with phosphorus oxychloride leads, after hydrolysis, to the selective formation of mixed nucleoside 2′(3′)-phosphates. Alkylation reactions are more restricted but reaction of 2′,3′-*O*-(dibutylstannylene)uridine with benzyl bromide and methyl iodide in dimethylformamide leads selectively to the monobenzylation and monomethylation of the 2′ and 3′ oxygens. The reaction of nucleoside 5′-phosphates with hexabutyldistannoxane leads to the formation, in high yield, of crystalline bis(tributyltin) esters with significant antifungal and antibacterial properties.

The ever-increasing interest in the chemistry of nucleosides and nucleotides has led to a continuing search for new and selective reactions that can be applied to predetermined sugar hydroxyl groups. Recent years have also witnessed an expanding interest in the chemistry of organotin compounds,[2] including the development of effective means for the synthesis of cyclic dialkoxytin derivatives.[3] It was therefore of interest to investigate the synthesis of some 2′,3′-*O*-stannylene derivatives of nucleosides (**2**), these compounds being tin analogs of the frequently used 2′,3′-*O*-alkylidene (*e.g.*, isopropylidene) nucleosides. Since tin-oxygen bonds have rather varied stabilities, the stannylene function could either serve as a protecting group for the 2′,3′-diol or as an activating group for further reactions.

The preparation of 2′,3′-*O*-(dibutylstannylene) nucleosides (**2**) proved to be very simple and was achieved by heating a methanolic suspension of the nucleoside (**1**) and an equimolar amount of dibutyltin oxide. A homogeneous solution resulted, usually within 30 min, and the solvent was then evaporated, leaving a solid residue that can be readily crystallized. In this way the 2′,3′-*O*-dibutylstannylene derivatives of uridine (**2a**), cytidine (**2b**), and adenosine (**2c**) were obtained in crystalline form in yields of 96, 91, and 70%, respectively. The reduced yield (70%) of **2c** was due to the necessity of two recrystallizations in order

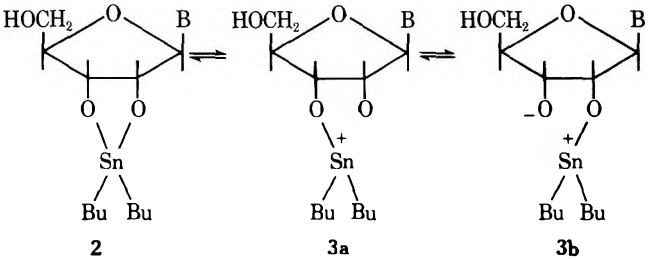


1a, B = uracil
b, B = cytosine
c, B = adenine
d, B = hypoxanthine

2a, B = uracil
b, B = cytosine
c, B = adenine
d, B = hypoxanthine

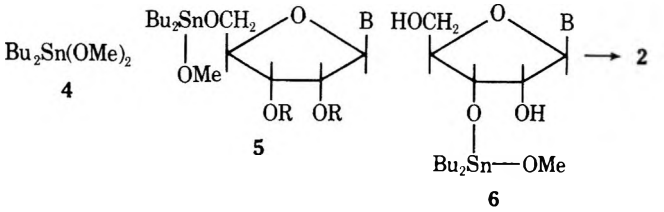
to remove a trace impurity. In all cases the reactions appear to be essentially quantitative and for practical purposes we usually generate the derivatives *in situ* as above and use them directly without crystallization.

The stannylene derivatives (**2**) have reasonable solubilities in polar solvents such as methanol, ethanol, and dimethylformamide but are poorly soluble in chloroform, acetone, and ether. On attempted thin layer chromatography on silica gel, and to a lesser degree on cellulose plates, the stannylene derivatives reverted to the parent nucleosides. The primary covalent nature of the compounds was, however, assured by mass spectrometry, which showed small but significant multiple peaks (tin isotopes) corresponding to the expected molecular ions. Other significant fragments in the higher molecular weight region corresponded to loss of butyl groups and of the heterocyclic bases. Unfortunately, we have been consistently unable to obtain well-resolved nmr spectra for these compounds, most signals being broad and lacking in fine structure. The nmr spectra of alkoxytin compounds have been a source of some confusion, since in some cases tin–hydrogen coupling is observed[4] while in others it is not.[5] Factors such as partial ionic character,[5] facile intermolecular alkoxy exchange,[4a] and self-association[4b] have been suggested to explain these effects. In the present case a general broadening of all signals can probably be attributed to intermolecular exchange. In support of this it was observed that the signals generally sharpened as the temperature was lowered until viscosity became a problem. Also, the spectrum of a mixture of **2a** and uridine showed broadened signals for, *e.g.*, the C_1′H of both compounds and these signals gradually coalesced as the temperature was raised. Upon recooling the original broad signals returned. Because of the problems described above in examining compounds of type **2** by either thin layer chromatography or nmr, it is difficult to determine with any precision the chemical stabilities of these substances.



2 **3a** **3b**

The selective formation of the 2′,3′-*O*-stannylene derivatives (**2**) is clearly a consequence of the greater thermodynamic stability of the cyclic 2-stanna-1,3-dioxolane structure relative to acyclic alkoxytin derivatives.[3b] It is well known that dibutyltin oxide and methanol rapidly form dibutyldimethoxytin (**4**),[2] which is presumably the reactive intermediate in subsequent condensations.

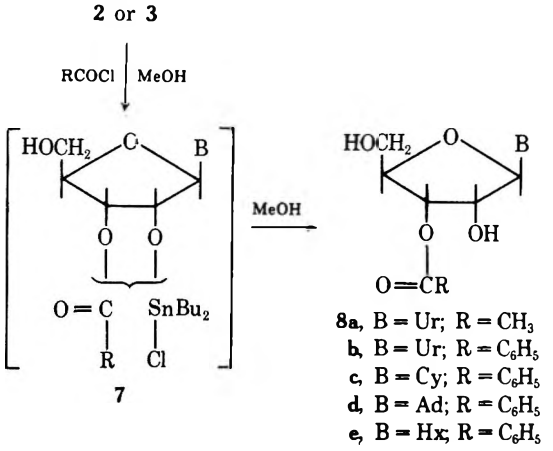


Whenever 4 undergoes alkoxy exchange with the 5′-hydroxyl group of the nucleoside the resulting derivative (5) can exchange once again with the solvent, regenerating 4. On the other hand, a single exchange reaction involving either the 2′ or 3′ hydroxyl group gives an intermediate (*e.g.*, 6) which undergoes an extremely rapid, second exchange to form the cyclic derivative (2) before methanolysis can occur. Since 2 is far more stable than 5 to methanol, or to traces of water formed during preparation of 4, the above process leads essentially quantitatively to this substance.

In an initial effort to determine the role of the stannylene derivative in other reactions of the nucleoside sugar moiety, pure **2a** was treated in dimethylformamide with a slight excess of acetic anhydride at 0°. Examination by thin layer chromatography (tlc) showed one major product which gave a negative test for vicinal diols using a periodate–benzidine spray.[6] Following extraction of tin compounds with chloroform the residue was shown by nmr spectroscopy to be a roughly equal mixture of 2′-*O*-acetyl- and 3′-*O*-acetyluridine similar to that prepared by mild hydrolysis of 2′,3′-*O*-(ethoxyethylidene)uridine.[7] As was shown by Fromageot, *et al.*,[7] crystallization of such a mixture from a polar solvent led to equilibration of the acyl functions and isolation of pure 3′-*O*-acetyluridine (**8a**) in 54% yield. From this experiment it was clear that the stannylidene group functions not as a protecting group, but rather as an activating group for the 2′- and 3′-hydroxyl functions of a nucleoside. It has previously been shown that various monoalkoxytin derivatives react with acid anhydrides or acid chlorides to form esters and the appropriate tin acetate or tin chloride.[8] Such a reaction has proved to be valuable in effecting a mild sulfamoylation in previous work from this laboratory,[9] but comparable acylations or alkylations do not appear to have been reported using cyclic stannylene derivatives. It is not clear whether such acylations are a direct consequence of equilibrium concentrations of ionic species (**3a,b**) or simply involve the well-known addition of tin alkoxides to reactive bonds, perhaps *via* a four-center transition state.[2,10]

In order to avoid multiple acylation in the above reaction only a slight excess of acetic anhydride was used. The apparent reactivity of the tin–oxygen bond, however, suggested that it might be possible to directly acylate the stannylene derivatives prepared *in situ* in methanol. In fact, the addition of 5–10 equiv each of acetyl chloride and triethylamine to a solution of **2a** prepared in methanol led to a very rapid and selective monoacetylation reaction. By crystallization of the mixed 2′(3′)-acetates, pure 3′-*O*-acetyluridine (**8a**) was obtained in 69% yield. Similar results were obtained using acetic anhydride rather than acetyl chloride but the yield of pure **8a** was lower.

From a preparative point of view the direct benzoylation of the stannylene derivatives was of greater interest. Treatment of a methanolic solution of **2a** with benzoyl chloride and triethylamine gave pure 3′-*O*-benzoyluridine (**8b**) in 78% yield following crystallization from aqueous ethanol. Very similar results were obtained from reactions of the other 2′,3′-*O*-stannylene nucleosides (**2b–d**) with acylating agents. Thus the reaction of methanolic **2b** with acetic anhydride and triethylamine gave a roughly 3:1 mixture of 3′-*O*-acetyl- and 2′-*O*-acetylcytidines in essentially quantitative yield. In this case, however, no selective crystallization of one isomer could be achieved. A similar reaction using benzoyl chloride gave pure crystalline 3′-*O*-benzoylcytidine (**8c**) in 87% yield. The method was also suitable in the purine series, since reactions of 2′,3′-*O*-(dibutylstannylene)adenosine (**2c**) and its inosine counterpart **2d** gave the crystalline 3′-*O*-benzoyl nucleosides (**8d, 8e**) in yields of 70 and 50%, respectively. In all cases the homogeneity of the final products and the location of the acyl group were readily apparent by nmr spectroscopy. The spectra of the crude products prior to crystallization always showed signals characteristic of both the 2′- and 3′-acyl derivatives, the relative assignments being possible through application of the rules developed by Fromageot, *et al.*[11] Following crystallization, the pure 3′-*O*-acyl derivatives (**8a–e**) were identified by use of the

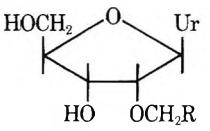


above rules,[11] by the characteristic downfield shift of the C_3′H signals, and by the presence of signals due to the C_2′OH and C_5′OH groups. The absolute location of those groups was confirmed by spin-decoupling studies in DMSO-d_6. The ribo configuration was in each case confirmed by deacylation and examination of the parent nucleosides by borate electrophoresis.[12]

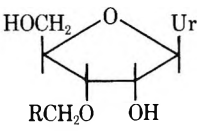
The useful feature of all the above reactions is the complete selectivity for acylation at C_2′ or C_3′ with no observable reaction at C_5′ or on heterocyclic amino groups. This is doubtless a consequence of the initial high reactivity of the Sn–O bonds, perhaps *via* intervention of equilibrium concentrations of ionic species such as **3a,b**. This reactivity leads to almost immediate reaction with the acyl halide, giving a mixture of monoacyl–monotin ethers (*e.g.*, **7**). The lability of acyclic tin ethers such as **7** in methanol or in the presence of the mole of water released during formation of **2** then leads to rapid methanolysis or hydrolysis of the remaining Sn–O bond, giving, after crystallization, the monoester **8** before a second acylation can occur. In the absence of tin activation at C_5′OH and at amino functions, these groups cannot compete effectively with methanol and remain unreacted. In contrast, it is known that selective N-acylation of cytidine can be accomplished using acid anhydrides in methanol[13] but these reactions occur in the absence of any base and require many hours under reflux. It should also be recalled that some selectivity for 2′(3′)-*O*-mono- and diacylation results from reaction of nucleosides with benzoic anhydride and tributylamine in aqueous ethanol.[14]

In the uridine series, the 2′,3′-*O*-stannylene function also provides an opportunity for selective monoalkylation of the 2′- and 3′-oxygen functions. Thus the reaction of **2a** with a slight excess of benzyl bromide in dimethylformamide led to the formation of a roughly equal (nmr) mix-

ture of 2′-*O*-benzyluridine (**9a**) and 3′-*O*-benzyluridine (**10a**) in a combined yield of 65% and with no indication of other benzylation products. The mixture could not be preparatively separated by chromatography under a variety of conditions, but it was possible to almost completely resolve the mixture by fractional crystallization, giving pure **9a** (31%) and **10a** (26%). Unequivocal syntheses of **9a** and **10a** have been described by Reese, *et al.*,[15] and by Blank and Pfleiderer[16] *via* benzylation of the appropriate di-*O*-trityluridines. Also, recent work by Christensen and Broom[17] has demonstrated the direct 2′(3′)-*O*-benzylation of unprotected uridine through reaction with phenyldiazomethane in the presence of stannous chloride. A similar reaction between **2a** and a large excess of methyl iodide in dimethylformamide at 37° led to a mixture of 2′-*O*-methyluridine (**9b**)[18] and 3′-*O*-methyluridine (**10b**)[18] in a ratio



9a, R = C_6H_5
b, R = H

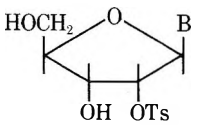


10a, R = C_6H_5
b, R = H

of 45:55 (by nmr) in 70% yield. There was once again no indication of methylation of C_5′OH or of the uracil ring. A preparative separation of these two compounds could not be achieved.

Unfortunately, extension of the selective alkylation reaction to the adenosine and cytidine series was not successful. Thus reaction of **2c** with a large excess of methyl iodide led to the predominant formation of N^1-methyladenosine, which was isolated in crystalline form and directly compared with an authentic sample.[19] In a similar way, reaction of the cytidine derivative (**2b**) led predominantly to a positively charged, periodate-positive material with an ultraviolet spectrum similar to that of N^3-methylcytidine.[20] An attempt to avoid base alkylation *via* preparation of the stannylene derivative of N^4-benzoylcytidine also failed, since the reaction was accompanied by debenzoylation. It is interesting that we observed no sign of *O*-alkylation during the above reactions.

The reactions of the stannylene derivatives of uridine and adenosine (**2a**, **2c**) with *p*-toluenesulfonyl chloride in methanol were extremely rapid and led to the isolation of the pure, crystalline 2′-*O*-*p*-toluenesulfonyl derivatives (**11a,b**) in yields of 62 and 70%, respectively. Since it is generally accepted that sulfonyl esters, unlike their carboxylate counterparts, do not undergo "acyl" migration,[21] this suggests a distinct preference for reaction at C_2′OH rather than at C_3′OH. Similar preference has previously been noted during sulfonylation of 5′-substituted nucleosides[22] and 5′-nucleotides[23] as well as during alkylation of unprotected nucleosides.[24] The present method provides a uniquely facile route to 2′-*O*-*p*-toluenesulfonyladenosine (**11b**), a versatile type of precursor to 8,2′-anhydro nucleosides,[25] which has previously been difficult to prepare in pure form and high yield.[22c] It is interesting to note that **11b** proves, rather unexpectedly, to be labile in base, brief



11a, B = Ur
b, B = Ad
c, B = Cy

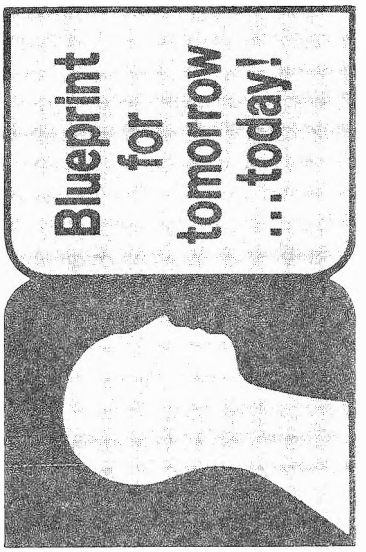
treatment with ethanolic sodium hydroxide leading to complete glycosidic cleavage and release of adenine. Similar cleavage was not observed upon treatment with aqueous pyridine or triethylamine at 100°, but attempted displacement of the sulfonyl group with sodium benzoate or lithium azide in dimethylformamide at 150° once again gave only adenine. The mechanism of this glycosidic cleavage is not at all certain at this time. One possibility involves the intermediacy of a 1′,2′-unsaturated nucleoside arising *via* an elimination reaction, and studies with such nucleosides[26] are currently underway.

The reaction of 2′,3′-*O*-(dibutylstannylene)cytidine (**2b**) with *p*-toluenesulfonyl chloride in methanol under conditions similar to those above led to a more complex mixture. At least in part this can be explained by the expected tendency of 2′-*O*-*p*-toluenesulfonylcytidine (**11c**) to undergo internal displacement with formation of O^2,2′-cyclocytidine. Indeed, an examination of the crude reaction product by paper chromatography and electrophoresis demonstrated the presence of O^2,2′-cyclocytidine. It has recently been demonstrated by Ikehara and Uesugi[27] that attempted tosylation of cytidine 5′-phosphate in aqueous base leads to a complex mixture of products mostly derived from initial reaction at C_2′ followed by cyclonucleoside formation. A clarification of the nature of the other products must await further work.

Finally, we have examined the reaction of the 2′,3′-*O*-stannylene nucleosides with phosphorochloridates. Our original studies made use of substituted phosphorylating agents such as diphenyl phosphorochloridate and it was shown that such compounds react with, *e.g.*, **2c** in methanol in the presence of triethylamine to form an unstable, neutral species which is presumably either a 2′(3′)-phospho triester (*e.g.*, **12a**) or a 2′,3′-cyclic triester. As expected,[28] this material was very sensitive to water and was very unstable in both acid and base, being rapidly converted to a monoanion as judged by paper electrophoresis at pH 7.5. Accordingly, it could not be freed from salts or obtained in a pure form.

A similar product could be obtained by reaction of a methanolic solution of **2c** with an excess of phosphorus oxychloride. In order to avoid the presence of water-soluble salts, hexabutyldistannoxane was used as a base, since both the compound itself and the resulting acid addition products (*e.g.*, Bu_3SnCl) are soluble in ether. Following the very rapid reaction of **2c** with phosphorus oxychloride as above, the adenosine derivatives were precipitated with ether. The nmr spectrum of the resulting product showed it to be a roughly 9:1 mixture of two compounds, the major one being dimethyladenosine 3′-phosphate (**12b**). There is no doubt that the compound is a dimethyl ester, the methyl groups appearing as a pair of three-proton doublets ($J_{P,H}$ = 11 Hz) at 3.84 and 3.91 ppm in DMSO-d_6 due to the diastereotopic nature of phospho triesters containing asymmetric functions.[29] The minor constituent, presumably the 2′-dimethylphosphoryl isomer, showed methyl ester protons, once again as a pair of doublets, at 3.60 and 3.65 ppm. The location of the phosphate ester grouping at C_3′ in the major isomer was apparent both from the fact that signal for C_3′H was shifted downfield and was superimposed upon that of C_2′H, and from the relative chemical shifts of the C_1′ protons in the two isomers,[11] the major signal being a doublet ($J_{1',2'}$ = 7 Hz) at 6.60, and the minor one a doublet at 6.66 ppm ($J_{1',2'}$ = 5 Hz). For the moment we have no evidence as to whether the formation of **12b** involves predominant opening of the stannylene derivative at C_3′ or an equilibration of the 2′- and 3′-phosphoryl derivatives with **12b** being the thermodynamically more stable product.

Storage of the above crude product in the presence of moisture led to the appearance of ionic materials and



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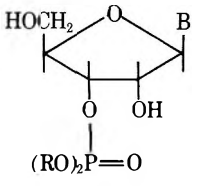
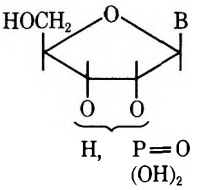
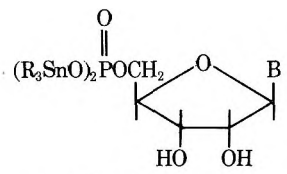
completion of this hydrolysis with aqueous sodium hydroxide at room temperature led to the isolation of the pure mixed barium salts of adenosine 2′(3′)-phosphates (**13a**, 60% 3′-phosphate by paper chromatography) in an overall yield of 78% from adenosine. The alkaline hydrolysis of compounds such as **12b** is well known and involves a series of events involving participation of the adjacent hydroxyl function.[28] In essentially the same way, the reactions of **2a** and **2b** with phosphorus oxychloride and hexabutyldistannoxane led to the isolation of the mixed uridine 2′(3′)-phosphates (**13b**) and cytidine 2′(3′)-phosphates (**13c**) in yields of 87 and 73%, respectively. The absence of any 5′-phosphate esters was confirmed by borate electrophoresis at pH 8 and by the complete resistance of the products toward dephosphorylation by the 5′-nucleotidase activity of crude *Crotalus adamanteus* venom.[30] The above method thus provides a novel and highly selective method for the direct 2′(3′)-phosphorylation of unprotected ribo nucleosides. Complementary methods involving reaction of nucleosides with aqueous trimetaphosphate[31] or with phosphite esters[32] have also been described.



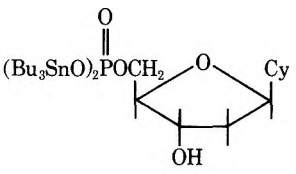
12a, B = Ad; R = C_6H_5
b, B = Ad; R = CH_3



13a, B = Ad
b, B = Ur
c, B = Cy



14a, B = Ad; R = C_4H_9
b, B = Cy; R = C_4H_9
c, B = Cy; R = CH_3



15

In the past many organotin esters of phosphoric acid and related derivatives have been prepared and examined for antifungal and insecticidal activities.[2,33] It seemed of interest to prepare some trialkyltin esters of nucleotides both for the above reasons and in the hope that such esters might serve as phosphate protected, organic solvent soluble derivatives suitable for chemical manipulations. Such esters have, in general, been prepared *via* reaction of the sodium salt of the phosphate with a tin halide. We have preferred, however, to briefly heat the free acid nucleoside 5′-phosphate with an equivalent amount of hexabutyldistannoxane or trimethyltin hydroxide in methanol or ethanol until a clear solution results. Evaporation of the solvent followed by crystallization then gives the pure bis(trialkyltin) nucleoside 5′-phosphates (**14**, **15**) in good yields.

The esters were indeed very stable in the crystalline form and freely soluble in solvents such as pyridine. By analogy with extensive studies on trialkyltin esters of a variety of acids, these compounds are considered to be covalent.[2] Their reactions are, however, polar in nature and strongly dependent upon the solvent. The ready polarization of the ester bond is apparent from the fact that they behave similarly to the parent nucleotide during chromatography and electrophoresis. The ester groups also do not appear to prevent participation of the phosphate group during attempted carbodiimide promoted phosphorylations of the sugar hydroxyl functions. The utility of compounds such as **14** or **15** as phosphate protected nucleotides thus appears to be severely limited.

Some biological properties of **14** and **15** have also been examined.[34] They were thus quite cytotoxic to mammalian cells in tissue culture (ED_{50} ~0.1-1 μg/ml) and showed a broad activity against a variety of gram-positive bacteria and fungi (minimum inhibitory concentrations of 0.3-5.0 μg/ml). Both the spectra of activities and the absolute activities are very similar to those shown by a variety of trialkyltin esters[2,33,35] and the present compounds do not appear to show any unique properties.

Thus, while the tin esters of nucleotides do not appear to be particularly useful compounds, the 2′,3′-*O*-dialkylstannylene nucleosides (**2**) have proved to be readily available and interesting intermediates permitting highly selective reactions at the C_2′- and C_3′-hydroxyl functions. Examples of the use of these compounds for specific purposes will be found in future publications.

Experimental Section

Thin layer chromatography (tlc) was conducted on commercial 250-μ thick layers of silica gel GF obtained from Analtech, Inc., Newark, Del., and preparative tlc on 20 × 100 cm glass plates coated with a 1.3-mm layer of silica gel HF. Nuclear magnetic resonance spectroscopy was performed using a Varian HA-100 spectrometer and is reported in parts per million downfield from an internal standard of tetramethylsilane. Elemental analyses were by Dr. A. Bernhardt, Mulheim, Germany, and other instrumental analyses were obtained by the staff of the Analytical Laboratory of Syntex Research. We are particularly grateful to Dr. M. L. Maddox and Mrs. J. Nelson for their cooperation with nmr spectroscopy.

2′,3′-*O*-(Dibutylstannylene)uridine (2a). A suspension of uridine (488 mg, 2 mmol) and dibutyltin oxide (500 mg, 2 mmol) in methanol (100 ml) was heated under reflux for 30 min and the resulting clear solution was then evaporated to dryness and dried *in vacuo*. The resulting crystalline residue (915 mg, 96%) was analytically pure and showed mp 232-234°. Recrystallization from ethanol did not change this melting point: λ_{max} (MeOH) 261 nm (ε 9400); mass spectrum (70 eV) *m/e* 473-481 (M^+), 415-423 (M − C_4H_9), 361-369 (M − uracil), 301-309 (M − uracil − C_4H_9).

Anal. Calcd for $C_{17}H_{28}N_2O_6Sn$ (475.10): C, 42.97; H, 5.94; N, 5.90. Found: C, 42.91; H, 5.91; N, 5.86.

2′,3′-*O*-(Dibutylstannylene)cytidine (2b). A suspension of cytidine (243 mg, 1 mmol) in methanol (25 ml) was heated under reflux in methanol (25 ml) in the presence of dibutyltin oxide (250 mg, 1 mmol). After 2 hr the resulting clear solution was evaporated to dryness and the residue was crystallized from ethanol–ether, giving 430 mg (91%) of **2b**: mp 217-218°; λ_{max} (H^+, MeOH) 282 nm (ε 13,300); λ_{max} (OH^-, MeOH) 275 nm (ε 8200); nmr (MeOh-d_4) 0.90 (t. 6, CH_3's), 1.2-1.8 (m, 12, CH_2's), 3.88 (m, 2, C_5′H_2), 4.3 (m, 2, C_2′H and C_3′H), 5.88 (s, 1, C_1′H), 5.92 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 7.97 ppm (d, 1, C_6H).

Anal. Calcd for $C_{17}H_{29}N_3O_5Sn$ (474.11): C, 43.06; H, 6.17; N, 8.86; Sn, 25.03. Found: C, 42.66; H, 6.23; N, 8.78; Sn, 24.69.

2′,3′-*O*-(Dibutylstannylene)adenosine (2c). A mixture of adenosine (267 mg, 1 mmol), dibutyltin oxide (250 mg, 1 mmol), and methanol (25 ml) was heated under reflux for 30 min and then evaporated to dryness. Two crystallizations from ethanol–acetone gave 350 mg (70%) of **2c**: mp 154-156°; λ_{max} (MeOH) 259 nm (ε 14,700); mass spectrum (70 eV) *m/e* 496-504 (M^+), 438-446 (M − C_4H_9), 361-369 (M − adenine).

Anal. Calcd for $C_{18}H_{29}N_5O_4Sn$ (498.14): C, 43.39; H, 5.86; N, 14.05; Sn, 23.82. Found: C, 43.23; H, 6.05; N, 14.11; Sn, 23.56.

3′-*O*-Acetyluridine (8a). A. A mixture of uridine (1.22 g, 5 mmol) and dibutyltin oxide (1.25 g, 5 mmol) was heated under reflux in methanol (150 ml) for 30 min. The resulting clear solution was cooled and to it was added triethylamine (7.0 ml, 50 mmol) and then acetyl chloride (3.56 ml, 50 mmol). After 10 min at room temperature the solution was evaporated to dryness and a solution of the residue in chloroform was applied to a 2 × 30 cm column of silicic acid. Elution with ethyl acetate–acetone (1:1) gave a mixture of 2′(3′)-*O*-acetyluridines (roughly 70% 3′ by nmr)[11] which was crystallized twice from ethanol, giving 992 mg (69%) of pure 8a: mp 171-172° (reported[7] mp 172-174°); λ_{max} (MeOH) 260 nm (ε 10,200); nmr (DMSO-d_6) 2.08 (s, 3, OAc), 3.63 (br s, 2, C_5′H_2), 4.05 (br d, 1, $J_{3',4'}$ = 2.5 Hz, C_4′H), 4.31 (m, 1,

becoming dd, $J_{1',2'}$ = 6.5, $J_{2',3'}$ = 5.5 Hz, C_2·H), 5.15 (dd, 1, C_3·H), 5.28 (t, 1, C_5·OH), 5.72 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.72 (d, 1, $J_{H,OH}$ = 6 Hz, C_2·OH), 5.86 (d, 1, C_1·H), 7.91 ppm (d, 1, C_6H).

B. A solution of **2a** (475 mg, 1 mmol) and acetic anhydride (0.1 ml, 1.05 mmol) in dimethylformamide (10 ml) was kept at 0° for 4 hr, the reaction being followed by tlc using chloroform–methanol (85:15). The mixture was then evaporated to dryness *in vacuo* and the residue was partitioned between water and chloroform. The aqueous phase was evaporated to dryness and the residue was crystallized from ethanol (1 ml) giving 154 mg (54%) of pure **8a** identical with that above.

C. A solution of **2a** in methanol (30 ml) was prepared *in situ* from uridine (488 mg, 2 mmol) and dibutyltin oxide (500 mg) as in A. Triethylamine (2.8 ml, 20 mmol) and acetic anhydride (2.0 ml, 20 mmol) were added and after 3 min at room temperature the mixture was evaporated to dryness. The residue was coevaporated several times with ethanol and then partitioned between methylene chloride and water. The aqueous phase was evaporated to dryness and the residue was crystallized from ethanol, giving 230 mg (34%) of pure **8a**, the purity being confirmed by tlc and nmr as above.

3′-*O*-Benzoyluridine (8b). A solution of 2a (2 mmol) in methanol (100 ml) was prepared *in situ* as above. Triethylamine (1.4 ml, 10 mmol) and benzoyl chloride (1.2 ml, 10 mmol) were added and the mixture was stirred at room temperature for 10 min, at which point tlc using ethyl acetate–acetone (1:1) showed no remaining uridine. The solvent was evaporated *in vacuo* and the residue was partitioned between ether (100 ml) and water and filtered. The aqueous phase was concentrated to about 30 ml and allowed to crystallize. Recrystallization from aqueous ethanol gave 570 mg (78%) of pure (nmr and tlc) **8b** as the dihydrate: mp 213–214° (reported[7] mp 212–214° for the anhydrous compound); λ_{max} (MeOH) 230 nm (ϵ 16,000), 260 (11,800); ORD (MeOH) $[\Phi]_{284}$ 0°, $[\Phi]_{282}$ (peak) 400°, $[\Phi]_{280}$ 0°, $[\Phi]_{253}$ (trough) −1300°, $[\Phi]_{226}$ 0°; nmr (DMSO-d_6) 3.70 (dd, 2, $J_{4',5'}$ = 3, $J_{H,OH}$ = 5 Hz, C_5·H_2, becoming d with D_2O), 4.23 (dt, 1, $J_{3',4'}$ = 3 Hz, C_4·H), 4.42 (ddd, 1, $J_{1',2'}$ = 7, $J_{2',3'}$ = 6, $J_{H,OH}$ = 6 Hz, C_2·H), 5.41 (dd, 1, C_3·H), 5.33 (t, 1, C_5·OH), 5.74 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.84 (d, 1, C_2·OH), 5.97 (d, 1, C_1·H), 7.6 and 8.05 (m, total 5, Ar), 7.93 (d, 1, C_6H), 11.38 ppm (br s, 1, NH).

Anal. Calcd for $C_{16}H_{16}N_2O_7 \cdot 2H_2O$ (366.33): C, 52.46; H, 4.95; N, 7.64. Found: C, 52.40; H, 5.04; N, 7.59.

After drying *in vacuo* at 100° the anhydrous compound (mp 212–213°) was obtained.

Anal. Calcd for $C_{16}H_{16}N_2O_7$ (348.31): C, 55.17; H, 4.63; N, 8.04. Found: C, 55.07; H, 4.76; N, 8.03.

2′-*O*-Benzyluridine (9a) and 3′-*O*-Benzyluridine (10a). A solution of **2a** (2.375 g, 5 mmol) and benzyl bromide (1.7 g, 10 mmol) in dimethylformamide (30 ml) was heated at 100° for 1 hr, at which point tlc using ethyl acetate–acetone (1:1) showed no uridine remaining. Following evaporation of the solvent the residue was chromatographed on a column of silicic acid using chloroform and chloroform–methanol (19:1) giving 1.2 g (65%) of a roughly equal mixture (nmr) of **9a** and **10a**. Crystallization of the mixture from ethanol removed almost all of the 3′-*O*-benzyl isomer (**10a**), giving 440 mg (26%) of the pure compound: mp 206–208°, raised to 208.5–209° upon recrystallization of an analytical sample (reported[15a] mp 204–206°, 205–207°[17]); λ_{max} (MeOH) 262 nm (ϵ 10,200); nmr (DMSO-d_6) 3.58 (br s, 2, C_5·H_2), 3.95 (m, 2, C_3·H and C_4·H), 4.22 (ddd, 1, $J_{1',2'}$ = 5.5, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 5 Hz, C_2·H), 4.53 and 4.70 (d, 1, J_{gem} = 12.5 Hz, ArCH_2), 5.10 (t, 1, C_5·OH), 5.46 (d, 1, C_2·OH), 5.61 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.80 (d, 1, C_1·H), 7.33 (s, 5, Ar), 7.86 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{18}N_2O_6$ (334.33): C, 57.48; H, 5.42; N, 8.37. Found: C, 57.31; H, 5.48; N, 8.58.

Continued crystallization from ethanol gave 510 mg (31%) of pure **9a** in three crops: mp 178.5–180° (reported[15b] mp 181–182°, 177–179°[17]); λ_{max} (MeOH) 262 nm (ϵ 9800); nmr (DMSO-d_6) 3.63 (br s, 2, C_5·H_2), 3.97 (dd, 1, $J_{1',2'}$ = 5, $J_{2',3'}$ = 5 Hz, C_2·H), 3.95 (m, 1, C_4·H), 4.18 (ddd, 1, $J_{3',4'}$ = 5, $J_{H,OH}$ = 5 Hz, becoming dd with D_2O, C_3·H), 4.55 and 4.74 (d, 1, J_{gem} = 12 Hz, ArCH_2), 5.10 (t, 1, C_5·OH), 5.19 (d, 1, C_3·OH), 5.56 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.96 (d, 1, C_1·H), 7.32 (s 5, Ar), 7.90 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{18}N_2O_6$ (334.33): C, 57.48; H, 5.42; N, 8.37. Found: C, 57.15; H, 5.36; N, 8.07.

2′(3′)-*O*-Methyluridine (9b, 10b). A solution of **2a** (475 mg, 1 mmol) and methyl iodide (2.0 ml) in dimethylformamide (15 ml) was kept at 37° for 18 hr, at which point tlc using ethyl acetate–acetone (1:1) showed a major spot giving a negative test with the periodate–benzidine spray.[6] After evaporating the solvent and washing the residue with hexane, the mixture was purified by preparative tlc using ethyl acetate–acetone (45:55) giving 180 mg (70%) of a clean mixture of **9b** and **10b** in a ratio of 55:45 by nmr. No resolution of this mixture was achieved.

2′-*O*-*p*-Toluenesulfonyluridine (11a). A solution of **2a** in methanol (250 ml) was prepared *in situ* as above from 1.22 g (5 mmol) of uridine. Triethylamine (8.5 ml, 60 mmol) was added followed by a solution of *p*-toluenesulfonyl chloride (11.5 g, 60 mmol) in acetone (20 ml). After 10 min at room temperature the solution was evaporated to dryness and the residue was dissolved in acetone and filtered to remove 4.8 g of triethylamine hydrochloride. The filtrate was evaporated and partitioned between water and ether, and the aqueous phase was concentrated to a small volume, giving 1.75 g (88%) of **11a** that was at least 90% pure by nmr. Recrystallization from water gave 1.23 g (62%) of pure **11a**: mp 172–174° (reported[36] mp 175–177°); λ_{max} (MeOH) 225 nm (ϵ 14,500), 261 (ϵ 9600); nmr (DMSO-d_6) 2.37 (s, 3, ArCH_3), 3.57 (m, 2, C_5·H_2), 3.95 (m, 1, C_4·H), 4.17 (ddd, 1, $J_{2',3'}$ = 5, $J_{3',4'}$ = 2, $J_{H,OH}$ = 5 Hz, becoming dd with D_2O, C_3·H), 4.88 (dd, 1, $J_{1',2'}$ = 7 Hz, C_2·H), 5.28 (t, 1, C_5·OH), 5.47 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.91 (d, 1, C_3·OH), 6.03 (d, 1, C_1·H), 7.40 and 7.73 (d, 2, J = 8.5 Hz, Ar), 7.60 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{18}N_2O_8S$ (398.39): C, 48.23; H, 4.56; N, 7.03. Found: C, 48.26; H, 4.57; N, 6.73.

Treatment of 10 mg of **11a** with 0.1 *N* sodium hydroxide (0.3 ml) at room temperature for 2 hr led to almost complete conversion to 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil which was identified by tlc (EtOAc–MeOH, 3:2) and uv (λ_{max} 223, 250 nm).

Uridine 2′(3′)-Phosphate (13b). A solution of **2a** (2 mmol) was prepared *in situ* in methanol (100 ml) and cooled to room temperature. After addition of hexamethyldistannoxane (6 ml, 12 mmol), phosphorus oxychloride (0.70 ml, 7.6 mmol) was added and the solution was kept at room temperature for 20 min before evaporation to dryness. The residue was shaken several times with 100-ml portions of ether to remove tin compounds and finally dissolved in water. After extraction with ether, the aqueous phase contained a predominant spot with the electrophoretic mobility of a monoanion. This material was treated overnight with 0.5 *N* sodium hydroxide and the solution was then adjusted to pH 8 with Dowex 50 (H^+) resin. The solvent was evaporated and the residue was crystallized from aqueous ethanol, giving 644 mg (87%) of the disodium salts of **13b** (3′:2′ = 3:2 by nmr). The product contained no uridine 5′-phosphate as judged by borate electrophoresis at pH 8[37] and by its complete resistance to incubation with crude *Crotalus adamanteus* venom,[30] λ_{max} (pH 2) 260 nm (ϵ 9200).

Anal. Calcd for $C_9H_{11}N_2O_9PNa_2$ (368.13): C, 29.36; H, 3.00; N, 7.60; P, 8.41. Found: C, 29.17; H, 3.34; N, 7.60; P, 8.27.

2′(3′)-*O*-Acetylcytidine. Triethylamine (2.8 ml, 20 mmol) and acetic anhydride (2.0 ml, 20 mmol) were added to a solution of **2b** in methanol (50 ml) prepared *in situ* from cytidine (973 mg, 4 mmol) as above. After 5 min at room temperature the mixture was evaporated to dryness and the residue was extracted several times with boiling ether. The final residue was dissolved in isopropyl alcohol (10 ml) and upon addition of ether gave 1.10 g (96%) of a mixture of 3′-*O*-acetylcytidine and its 2′ isomer in a ratio of 3:1 by nmr. The mixture had mp 120–130° and no selective crystallization could be achieved: λ_{max} (pH 2) 278 nm (ϵ 12,300), 211 (9600); λ_{max} (pH 12) 229 nm (ϵ 8000), 270 (8600).

Anal. Calcd for $C_{11}H_{15}N_3O_6$ (285.26): C, 46.31; H, 5.30; N, 14.73. Found: C, 45.83; H, 5.04; N, 14.84.

3′-*O*-Benzoylcytidine (8c). Triethylamine (1.4 ml, 10 mmol) and benzoyl chloride (1.20 ml, 10 mmol) were added to a solution of **2b** prepared *in situ* in methanol (25 ml) from cytidine (486 mg, 2 mmol) and dibutyltin oxide (500 mg, 2 mmol) as above. After 5 min at room temperature the solvent was evaporated and the residue was partitioned between water (100 ml) and ether. The aqueous phase was concentrated to about 15 ml and upon storage gave 670 mg (87%) of pure 3′-*O*-benzoylcytidine (**8c**) as the dihydrate: mp 136–137°; λ_{max} (pH 1) 230 nm (ϵ 16,300), 278 (14,600); λ_{max} (pH 12) 221 nm (ϵ 16,200), 271 (9200); ORD (pH 2) $[\Phi]_{298}$ (peak) 3000°, $[\Phi]_{284}$ 0°, $[\Phi]_{235}$ (trough) −5900°, $[\Phi]_{226}$ 0°; nmr (DMSO-d_6) 3.68 (m, 2, C_5·H_2), 4.21 (dt, 1, $J_{4',5'}$ = 3.5, $J_{3',4'}$ = 3.5 Hz, C_4·H), 4.41 (ddd, 1, $J_{1',2'}$ = 6, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 6 Hz, becoming dd with D_2O, C2·H), 5.34 (dd, 1, C_3·H), 5.25 (t, 1, C_5·OH), 5.73 (d, 1, C_2·OH), 5.79 (d, 1, $J_{5,6}$ = 6.5 Hz, C_5H), 5.96 (d, 1, C_1·H), 7.22 (br s, 2, NH_2), 7.6 and 8.07 (m, total 5, Ar), 7.88 ppm (d, 1, C_6H).

Anal. Calcd for $C_{16}H_{17}N_3O_6 \cdot 2H_2O$ (383.36): C, 50.15; H, 5.51; N, 10.96. Found: C, 50.33; H, 5.34; N, 10.89.

Upon drying *in vacuo* at 100° the compound lost its crystalline form and gave anhydrous **8c** which sintered at 136° but did not fully melt until 144.5°.

Anal. Calcd for $C_{16}H_{17}N_3O_6$ (347.33): C, 55.33; H, 4.93; N, 12.10. Found: C, 54.99; H, 5.47; N, 12.19.

Cytidine 2′(3′)-Phosphate (13c). Hexabutyldistannoxane (6 ml, 12 mmol) and then phosphorus oxychloride (0.7 ml, 7.5 mmol) were added at room temperature to a solution of 2b (2 mmol) prepared *in situ* in methanol (60 ml) as above. After 20 min the mixture was evaporated to dryness and the residue was extracted several times with boiling ether. The final residue was dissolved in 1 *N* sodium hydroxide and stored overnight. The solution was then adjusted to pH 8 by addition of Dowex 50 (H^+) resin, and then passed through a column of Dowex 50 (Et_3N) resin. The eluates were evaporated to dryness, dissolved in water (1 ml) and ethanol (6 ml), and adjusted to pH 2 with concentrated hydrochloric acid, giving 460 mg (73%) of a crystalline mixture of cytidine 2′(3′)-phosphates with chromatographic and electrophoretic mobilities identical with those of the authentic compounds: λ_{max} (pH 2) 278 nm (ϵ 12,700); λ_{max} (pH 12) 230 nm (sh, ϵ 8300), 270 (9100).

Anal. Calcd for $C_9H_{14}N_3O_8P$ (323.21): C, 33.44; H, 4.36; N, 13.00; P, 9.58. Found: C, 33.48; H, 4.48; N, 12.89; P, 9.66.

3′-*O*-Benzoyladenosine (8d). Triethylamine (14.0 ml, 100 mmol) and benzoyl chloride (12 ml, 100 mmol) were added to a solution of 2c (20 mmol) prepared *in situ* in methanol (250 ml). After 15 min at room temperature the solvent was evaporated and the residue was thoroughly triturated with ether (250 ml) several times. The residue was then triturated twice with 50-ml portions of water and then dried *in vacuo*. Two crystallizations from aqueous ethanol gave 5.14 g (70%) of pure **8d:** mp 205–206°; λ_{max} (pH 2) 237 nm (ϵ 17,100), 256 (15,800); λ_{max} (ph 11) 231 nm (ϵ 13,100), 259 (14,900); nmr (DMSO-d_6) 3.76 (br s, 2, $C_5{\cdot}H_2$), 4.36 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_4{\cdot}H$), 5.05 (ddd, 1, $J_{1',2'}$ = 7.5, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 5.5 Hz, becoming dd with D_2O, $C_2{\cdot}H$), 5.58 (dd, 1, $C_3{\cdot}H$), 5.91 (d, 1, $C_2{\cdot}OH$), 6.06 (d, 1, $C_1{\cdot}H$), 7.39 (s, 2, NH_2), 7.1 and 8.13 (m, total 5, Ar), 8.20 and 8.44 ppm (s, 1, C_2H and C_8H).

Anal. Calcd for $C_{17}H_{17}N_5O_5$ (371.36): C, 54.98; H, 4.61; N, 18.86. Found: C, 54.75; H, 5.02; N, 18.73.

2′-*O*-*p*-Toluenesulfonyladenosine (11b). Triethylamine (10.5 ml, 75 mmol) and *p*-toluenesulfonyl chloride (14.25 g, 75 mmol) were added to a solution of **2c** (5 mmol) prepared *in situ* in methanol (100 ml). After 5 min at room temperature the solvent was evaporated and the residue was partitioned between water and ether. The aqueous phase was concentrated and stored at 4°, giving 1.47 g (70%) of **11b:** mp 229–230° (reported[22c] mp 224°); λ_{max} (pH 2) 229 nm (ϵ 12,900), 257 (12,400); λ_{max} (pH 11) 228 nm (ϵ 12,300), 261 (12,700); nmr (DMSO-d_6) 2.25 (s, 3, $ArCH_3$), 3.62 (m, 2, $C_5{\cdot}H_2$), 4.07 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_4{\cdot}H$), 4.39 (ddd, 1, $J_{2',3'}$ = 5, $J_{H,OH}$ = 5 Hz, becoming dd with D_2O, $C_3{\cdot}H$), 5.49 (dd, 1, $J_{1',2'}$ = 7.5 Hz, $C_2{\cdot}H$), 5.75 (t, 1, $C_5{\cdot}OH$), 6.03 (d, 1, $C_3{\cdot}OH$), 6.11 (d, 1, $C_1{\cdot}H$), 7.03 and 7.42 (d, 2, Ar), 7.37 (s, 2, NH_2), 8.02 and 8.19 ppm (s, 1, C_2H and C_8H).

Anal. Calcd for $C_{17}H_{19}N_5O_6S$ (421.44): C, 48.45; H, 4.54; N, 16.61; S, 7.60. Found: C, 48.29; H, 5.18; N, 16.52; S, 7.71.

Reaction of 11b with Alkali. Sodium hydroxide (4 ml of 1 *N*) was added to a solution of **11b** (421 mg, 1 mmol) in ethanol (20 ml) and the mixture was heated under reflux for 10 min. Tlc using ethyl acetate–methanol (4:1) showed complete conversion to adenine. The mixture was evaporated and purified by preparative tlc using the above solvent, and crystallization from water gave 110 mg (81%) of adenine, mp >300°, having a uv spectrum identical with that of an authentic sample. Treatment of **11b** with 90% pyridine at 100° for 24 hr or with aqueous triethylamine did not lead to any change, but treatment with sodium benzoate or lithium azide in dimethylformamide at 150° for 10 min gave only adenine.

Adenosine 2′(3′)-Phosphate (13a). Hexabutyldistannoxane (6.0 ml, 11.8 mmol) and phosphorus oxychloride (0.70 ml, 7.5 mmol) were added to a solution of **2c** (2 mmol) prepared *in situ* in methanol (30 ml). After 20 min the solvent was evaporated and the residue was washed carefully with ether, leaving 525 mg of a dry, white precipitate, the nmr spectrum of which suggested it to be dimethyl adenosine 3′-phosphate and its 2′ isomer in a ratio of 9:1 (see text). Upon storage of the mother liquors in an open flask a further 280 mg of precipitate separated and was shown by paper electrophoresis to be a monoanion. The combined precipitates were dissolved in 1 *N* sodium hydroxide and kept overnight before being adjusted to pH 8 with Dowex 50 (H^+) resin. Addition of barium acetate (2 ml of 2 *M*) followed by two volumes of ethanol gave a white precipitate that was collected by centrifugation and reprecipitated twice with aqueous ethanol. The final precipitate was washed with ethanol and ether and dried *in vacuo* at 100°, giving 750 mg (78%) of the barium salt of adenosine 2′- and 3′-phosphates [roughly 2:3 by paper chromatography using saturated ammonium sulfate–2-propanol–1 *M* sodium acetate (80:2:18)]: λ_{max} (pH 2) 256 nm (ϵ 14,200); λ_{max} (pH 12) 259 nm (ϵ 15,000).

Anal. Calcd for $C_{10}H_{12}N_5O_7PBa$ (482.54): C, 24.89; H, 2.51; N, 14.51; P, 6.42. Found: C, 24.81; H, 3.12; N, 14.41; P, 6.24.

3′-*O*-Benzoylinosine (8e). A suspension of inosine (536 mg, 2 mmol) in methanol (100 ml) containing dibutyltin oxide (500 mg, 2 mmol) and triethylamine (2.8 ml, 20 mmol) was heated under reflux for 30 min.[38] After cooling, benzoyl chloride (2.4 ml, 20 mmol) was added and after 10 min the solvent was evaporated. The residue was washed thoroughly with ether and then partitioned between water and ether. The aqueous phase was evaporated to dryness and the residue was extracted with acetone, leaving much of the triethylamine hydrochloride as white crystals. Evaporation of the acetone solution and crystallization from water gave 465 mg (63%) of a 2:1 mixture of 3′-*O*-benzoyl- and 2′-*O*-benzoylinosine ($C_1{\cdot}H$ 6.04 ppm in 3′-OBz and 6.35 ppm in 2′-OBz). Recrystallization from aqueous ethanol gave 372 mg (50%) of the pure 3′-*O*-benzoate (**8e**): mp 155–159°, unchanged upon recrystallization; λ_{max} (pH 2) 234 nm (ϵ 20,400), 248 (sh, 16,300); λ_{max} (pH 11) 230 nm (ϵ 13,700), 254 (11,900); nmr (DMSO-d_6) 3.75 (m, 2, $C_5{\cdot}H_2$), 4.35 (br d, 1, $J_{3',4'}$ = 2 Hz, $C_4{\cdot}H$), 4.95 (ddd, 1, $J_{1',2'}$ = 7, $J_{2',3'}$ = 5.5, $J_{H,OH}$ = 5.5 Hz, becoming dd with D_2O, $C_2{\cdot}H$), 5.33 (t, 1, $C_5{\cdot}OH$), 5.56 (dd, 1, $C_3{\cdot}H$), 5.97 (d, 1, $C_2{\cdot}OH$), 6.04 (d, 1, $C_1{\cdot}H$), 7.65 and 8.12 (m, total 5, Ar), 8.44 ppm (s, 1, C_8H).

Anal. Calcd for $C_{17}H_{16}N_4O_6$ (372.34): C, 54.83; H, 4.33; N, 15.05. Found: C, 54.80; H, 4.43; N, 14.96.

Bis(tributyltin) Adenosine 5′-Phosphate (14a). A suspension of adenosine 5′-phosphate (346 mg, 1 mmol) and hexabutyldistannoxane (606 mg, 1.02 mmol) in ethanol (60 ml) was heated under reflux for 10 min, giving a clear solution. The solvent was then concentrated to 10 ml, and water (50 ml) was gradually added, giving 740 mg (80%) of **14a:** mp 197–198°; λ_{max} (MeOH) 259 nm (ϵ 14,500); nmr (DMSO-d_6) 0.7–1.8 (m, 54, Bu), 4.66 (dd, 1, $J_{1',2'}$ = 5, $J_{2',3'}$ = 5 Hz, $C_2{\cdot}H$), 5.90 (d, 1, $C_1{\cdot}H$), 8.17 and 8.21 ppm (s, 1, C_2H and C_8H).

Anal. Calcd for $C_{34}H_{66}N_5O_7PSn_2$ (925.24): C, 44.13; H, 7.19; N, 7.57; P, 3.35. Found: C, 43.75; H, 6.99; N, 7.74; P, 3.37.

Bis(tributyltin) Cytidine 5′-Phosphate (14b). A suspension of cytidine 5′-phosphate (646 mg, 2 mmol) and hexabutyldistannoxane (1.19 g, 2 mmol) in methanol (30 ml) was heated under reflux for 2 hr and the resulting clear solution was then evaporated to dryness. The resulting residue was crystallized twice from ethanol–ether, giving 1.25 g (69%) of **14b:** mp 163–166°; λ_{max} (MeOH, H^+) 283 nm (ϵ 13,700); λ_{max} (MeOH, OH^-) 273 nm (ϵ 8300).

Anal. Calcd for $C_{33}H_{66}N_3O_8PSn_2$ (901.27): C, 43.98; H, 7.38; N, 4.66. Found: C, 43.95; H, 7.30; N, 4.98.

Bis(trimethyltin) Cytidine 5′-Phosphate (14c). A suspension of cytidine 5′-phosphate (323 mg, 1 mmol) and trimethyltin hydroxide (360 mg, 2 mmol) in ethanol (30 ml) was heated under reflux for 1 hr and the resulting clear solution was evaporated to dryness. Crystallization from ethanol–chloroform gave 584 mg (90%) of **14c:** mp >300°; λ_{max} (MeOH, H^+) 279 nm (ϵ 12,200); λ_{max} (MeOH, OH^-) 227 nm (sh, ϵ 8200), 271 (8600).

Anal. Calcd for $C_{15}H_{30}N_3O_8PSn_2$ (648.80): C, 27.77; H, 4.66; N, 6.47; P, 4.77. Found: C, 27.76; H, 4.87; N, 6.29; P, 4.70.

Bis(tributyltin) 2′-Deoxycytidine 5′-Phosphate (15). An ethanolic suspension (35 ml) of 2′-deoxycytidine 5′-phosphate (1 mmol) and hexabutyldistannoxane (1 mmol) was heated under reflux for 10 min and then evaporated to dryness. Crystallization of the residue from ethanol–acetone and then from ethanol–ether gave 725 mg (82%) of **15:** mp 190–191°, λ_{max} (MeOH) 273 mm (ϵ 10,000).

Anal. Calcd for $C_{33}H_{66}N_3O_7PSn_2$ (885.27): C, 44.77; H, 7.51; N, 4.74; P, 3.49. Found: C, 44.44; H, 7.83; N, 5.22; P, 3.29.

Registry No. 2a, 42822-78-6; **2b,** 42822-79-7; **2c,** 42822-80-0; **8a,** 4873-68-1; **8b,** 16667-60-0; **8c,** 42822-83-3; **8d,** 42822-84-4; **8e,** 42822-85-5; **9a,** 6554-02-5; **9b,** 2140-76-3; **10a,** 4710-74-1; **10b,** 6038-59-1; **11a,** 6206-10-6; **11b,** 42776-78-3; **13a** 2′ isomer barium salt, 42829-41-4; **13a** 3′ isomer barium salt, 42829-42-5; **13b** 2′ isomer disodium salt, 42829-43-6; **13b** 3′ isomer disodium salt, 35170-03-7; **13c** 2′ isomer, 85-94-9; **13c** 3′ isomer, 84-52-6; **14a,** 42829-47-0; **14b,** 42829-48-1; **14c,** 42829-49-2; **15,** 42829-50-5; uridine, 58-96-8; dibutyltin oxide, 818-08-6; cytidine, 65-46-3; adenosine, 58-61-7; 2′-*O*-acetylcytidine, 36963-55-0; 3′-*O*-acetylcytidine, 42829-52-7;

adenosine 5′-phosphate, 61-19-8; hexabutyldistannoxane, 56-35-9; cytidine 5′-phosphate, 63-37-6; trimethyltin hydroxide, 56-24-6; 2′-deoxycytidine 5′-phosphate, 1032-65-1

References and Notes

(1) Syntex Postdoctoral Fellow, 1968–1970.
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Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. IV.[1] A Facile Synthesis of 2′,3′-Unsaturated Nucleosides Using Chromous Acetate

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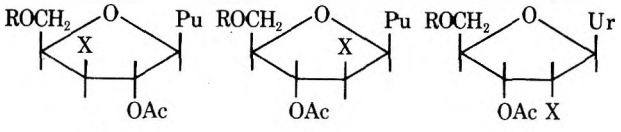
The halo acetates obtained from ribo nucleosides and 2-acetoxyisobutyryl halides have been shown to readily react with chromous acetate and ethylenediamine in ethanol at −78° to produce 2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl nucleosides. In this way 2′,3′-unsaturated analogs of adenosine, formycin, inosine, 5′,N^2-dibenzoylguanosine, and uridine have been prepared. Simple 3′-deoxy nucleosides and 3′-deoxy-β-D-*glycero*-pent-3-enofuranosyl nucleosides are sometimes obtained as by-products. An alternative synthesis of the 3′,4′-unsaturated analog of adenosine has been achieved *via* a base-catalyzed elimination reaction. Some interesting features of the nmr and ORD spectra of 2′,3′-unsaturated nucleosides are reported. An alternative synthesis of 9-(2-*O*-acetyl-3-deoxy-3-halo-β-D-xylofuranosyl)adenines has been developed *via* the reaction of 2′,3′-*O*-ethoxyethylideneadenosine with boron trifluoride etherate in the presence of anhydrous halide salts.

Nucleosides containing unsaturated sugars have been found to exist in nature in antibiotics such as Angustmycin A[3] and Blasticidin S.[4] In addition, the olefinic functionality in these molecules provides an interesting site for a variety of chemical transformations.[5,6] For these reasons considerable chemical effort has been devoted to the development of synthetic routes to 2′,3′-,[7] 3′,4′-,[8] and 4′,5′-[9] unsaturated nucleosides.[10] The available syntheses of 2′,3′-unsaturated nucleosides have generally involved base-catalyzed elimination reactions of either 3′-*O*-methanesulfonyl or O^2,3′-anhydro derivatives of 2′-deoxy nucleosides.[7] As yet, preparations starting from the more readily available ribo nucleosides have been very limited. Thus 1-(2,3-dideoxy-5-*O*-trityl-β-D-*glycero*-pent-2-enofuranosyl)uracil was obtained in the low yield *via* treatment of 5′-*O*-trityluridine 2′,3′-thionocarbonate with Raney nickel,[11a] and a blocked 2′,3′ olefin was very recently obtained from a 2′,3′-dimesyl derivative of tubercidin with zinc and sodium iodide.[11b]

Recent work from this laboratory has led to the development of efficient and novel methods for the replacement of the $C_{2'}$- or $C_{3'}$-hydroxyl groups of ribo nucleosides by chlorine or bromine atoms.[1,12] In particular, the reactions of ribo nucleosides with 2-acetoxyisobutyryl halides have led to interesting results. This reagent has been shown to react with purine nucelosides such as adenosine,[12b] tubercidin,[1] formycin,[1] and guanosine[12d] to form trans halo acetates (1 and 2) with the 2′-*O*-acetyl-3′-deoxy-3′-halo-β-D-xylofuranoside isomers (1) predominating. The formation of these trans halo acetates has been explained *via* the opening of 2′,3′-*O*-acetoxonium ion intermediates by halide ion.[12a,b] On the other hand, 2-ace-

toxyisobutyryl halides react with uridine derivatives to form 3′-*O*-acetyl-2′-deoxy-2′-halo-β-D-ribofuranosyl nucleosides (3), the cis halo acetate configuration being due to participation of the uracil ring with the 2′,3′-*O*-acetoxonium ion giving an O^2,2′-anhydro nucleoside which is finally opened by halide attack.[12a] In all the above compounds (1–3) the 5′-hydroxyl is substituted as either a



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2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl ether or a 2-acetoxyisobutyryl ester, the choice being both solvent and substrate dependent.

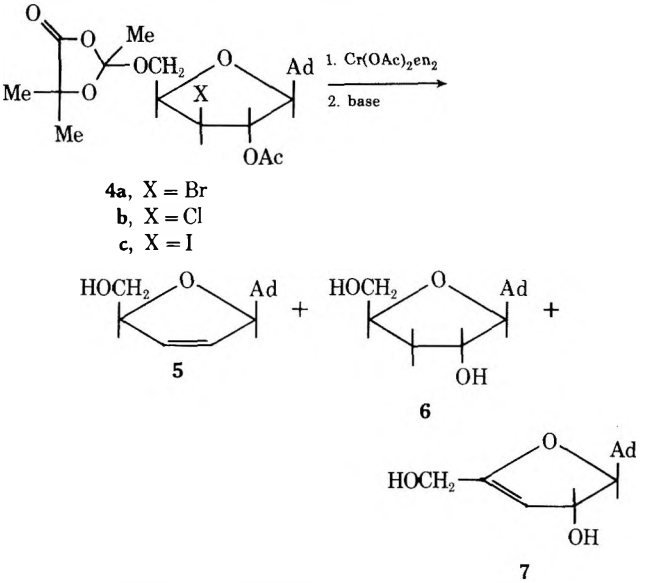
The ready availability of the above vicinal halo acetates suggested that these compounds might provide a direct route to 2′,3′-unsaturated nucleosides *via* appropriate elimination reactions.[13] A particularly attractive possibility was the use of chromous salts which, particularly when complexed with ethylenediamine, are well known to reduce simple alkyl halides[14] and to convert vicinal dihalides or halo esters to olefins.[15,16]

Most of the extensive studies by Kochi, *et al.*,[14,15] have been carried out using the ethylenediamine complex of chromous perchlorate, and our initial studies were carried out using this species as a solution in aqueous dimethylformamide.[14] In view of the extreme sensitivity of these solutions to traces of oxygen we prefer to use chromous acetate, which is a dry solid readily prepared from chromous perchlorate[17,18] and sodium acetate and readily handled in a drybox under nitrogen or argon. The acetate has previously been prepared from chromous chloride,[19] but since we have obtained consistently active preparations from the perchlorate we have continued to use this material.

Our initial study was done using crystalline 9-[2-*O*-acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (**4a**), which was obtained from adenosine and 2-acetoxyisobutyryl bromide.[12b] The reaction of **4a** with 5 molar equiv of chromous acetate and 10 equiv of ethylenediamine was carried out in ethanol at −78° for 30 min. Following removal of residual protecting groups by treatment with methanolic ammonia the mixture was separated by direct crystallization and preparative tlc into two major crystalline compounds. The major product, isolated crystalline in 59% yield, proved to be the desired 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)adenine (**5**), a compound that has previously been prepared by both McCarthy, *et al.*,[7b] and Horwitz, *et al.*,[20] by treatment of 3′-*O*-tosyl-2′-deoxyadenosine with sodium alkoxides. The structure of **5** was unequivocal from an examination of its nmr spectrum in DMSO-d_6. The spectra of all the 2′,3′-unsaturated nucleosides prepared in this study (see Tables I and II) were all very similar and showed some interesting features. Thus the vinyl protons appear as well-defined doublets of doublets of doublets showing values of $J_{1',2'}$ = 1.5, $J_{2',3'}$ = 6, $J_{3',4'}$ = 2–2.5, and $J_{2',4'}$ = 1.5 Hz. The $C_{1'}$ proton characteristically appeared as a sharp five-line pattern with couplings to $C_{2'}$H, $C_{3'}$H, and $C_{4'}$H of 1.5, 1.5, and 3 Hz.[21] The very large 1′,4′-homoallylic coupling is noteworthy and has been previously reported in our earlier work on the thymine analog (**12c**).[23]

The second major product, isolated crystalline in 30% yield, proved to be 3′-deoxyadenosine (**6**), which was physically and spectrally identical with a previously prepared sample.[12b] Clearly simple chromous ion reduction of the bromo function[14] competes to some degree with the desired elimination reaction.

The presence of the chiral 5′-dioxolanone ether group allows the crystallization of a single diastereomer of **4a** in only 30–35% yield from adenosine.[12b] Accordingly, it was of practical interest to examine the chromous ion reaction with the crude mixture of 3′- and 2′-halo nucleosides (**1** and **2**, roughly 9:1) that can be obtained in greater than 90% yield from adenosine and 2-acetoxyisobutyryl halides.[12b] The reaction between the crude mixture of chloro nucleosides (**4b** and **2**, Pu = Ad, X = Cl, R = Me_3-dioxolanone) with the chromous acetate–ethylenediamine reagent was carried out exactly as with the pure 3′-bromo compound **4a**. From this reaction the crystalline 2′ olefin **5** was isolated in almost the same yield (62%) as from pure **4a**. The yield of 3′-deoxyadenosine was, however, considerably lower (10%) and a very small amount of 2′-deoxyadenosine could also be detected chromatographically. In addition to the above products a new substance was also formed in this reaction and isolated in crystalline form in 6% yield. From analytical data, a positive test for olefins upon spraying a tlc plate with aqueous potassium permanganate, and nmr spectroscopy, this compound was shown to be 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**7**). From the nmr spectrum of **7** in DMSO-d_6



4a, X = Br
b, X = Cl
c, X = I

5 6 7

the presence of a free 5′-hydroxyl group and a single secondary hydroxyl function were apparent. No signal for $C_{4'}$H could be detected and the $C_{2'}$ and $C_{3'}$ protons were superimposed at 5.27 ppm, suggesting the vinylic nature of $C_{3'}$.

An alternative synthesis of **7** was also achieved in 59% yield *via* treatment of **4a** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in acetonitrile at 80°. Under these conditions a considerable amount of 2′,3′-anhydroadenosine was also produced but the two compounds could be easily separated by crystallization. Several 3′,4′-unsaturated 2′-deoxynucleosides have been prepared by Žemlička, *et al.*,[8] by base-catalyzed eliminations on 2′-deoxy nucleoside 5′-uronates followed by complex hydride reduction of the ester function.[8] The only 3′,4′-unsaturated ribo nucleosides that have been described are the result of silica gel or base-catalyzed elimination of the acetal function from 2′,3′-*O*-benzylidene nucleoside 5′-aldehydes followed by borohydride reduction of the aldehyde.[24]

In order to complete the series of 3′-halogenated adenosine derivatives it was of interest to study the iodo compound. Our previous efforts to isolate pure 2-acetoxyisobutyryl iodide were unsuccessful owing to its thermal insta-

Table I
Nmr Chemical Shifts at 100 MHz (Parts per Million)

Compd	Solvent[b]	C_1'H	C_2'H	C_3'H	C_4'H	$C_{5'a}$H	$C_{5'b}$H	C_2H, C_8H[a]	Other
4c	D	6.07 (d)	5.98 (dd)	4.75 (m)	4.14 (m)	3.77 (dd)	3.95 (dd)	8.12, 8.23	1.72 (s, 3, $MeCO_3$), 1.46 (s, 3, CMe_2), 1.50, 1.52 (s, total 3, CMe_2), 2.05 (s, 3, OAc), 7.29 (s, 2, NH_2)
5	D	6.90 (ddd)	6.42 (ddd)	6.07 (ddd)	4.84 (m)	3.55 (dd)		8.12, 8.14	4.98 (t, 1, C_5'OH), 7.21 (s, 2, NH_2)
7	D	6.31 (d)	5.27 (m)	5.27 (m)		4.07 (d)		8.20, 8.24	5.27 (t, 1, C_5'OH), 5.75 (d, 1, C_2'OH), 7.35 (s, 2, NH_2)
9	D	5.98 (ddd)	6.02 (ddd)	5.92 (ddd)	4.90 (m)	3.57 (dd)	3.74 (dd)	8.02 (s, C_3H)	
12a	D	6.86 (m)	6.58 (ddd)	6.30 (m)	5.23 (m)	4.47 (d)		With Ar	7.6–8.1 (m, 11, Ar and C_2H)
12b	D	6.78 (ddd)	6.45 (ddd)	6.09 (ddd)	4.88 (m)	3.55 (d)		8.03, 8.08	
13	D	6.21 (d)	5.12 (m)	5.22 (br d)		4.01 (s)		8.07, 8.07	
15a	D	6.80 (ddd)	6.38 (ddd)	5.90 (ddd)	4.78 (m)	3.59 (d)			5.56 (d, 1, C_3H), 7.74 (d, 1, C_6H)
15b	D	6.76 (ddd)	6.39 (ddd)	6.01 (ddd)	5.00 (m)	3.82 (d)			5.57 (d, 1, C_3H), 7.45 (d, 1, C_6H)
15c	C	7.00 (ddd)	6.28 (ddd)	5.89 (ddd)	5.07 (m)	4.22 (dd)	4.50 (dd)		1.52, 1.55 (s, 3, CMe_2), 2.01 (s, 3, OAc), 5.76 (s, 1, C_5H), 7.54 (s, 1, C_6H)
15d	C	7.09 (ddd)	6.37 (ddd)	5.99 (ddd)	5.12 (m)	4.27 (dd)	4.45 (dd)		2.08 (s, 3, OAc), 5.79 (s, 1, C_3H), 7.57 (s, 1, C_6H)
17	D	6.10 (d)	4.93 (dd)	5.20 (dd)	4.30 (m)	4.30 (br s)			5.70 (dd, 1, C_3H), 7.65 (d, 1, C_6H), 1.46 (s, 6, CMe_2), 1.96 (s, 3 *t*-OAc), 2.11 (s, 3, 3'-OAc)
18	D	6.11 (d)	4.95 (dd)	5.22 (dd)	4.25 (m)	4.25 (m)			2.04 and 2.10 (s, 3, OAc), 5.73 (dd, 1, C_3H), 7.66 (d, 1, C_6H)
21c	D	6.03 (d)	5.95 (dd)	4.75 (dd)	4.04 (m)	3.76 (m)		8.14, 8.33	2.04 (s, 3, OAc), 5.56 (t, 1, C_5'OH), 7.33 (s, 2, NH_2)

[a] Specific assignments are not implied. [b] Solvents are DMSO-d_6 (D) and $CDCl_3$ (C).

bility during distillation. We have, however, shown that the acyl iodide can be prepared *in situ* by reaction of 2-acetoxyisobutyryl chloride with carefully dried sodium iodide in acetonitrile. The direct reaction of this mixture with adenosine in the presence of an excess of sodium iodide proceeds readily to give a mixture containing only two significant ultraviolet-absorbing spots upon tlc. The faster of these (15–30% in different experiments) proved to be 2',3',5'-tris-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) adenosine, which was isolated in crystalline form and shown to be identical with an authentic sample.[12b] The major product crystallized readily from ethyl acetate–ether and proved to be the 3'-iodoacetate **4c**. As in our earlier studies with adenosine, the 5' position was blocked as the trimethyldioxolanon-2-yl ether as shown by its infrared spectrum (ν_{max} 1810 cm^{-1}) and its nmr spectrum. While the latter clearly showed the 2'-*O*-acetyl and the CH_3CO_3 group of the dioxolanone moiety as three-proton singlets at 2.05 and 1.72 ppm, the usual pair of three-proton singlets due to the nonequivalent *gem*-dimethyl group was not present. In its place were three singlets totaling six protons and in a ratio of 2:1:1 at 1.46, 1.50, and 1.52 ppm. This suggests that the sharp-melting crystalline product is still a mixture of diastereoisomers due to the chiral dioxolanone group. Of the other protons in the molecule, only C_3'H reflected this diastereomerism and appeared as a complex multiplet while all other signals were sharp. The xylo configuration of the iodo group was apparent from the conversion of **4c** to 2',3'-anhydroadenosine[12b] upon treatment with sodium methoxide. We cannot rule out the presence of minor amounts of chloro nucleoside **4a** or of 2'-halogenated material in the crude product prior to crystallization. Nevertheless, the crude reaction product was treated with chromous acetate under the usual conditions, giving 48% of the 2' olefin **5**, 9% of 3'-deoxyadenosine (**6**), and 7% of the 3' olefin **7** in addition to adenosine coming from the trisdioxolanone.

From the above it is clear that there is relatively little difference in the distribution of products resulting from the chloro, bromo, and iodo nucleosides (**4a–c**). In view of the known relative reactivities (I > Br > Cl) of alkyl halides toward simple reduction by chromous ion,[14] it is perhaps surprising that considerably more 3'-deoxyadenosine (**6**) arose from the bromo nucleoside **4a** than from its chloro or iodo counterparts. It is established[14-16] that both chromous ion promoted reductions and eliminations involve radical and organochromium intermediates. It is assumed that the formation of the 3' olefin **7** is the consequence of an alternative pathway of decomposition of the initial C_3' radical rather than of a base-catalyzed elimination of bromide due to ethylenediamine. This conclusion is based upon the fact that the base-catalyzed conversion of **4a** to **7** using DBN requires heating in acetonitrile while the chromous reaction took place at low temperature.

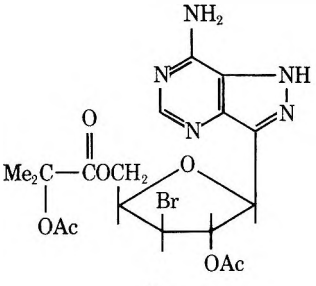
We have previously described the reaction of the biologically active adenosine analog formycin with 2-acetoxyisobutyryl bromide to give a 3:1 mixture of 7-amino-3-[5-*O*-(2-acetoxyisobutyryl)-2-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl]pyrazolo[4,3-*d*]pyrimidine (**8**) and its 3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl isomer in quantitative yield.[1] The reaction of this mixture with chromous acetate in the usual way followed by removal of the acetoxyisobutyryl ester with sodium methoxide gave the 2',3'-unsaturated nucleoside **9** in 43% yield. While free **9** was not obtained in crystalline form its purity was confirmed by its elemental analysis, chromatographic behavior, and characteristic nmr spectrum. In addition, a 9% yield of pure 3'-deoxyformycin (**10**) was isolated as its crystalline hydrochloride and found to be identical with a

Table II
Coupling Constants for Compounds in Table I (Hertz)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	Other
4c	4	6.5	*a*	3	2.5	11.5	
5	1.5	6	2	3.5	3.5	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5'H,OH} = 5$
7	2.5	*a*				0	$J_{H,OH} = 5$
9	*a*	*a*	*a*	3	3	12	
12a	1.5	5.5	*a*	4	4	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$
12b	1.5	6	2.5	4	4	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$
13	2.5	~2				0	$J_{3',5'} \cong 0.5$
15a	1.5	6	2	3.5	3.5	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
15b	1.5	6	2.5	4.5	4.5	0	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
15c	1.5	6	2.5	3.5	4	12.5	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
15d	1.5	6	2.5	3.5	3.5	12	$J_{1',3'} = 1.5$, $J_{1',4'} = 3$, $J_{2',4'} = 1.5$, $J_{5,6} = 8$
17	7	6	1	~1	~1	0	$J_{5,NH} = 2$, $J_{5,6} = 8$
18	7	6	3	*a*	*a*	*a*	$J_{5,NH} = 1$
21c	4.5	4.5	5.5	*a*	*a*	*a*	$J_{5',OH} = 5$

[a] Unresolved.

sample previously obtained by catalytic hydrogenolysis of **8**.[1] While the formation of a small amount of 2′-deoxyformycin[1] in the chromous acetate reaction was indicated by tlc, this compound was not isolated.



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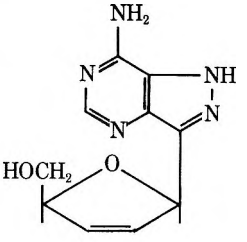

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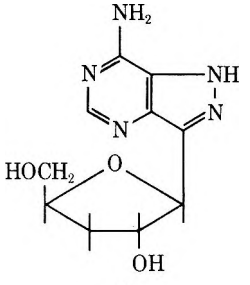
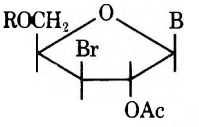
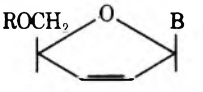


10

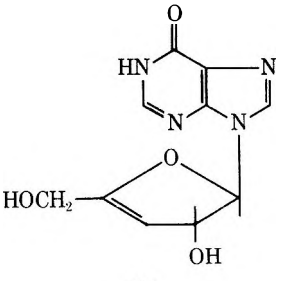
The reactions of N^6,5′-*O*-dibenzoylguanosine[25] and of inosine with α-acetoxyisobutyryl halides have also been examined and shown to lead predominantly to the 2′-*O*-acetyl-3′-bromo-3′-deoxy-β-D-xylofuranosyl nucleosides (**11a,b**).[12d] The reaction of **11a** with chromous acetate gave a mixture of products from which 9-(5-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-N^2-benzoylguanine (**12a**) was isolated in 24% yield by direct crystallization. Attempts to raise this yield and to isolate other products following debenzoylation of the mother liquors with methanolic dimethylamine[26] met with failure, since the mixture so obtained was not sufficiently soluble for chromatographic separation and could not be successfully crystallized. The analogous reaction with the bromo acetyl derivative **11b** in the inosine series was far more successful. Following cleavage of protecting groups with methanolic ammonia and chromatography on silicic acid, the desired 2′,3′ olefin **12b** was isolated in crystalline form in 53% yield. In addition, crystalline 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)hypoxanthine (**13**) was obtained in 3% yield, and, while we have been unable to isolate it in crystalline form owing to chromatographic overlapping with residual **13**, 3′-deoxyinosine was clearly also present on the basis of tlc comparison with an authentic sample. The latter compound has previously been shown to be the biologically inactive deamination product of Cordycepin (3′-deoxyadenosine)[27] and has been obtained by synthesis.[28]



11a B = N^2-Bz-guanine; R = Bz
b, B = hypoxanthine; R = trimethyldioxolanone



12a, B = N^2-Bz-guanine; R = Bz
b, B = hypoxanthine; R = H
c, B = thymine; R = H

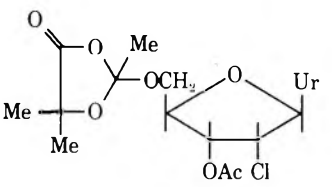


13

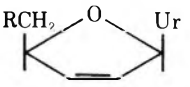
The above reactions using purine nucleosides have the common feature that they all are substituted with trans bromo acetate functions at $C_{2'}$ and $C_{3'}$ of the sugar moiety. Since chromous ion promoted reductive eliminations are radical in nature, Singleton and Kochi[15a] have shown that both *cis*- and *trans*-1,2-dibromocyclohexane are converted to cyclohexene, although at different rates. Accordingly, it seemed likely that the cis bromo acetates produced by reaction of uridine with 2-acetoxyisobutyryl halides[12a] should also be converted to 2′,3′ olefins. Our initial experiments were carried out on the crude product from uridine and 2-acetoxyisobutyryl chloride in acetoni-

trile which has been shown by nmr and by isolation to be predominantly (at least 80%) 3′-*O*-acetyl-2′-chloro-2′-deoxy-5′-*O*-(2,5,5,-trimethyl-1,3-dioxolan-4-on-2-yl)uridine (**14**)[12a] together with lesser amounts of the corresponding 5′-*O*-acetoxyisobutyrate. The reaction of this product with chromous acetate led, unexpectedly, to quite extensive glycosidic cleavage with release of uracil. Following removal of protecting groups with sodium methoxide and separation by preparative tlc the desired 2′,3′ olefin **15a** was isolated in crystalline form in an overall yield of 26%. This product has previously been prepared by Horwitz, *et al.*,[7a] from derivatives of 2′-deoxy-3′-*O*-methanesulfonyluridine. The only other nucleoside isolated from this reaction proved to be 2′-deoxyuridine (5%), the result of simple reduction of **14**. Another reaction was carried out using as starting material the crude product from uridine and 2-acetoxyisobutyryl chloride in dimethylformamide.[12a] This material was also shown to be predominantly the 5′-dioxolanone **14** although the proportion of by-products was somewhat higher than in the reaction in acetonitrile. In this case the distribution of products from the chromous acetate reaction was very similar to that described above, but in addition a single, less polar band was also isolated by preparative tlc. This compound, isolated crystalline in 11% yield, proved to be 1-(5-chloro-2,3,5-trideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (**15b**), this structure being confirmed by an independent synthesis *via* chlorination of **15a** with triphenylphosphine and carbon tetrachloride.[12c] The isolation of **15b** suggests that one of the by-products accompanying reaction of uridine with 2-acetoxyisobutryl chloride in hot dimethylformamide is 3′-*O*-acetyl-2′,5′-dichloro-2′,5′-dideoxyuridine (**16**).[12c] While the chloro and acetyl functions of **16** would serve as precursors of the 2′,3′ olefin, the primary alkyl chloride would be relatively resistant to reaction with chromous ion at low temperatures.[14] In support of the above we have shown that treatment with methanolic hydrogen chloride of crude **14** from a reaction in dimethylformamide readily cleaves the dioxolanone substituent.[12a] Preparative tlc of the mother liquors from the resulting 3′-*O*-acetyl-2′-chloro-2′-deoxyuridine led to the isolation, in modest yield, of an acid-resistant fraction, the nmr spectrum of which clearly showed the major constituent to be **16**.[12c] By-products such as **16** are apparently not formed in comparable reactions between uridine and 2-acetoxyisobutyryl chloride in solvents such as acetonitrile.

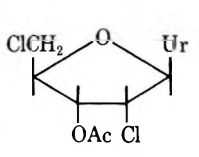
In the hope that the extent of glycosidic cleavage could be reduced by using a bromo- rather than a chlorouridine, the reaction between uridine and 2-acetoxyisobutyryl bromide in acetonitrile was investigated. The crude product of this reaction, isolated in essentially quantitative yield, proved to be a roughly 9:1 mixture of two compounds. The major, less polar, product was isolated in pure form by chromatography on silicic acid and proved to be 5′-*O*-(2-acetoxyisobutyryl)-3′-*O*-acetyl-2′-bromo-2′-deoxyuridine (**17**). The unexpected formation of the acetoxyisobutyryl derivative rather than the dioxolanone found with the chloro analog **14** was confirmed by its nmr spectrum, which showed the *gem*-dimethyl group as a six-proton singlet at 1.46 ppm and the tertiary acetoxyl as a three-proton singlet at 1.96 ppm.[12a] In addition, the infrared spectrum showed only normal ester bands in the 1700–1800-cm^{-1} region and no indication of the typical dioxolanone carbonyl frequency at 1805–1810 cm^{-1}.[12a] We have previously found that during reactions of 2-acetoxyisobutyryl halides with nucleosides the choice between the dioxolanone ether and 2-acetoxyisobutyryl ester varies according to both the solvent[12a] and the nature of the heterocyclic base.[1] The present case provides yet another example of the delicate balance between these two alternative substituents. One possible explanation is that the 2-acyloxyisobutyryl halides are themselves in equilibrium with cyclic oxonium ion or 2-halodioxolanone tautomers, the formation of which is dependent upon both the nature of the halide and steric requirements. Examination of these compounds by infrared and nmr spectroscopy, however, reveals no indication of the presence of appreciable amounts of such species.



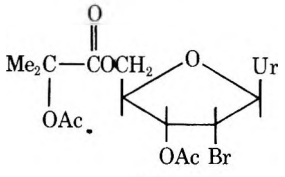
14



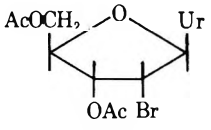
15a, R = OH
b, R = Cl
c, R = O—COCMe$_2$ (OAc)
d, R = OCOCH$_3$



16



17



18

The minor product from the above reaction was also isolated and shown to be 3′,5′-di-*O*-acetyl-2′-bromo-2′-deoxyuridine (**18**). The chromatographic behavior and the nmr and infrared spectra of this substance were identical in every way with those of a sample of **18** prepared by acetylation of 2′-bromo-2′-deoxyuridine according to Cushley, *et al.*[29] It is interesting to note that the reaction of uridine with 2-acetoxyisobutyryl chloride and an excess of anhydrous lithium bromide rather than with pure 2-acetoxyisobutyryl bromide leads to a similar mixture of **17** and **18** in which the proportion of **18** is markedly increased. For the present purposes, of course, both **17** and **18** are equally suitable substrates for the chromous reaction. The mechanism by which the 5′-*O*-acetyl substituent arises is unclear and perhaps involves a decomposition of the reagent to acetyl bromide. The chloro analog of **18** was the sole product from uridine and 2-acetoxyisobutyryl chloride in glacial acetic acid.[12a]

The reaction of crude **17** with chromous acetate was found to give results very similar to those using the chloro nucleoside **14**. Once again, quite extensive glycosidic cleavage resulted, and following removal of the 5′ substituent and preparative tlc the 2′,3′ olefin **15a** and 2′-deoxyuridine were isolated in yields of 33 and 3%, respectively. It would appear that the extensive glycosidic cleavage leading to uracil is due to the fact that only in the uridine series the 2′ position is the principal site of halogenation. Presumably the initial chromous ion promoted 2′ radical can lead to either the desired 2′,3′ olefin or to glycosidic cleavage by alternative pathways.

In one reaction between **17** and chromous perchlorate the direct product was isolated by crystallization prior to deacylation, giving the 5′-*O*-(2-acetoxyisobutyryl) olefin

(**15c**). As part of the characterization of **15a** we have also acetylated the free 5′-hydroxyl group, giving crystalline **15d**. The nmr spectra of both **15c** and **15d** showed the expected downfield shift of the $C_{5'}$ protons relative to those of **15a**. In addition, the ester functions at $C_{5'}$ led to nonequivalence of the two $C_{5'}$ protons, presumably owing to restriction of rotation. The compound **15c** is also the first example of a 5′-*O*-(2-acetoxyisobutyryl) nucleoside that we have encountered in which the *gem*-dimethyl groups are magnetically nonequivalent and appear as a pair of three-proton singlets at 1.52 and 1.55 ppm.

It has previously been noted that the optical rotatory dispersion (ORD) spectra of the 2′,3′-unsaturated uridine and adenosine analogs **15a** and **5** are anomalous. Thus, while simple β-nucleosides in the pyrimidine and purine series normally exhibit positive and negative Cotton effects, respectively,[30] **15a** was found to be negative[11,30a] and **5** positive.[31] Our results confirm the above observations and extend them to a variety of related compounds. Thus, like **15a**, several 5′-substituted derivatives (**15b–d**) also exhibit negative Cotton effects. Similarly, the 2′,3′-unsaturated analog of formycin (**9**) showed an anomalous positive Cotton effect while that from inosine (**12b**) gave a positive plain dispersion curve. The ORD spectrum of the 5′,N^2-dibenzoylguanosine olefin (**12a**) is considerably more complex and shows a multiple Cotton effect. This is presumably related to the presence of two intense maxima in the ultraviolet spectrum of **12a**. As yet we have not debenzoylated this compound so as to obtain a more simple spectrum. It seems, nevertheless, clear that inverted Cotton effects are a general consequence of the introduction of 2′,3′ unsaturation into both purine and pyrimidine nucleosides.

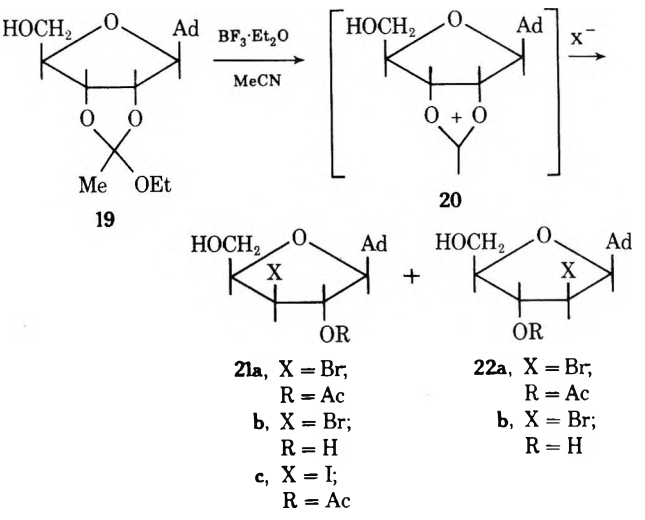
Finally, we would like to briefly describe an alternative method for the synthesis of sugar halogenated purine nucleosides of types **1** and **2** (X = Br and I) in which the 5′ hydroxyl is unsubstituted. This method is based upon the observation, made during a separate study in this laboratory,[32] that reaction of uridine 2′,3′-ortho esters with nitrosonium tetrafluoroborate in acetonitrile led readily to 3′-*O*-acyl-O^2,2′-cyclouridine derivatives, presumably *via* intermediate 2′,3′-acyloxonium ions. This is also clearly related to reports by Robins, *et al.*,[33] that treatment of 2′,3′-*O*-methoxyethylideneadenosine with pivaloyl chloride in refluxing pyridine leads, *inter alia*, to 9-(2-*O*-acetyl-3-chloro-3-deoxy-5-*O*-pivaloyl-β-D-xylofuranosyl)-N^6-pivaloyladenine, once again presumably *via* a 2′,3′-acetoxonium intermediate. In the presence of excess iodide ion a related 3′-iodo nucleoside bearing a bizarre enol ester function at $C_{2'}$ was obtained.[33b] Along similar lines, Newman and Chen[34] have recently described the conversion of simple cyclic ortho esters into chloroacetates *via* treatment with chlorotriphenylmethane.

Both the above reactions would appear to involve only the conversion of an ortho ester to an acetoxonium ion utilizing pivaloyl chloride or chlorotriphenylmethane as a source of anhydrous acid. Previous work by Meerwein[35] has shown that such a conversion can be accomplished using model cyclic ortho esters in the presence of Lewis acids such as boron trifluoride. We felt that the reaction of a nucleoside 2′,3′-ortho ester with boron trifluoride would generate the desired acyloxonium ion without the complications introduced by the presence of acylating species such as pivaloyl chloride or of nucleophilic halide ions originating from the reagent. We have accordingly treated the mixed diastereoisomers of 2′,3′-*O*-ethoxyethylideneadenosine (**19**)[36] with boron trifluoride etherate in acetonitrile at 0° in the presence of an excess of anhydrous lithium bromide. Examination of the reaction mixture by tlc showed the presence of two major spots, the more polar of which proved to be 2′(3′)-*O*-acetyladenosine arising from simple hydrolysis of the intermediate acetoxonium ion **20**. The less polar product was isolated by preparative tlc and shown by nmr to be a roughly 5:1 mixture of 9-(2′-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**21a**) and 9-(3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl)adenine (**22a**). By direct crystallization it was possible to isolate an overall 33% yield of pure **21a** which was found to be identical with a sample previously prepared by acidic hydrolysis of the corresponding 5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl) derivative obtained from adenosine and 2-acetoxyisobutyryl bromide.[12b]

While pure **22a** was not isolated as such, its presence was confirmed by treatment of the mother liquors from crystallization of **21a** with methanolic ammonia, which converts the 3′-bromo isomer **21a** into a mixture of the bromohydrin **21b** and 2′,3′-anhydroadenosine as previously described.[12b] At the same time **22a** is deacetylated giving, in low yield, the crystalline bromohydrin **22b** which was identical with an authentic sample.[12b]

In a very similar way, **19** was treated with boron trifluoride etherate in the presence of anhydrous sodium iodide. By a combination of chromatography on silicic acid and crystallization the pure 2′-*O*-acetyl-3′-iodo nucleoside **21c** was isolated in 35% yield. Identically the same compound was obtained by mild acidic hydrolysis of the product **4c** from adenosine and 2-acetoxyisobutyryl chloride in the presence of excess sodium iodide.

The above method constitutes a useful alternative to the use of 2-acetoxyisobutyryl halides for the preparation of compounds such as **21** and **22**. Clearly, in principle, such a reaction could also be used for the introduction of substituents other than halogen by reaction of the intermediate acetoxonium ion (**20**) with the appropriate nucleophile. Progress in this direction will be reported at a later date. Regardless of their mode of preparation, nucleoside halo acetates of types **1–3** constitute versatile intermediates for the preparation of deoxy, dideoxy, and unsaturated nucleosides.



Experimental Section

General Methods. The general methods used are similar to those described in previous papers in this series.[4] The assignments of sugar protons in the nmr spectra are generally confirmed by spin-decoupling studies and are presented in Tables I and II. We are particularly grateful to Mrs. J. Nelson and Dr. M. L. Maddox for their generous help with nmr studies.

Chromous Acetate. Electrolytically purified chromium metal chips (99.996% purity from Varlacoid Chemical Co., Elizabeth, N. J.) was rapidly, successively washed by decantation with concentrated hydrochloric acid, water, 70% perchloric acid, and water in a drybox under argon. The metal was then treated for roughly 1 min with 18% perchloric acid (40 ml) with vigorous passage of argon through the liquid. The solution was decanted, and the metal was added to 200 ml of 70% perchloric acid that had been thoroughly deoxygenated with argon. The mixture was then stored under argon for 60 hr, giving a deep blue solution which was added to a stirred, deoxygenated solution of sodium acetate (80 g) in water (160 ml). The resulting precipitate was collected under argon and successively washed with deoxygenated water, ethanol, and ether. The final material was dried and stored *in vacuo*, giving 44.3 g of chromous acetate as a brick red powder.

9-[2-*O*-Acetyl-3-deoxy-3-iodo-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (4c). 2-Acetoxyisobutyryl chloride (6.8 ml, 48 mmol) was added to a solution of carefully dried (100° *in vacuo* for 2 days) sodium iodide (10.8 g, 72 mmol) in anhydrous acetonitrile (100 ml). After 15 min, adenosine (3.2 g, 12 mmol) was added to the resulting suspension and the mixture was stirred for 30 min. The solvent was then largely removed *in vacuo* and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate containing sodium thiosulfate. The organic phase was further washed with sodium bicarbonate, then with water, dried ($MgSO_4$), and evaporated, leaving 6.38 g of a foam which by tlc (chloroform–methanol, 9:1) contained two major spots (~3:1) with very similar mobilities and only traces of more polar products. For analytical purposes a portion of this (500 mg) was partially separated by repeated preparative tlc on two plates. The less polar, minor product was crystallized from ethyl acetate–ether, giving 40 mg of an essentially single diastereoisomer of 2′,3′,5′-tris(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)adenosine with mp 140–141° and with an nmr spectrum identical with that of an authentic sample.[12b] Crystallization on the more polar band gave 200 mg of **4c**: mp 134.5–135.5°; λ_{max} (MeOH, H^+) 259 nm (ε 15,400); $[\alpha]^{23}D$ 16.9° (*c* 0.5, MeOH); ORD (MeOH) $[\Phi]_{242}$ (peak) 10,500°, $[\Phi]_{261}$ 0°, $[\Phi]_{278}$ (trough) −4900°.

Anal. Calcd for $C_{18}H_{22}N_5O_5I$ (547.31): C, 39.49; H, 4.05; N, 12.80; I, 23.19. Found: C, 39.66; H, 4.19; N, 12.60; I, 23.35.

Treatment of the crude product with methanolic sodium methoxide for 5 min at room temperature gave only 2′,3′-anhydroadenosine with melting point and nmr spectrum identical with those of an authentic sample[12b] and adenosine from the trisdioxolanone.

General Procedure for Chromous Acetate Reactions. The halogenated nucleoside (5 mmol) was dissolved in 100–150 ml of ethanol and deoxygenated by thorough bubbling with argon. This solution was then added, under argon, to a stirred, deoxygenated mixture of chromous acetate (4.25 g, 25 mmol) and ethylenediamine (3.4 ml, 50 mmol) in ethanol at −78° for 0.5–4 hr as specified below. Air was then bubbled through the still cooled solution for several minutes and ice (~5 g) and glacial acetic acid (4.5 ml) were added. The mixture was llowed to warm to room temperature and the purple solution was evaporated *in vacuo*. The residue was partitioned between ethyl acetate and water and the dried ($MgSO_4$) solution was treated as described below.

Reaction of Chromous Acetate with Adenosine Derivatives. A. With Crude 9-[2-*O*-Acetyl-3-chloro-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (4b). The reaction was carried out for 2.5 hr as above using 2.28 g (5 mmol) of the crude extracted product (principally **4b** and its 3′-*O*-acetyl-2′-bromo-β-D-arabino isomer in a ratio of ~9:1) from adenosine and 2-acetoxyisobutyryl chloride.[12b] The crude extract (2.0 g) was treated for 22 hr with saturated methanolic ammonia and the evaporated residue was crystallized from methanol, giving 430 mg of 9-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-adenine (**5**): mp 194–195° (reported[7b] mp 187–190°[20]); λ_{max} (MeOH) 260 nm (ε 15,200); $[\alpha]^{23}D$ 22.8° (*c* 0.25, MeOH); ORD (MeOH) $[\Phi]_{266}$ (peak) 4900°, $[\Phi]_{246}$ 0°, $[\Phi]_{234}$ (trough) −2600°.

Anal. Calcd for $C_{10}H_{11}N_5O_2$ (233.23): C, 51.49; H, 4.75; N, 30.03. Found: C, 51.21; H, 4.77; N, 30.19.

The mother liquors from **5** were separated into three major bands by preparative tlc on three plates using four developments with chloroform–methanol (9:1). Elution of the fastest band followed by crystallization from methanol gave a further 290 mg (total yield 720 mg, 62%) of **5** identical with that above. Elution of the middle band followed by crystallization from methanol gave 130 mg (10%) of pure 3′-deoxyadenosine (**6**), mp 226–228°, in every way identical with an authentic sample.[12b]

Elution of the slowest band gave 330 mg of a mixture of products containing a small amount of 2′-deoxyadenosine which was identified chromatographically. Crystallization from methanol gave 80 mg (6%) of essentially pure 9-(3-deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (**7**) which after one further crystallization from aqueous methanol had mp 240–241°: λ_{max} (MeOH, H^+) 258 nm (ε 15,000); λ_{max} (MeOH, OH^-) 259 nm (ε 14,800); $[\alpha]D$ 307° (*c* 0.1, H_2O); ORD (MeOH) $[\Phi]_{272}$ (trough) −13,300°, $[\Phi]_{258}$ (peak) −10,300°, $[\Phi]_{226}$ (trough) −50,000°, $[\Phi]_{216}$ 0°.

Anal. Calcd for $C_{10}H_{11}N_5O_3$ (249.23): C, 48.19; H, 4.45; N, 28.10. Found: C, 48.22; H, 4.48; N, 28.13.

B. With 9-[2-*O*-Acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (4a). The reaction with pure crystalline **4a**[12b] was carried out for 0.5 hr, giving 1.9 g of crude ethyl acetate extract. Following treatment with methanolic ammonia, initial crystallization from methanol followed by preparative tlc as above gave 685 mg (59%) of **5**, 370 mg (30%) of **6**, and only a trace of **7**, all with physical constants similar to those above.

C. With Crude Iodo Nucleoside (4c). The crude product from adenosine, 2-acetoxyisobutyryl chloride, and sodium iodide as above (2.73 g, ~5 mmol) was treated with chromous acetate for 30 min, giving 2.1 g of crude ethyl acetate extract. This material was treated for 24 hr with saturated methanolic ammonia and evaporated to dryness. Initial crystallization from methanol followed by preparative tlc and crystallization from methanol as above gave 554 mg (48%) of **5**, 110 mg (9%) of **6**, and 90 mg (7%) of **7**, all identical with those above.

9-(3′-Deoxy-β-D-*glycero*-pent-3-enofuranosyl)adenine (7). A solution of **4a** (2.0 g, 4 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (0.66 ml, 8 mmol) in acetonitrile (20 ml) was heated at 80° for 30 min. Methanol (20 ml) was then added to the cooled solution and the mixture was stored at room temperature for 5 hr, giving 0.83 g of crude **7** contaminated with some 2′,3′-anhydrodenosine. Crystallization from water gave 0.59 g (59%) of pure **7** which was identical with the product of the chromous acetate reaction above by tlc and by nmr and infrared spectroscopy.

7-Amino-3-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)pyrazolo[4,3-*d*]pyrimidine (9) and 3′-Deoxyformycin (10). A sample of a 3:1 mixture of **8** and its 3-*O*-acetyl-2-bromo-2-deoxy-β-D-arabinofuranosyl isomer[1] (1.0 g, 2 mmol) was treated with chromous acetate as above for 2 hr, giving 850 mg of crude ethyl acetate extract. This material was treated for 24 hr with 0.38 *N* methanolic sodium methoxide, neutralized with Dowex 50 (H^+) resin, and evaporated to dryness. The resulting syrup (500 mg) was purified by preparative tlc using three developments with chloroform–methanol (85:15) giving two major bands. Elution of the faster of these gave 200 mg (43%) of **9** as a white solid that could not be crystallized but which was pure by tlc and nmr: λ_{max} (MeOH, H^+) 237 nm (ε 5800), 296 (9000); λ_{max} (MeOH, OH^-) 236 nm (ε 14,400), 306 (5900); $[\alpha]^{23}D$ 17.6° (*c* 0.9, MeOH); ORD (MeOH) $[\Phi]_{302}$ (peak) 4700°, $[\Phi]_{280}$ (trough) 4000°, $[\Phi]_{268}$ (peak) 5100°, $[\Phi]_{246}$ 0°, $[\Phi]_{232}$ −5100°; mass spectrum (70 eV) molecular ion *m/e* 233.

Anal. Calcd for $C_{10}H_{11}N_5O_2$ (233.23): C, 51.49; H, 4.75. Found: C, 51.22; H, 5.35.

Elution of the slower band gave 120 mg of a syrup that was converted into its hydrochloride and crystallized from ethanol, giving 50 mg (9%) of 3′-deoxyformycin hydrochloride (**10**), mp 207–209°, in all ways identical with an authentic sample[1].

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)hypoxanthine (12b). Crude **11b** (from inosine and 2-acetoxyisobutyryl bromide)[37] was treated as usual with chromous acetate for 1 hr, giving 2.1 g of crude ethyl acetate extract. This material was chromatographed on a column of silicic acid using chloroform–methanol (19:1) to remove a lttle hypoxanthine and giving 1.4 g of a white foam. This was treated for 20 hr with methanolic ammonia at room temperature to give one major, permanganate-positive spot and several minor products. Crystallization from methanol gave a total of 606 mg (53%) of **12b**: mp above 300°; λ_{max} (MeOH, H^+) 250 nm (ε 10,300); λ_{max} (MeOH, OH^-) 255 nm (ε 12,600); $[\alpha]^{23}D$ −34.8° (c 0.09, H_2O); ORD (MeOH) plain positive dispersion curve with $[\Phi]_{300}$ 400°, $[\Phi]_{250}$ 3000°, $[\Phi]_{220}$ 7100°.

Anal. Calcd for $C_{10}H_{10}N_4O_3$ (234.21): C, 51.28; H, 4.30; N, 23.92. Found: C, 51.10; H, 4.28; N, 23.65.

The mother liquors from **12b** were carefully chromatographed on silicic acid using chloroform–methanol (4:1) to give 70 mg of a permanganate-positive material more polar than **12b** and with an R_f very close to that of 3′-deoxyinosine. Crystallization from methanol gave 39 mg (3%) of the pure 3′ olefin **13**: mp 206–208° dec; λ_{max} (MeOH, H^+) 251 nm (ε 10,200); λ_{max} (MeOH, OH^-)

255 nm (ε 11,600); $[\alpha]^{23}D$ −129° (c 0.1, MeOH); ORD (MeOH) $[\Phi]_{300}$ −2800°, $[\Phi]_{224}$ (trough) −22,500°, $[\Phi]_{216}$ −11,000°.

Anal. Calcd for $C_{10}H_{10}N_4O_4$ (250.21): C, 48.00; H, 4.02; N, 22.39. Found: C, 47.97; H, 4.41; N, 22.21.

The mother liquors from **13** were shown by tlc to be a mixture of **13** and 3′-deoxyinosine[37] that could not be further resolved.

9-(5-*O*-Benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-*N*²-benzoylguanine (12a). The reaction between chromous acetate and crude **11a** (3.3 g, 5 mmol, from 2-acetoxyisobutyryl bromide and N^6, 5′-dibenzoylgluanosine)[12d] was carried out for 30 min, giving 2.04 g of ethyl acetate extract. Direct crystallization of this material from methanol gave 500 mg (24%) of **12a** which softened at 280° and melted with decomposition at 289–294°: λ_{max} (MeOH, H^+) 232 nm (ε 25,100), 274 (20,000); λ_{max} (MeOH, OH^-) 231 nm (ε 27,300), 275 (14,000), 318 (17,600); $[\alpha]^{23}D$ −149° (c 0.1, pyridine); ORD (MeOH) $[\Phi]_{318}$ (trough) −4900°, $[\Phi]_{286}$ (peak) −1700°, $[\Phi]_{250}$ (trough) −8300°, $[\Phi]_{236}$ 0°, $[\Phi]_{220}$ (peak) 16,200°.

Anal. Calcd for $C_{24}H_{19}N_5O_5$ (457.43): C, 63.01; H, 4.19; N, 15.31. Found: C, 62.81; H, 4.36; N, 15.13.

5′-*O*-(2-Acetoxyisobutyryl)-3′-*O*-acetyl-2′-bromo-2′-deoxyuridine (17). 2-Acetoxyisobutyryl bromide (3.6 g, 17 mmol) was added to a suspension of uridine (1.4 g, 5.7 mmol) in acetonitrile (25 ml) and the mixture was heated at 80° for 3 hr. The resulting clear solution was largely evaporated *in vacuo* and the residue was dissolved in ethyl acetate, extracted several times with aqueous bicarbonate and then with water, dried ($MgSO_4$), and evaporated, leaving 3.0 g of a froth. This material contained one major spot and roughly 10% of a slightly more polar compound. For analytical purposes this material was chromatographed on a column of silica gel using 1% methanol in chloroform. In this way 1.57 g (58%) of pure **17** was obtained as a white froth followed by a further 1.17 g of a mixture of the two products (total yield quantitative). The major product (**17**) had λ_{max} (MeOH, H^+) 258 nm (ε 9900); $[\alpha]^{23}D$ 26.8° (c 0.22, $CHCl_3$); ν_{max} (KBr) 1755, 1700 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}N_2O_9Br$ (477.27): C, 42.78; H, 4.44; N, 5.87. Found: C, 42.33; H, 4.46; N, 5.72.

A sample of the minor component was purified by preparative tlc of an enriched fraction using chloroform–methanol (19:1) giving **18** as a chromatographically homogeneous foam: λ_{max} (MeOH, H^+) 258 nm (ε 9200); $[\alpha]^{23}D$ 14.3° (c 0.6, MeOH); ORD (MeOH) $[\Phi]_{278}$ (peak) 4500°, $[\Phi]_{266}$ 0°, $[\Phi]_{250}$ (trough) −5100°. The nmr spectrum of **18** was identical with that of a sample prepared by acetylation of 2′-bromo-2′-deoxyuridine according to Cushley, *et al.*[29]

Anal. Calcd for $C_{13}H_{15}N_2O_7Br$ (391.18): N, 7.16. Found: N, 7.17.

In a separate reaction uridine (9.76 g, 40 mmol) was added to a solution of 2-acetoxyisobutyryl chloride (160 mmol) and lithium bromide (400 mmol) in acetonitrile (300 ml) and the mixture was heated at 80° for 6 hr. A work-up as above gave 20 g of a roughly 2:1 mixture of **17** and **18** as judged by tlc and nmr. This material was used directly for the preparation of **15a**.

1-(2′,3′-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (15a). A. From the Bromo Nucleoside 17. The reaction with chromous acetate was carried out in the usual way for 4 hr using crude, unchromatographed **17** (2.38 g, ~5 mmol). The ethyl acetate extract gave only 1.33 g of crude product and the aqueous phase was found to contain predominantly uracil. The organic extract was evaporated and treated for 30 min with 0.38 *M* methanolic sodium methoxide (30 ml), neutralized with Dowex 50 (H^+) resin, and evaporated. The residue was purified by preparative tlc using two developments with chloroform–methanol (85:15) giving one major and two minor bands. Elution of the fastest, major band gave 530 mg of chromatographically pure **15** which was crystallized from methanol to give 350 mg (33%): mp 154.5–155.5° (reported[7a] mp 153–154°); λ_{max} (MeOH, H^+) 260 nm (ε 9800); λ_{max} (MeOH, OH^-) 260 nm (ε 7200); $[\alpha]^{23}D$ −15.4° (c 0.2, MeOH); ORD (MeOH) $[\Phi]_{283}$ (trough) −3700°, $[\Phi]_{258}$ 0°, $[\Phi]_{220}$ 10,400°.

Anal. Calcd for $C_9H_{10}N_2O_4$ (210.19): C, 51.42; H, 4.80; N, 13.33. Found: C, 51.57; H, 4.82; N, 13.21.

Elution of the middle band and crystallization from methanol gave 30 mg (5%) of uracil with mp >300° and in all ways identical with an authentic sample. Elution of the slowest band gave 35 mg (3%) of 2′-deoxyuridine which was chromatographically identical with an authentic sample and could be distinguished from 3′-deoxyuridine by tlc using chloroform–methanol (85:15).

B. From the Chloro Nucleoside 14. The reaction with chromous acetate was carried out for 4 hr using the crude product obtained essentially quantitatively from uridine and 2-acetoxyisobutyryl chloride in acetonitrile and known to be predominantly the 5′-dioxolanone (**14**).[12a] Once again much uracil was present in the aqueous phase and the ethyl acetate extracts were treated with sodium methoxide and purified by preparative tlc as in A. In this way 270 mg (26%) of crystalline **15a**, 60 mg (11%) of uracil, and 60 mg (5%) of 2′-deoxyuridine were isolated and shown to be identical with the same compounds from A.

1-[5-*O*-(2-Acetoxyisobutyryl)-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl]uracil (15c). In one experiment on the reaction of crude **17** with chromous perchlorate and ethylenediamine in dimethylformamide, the crude ethyl acetate extract was directly crystallized from ethyl acetate without prior deacylation. In this way **15c** was obtained as white crystals, mp 159–160°, in 15% yield: λ_{max} (MeOH) 259 nm (ε 10,300); $[\alpha]^{23}D$ −25.9° (c 1, MeOH); ORD (MeOH) $[\Phi]_{270}$ (trough) −4300°, $[\Phi]_{254}$ 0°, $[\Phi]_{240}$ (sh) 5100°.

Anal. Calcd for $C_{15}H_{18}N_2O_7$ (338.31): C, 53.25; H, 5.36; N, 8.28. Found: C, 53.12; H, 5.38; N, 8.30.

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (15d). Acetylation of **15a** using acetic anhydride in pyridine at room temperature for 1 hr followed by crystallization from ethyl acetate gave **15d**: mp 127–128°; λ_{max} (MeOH) 259 nm (ε 9700); ORD (MeOH) $[\Phi]_{271}$ (trough) −6600°, $[\Phi]_{255}$ 0°, $[\Phi]_{220}$ (peak) 9200°.

Anal. Calcd for $C_{11}H_{12}N_2O_5$ (252.23): C, 52.38; H, 4.80; N, 11.11. Found: C, 52.33; H, 4.83; N, 10.98.

1-(5-Chloro-2,3,5-trideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (15b). A. A solution of **15a** (80 mg, 0.4 mmol) in dimethylformamide (1 ml) was treated overnight at room temperature with triphenylphosphine (150 mg, 0.6 mmol) and carbon tetrachloride (100 mg, 0.65 mmol). The solvent was evaporated and the residue was purified by preparative tlc using chloroform–methanol (9:1). This separated triphenylphosphine oxide from a new product which was eluted and crystallized from methanol–ethyl acetate, giving 50 mg (57%) of **15b**: mp 166.5–167.5°; λ_{max} (MeOH, H^+) 259 nm (ε 9800); λ_{max} (MeOH, OH^-) 258 nm (ε 6700); $[\alpha]^{23}D$ −67.0° (c 0.55, MeOH); ORD (MeOH) $[\Phi]_{274}$ (trough) −8700°, $[\Phi]_{257}$ 0°, $[\Phi]_{228}$ (peak) 12,800°.

Anal. Calcd for $C_9H_9N_2O_3Cl$ (228.63): C, 47.28; H, 3.97; N, 12.25; Cl, 15.51. Found: C, 47.50; H, 4.04; N, 12.07; Cl, 15.47.

Upon storage at room temperature for several weeks **15b** decomposed to a black resin.

B. A reaction between chromous acetate and the crude product from uridine and 2-acetoxyisobutyryl chloride in dimethylformamide and known to be predominantly **14**[12a] was carried out for 4 hr as above. In addition to the products isolated above as in B a new, fast-moving band was observed. Elution of this material gave 130 mg (11%) of pure **15b** which was chromatographically and spectroscopically identical with that above.

9-(2-*O*-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (21a). A solution of the mixed diastereoisomers of 2′,3′-*O*-ethoxyethylideneadenosine (1.68 g, 5 mmol)[35] and carefully dried (100° *in vacuo*) lithium bromide (1.74 g, 20 mmol) in acetonitrile (300 ml) was stirred at 0° while boron trifluoride etherate (5 ml) was added. After 1 hr an excess of saturated aqueous sodium bicarbonate was added and the acetonitrile was largely removed *in vacuo*. The aqueous residue was extracted several times with chloroform and some minor, fast-moving impurities were removed by chromatography on silica gel using chloroform–methanol (9:1) giving 1.40 g of a froth that showed two spots upon tlc. The slower, minor spot contained mainly 2′(3′)-*O*-acetyladenosine while the major product was a roughly 5:1 mixture of **21a** and **22a** by nmr.[12b] Preparative tlc on three plates using chloroform–methanol (9:1) gave 861 mg of the less polar band which was crystallized from methanol–chloroform, giving 646 mg (33%) of **21a**, mp 205–206°, identical with an authentic sample[12b] by nmr.

The mother liquors from **21a** were evaporated to dryness and treated for 1.5 hr with saturated methanolic ammonia. Preparative tlc using five developments with chloroform–methanol (9:1) cleanly separated a fast band containing a mixture of **21b** and 2′,3′-anhydroadenosine from a slightly more polar band which was crystallized from ethyl acetate giving 34 mg (2%) of **22b**, mp 215–216°, in every way identical with an authentic sample.[12b]

9-(2-*O*-Acetyl-3-deoxy-3-iodo-β-D-xylofuranosyl)adenine (21c). Boron trifluoride etherate (5 ml) was added to a stirred solution of **19** (1.68 g, 5 mmol) and dried sodium iodide (1.8 g, 12 mmol) in acetonitrile at 0°. After 2 hr at 0° water (3 ml) was added followed by solid sodium thiosulfate to discharge the iodine color. The solution was dried ($MgSO_4$) and evaporated, leaving

3.0 g of a yellow syrup that was directly chromatographed on a column of silicic acid using chloroform–methanol (9:1).[38] Following removal of unreacted **19** a crude product (1.35 g) was obtained which was crystallized from ethyl acetate–methanol, giving 450 mg of **21c**. Preparative tlc of the mother liquors followed by crystallization as above gave a further 300 mg (total yield 750 mg, 35%) of pure **21c**: mp 199–201°; λ_{max} (MeOH, H^+) 259 nm (ϵ 16,800); λ_{max} (MeOH, OH^-) 260 nm (ϵ 15,800); $[\alpha]^{23}D$ 30.2° (*c* 0.1, pyridine); ORD (MeOH) $[\Phi]_{280}$ (trough) −5300°, $[\Phi]_{265}$ 0°, $[\Phi]_{240}$ (peak) 11,300°; ν_{max} (KBr) 1740, 1670, 1610 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_5O_4I$ (435.18): C, 33.12; H, 3.24; N, 16.09; I, 29.16. Found: C, 33.22; H, 3.34; N, 15.98; I, 29.10.

Registry No. **4a**, 37731-72-9; **4b**, 37731-76-3; **4c**, 42867-59-4; **5**, 7057-48-9; **6**, 73-03-0; **7**, 42867-61-8; **8**, 40627-32-5; 8 3-*O*-acetyl-2-bromo isomer, 42867-63-0; **9**, 42867-64-1; **11a**, 42867-65-2; **11b**, 42867-66-3; **12a**, 42867-67-4; **12b**, 42867-68-5; **13**, 42867-69-6; **14**, 42867-70-9; **15a**, 5974-93-6; **15b**, 42867-72-1; **15c**, 42867-73-2; **15d**, 42867-74-3; **17**, 42867-75-4; **18**, 19325-92-9; **19**, 42867-77-6; **21a**, 42867-78-7; **21c**, 42867-79-8; chromous acetate, 628-52-4; 2-acetoxyisobutyryl chloride, 40635-66-3; adenosine, 58-61-7; 2-acetoxyisobutyryl bromide, 40635-67-4; uridine, 58-96-8.

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(38) This work-up gave better results than the normal partitioning process where some of the nucleosides became water soluble.

Synthesis and Stereochemistry of Telomers of Vinylene Carbonate as Synthetic Intermediates for Carbohydrates[1]

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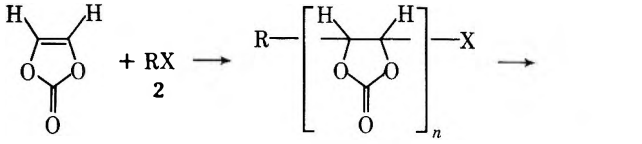
Vinylene carbonate underwent smooth telomerization with various polyhalogenomethanes as telogens in the presence of the radical initiator, BPO or AIBN, to give rise to type 3 telomers which could be synthetic key intermediates for carbohydrates. Isolation and stereochemistry of the lower telomers 3 ($n \leq 3$ or 4) stereoselectively formed were described. Stereochemistry of the $n = 2$ telomers **17a** and **17b** (**18a** and **18b**) was determined as trans,syn,trans and trans,anti,trans configuration by chemical correlation with lyxose and xylose derivatives **31**, and **34**, respectively. Abnormal telomerization involving unusual hydrogen abstraction from telogens by the radicals derived from peroxide was observed in the cases of bromoform and methylene bromide employed as telogens in contrast to those of polychloromethanes.

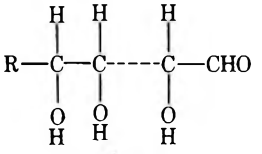
Apart from chemical modifications of naturally occurring monosaccharides, previously reported syntheses of carbohydrates from simple nonsugar substances mostly involve nonspecific processes at the stage of extension of the carbon chain or introduction of functional groups.[2] This paper deals with the stereoselective synthesis of car-

bohydrates starting with simple achiral compounds, vinylene carbonate (1) and polyhalogenomethanes, in two steps (telomerization and hydrolysis).

There have appeared structural and kinetic investigations on the polymers[3] derived from substituted or nonsubstituted vinylene carbonates as well as the chemical reactions involving the photocycloaddition[4] and the Diels–Alder reaction,[5] since the first preparation of parent compound 1 by Newman and coworker in 1953.[6] So far there seems to be no information on the telomerization of vinylene carbonates, which could be of significance in the synthesis of carbohydrates.

Careful control of the telomerization of 1 as a taxogen with polyhalogenomethanes (2) as telogens to give type 3 telomers followed by hydrolysis would provide a novel and facile route to both natural and unnatural polyalcohols, including carbohydrates. Highly stereoselective product formation would be expected owing to the strong tendency of trans radical addition.[7]



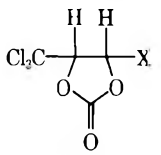


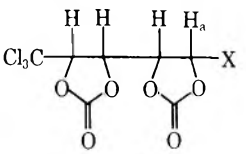
In this paper we describe the first radical telomerization of 1 with such polyhalides as carbon tetrachloride, chloroform, carbon tetrabromide, bromoform, dibromomethane, and bromotrichloromethane, as telogens to afford telomers **3**, especially lower telomers with n values less than four, which could play an important role as synthetic intermediates for carbohydrates and polyalcohols.

Results and Discussion

Telomerization of Vinylene Carbonate. Carbonate 1 underwent smooth telomerization with polyhalogenomethanes in the presence of benzoyl peroxide (BPO) or azobisisobutyronitrile (AIBN) as radical initiator under a nitrogen atmosphere to give telomers 3 in yields depending on the conditions (Table I). After 1 was almost consumed, treatment of the reaction mixture with hot methylene chloride gave as insoluble portions the higher telomers 3 with average n values of ten or more in addition to soluble products which consisted mainly of the lower telomers 3 with n values less than four. The soluble products could be separated into stereochemically pure telomers 3 (n = 1, 2, 3, and 4) by careful column chromatography on silica gel.[8]

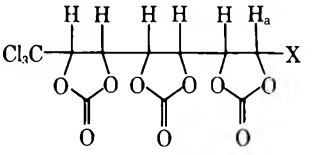
The 1:1 adducts of 1 with carbon tetrachloride and chloroform were identified as 4-chloro-5-trichloromethyl-1,3-dioxolan-2-one (5) and 4-trichloromethyl-1,3-dioxolan-2-one (6), respectively, on the basis of spectral data (ir, nmr) and elemental analyses. Repeated attempts to detect another n = 1 isomer by nmr, tlc, and glpc analyses were unsuccessful.





Among eight possible isomers two isomeric n = 2 telomers, **7a** and **7b**, were preferentially obtained in the reaction using carbon tetrachloride as telogen and identified as stereoisomers of 5-chloro-5′-trichloromethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione. The nmr spectra of **7a** and **7b** showed doublet signals at δ 6.50 (J = 2 Hz) and 6.55 (J = 2 Hz) due to terminal methine protons and multiplet peaks centered at δ 5.20 and 5.35, with a ratio of 1:3, respectively. Chloroform as a telogen gave as the n = 2 telomers 5-trichloromethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione (**8a** and **8b**), which showed multiplet signals centered at δ 4.90 and 4.85 in the nmr spectra, respectively. Despite an extensive search for the other n = 2 isomers they could not be found in the reaction mixture. This indicates that the reaction proceeded with high stereoselectivity.

As for the n = 3 telomers with 32 possible isomers (carbon tetrachloride as telogen), only three isomeric compounds, **9a**, **9b**, and **9c**, could be selectively isolated in nearly equal amounts. Their nmr spectra, whose pattern was similar to those of **7a** and **7b**, showed two peaks at δ 6.6 and 5.2 in an intensity of 1:5. Further elution on the column gave a small amount of the n = 4 telomer **10**. The n = 3 telomer **11** derived from chloroform was also isolated, presumably in an isomeric mixture.



Further studies on the distribution of telomers formed showed that the molar ratios 1:7 and 1:25 of 1 to carbon tetrachloride and chloroform gave the best results for the lower telomers ($n \leq 4$), respectively, while the increased ratios of taxogen to telogen resulted in high yields of the higher telomers (Table I). On the contrary, bromotrichloromethane as telogen even in 2 molar equiv gave exclusively the n = 1 adduct **12**, reflecting the large chain transfer constant.[9] This chain transfer reaction was remarkably affected by the ratio of 1 to telogens. Analyses of the higher telomer fractions which were obtained in the telomerization at the molar ratios 1:3, 1:7, and 1:12 of 1 to carbon tetrachloride gave average n values of 15.5, 8.5, and 6.5, respectively. A similar tendency was also observed in the case of chloroform.

The situation was more complicated when poly*bromo*methanes were used as telogens; unusual telomers were obtained in fairly good yields in addition to the normal ones. Thus, the reaction of 1 with methylene bromide free from bromoform and carbon tetrabromide gave four abnormal lower telomers which were identified as 4-dibromomethyl-1,3-dioxolan-2-one (**14**), 4-bromo-5-dibromomethyl-1,3-dioxolan-2-one (**15**), 5-bromo-5′-dibromomethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione (**18a** and **18b**), together with the expected 4-bromo-5-bromomethyl-1,3-dioxolan-2-one (**13**) and 5-bromo-5′-bromomethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione (**17a** and **17b**).

The isomeric structures of **13** and **14** were established by nmr spectra, which showed doublet peaks at δ 6.48 (J = 1.5 Hz) assignable to the bromomethine proton and δ 5.80 (J = 3.5 Hz) due to the dibromomethine proton, respectively. In the nmr spectra, **17a** and **17b** showed signals due to bromomethylene protons at δ 3.65 and 3.73 as an AB part of an ABX pattern, respectively, while **18a**

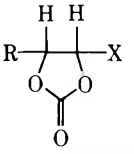
Table I
Isolated Yields (%) of Telomers 3 of Vinylene Carbonate with Polyhalogenomethanes[a]

Mole ratio (telogen/1)	Telogen	Lower telomers			Higher telomers[b]
		$n = 1$	$n = 2$	$n = 3$	
3	CCl_4	4.9 (**5**)	4.2 (**7**)	1.4 (**9**)	43.0 (n = 15.5)[c]
7	CCl_4	28.5 (**5**)	15.6 (**7**)	3.6 (**9**)	15.4 (n = 8.5)[d]
12	CCl_4	45.3 (**5**)	12.2 (**7**)		4.9 (n = 6.5)[e]
8	$CHCl_3$	1.1 (**6**)	1.4 (**8**)		61.0 (n = 17.5)[f]
20	$CHCl_3$	4.8 (**6**)	6.3 (**8**)		4.3 (n = 12.5)[g]
25	$CHCl_3$	15.9 (**6**)	10.3 (**8**)	2.6 (**11**)	5.4 (n = 10.5)[h]
4	$CBrCl_3$	92.0 (**12**)			
15	CH_2Br_2	19.5 (**13, 14, 15**)	4.8 (**17, 18**)		
5	$CHBr_3$	41.0 (**15, 16**)	17.0 (**19**)		
2	CBr_4	35.0 (**16**)			

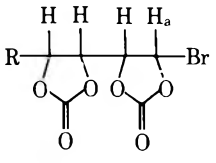
[a] Benzoyl peroxide was used as a radical initiator. [b] Obtained as insoluble products in hot methylene chloride and given in yields (%) based on the average molecular weight determined by elementary analyses. An average of n value was also calculated on the basis of chlorine analyses. [c] Found: C, 41.61; H, 3.88; Cl, 12.92. [d] Found: C, 38.44; H, 3.55; Cl, 20.19. [e] Found: C, 37.46; H, 3.38; Cl, 24.59. [f] Found: C, 42.64; H, 3.89; Cl, 9.36. [g] Found: C, 41.21; H, 3.66; Cl, 15.76. [h] Found: C, 39.19; H, 3.47; Cl, 18.57.

and **18b** gave doublet peaks at δ 5.90 (J = 3 Hz) and 6.05 (J = 3 Hz) assignable to dibromomethine protons, respectively.

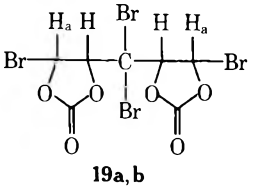
Bromoform as a telogen gave three unusual lower telomers, 4-bromo-5-tribromomethyl-1,3-dioxolan-2-one (**16**) and dibromomethylene-4,4′-bis(5-bromo-1,3-dioxolan-2-one) (**19a** and **19b**) in addition to **15** with no formation of the expected **18a** and **18b**. The addition of carbon tetrabromide to **1** afforded **16** in 35% yield. Failure to convert



13, R = CH_2Br; X = Br **20**, R = OCOPh; X = Cl
14, R = $CHBr_2$; X = H **21**, R = OCOPh; X = H
15, R = $CHBr_2$; X = Br **22**, R = OCOPh; X = Br
16, R = CBr_3; X = Br **23**, R = $C(CH_3)_2CN$; X = Br



17a,b, R = CH_2Br
18a,b, R = $CHBr_2$

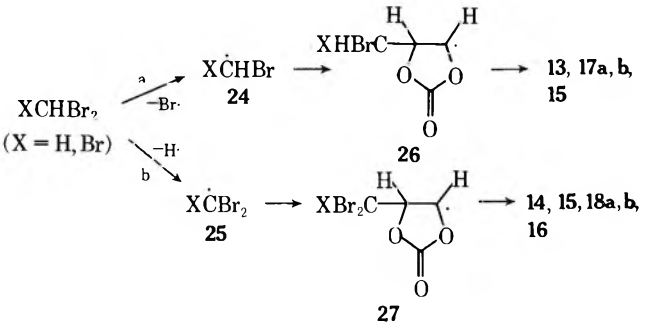


19a,b

13 into **15** and **15** into **16** in the presence of BPO and polybromomethanes would preclude **13** and **15** as the possible intermediates in the reaction. The nmr spectra of **19a** and **19b**, which closely resemble that of **16**, showed two doublets at δ 6.55 (J = 2.5 Hz) and 5.25 (J = 2.5 Hz) and δ 6.60 (J = 2.5 Hz) and 5.30 (J = 2.5 Hz), respectively, indicative of the symmetrical structures. Treatment of **1** with **16** in the presence of BPO gave a mixture of **19a** and **19b** in a ratio of 5:4 (75% yield).

The additional products, **20**, **21**, **22**, and **23**, which were undoubtedly derived from the direct participation of the decomposed radicals of BPO and AIBN, were isolated in low yields.

Reaction Pathways. First, mention should be made of the formation of unusual telomers in the reactions using polybromomethanes as telogens.[7] Bromine and hydrogen abstractions (paths a and b) from polybromides by the radicals, PhCOO· and/or Ph· derived from an initiator BPO could take place in the radical reactions described above and result in the formation of radicals **24** and **25**, which could account for the isolated products **13**–**18** *via* the ethylene carbonate radicals **26** and **27**. Path b, which was further supported by a fair yield of benzoic acid formed in the telomerization of **1** with methylene bromide and bromoform, provides a unique example of hydrogen abstraction by radicals derived from peroxide with one precedent of similar type of unusual telomerization of polyhaloethylenes.[10]



The initial formation of trichloromethyl radicals from carbon tetrachloride and chloroform by BPO or AIBN followed by the telomerization with **1** would explain all the isolated products derived from polychloromethanes as telogens.

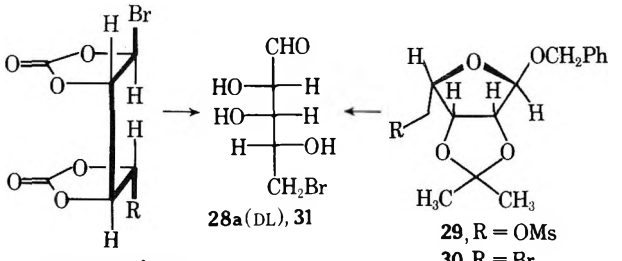
The products **19a** and **19b** are formed by radical addition of **16** to **1** as disclosed in the separate experiment.

Stereochemistry of Lower Telomers. Steric effects are most important in the highly stereoselective formation of telomers during radical telomerizations;[7] products of trans configuration might be expected to be formed preferentially in the rather nonflexible cyclic carbonate system, because the eclipsing approach of telogens to the halogenomethyl substituents (radicals) in the product-forming step of the chain process is energetically very disfavored.[11]

Just as predicted on the basis of mechanistic considerations, the expected trans stereochemistry of the n = 1 products **5**, **12**, **13**, **15**, and **16** as well as of the adducts **20**, **22**, and **23** was substantiated by the small coupling constants ($J_{vic} \cong$ 2.0 Hz) of the vicinal protons on the carbonate rings[12,14] which are in good accord with the value, J_{vic} = 2.0 Hz, of monochloroethylene carbonate, attributable to trans coupling[14,15] (Table II). Such small values for **5** and its analogs, unlike the large coupling constant J_{vic} = 6.0 Hz (presumably trans) for **6**, may reflect the significant steric effects of electronegative substituent groups on conformation.[15]

Application of this general tendency in the n = 1 series to the stereoselectively formed n = 2 telomers would make it possible to assign the trans,syn,trans and trans,anti,trans structures to **17a** (**18a**) and **17b** (**18b**),

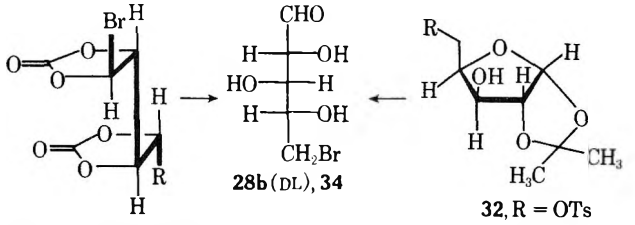
which on hydrolysis of the carbonate groups give 5-substituted 5-deoxy-DL-lyxose and -xylose, respectively. Such a stereochemistry was unequivocally proven by selective reduction of **18a** and **18b** with nickel carbonyl in tetrahydrofuran[16] to **17a** and **17b** followed by their successful conversion into 5-bromo-5-deoxy-DL-lyxose (**28a**) and -xylose (**28b**), respectively.[2] The authentic sugar derivatives **31** and **34** were obtained as syrups by simultaneous removal of protecting groups of benzyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-α-D-lyxofuranoside (**30**) and 5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**33**) which were prepared from the corresponding mesylate **29**[17] and tosylate **32**,[18] respectively. Identity of the hydrolyzates **28a** and **28b** with the authentic specimens **31** and **34** was established, respectively, except for the optical activity by paper chromatography and gas chromatographic analysis (as trimethylsilates).



trans,syn,trans form
17a, R = CH_2Br
18a, R = $CHBr_2$

28a(DL), **31**

29, R = OMs
30, R = Br

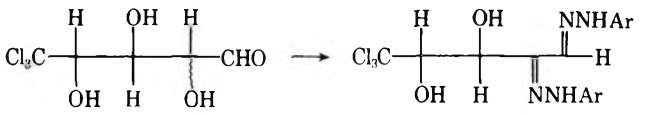


trans,anti,trans form
17b, R = CH_2Br
18b, R = $CHBr_2$

28b(DL), **34**

32, R = OTs
33, R = Br

All of the n = 2 and 3 telomers isolated except **8** and **11** which gave intricate nmr spectra showed well-defined doublet peaks due to H_a protons with small coupling constants (J_{vic} = 2.0 Hz) (Table III), which were comparable to those of the n = 1 products and hence suggested trans-substituted 1,3-dioxolan-2-one structures, though the complexity of the spectra prevented further assignments of configuration. On the other hand, acid hydrolysis of **7a** and **7b** gave high yields of 5-deoxypentoses **35a** and **35b**, which afforded identical 2,4-dinitrophenylosazones (**36**), indicative of a configurational difference only at C-2. These findings strongly suggest trans,syn,trans and trans,anti,trans configurations or their homologs for **7a** and **7b** and **19a** and **19b** in analogy with **17a,b** and **18a,b**.



35a, b

36, Ar = 2,4-$(NO_2)_2C_6H_3$

Similar considerations regarding the stereochemistry of **9a-c** would assign to these substances three configurations among four isomeric structures **37**, **38**, **39**, and **40**, hydrolysis of which would give glycero-manno-, glycero-gluco-, glycero-gulo, and glycero-idoheptose derivatives.

Table II
Vicinal Coupling Constants for 4,5-Disubstituted 1,3-Dioxolan-2-ones (3, n = 1)[a]

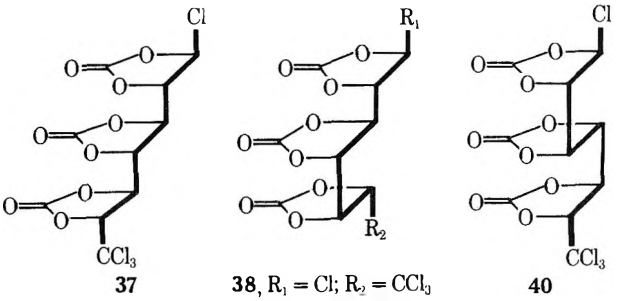
Compd	R	X	J_{vic}, Hz	Solvent
3 (n = 1)	H	Cl	2.0, 5.5	$CDCl_3$
5	CCl_3	Cl	2.0	CCl_4
6	CCl_3	H	6.0, 7.5	$CDCl_3$
12	CCl_3	Br	2.0	$CDCl_3$
13	CH_2Br	Br	1.5	CCl_4
15	$CHBr_2$	Br	2.5	CCl_4
16	CBr_3	Br	2.0	CCl_4
20	OCOPh	Cl	0	$CDCl_3$
21	OCOPh	H	3.0, 5.5	$CDCl_3$
22	OCOPh	Br	0	CCl_4
23	$C(CH_3)_2CN$	Br	3.0	CCl_4

[a] All spectra were obtained at 60 MHz.

Table III
Nmr Data on the n = 2 and 3 Telomers[a]

Compd	X	H_a δ, ppm	H_a J, Hz
7a	Cl	6.50	2.0
7b	Cl	6.65	2.0
9a	Cl	6.60	2.0
9b	Cl	6.65	2.0
9c	Cl	6.65	2.0
17a	Br	6.75	2.0
17b	Br	6.75	2.0
18a	Br	6.65	2.0
18b	Br	6.85	2.0
19a[b]	Br	6.55	2.5
19b[b]	Br	6.60	2.5

[a] Spectra were obtained in CH_3CN at 60 MHz. [b] In $CDCl_3$.



37

38, R_1 = Cl; R_2 = CCl_3
39, R_1 = CCl_3; R_2 = Cl

40

Telomerization of **1** described above, which could be appreciably controlled with regard to the length of carbon chain by simple alteration of the ratios of **1** to telogens, provides an interesting potential for stereoselective synthesis of carbohydrates and polyalcohols.

Experimental Section

All melting points were taken in a Yanaco micro melting point apparatus and are uncorrected. Ir spectra were determined on a Nihon Bunko Model DS-402G spectrophotometer. Nmr spectra were recorded on a Nihon Denshi Model JMN-3H-60 spectrometer using TMS as an internal standard. Determination of molecular weight was performed with a Hitachi Perkin-Elmer Model 115 vapor pressure osmometer. Glc analysis was carried out with a Yanaco G800-T gas chromatograph using a 10% SE-30 (A) or a 15% PEGS (B) column (2 m × 3 mm). Tlc plates coated with silica gel (Camag D-5) were used.

Polyhalogenomethanes. Commercially available halides, carbon tetrachloride, chloroform, bromoform, carbon tetrabromide, and bromotrichloromethane were purified by distillation or recrystallization immediately before use. Bromoform-free methylene bromide was prepared by the literature methods[19] and purified by repeated distillation.

Vinylene Carbonate (1). Ethylene carbonate (88 g, 1 mol) was placed in a 300-ml three-necked flask equipped with a thermometer and gas inlet and exhausting tubes and chlorine gas was bub-

bled through the liquefied carbonate at 100–105°, while BPO (0.1 g) was added at 1.5-hr intervals. After the chlorination for 6 hr, the gas chromatogram (column A at 120°) indicated that the reaction products consisted of dichloroethylene carbonate, ethylene carbonate, and monochloroethylene carbonate in a ratio of 1:1:8. Fractional distillation under reduced pressure gave monochloroethylene carbonate, nmr ($CDCl_3$) δ 6.72 (1 H, d, d, J = 2.0 Hz, J' = 5.5 Hz), 4.88 (1 H, d, d, J = 5.5 Hz, J' = 10 Hz), 4.57 (1 H, d, d, J = 2.0 Hz, J' = 10 Hz), bp 105–110° (9 mm) [lit.[6] bp 106–107° (10–11 mm)], in 70% yield (85 g) in addition to a small amount of 1,2-dichloroethylene carbonate, bp 78–80° (20 mm). According to Newman's method,[6] vinylene carbonate (1) was prepared from monochloroethylene carbonate by action of triethylamine in 45%, bp 73° (30 mm) [lit.[6] bp 73–74° (32 mm)].

General Procedure for Telomerization. A solution of **1** in telogens was placed in a four-necked flask equipped with thermometer, condenser, and tubes for nitrogen gas and warmed under stirring in a slow stream of nitrogen. Radical initiator, BPO or AIBN, was added every *ca.* 4 hr and the reaction was checked by glpc (column A, at 120°). After removal of unchanged telogens and **1** by distillation, the products were separated by column chromatography on silica gel.

Reaction of 1 with Carbon Tetrachloride. A typical run was provided as follows. A mixture of **1** (17.2 g, 0.2 mol) and carbon tetrachloride (216 g, 1.4 mol) was refluxed in the presence of BPO (0.1 g) under a nitrogen atmosphere and the radical initiator (0.1 g) was added every 3 hr. Within 28 hr **1** was completely consumed. After removal of the low-boiling materials, the residue was repeatedly extracted with hot methylene chloride (300 ml). The insoluble products were purified by reprecipitation with acetone and *n*-hexane to give the higher telomers (3.2 g) as a colorless, amorphous powder. The combined extracts and washings were evaporated *in vacuo* to leave the oily residue (32.9 g), which was dissolved in methylene chloride and placed on a column containing silica gel (250 g). The column was eluted with successive solvents of *n*-hexane–benzene, benzene, benzene–methylene chloride, methylene chloride, and methylene chloride–acetone and fractions of 100 ml each were collected. Elution with *n*-hexane–benzene (7:3) and benzene gave **5** (13.7 g) and **20** (0.16 g) as crystalline products, respectively, in addition to a mixture (0.19 g) of **5** and **20**. Further elution with benzene gave **7a** (2.3 g) and **7b** (2.2 g), which were readily crystallized on standing, together with a solid (0.58 g) as a mixture of **7a** and **7b**. The n = 3 telomers **9a** (0.27 g), **9b** (0.25 g), and **9c** (0.27 g) were obtained from the pooled fractions eluted with methylene chloride–acetone (98:2). The fractions eluted with methylene chloride–acetone (9:2) gave a solid **10** (0.18 g) identified as the n = 4 telomer on the basis of elementary analysis. Mixed fractions of the components were rechromatographed on silica gel with the same solvent systems as above and total yields were summarized in Table I. The physical and spectral data of the products follow.

5: mp 53–54° from *n*-hexane as colorless needles; ir (KBr) 1840 cm^{-1}; nmr (CCl_4) δ 6.40 (1 H, d, J = 2 Hz), 5.20 (1 H, d, J = 2 Hz). *Anal.* Calcd for $C_4H_2O_3Cl_4$: C, 20.03; H, 0.84; Cl, 59.12. Found: C, 19.77; H, 1.11; Cl, 59.85.

20: mp 109–110° from *n*-hexane; ir (KBr) 1855 and 1740 cm^{-1}; nmr ($CDCl_3$) δ 8.00 (2 H, m), 7.50 (3 H, m), 6.83 (1 H, s), 6.28 (1 H, s). *Anal.* Calcd for $C_{10}H_7O_5Cl$: C, 49.51; H, 2.91; Cl, 14.61. Found: C, 49.32; H, 3.00; Cl, 15.08.

7a: mp 185–186° from CCl_4; ir (KBr) 1825 and 1805 cm^{-1}; nmr (CH_3CN) δ 6.50 (1 H, d, J = 2 Hz), 5.20 (3 H, m). *Anal.* Calcd for $C_7H_4O_6Cl_4$: C, 25.80; H, 1.24; Cl, 43.51; mol wt, 326. Found: C, 25.94; H, 1.21; Cl, 43.72; mol wt, 345.

7b: mp 159–160° from CCl_4; ir (KBr) 1845, 1830, and 1810 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.35 (3 H, m). *Anal.* Calcd for $C_7H_4O_6Cl_4$: C, 25.80; H, 1.24; Cl, 43.51; mol wt, 326. Found: C, 25.75; H, 1.38; Cl, 43.49; mol wt, 354.

9a: mp 244° dec from CH_2Cl_2; ir (Nujol) 1840 and 1820 cm^{-1}; nmr (CH_3CN) δ 6.60 (1 H, d, J = 2 Hz), 5.15 (5 H, m). *Anal.* Calcd for $C_{10}H_6O_9Cl_4$: C, 29.16; H, 1.47. Found: C, 29.24; H, 1.83.

9b: mp 225–230° dec from CH_2Cl_2; ir (Nujol) 1845, 1825, and 1805 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.25 (5 H, m). *Anal.* Calcd for $C_{10}H_6O_9Cl_4$: C, 29.16; H, 1.47; Cl, 34.18. Found: C, 29.16; H, 1.84; Cl, 34.08.

9c: mp 290° dec from CH_2Cl_2; ir (Nujol) 1830–1810 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.25 (5 H, m). *Anal.* Calcd for $C_{10}H_6O_9Cl_4$: C, 29.16; H, 1.47. Found: C, 29.16; H, 1.64.

10: mp 280° dec from CH_2Cl_2; ir (Nujol) 1845–1810 cm^{-1}. *Anal.* Calcd for $C_{13}H_8O_{12}Cl_4$: C, 31.35; H, 1.62; Cl, 28.47. Found: C, 31.59; H, 1.84; Cl, 29.02.

Reaction of 1 with Chloroform. A solution of **1** (17.2 g, 0.2 mol) in chloroform (600 g, 5 mol) was refluxed in the presence of BPO for 59 hr in a similar way to that described for the reaction with carbon tetrachloride. After removal of the excess telogen, the unreacted **1** (8.9 g) was recovered by distillation. On treatment of the residue with hot methylene chloride, the higher telomers as insoluble products (0.51 g) were obtained in addition to the soluble lower telomers, of which separation was achieved by careful chromatography on silica gel, analogously to the telomers with carbon tetrachloride, and the products **6** (3.4 g), **21** (0.07 g), **8a** (0.83 g), **8b** (0.64 g), and **11** (0.24 g) were obtained in pure forms. Telomers obtained had the following properties.

6: mp 98–99° from *n*-hexane; ir (Nujol) 1810 and 1800 cm^{-1}; nmr ($CDCl_3$) δ 5.25 (1 H, d, d, J = 7.5 Hz, J' = 6.0 Hz), 4.75 (2 H, m). *Anal.* Calcd for $C_4H_3O_3Cl_3$: C, 23.39; H, 1.47; Cl, 51.77. Found: C, 23.66; H, 1.50; Cl, 51.49.

21: mp 112–113° from CCl_4; ir (KBr) 1827, 1808, and 1735 cm^{-1}; nmr ($CDCl_3$) δ 7.97 (2 H, m], 7.55 (3 H, m), 6.95 (1 H, d, d, J = 6 Hz, J' = 3 Hz), 4.7 (2 H, m). *Anal.* Calcd for $C_{10}H_8O_5$: C, 57.69; H, 3.87; Found: C, 56.96; H, 3.98.

8a: mp 185–186° from benzene; ir (Nujol) 1840, 1820, 1800, and 1785 cm^{-1}; nmr (CH_3CN) δ 5.35–4.45 (m). *Anal.* Calcd for $C_7H_5O_6Cl_3$: C, 28.84; H, 1.73; Cl, 36.49. Found: C, 29.38; H, 2.12; Cl, 36.71.

8b: mp 152° from benzene; ir (Nujol) 1840–1784 cm^{-1}; nmr (CH_3CN) δ 5.40–4.30 (m). *Anal.* Calcd for $C_7H_5O_6Cl_3$: C, 28.84; H, 1.73. Found: C, 28.95; H, 1.91.

11: mp 227–235° dec from CH_2Cl_2; ir (Nujol) 1830–1810 cm^{-1}. *Anal.* Calcd for $C_{10}H_7O_9Cl_3$: C, 31.82; H, 1.87. Found: C, 31.50; H, 1.91.

Reaction of 1 with Methylene Bromide. A mixture of **1** (17.2 g, 0.2 mol), methylene bromide (522 g, 3 mol), and BPO was heated at 90° in a similar manner to that described above. After excess methylene bromide was removed *in vacuo*, the distillation gave a recovery of the unchanged **1** (1.6 g). The residue was chromatographed on silica gel to afford the lower telomers in pure forms. The unusual adduct **15** (4.68 g) was first eluted with benzene–*n*-hexane (3:7) and was indistinguishable from the normal n = 1 telomer in the reaction of bromoform as a telogen. Subsequent elution with the same solvent gave the n = 1 adduct **13**, bp 100° (0.1 mm), 4.46 g, as a viscous oil and a crystalline isomer **14** (0.34 g) recrystallized from carbon tetrachloride as colorless needles, mp 68–69°, which showed distinct difference in the nmr spectral data as given below. A small amount of **22** was also isolated. Subsequent fraction eluted out with benzene–chloroform (1:1) gave the unusual n = 2 telomers **18a** (0.22 g) and **18b** (1.07 g) which were recrystallized from carbon tetrachloride to give colorless needles, mp 147–148 and 131–132°, respectively. On the continuing elution the normal n = 2 telomers, **17a** (0.04 g) and **17b** (0.39 g), were obtained, which afforded colorless prisms, mp 170–171 and 126–128°, on recrystallization from chloroform, respectively. Further elution with chloroform–acetone (10:1) gave an amorphous powder (7.09 g), presumably the higher telomers.

When AIBN was used in the place of BPO under the same conditions as described above, the identical products **13** (1.5 g, 5.7%), **15** (1.3 g, 3.8%), **17a** (50 mg, 0.2%), **17b** (101 mg, 0.4%), **18a** (65 mg, 0.3%), and **18b** (180 mg, 0.7%) were isolated in addition to the recovered **1** (8.6 g) and the adduct **23** (138 mg, 0.6%), mp 80–81° (from CCl_4). No formation of **14** was observed. Data on the spectra and combustion analyses were as follows.

13: ir (neat) 1845 and 1825 cm^{-1}; nmr (CCl_4) δ 6.48 (1 H, d, J = 1.5 Hz), 5.20 (1 H, m), 3.65 (2 H, m). *Anal.* Calcd for $C_4H_4O_3Br_2$: C, 18.49; H, 1.55. Found: C, 18.84; H, 1.58.

14: ir (Nujol) 1825 and 1800 cm^{-1}; nmr ($CDCl_3$) δ 5.80 (1 H, d, J = 3.5 Hz), 4.95 (1 H, m), 4.55 (2 H, m). *Anal.* Calcd for $C_4H_4O_3Br_2$: C, 18.49; H, 1.55; Br, 61.50. Found: C, 18.74; H, 1.57; Br, 61.43.

18a: ir (Nujol) 1845, 1820, and 1795 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.90 (1 H, d, J = 3 Hz), 5.00 (3 H, m). *Anal.* Calcd for $C_7H_5O_6Br_3$: C, 19.78; H, 1.19. Found: C, 20.03; H, 1.22.

18b: ir (Nujol) 1840–1815 cm^{-1}; nmr (CH_3CN) δ 6.85 (1 H, d, J = 2 Hz), 6.05 (1 H, d, J = 3 Hz), 5.35 (3 H, m). *Anal.* Calcd for $C_7H_5O_6Br_3$: C, 19.78; H, 1.19. Found: C, 20.36; H, 1.20.

17a: ir (Nujol) 1835 and 1795 cm^{-1}; nmr (CH_3CN) δ 6.75 (1 H, d, J = 2 Hz), 4.60–5.20 (3 H, m), 3.65 (2 H, m). *Anal.* Calcd for $C_7H_6O_6Br_2$: C, 24.30; H, 1.75; Br, 46.20. Found: C, 24.35; H, 1.85; Br, 45.60.

17b: ir (Nujol) 1845 and 1795 cm^{-1}; nmr (CH_3CN) δ 6.75 (1 H, d, J = 2 Hz), 4.60–5.50 (3 H, m), 3.73 (2 H, m). *Anal.* Calcd for $C_7H_6O_6Br_2$: C, 24.30; H, 1.75. Found: C, 24.30; H, 1.85.

23: ir (Nujol) 2280 (vw), 1845, and 1825 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (6 H, s), 4.83 (1 H, d, J = 3.0 Hz), 6.05 (1 H, d, J = 3.0 Hz). *Anal.* Calcd for $C_7H_8NO_3Br$: C, 35.90; H, 3.44; N, 5.97; Br, 33.29. Found: C, 35.91; H, 3.46; N, 5.73; Br, 33.75.

Reaction of 1 with Carbon Tetrabromide. The mixture of 1 (6.88 g, 0.08 mol), carbon tetrabromide (53 g, 0.16 mol), and BPO (0.2 g) was heated at 90° under an atmosphere of nitrogen for 5 hr. Removal of the excess carbon tetrabromide gave a crystalline product (11.68 g) which was recrystallized from *n*-hexane to give **16** as colorless needles: 35% yield; mp 85–86°; ir (KBr) 1883, 1826, and 1790 cm^{-1}; nmr (CCl_4) δ 6.42 (1 H, d, J = 2 Hz), 5.38 (1 H, d, J = 2 Hz). *Anal.* Calcd for $C_4H_2O_3Br_4$: C, 11.49; H, 0.48; mol wt, 418. Found: C, 12.13; H, 0.63; mol wt, 424.

Reaction of 1 with Bromoform. A solution of 1 (9.46 g, 0.11 mol) and bromoform (140 g, 0.55 mol) was heated at 90° under an atmosphere of nitrogen for 18 hr, while BPO (0.1 g) was occasionally added. Excess bromoform was removed by distillation *in vacuo* and a part (15.4 g) of the residue (30.1 g) was chromatographed on silica gel to give a small amount of benzoic acid in addition to the telomers. Separation of the lower telomers was achieved by eluting the column with a mixture of *n*-hexane and benzene in the ratio of 2:1 to 1:2. Elution with benzene–*n*-hexane (1:2) gave **16**, mp 85–86° (3.23 g), which was identical with the n = 1 telomer in the reaction of carbon tetrabromide as a telogen with respects to melting points and ir and nmr spectra. Subsequent elution with the same solvent gave 15 (5.27 g) and a small amount of 22 (0.15 g) which were purified by distillation under diminished pressure and recrystallization, respectively. A mixture of benzene–*n*-hexane (2:1) as an eluting solvent gave the n = 2 unusual telomers **19a** (1.93 g) and **19b** (1.33 g). An amorphous solid (5.0 g) was obtained by elution with more polar solvent (chloroform–methanol, 10:1).

Physical and spectral data of the products isolated were as follows.

15: bp 105° (0.03 mm); ir (neat) 1825 cm^{-1}; nmr (CCl_4) δ 6.55 (1, H, d, J = 2.5 Hz), 5.75 (1 H, d, J = 3.5 Hz), 5.20 (1 H, q, J = 2.5 Hz, J' = 3.5 Hz). *Anal.* Calcd for $C_4H_3O_3Br_3$: C, 14.17; H, 0.89; mol wt, 339. Found: C, 14.70; H, 0.93; mol wt, 342.

22: mp 87–88° from *n*-hexane; ir (Nujol) 1850 and 1730 cm^{-1}; nmr (CCl_4) δ 8.00 (2 H, m), 7.50 (3 H, m), 6.87 (1 H, s), 6.40 (1 H, s). *Anal.* Calcd for $C_{10}H_7O_5Br$: C, 41.83; H, 2.47; mol wt, 287. Found: C, 41.66; H, 2.42; mol wt, 283.

19a: mp 147–148° from CCl_4; ir (KBr) 1840, 1827, and 1790 cm^{-1}; nmr ($CDCl_3$) δ 6.55 (1 H, d, J = 2.5 Hz), 5.25 (1 H, d, J = 2.5 Hz). *Anal.* Calcd for $C_7H_4O_6Br_4$: C, 16.68; H, 0.81; Br, 63.46; mol wt, 504. Found: C, 16.82; H, 0.87; Br, 63.74; mol wt, 504.

19b: mp 131–132° from CCl_4; ir (KBr) 1855, 1820, and 1790 cm^{-1}; nmr ($CDCl_3$) δ 6.60 (1 H. d, J = 2.5 Hz), 5.30 (1 H, J = 2.5 Hz). *Anal.* Calcd for $C_7H_4O_6Br_4$: C, 16.68; H, 0.81; Br, 63.46; mol wt, 504. Found: C, 16.73; H, 0.75; Br, 64.46; mol wt, 515.

Reaction of 1 with Bromotrichloromethane. The mixture of 1 (17.2 g, 0.2 mol), bromotrichloromethane (162 g, 0.82 mol), and BPO was kept at 90° in a slow stream of nitrogen overnight. Evaporation of the solvent *in vacuo* left the pale yellow residue, which was crystallized on trituration with *n*-hexane. Recrystallization from *n*-hexane gave the 1:1 adduct **12** (52.0 g, 91.4%) as colorless prisms: mp 51–52°; ir (Nujol) 1860 cm^{-1}; nmr ($CDCl_3$) δ 6.55 (1 H, d, J = 2 Hz), 5.37 (1 H; d, J = 2 Hz). *Anal.* Calcd for $C_4H_2O_3BrCl_3$: C, 16.87; H, 0.70. Found: C, 17.11; H, 0.68.

Reaction of 1 with 16. The mixture of 1 (1.72 g, 0.02 mol), **16** (21.31 g, 0.05 mol), and BPO was dissolved in benzene (50 ml) and refluxed under nitrogen for 20 hr, whereupon glpc indicated that 1 was almost consumed. The benzene was removed *in vacuo* and the residue was chromatographed on silica gel to give **19a** (2.02 g) and **19b** (1.74 g), which were identical with the isomeric telomers prepared by the reaction of 1 with bromoform described above. The starting material **16** was recovered (17.23 g) and a total yield of **19a** and **19b** was 75% based on the unrecovered **16**.

Benzyl 5-Bromo-5-deoxy-2,3-*O*-isopropylidene-α-D-lyxofuranoside (30). The mixture of benzyl 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-lyxofuranoside (**29**, 7.2 g, 0.2 mol) prepared from D-mannose according to the Brimacombe method,[17] lithium bromide (10.5 g), and hexamethylphosphoric triamide (21.48 g) was refluxed in dry toluene (500 ml) for 2 hr. The mixture, after cooling in an ice bath, was washed with water (80 ml) three times. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give a syrup (10.09 g) from which chromatography on alumina (*n*-hexane–benzene, 1:1) gave the crude product **30** (4.9 g) in addition to **29** (2.97 g). Distillation under diminished pressure gave **30** (3.9 g, 97% based on the unrecovered **29**) as a colorless liquid: bp 130° (0.03 mm); $[\alpha]^{20}D$ +91.6° (c 1.31, MeOH); ir (neat) 1610, 1590, 1385, 740,and 700 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (5 H, s), 5.15 (1 H, s), 4.49 (2 H, q, J = 12 Hz, J' = 24 Hz), 3.52 (2 H, m), 1.52 (3 H, s), 1.36 (3 H, s). *Anal.* Calcd for $C_{15}H_{19}O_4Br$: C, 52.49; H, 5.58; Br, 23.28. Found: C, 52.59; H, 5.59; Br, 22.81.

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (33). The mixture of 1,2-*O*-isopropylidene-5-*O*-p-toluenesulfonyl-α-D-xylofuranose (**32**, 10.0 g, 0.03 mol) prepared from D-xylose by the method of Levin,[18] lithium bromide (16 g), and hexamethylphosphoric triamide (32 g) was refluxed in dry toluene (600 ml) for 2 hr. Analogous treatment of the mixture to that described for **30** gave the crude product, which was purified by recrystallization from *n*-hexane to give **33** (6.87 g, 93%) as colorless needles: mp 93–94°; $[\alpha]^{20}D$ −22.2° (c 1.58, MeOH); ir (Nujol) 3420 and 1385 cm^{-1}; nmr ($CDCl_3$) δ 5.95 (1 H, d, J = 4 Hz), 3.55 (2 H, m), 1.56 (3 H, s), 1.36 (3 H, s). *Anal.* Calcd for $C_8H_{13}O_4Br$: C, 37.96; H, 5.18; Br, 31.57. Found: C, 38.02; H, 5.29; Br, 31.07.

5-Bromo-5-deoxy-D-lyxose (31). A suspension of **30** (686 mg) in 2 *N* sulfuric acid (40 ml) was heated at 100° for 4 hr. A homogeneous solution resulted and then was neutralized with barium carbonate. The precipitate was removed by a centrifugation and the clear supernatant was evaporated *in vacuo* to leave an oil which was washed with five 5-ml portions of benzene and extracted with dry ethanol. The extracts were decolorized with charcoal and evaporated to give **31** (440 mg) as a colorless syrup. This compound gave a single pink spot (R_f 0.69) on the paper chromatogram[20] and a single peak with a retention time of 6 min for the trimethylsilyl derivative by gas chromatographic analysis.[21]

5-Bromo-5-deoxy-D-xylose (34). Compound **33** (506 mg) was treated with 0.3 *N* sulfuric acid (20 ml) at 90° for 2.5 hr. The solution was neutralized with barium carbonate and centrifuged. The supernatant decolorized was evaporated *in vacuo* to leave a syrup. The ethanol solution was centrifuged to remove insoluble materials and evaporated to give a quantitative yield of **34** (420 mg) as a colorless syrup, which gave a pink spot (R_f 0.65) and a peak with a retention time of 7.0 min for the trimethylsilyl ether on paper[20] and gas[21] chromatograms, respectively.

5-Bromo-5-deoxy-DL-lyxose (28a). The mixture of **17a** (215 mg) and 1 *N* sulfuric acid (10 ml) was kept under stirring at 90° for 16 hr. After neutralization with barium carbonate, the reaction mixture was centrifuged in order to remove the insoluble compounds, and treatment of the supernatant with charcoal followed by evaporation *in vacuo* gave a syrup which was dissolved in absolute ethanol and filtered. The filtrate was evaporated to give **28a** as a syrup quantitatively. This product was identical with an authentic sample **31** with respect to R_f value (0.69)[20] and retention time (6.0 min).[21]

5-Bromo-5-deoxy-DL-xylose (28b). A suspension of 17b (346 mg) and 1 *N* sulfuric acid (15 ml) was stirred on heating at 90° for 16 hr. The homogeneous mixture was treated in an analogous manner for **28a** to afford **28b** as a colorless syrup, which was identical with the authentic compound 34 on behavior to paper and gas chromatography (R_f 0.65,[20] retention time 7.0 min[21]).

5-Trichloro-5-deoxypentoses (35a and 35b). Telomers **7a** (0.65 g) and **7b** (0.22 g) were treated with 2 *N* HCl (20 ml) at 80° for 10 hr. Thorough removal of the solvent gave syrupy products **35a** [0.38 g, ir (neat) 3400 and 1780 cm^{-1}] and **35b** [0.14 g, ir (neat) 3400 and 1735 cm^{-1}], respectively, which were positive against the Fehling reagent. 2,4-Dinitrophenylosazones, mp 253–254° (from AcOEt), prepared from **35a** and **35b** were identical with regard to melting point, tlc, and ir spectra (KBr). *Anal.* Calcd for $C_{17}H_{13}N_8O_{10}Cl_3$: N, 18.81; Cl, 17.85. Found: N, 19.16; Cl, 17.93.

Registry No. **1**, 872-36-6; **3** (n = 1, R = H, X = Cl, 3967-54-2; **5**, 39010-29-2; **6**, 42854-66-0; **7a**, 42854-67-1; **7b**, 42854-68-2; **8**, 42854-69-3; **9**, 42854-70-6; **10**, 42854-71-7; **11**, 42854-72-8; **12**, 38987-59-6; **13**, 42854-74-0; **14**, 42854-75-1; **15**, 42854-76-2; **16**, 39189-28-1; **17a**, 42854-78-4; **17b**, 42854-79-5; **18a**, 42854-80-8; **18b**, 42854-81-9; **19a**, 42854-82-0; **19b**, 42854-83-1; **20**, 42854-84-2; **21**, 42854-85-3; **22**, 42854-86-4; **23**, 42854-87-5; **28a**, 36663-35-1; **28b**, 36663-36-2; **29**, 20689-04-7; **30**, 42854-91-1; **31**, 42854-92-2; **32**, 20513-95-5; **33**, 42854-94-4; **34**, 42854-95-5; **35a**, 42854-96-6; **35b**, 42854-97-7; **36**, 42854-98-8; ethylene carbonate, 96-49-1; 1,2-dichloroethylene carbonate, 3967-55-3; carbon tetrachloride, 56-23-5; chloroform, 67-66-3; methylene bromide, 74-83-9; carbon tetrabromide, 558-13-4; bromoform, 75-25-2; bromotrichloromethane, 75-62-7.

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Preparation and Use of Benzhydrylamine Polymers in Peptide Synthesis. II. Syntheses of Thyrotropin Releasing Hormone, Thyrocalcitonin 26–32, and Eledoisin[1]

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Three procedures have been developed for the synthesis of a benzhydrylamine polymer for the preparation of C-terminal amide peptides by solid-phase synthesis. From a common keto intermediate, prepared by acylation of polysterene–1% divinylbenzene with benzoyl chloride, the desired product can be obtained directly by the Leukart reaction, by reduction of an oxime intermediate, or by ammonolysis of the benzhydryl bromide intermediate. The application of this support to the syntheses of the wide range of peptide hormones possessing a C-terminal amide is illustrated by the syntheses of TRH, the C-terminal heptapeptide fragment of thyrocalcitonin, and the endecapeptide, eledoisin.

The original synthesis of a biologically active peptide hormone was that of oxytocin by du Vigneaud.[5] Both oxytocin and antidiuretic hormone are of neurohypophyseal origin and are characterized by the presence of the C-terminal amide group. Recent advances in endocrinology have led to the isolation and sequence analysis of a number of other peptides which are also characterized by the presence of the C-terminal amide group. The presence of the masked carboxyl function may serve to protect these peptides from degradation by exopeptidases with carboxypeptidase specificity. Examples of such physiologically important peptides would be thyrotropin releasing hormone (TRH) and follicle stimulating hormone-luteinizing hormone-releasing hormone (FSH-LH-RH) from the hypothalamus,[6] gastrin,[7] cholecystokinin–pancreozymin and secretin from the gastrointestinal tract,[8] thyrocalcitonin from the thyroid,[9] and substance P, which was also isolated from the hypothalamus.[10]

Concurrent advances in peptide synthesis have seen the development of the solid-phase method.[11] As originally outlined by Merrifield[12] and most commonly employed, the solid-phase method utilizes a polymeric benzyl ester for carboxyl protection. Cleavage of this link to the polymeric support by ammonolysis either with NH_3–CH_3OH or NH_3–dimethylformamide[13-15] or with liquid ammonia[16] to give the desired peptide amide has been reported. Minor difficulties with the side reaction of transesterification or with hindered release of product have been noted.[17-20] A more serious consideration is the problem of protection of side chain carboxyl groups such as those of glutamic or aspartic acid residues. Restriction of side chain protection to the labile *tert*-butyl esters which are resistant to ammonolysis imposes concomitant restraints on the choice of amino group protection to ones even more labile.

In order to circumvent these problems when the desired product possesses a C-terminal amide function, we have conceived of a new type of polymeric carboxyl protecting group.[21] In this case, the covalent link to the support is through an amide bond between the C-terminal amino acid residue and the amine function of the polymer. Selective cleavage of the bond between the amino group and the support allows the peptide to be cleaved with the C-terminal amide function intact. The benzhydrylamine (diphenylmethylamine) support is the first of such supports which allow the selective placement of the amide function. Three methods[22] for the preparation of this sup-

port are compared and the application of this approach is demonstrated by the syntheses of the C-terminal heptapeptide fragment of thyrocalcitonin and of two biologically active peptides, TRH and eledoisin,[23] a hypotensive peptide isolated[24] from the salivary glands of the mollusk *Eledone* and similar in structure to substance P.

Results and Discussion

Three synthetic routes to the benzhydrylamine support are outlined in Figure 1. A common intermediate is the phenyl keto derivative of polystyrene–1%-divinylbenzene copolymer prepared by Friedel–Craft acylation of the polymer with benzoyl chloride. Initial preparation was by reduction of the ketone with sodium borohydride or sodium bis(2-methoxyethoxy)aluminum hydride;[25] treatment of the resulting carbinol with HBr in methylene chloride gave the benzhydryl bromide polymer essentially as outlined by Southard and coworkers.[26] The desired amine derivative was obtained by treatment with ammonia in methylene chloride. The amine content was determined by titration as described by Dorman,[27] by substitution with an amino acid and subsequent hydrolysis and amino acid analysis, or by the procedure of Esko.[28]

A second procedure involved the preparation of an intermediate oxime resin by treatment of the ketone polymer with hydroxylamine hydrochloride in ethanol–pyridine. This intermediate was easily converted to the desired benzhydrylamine support by reduction with sodium bis(2-methoxyethoxy)aluminum hydride in benzene or with lithium aluminum hydride in ether.

The third procedure[29] is direct reductive amination by the Leukart reaction of the ketone polymer with ammonium formate and hydrolysis of the formyl derivative to give the free amine. While this procedure is the most direct, it also has been the most sensitive to reaction conditions. For this reason, the preparation of the intermediate oxime has been favored in our laboratories except when the benzhydryl bromide polymer, which is an intermediate in the first scheme, is also desired.

For any modification of the solid-phase procedure to be useful and to gain acceptance, it should offer advantages over existing techniques and be applicable to the wide range of biologically active peptides. The amide support offers decided advantages over the benzyl ester support in the synthesis of C-terminal amide peptides. It allows the selective placement of the amide function at the C-terminal residue in the presence of a side chain carboxyl group as has been demonstrated in the synthesis of gastrin tetrapeptide.[22] The amide bond to the polymer offers the advantage of being synthesized under identical conditions with those of the subsequent peptide bonds. In other words, a particular amino acid polymer does not have to be prepared under conditions different, *i.e.*, refluxing ethanol, from those used for the subsequent peptide synthesis. The presence of excess chloromethyl groups and the formation of quaternary amine is also eliminated. Another advantage is the elimination of possible side chain alkylation by the chloromethyl group of such amino acids as methionine and histidine, which has presented difficulties in polymer attachment procedures. The stability of the amide linkage compared to the ester bond also offers advantages. Loss of the peptide from the support by ester hydrolysis during synthesis and by intramolecular aminolysis[30] to give the diketopiperazine when the C-terminal amino acid is an *N*-methyl derivative such as proline should be reduced. In addition, removal of the peptide from the support is by hydrogen fluoride treatment, which removes a wide variety of protecting groups and, in most cases, would simplify the synthetic procedure.

The syntheses of TRH[31] and thyrocalcitonin 26–32 demonstrate the usefulness of this approach with C-terminal proline peptides. An overall yield of 36% of TRH based on the original amount of amine on the polymer and a yield on cleavage of 88% of the proline originally bound in the synthesis of the calcitonin heptapeptide indicate that very little, if any, formation of proline diketopiperazine with resulting cleavage from the support had occurred. In the case of TRH, comparison of the synthetic product prepared on the polymer with authentic TRH prepared by classical solution procedures[32] gave identical results on thin layer chromatography in five different solvent systems and the biological activity (Table I) of the two compounds is similar. The successful synthesis of the C-terminal heptapeptide of thyrocalcitonin demonstrates the applicability of solid phase, in general, and this approach, in particular, to that hormone.

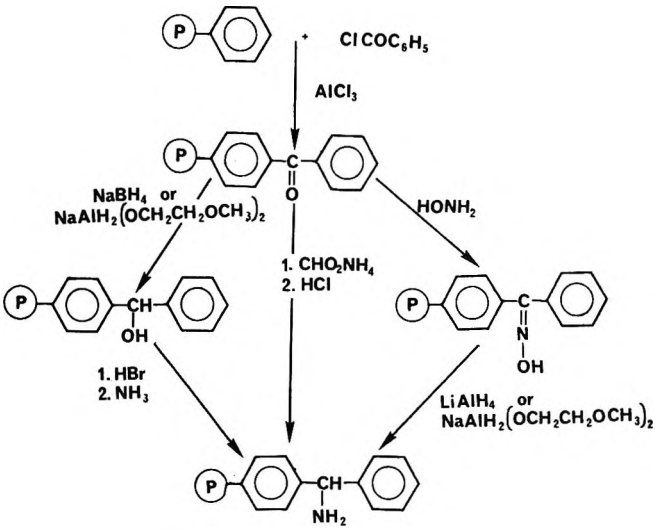

Figure 1. Synthesis of benzhydrylamine polymer by three different procedures.

Table I
Comparison of the Present Synthetic TRH to Standard TRH

	Ng/mouse	CPM
Saline		−24 ± 42
Synthetic TRH	5.0	214 ± 66
	25.0	860 ± 264
Standard TRH	5.0	300 ± 72
	25.0	930 ± 286

The synthesis of the endecapeptide, eledoisin,[33] demonstrates the applicability of this approach to peptides in the eledoisin, physaelamin, and substance P[34] series. The problems of S-alkylation associated with attachment of C-terminal methionine to the normal chloromethyl support are eliminated with the use of the benzhydrylamine support. The chemical properties and biological activity of this peptide were also compared with those of an authentic standard and found to be similar. The synthesis of other C-terminal methionine amide peptides isolated from amphibian skin such as alytesin, bombesin,[35] and ranatensin[36] is also feasible using the benzhydrylamine support. In addition, two toxic peptides, apamin[37] and melittin,[38] have been isolated from bee venom which contain a C-terminal histidine amide and glutamine amide, respectively. The synthesis of analogs of these compounds should also be facilitated by the use of the benzhydrylamine support.

The question of increased stability of the growing peptide chain to deprotection has been examined.[22] These successful syntheses are certainly consistent with this hypothesis, but do little to substantiate it. The use of the benzhydrylamine polymer in the synthesis of longer pep-

tides should confirm this suggestion. In this connection, it is not necessary to require a C-terminal amide function for the use of this support. The use of this support as polymeric side chain protection[11] by the attachment of either the β-carboxyl of aspartic acid to give an asparagine derivative or the γ-carboxyl of glutamic acid to give a glutamine derivative would allow elongation at either the carboxyl or amino end. This concept has been amply illustrated,[39] but not yet utilized for the synthesis of longer peptide chains.

Experimental Section

All solvents used were purified according to standard procedures.[40] Acid hydrolyses of peptide polymer were performed according to Scotchler, *et al.*[41] Acid hydrolysates of free peptides were prepared using 6 *N* HCl (110°, 16 hr) and the amino acid composition was determined with an Auto-Analyzer or a Spinco 120C. Optical rotations were determined with a Perkin-Elmer polarimeter, Model 141, or a Cary 60. Melting points (uncorrected) were determined in capillary tubes in a Tottoli melting point apparatus (manufactured by Buchi). Thin layer chromatography (tlc) was done on silica gel G plates (Analtech) in the following systems: (I) methanol–chloroform (60:30); (II) chloroform–methanol–concentrated ammonia (60:45:20); (III) 1-butanol–ethyl acetate–acetic acid–water (1:1:1:1); (IV) chloroform–methanol–38% acetic acid (60:40:20); (V) 1-butanol–acetic acid–water (4:1:1). The bioassay method for TRH was that described by Bowers and Shally.[42]

Benzoyl–Polystyrene–1% Divinylbenzene (Keto Polymer). Cross-linked polystyrene (1%, 30 g, BioBead SX1) was suspended in 200 ml of nitrobenzene containing 10 ml (86 mmol) of benzoyl chloride. Anhydrous aluminum chloride (16 g, 160 mmol) was added slowly with vigorous stirring. The reaction mixture was then refluxed at 90–100° for 24 hr while stirring. The polymer was filtered and washed as follows: nitrobenzene (3 × 100 ml), ethanol (3 × 100 ml), ethanol–water (1:1) (3 × 100 ml), ethanol (3 × 100 ml), CH_2Cl_2 (3 × 100 ml). After drying *in vacuo*, a strong carbonyl absorption at 1670 cm^{-1} was observed by ir.

Phenylketoximyl–Polystyrene–1% Divinylbenzene (Oxime Polymer). Keto polymer (4 g) was suspended in 40 ml of ethanol and 5 ml of pyridine. Hydroxylamine hydrochloride (5 g, 73 mmol) was added and the mixture was refluxed with stirring for 24 hr. The polymer was filtered and washed as follows: ethanol (3 × 50 ml), ethanol–water (1:1) (3 × 50 ml), ethanol (3 × 50 ml), CH_2Cl_2 (3 × 50 ml). After drying *in vacuo* at 45°, ir (KBr pellet) showed absence of the carbonyl absorption at 1670 cm^{-1}.

Phenylhydroxymethyl–Polystyrene–1% Divinylbenzene (Hydroxy Polymer). To a suspension of keto polymer (12 g) in 100 ml of 2-(2-ethoxy)ethanol was added 3 g (79 mmol) of $NaBH_4$ portionwise while stirring at 55°. After 4 hr, the mixture was filtered and washed as described above (see keto polymer) with the substitution of 2-(2-ethoxyethoxy)ethanol for nitrobenzene. Ir showed the disappearance of the absorption at 1670 cm^{-1} and the appearance of a strong band at 3500 cm^{-1} (OH).

Phenylbromomethyl–Polystyrene–1% Divinylbenzene (Benzhydryl Bromide Polymer). A suspension of hydroxy polymer (11 g) in 250 ml of methylene chloride was cooled to 0° and HBr gas was bubbled into the mixture for 4 hr. The polymer was allowed to warm to room temperature, filtered, and washed with methylene chloride (3 × 40 ml) and ethanol (3 × 40 ml). An aliquot of the polymer was heated in pyridine for 2 hr and the bromine content was determined by Volhard titration to be 0.6 mmol/g.

Phenylaminomethyl–Polystyrene–1% Divinylbenzene (Benzhydrylamine Polymer). A. From the Benzhydryl Bromide Polymer. Phenylbromomethyl polymer (10 g) was suspended in 250 ml of methylene chloride cooled to 0°. Ammonia was bubbled through this mixture for 8 hr. The reaction mixture was stirred for an additional 12 hr at 0°. The polymer was then filtered, washed, and dried as indicated for the bromo polymer and contained 0.6 mmol of NH_2/g as the hydrobromide salt.

B. From the Oxime Polymer. 1. $LiAlH_4$ Reduction. Oxime polymer (4 g) was suspended in 50 ml of ether and added to a slurry of $LiAlH_4$ (3.79 g) in 300 ml of anhydrous ether. The reaction mixture was refluxed for 24 hr. Excess $LiAlH_4$ was treated with ethanol, then 10% concentrated HCl was added to dissolve the reduction by-product. The polymer was filtered, and washed repeatedly with 10% HCl, ethanol (3 × 50 ml), and CH_2Cl_2 (3 × 50 ml). The polymer was washed with 10% triethylamine in $CHCl_3$ to convert the hydrochloride to the free amine. After drying, the ir indicated broad absorption at 3500–3100 cm^{-1} (amine). A test sample was substituted with Boc-Tyr(Bzl) at 0.52 mmol/g.

2. $NaAlH_2(OCH_2CH_2OCH_3)_2$ Reduction. Oxime polymer (3 g, solid) was added to a stirred solution of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (12 mmol) in 50 ml of benzene at 60°. The mixture was allowed to react overnight, when excess reagent was treated with dilute HCl. The polymer was then filtered, and washed with benzene (3 × 50 ml), ethanol (3 × 50 ml), H_2O (3 × 50 ml), ethanol (3 × 50 ml), and CH_2Cl_2 (3 × 50 ml). The polymer was washed with 10% triethylamine in $CHCl_3$ to convert the hydrochloride to the free amine. After drying, the ir and test substitution gave identical results with those prepared above.

C. By Leukart Reduction. Keto polymer (2.0 g) was suspended in 20 ml of nitrobenzene. To a three-necked flask fitted with a thermometer and reflux condenser containing 8.0 ml (0.2 mol) of 97% formic acid was added 13.5 ml (0.2 mol) of 28% NH_4OH. The contents were stirred and heated to distil off water until the temperature of the mixture reached 160°. Then the suspension of keto polymer in nitrobenzene was added. The reaction mixture was stirred for 22 hr at 160–170°. Then 20 ml of concentrated HCl was added to the flask and the mixture was refluxed for 8 hr. The mixture was allowed to stand at room temperature for an additional 10 hr; 50 ml of H_2O was added; and the polymer product was filtered and washed with nitrobenzene (3 × 20 ml), ethanol (3 × 20 ml), ethanol–H_2O (1:1) (3 × 20 ml), ethanol (3 × 20 ml), and CH_2Cl_2 (3 × 20 ml). The polymer was dried *in vacuo* at 45° to give 2.23 g of benzhydrylamine polymer as the hydrochloride. Treatment with 10% triethylamine in $CHCl_3$ gave the free amine. Ir indicated loss of the CO absorption (1720 cm^{-1}) and presence of the NH_2 band. A sample was treated with acetic anhydride and Et_3N and ir showed reappearance of CO absorption. To another sample, Boc-glycine was added by the normal procedure and substitution of 0.41 mmol/g was obtained.

L-Pyroglutamyl-L-histidyl-L-proline Amide (TRH). Benzhydrylamine polymer (2 g, 0.47 mmol of amine/g of resin) prepared by the Leukart method was loaded into the reaction vessel, swollen in CH_2Cl_2 for a few minutes, and washed with CH_2Cl_2 (3 × 20 ml). Further steps of peptide synthesis were as follows. (1) Boc-L-Pro (2.35 mmol) dissolved in CH_2Cl_2 was added to the reaction vessel and mixed with resin for a few minutes. Then an equimolar amount of *N,N*-dicyclohexylcarbodiimide (DCCI) in CH_2Cl_2 was added and the reaction mixture was maintained for 2 hr. (2) Resin was washed with CH_2Cl_2 (3 × 20 ml) and then the Boc protecting group was removed by 20 ml of 50% (v/v) trifluoroacetic acid in CH_2Cl_2 for 1 hr. Deprotection was followed by three washings each (20 ml) with CH_2Cl_2, 95% (v/v) *tert*-butyl alcohol in CH_2Cl_2, and CH_2Cl_2. (3) Resin was washed with $CHCl_3$ (3 × 20 ml) and then was neutralized by 10% (v/v) triethylamine in $CHCl_3$ for 10 min followed by washes with $CHCl_3$ and CH_2Cl_2 (3 × 20 ml). (4) Boc-Im-DNP-L-His (2.35 mmol) was attached to the resin as for Boc-Pro and deprotection and neutralization were carried out the same as in 2 and 3. (5) Neutralization after the second addition was followed by washes (3 × 20 ml) with CH_2Cl_2 and DMF. L-Pyroglutamic acid and DCCI (2.35 mmol) dissolved in DMF were added to the reaction vessel and reaction was maintained for 2 hr. The resin was then washed with DMF (3 × 20 ml). (6) To remove DNP from the histidine imidazole ring, thiophenol (20 molar excess) in DMF was added to the reaction vessel and shaken for 1 hr.[43] The resin was washed with DMF and CH_2Cl_2 three times, respectively. (7) The final product was cleaved from the resin in an apparatus described by Pourchot and Johnson[44] with HF as described below. After the final wash of resin with CH_2Cl_2, it was vacuum dried overnight and then transferred into a polypropylene reaction vessel for HF cleavage. Anisole (3 ml) was added to protect the product. After the reaction and reservoir vessels were placed on the HF line, nitrogen gas was passed through the HF line. HF was distilled into the reservoir vessel (20 ml) and then transferred to the reaction vessel. The reaction mixture was stirred for 1 hr at room temperature. After the reaction was completed, the HF was evaporated from the reaction vessel with a stream of nitrogen gas. The cleavage mixture was dried completely *in vacuo*. The crude product was then extracted with 1% acetic acid and freeze-dried immediately. (8) Purification of the peptide was by means of countercurrent distribution (CCD) in 1-butanol–acetic acid–water (4:1:5) with 200 transfers. After completion of the CCD run, the peptide peaks were located by the Pauly reaction. The peak fraction (K = 0.10) was pooled, the 1-butanol was evaporated *in vacuo*, and the remaining liquid was lyophilized; 121 mg (36% yield) of white powder was obtained. The purified compound was homogenous on tlc in five different systems: R_f I 0.52, R_f II 0.69, R_f III 0.54, R_f IV 0.56, R_f V 0.21. Standard synthetic TRH supplied by Abbott Labs showed identical behavior when compared with the product

on tlc in the above systems. Amino acid ratios were Glu, 1.0; His, 1.1; Pro, 1.0.

Anal. Calcd for $C_{16}H_{22}O_4N_6 \cdot CH_3CO_2H \cdot 1\frac{1}{2}H_2O$: C, 48.40; H, 6.5; N, 18.7. Found: C, 48.16; H, 6.13; N, 18.64.

Boc-L-prolylbenzhydrylamine Polymer. A solution of 0.9 g (4.2 mmol) of Boc-L-proline in 5 ml of methylene chloride was added to 2 g of benzhydrylamine polymer (prepared from oxime polymer) suspended in 5 ml of methylene chloride. After 5 min of shaking, 0.86 g (4.2 mmol) of DCCI in 2 ml of methylene chloride was added and the mixture was shaken for 2 hr. The solvent was filtered off and the resin was washed with methylene chloride (three times). This coupling was repeated using the same amount of Boc-L-proline and of DCCI. The resin was then treated with acetic anhydride to mask the remaining amino groups. After washing with methylene chloride (three times), ethanol (three times), and again with methylene chloride (three times), the resin was dried *in vacuo*, yield 2.14 g. Amino acid analysis of an acid hydrolysate showed the product to contain 0.29 mmol of proline/g coupled to the resin.

Boc-glycyl-L-phenylalanylglycyl-L-prolyl-γ-benzyl-L-glutamyl-*O*-(2,2,2-trifluoro-1-benzyloxycarbonylaminoethyl)-L-threonyl-L-prolylbenzhydrylamine Polymer. The Boc-L-prolylbenzhydrylamine polymer (1.2 g) was placed in the reaction vessel. The following cycle of deprotection, neutralization, and coupling was carried for the introduction of each new residue: (1) three washings with 10-ml portions of glacial acetic acid; (2) cleavage of the Boc group by treatment with 1 *N* HCl in glacial acetic acid (10 ml) for 5 min followed by 10 ml for 30 min; (3) three washings with 10-ml portions of glacial acetic acid; (4) three washings with 10-ml portions of absolute ethanol; (5) three washings with 10-ml portions of methylene chloride; (6) neutralization of the hydrochloride with 1 ml of triethylamine in 9 ml of methylene chloride for 10 min; (7) three washings with 10-ml portions of methylene chloride; (8) addition of 1.04 mmol (300% excess) of the appropriate Boc-amino acid in 8 ml of methylene chloride and mixing for 5 min; (9) addition of 1.04 mmol of DCCI in 2 ml of methylene chloride, followed by a reaction period of 3 hr; (10) three washings with 10-ml portions of methylene chloride; (11) three washings with 10-ml portions of absolute ethanol.

The polypeptide resin was washed three times with 10-ml portions of methylene chloride followed by three washings with 10-ml portions of absolute ethanol and dried *in vacuo*, yield 1.57 g (0.27 mmol of peptide/g).

Glycyl-L-phenylalanylglycyl-L-prolyl-L-glutamyl-L-threonyl-L-prolinamide (Thyrocalcitonin 26–32). The protected peptide resin (1.57 g) was treated with hydrogen fluoride (10 ml) and excess anisole (1 ml) and stirred at 0° for 2 hr. The reaction mixture was then brought to room temperature and the hydrogen fluoride was allowed to evaporate. The crude peptide was separated from the resin by repeated washing of the resin with trifluoroacetic acid. After evaporation of the combined washings under reduced pressure, the residue was treated with dry ether and filtered. The precipitate was washed three times with ether and dried *in vacuo*. The yield of the crude heptapeptide amide from the cleavage was 214 mg (88% on the amount of proline originally bound to the resin).

The crude heptapeptide amide was dissolved in 15 ml of 1 *M* acetic acid and applied to a Sephadex LH-20 column (4.5 × 40 cm) which had been equilibrated with 1 *M* acetic acid. The column was eluted with the same solvent and 90 fractions of 7.5 ml each were collected. The maximum of the desired peptide was in tube 44, as shown by measurement of ninhydrin color values of the various fractions. The fractions corresponding to this maximum were pooled and lyophilized to give 99 mg of white powder.

This lyophilized material was subjected again to gel filtration under the same conditions. The shape of the distribution curve suggested that the peptide was homogeneous. The fractions corresponding to the maximum were combined and lyophilized, yield 89 mg (36% overall yield).

In paper chromatography (Whatman No. 4) in the solvent system 1-butanol–acetic acid–water (4:1:1), the peptide showed a single spot (R_f 0.32) visible with ninhydrin. In paper electrophoresis at pH 1.9 in the solvent system formic acid–acetic acid–water (15:10:75), it moved as a spot toward the cathode with migration relative to histidine of 0.23 and relative to leucine of 0.37, $[\alpha]^{20}n$ −0.75° (c 1, acetic acid). Amino acid analysis gave Gly, 1.97; Phe, 1.00; Pro, 2.02; Glu, 1.00; Thr, 0.93.

Boc-L-methionylbenzhydrylamine Polymer. Benzhydrylamine polymer (2 g) was treated with Boc-L-methionine (1.04 g, 4.2 mmol) and DCCI (0.86 g, 4.2 mmol) as described for Boc-L-prolyl benzhydrylamine polymer. Amino acid analysis of an acid hydrolysate showed the product to contain 0.26 mmol of methionine/g of coupled resin.

Boc-L-pyroglutamyl-L-prolyl-*O*-(2,2,2-trifluoro-1-benzyloxycarbonylaminoethyl)-L-seryl-*N*$^{\epsilon}$-benzyloxycarbonyl-L-lysyl-β-benzyl-L-aspartyl-L-alanyl-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionylbenzhydrylamine Polymer. The Boc-L-methionylbenzhydrylamine polymer (1.5 g) was placed in the reaction vessel. The same cycle described for the the synthesis of C-terminal heptapeptide of thyrocalcitonin was carried out for the introduction of each new residue.

The fully protected endecapeptide resin weight was 2.12 g (90% based on the amount of methionine originally bound to the resin).

L-Pyroglutamyl-L-prolyl-L-seryl-L-lysyl-L-aspartyl-L-alanyl-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine Amide (Eledoisin). Treatment of protected peptide resin (2.12 g) with hydrogen fluoride and extraction of the reaction mixture with trifluoroacetic acid as previously described gave 415 mg of crude peptide.

Crude peptide (200 mg) was purified by passing through a Sephadex LH-20 column (3 × 100 cm) which had been equilibrated with 1 *M* acetic acid. The column was eluted with the same solvent and 120 fractions of 6 ml each were collected. Eledoisin appeared to be in fractions 44–52, which were pooled and lyophilized. A further purification under the same conditions gave 55 mg of homogeneous product (18.5% yield), mp 230° dec, $[\alpha]^{22}D$ −48° (c 2, glacial acetic acid).

In paper chromatography (Whatman No. 4) in the solvent system 1-butanol–acetic acid–water (4:1:5), the peptide showed a single spot (R_f 0.4). In paper electrophoresis at pH 1.9 in the solvent system formic acid–acetic acid–water (15:10:75), it moved as a spot toward the cathode with migration relative to histidine of 0.34 and relative to leucine of 0.50.

Amino acid analysis gave Lys, 0.88; Asp, 0.93; Ser, 0.97; Glu, 0.98; Pro, 1.04; Gly, 1.00; Ala, 1.06; Met, 0.99; Ileu, 1.01; Leu, 1.08; Phe, 1.03.

The synthetic product showed the same activity as natural eledoisin when tested in rabbit blood pressure and guinea pig ileum assays.

Registry No. TRH, 24305-27-9; thyrocalcitonin 26–32, 42790-39-6; eledoisin, 69-25-0.

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Reactions Catalyzed by $Co_2(CO)_8$. Selective Deuterium Incorporation into Some Polycyclic Hydrocarbons

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Anthracene and anthraquinone can be converted to 9,9,10,10-tetradeuterio-9,10-dihydroanthracene in the presence of excess D_2 (or D_2O), CO, and catalytic amounts of $Co_2(CO)_8$. Pyrene also undergoes reduction and H-D exchange at the 4 and 5 positions; phenanthrene fails to react. When 1-octene is treated with CO and $Co_2(CO)_8$ in the presence of the tetradeuteriodihydroanthracene, as a deuterium source, C_9 aldehydes, randomly substituted with deuterium, result.

Both heterogeneous and homogeneous metal catalytic systems effect random hydrogen-deuterium exchange between water (or D_2O) and alkylbenzenes, benzene, and polycyclic aromatics.[1-7] Garnett and coworkers have extensively studied the homogeneous aqueous system for H-D exchange based on $PtCl_4^{2-}$.[2-7] Recently, a homogeneously catalyzed exchange between deuterium gas and an aromatic compound has been reported.[8]

We wish to report that $Co_2(CO)_8$ will catalyze selective hydrogen-deuterium addition and exchange involving anthracene (or 9,10-dihydroanthracene) and anthraquinone with either deuterium gas or D_2O. To our knowledge, this is the first example of an exchange catalyst that has high selectivity for specific hydrogens and that can use either D_2 or D_2O as its isotope source.

When anthracene is treated with synthesis gas and catalytic amounts of $Co_2(CO)_8$,[9] quantitative yields of 9,10-dihydroanthracene are obtained.[10] The reduction has now been done using D_2 or D_2O, CO, and $Co_2(CO)_8$. We find, accompanying the reduction of anthracene, exchange at the 9 and 10 positions takes place, resulting in formation of 9,9,10,10-tetradeuterio-9,10-dihydroanthracene (I). The same product is formed when anthraquinone is treated with D_2 or D_2O in the presence of CO and $Co_2(CO)_8$. This reaction, using successive equilibrations, offers a synthetic route to I. By chemical, rather than catalytic, dehydrogenation of I, it should be possible to prepare anthracene isotopically labeled on the 9 and 10 carbon atoms (V).

Experimental Section

Mass spectral analysis was done on a Consolidated Electrodynamics Corp. Model 110-B high-resolution instrument.[11] The inlet system was operated at 160°[12] and 10^{-6} Torr. It has been shown that deuteration does not change the sensitivity of the component in the mass spectrometer.[13] The data therefore are shown as a per cent of total ionization, which assumes equal sensitivities for all components.

Nmr spectra were run on a Varian A-60 spectrometer with chemical shifts reported in parts per million from TMS (δ).

Reduction-Exchange of Anthracene Using $Co_2(CO)_8$, and D_2. To a 200-ml rocking autoclave were added 0.2 g of $Co_2(CO)_8$, 2 g of anthracene, and 30 ml of benzene. The system was flushed several times with CO and pressured with a mixture of D_2 (98 atom %) and CO (see Table I). Upon completion of the reaction, the mixture was refluxed in air for 8 hr to decompose the $Co_2(CO)_8$ and filtered, and the solvent was removed. The product was recrystallized from ethanol.

Reduction-Exchange of Anthracene Using $Co_2(CO)_8$ and D_2O. To a 200-ml rocking autoclave were added 0.2 g of $Co_2(CO)_8$, 2 g of anthracene, 30 ml of dioxane, and 5 ml of D_2O. The system was flushed several times with CO and pressured to 3000 psi with CO. The work-up of the reaction product was the same as above.

Table I
Hydrogen–Deuterium Exchange Products

Substrate, g	Anthracene, 2.0	Anthracene, 2.0	Anthracene, 2.0	Anthracene, 2.0	Anthracene, 2.0	9,10-Dihydroanthracene, 2.0	Phenanthrene, 2.0	9,10-Dihydrophenanthrene, 1.0	Anthraquinone, 10	Pyrene, 2.3
Solvent, 30 ml	Benzene	Benzene	Benzene	Dioxane (5 ml) D_2O	Dioxane	Benzene	Benzene	Benzene	Benzene (250 ml)	Benzene
Reaction temp, °C	200	160	200	175	175	135	160	180	250	175
Time at reaction temp, hr	5	13	11.2	6	6	6	5	6	6	6
Starting gas[a] compn, psi	500 D_2 700 CO	1000 D_2 1000 CO	1300 D_2 1350 CO	3000 CO	1400 D_2 1400 CO	1200 D_2 1200 CO	900 D_2 1100 CO	600 D_2 800 CO	800 D_2 1200 CO	800 D_2 1100 CO	500 D_2 700 CO
Mass spectral analysis, %											
m/e 178	1.0	0.7		2.3	0.1	1.1	3.8	96.7	3.0		*m/e* 202	39.0
179	0.5	1.6	0.3	0.6	0.6	5.1	5.6	0.1	1.4	0.4	203	31.0
180	2.4	4.4	1.6	2.2	2.3	14.1	25.0	1.4	93.7	4.2	204	20.0
181	3.3	13.3	1.0	1.0	3.5	28.1	19.9		0.9	1.0	205	5.0
182	12.9	26.7	4.3	6.6	19.2	37.5	23.6	1.0	1.0	7.5	206	3.0
183	29.0	35.6	21.5	28.5	36.5	12.2	16.6	0.4		19.8	207	1.3
184	50.9	17.7	71.3	57.4	37.8	1.7	5.5	0.4		66.0	208	0.3
% of isotopic equilibrium[b]	84	64	93	88	79	40	39					

[a] CO necessary to keep $Co_2(CO)_8$ from decomposing. [b] Equilibrium concentration of deuterium was between 93 and 97% for all experiments, depending on deuterium source and available protons from substrate.

Conversion of Anthraquinone to Deuterated Dihydroanthracenes. To a 500-ml stainless steel rocking autoclave were added 10 g of anthraquinone, 0.5 g of $Co_2(CO)_8$, and 250 ml of benzene. The system was flushed with CO and pressured with 800 psi of D_2 (D_2O may also be used as the deuterium source) and 1100 psi of CO. Upon completion of the reaction, the mixture was refluxed for 8 hr to decompose the $Co_2(CO)_8$ and filtered, and the D_2O was removed. The resulting solution was evaporated to dryness and the product was recrystallized from ethanol.

Results and Discussion

When anthracene is treated with $Co_2(CO)_8$, CO, and D_2 in benzene or with $Co_2(CO)_8$, CO, and D_2O in dioxane, selective reduction and exchange at the 9 and 10 positions occur (as shown by vpc, uv, and nmr analysis), giving varying amounts of compounds I–VII (Scheme I; not all possible equilibria are shown). Table I shows the conditions under which the reactions were run and the various hydroaromatic products formed as determined by mass spectral analysis. The reaction goes in either benzene or dioxane solvent and in dioxane either D_2 or D_2O can be used as the isotope source, both giving good yields of I–III.

Scheme I
The Reductive Hydrogen–Deuterium Exchange of Anthracene Showing Some of the Possible Equilibrium Reactions

In each experiment shown in Table I, the product distribution makes it clear that anthracene is readily reduced to II (*m/e* 182) followed by H–D exchange to give III and I. The exchange may be directly on II to give III and then I, or it may involve successive dehydrogenation–hydrogenation, such as II → IV → III. Very little unre-

duced anthracene is observed by either uv or vpc; the small peaks in the mass spectra at m/e 178–180 are believed due largely to dehydrogenation of I–III in the mass spectrometer[12] and not exchange of the protons on anthracene to form IV and V. Some of the 180 peak is due to VII formed by back-equilibration with H_2.

The distribution of products I–III as a function of temperature and time is further indication that reduction is faster than exchange and that an equilibrium amount of I is formed only after considerable time at higher temperature.

The selective nature of the reduction–exchange reaction can be evaluated from the mass spectral data. No significant peaks in the mass spectra, above m/e 184 (I), have been observed. If exchange of ring protons 1–8 did occur, incorporation of more than four deuterium atoms would be expected and peaks above m/e 184 would be observed. The specific selectivity for positions 9 and 10 in anthracene is further substantiated by the nmr spectra. The nmr spectra of 9,10-dihydroanthracene has sharp singlets at 3.87 and 7.18 ppm, corresponding to the 9,10 protons and protons 1–8, respectively. The nmr spectra of the mixtures of deuterated products were run and compared with the spectrum of pure 9,10-dihydroanthracene (using solutions of equal weight concentration). The peak at 7.2 ppm is a sharp singlet of nearly equal intensity in each sample. The peak at 3.8 ppm, however, is broadened and considerably reduced in intensity in the deuterated samples; the broadening is due to H–D coupling. The fact that no loss in intensity is observed in the peaks at 7.2 ppm for the deuterated samples further demonstrates the lack of exchange of protons 1–8.

In order to test the hypothesis that reduction is the faster of the two reactions and that exchange occurs predominantly in the dihydro species, II, the exchange reaction was carried out using 9,10-dihydroanthracene as the starting substrate. Exchange of the 9 and 10 protons does occur, resulting in a distribution of deuterated products (Table I). Equilibration is slower when starting with the dihydro compound, since all four protons must exchange.

When anthraquinone is treated with D_2 in benzene or D_2O in dioxane, in the presence of $Co_2(CO)_8$ and CO, it is readily converted to the deuterated dihydroanthracenes, I–III. A product from an anthraquinone reduction containing 66% I and 20% III was treated for 5 hr, in benzene, with CO and an equimolar amount of 1-octene in the presence of $Co_2(CO)_8$ at 160° to determine if dihydroanthracene would act as a hydrogen source in the oxo reaction. The olefin was readily converted to the C_9 aldehydes and the dihydroanthracenes were converted to a mixture of 50% anthracene, 40% 9-deuterioanthracene, and 10% 9,10-dideuterioanthracene.

Mass spectral analysis of the aldehydes indicates considerable deuterium substitution throughout the molecule, thus accounting for the low deuterium content of the anthracene. Deuterium substitution in the aldehyde probably results from isomerization of the olefin, involving exchange with $DCo(CO)_4$, followed by hydroformylation.

Phenanthrene, which is relatively inert to $Co_2(CO)_8$-catalyzed hydrogenation,[10,14] 9,10-dihydrophenanthrene, and diphenylmethane were also used as substrates for the reduction–exchange. No reaction occurred with diphenylmethane and little, if any, reaction occurred with phenanthrene and 9,10-dihydrophenanthrene (Table I). The reduction of pyrene at the 4 and 5 position has been reported,[10] and we have found that exchange at these positions does occur. No tetrahydropyrene is formed and no exchange other than at the 4 and 5 positions is observed. Exchange seems to occur only at positions which undergo reduction, and where some sort of activation is present, *i.e.*, an aromatic ring α to the point of exchange, in both reduced and unreduced compounds.

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Registry No. Anthracene, 120-12-7; 9,10-dihydroanthracene, 613-31-0; phenanthrene, 85-01-8; 9,10-dihydrophenanthrene, 776-35-2; anthraquinone, 84-65-1; pyrene, 129-00-0; $Co_2(CO)_8$, 10210-68-1.

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Reactions of *pentahapto*-Cyclohexadienyliron Tricarbonyl Cations with Enamines

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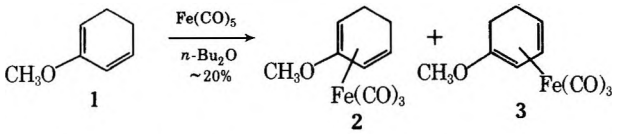
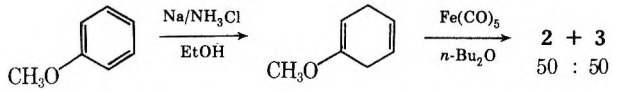
Complexes of the type $CH_3OC_6H_6Fe(CO)_3^+BF_4^-$ were reinvestigated. A previously predicted isomer was isolated and identified as **6**. The structure of an isomer of $CH_3OC_6H_5CH_3Fe(CO)_3^+BF_4^-$ (**8**) was reassigned on the basis of new spectral, chemical, and X-ray evidence. In addition isomers of the salts were shown to react with enamines in ~65% yield.

(*pentahapto*-Pentadienyl)(tricarbonyl)iron cations have been studied by a number of investigators.[3-9] The (*pentahapto*-methoxycyclohexadienyl)(tricarbonyl)iron cations have been examined in their reactions with nucleophiles[10] and have been shown to yield substituted anisole compounds on the removal of the iron tricarbonyl group.[3] In addition to extending the scope of the reaction with nucleophiles to enamines, we have oxidatively removed the iron tricarbonyl group with hydrolysis. This seems to be a convenient method of synthesizing cyclohexenones substituted in the 4 position. Such compounds have structural similarities to agents useful in herbicides.[11]

Treatment of 2-methoxycyclohexa-1,3-diene (**1**) with $Fe(CO)_5$ in refluxing di-*n*-butyl ether[5,12] gave a 70:30 mixture of complexes **2** and **3**. Treatment of 1-methoxycyclohexa-1,4-diene with $Fe(CO)_5$ in refluxing di-*n*-butyl ether gave a 50:50 mixture of **2** and **3**. The pure complex **2**

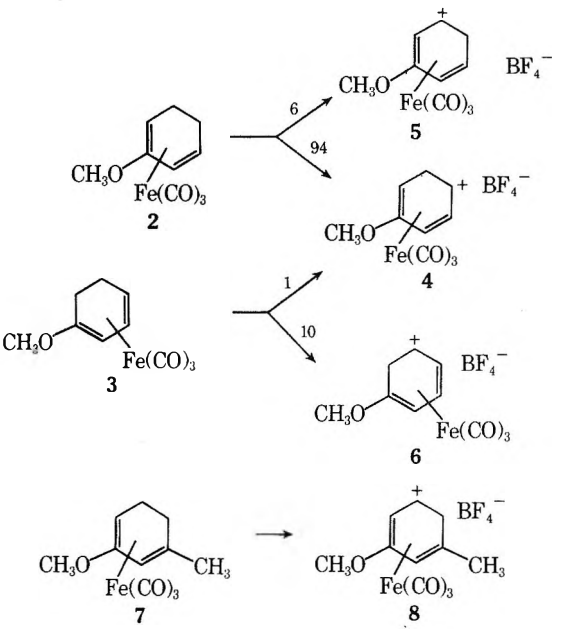


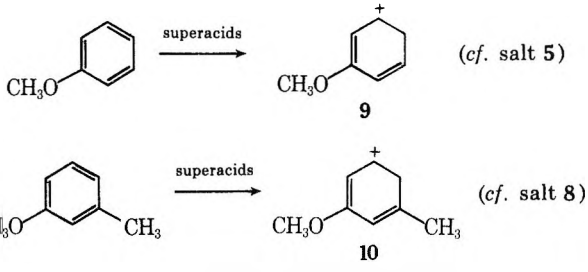


and the pure complex **3** each gave a 70:30 mixture of **2** and **3** on heating in refluxing di-*n*-butyl ether. This is despite the report that **2** and **3** do not isomerize upon heating in refluxing benzene or upon irradiation.[3]

Treatment with triphenylmethyl fluoroborate converts complex **2** to a 94:6 mixture of the salts (1,2,3,4,5-*pentahapto*-2-methoxycyclohexadienyl)(tricarbonyl)(iron fluoroborate (**4**) and (1,2,3,4,5-*pentahapto*-3-methoxycyclohexadienyl)(tricarbonyl)iron fluoroborate (**5**). The corresponding reaction of **3** gave a 10:1 mixture of the salts (1,2,3,4,5-*pentahapto*-1-methoxycyclohexadienyl)(tricarbonyl)iron fluoroborate (**6**) and **4**. Treatment of 3-methoxy-1-methylcyclohexa-1,3-dieneiron tricarbonyl (**7**) with triphenylmethyl fluoroborate gave exclusively (1,2,3,4,5-*pentahapto*-3-methoxy-1-methylcyclohexadienyl)(tricarbonyl)iron fluoroborate (**8**).

The directing effect of the methyl group on hydride abstraction from the complex **7** is not clearly understood but may be the result of steric interactions. However, all the abstractions above are likely to be under kinetic control. It is interesting to note that the cations of the salts **4**, **5**, **6**, and **8** can be viewed as protonated anisoles complexed with iron tricarbonyl. The pmr spectra of protonated anisoles have recently appeared.[13] The protonated species presumably form under thermodynamic control and give the predicted products when C-protonation occurs.





The pmr spectra of the salts of **4**, **5**, **6**, **8**, **9**, and **10** are shown in Table I. Salt **4** has been reported previously with its pmr spectrum.[3] Birch and coworkers found that **4** reacts with cyanide, and the product was transformed to

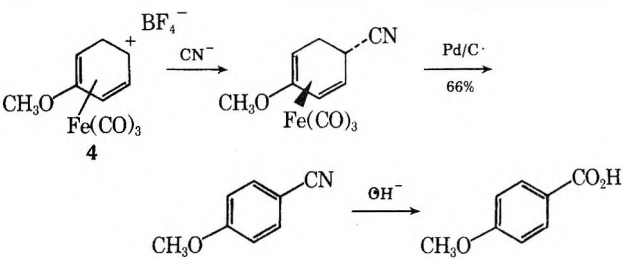
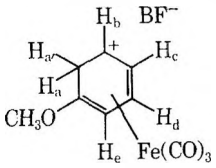
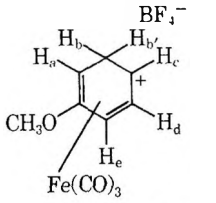
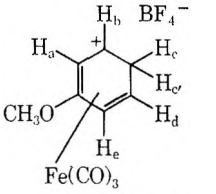
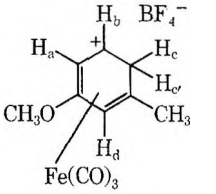
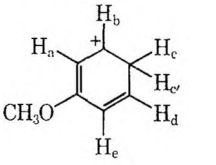
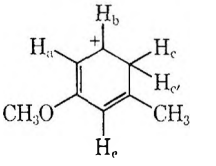
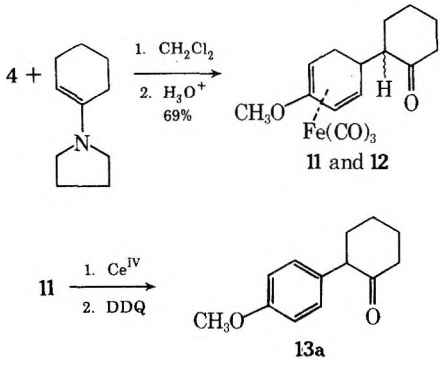


Table I[a]

Compd	Structure	H_a	H_b	H_c	H_d	H_e	$H_{x'}$	OCH_3
6 R = H x = a		3.47 (dd) J = 18 J = 6	4.37 (t) J = 6 J = 6	6.44 (t) J = 6 J = 6	7.23 (t) J = 6 J = 6	4.92 (d) J = 6	2.90 (d) J = 18	4.05 (s)
4 R = H x = b		4.25 (d) J = 6	3.17 (m) J = 16 J = 7 J = 6	4.49 (dd) J = 7 J = 6	6.23 (t) J = 6 J = 6	7.34 (d) J = 6	2.16 (d) J = 6	3.94 (s)
5 R = H x = c		6.46 (d) J = 7	4.33 (r) J = 7 J = 7	3.10 (m) J = 16 J = 7 J = 7	4.33 (d) J = 7 J = 7	6.46 (d) J = 7	2.07 (d) J = 16	4.37 (s)
8 R = CH_3 x = c		6.39 (d) J = 8	4.10 (dd) J = 8 J = 6	3.03 (dd) J = 16 J = 6	1.97 (s)	6.23 (s)	2.28 (d) J = 16	4.25 (s)
9 R = H x = c		7.8 (d) J = 10	9.0 (d) J = 10	4.5 (s)	8.6 (d) J = 10	7.5 (d) J = 10	4.5 (s)	4.80 (s)
10 R = CH_3 x = c		7.42 (d) J = 10	8.5 (d) J = 10	4.3 (s)	2.83 (s)	7.50 (s)	4.3 (s)	4.69 (s)

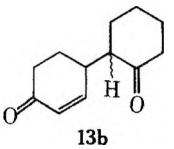
[a] The pmr spectra of the iron complexes were taken in CD_3COCD_3. The chemical shifts are given in δ relative to internal TMS. The coupling constants (J) are in hertz. Values for the uncomplexed ions are from ref 13 and were taken in superacids.

known compounds. We have found that **4** reacts with 1-pyrrolidinocyclohexene to give ketones **11** and **12** after hydrolysis. Pure **11** was converted to the known aromatic compound **13a**.[14] Oxidation of the ketone **12** with Jones



13a

reagent or with ferrous perchlorate gave a new compound with a saturated and unsaturated ketone as well as two vinyl hydrogens. The new compound was assigned the diketone structure **13b**.



13b

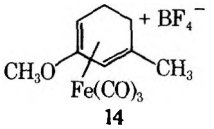
The C_s symmetry of the cation in the salt **5** was evident in the pmr pattern. This evidence for the structure of the salt **5** was supplemented by the formation of **5** from the diene complex **2** and the absence of the salt **5** in the hydride abstraction products of the diene complex **3**. The structure of the salt **6** is consistent with its formation from the diene complex **3** as is the absence of **6** in the hydride abstraction products of the diene complex **2**. The resonances of the salt **6** at δ 4.37 (proton b) and 6.44 (proton c) were found to be coupled. Resonances at δ 4.92 (proton e) and 7.23 (proton d) were also coupled, justifying the assignments given in Table I.

The structure **14** was previously assigned to the salt **8** on the basis of an unreported pmr spectrum.[3] However, our pmr spectrum of **8** is very similar to the spectrum of the salt **5**. Additional new evidence for the identity of the salt **8** was obtained by treating **8** with the pyrrolidine ena-

Table II
Bond Distances and Angles and Their Standard Deviations Involving the Heavier Atoms[a]

Bond	Length, Å	Bond	Angle, deg	Bond	Angle, deg
C(2)–C(1)	1.424 (5)	C(2)–C(1)–C(6)	118.3 (3)	C(2)–C(1)–Fe(23)	67.8 (2)
C(6)–C(1)	1.510 (5)	C(6)–C(1)–C(16)	114.0 (3)	C(6)–C(1)–Fe(23)	109.5 (2)
C(16)–C(1)	1.512 (6)	C(16)–C(1)–Fe(23)	121.0 (2)	C(16)–C(1)–C(2)	118.5 (3)
Fe(23)–C(1)	2.116 (3)				
C(3)–C(2)	1.405 (5)	C(3)–C(2)–C(1)	115.0 (3)	C(3)–C(2)–Fe(23)	70.8 (2)
Fe(23)–C(2)	2.057 (3)	Fe(23)–C(2)–C(1)	72.3 (2)		
C(4)–C(3)	1.421 (4)	C(4)–C(3)–C(2)	115.0 (3)	C(4)–C(3)–O(4)	118.6 (3)
O(14)–C(3)	1.364 (4)	O(14)–C(3)–C(2)	126.3 (3)	O(14)–C(3)–Fe(23)	126.2 (2)
Fe(23)–C(3)	2.074 (3)	Fe(23)–C(3)–C(2)	69.5 (2)	Fe(23)–C(3)–C(4)	71.1 (2)
C(5)–C(4)	1.514 (4)	C(5)–C(4)–C(3)	120.5 (2)	C(5)–C(4)–Fe(23)	110.3 (2)
Fe(23)–C(4)	2.100 (3)	Fe(23)–C(4)–C(3)	69.1 (2)		
C(6)–C(5)	1.540 (5)	C(6)–C(5)–C(4)	108.8 (3)	C(1)–C(6)–C(5)	112.4 (2)
C(7)–C(5)	1.534 (4)	C(7)–C(5)–C(4)	112.9 (2)	C(7)–C(5)–C(6)	112.8 (2)
C(8)–C(7)	1.534 (5)	C(8)–C(7)–C(5)	114.8 (3)	C(8)–C(7)–C(12)	109.8 (3)
C(12)–C(7)	1.519 (5)	C(12)–C(7)–C(5)	113.0 (2)		
C(9)–C(8)	1.524 (5)	C(9)–C(8)–C(7)	111.8 (3)		
C(10)–C(9)	1.511 (6)	C(10)–C(9)–C(8)	110.1 (3)		
C(11)–C(10)	1.519 (6)	C(11)–C(10)–C(9)	111.6 (3)		
C(12)–C(11)	1.500 (6)	C(12)–C(11)–C(10)	113.9 (3)	C(7)–C(12)–C(11)	115.7 (3)
O(13)–C(12)	1.198 (4)	O(13)–C(12)–C(7)	122.4 (3)	O(13)–C(12)–C(11)	121.9 (3)
O(14)–C(15)	1.426 (5)	C(3)–O(14)–C(15)	116.8 (3)		
C(17)–O(18)	1.142 (5)	Fe(23)–C(17)–O(18)	179.3 (3)		
C(17)–Fe(23)	1.788 (4)	C(17)–Fe(23)–C(1)	96.5 (1)	C(17)–Fe(23)–C(2)	93.3 (2)
		C(17)–Fe(23)–C(3)	121.4 (1)	C(17)–Fe(23)–C(4)	161.2 (1)
C(19)–O(20)	1.142 (4)	Fe(23)–C(19)–O(20)	177.3 (3)		
C(19)–Fe(23)	1.774 (3)	C(19)–Fe(23)–C(1)	88.6 (1)	C(19)–Fe(23)–C(2)	128.1 (1)
		C(19)–Fe(23)–C(3)	134.0 (1)	C(19)–Fe(23)–C(4)	97.1 (1)
C(21)–O(22)	1.142 (4)	Fe(23)–C(21)–O(22)	175.9 (3)		
C(21)–Fe(23)	1.780 (3)	C(21)–Fe(23)–C(1)	163.0 (1)	C(21)–Fe(23)–C(2)	126.5 (1)
		C(21)–Fe(23)–C(3)	93.8 (1)	C(21)–Fe(23)–C(4)	89.2 (1)
		C(1)–Fe(23)–C(2)	39.8 (1)	C(1)–Fe(23)–C(3)	69.4 (1)
		C(1)–Fe(23)–C(4)	76.4 (1)	C(2)–Fe(23)–C(3)	39.8 (1)
		C(2)–Fe(23)–C(4)	69.9 (1)	C(3)–Fe(23)–C(4)	39.8 (1)
		C(17)–Fe(23)–C(19)	100.2 (2)	C(17)–Fe(23)–C(21)	94.4 (1)
		C(19)–Fe(23)–C(21)			

[a] The values for the standard deviations in bond lengths have been multiplied by 10^3. The values for the standard deviations in bond angles have been multiplied by 10.



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mine of cyclohexanone. Subsequent hydrolysis of the product gave ketone **15**. Ketone **15** was characterized by single-crystal X-ray structure analysis. The crystal structure was solved by the heavy atom method. Refinement to an *R* factor of 5.7% was obtained by the method of least squares on 1860 nonzero structure factors. The intensity data were collected on a diffractometer (Co Kα radiation).

A view of the ketone **15**, drawn by a Calcomp plotter controlled by an IBM 370/155 computer using the ORTEP program,[15] is shown in Figure 1. The bond distances and angles involving the heavier atoms, along with their respective standard deviations, are listed in Table II. The standard deviations in atomic coordinates (Tables III and IV) correspond to positional uncertainties of approximately 0.004 Å for carbon atoms, 0.003 Å for oxygen atoms, 0.0006 Å for the iron atom, and 0.04 Å for hydrogen atoms. Distances and angles involving hydrogen atoms are listed in Table V.

The cyclohexadiene ring is distorted in the complex. Carbons 1–4 are nearly planar and the methoxy oxygen (O-14) does not deviate much from the best plane through the four carbon atoms. Carbons 5 and 6, the bridging carbon atoms, are bent substantially away from the iron atom, and the methyl group (C-16) is bent toward the metal atom (see Table VI). Also the bond between C-2 and C-3, a formal single bond, is shorter than the formal

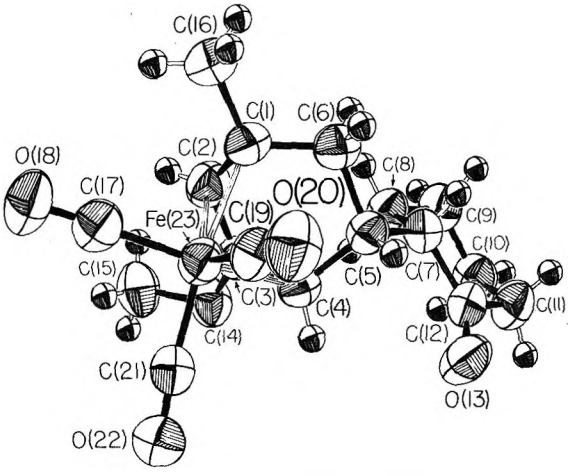


Figure 1. The carbon, iron, and oxygen atoms in the top figure of 3-methoxy-1-methyl-5-(2-oxocyclohexyl)cyclohexadieneiron tricarbonyl are drawn as ellipsoids at 50% thermal probability. The hydrogen atoms are shown as spheres of radius 1 nm.

double bond between C-3 and C-4. This distortion was also found by Churchill and Mason,[16] who studied the structure of octafluorocyclohexa-1,3-dieneiron tricarbonyl, and is discussed at length by them.

Additional reactions of the salts **4** and **8** are shown in Schemes I and II. Of particular interest is the reaction of the salt **4** with the dienamine 3-pyrrolidinocholesta-3,5-diene (**16**). Reagents such as diketone,[17] methyl iodide,[18] *m*-methoxybenzyl bromide,[19] ethyl acrylate,[20] acryloyl chloride,[21] 1,3-dichlorobut-2-ene,[22] methyl vinyl ketone,[23] methyl vinyl sulfone,[23] α,β-unsaturated nitriles,[24] cyano-

Table III
Heavy-Atom Parameters and Their Standard Deviations[a]

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	4125 (4)	6100 (3)	1310 (1)	245 (8)	154 (4)	21 (1)	50 (9)	−39 (3)	2 (2)
C(2)	4030 (5)	7575 (4)	1412 (1)	262 (8)	167 (4)	20 (1)	−44 (10)	−39 (4)	−4 (2)
C(3)	2347 (5)	8263 (3)	1284 (1)	284 (9)	134 (4)	18 (1)	17 (9)	−26 (3)	0 (2)
C(4)	960 (5)	7369 (3)	1094 (1)	234 (8)	136 (4)	18 (1)	51 (9)	−29 (3)	1 (2)
C(5)	1692 (4)	6274 (3)	679 (1)	240 (8)	131 (3)	19 (1)	−10 (9)	−28 (3)	−3 (2)
C(6)	3611 (5)	5583 (4)	802 (1)	288 (9)	150 (4)	20 (1)	55 (10)	−31 (3)	−1 (2)
C(7)	1977 (5)	6869 (3)	123 (1)	277 (8)	136 (4)	16 (1)	2 (8)	−32 (3)	−7 (2)
C(8)	3363 (6)	8158 (4)	24 (1)	289 (10)	174 (4)	21 (1)	−60 (10)	−40 (4)	8 (3)
C(9)	3670 (6)	8637 (4)	−543 (1)	353 (10)	190 (5)	20 (1)	−87 (12)	−21 (4)	13 (3)
C(10)	1676 (6)	9034 (4)	−686 (2)	403 (11)	185 (5)	20 (1)	14 (12)	−34 (4)	14 (3)
C(11)	176 (6)	7831 (5)	−584 (2)	368 (11)	206 (6)	22 (1)	−12 (13)	−68 (4)	9 (3)
C(12)	2 (5)	7184 (4)	−52 (1)	279 (9)	156 (4)	19 (1)	−18 (0)	−43 (3)	−10 (2)
O(13)	−1594 (4)	6889 (3)	208 (1)	269 (7)	266 (5)	25 (1)	−68 (8)	−48 (3)	19 (2)
O(14)	1903 (4)	9661 (2)	1350 (1)	387 (7)	127 (3)	20 (1)	14 (7)	−47 (3)	−4 (2)
C(15)	2810 (7)	10399 (4)	1723 (2)	468 (14)	154 (5)	22 (1)	−54 (12)	−48 (4)	−18 (3)
C(16)	5735 (6)	5245 (5)	1498 (2)	320 (10)	197 (6)	27 (1)	107 (12)	−64 (4)	−2 (3)
C(17)	2455 (5)	6553 (4)	2413 (1)	326 (10)	166 (5)	22 (1)	26 (10)	−48 (4)	−3 (2)
O(18)	3074 (5)	6475 (3)	2792 (1)	517 (10)	272 (5)	22 (1)	109 (11)	−114 (4)	−7 (2)
C(19)	574 (5)	4928 (3)	1782 (1)	306 (9)	151 (4)	17 (1)	3 (10)	−44 (3)	8 (2)
O(20)	74 (4)	3791 (3)	1740 (1)	480 (9)	146 (3)	26 (1)	−68 (8)	−74 (3)	5 (2)
C(21)	−760 (5)	7582 (4)	2126 (1)	297 (9)	159 (4)	17 (1)	1 (10)	−35 (3)	−5 (2)
O(22)	−2238 (4)	8130 (3)	2296 (1)	327 (7)	210 (4)	26 (1)	77 (8)	−32 (3)	−26 (2)
Fe(23)	1456 (1)	6677 (1)	1825 (0)	273 (2)	139 (1)	18 (0)	9 (2)	−40 (1)	1 (0)

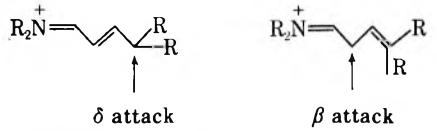
[a] The values have been multiplied by 10^4. The temperature factor is in the form $T = \exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$.

Table IV
Hydrogen Atom Parameters and Their Standard Deviations[a]

Atom	x	y	z	B
H(24)	475 (4)	802 (3)	158 (1)	46 (7)
H(25)	−22 (4)	780 (3)	107 (1)	38 (6)
H(26)	71 (4)	558 (3)	72 (1)	36 (5)
H(27)	341 (5)	452 (4)	82 (1)	63 (8)
H(28)	478 (4)	584 (3)	54 (1)	46 (6)
H(29)	257 (4)	618 (3)	−10 (1)	42 (6)
H(30)	462 (5)	792 (4)	11 (1)	64 (8)
H(31)	274 (4)	898 (4)	26 (1)	56 (7)
H(32)	430 (6)	780 (4)	−78 (1)	81 (10)
H(33)	469 (6)	939 (4)	−60 (1)	75 (9)
H(34)	191 (5)	934 (4)	−104 (1)	70 (9)
H(35)	121 (6)	985 (4)	−46 (2)	76 (9)
H(36)	70 (5)	716 (4)	−83 (1)	60 (8)
H(37)	−115 (6)	814 (4)	−59 (1)	76 (10)
H(38)	246 (5)	994 (4)	205 (1)	70 (9)
H(39)	217 (6)	1134 (5)	177 (2)	91 (11)
H(40)	422 (6)	1044 (4)	159 (1)	76 (10)
H(41)	596 (5)	561 (4)	182 (1)	71 (9)
H(42)	530 (5)	429 (4)	155 (1)	57 (8)
H(43)	688 (6)	519 (5)	122 (2)	84 (10)

[a] The values for the coordinates have been multiplied by 10^3. The values for the isotropic temperature factors have beed multiplied by 10.

gen chloride,[25] and diethyl azodicarboxylate[26] attack the β carbon of the dienamine.[27] This is a result of attack at the position of greatest electron density. However, the product from attack at the δ carbon gives the more stable product after nucleophilic attack. The relationship between the stability of a cation and its selectivity in reaction has long been appreciated.[27-29] In particular, electrophilic reagents which stabilize positive charge especially well tend to give terminal substitution at the δ carbon with dienamines.[27] Examples include the Vilsmeier reagent $HC(Cl)=NMe_2^+$,[30] protons,[31] 1,2-diphenyl-3-dicyanomethylenecyclopropene,[32] and benzyl sulfonyl chloride.[26]



Since the salt 4 is stable to recrystallization from hot water[3] and is stable in air for several weeks, its chemistry would be expected to display a similar selectivity with the latter reagents. The salt 4 attacked the β carbon atom of isobutyraldehyde enamine, unlike alkyl halides that usually attack the nitrogen of β-disubstituted enamines that are derived from aldehydes.[33]

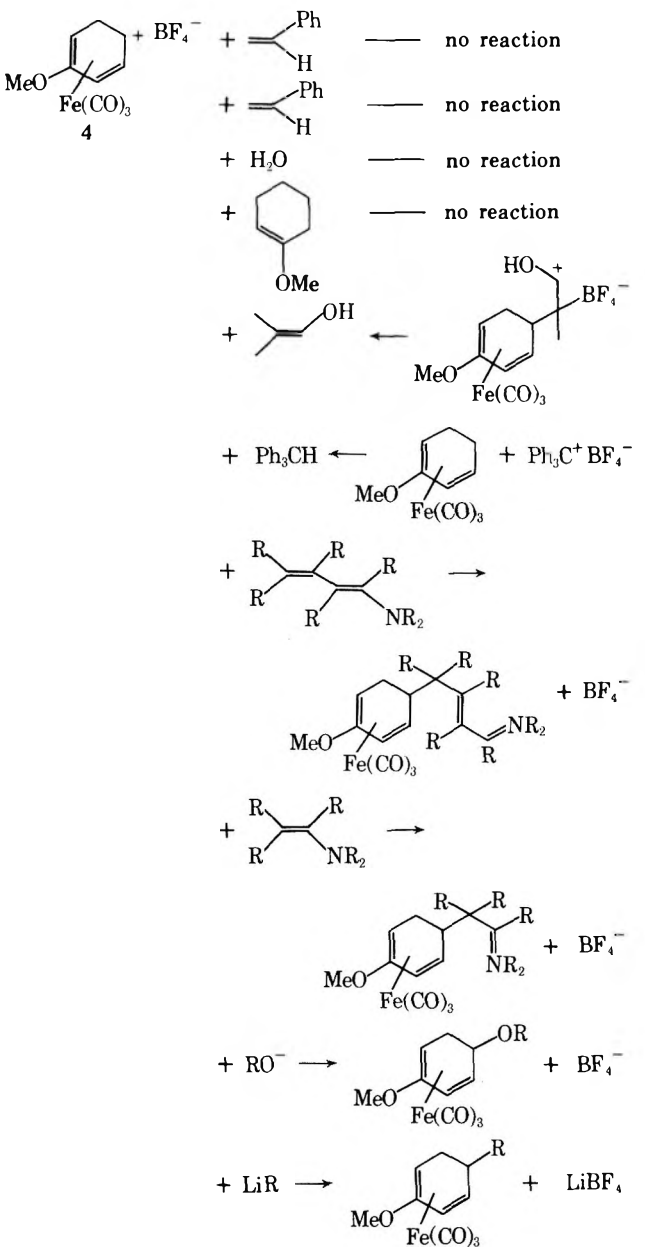
Experimental Section[34]

Preparation of 2-Methoxycyclohexa-1,3-dieneiron Tricarbonyl (2) and 1-Methoxycyclohexa-1,3-dieneiron Tricarbonyl (3).[35] To 146 g (6.35 g-atoms) of sodium in 2 l. of ammonia was added 130 g (1.30 mol) of anisole with 100 ml of ether. The addition required 40 min. The mixture was stirred for an additional 30 min before 600 ml (10.3 mol) of ethanol was added. After the reaction mixture turned colorless, the ammonia was boiled off; then 500 ml of ether was added. The organic layer was separated, washed with 3 × 100 ml of water, and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure, leaving 69.3 g of colorless oil: pmr spectrum (CCl_4) δ 3.75 (s, rel intensity 4, methoxy group in anisole), 3.51 (s, rel intensity 15, methoxy group in 1-methylcyclohexa-1,4-diene), 3.43 (s, rel intensity 4, methoxy group in 1-methoxycyclohexene).

To 15.6 g of the colorless oil was added 250 ml of di-*n*-butyl ether and 25 g (128 mmol) of iron pentacarbonyl. The reaction mixture was stirred under argon in an oil bath at 135–145° for 55 hr. The reaction mixture was filtered through Celite. Solvent was removed at vacuum pump pressure. The remaining 14.6 g of crude product contained about a 50:50 mixture of **2** and **3**. Chromatography on 500 g of silica gel with petroleum ether gave a first major yellow band containing 7.2 g (10% yield, two steps) of **2**: pmr spectrum ($CHCl_3$) δ 5.06 (dd, J = 6, 2 Hz, 1 H, C_3 H), 3.56 (s, 3 H, methoxy), 3.43 (q, J = 2 Hz, 1 H, C_1 H), 2.75 (dd, J = 6, 3 Hz, C_4 CH), 2.5–0.8 (m, 4 H); ^{13}C nmr spectrum ($CDCl_3$) δ 201.0 (carbonyl on iron), 133.2 (C_2), 64.4 (C_3), 52.4 (methoxy), 51.3 (C_1), 48.4 (C_4), 23.7, 22.6 (C_5 and C_6); ir spectrum ($CHCl_3$) 3005, 2935, 2925, 2900, 2875 (CH stretch), 2045 (vs, symmetrical carbonyl stretch on iron ligands), 1975 (vs, asymmetrical carbonyl stretch on iron ligands), 1480 cm^{-1} (alkene ligand).

The second major yellow band was eluted with ether–petroleum ether and gave 6.3 g (9% yield) of **3**: pmr spectrum ($CDCL_3$) δ 5.33 (dd, J = 5, 2 Hz, 1 H, C_2 H), 5.05 (dd, J = 7, 5 Hz, 1 H, C_3 H), 3.47 (s, 3 H, methoxy), 2.98 (m, 1 H, C_4 H), 2.5–0.8 (m, 4 H); ^{13}C nmr spectrum ($CDCl_3$) δ 201.7 (carbonyl on iron), 134.0 (C_1), 74.5 (C_2), 73.6 (C_3), 55.3 (methoxy), 53.5 (C_4), 24.0, 22.3 (C_5 and

Scheme I
Reactivity of (1,2,3,4,5-*pentahapto*-2-Methoxycyclohexadienyl)(tricarbonyl)iron Fluoroborate

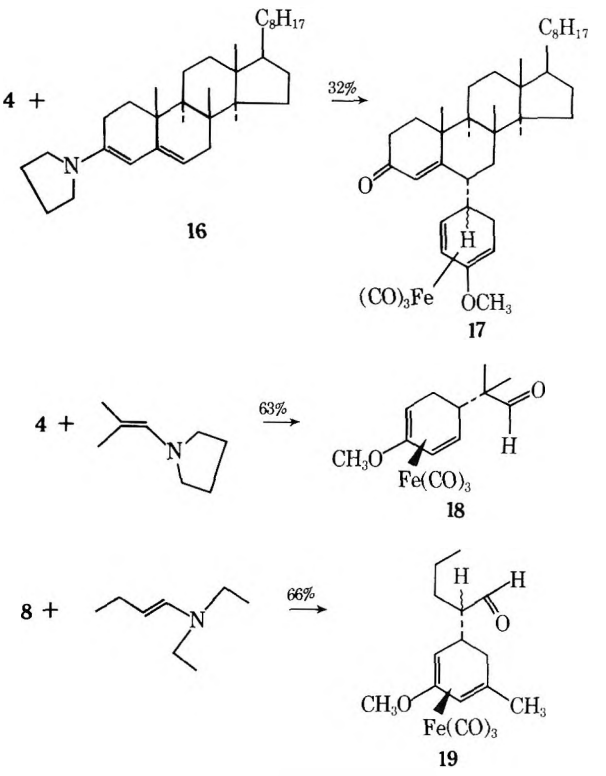


C_6); ir spectrum ($CHCl_3$) 3015, 2965, 2940, 2905, 2865 (CH stretch), 2030 (vs, symmetrical carbonyl stretch on iron ligands), 1960 (vs, asymmetrical carbonyl stretch on iron ligands), 1475 cm^{-1} (s, alkene ligands).

Preparation of (1,2,3,4,5-*pentahapto*-2-Methoxycyclohexadienyl)(tricarbonyl)iron Fluoroborate[36,37] (4) and (1,2,3,4,5-*pentahapto*-3-Methoxycyclohexadienyl)(tricarbonyl)iron Fluoroborate (5). To a warm solution of 3.22 g (12.4 mmol) of triphenylcarbinol in 32 ml of acetic anhydride was added 1.9 ml (10.4 mmol) of 48–50% aqueous fluoroboric acid under argon. After the solution had stood for 15 min, a 3.11-g (12.4 mmol) portion of **2** was added. The reaction mixture was stirred for 40 min. As 92 ml of ether was added, a precipitate formed. The precipitate was collected and washed with 10 ml of ether. On drying 3.72 g (89% yield) of **4** was obtained: nmr spectrum, see Table I; ir spectrum (mineral oil) 2100, 2055, 2045 (vs, carbonyl stretching), 1515, 1495 (alkene stretching), 1095, 1050, 1025 cm^{-1} (s, fluoroborate).

An additional 100 ml of ether was added to the mother liquor and wash solution. A second precipitate formed. Filtration gave 0.26 g (6% yield) of a yellow powder after washing with 10 ml of ether and drying. The pmr spectrum showed **5** with about 5% of **4** as a contaminant. Purer material was obtained by dissolving the solid in acetone and precipitating the yellow powder with petroleum ether: pmr spectrum, see Table I; ir spectrum (mineral oil) 2100, 2060, 2040 (vs, carbonyl stretching), 1540 (alkene stretching), 1100, 1055, 1045 cm^{-1} (fluoroborate). *Anal.* Calcd for $C_{10}H_9BF_4FeO_4$: C, 35.77; H, 2.70. Found: C, 35.82; H, 2.46.

Scheme II
Hydrolysis Products after Treating 8 and 4 with the Enamines Drawn



Preparation of (1,2,3,4,5-*pentahapto*-1-Methoxycyclohexadienyl)(tricarbonyl)iron Fluoroborate (6).[37] To a warm solution of 1.6 g (6.2 mmol) of triphenylcarbinol in 17 ml of acetic acid was added 0.95 ml (5.2 mmol) of 48–50% aqueous fluoroboric acid under argon. The mixture was stirred with cooling for 15 min. Next 1.55 g (6.2 mmol) of **3** was added with 2 ml of acetic anhydride. After stirring for 30 min under argon, the reaction was quenched with 30 ml of ether. The solid that formed was filtered and washed with 10 ml of ether. On drying the precipitate amounted to 0.647 g. The pmr spectrum showed about 10% impurity of **4**. The filtrate and wash solution were treated with a second 30-ml portion of ether and after washing with 10 ml of ether gave 0.296 g of yellow solid with an pmr spectrum identical with that of the first precipitate. The combined solid was dissolved in acetone and precipitated with petroleum ether. The resulting material was redissolved and precipitated twice more. After drying, the resulting residue was a yellow powder: pmr spectrum, see Table I; ir spectrum (mineral oil) 2105, 2030 (vs, carbonyl stretching), 1539 (alkene stretching), 1095, 1050, 1035 cm^{-1} (s, fluoroborate). *Anal.* Calcd for $C_{10}H_9BF_4FeO_4$: C, 35.77; H, 2.70. Found: C, 35.63; H, 2.61.

Preparation of 2-Methoxy-5-(2-oxocyclohexyl)cyclohexa-1,3-dieneiron Tricarbonyl (11, 12). To a solution of 3.35 g (10 mmol) of **4** in 50 ml of dichloromethane was added 1.51 g (10 mmol) of 1-pyrrolidinocyclohexene. The mixture was stirred under argon for 17 hr; then 600 mg of sodium acetate, 10 ml of acetic acid, and 10 ml of water were added. The resulting mixture was stirred and refluxed for 3 hr under an argon atmosphere. The organic layer was separated, washed with 4 × 25 ml of water, and dried over anhydrous $MgSO_4$. Removal of solvent at reduced pressure left 3.46 g of yellow solid. The solid was chromatographed on 400 g of silica gel. Dichloromethane was used to elute 2.40 g (69% yield) of crude product. The crude material was recrystallized from petroleum ether, giving 596 mg of crystals of **11**, mp 97–102°, and 668 mg of less soluble crystals of **12**, mp 108–114°.

The crude **11** was recrystallized twice more from petroleum ether to give yellow crystals: mp 102–103°; pmr spectrum ($CDCl_3$) δ 5.13 (dd, J = 7, 2 Hz, 1 H, C_3 H), 3.47 (s, 3 H, methoxy), 3.34 (m, 1 H, C_1 H), 2.74 (dd, J = 6, 3 Hz, 1 H, C_4 H), 2.5–0.8 (m, 12 H); ^{13}C nmr spectrum ($CDCl_3$) δ 211.8 (carbonyl on iron), 66.7 (C_3), 58.7 (C_1), 55.3 (C_4), 53.1 (methoxy carbon), 51.3 (C_1), 42.4

Table V
Bond Distances and Angles and Their Standard Deviations Involving the Hydrogen Atoms[a]

Bond	Length, Å	Bond	Angle, deg	Bond	Angle, deg
H(24)–C(2)	0.82 (3)	H(24)–C(2)–C(1)	126 (2)	H(24)–C(2)–C(3)	118 (2)
		H(24)–C(2)–Fe(23)	118 (2)		
H(25)–C(4)	0.91 (3)	H(25)–C(4)–C(3)	114 (2)	H(25)–C(4)–C(5)	115 (2)
		H(25)–C(4)–Fe(23)	120 (1)		
H(26)–C(5)	0.93 (2)	H(26)–C(5)–C(4)	106 (2)	H(26)–C(5)–C(6)	107 (2)
		H(26)–C(5)–C(7)	109 (2)		
H(27)–C(6)	1.02 (4)	H(27)–C(6)–C(1)	110 (2)	H(27)–C(6)–C(5)	109 (2)
		H(27)–C(6)–H(28)	111 (2)		
H(28)–C(6)	0.98 (3)	H(28)–C(6)–C(1)	105 (2)	H(28)–C(6)–C(5)	111 (2)
H(29)–C(7)	0.91 (3)	H(20)–C(7)–C(5)	107 (2)	H(29)–C(7)–C(8)	106 (2)
		H(29)–C(7)–C(12)	105 (2)		
H(30)–C(8)	0.94 (4)	H(30)–C(8)–C(7)	109 (2)	H(30)–C(8)–C(9)	109 (2)
		H(30)–C(8)–H(31)	108 (3)		
H(31)–C(8)	1.04 (3)	H(31)–C(8)–C(7)	109 (2)	H(31)–C(8)–C(9)	109 (2)
H(32)–C(9)	1.05 (4)	H(32)–C(9)–C(8)	108 (2)	H(32)–C(9)–C(10)	110 (2)
		H(32)–C(9)–H(33)	105 (3)		
H(33)–C(9)	0.98 (4)	H(33)–C(9)–C(8)	110 (2)	H(33)–C(9)–C(10)	114 (2)
H(34)–C(10)	0.95 (4)	H(34)–C(10)–C(9)	108 (2)	H(34)–C(10)–C(11)	113 (2)
		H(34)–C(10)–H(35)	109 (3)		
H(35)–C(10)	0.99 (4)	H(35)–C(10)–C(9)	104 (2)	H(35)–C(10)–C(11)	111 (2)
H(36)–C(11)	0.93 (3)	H(36)–C(11)–C(10)	104 (2)	H(36)–C(11)–C(12)	108 (2)
		H(36)–C(11)–H(37)	116 (3)		
H(37)–C(11)	0.95 (4)	H(37)–C(11)–C(10)	111 (2)	H(37)–C(11)–C(12)	104 (2)
H(38)–C(15)	0.95 (4)	H(38)–C(15)–O(14)	109 (2)	H(38)–C(15)–H(39)	106 (3)
H(39)–C(15)	0.98 (5)	H(39)–C(15)–O(14)	107 (3)	H(39)–C(15)–H(40)	113 (3)
H(40)–C(15)	0.95 (4)	H(40)–C(15)–O(14)	108 (2)	H(40)–C(15)–H(38)	114 (3)
H(41)–C(16)	0.95 (4)	H(41)–C(16)–C(1)	110 (2)	H(41)–C(16)–H(42)	109 (3)
H(42)–C(16)	0.95 (3)	H(42)–C(16)–C(1)	109 (2)	H(42)–C(16)–H(43)	104 (3)
H(43)–C(16)	0.97 (4)	H(43)–C(16)–C(1)	108 (3)	H(43)–C(16)–H(41)	117 (3)

[a] The values for the standard deviations in bond lengths have been multiplied by 10^2.

Table VI
Least-Squares Plane of the Diene Carbon Atoms and Atomic Deviations from the Plane[a]

Atom	Deviation, Å	Atom	Deviation, Å
C(1)	−0.006	C(5)	−0.907
C(2)	0.012	C(6)	−0.946
C(3)	−0.012	O(14)	0.012
C(4)	0.006	C(16)	0.196

[a] Coefficients are direction cosines relative to the crystallographic axis. Plane through atoms C(1), C(2), C(3), and C(4): $-0.3239x - 0.1653y + 0.8563z = 1.068$.

($C_{3'}$), 36.5 (C_5), 32.3 ($C_{6'}$), 31.6 (C_4), 28.3 ($C_{5'}$), 25.1 (C_6); ir spectrum ($CHCl_3$) 3030, 3020, 2940, 2865 (CH stretch), 2045 (vs, symmetrical carbonyl stretch of iron ligands), 1965 (vs, asymmetrical carbonyl stretch of iron ligands), 1705 (s, carbonyl of cyclohexanoyl), 1485 cm^{-1} (s, alkene ligand). *Anal.* Calcd for $C_{16}H_{18}FeO_5$: C, 55.51; H, 5.24. Found: C, 55.55; H, 5.46.

The crude 12 was recrystallized twice more from petroleum ether to give crystals: mp 113–114°; pmr spectrum ($CDCl_3$) δ 5.12 (dd, J = 7, 2 Hz, 1 H, C_3 H), 3.47 (s, 3 H, methoxy), 3.28 (m, 1 H, C_1 H), 2.55 (dd, J = 7, 2 Hz, 1 H, C_4 H), 2.4–0.8 (m, 12 H); ^{13}C nmr spectrum ($CDCl_3$) δ 212.2 (carbonyls on iron), 211.2 (cyclohexanoyl carbonyl), 139.7 (C_2), 67.4 (C_3), 57.6 ($C_{1'}$), 54.3 C_4), 52.9 (methoxy), 51.3 (C_1), 42.1 ($C_{3'}$), 37.1 (C_5), 30.6 ($C_{6'}$), 28.7 ($C_{4'}$), 27.8 ($C_{5'}$), 24.3 (C_6); ir spectrum ($CHCl_3$) 3005, 2940, 2865, 2830 (CH stretch), 2040 (vs, symmetrical carbonyl strength of iron ligands), 1960 (vs, asymmetrical carbonyl stretch or iron ligands), 1705 (s, carbonyl of cyclohexanoyl), 1485 cm^{-1} (s, alkene ligands). *Anal.* Calcd for $C_{16}H_{18}FeO_5$: C, 55.51; H, 5.24. Found: C, 55.30; H, 5.09.

Preparation of 5-(1,1-Dimethyl-2-oxoethyl)-2-methoxycyclohexa-1,3-dieneiron Tricarbonyl (18). To a mixture of 336 mg (1.0 mmol) of 4 and 5 ml of CH_2Cl_2 was added 125 mg (1.0 mmol) of 2,2-dimethyl-1-pyrrolidinoethene. The mixture was stirred under argon for 19 hr. A solution of 300 mg of sodium acetate, 6 ml of acetic acid, and 6 ml of water was added to the reaction mixture and stirring was continued for 3 hr. Then the organic layer was separated, washed with 5 × 5 ml of saturated sodium bicarbonate, washed with 2 × 5 ml of water, and dried over anhydrous $MgSO_4$. Removal of the solvent at vacuum pump pressure left 266 mg of a yellow oil.

Bulb-to-bulb distillation of the oil (95°, 0.05 mm) gave 203 mg (63° yield) of 18: pmr spectrum ($CDCl_3$) δ 9.59 (s, 1 H, aldehyde proton), 5.28 (dd, J = 6, 2 Hz, 1 H, C_3 H), 3.76 (s, 3 H, methoxy), 3.44 (m, 1 H, C_1 H), 3.0–0.8 (m, 4 H), 1.12 (s, 3 H, methyl), 1.08 (s, 3 H, methyl); ir spectrum ($CHCl_3$) 3010, 2965, 2940, 2875 (CH stretch), 2760 (CH aldehyde stretch), 2045 (vs, symmetrical carbonyl stretch of iron ligands), 1965 (vs, asymmetrical carbonyl stretch of iron ligands), 1725 (s, aldehyde carbonyl), 1490 cm^{-1} (s, alkene ligand). *Anal.* Calcd for $C_{14}H_{16}FeO_5$: C, 52.52; H, 5.04. Found: C, 52.58; H, 5.03.

Preparation of 6α-(4-Methoxycyclohexa-2,4-dieneiron Tricarbonyl)cholest-4-en-3-one (17). To 1.46 g (4.35 mmol) of 4 with 50 ml of CH_2Cl_2 was added 1.9 g (4.35 mmol) of 3-pyrrolidinocholesta-3,5-diene.[38] The mixture was stirred under an argon atmosphere for 31 hr. A solution of 1 g of sodium acetate, 20 ml of water, and 20 ml of acetic acid was added to the reaction mixture and stirring was continued for 14 hr. The organic layer was separated, washed with 4 × 25 ml of saturated sodium bicarbonate, washed with 25 ml of water, and dried over anhydrous $MgSO_4$. The solvent was removed at reduced pressure, leaving 2.62 g of brown foam, mp 90–93°. A 1.22-g portion of the form was chromatographed on 15 g of silica gel. A solution of 25% ethyl acetate–hexane was used to elute a yellow oil that gave 846 mg of brown foam at vacuum pressure. The foam was then chromatographed on 115 g silica gel H (10–40) in a column 2.54 cm in diameter. A solution of 25% ethyl acetate–hexane was pumped through the column to elute the sample. After an initial 150 ml of solvent was collected from the high-pressure column at the rate of 1.5 ml/min, the fractions were collected every 4 min. Fractions 29–55 contained 431 mg (32% yield) of chromatographically homogeneous foam.

The chromatographed foam was recrystallized from 12 ml of methanol to give 181 mg of white, fibrous solid, mp 167–169°. Repeated recrystallization from methanol gave a white, fibrous solid: mp 172–173°; pmr spectrum ($CDCl_3$) δ 5.63 (s, 1 H, $C_{4'}$ vinyl hydrogen), 5.12 (dd, J = 7, 2 Hz, 1 H, $C_{3'}$ H), 3.63 (s, 3 H, methoxy), 3.26 (m, 1 H, $C_{5'}$ H), 2.80 (m, 1 H, $C_{2'}$ H), 2.5–0.8 (m, 33 H), 1.08 (s, 3 H, methyl), 0.9 (s, 3 H, methyl); ir spectrum ($CHCl_3$) 3010, 2950, 2890, 2870 (CH stretch), 2045 (vs, symmetrical carbonyl stretch of iron ligands), 1965 (vs, asymmetrical carbonyl stretch of iron ligands), 1660 (s, enone carbonyl), 1605 (alkene), 1490 cm^{-1} (s, alkene ligands); uv spectrum λ_{max} (MeOH) 225 nm (ϵ 20,000). *Anal.* Calcd for $C_{37}H_{52}FeO_5$: C, 70.24; H, 8.29. Found: C, 70.48; H, 8.53.

Preparation of 3-Methoxy-1-methylcyclohexa-1,3-dieneiron Tricarbonyl (7), 1-Methoxy-5-methylcyclohexa-1,3-dieneiron Tricarbonyl, and 1-Methoxy-3-methylcyclohexa-1,3-dieneiron Tricarbonyl.[34] To a solution of 21 g (0.875 g-atom) of sodium in 500 ml of ammonia was added 20 g (164 mmol) of 3-methylanisole and 250 ml of ether. The addition was complete in 50 min. The reaction mixture was stirred for 30 min and then 75 ml (1.28 mol) of ethanol was added over a 20-min period. The ammonia was boiled off. After 200 ml of water and 200 ml of ether were added, the organic layer was separated, washed with 4 × 50 ml of water, and dried over anhydrous $MgSO_4$. Removal of solvent at reduced pressure left 16.6 g (82% yield) of 1-methoxy-5-methylcyclohexa-1,4-diene. Distillation gave 12.9 g of a colorless oil: bp 75–77° (aspirator pressure); pmr spectrum (CCl_4) δ 5.35 (m, 1 H, C_4 H), 4.52 (m, 1 H, C_2 H), 3.42 (s, 3 H, methoxy), 2.58 (m, 4 H, C_3 H and C_6 H), 1.68 (s, 3 H, methyl).

To 6.0 g (48.3 mmol) of 1-methoxy-5-methylcyclohexa-1,4-diene in 120 ml of di-*n*-butyl ether was added 26 g (133 mmol) of iron pentacarbonyl. The reaction mixture was stirred and refluxed under argon in a oil bath at 135–145°. The reaction was followed by examining aliquots by ir. The reaction was stopped after 45 hr at reflux when absorption at 1670 and 1710 cm^{-1} had diminished. The reaction mixture was filtered through Celite, which was washed with ether until the wash solution was colorless. The solvents were removed at reduced pressure. After treatment at vacuum-pump pressure, a crude yield of 9.33 g of oil was collected. A 9.05-g portion of oil was loaded onto 500 g of silica gel and eluted with petroleum ether. The petroleum ether was collected in 500-ml fractions. Fractions 5 and 6 consisted of yellow material, 280 mg, of unknown structure. The next three fractions contained a trace of green material, possibly $Fe_3(CO)_{12}$.[39] Fractions 10–18 contained 2.65 g (21% yield) of **7**: pmr spectrum ($CDCl_3$) δ 5.02 (d, J = 2 Hz, 1 H, C_2 H), 3.56 (s, 3 H, methoxy), 3.33 (m, 1 H, C_4 H), 2.0–0.8 (m, 4 H, C_5 H and C_6 H), 1.61 (s, 3 H, methyl); ir spectrum ($CHCl_3$) 3010, 2960, 2940, 2920, 2880, 2860, 2840 (CH stretch), 2035 (vs, symmetrical carbonyl stretch of iron ligands), 1490 cm^{-1} (s, alkene ligand). On elution of the column with ether–petroleum ether, 4.56 g of a mixture of 1-methoxy-5-methylcyclohexa-1,3-dieneiron tricarbonyl and 1-methoxy-3-methylcyclohexa-1,3-dieneiron tricarbonyl was collected.

Preparation of (1,2,3,4,5-*pentahapto*-3-Methoxy-1-methylcyclohexadienyl)(tricarbonyl)iron Fluoroborate (8).[37] To a warm solution of 520 mg (2 mmol) of triphenylcarbinol in 5.2 ml of acetic anhydride was added 0.325 ml (1.7 mmol) of 48–50% aqueous fluoroboric acid under argon atmosphere. The mixture was stirred for 30 min, and then 528 mg (2 mmol) of **7** was added. The reaction mixture was stirred for 1 hr in an ice bath and then quenched with 10 ml of ether. The precipitate was filtered and washed with 2 × 10 ml of ether. Further precipitate which formed in the combined mother liquor and wash solution was collected and added to the original precipitate. Drying the combined precipitates at vacuum pump pressure left 561 mg (80% yield) of yellow powder: pmr spectrum, see Table I; ir spectrum (mineral oil) 2090, 2045, 1975 (vs, carbonyl stretch on iron ligands), 1555 (alkene ligands), 1100, 1060, 1040 cm^{-1} (s, fluoroborate). *Anal.* Calcd for $C_{11}H_{11}BF_4FeO_4$: C, 37.76; H, 3.17 Fe, 15.96. Found: C, 37.87; H, 3.29; Fe, 15,80.

Preparation of 5-(1-Ethyl-2-oxoethyl)-3-methoxy-1-methylcyclohexa-1,3-dieneiron Tricarbonyl (19). To 1.50 g (4.29 mmol) of 8 and 75 ml of CH_2Cl_2 was added 550 mg (4.86 mmol) of 1-(*N*,*N*-diethylamino)-1-butene. The mixture was stirred under argon for 14 hr. The solvent was removed from the reaction mixture at reduced pressure, and then the gummy residue was shaken with 50 ml of ether and 20 ml of water. The ether layer, the water layer, and the remaining gum were separated. The gum was extracted with an additional 50 ml of ether. The combined ether layers were dried over anhydrous $MgSO_4$. A residue remained after the solvent was removed at reduced pressure.

The residue was chromatographed on 20 g of silica gel. Elution of the second band with petroleum ether gave 937 mg (66% yield) of yellow oil. A portion of the oily product was distilled bulb to bulb (95%, 0.05 mm) to give a purer product: nmr spectrum ($CDCl_3$) δ 9.63 (t, J = 2 Hz, 1 H, aldehyde hydrogen), 5.12 (s, 1 H, C_2 H), 3.62 (s, 3 H, methoxy), 3.24 (m, 1 H, C_4 H), 3.0–0.8 (m, 9 H), 1.57 (3 H, methyl); ir spectrum ($CHCl_3$) 3020, 2970, 2940 (CH stretch), 2725 (w, aldehyde CH stretch), 2040 (vs, symmetrical carbonyl stretch on iron ligands), 1960 (vs, asymmetrical carbonyl stretch on iron ligands), 1720 (aldehyde carbonyl), 1490 cm^{-1} (alkene ligands). *Anal.* Calcd for $C_{15}H_{18}FeO_5$: C, 53.91; H, 5.42; Fe, 16.71. Found: C, 54.03; H, 5.41; Fe, 16.63.

Preparation of 3-Methoxy-1-methyl-5-(2-oxocyclohexyl)cyclohexa-1,3-dieneiron Tricarbonyl (15). To 30 ml of CH_2Cl_2 were added 750 mg (.0 mmol) of 1-pyrrolidinocyclohexene and 200 mg (0.573 mmol) of **11**. The reaction mixture was stirred under argon for 20 hr. A solution of 250 mg of sodium acetate, 5 ml of water, and 5 ml of acetic acid was added to the reaction mixture and stirring was continued for 1.5 hr. The organic layer was separated, washed with 2 × 15 ml of water, and dried over anhydrous $MgSO_4$. Removal of the solvents at vacuum-pump pressure left 194 mg of dark oil.

The crude product dissolved in methanol. The methanol solution was filtered and evaporated at reduced pressure to give 139 mg of oily solid (67% yield). A portion of the product was recrystallized twice from methanol to give yellow crystals: mp 142–143°; pmr spectrum ($CDCl_3$) δ 5.12 (d, J = 2 Hz, 1 H, C_2 H), 3.60 (s, 3 H, methoxy), 3.26 (m, 1 H, C_4 H), 3.0–0.8 (m, 12 H), 1.53 (s, 3 H, methyl); ir spectrum ($CHCl_3$) 2945, 2870, 2865 (CH stretch), 2040 (vs, symmetrical carbonyl stretch on iron ligands), 1960 (vs, asymmetrical carbonyl stretch on iron ligands), 1705 (cyclohexanoyl carbonyl), 1490 cm^{-1} (s, alkene ligands). *Anal.* Calcd for $C_{17}H_{20}FeO_5$: C, 56.68; H, 5.60; Fe, 15.50. Found: C, 56.77; H, 5.56; Fe, 15.41.

Collection of the X-Ray Data for Compound 15. Crystals in the form of yellow prisms were obtained from petroleum ether. All the data were obtained from one crystal with dimensions of 0.6 × 0.3 × 0.2 mm. Unit cell parameters were determined from least-squares refinement of the 2θ angles of 27 reflections measured on a General Electric diffractometer. The resulting values were a = 6.769 ± 0.001 Å, b = 9.487 ± 0.002 Å, c = 26.054 ± 0.003 Å, β = 100.57 ± 0.02°. The absence of $0k0$ reflections for k odd and $h0l$ reflections for l odd indicated that the space group was $P2_1/c$. The crystal density, measured by the flotation method, was found to be 1.43 ± 0.02 g cm^{-3}. The calculated density is 1.45 g cm^{-3} for four molecules of molecular weight 360.20 per unit cell.

Intensity data were collected by the θ–2θ scan method on a Datex-automated General Electric diffractometer using iron-filtered Co Kα radiation (λ 1.79021 Å). Reflections were collected to a maximum value of 2θ = 135° with a scan rate of 2°/min. Background counts were taken for 30 sec at the beginning and the end of each scan. The reflections whose peak counting rate exceeded 20,000 counts/sec were remeasured with a lower beam intensity to minimize counting losses. Three reflections, monitored at regular intervals during the data collection, showed no significant variation in intensity.

The intensities of 1875 reflections were measured. The intensities of 15 of these reflections were observed to be less than one standard deviation above background and were assigned a value of zero with zero weight throughout the refinement process. The data were corrected for Lorentz–polarization effects but not for absorption (μ 23 cm^{-1}). The data were placed on an approximately absolute scale by Wilson's method.[40] A Howells', Phillips', and Rogers' plot[41] confirmed that the crystal was centrosymmetric.

Solution and Refinement of the Structure of 15. The phases of the 211 reflections with an E value greater than 1.60 were assigned by Long's program,[42] which uses a reiterative application of Sayre's[43] equation. Long's procedure yielded 16 possible phase assignment combinations for the 211 chosen reflections. Of these 16 combinations, two clearly had much higher consistency indices and of these the more consistent had also converged more quickly.

The reflections whose phases had been determined as described above were used to calculate an E map. The iron atom was easily located in this map. The alternate calculation of structure factors and electron-density maps quickly led to the complete elucidation of the structure.

All calculations were carried out on the IBM 370/155 computer with subprograms operating under the CRYM system.[44] The atomic scattering factors for carbon, oxygen, and iron were taken from "International Tables for X-Ray Crystallography."[45] The atomic scattering factor for hydrogen is that given by Stewart, Davidson, and Simpson.[46] The least-squares routine minimizes the quantity $\Sigma w(F_o^2 - F_c^2)^2$. The weights, w, used throughout the refinement of the structure, were set equal to $1/\sigma^2(F_o^2)$ which were derived from counting statistics. The variance of the intensity was calculated by the formula

$$\sigma^2(I) = S + \alpha^2(B_1 + B_2) + (dS)^2$$

where S is the total counts collected during the scan, B_1 and B_2 are the numbers of counts collected for each background, α is the scan time to total background time ratio, and d is an empirical constant of 0.02.

Least-squares refinement of the coordinates of the 23 heavier atoms reduced the R index to 0.173. The nonmethyl group hydrogens were introduced at their expected positions. After two cycles of least-squares refinement of the heavier atoms including isotropic temperature factors followed by two additional cycles of refinement with anisotropic temperature factors, a difference Fourier synthesis revealed the positions of the six hydrogens on the two methyl groups. The coordinates of all atoms were placed in one matrix. The temperature factors, including isotropic temperature factors for the hydrogen atoms, and the scale factor were contained in a second matrix, and the refinement was continued. The R index $\Sigma||F_o|-|F_c||/\Sigma|F_o|$ was reduced to 0.073 and the weighted R, $\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4$, to 0.040. The "goodness-of-fit" $[\Sigma w(F_o^2 - F_c^2)^2/(m - s)]^{1/2}$, where m is the number of observations and s is the number of parameters refined, was 7.0

This rather large value for the "goodness-of-fit" and the unreasonableness of some of the refined temperature factors led us to reexamine the data. The most evident error was the fact that the crystal was larger in one dimension than the diameter of the X-ray beam. The crystal was mounted on the diffractometer with its long needle axis coincident with the ϕ axis. Under these conditions it can be easily shown that the volume of the crystal bathed by the X-ray beam is proportional to sec θ and to sin χ. The intensity data were, therefore, all multiplied by $(1 + \tan^2\theta \sin^2\chi)^{-1/2}$; additional least-squares refinement was performed with this corrected data. In the final stages of refinement, a secondary extinction factor[47] was included and the anomalous dispersion contribution was included in the atomic scattering factor for iron. The final value obtained for the secondary extinction factor, g, was $20.1 \pm 0.5 \times 10^{-6}$. The final R index was 0.057, the weighted R was 0.019, and the "goodness-of-fit" was 5.1.

The observed and calculated structure factors $|F_o|$ and F_c are listed in Table VII.[48] The coordinates and anisotropic temperature factors of the heavier atoms and their standard deviations are given in Table III. The positional parameters and isotropic temperature factors for the hydrogen atoms and their standard deviations are given in Table IV. During the final cycle of refinement, the average parameter shift was less than one-tenth of its standard deviation, and no parameter shifted more than one-quarter of its standard deviation.

Oxidation of 12 to 2-(*p*-Anisyl)cyclohexanone (13a). To a mixture of 190 mg (0.55 mmol) of **12** and 5 ml of methanol was added 1.0 g (1.83 mmol) of ceric ammonium nitrate in 10 ml of methanol. The addition was completed in 5 min. The reaction mixture was stirred for an additional 10 min before 0.125 g (0.55 mmol) of dichlorodicyanoquinone (DDQ) in 20 ml of ether was added over a 5-min period. The reaction mixture was stirred for 1-hr. Then 10 ml of water and 20 ml of ether were added. The ether layer was separated. The aqueous layer was extracted with 3 × 20 ml of ether, and the combined ether layers were washed with 10 ml of brine and dried over anhydrous $MgSO_4$. Removal of the ether at reduced pressure left 198 mg of crude product. After the solid was washed with 1 ml of warm benzene and 6 ml of warm chloroform, the product was eluted on a silica gel plate (EM reagents silica gel F-254, 20 × 200 cm) with ether. The band of higher R_f contained 47 mg (42% yield) of **13a**, mp 69–78°. Four recrystallizations from petroleum ether gave white crystals of **13a**, mp 88–89° (lit.[12] mp 89–89.2°). The 2,4-dinitrophenylhydrazone was prepared[49] and had mp 143–144° (lit.[12] mp 144–145°).

The band of lower R_f contained 32 mg of what was presumably an isomer or a mixture of isomers of 4-(2-oxocyclohexyl)cyclohex-2-en-1-one: ir spectrum ($CHCl_3$) 2940, 2865 (CH stretch), 1710 (unconjugated carbonyl), 1675 (conjugated carbonyl), 1450 cm^{-1} (alkene); pmr spectrum ($CDCl_3$) δ 6.82 (m, J = 10 Hz, 1 H, alkene β to carbonyl), 5.99 (dd, J = 10, 2 Hz, 1 H, alkene α to carbonyl), 3.3–0.8 (m, 14 H).

Conversion of 11 to 4-(2-Oxocyclohexyl)cyclohex-2-en-1-one (13b). To 180 mg (0.52 mmol) of **11** in 5 ml of acetone was added 0.59 ml of Jones reagent (approximately 8 N in chromic acid or about 0.47 mmol of CrO_3). Bubbles evolved from the mixture until the last few drops of oxidant were added. The organic layer was partitioned between ether and saturated aqueous $NaHCO_3$. The ether solution was dried over anhydrous $MgSO_4$. Removal of ether at reduced pressure left 69 mg (69% yield) of a yellow oil which solidified, mp 74–79°. Three recrystallizations from petroleum ether gave crystals of **13b**: mp 85–86°; ir spectrum ($CHCl_3$) 2940, 2865 (CH stretch), 1710 (unconjugated carbonyl), 1675 (conjugated carbonyl), 1450 cm^{-1} (alkene); pmr spectrum ($CDCl_3$) δ 6.83 (m, J = 10 Hz, 1 H, vinyl hydrogen β to carbonyl), 5.99 (dd, J = 10, 2 Hz, 1 H, vinyl hydrogen α to carbonyl), 3.10 (m), 2.8–0.8 (m); uv spectrum λ_{max} (MeOH) 226 nm (ϵ 1.01×10^4). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.56.

Acid-Catalyzed Cleavage of 5-(1,1-Dimethyl-2-oxoethyl)-2-methoxycyclohexa-1,3-dieneiron Tricarbonyl. To 160 mg (0.5 mmol) of 5-(1,1-dimethyl-2-oxoethyl)-2-methoxycyclohexa-1,3-dieneiron tricarbonyl in 1.5 ml of acetic anhydride was added 0.08 ml (0.45 mmol) of 48–50% aqueous fluoroboric acid. The mixture turned orange and was stirred under argon for 30 min. Then 5 ml of ether was added. The precipitate was collected and dried at vacuum-pump pressure. The residue contained 103 mg (62% yield) of (1,2,3,4,5-*pentahapto*-2-methoxycyclohexadienyl)(tricarbonyl)iron fluoroborate (**4**).

Rate of Hydride Abstraction from 2-Methoxycyclohexa-1,3-dieneiron Tricarbonyl. To 3.22 g (12.4 mmol) of triphenylcarbinol in a 200-ml flask was added 32 ml of acetic anhydride. The solid was dissolved by heating the mixture on a steam bath. Then 1.9 ml (10.4 mmol) of 48–50% aqueous fluoroboric acid was added. The mixture was stirred and cooled under an argon atmosphere for 15 min. Then 3.11 g (12.4 mmol) of 2-methoxycyclohexa-1,3-dieneiron tricarbonyl was added.

The first 5-ml aliquot was taken 5 min after the addition of reagents was complete. The aliquots were treated with 25 ml of ether. The precipitate formed was collected, washed with 5 ml of ether, and dried at vacuum-pump pressure for each aliquot.

Successive aliquots were taken 10, 20, 30, 40, 60, and 90 min after all reagents had been mixed. The 5-ml aliquoots contained 424, 411, 430, 425, 418, 432, and 448 mg. The last aliquot taken was a 6.8-ml sample at 120 min and contained 549 mg. The total yield of salts was 3.54 g (86%). The pmr spectra of the 5-min aliquot, the 40-min aliquot, and the 120-min aliquot were identical. The spectra showed that the aliquots contained about 90% (1,2,3,4,5-*pentahapto*-2-methoxycyclohexadienyl)(tricarbonyl)iron fluoroborate (**4**) and about 10% of (1,2,3,4,5-*pentahapto*-3-methoxycyclohexadienyl)(tricarbonyl)iron fluoroborate.

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Registry No. **2**, 12318-19-3; **3**, 12318-18-2; **4**, 12307-15-2; **5**, 42531-68-0; **6**, 42531-69-1; **7**, 12318-45-5; **8**, 42531-71-5; **9**, 42540-81-8; **10**, 42540-82-9; **11**, 42531-72-6; **13a**, 37087-68-6; **13b**, 42540-84-1; **15**, 42531-73-7; **17**, 42531-74-8; **18**, 42531-75-9; **19**, 42531-76-0; triphenylcarbinol, 76-84-6; 1-pyrrolidinocyclohexene, 1125-99-1; 2,2-dimethyl-1-pyrrolidinoethene, 2403-57-8; 3-pyrrolidinocholesta-3,5-diene, 2309-31-1; 3-methylanisole, 100-84-5; 1-methoxy-5-methylcyclohexa-1,4-diene, 13697-84-2; 1-(*N*,*N*-diethylamino)-1-butene, 15430-99-6; DDQ, 84-58-2.

Supplementary Material Available. Table VII, listing the observed and calculated structure factors, 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 Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy of $2.00 for microfiche, referring to code number JOC-74-51.

References and Notes

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Reaction Intermediates in the Alkylation of Pyridine with *tert*-Butyllithium[1]

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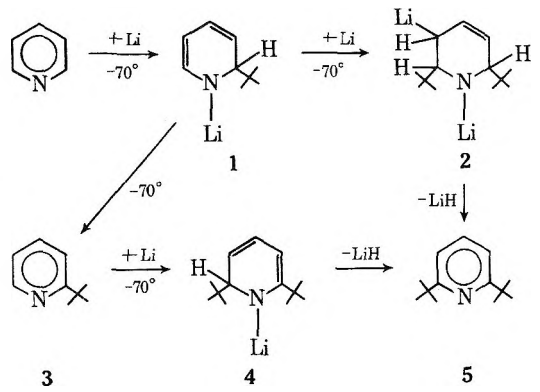
The complex 1,3-dilithio-2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine (**2**) is formed from pyridine and excess *tert*-butyllithium and decomposes on heating to 2,6-di-*tert*-butylpyridine (**5**). Complex **2** has been isolated as the protonated analog 2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine (**10**), which can be catalytically dehydrogenated to **5**. The precursor of 2-*tert*-butylpyridine (**3**), 1-lithio-2-*tert*-butyl-1,2-dihydropyridine (**1**), was isolated from a reaction of pyridine with *tert*-butyllithium at −70°. Treatment of **1** with methanol gives a mixture containing 2-*tert*-butyl-1,2-dihydropyridine (**6**) and 2-*tert*-butyl-2,5-dihydropyridine (**7**). When heated, dihydropyridines **6** and **7** form 2-*tert*-butylpyridine (**3**) and 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**8**). Pyridine and excess *tert*-butyllithium above room temperature also give 2,4,6-tri-*tert*-butylpyridine (**9**) which is formed only by alkylation of **5**.

The reactions of pyridine with organolithium compounds have provided a variety of products resulting from monoalkylation or arylation of pyridine α to nitrogen.[2] We recently reported[3] isolation of 4-alkyl- and 2,4- and 2,6-dialkylpyridines in addition to the expected 2-alkylpyridine from reactions in which an excess of the appropriate alkyllithium compound was used. This investigation led to the direct synthesis in good yield of a variety of 2,6-dialkylpyridines.[3] The reaction of pyridine with excess *tert*-butyllithium is significant because it gives 2,4,6-tri-*tert*-butylpyridine (**9**)[3,4] in addition to other products. However, trialkylated products were not observed in reactions of pyridine with other alkyllithium compounds.

Intermediates which are precursors to dialkyl- and trialkylpyridines have not been reported previously. However, the recent conclusive evidence[5] for the existence of intermediate σ complexes in monoalkylation and arylation of pyridine with organolithium compounds suggested that isolation and characterization of similar complexes leading directly to *tert*-butylpyridines **5** and **9** might also be possible.

Two reaction schemes were considered as the most likely pathways to 2,6-di-*tert*-butylpyridine (**5**). Direct alkylation of intermediate **1** and alkylation of 2-*tert*-butylpyridine (**3**) formed by decomposition of **1** could give intermediates **2** and **4**, respectively. These intermediates could form dialkylpyridine **5** by loss of lithium hydride. Formation of **5** by decomposition of intermediate **1** followed by a second alkylation step corresponds to the previously utilized[2d] two-step synthesis of 2,6-dialkylpyridines. Intermediate **2** could result from direct alkylation of **1**, a reaction not unlike the known[6] addition of *tert*-butyllithium to 1,3-butadiene, or from alkylation of the isomeric 5-lithio-2-*tert*-butyl-2,5-dihydropyridine.



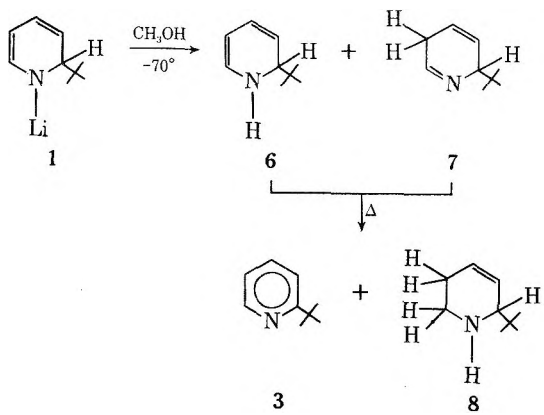
Results and Discussion

The results of a series of reactions of pyridine with excess *tert*-butyllithium conducted under varied conditions are summarized in Table I. A reaction in which reagents were mixed at −70° and stirred at room temperature for 5 days (reaction 1, Table I) afforded the best yield (58%) of 2,6-di-*tert*-butylpyridine (**5**). Thus, isolation and identification of an intermediate leading directly to **5** initially was attempted under similar conditions.

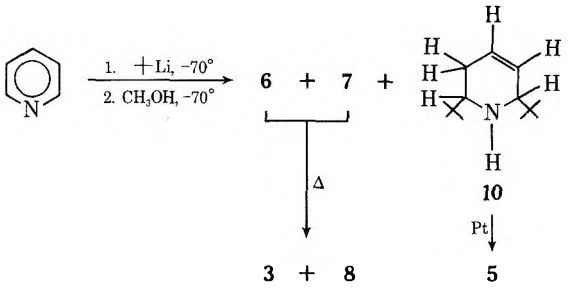
1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (**1**), the precursor of 2-*tert*-butylpyridine (**3**), was isolated as a crystalline solid from a mixture of *tert*-butyllithium and an equivalent amount of pyridine in ether or pentane at −70°. The assigned structure **1** follows from its nmr spectrum[5c] and from the properties of products resulting from protonation of **1**.

Addition of methanol to intermediate **1** at −70° resulted in formation of a yellow oil which gave two products by preparative glc identified as 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**8**) and 2-*tert*-butylpyridine (**3**). Assignment of **8** is based on a correct elemental analysis, nmr and ir spectra, and catalytic dehydrogenation (Pt–asbestos) of **8** to 2-*tert*-butylpyridine (**3**).

Tetrahydropyridine **8** and alkylpyridine **3** clearly were not present in a sample of the crude product which had not been subjected to glc analysis, as shown by the ir and nmr spectra of the mixture. These revealed the absence of aromatic hydrogens but showed absorptions not found in the spectra of either **3** or **8**, including those in the ir at 1580 and 1640 cm^{-1} characteristic of 1,2-dihydropyridines[7] and absorptions at 1675 cm^{-1} in the ir[8] and δ 7.92 (broad doublet) in the nmr assigned to the HC=N moiety of **7**. Compounds **3** and **8** are assumed to result, therefore, from decomposition of dihydropyridines **6** and **7** *via* hydride transfer from **6** to **7** and/or disproportionation of **6** and **7**. That decomposition had occurred was substantiated by observing that a mixture prepared from intermediate **1** and methanol at −70° contained only **3** and **8** after the sample had been heated on a steam bath for 1 hr. Formation of **7** by protonation of intermediate **1** at position 5 is analogous to a proposed[9] intermediate formed in the synthesis of 2,5-disubstituted pyridines from 1-lithio-2-phenyl-1,2-dihydropyridine. Although 1,2-dihydropyridines are common,[10] 2,5-dihydropyridines are virtually unknown,[8] presumably owing to the greater stability of 1,2- and 1,4-dihydropyridines. Nonisolable 2,5-dihydropyridines have been proposed,[11] however, as intermediates in the hydride reduction of pyridinium ions.



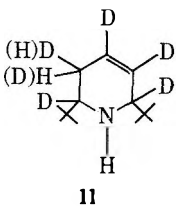
Evidence supporting intermediate **2** as a precursor of 2,6-di-*tert*-butylpyridine (**5**) was obtained initially from a reaction of pyridine with 10 equiv of *tert*-butyllithium at room temperature for 72 hr (reaction 2, Table I). After the reaction had been terminated at −70° with methanol, work-up gave a yellow oil which according to glc analysis contained several products, including alkylpyridines **3** and **5**. A third compound present in substantial amount was collected by preparative glc and identified as 2,6-di-*tert*-butyl-1,2,3,6-tetrahydropyridine (**10**), which is logically derived from protonation of intermediate **2**. An analogous reaction conducted at −70° gave on work-up an oil from which only three alkylation products were obtained by preparative glc. These were identified as tetrahydropyridine **8** and 2-*tert*-butylpyridine (**3**) (derived from decomposition of dihydropyridines **6** and **7** as previously described) and tetrahydropyridine **10**.



The assigned structure **10** is based on a correct elemental analysis, the dehydrogenation (Pt–asbestos) of **10** to 2,6-di-*tert*-butylpyridine (**5**), and the ir and nmr spectra of **10** and a deuterated analog.

The nmr spectrum of **10** showed two singlets (18 H) at δ 0.93 and 0.96 assigned to the two nonequivalent *tert*-butyl groups and a multiplet at δ 5.85 (2 H) attributed to the CH=CH moiety. The single hydrogen at position 6 adjacent to diastereotopic hydrogens at position 5 appeared as a doublet of doublets centered at δ 2.57.

Treatment of pyridine-d_5 with 10 equiv of *tert*-butyllithium at −70° followed by the appropriate work-up gave tetrahydropyridine **11**. The nmr spectrum of this compound revealed two broad absorptions at δ 1.70 and 1.90 for the diastereotopic hydrogens at position 5 which integrated for one hydrogen relative to the 18 hydrogens of the two *tert*-butyl groups. An absorption at δ 1.42 was assigned to NH. This was confirmed by observing that a decrease in the area of this peak relative to the *tert*-butyl absorptions occurred and a new absorption at δ 4.58 due to DOH appeared when a drop of D_2O was added to the nmr sample tube.



Tetrahydropyridine **10** and 2,6-di-*tert*-butylpyridine (**5**) were shown to originate from the same intermediate by the following experiments. Analysis (glc) of one half of a mixture of pyridine and 10 equiv of *tert*-butyllithium (−70°, 48 hr) which was quenched with methanol at −70° revealed the presence of tetrahydropyridine **10** (ir and nmr of a glc-collected sample) but showed no evidence of 2,6-di-*tert*-butylpyridine (**5**). A similar analysis of the remainder of the solution which had been refluxed (35°) for 24 hr revealed the presence of **5** but not tetrahydropyridine **10**.

Although 2-*tert*-butylpyridine (**3**) is readily converted by *tert*-butyllithium to 2,6-di-*tert*-butylpyridine (**5**) at room temperature (90% after 24 hr), no detectable conversion to **5** occurred at −70° after 24 hr. This result precludes formation of **5** at −70°. This conclusion is supported by reactions of pyridine with *tert*-butyllithium below room temperature (Table II) which did not give 2,6-di-*tert*-butylpyridine (**5**). That the sequence **1** → **3** → **4** was not a major source of **5** even at room temperature was suggested by an experiment which demonstrated the stability of intermediate **1** in solution at room temperature even after several days.

In order to optimize the yield of intermediate **2**, pyridine was treated with excess *tert*-butyllithium in a series of reactions (Table II) conducted below room temperature. However, the yield of **2** seldom exceeded 50% based on the yields of tetrahydropyridine **10**. Similar results were obtained from a reaction of intermediate **1** with excess *tert*-butyllithium, which gave 50% of **10**. Intermediate **2** could not be characterized by nmr from these solutions because of the presence of substantial quantities of **1**. Efforts to isolate **2** from **1** by crystallization were also unsuccessful.

In reactions in which intermediate **2** was converted by protonation to tetrahydropyridine **10** before decomposition of **2** occurred, 2,4,6-tri-*tert*-butylpyridine (**9**) was not formed. However, **9** was formed in reactions conducted above room temperature and became the major alkylpyridine formed (80%) in refluxing heptane at 80° (Table I). Thus, the only source of **9** is from the reactions of 2,6-di-*tert*-butylpyridine (**5**) with *tert*-butyllithium. This was confirmed by reactions of **5** with *tert*-butyllithium, which did not give **9** after 24 hr at room temperature but gave **9** in 50% yield after 24 hr in refluxing hexane at 60°. In an attempt to isolate the protonated analog of an intermediate leading to **9**, reactions in which **5** was only partially converted to **9** were cooled to −70° and quenched with methanol, and the temperature was not allowed to exceed 10° during work-up. Only aromatic species could be detected in an nmr spectrum of the residue. This result suggests that the temperature required to effect conversion of **5** to **9** is sufficient to cause immediate decomposition of the precursor of **9**.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained from Varian T-60 and HA-100 instruments using $DCCl_3$ and CCl_4 as solvents and TMS as the internal standard. Infrared spectra were taken as thin films from a Perkin-Elmer 257 instrument. Chemical analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Actual yields or relative percentages of products as specified in Tables I and II were determined by glc analysis utilizing standardized 20 ft × 0.25 in. 30% SE-30 on Chromosorb W and 20 ft × 0.25 in. 20% Versamid 900 on Chromosorb W columns on Hewlett-Packard F & M 5750 and Aerograph 90-P3 chromatographs.

Samples of products for chemical and spectral analyses and for preparation of derivatives were obtained by preparative glc using an Aerograph 90-P3 instrument equipped with a 20 ft × 0.375 in. column of 20% SE-30 on Chromosorb W.

Alkyllithium compounds were obtained from Lithium Corp. of America.

Synthesis of *tert*-Butylpyridines. A solution of pyridine and solvent (60 ml of solvent per 0.01 mol of pyridine) under a nitrogen atmosphere was cooled to −70° using a Dry Ice–acetone mixture. The pyridine–solvent mixture was mechanically stirred as a solution of *tert*-butyllithium in pentane was added at a rate necessary to maintain the temperature within a few degrees of −70° (2–4 hr required). The mixture was stirred for an additional period at a higher temperature. When a reflux temperature higher than that afforded by pentane (36°) was desired, pyridine and a higher boiling solvent were used and pentane from the addition of *tert*-butyllithium solution was removed by distillation.

The mixture was cooled in an ice–water or a Dry Ice–acetone mixture and treated with cold water or methanol, respectively, to destroy unchanged *tert*-butyllithium. The mixture was subjected to continuous liquid–liquid extraction with ether for 48 hr. The extract was dried (K_2CO_3), concentrated by rotary evaporation, and analyzed by glc. Specific conditions and results are summarized in Table I.

1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (1). A 25 × 200 mm test tube containing 10 ml of dry ether or pentane and 3.2 g (0.04 mol) of pyridine was flushed with nitrogen, fitted with a serum cap, and cooled in a Dry Ice–acetone mixture (−70°). Subsequent addition and removal of liquids was accomplished using a syringe. Ten milliliters of 0.40 *M* *tert*-butyllithium in pentane was added slowly to the mixture. Pale yellow crystals of **1** formed in 15–20 min. After standing for an additional 2–3 hr, the remaining liquid was removed and the solid was washed with two 5-ml portions of dry ether or pentane. Additional solvent was removed by pulling a vacuum on the crystals. The nmr spectrum of **1** was obtained from a solution of the solid (approximately 40%) in tetramethylethylenediamine: δ 0.85 (s, 9, *tert*-butyl), 3.40 (d, 1, C-2), 4.13 (m, 1, C-3), 4.45 (t, 1, C-5), 5.98 (m, 1, C-4), 6.72 (d, 1, C-6).

A mixture containing **1** in ether prepared as described above was allowed to stand at room temperature for 8 days. During this period nmr spectra of the solution showed that no decomposition of intermediate **1** had occurred.

Hydrolysis of 1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (1). A crystalline sample of **1** was prepared as described above, and the crystals were dissolved in anhydrous ether at room temperature. The solution was cooled to −70°, quenched with methanol, and warmed to room temperature. The ethereal solution was dried (K_2CO_3), and ether was removed by rotary evaporation. Analysis (glc) of the residue revealed the presence of two major products which were collected by preparative glc and identified as 2-*tert*-butylpyridine (nmr, ir) and 2-*tert*-butyl-1,2,5,6-tetrahydropyridine (**8**).

Tetrahydropyridine **8** was characterized by ir and nmr spectra: ir 1655 cm^{-1}; nmr δ 0.93 (s, 9, *tert*-butyl), 1.63 (s, 1, NH), 2.00 (m, 2, C-6), 3.03 (m, 3 C-2, C-5), 5.77 (m, 2, CH=CH).

Anal. Calcd for $C_9H_{17}N$ (**8**): C, 77.61; H, 12.33; N, 10.06. Found: C, 77.40; H, 12.43; N, 9.71.

A second sample of **1** in ether was hydrolyzed (CH_3OH) at −70°. The major components of the residue obtained on work-up at room temperature were assigned as 2-*tert*-butyl-1,2-dihydropyridine (**6**) and 2-*tert*-butyl-2,5-dihydropyrieine (**7**) based on the ir and nmr spectra of the residue and the products (**3** and **8**) obtained on heating the mixture. The spectra showed ir 1580, 1640 (conjugated diene), 16.75 cm^{-1} (C=N); nmr δ 0.85 and 0.95 (*tert*-butyl), 2.00, 2.65, 3.08, 3.85, 4.45, 5.02, 5.96 (complex multiplets, allylic and vinylic hydrogens), 7.92 (broad doublet, N=CH).

An nmr spectrum obtained from a sample of the reaction residue which had been heated (steam bath) for 1 hr was clearly that of a mixture of tetrahydropyridine **8** and 2-*tert*-butylpyridine (**3**).

Catalytic Dehydrogenation[12] of Tetrahydropyridine 8. A 0.66-g (0.0034 mol) sample of **8** was placed in a 100-ml flask connected by an L-shaped adapter to a catalyst chamber consisting of a 20-cm section of 12-mm glass tubing loosely packed with 30% platinized asbestos. The catalyst chamber was connected to a cold trap followed by a mineral oil bubbler. The system was flushed with nitrogen, the catalyst chamber was heated to 300° with a Lindberg Hevi-duty tube furnace, and hydrogen was allowed to pass slowly through the system (about 3 hr). The sample of tetrahydropyridine **8** was evaporated into the catalyst chamber by heating it at 150° in an oil bath. The reaction afforded as the only product 0.24 g (37%) of 2-*tert*-butylpyridine (**3**) identified by the ir and nmr spectra of a glc-collected sample.

2,6-Di-*tert*-butyl-1,2,3,6-tetrahydropyridine (10). The gener-

Table I
Synthesis of *tert*-Butylpyridines[a]

Reaction no.	Solvent, temp,[b] °C	Time, hr	*tert*-Butylpyridines,[c] %[d] 2-	4-	2,4-	2,6-	2,4,6-
1	*n*-Hexane, ambient	120	9	7	22	58	
2[e]	*n*-Hexane, ambient	72	49			13	
3	*n*-Hexane, 60	48	3	3	3	16	38
4[a]	*n*-Hexane, 60	48			6	22	33
5	*n*-Heptane, 80	48			1	5	76

[a] A 10:1 mole ratio of *tert*-butyllithium to pyridine was used in all reactions except 3, which employed a 3:1 ratio. [b] Following addition of *tert*-butyllithium at −70°. [c] Except for 2,4,6-tri-*tert*-butylpyridine, nmr and ir spectra of glc-collected samples were compared with those of authentic samples. Derivatives were 2-picrate, mp 104–105° [lit. mp 104.6–105.2°: H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951)]; 4-picrate, mp 129–130° (lit. mp 130.9–131.4°: Brown and Murphey); 2,4-chloroplatinate, mp 201.5–202.0°; 2,6-chloroaurate, mp 183.5–184.0° (lit.[3d] mp 184.2–184.5°); 2,4,6-tri-*tert*-butylpyridine, mp 68.0° [lit. mp 69.0°: K. Dimroth and W. Mack, *Angew. Chem., Int. Ed. Engl.*, **7**, 460 (1968)]. [d] Glc analyses of weighed residues obtained after work-up. [e] This reaction also provided 38% of tetrahydropyridine **10**. Yields given are relative percentages of the three major products. Small quantities of other products were not identified.

Table II
Some Reactions of Pyridine with *tert*-Butyllithium[a] below Ambient Temperature

Reaction no.	Temp, °C	Time, hr	Products, relative %[b] 3	8	5	10
1	−70	48	9	9		52
2	−70	48	22	16		55
3[c]	−70	48	23	13		45
4[d]	0	24	35	13		
5	−40	48	25	25		48
6	−90	24	29	33		24
7	−70	24	27	22		41
8	−90	96	39	9		44

[a] *tert*-Butyllithium was added to pyridine in *n*-hexane (reaction 1) or ethyl ether (other reactions). A 10:1 mole ratio of *tert*-butyllithium to pyridine was used in all reactions except reaction 1, which employed a 5:1 ratio. [b] The material balance consisted of small quantities of 4-*tert*-butylpyridine, bipyridyl, and unchanged pyridine. [c] Pyridine in ethyl ether was added to *tert*-butyllithium at −70°. [d] The major product was bipyridyl.

al procedure described previously for synthesis of alkylpyridines was used with the following modification. After addition of *tert*-butyllithium, the reaction period and termination with methanol were completed below room temperature. Specific reaction conditions and relative percentages of **10** are summarized in Table II. Tetrahydropyridine **10** was characterized from a glc-collected sample: ir 1648 cm^{-1}; nmr δ 0.93 and 0.96 (two singlets, 18, *tert*-butyl), 1.37 (s, 1, NH), 1.52 and 1.84 (two multiplets, 2, C-5), 2.57 (doublet of doublets, 1, C-6), 2.93 (m, 1 C-2), 5.82 (m, 2, C-3 and C-4).

Anal. Calcd for $C_{13}H_{25}N$ (**10**): C, 79.93; H, 12.90; N, 7.17. Found: C, 80.19; H, 12.61; N, 7.13.

2,6-Di-*tert*-butyl-1,2,3,6-tetrahydropyridine-*2,3,4,5,6-d*$_5$ (11). The procedure described for the synthesis of tetrahydropyridine **10** was followed, treating pyridine-d_5 with 10 equiv of *tert*-butyllithium for 48 hr at −70°. Termination of the reaction at this temperature by addition of methanol followed by work-up afforded **11** collected as a colorless oil by preparative glc: nmr δ 0.90 and 0.94 (two singlets, 18, *tert*-butyl), 1.70 and 1.90 (two broad singlets, 1, C-5), 1.42 (s, 1, NH). The δ 1.70 and 1.90 absorptions integrated for one proton relative to the *tert*-butyl absorption. The NH assignment was confirmed by a simple exchange experiment by adding a drop of deuterium oxide to the nmr sample tube. A decrease in the area of the NH absorption relative to the *tert*-butyl absorption was observed and was accompanied by the appearance of an absorption due to DOH (δ 4.58).

Catalytic Dehydrogenation of Tetrahydropyridine 10. The procedure described previously for dehydrogenation of tetrahydropyridine 8 was followed. A 0.40-g (0.0020 mol) sample of **10** gave as the only product 0.26 g (60%) of 2,6-di-*tert*-butylpyridine (**5**) identified by ir and nmr spectra of a glc-collected sample.

Reaction of 1-Lithio-2-*tert*-butyl-1,2-dihydropyridine (1) with Excess *tert*-Butyllithium. A crystalline sample of **1** was prepared from 10 ml of 2 *M* *tert*-butyllithium added to 1.6 g (0.02 mol) of pyridine in 10 ml of anhydrous ether at −70° in a 250-ml flask. The solvent was removed with a syringe, the crystals were washed with ether, and additional ether (50 ml) was added. To the stirred mixture 90 ml of 2 *M* *tert*-butyllithium was added from an addition funnel over a 1-hr period. The mixture was stirred for 48 hr at −70° and worked up as previously described in the preparation of tetrahydropyridine 8. Analysis (glc) of the reaction residue gave **10** (50%), which was identified by ir and nmr spectra of a glc-collected sample.

Reaction of 2-*tert*-Butylpyridine (3) with *tert*-Butyllithium. A 4.0-g (0.03 mol) sample of 3 in 200 ml of ether was treated with 150 ml of 2 *M* *tert*-butyllithium at −70° using the procedure previously described for the synthesis of *tert*-butylpyridines.

A sample of the mixture was removed after 24 hr at −70°, terminated with methanol at −70°, and worked up as described in the synthesis of alkylpyridines. Analysis (glc) of the residue showed only unchanged **3**.

The remainder of the mixture was stirred at room temperature for 24 hr and terminated with methanol at −70°. Analysis (glc) of the residue after work-up showed 2,6-di-*tert*-butylpyridine (90%).

2,4,6-Tri-*tert*-butylpyridine (9). A 115-ml sample of 1.24 *M* *tert*-butyllithium in pentane was added to 2.5 g (0.013 mol) of 2,6-di-*tert*-butylpyridine (**5**) in 100 ml of pentane at −70° using the general procedure described in the synthesis of *tert*-butylpyridines. The solution was warmed to room temperature, 100 ml of hexane was added, and the pentane was removed by distillation. The mixture was refluxed at 60° overnight, terminated at 0° with water, and worked up in the usual manner. Analysis (glc) showed a 50% conversion to **9**.

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Registry No. 1, 42540-75-0; **6**, 42540-76-1; **7**, 42540-77-2; **8**, 42540-78-3; **10**, 42540-79-4; pyridine, 110-86-1; *tert*-butyllithium, 594-19-4.

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1-Phenyl-1-azaspiro[2.2]pentanes. Synthesis and Reactions[1a]

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Phenyl azide adds to methylenecyclopropanes **2a–c** to produce the corresponding triazolines, which are photochemically converted to azaspiropentanes **1a–c**. These novel heterocycles isomerize to imines **5a–c**; the first two add methanol to yield **7a** and **7b**. Azaspiropentane **1a** also adds HCl to generate chloride **6a**, which can be reconverted to **1a** by the DMSO anion. Pyrolysis of **1a** leads to **5a** and *N*-phenylketenimine. The same products are obtained from vapor phase pyrolysis of its triazoline precursor. Benzene-sensitized irradiation of **1a** also gives **5a**. These reactions are discussed in mechanistic terms.

Substantial recent interest has focused on the synthesis and characterization of heterocyclic analogs of various highly strained, small-ring hydrocarbons. Several laboratories have reported upon oxaspiropentanes in recent years[2] and examples of a thiaspiropentane[3] and dioxaspiropentanes[4] are known. The synthesis of 2-phenyl-1-azaspiro[2.2]pent-1-ene is briefly mentioned in the literature,[5] but this novel unsaturated azaspiropentane derivative constitutes the only example of this structural type previously described. The present report details our studies of this heterocyclic system.[6]

The key step of our synthetic approach to **1a–c** exploits the well-known photochemical ring contraction of the appropriate triazolines.[7] The requisite triazolines were obtained from the thermal addition[7] of phenyl azide to methylenecyclopropanes **2a–c**. The adducts were obtained as sharply melting, crystalline solids whose nmr spectra confirmed their homogeneity and gross structure. The tentative assignment of structures **3a–c** is based upon the general observation that the substituent-bearing nitrogen of phenyl azide ordinarily bonds to the olefinic carbon best able to bear positive charge.[7] Nonetheless, alternate structures **4a–c** which would result from the alternate mode of addition cannot be rigorously excluded on the basis of the available data. This ambiguity is of little practical consequence, however, since the photochemical expulsion of nitrogen from either of the triazoline isomers should lead to the desired azaspiropentanes.

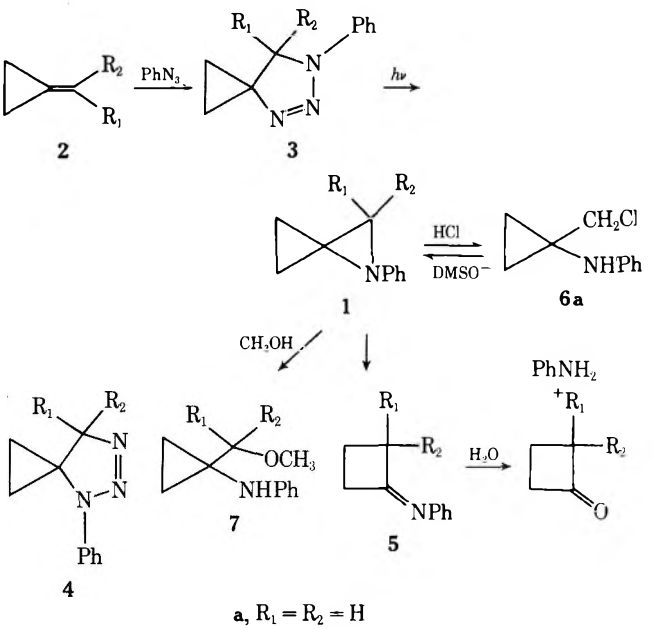
Irradiation of the appropriate triazoline in halocarbon solvents through Pyrex with 3100-Å bulbs gave azaspiropentanes **1a–c** cleanly. However, the photolysis leading to **1c** had to be performed at −78°, since this material underwent facile rearrangement to cyclobutanone anil **5c** upon warming to room temperature. Performing the photolysis of **1c** at room temperature gave only **5c**. The structure of this material was unambiguously established by its spectral data and clean hydrolytic conversion to aniline and 2,2-diphenylcyclobutanone.

The nmr spectrum of azaspiropentane **1a** is temperature dependent. Under ambient conditions there are only three signals for the aliphatic methylene groups at δ 0.77 (m), 1.07 (m), and 2.48 (s). However, at −50° each of these signals is split into a pair. This behavior is in accord with a relatively slow inversion at the nitrogen center at −50°, whereas a time-averaged spectrum is observed at the normal probe temperature where inversion is more rapid.

Prolonged irradiation of azaspiropentane **1a** in CH_2Cl_2 resulted in its conversion into chloride **6a**. This material is thought to result from the nonphotochemical addition of HCl to **1a**. The HCl apparently arises from a photochemically initiated decomposition of the solvent. Dry HCl in ether also transformed **1a** into **6a**. Performing this reaction at −20° allowed the isolation of a white, crystalline solid (tentatively identified as the hydrochloride of **1a**) which could be kept at this temperature in the solid state, but which was converted into **6a** by warming or more simply by dissolving it in $CDCl_3$ at −50°. On the other hand, azaspiropentane **1b** was transformed to cyclobutanone anil **5b** in high yield by HCl in benzene. Compound **5b** hydrolyzed to aniline and 2-phenylcyclobutanone as expected. Prolonged photolyses of **1b** in CH_2Cl_2 also gave **5b**, perhaps by HCl formation and acid-catalyzed rearrangement (*vide infra*).

Chloride **6a** was reconverted to azaspiropentane **1a** in good yield upon reaction with the sodium salt of DMSO. This process constitutes a second synthetic pathway to the subject heterocyclic system which may be employed in future synthetic approaches to azaspiropentanes.

Azaspiropentane **1a** reacted remarkably easily with methanol which added to the heterocyclic ring yielding **7a**. A similar process occurred with **1b** which gave **7b**. In



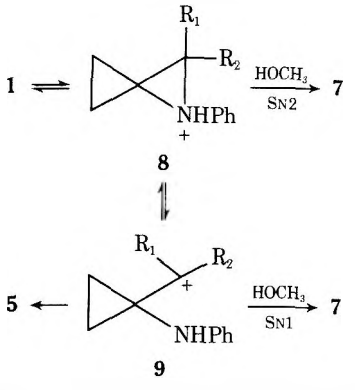
a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = Ph$
c, $R_1 = R_2 = Ph$

this case it was demonstrated that performing the reaction in the presence of $NaHCO_3$ retarded the reaction slightly, whereas the addition of minute quantities of acetic acid accelerated the conversion substantially. An attempt to add methanol to **1c** by carrying out the photolysis of **3c** in methanol was unsuccessful; the previously indicated rearrangement to **5c** was observed instead.

Interestingly, azaspiropentane **1a** was not reactive toward strong bases such as KO-*t*-Bu or $LiNEt_2$. A provocative, but obscure, transformation resulted in the formation of acetone and aniline in modest yields upon prolonged treatment with the sodium salt of DMSO.

In general, the azaspiropentanes obtained in this study undergo two types of reactions under protonic conditions:

ring expansion to the cyclobutyl isomer **5** and addition of methanol (or HCl) to the peripheral C–N bond of the heterocyclic ring. The former reaction appears to be more efficient with an increase in the number of phenyl groups on the carbon adjacent to the heteroatom. The second reaction type apparently displays an opposite response to this substitution change, since no **7c** was obtained from **1c** in methanol. The ring-expansion process is at least formally analogous to both the spiropentane–methylenecyclobutane[8] and oxaspiropentane–cyclobutanone[2] rearrangements. This isomerization of **1** is probably catalyzed by acid which transforms the nitrogen into a better leaving group as indicated in structure **8**. Ring opening leads to cyclopropylcarbinyl cation **9**, which then undergoes a 1,2-



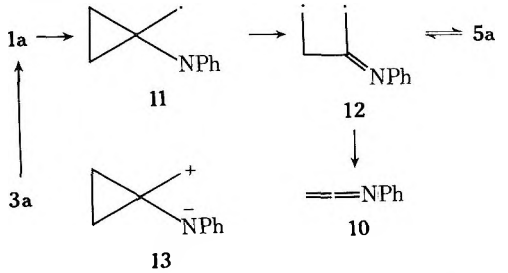
alkyl migration to the electron-deficient center and subsequently deprotonates to produce **5**. Concerted and uncatalyzed variants of this mechanism are also possible. The competing reaction, involving the acid-catalyzed addition of methanol, may occur either by nucleophilic displacement on **8** (SN2) or by nucleophilic capture of cation **9** (SN1). In the first case the substituent effect of the phenyls could result from their steric retardation of SN2 attack on **8** coupled with the simultaneous enhancement of the bond-breaking process leading to **9**. On the other hand, if the competition is simply between rearrangement of **9** leading to **5** and nucleophilic attack giving **7**, the phenyl substituents should serve to stabilize **9** and thereby decrease both rearrangement and methanol attack. If the latter is affected to a much greater degree than the former, the results are understandable. It is not clear, however, that this should be the case, and consequently the first description is tentatively preferred.

The thermal chemistry of **1a** was also examined in some detail. This azaspiropentane can be vacuum transferred through a tube heated to 250° without change. However, raising the temperature to 275° gives a mixture of starting material, cyclobutanone anil (**5a**), and *N*-phenylketenimine[9] (**10**) in a 56:18:16 ratio. At 400° complete conversion of **1a** to a 50:50 mixture of **5a** and **10** occurred. Upon increasing the temperature further there was a decrease in the ratio of **5a** to **10**. This is accountable by a secondary pyrolysis of **5a** to **10** and, presumably, ethylene. This reaction was demonstrated by the independent pyrolysis of **5a** to **10** at temperatures above 400°. However, the presence of the ketenimine in the pyrolysates from **1a** at lower temperature indicates that some of this material is formed directly. Interestingly, refluxing a benzene solution of **1a** for 48 hr gave 20% conversion of **1a** to a 50:50 mixture of **5a** and **10**. Under comparable conditions product **10** was stable.

The most straightforward explanation of these thermal reactions invokes homolytic rupture of the peripheral C–N bond of **1a**, yielding biradical **11**. Ring opening of this species generates new biradical **12**, which can lead to **5a** by bond formation and to ketenimine **10** by bond fission of the 1,4-biradical moiety. The pyrolytic transformation of **5a** to **10** undoubtedly results from the reversible formation of **12**. It is remarkable that the fragmentation of **12** leading to **10** is competitive with rearrangement to **5a** even in refluxing benzene. Dipolar species **13** could be considered as an alternate intermediate in the thermal **1a** to **5a** conversion, but it is not an attractive precursor of **10**.

Azaspiropentane **1b** was isomerized to **5b** by heating a $CDCl_3$ solution to 100° and, as indicated previously, **1c** undergoes spontaneous transformation to **5c** below room temperature. These reactions may be related to the thermal conversion of **1a** just described, but acid-catalyzed processes appear to be equally likely.

The vacuum transfer of triazoline **3a** through a heated chamber at 550° also produced **5a** and **10** in a 34:66 ratio. The similarity of this product mixture with that from **1a** under these conditions suggests strongly that the former process intersects the pathway of the latter somewhere along the way from **1a** to **5a** and **10**. The thermolysis of **3a** probably leads initially to either **1a** itself or to the derived biradical **11**.



Finally, irradiation of **1a** in benzene with 2537-Å light results in very slow conversion to **5a**; direct irradiation with light of this wavelength was ineffective. It appears that energy is transferred from excited benzene to **1a**, resulting in the formation of a species capable of giving **5a**. The most likely candidate for this important intermediate is the triplet state of **11**.

Experimental Section

General. All nmr spectra were recorded on a Varian HR-220 spectrometer. Mass spectra were obtained on MS-9 and CH-4 spectrometers. Infrared spectra were obtained on a Perkin-Elmer IR-37. Analyses were performed by Midwest Microanalytical Laboratories. Anhydrous $MgSO_4$ was routinely used as drying agent.

Addition of Phenyl Azide to Methylenecyclopropane. A mixture of 1 g of methylenecyclopropane[10] and 3 g of phenyl azide[11] was refluxed for 72 hr under nitrogen using a Dry Ice–acetone condenser. After the addition of 50 ml of pentane, the solution was cooled to 0° and filtered to give 1.8 g (56%) of light yellow crystals: mp 108–110°; ir (CCl_4) 6.25, 6.70, 6.75, 9.05, 9.2, 9.4, 10.8 μ; nmr δ 1.01 (m, 2), 1.52 (m, 2), 3.50 (s, 2), 6.90 (t, 1, J = 6 Hz), 2.08 (d, 2, J = 6 Hz), and 7.20 (t, 2, J = 6 Hz).

Anal. Calcd for $C_{10}H_{11}N_3$: C, 69.34; H, 6.40; N, 24.26. Found: C, 69.4; H, 6.3; N, 24.1.

A 1-g sample of methylenecyclopropane and 3 g of phenyl azide were placed in a 100-ml glass tube, cooled in liquid N_2, and sealed under vacuum. The tube was heated to 50° for 24 hr, cooled in liquid N_2, and opened to give a yellow slurry which was diluted with pentane. The solid was collected by filtration to give 2.6 g (80%) of product. Several other reaction mixtures heated for 48 hr under identical conditions resulted in shattering of the tube.

1-Phenyl-1-azaspiro[2.2]pentane (1a). A 100-mg sample of triazoline in 10 ml of CH_2Cl_2 in a Pyrex flask was irradiated for 2 hr with 3100-Å bulbs in a Rayonet reactor. Removal of the solvent under vacuum gave 75 mg (90%) of **1a** as a dark yellow oil: ir (CCl_4) 6.25, 6.85, 7.9, 9.9, 11.2 μ; nmr δ 0.77 (m, 2), 1.07 (m, 2), 2.48 (s, 2), 6.66 (d, 2, J = 7 Hz), 6.82 (t, 1, J = 7 Hz), and 7.08 (t, 2, J = 7 Hz). A sample was purified by column chromatography on basic alumina for analysis.

Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.8; H, 7.6; N, 9.5.

A 25-mg sample of **1a** in acetone-d_6 was cooled to −50°: nmr δ 0.74 (m, 1), 0.88 (m, 1), 1.09 (m, 1), 1.13 (m, 1), 2.48 (s, 1), 2.66 (s, 1), 6.60 (d, 2, J = 6 Hz), 6.91 (t, 1, J = 6 Hz), and 7.15 (t, 2, J

= 6 Hz). The singlets at δ 2.48 and 2.66 broadened and merged into one peak at δ 2.48 upon warming the sample. The coalescence temperature for this process was −22°. The complex multiplets at δ 0.74 and 0.88 and those at δ 1.09 and 1.13 also merged into single signals at δ 0.77 and 1.11, respectively.

A 5% impurity in the sample from photolysis in CH_2Cl_2 continued to increase upon prolonged irradiation as **1a** decreased. After 4 hr of irradiation the sample was quantitatively converted to **6a**: ir (CCl_4) 2.93, 6.25, 6.70, 6.75, 8.0, 9.7, 13.9, and 14.5 μ; nmr δ 0.91 (m, 2), 1.02 (m, 2), 3.59 (s, 2), 4.36 (broad s, 1), 6.5–7.5 (m, 5); mass spectrum *m/e* (rel intensity) 183 (8), 181 (21), 146 (100), 132 (58), 119 (14), 118 (30), 117 (29), 104 (71), 91 (33), 77 (83).

Photolysis of the triazoline in ether solution under the same conditions gave only **1a** after 5 hr.

Reaction of 1a with HCl. A 100-mg sample of **1a** in 10 ml of ether was cooled to 0° and HCl gas was bubbled into the solution. A white solid formed which turned into a brown oil upon filtration. Extraction of the oil into $CDCl_3$ and examination by nmr revealed the formation of **6a**, pure by nmr.

When the HCl was added at −20°, the white solid could be collected and was stable at −20°. The solid was dissolved in $CDCl_3$ at −50°; examination of the nmr indicated only **6a**.

A 10-mg sample of azaspiropentane **1a** was dissolved in 1.0 ml of acetone-d_6 and 0.5 equiv of gaseous HCl was added. Analysis by nmr revealed **6a** (45%) and **1a** (55%).

Reaction of 1a with Methanol. A mixture of 100 mg of **1a** and 1 ml of methanol was stirred at 130° for 24 hr. Removal of methanol under vacuum and vacuum transfer (0.01 mm) gave 100 mg (82%) of **7a**: ir 3.0, 6.3, 6.75, 9.1, and 9.8 μ; nmr (100 MHz) δ 0.78 (m, 4), 3.18 (s, 3), 3.32 (s, 2), 3.8 (br s, 1), and 6.8 (m, 5); mass spectrum *m/e* (rel intensity) 177 (61), 176 (26), 146 (24), 144 (45), 132 (100), 130 (27), 118 (24), 117 (45), 93 (100), 91 (68), 86 (92), 84 (100), 77 (73), 51 (81), 49 (100); exact mass, 177.116 (calcd for $C_{11}H_{15}ON$, 177.115).

Treatment of 6a with Base. A 1-g sample of **6a** was dissolved in 50 ml of DMSO and 4 equiv of NaH was added at 0° under nitrogen. The solution was stirred at 0° for 30 min and the reaction was quenched by the addition of 100 ml of water. The solution was extracted twice with ether and the ether extract was washed with water and dried. Solvent removal gave 750 mg (~100%) of crude **1a**. A similar reaction run for 15 min gave 85% conversion to **1a**.

Treatment of 1a with Base. A 100-mg sample of **1a** in 50 ml of ether was treated with 4 equiv of lithium diethylamide at 20° for 72 hr. The addition of water, separation of the ether layer, drying, and solvent removal gave a sample whose nmr indicated a mixture of diethylamine and **1a**.

A 100-mg sample of **1a** in 50 ml of ether was refluxed with 5 equiv of *t*-BuOK for 72 hr. The addition of 10 ml of water, separation of the ether layer, and solvent removal gave a sample whose nmr showed only *tert*-butyl alcohol and **1a**.

Treatment of 1a with DMSO Anion. A 100-mg sample of **1a** in 50 ml of DMSO was stirred at 0° while 4 equiv of NaH was added. The reaction was stirred for 72 hr at 30°. The addition of 10 ml of water followed by vacuum transfer (20 mm) of the volatile material into a Dry Ice trap gave 10 mg (25%) of acetone. Addition of 100 ml of water to the reaction mixture, extraction with ether, drying, and solvent removal gave a sample whose nmr indicated aniline and **1a** in a 1:5 ratio. Column chromatography of this mixture gave 50 mg of **1a** and 10 mg of aniline (15%).

Pyrolysis of 1a. Seven 25-mg samples of **1a** were transferred under vacuum (0.1 mm) through a chamber filled with quartz chips and heated to the temperature indicated. Only two products were observed by nmr analysis of the crude pyrolysate: *N*-phenylketenimine (**10**) and **5a** (Table I).

A sample of **5a**, isolated by column chromatography, was subjected to the pyrolysis conditions above. No reaction was observed below 400°; at 400°, <5% of **10** was formed; at 550°, 10% of **10** was observed; at 600°, 20% was observed.

A 25-mg sample of **1a** was refluxed in benzene for 48 hr. Solvent removal by vacuum (20 mm) and nmr analysis indicated **1a**, **10**, and **5a** in a 80:10:10 ratio. Refluxing a solution of **5a** in benzene for 72 hr gave no **10**.

Vacuum transfer (0.001 mm) of 1.0 g of **1a** through a 600° chamber filled with quartz required 72 hr and gave 0.50 g (54%) of **10** pure by nmr.

Photolysis of 1a. A 100-mg sample of **1a** in 100 ml of ether was irradiated through quartz using 2537-Å bulbs in a Rayonet reactor for 72 hr. Solvent removal gave 97 mg of recovered starting material. A similar experiment with benzene as the solvent gave 10% conversion to **5a** with 85% recovery of **1a**.

Table I

Temp, °C	1a, %	5a, %	10, %
200	100		
250	100		
275	66	18	16
300	42	36	22
400		50	50
550		46	54
600		25	75

Pyrolysis of 3a. A 100-mg sample of **3a** was transferred under vacuum through a chamber filled with quartz chips at 550°. The material collected was shown by nmr and ir to be a 66:34 ratio of **10** and **5a**. *N*-Phenylketenimine[9] gave ir 4.93 and 11.0 μ; nmr δ 3.41 (s, 2), 7.0–7.3 (m, 5). Imine **5a** gave ir 5.89 μ; nmr δ 1.97 (quintet, 2, *J* = 7 Hz), 2.83 (t, 2, *J* = 7 Hz), 3.04 (t, 2, *J* = 7 Hz), 6.68 (d, 2, *J* = 7 Hz), 6.91 (t, 1, *J* = 7 Hz), and 7.15 (t, 2, *J* = 7 Hz).

The crude reaction mixture was hydrolyzed with 10% HCl. The reaction mixture was extracted with ether and the extract was concentrated and purified by glpc to give 5 mg (40%) of cyclobutanone and 38 mg (75%) of acetanilide. The water layer was neutralized with $NaHCO_3$ and an ether extract was shown to contain 30 mg (74%) of aniline.

Addition of Phenyl Azide to Benzylidenecyclopropane[12] (2b). A mixture of 2 g of **2b** and 2 g of phenyl azide was heated on a steam bath for 24 hr. The addition of pentane caused 1.5 g (38%) of **3b** to precipitate as tan crystals, mp 136–140°. Recrystallization from cyclohexane gave a pure sample: mp 147–148° (gas evolution at 180–185°); ir ($CHCl_3$) 3.29, 3.48, 6.25, 6.75, 6.92, 7.42, 9.03, 9.3, 9.4, and 9.71 μ; nmr δ 0.55 (m, 1), 1.00 (m, 1), 1.29 (m, 1), 1.70 (m, 1), 4.79 (s, 1), and 7.0–7.3 (m, 10).

Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.1; H, 6.3; N, 16.8.

Photolysis of 3b. A solution of 100 mg of **3b** in 10 ml of CH_2Cl_2 was irradiated at 0° through a Pyrex test tube in a Rayonet reactor using 3100-Å bulbs until gas evolution ceased (~4 hr). Removal of the solvent gave 92 mg (99%) of a brown liquid identified as 1,2-diphenyl-1-azaspiro[2.2]pentane (**1b**) which could not be further purified without decomposition. This crude sample gave ir 6.25, 6.70, 6.89, 7.16, 8.0, 9.0, and 9.7 μ; nmr δ 0.82 (m, 1), 0.91 (m, 1), 1.14 (m, 1), 1.38 (m, 1), 3.57 (s, 1), and 6.9–7.5 (m, 10). No change in the nmr was observed after storage of a pure sample of **1b** for 1 year at 0°. Photolysis in cyclohexane or chloroform did not proceed as rapidly or give as pure a product.

Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.9; H, 6.8; N, 6.4.

Pyrolysis of 1b. A solution of 20 mg of **1b** in 1 ml of $CDCl_3$ was sealed in an nmr tube. The sample was heated to 100° and its spectrum was recorded at 15-min intervals. Conversion to one product in 55% yield was complete in 100 min as judged by nmr integration. Solvent removal and purification of the residue by column chromatography under a nitrogen atmosphere using basic alumina which had been pretreated by elution with 400 ml of anhydrous ether gave 7 mg of **5b**: ir ($CHCl_3$) 3.3, 5.9, 6.28, 6.74 μ; nmr δ 2.10 (m, 1), 2.65 (m, 1), 2.86 (m, 2), 4.45 (t, 1, *J* = 7 Hz), and 6.8–7.2 (m, 10).

Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 87.0; H, 6.8; N, 6.1.

Hydrolysis of 5b. A 34-mg sample of **5b** was stirred with 5 ml of 10% HCl for 6 hr. The solution was extracted with ether, the extract was dried, and the solvent was removed to give 20 mg (89%) of 2-phenylcyclobutanone which was purified by glpc: ir 3.41, 5.62, 6.72, 6.93, 13.3, and 14.4 μ; nmr δ 2.2 (m, 1), 2.5 (m, 1), 3.0 (m, 1), 3.1 (m, 1), 4.44 (t, 1, *J* = 7 Hz), and 7.19 (m, 5).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.4; H, 6.7.

The acid solution was neutralized with $NaHCO_3$ and extracted with ether. Solvent removal after drying gave 12 mg (84%) of aniline.

Photolysis of 1b. A 100-mg sample of **1b** in 3 ml of CH_2Cl_2 was irradiated through Pyrex with 3100-Å bulbs in a Rayonet reactor for 24 hr. Solvent removal gave a brown liquid whose nmr was identical with that of **5b** except for an excess of absorption in the aromatic region. Purification by column chromatography as described above gave 48 mg (48%) of **5b**. Hydrolysis as described above gave 25 mg (89%) of 2-phenylcyclobutanone and 18 mg (82%) of aniline.

Reaction of 1b with HCl. An 80-mg sample of **1b** in 10 ml of benzene was stirred at 0° while 1 drop of a saturated solution of

dry HCl in benzene was added. The benzene was removed under vacuum to give 73 mg of **5b** (90%).

Reaction of 1b with Methanol. An 80-mg sample of **1b** in 0.3 ml of methanol was stirred at 25° for 6 hr. Solvent removal gave 81 mg (93%) of **7b**: ir 2.95, 3.34, 6.25, 6.70, 9.15, 13.3, 14.3 μ; nmr δ 0.57 (m, 1), 0.75 (m, 2), 1.02 (m, 1), 3.15 (s, 3), 3.97 (broad s, 1), 4.48 (s, 1), 6.60 (d, 3, J = 7 Hz), 7.03 (t, 2, J = 7 Hz), and 7.18 (m, 5) purified by column chromatography.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.3; H, 7.8; N, 5.4.

An 80-mg sample of **1b** was dissolved in 0.3 ml of CD_3OD and its disappearance was followed by nmr at 15° to determine its approximate half-life. For CD_3OD stirred over solid $NaHCO_3$, $\tau_{1/2}$ was ~58 min; for neutral CD_3OD, $\tau_{1/2}$ was ~42 min; and for 0.01% AcOD in CD_3OD, $\tau_{1/2}$ was ~4 min. The reaction was over in 1% AcOD in CD_3OD before a spectrum could be recorded.

Reaction of Diphenylmethylenecyclopropane[12] (2c) with Phenyl Azide. A 1.0-g sample of **2c** and 1.0 g (1.7 equiv) of phenyl azide were heated on a steam bath for 48 hr, after which time **2c** had completely reacted upon nmr examination. Addition of 100 ml of pentane gave 0.1 g of a dark brown solid whose nmr had only aromatic absorption. Removal of this solid by filtration, concentration of the pentane solution to 25 ml, and cooling to −20° gave 0.8 g (51%) of solid **3c** (mp 145–147°, gas evolution at 180°): ir 3.3, 6.25, 6.80, 6.90, 7.5, and 9.4 μ; nmr δ 0.55 (m, 2), 1.50 (m, 2), and 6.6–7.2 (m, 15); mass spectrum m/e (rel intensity) 325 (<1), 297 (19), 296 (38), 282 (11), 269 (46), 170 (100), and 165 (23).

Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.0; H, 5.8; N, 12.6.

Photolysis of 3c. A 100-mg sample of **3c** in 1 ml of CH_2Cl_2 was irradiated with a medium-pressure Hanovia system through Pyrex. Observation by nmr indicated a reaction time of 60 min. Solvent removal gave a dark brown oil identified as **5c**: ir 5.90, 6.27, 6.82, 6.93, 7.91, 9.0, 9.8 μ; nmr δ 2.83 (m, 4), 6.8–7.8 (m, 15). Purification by column chromatography on basic alumina gave 80 mg (91%) of a light yellow oil.

Anal. Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 89.0; H, 6.3; N, 4.5.

Photolysis of **3c** in $CDCl_3$ under the same conditions as above at −78° gave 90% conversion of **3c** to **1c** as observed by low-temperature nmr: δ 1.11 (m, 2), 1.55 (m, 2), and 6.4–7.4 (m, 15). This sample of **1c** was stable up to −30° for periods up to 6 hr. Rapid warming to 20° gave quantitative conversion to **5c** in 10 min as monitored by nmr.

Photolysis of 3c in Methanol. A 100-mg sample of **3c** in 5 ml of MeOH was irradiated with 3100-Å bulbs in a Rayonet reactor for 3 hr. Removal of the MeOH under vacuum gave 82 mg (92%) of **5c**, pure by nmr.

Hydrolysis of 5c. A 100-mg sample of **5c** was stirred with 100 ml of a 5% HCl solution for 2 hr. The HCl solution was extracted with ether, the ether was dried, and the solvent was removed under vacuum to give 70 mg (93%) of 2,2-diphenylcyclobutanone: ir 5.61 μ; nmr δ 2.76 (t, 2, J = 8.5 Hz), 3.08 (t, 2, J = 8.5 Hz), 7–7.8 (m, 10).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 5.92. Found: C, 86.4; H, 5.9.

The HCl aqueous layer was neutralized with $NaHCO_3$ and extracted with ether. Drying and solvent removal gave 25 mg (80%) of aniline.

Registry No. **1a**, 42540-58-9; **1b**, 40323-60-2; **1c**, 42540-60-3; **2a**, 6142-73-0; **2b**, 7555-67-1; **2c**, 7632-57-7; **3a**, 42540-63-6; **3b**, 40323-62-4; **3c**, 42540-65-8; **5a**, 42540-66-9; **5b**, 40323-63-5; **5c**, 42540-68-1; **6a**, 42540-69-2; **7a**, 42540-70-5; **7b**, 40323-64-6; **10**, 42540-72-7; phenyl azide, 622-37-7; 2-phenylcyclobutanone, 42436-86-2; 2,2-diphenylcyclobutanone, 24104-20-9.

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Octahydrophenanthreneaziridines. *syn*- and *anti*-9,10-Imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene

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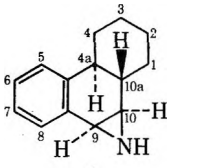
Preparation of *anti*-9,10-imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (2) is reported. A comparison of the results of ring opening reactions of these syn and anti aziridines (1 and 2) is made. Both isomers are converted to β-chloro amides when treated with benzoyl chloride and subsequently converted to the isomeric oxazolines. Acid-catalyzed ring opening produces amino alcohols in both cases with 1 affording a 57:43 ratio of cis and trans products, 22 and 23. Opening of 2 afforded a 10:90 mixture of cis and trans amino alcohols, 24 and 25.

Current studies required finding suitable methods for the preparation of the isomeric aziridines 1 and 2. Obtention of these aziridines provided a convenient system for study of the stereochemistry of the ring opening process. These compounds offer advantages similar to steroidal aziridines, with the additional quality of the regioselectivity of opening being somewhat predetermined because of the adjacent phenyl group; thus C–N bond breaking would occur primarily at the benzylic position. In previous studies, products of both carbonium ion opening and displacement mechanisms had been reported from styrylaziridines and aziridinium ions.[1-3]

In a previous study,[4] *syn*-9,10-imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**1**)[5,6] was prepared. Reaction of **1** with benzoyl chloride afforded oxazoline **5**. More carefully controlled conditions (0°, ether, 1 equiv of pyridine) led to an intermediate 9(a)-chloro-10(e)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene[7] (**3**), which was readily converted to **5** (75°, $CHCl_3$, 30 min). We therefore sought to prepare the analogous anti aziridine, **2**, to look at this process, as well as to study the ring opening process under hydrolytic conditions.



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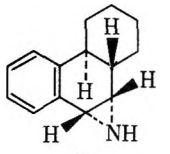

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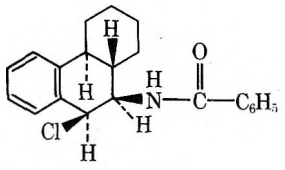

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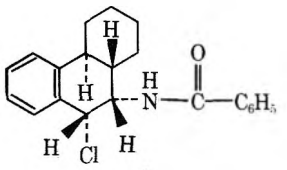

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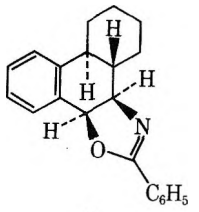

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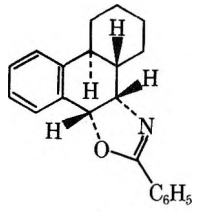

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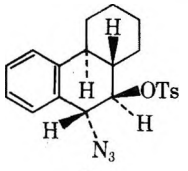
A successful route to **2** was found in the method of Ponsold,[8] which involved the reductive cyclization of 9(e)-azido-10(e)-tosyloxy-1,2,3,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**7**) using hydrazine and a Raney



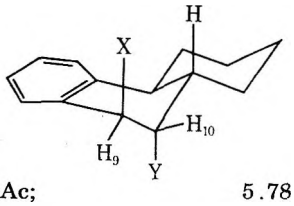
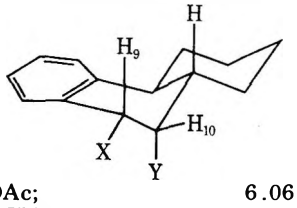
7

nickel catalyst. This method has previously been applied to 1,2-trans-diaxial azido mesylates in steroidal systems.[8-11] The process of preparation of an azido mesylate or tosylate from an epoxide, followed by reaction with hydrazine–Raney nickel, affords a convenient route to aziridines of opposite stereochemistry from the starting epoxide.

The azide function of **7** had been shown to undergo a facile 1,2 shift under acetolysis conditions.[12] The success of that process suggested possible utilization of **7** in the Ponsold reaction, although no precedent of a diequatorial[7] system has previously been reported. Under these conditions aziridine **2** was produced in 80% yield. The nmr spectrum was consistent with the structure, showing signals for H_9 and H_{10} at δ 2.97 and 2.48, respectively, $J_{9,10} = 6$, $J_{10,10a} \cong 0$ Hz.

Reaction of **2** with benzoyl chloride afforded a β-chloro benzamide, **4**, which cyclized to the oxazoline **6** only upon heating at 80° for several hours, more strenuous conditions than those necessary to convert **1** to **5**.[4] The structure of oxazoline **6** was confirmed by converting a sample of amino alcohol **10** to **6** by reaction with ethyl benzimidate.[12] The isolation of an intermediate β-halo amide is consistent with previous results and speculation concerning the conversion of *N*-acylaziridines to oxazolines.[4,13,14]

Table I
60-MHz Nmr Data on Selected 9(e),10(a)- and 9(a),10(a)-Disubstituted Octahydrophenanthrenes

Compd	δ, H_9	$J_{9,10(e)}$, Hz
		
8,[a] X = OAc; Y = NHAc	5.78	3.0
9,[a] X = OAc; Y = N_3	5.95	3.0
10,[a] X = OH; Y = Br	4.75	2.3
11,[a] X = $NHCO_2Me$; Y = I	5.59	2.0
12,[b] X = Y = OH	4.30	2.5
13,[b] X = Y = OCOPh	6.02	2.5
14,[b] X = Y = $OCNH_2$	5.55	2.0
15,[c] 6β,7α-Dichloroestrone	5.28	2.2
		
16,[a] X = OAc; Y = NHAc	6.06	5.0
17,[a] X = OAc; Y = N_3	6.18	4.5
18,[b] X = Y = OH	4.57	4.0
19,[b] X = Y = OCOPh	6.08	4.0
20,[b] X = Y = $OCNH_2$	5.83	4.0
21,[c] 6α,7α-Dichloroestrone	5.54	4.0

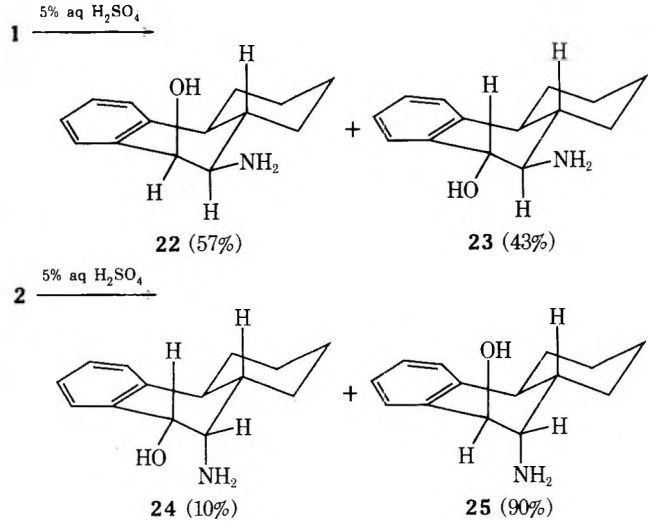
[a] Reference 12. [b] B. E. Sherwood, Ph.D. Thesis, University of Washington, 1973. [c] Y. Osawa and M. Newman, *J. Amer. Chem. Soc.*, **85**, 2856 (1963).

The stereochemistry of the chlorine atom in **4** is tentatively assigned the 9(e) position on the basis of the nmr spectrum, requiring **4** to be a *cis*-β-chlorobenzamide. The nmr spectrum showed $J_{9,10} = 4.5$ Hz, consistent with either a 9(e) or 9(a) proton. However, in related systems (Table I), consistently larger J values are observed for the 9(a),10(e) coupling than for the 9(e),10(e) disposition of protons. Dreiding models show that $\theta_{9(e),10(e)}$ is *ca.* 70–75°, consistent with an expected larger J value for the former distribution of protons.[15]

The similarity in stereochemistry of **3** and **4**, both cis, would suggest that similar processes are involved. However, the structures of these two compounds, and the subsequent oxazoline formation under the described conditions, are not consistent with the normal displacement mechanisms expected for opening of *N*-acylaziridines or their conversion to oxazolines. The difference in ease of conversion of the two intermediate β-halo amides to oxazolines may be a consequence of small differences in energy of the transition states of the processes involved. Additional work on these and other compounds would be needed to validate this interpretation.

The distribution of products of ring opening of **1** and **2** under aqueous acid (5% aqueous H_2SO_4) conditions were

determined. These products are the amine alcohols, **22, 23, 24,** and **25.** Ring opening of **1** afforded a 57:43 ratio of cis and trans amino alcohols **22** and **23.** Under similar conditions **2** is converted to a 10:90 ratio of cis and trans amino alcohols **24** and **25.** The products of opening of **1** are determined by acetylation of the amino alcohols followed by glpc determination of the diacetates (see Experimental Section). No difficulties were encountered in a direct glpc determination of alcohols **24** and **25.** Under these conditions all of the aziridine is consumed as determined by glpc.



These results suggest that, while the acid-catalyzed opening of **1** may occur through a benzylic carbonium ion which is nearly equally accessible from either side of the molecule, the opening of **2** may be more of a concerted process in which water molecules approach the β face of the molecule during bond-breaking process.

It would seem that, if both SN1 and SN2 processes are occurring in both openings, the SN2 process in the opening of **1** may require a greater activation energy because in the transition state a colinear disposition of functional groups would require a boat conformation, in contradistinction to a half-chair conformation for a similar transition state in the opening of **2.**

Small differences in the activation energies of the processes in each opening may be reflected in these product ratios. Additional experiments to consider some of these factors are in progress. The preparation of the aziridines and the relatively simple method for determination of product ratios will facilitate additional work.

Experimental Section

Peaks given in the mass spectral fragmentations are within 5.0 millimass units from calculated values. Unless otherwise stated, anhydrous sodium sulfate was used to dry solutions in organic solvents.

***syn*-9,10-Imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (1).** This compound was prepared by the method of Nelson and Miller,[4] mp 125–127° (lit.[4] mp 129–130°).

***anti*-9,10-Imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (2).** A mixture of 9(e)-azido-10(e)-*p*-toluenesulfonyloxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**7**,[12] 795 mg, 2.0 mmol), hydrazine hydrate (99%, 25 g, 0.5 mol), and Raney nickel [activity W-4, 348 mg (6.0 mg-atoms)] in 80 ml of MeOH was stirred at room temperature for 20 hr, during which the time 5.0-g portions of hydrazine were added every 3 hr. The mixture was diluted with H_2O and extracted with ether. The combined ether solutions were washed with H_2O, dried, and evaporated. The residual oil crystallized on standing and was recrystallized from hexane, affording 320 mg (80%) of **2**: mp 109–110°; ir (KBr) 3300 (NH), 3050 (ArCH), 2970 and 2900 (aliphatic CH), 1490, 1450, 1410, 1260, 1240, 1050, 890, 880, 860, 845, 820, 805 and 785, 725 and 755 cm^{-1}; nmr ($CDCl_3$) δ 7.23 (s, 4, ArH), 2.97 (d, broadened, 1, $J_{9,10}$ = 6.0, $J_{9,NH} \cong$ 0–1 Hz, H_9), 2.50–1.10 (m, 12, NH, H_{10} and $CHCH_2$ envelope); nmr ($CDCl_3$ + D_{20}) δ 4.53 (s, 1, HDO), 2.48 (d, 1, $J_{10,10a} \cong$ 0 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 201 (9, M + 2), 200 (55, M + H), 199 (100, M), 198 (61, M − 1), 182 (61, M − NH_3), 181 (17, M − NH_4), 170 (39, $C_{12}H_{12}N$), 156 (52, $C_{11}H_{10}N$), 141 (90, $C_{11}H_9$), 128 (74, $C_{10}H_8$), 91 (23, C_7H_7), 77 (23, C_6H_5); *m/e* 199.1362 (calcd for $C_{14}H_{17}N$, 199.1358).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.51; H, 8.45; N, 6.91.

9(e)-Chloro-10(a)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,-10a)-octahydrophenanthrene (4). To a stirred solution of *anti*-9,10-imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**2**, 80 mg, 0.42 mmol) and pyridine (33 mg, 0.42 mmol) in 40 ml of ether was added dropwise benzoyl chloride (141 mg, 1.0 mmol) in 10 ml of ether, maintaining the temperature below 5° with an ice bath. The mixture was stirred for 3.5 hr, filtered, and evaporated. The solid residue liquefied upon exposure to air; so it was redissolved in ether and the ether solution was washed with water, dried, concentrated to 2 ml, and placed in the refrigerator. The solute crystallized to give 9(e)-chloro-10(e)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**4**): 74 mg (58%); mp 151–151.5°; ir (KBr) 3350 (NH), 3100 (aromatic CH), 2950 and 2880 (aliphatic CH), 1640 (amide I), 1580 (amide II), and 740, 715, and 690 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 7.83–7.60 (m, 2, ArH), 7.55–7.27 (m, 7, ArH), 6.17 (d, br, 1, $J_{10,NH}$ = 11 Hz, NH), 5.60 (d, 1, $J_{10,9}$ = 4.5 Hz), 4.91 (dd, 1, $J_{10,NH}$ = 11, $J_{9,10}$ = 4.5, $J_{10,10a} \cong$ 0.1 Hz, H_{10}), 2.85–1.10 (m, 10, CH_2CH envelope); nmr (DMSO-d_6, D_2O) absorption at δ 6.17 is exchangeable with D_2O and the signal at δ 4.91 collapses to a slightly broadened doublet ($J_{10,9}$ = 4.5, $J_{10,10a}$ = 0–1 Hz, H_{10}); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 304 (12, M − Cl), 303 (47, M − HCl), 302 (7, M − H_2Cl), 275 (5, M − C_2H_5Cl), 274 (22, M − C_2H_6Cl), 198 (16, $C_{14}H_{16}N$), 182 (100, $C_{14}H_{14}$), 154 (43, $C_{12}H_{10}$), 122 (100, C_7H_8NO), 105 (100, C_7H_5O), 91 (11, C_7H_7), 77 (100, C_6H_5); *m/e* 304.1644 (calcd for $C_{21}H_{22}NO$, 304.1680); *m/e* 303.1600 (calcd for $C_{21}H_{21}NO$, 303.1622).

Anal. Calcd for $C_{21}H_{22}NOCl$: C, 74.22; H, 6.53; N, 4.12. Found: C, 74.22; H, 6.50; N, 4.12

2-Phenyloxazoline of 9(e)-Hydroxy-10(a)-amino-1,2,3,4,4a,-9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (6). A solution of 9(e)-chloro-10(a)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**4**, 20 mg, 0.06 mmol) in 0.5 ml of deuteriochloroform ($CDCl_3$) was heated at 80° for 67 hr while progress of the reaction was monitored by nmr, since during the conversion the H_9 signal at δ 5.60 ($J_{9,10}$ = 4.5 Hz) is replaced by a new H_9 signal at δ 6.60 (J = 9 Hz). The solution was treated with 10% aqueous sodium bicarbonate and ether, the phases were separated, and the ether phase was washed with water, dried, and evaporated. The crude product was chromatographed on 12 g of alumina (Merck, reagent aluminum oxide, neutral) using benzene as the eluent. Evaporation of the first 100 ml of eluent afforded 16 mg of white solid which was recrystallized from hexane to give the 2-phenyloxazoline of 9(e)-hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**6**): 14 mg (77%); mp 111–112° (lit.[12] mp 111°); nmr ($CDCl_3$) δ 8.07–7.83 (m, 2, ArH), 7.55–7.20 (m, 7, ArH), 5.80 (d, 1, $J_{9,10}$ = 10.0 Hz, H_9, appears at 6.60 in the HCl salt), 4.61 (dd, 1, $J_{10,10a}$ = 4.0 Hz, H_{10}), 2.73–0.80 (m, 10, CH_2CH envelope); mass spectrum (70 eV) *m/e* (rel intensity, fragment) 305 (1, M + 2), 304 (2, M + 1), 303 (12, M), 302 (2, M − 1), 275 (1, M − C_2H_4), 274 (7, M − C_2H_5), 200 (1, $C_{14}H_{16}O$), 198 (2, $C_{14}H_{16}N$), 182 (100, $C_{14}H_{14}$), 154 (15, $C_{12}H_{10}$), 122 (19, C_7H_8NO), 105 (46, C_7H_5O), 103 (2, C_7H_5N), 91 (12, C_7H_7), 77 (29, C_6H_5).

Hydrolysis of *syn*-9,10-Imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,-10a)-octahydrophenanthrene (1). A solution of *syn*-9,10-imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**1**, 10 mg, 0.05 mmol) in 10 ml of 5% aqueous sulfuric acid was refluxed for 1 hr, cooled, made alkaline (to pH 11) with 4 *N* aqueous sodium hydroxide, and extracted with ether. The ether solution was washed with water, dried, and treated with 0.5 ml of pyridine and 0.5 ml of acetic anhydride for 30 hr at room temperature. The ether solution was washed with water followed by 10% aqueous hydrochloric acid, 10% aqueous sodium hydroxide, and water, dried, and evaporated. The solid residue was dissolved in 0.5 ml of methanol and analyzed by glc using a 1.88 m × 0.32 cm 10% UC-W98 silicone rubber column, operating temperature 230°, helium flow rate 50 ml/min. The product composition was determined to be 57% 9(a)-acetoxy- and 43% 9(e)-acetoxy-10(e)-acet-

amido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (26 and 27) by comparison of the glc retention times of the product components with those of authentic samples of these acetoxy acetamides prepared in this laboratory[12] and by adding authentic samples to the unknown. Retention times were 35.4 min for 26 and 11.2 min for 27.

Hydrolysis of *anti*-9,10-Imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (2). A solution of *anti*-9,10-imino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (2, 10 mg, 0.05 mmol) in 10 ml of 5% aqueous sulfuric acid was refluxed for 1 hr, cooled, made alkaline (to pH 11) with 4 *N* aqueous sodium hydroxide, and extracted with ether. The ether solution was washed with water, dried, and evaporated. The solid remaining was dissolved in 0.5 ml of methanol and analyzed by glc using a 1.88 m × 0.32 cm 10% UC-W98 silicone rubber column (Hewlett-Packard, F & M Scientific Division), operating temperature 230°, helium carrier gas flow rate 50 ml/min. The product composition was determined to be 90% 9(a)-hydroxy- and 10% 9(e)-hydroxy-10(a)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (25 and 24) by comparison of the glc retention times of the product components with the retention times of authentic samples of these amino alcohols prepared in this laboratory[12] and adding authentic amino alcohols to the unknown samples. Retention times were 11.2 min for 25 and 12.2 min for 24.

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Registry No. 1, 28352-29-6; 2, 42822-53-7; 4, 42822-54-8; 6, 28352-40-1; 7, 28387-39-5.

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Some Reactions of Tetrahydrocarbazolechloroindolenine

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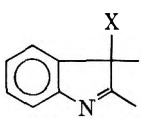
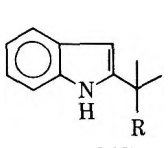
Tetrahydrocarbazolechloroindolenine (**9**), when allowed to react with NaOMe at −10°, gave 4a-methoxy-1,2,3,4-tetrahydrocarbazoleindolenine (**10**), while reaction with NaOH–MeOH under reflux gave 2-methoxyspiro[cyclopentane-1,3′-indolenine] (**12**). The relative proportion of **10** and **12** formed was dependent upon both base and temperature. When **10** was allowed to react with $LiAlH_4$, tetrahydrocarbazole was the product, while acid treatment gave bis[1,9-(1,2,3,4-tetrahydrocarbazole)] (**11**). $LiAlH_4$ reduction of **12** followed by Ac_2O–pyridine gave 1-acetoxyspiro[cyclopentane-1,3′-indoline] (**14**). Acid treatment of **12** gave spiro[cyclopentane-1,3′-indolin]-2′-one (**13**). 1-Methoxy-1,2,3,4-tetrahydrocarbazole (**16**) was prepared by NaOMe treatment of 1-pyridinium 1,2,3,4-tetrahydrocarbazole bromide (**15**).

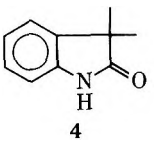
The reaction of indole derivatives with *tert*-butyl hypochlorite or sodium hypochlorite to yield chloroindolenines (**1**) is a well-known reaction.[1-3] Transformation of these highly reactive intermediates has yielded a variety of products depending on the conditions used. Buchi[4] found that the chloroindolenine of ibogaine, when treated with methanolic HCl, gave a methoxy derivative of structure **2**, and reaction with potassium cyanide gave structure **3**. The formation of oxindoles (**4**) has been reported by gentle acid treatment in aqueous media of the chloroindolenines of certain yohimbine alkaloids by Zinnes and Shavel.[5] Taylor and Finch[6] reported the formation of imido ethers of structure **5** by treating the chloroindolenines of various yohimbine alkaloids with methanolic base. Treatment of these imido ethers with aqueous acetic acid readily provided the corresponding oxindoles of structure **4**. Recently, Gassman, *et al.*,[3] have reported a series of reactions on the chloroindolenine of 2,3-dimethylindole, where they found that treatment with silver ion and methanol gave direct substitution of the chlorine atom and formation of the 3-methoxyindolenine **6**. They reported that



1, X = Cl
6, X = OCH_3



2, R = OCH_3
3, R = CN
7, R = OAc



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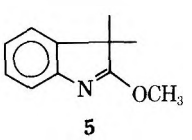

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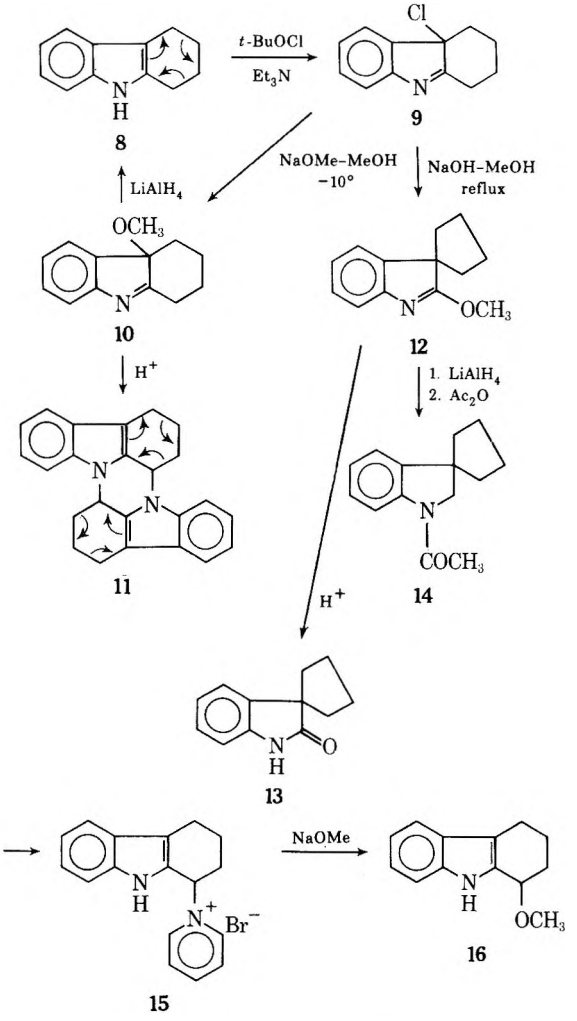
brief warming of a solution of the chloroindolenine caused rearrangement, evidenced by alteration of the ultraviolet and nmr spectra. When treated with NaOMe or $Th(OAc)_2$, the rearranged product gave derivatives of structure **2** and **7**, respectively.

Because of our interest in certain aspects of tetrahydrocarbazole (THC, **8**) chemistry, we decided to study some

reactions of its chloroindolenine, **9**. Generation of **9** at 0° was readily achieved using either *tert*-butyl hypochlorite or *N*-chlorobenzotriazole in the presence of triethylamine, as evidenced by disappearance of the 292- and 283-nm bands and emergence of an absorption maximum at 264 nm in the ultraviolet (CH_2Cl_2). The nmr spectrum of **9** showed a complex of aromatic protons at δ 6.8–7.6, a multiplet at δ 1.98–2.72, and another at δ 1.24–1.91 in approximately 4:4:4 ratio, the latter two groupings having the chemical shifts to be expected for four aliphatic protons, two protons α to a chlorine, and two protons α to a C=N bond. Isolation of this material in pure form was not possible, as it spontaneously and violently reacted when solvent was removed. A mass spectrum of this crude material gave *m/e* peaks compatible with THC (*m/e* 171, 143), carbazole (*m/e* 167), a chlorinated product (*m/e* 205, 207), and the dimer **11** (*m/e* 338, 310, 282). In contrast with the chloroindolenine of 2,3-dimethylindole,[3] the THC chloroindolenine **9** did not undergo rearrangement while in solution on warming, even at 70° for 1 hr, as shown by uv and nmr spectra identical with those obtained at 0°. Product formation (to be discussed later) after reaction of these solutions with NaOMe and NaOH–MeOH was also the same for both samples.



Treatment of THC chloroindolenine **9** with sodium methoxide at 0° gave **10** in 88% yield. This product had a uv absorption band 260 nm expected for an indolenine, which was unchanged in acid solution, and a C=N stretching band at 1650 cm^{-1} (indicating a strain in the five-membered ring) and did not show an NH stretching band (3425 cm^{-1} for THC). The nmr spectrum[13] established the remainder of the structure unequivocally, with a multiplet of four aromatic protons at δ 6.90–7.67, a singlet of three protons at δ 2.78 from the aliphatic methoxyl, and a very broad complex of eight aliphatic protons at δ 0.75–3.15. That the aliphatic proton signals were so widely spread out was in contrast to THC, where two broad signals occur at δ 1.77 and 2.55. When a model of **10** was made, it was seen that the six-membered ring was neither planar nor of the classical chair or boat conformation. Instead, the C-1 carbon must be coplanar with the nitrogen and the 9a carbon due to the double bond, while the C-4 carbon lies above the plane of the five-membered ring by approximately 54°. This imparts a spiral strained twist to the six-membered ring, making each proton around the ring nonequivalent to any other, and giving the complex nmr pattern seen. Strain in the five-membered ring, and consequently the six-membered ring as well, was already noted in the C=N stretching band. The mass spectrum of **10** had an intense M^+ ion at *m/e* 201, confirming the displacement of chlorine with a methoxyl group, and peaks which indicated loss of a methyl ($M^+ - 15$) and a methoxy ($M^+ - 31$) group.

Treatment of **10** with $LiAlH_4$ gave a 71% yield of THC (**8**) identical in the uv and mixture melting point with an authentic sample. Reduction can be rationalized as attack of an hydride ion on the nitrogen, followed by migration of the double bond to the indole position, and elimination of a methoxide anion.

When **10** was treated with dilute hydrochloric acid in aqueous methanol, a yield of 41% of crystalline product melting at 253–255° was formed. This dimer **11** has been reported with two different melting points (255 and 313° after resolidification[7] and 293–295°[8]). The mass spectrum of **11** had a molecular ion of *m/e* 338, and there were two ions at M − 28 and M − 56, as one might expect for this structure (see arrows in **11**), after comparing it with that of THC, where the major fragment is the M − 28 ion, the elements of ethylene having been lost from the saturated ring (see arrows in **8**). The uv spectrum was that of an indole, and the ir had no NH absorption band. An nmr of **11** was not possible because of its limited solubility in all solvents attempted.

When the chloroindolenine of THC (**9**) was treated with sodium hydroxide in methanol under reflux, a second product **12**, isomeric with **10**, was obtained in 82% yield. This compound was also an indolenine, as evidenced by the uv absorption at 255 nm, with no alteration in acid media. The ir had no NH band, but did have a C=N band at 1618 cm^{-1}. That this latter band is at a lower wavelength than in **10** is consistent with the less strained five-membered indolenine ring as shown in **12**. The molecular weight by mass spectral measurement was 201, and the spectrum was almost identical with that of **10**. The nmr spectrum[13] allowed firm assignment of the structure, since the eight protons of the spiro ring gave a singlet at δ 1.95, in contrast to the widely spread signal for the eight aliphatic protons in **10**. In addition, the methoxyl protons were much further downfield at δ 4.02, consistent with their proximity to the C=N bond.

When the spiro compound **12** was treated with aqueous methanolic HCl, it gave the oxindole **13** in 69% yield, previously reported by Witkop[9] and Moore.[10] All of the physical data were consistent with **13**, save the melting point of 95–96° (reported mp 113°). Preparation of **13** by Moore's method gave an ir, a melting point, and a mixture melting point identical with those of our products.

Treatment of **12** with $LiAlH_4$ gave a basic product which was difficult to characterize, and so it was derivatized with acetic anhydride in pyridine. This gave **14** in 65% overall yield. The uv spectrum of **14** was compatible with an *N*-acylindoline, with an absorbance at 252 nm.

Table I

Base	Reaction temp, °C	Ratio of 10/12
NaOMe	−10	4.00
	25	1.30
	65	0.90
NaOH	−10	1.92
	45	0.29
	65	0.17

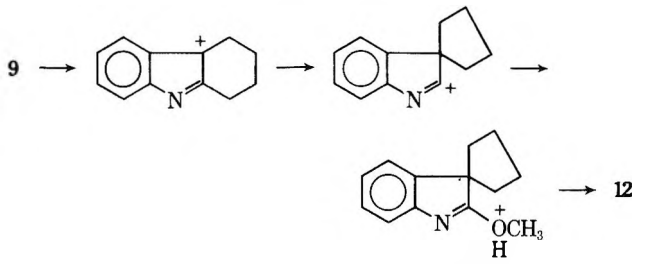
This structure was further supported by the ir with a band at 1660 cm^{-1} and disappearance of the NH absorbance, consistent with formation of an amide. The nmr had a singlet of two aliphatic protons α to the NAc at δ 3.82, a three-proton singlet at δ 2.22 from the *N*-acetyl group, and an eight-proton singlet from the spiro ring protons.

One product which might have been expected from reaction of **9** with either NaOMe or NaOH–MeOH is 1-methoxy-1,2,3,4-tetrahydrocarbazole (**16**). Since no product **16** was found, we decided to investigate the reaction of NaOMe with the known pyridinium salt **15**.[11] When the compound **15** was treated at room temperature with excess NaOMe, work-up gave a crystalline product in 52% yield, which had a molecular ion of *m/e* 201 and a pattern of fragmentation very similar to those of **10** and **12**, save that the intensity of the *m/e* 201 ion was much less and the *m/e* 186 fragment was shifted to *m/e* 185. The uv, in contrast to that of either **10** or **12**, is that of an indole, with peaks of almost equal intensity at 276, 283, and 291 nm. The ir had an indolic NH stretching band at 3300 cm^{-1}, and lacked a band in the 1600-cm^{-1} region. The nmr again provided confirmation of the structure,[13] with NH and methoxyl singlets at δ 8.13 and 3.38, respectively, a single proton at δ 4.48, α to the methoxyl group, a multiplet of two protons at C-4 at δ 2.67, and a multiplet of four protons from the C-2 and C-3 positions at δ 1.93. Especially important is the single proton at δ 4.48, adjacent to both a methoxyl and the indole system, and the two-proton multiplet at δ 2.67 on a carbon α to the indole ring. This locates the methoxyl at either C-1 or C-4, and, from the past behavior of **15**, we obviously prefer C-1.

That the two products **10** and **12** are obtainable from the chloroindolenine **9** is not surprising in view of prior studies with compounds of structure **1**. What was unusual and interesting was the dependence of product formation upon the conditions used. To further explore this phenomenon, we decided to study variations in both base and temperature upon the reaction. Since the two products **10** and **12** have sharp, easily integrated, and well-separated peaks in the nmr, we elected to run spectra on the crude reaction products without purification. Thus, each reaction mixture was run in the same manner as for **10** or **12** in the Experimental Section, save that the reaction temperature was varied. The chloroform extract of the crude reaction mixture was evaporated *in vacuo* to a viscous oil. This oil was then analyzed in the nmr in $CDCl_3$–TMS directly. The results are shown in Table I.

As the temperature was raised, both with NaOMe and NaOH, the spiro compound **12** increased in proportion to **10**. Also noticeable was the persistently higher proportion of **12** when NaOH was used, at each temperature. Rearrangement of **10** to **12** (or vice versa) under the reaction conditions used was ruled out when both products were recovered completely unchanged (nmr) after reflux in NaOMe–MeOH for several hours. Formation of **10** obviously follows from direct substitution at 4a, probably as an SN2 reaction. On the other hand, **12** is most probably formed *via* the C-4a carbonium ion, with subsequent Wagner–Meerwein rearrangement to the C-2 cation, and consequent reaction with methanol, as shown in Scheme I.

Scheme I



Since no **16** was formed in the reactions of the chloroindolenine **9**, even when the nmr of the crude reaction products was examined, we assume that generation of the C-1 carbonium ion, or similar C-1 activated species, did not occur under these conditions, in contrast with 2,3-dimethylindole.[3]

Experimental Section[12]

Tetrahydrocarbazolechloroindolenine (9). 1,2,3,4-Tetrahydrocarbazole (2.50 g) and triethylamine (1.60 ml) in benzene (45 ml) were stirred in an ice bath while *tert*-butyl hypochlorite (1.60 ml) (or an equivalent amount of *N*-chlorobenzotriazole) was added dropwise. The mixture was stirred for 30 min; then a portion was used directly for nmr determinations. For uv determination, the above reaction was repeated substituting methylene chloride as solvent in place of benzene: uv 235 nm (ϵ 13,700), 264 (3650); nmr δ 6.2–7.6 (multiplet, 4 H, aromatic), 1.98–2.72 (multiplet, 4 H, α aliphatic), 1.24–1.91 (multiplet, 4 H, β aliphatic).

4a-Methoxy-1,2,3,4-tetrahydrocarbazoleindolenine (10). Tetrahydrocarbazolechloroindolenine (**9**) from 2.00 g of THC in benzene solution was run rapidly into a stirred solution of sodium (1 g) in 35 ml of absolute methanol precooled to −10° in an ice–methanol bath. After 30 min of stirring at −10°, the mixture was evaporated *in vacuo*, 30 ml of ice water was added, and the solution was extracted four times with 25-ml portions of chloroform. The chloroform extract was dried over sodium sulfate and evaporated to a viscous oil (2.06 g, 88%). Crystallization from hexane gave large, colorless prisms: mp 47–51°; ir 3080, 1585, 1440, 1275, 1110, 1060, 760 cm^{-1}; nmr[13] δ 6.90–7.68 (4 H, aromatic), 2.78 (3 H, OCH_3), 0.75–3.15 (8 H, aliphatic); mass spectrum *m/e* 201, 186, 170, 168, 160, 158, 130; uv 228 nm (ϵ 12,300), 260 (4100), unchanged in HCl solution. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.46; N, 6.97. Found: C, 77.69; H, 7.45; N, 6.90.

Bis[1,9-(1,2,3,4-tetrahydrocarbazole)] (11). One gram of the 4a-methoxy compound **10** was heated under reflux in 25 ml of methanol and 1 ml of 1 *N* HCl in a nitrogen atmosphere. The solution was cooled and filtered to give 342 mg (41%) of white, powdery crystals: mp 253–255°; ir 1460, 1335, 1320, 1290, 1240, 1165, 735 cm^{-1}; mass spectrum *m/e* 338, 310, 282, 168, 141; uv 238 nm (ϵ 20,100), 285 (8200), 293 (sh, 7100). *Anal.* Calcd for $C_{24}H_{22}N_2$: C, 85.25; H, 6.51; N, 8.28. Found: C, 85.09; H, 6.52; N, 8.38.

2-Methoxyspiro[cyclopentane-1,3′-indolenine] (12). Tetrahydrocarbazolechloroindolenine (**9**), from 1.25 g of THC in benzene solution, was run rapidly into a stirred refluxing solution of NaOH (3 g) in methanol (35 ml), and the mixture was refluxed for 30 min. The solvent was evaporated *in vacuo*, ice water (30 ml) was added, and the mixture was extracted four times with chloroform (25 ml). The chloroform was dried with Na_2SO_4 and evaporated to a viscous oil (1.20 g, 82%), which crystallized on standing at −20°. Recrystallization from diethyl ether gave white prisms: mp 66–68; ir 1618, 1570, 1335, 1275, 1190, 1015, 1000, 750 cm^{-1}; nmr[13] δ 6.90–7.50 (4 H, aromatic), 4.02 (singlet, 3 H, OCH_3), 1.95 (singlet, 8 H, aliphatic spiro ring); mass spectrum *m/e* 201, 186, 170, 160, 158, 130; uv 225 nm (ϵ 7500), 255 (7200), unchanged in HCl solution. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.46; N, 6.97. Found: C, 77.49; H, 7.29; N, 6.95.

Spiro[cyclopentane-1,3′-indolin]-2′one (13). The spiro compound **8** (300 mg) in 30 ml of methanol–water (1:1) and 1 ml of concentrated HCl was heated under reflux in a nitrogen atmosphere for 1 hr. The solution was cooled and evaporated *in vacuo*, and 25 ml of benzene and dilute NH_4OH were added. The aqueous layer was reextracted four times with benzene. The benzene was pooled, dried over Na_2SO_4, and evaporated to yield a crystalline product (193 mg, 69%) which recrystallized from hexane to give pale pink needles melting at 95–96°: ir 3220, 3100, 1710, 1620, 1340, 1310, 1220, 810, 755, 640 cm^{-1}; nmr δ 9.40 (1 H, NH), 6.78–7.35 (4 H, aromatic), 2.03 (8 H, aliphatic spiro ring); mass spectrum *m/e* 187, 158, 146, 130, 117; uv 251 nm (ϵ 9100), 280 (1600).

1-Acetoxyspiro[cyclopentane-1,3′-indoline] (14). Two grams of the spiro indolenine compound **9** was treated with 2.0 g of $LiAlH_4$ in refluxing diethyl ether for 3 hr, then 0.5 ml of water, 0.5 ml of 15% NaOH, and 1.5 ml of water were added in succession. The ether phase was removed by filtration and to it 4.0 ml of pyridine and 2.0 ml of Ac_2O were added. After standing overnight at 10°, the solvent was evaporated to give 1.4 g (65%) of white crystals, which when recrystallized from hexane melted at 122–123.5: ir 1660, 1600, 1480, 1460, 1410, 755 cm^{-1}; nmr δ 6.92–7.32 (4 H, aromatic), 3.82 (singlet, 2 H, aliphatic), 2.22 (singlet 3 H, Ac), 1.83 (singlet, 8 H, aliphatic, spiro); mass spectrum *m/e* 215, 173, 130; uv 222 nm (ϵ 2000), 252 (8600), 280 (2300), 290 (1950). *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.85; H, 8.28; N, 6.22.

1-Methoxy-1,2,3,4-tetrahydrocarbazole (16). To 1,2,3,4-tetrahydrocarbazole (3.00 g) and pyridine (3.6 ml) in benzene (60 ml) was added at once *N*-bromosuccinimide (3.3 g) and dibenzoyl peroxide (1 mg), and the mixture was stirred overnight at room temperature. The clear benzene layer was decanted from the oily product which separated, and the oil was dissolved in methanol (20 ml) and run into excess sodium methoxide in methanol at room temperature. This mixture was stirred for 1 hr, then evaporated under vacuum, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with water twice, dried over Na_2SO_4 and evaporated to an oil which crystallized on standing (1.85 g, 52% yield). Recrystallization from hexane gave pale yellow rosettes melting at 74–76°: ir 3300, 1390, 1335, 1065, 910, 740; nmr[13] δ 8.13 (singlet, 1 H, NH), 6.92–7.50 (multiplet, 4 H, aromatic), 4.48 (1 H, α to OCH_3 at C-1), 3.38 (singlet, 3 H, OCH_3), 2.67 (multiplet, 2 H, aliphatic at C-4), 1.93 (multiplet, 4 H, aliphatic at C-2,3); mass spectrum *m/e* 201, 185, 170, 168; uv 230 nm (ϵ 17,800), 276 (7650), 283 (8150), 291 (6700). *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.61; H, 7.46; N, 6.97. Found: C, 77.73; H, 7.53; N, 6.89.

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Registry No. **8**, 942-01-8; **9**, 42540-51-2; **10**, 42540-52-3; **11**, 42540-53-4; **12**, 42540-54-5; **13**, 41058-67-7; **14**, 42540-56-7; **16**, 42540-57-8.

Supplementary Material Available. Full nmr data for compounds **10**, **12**, and **16** 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 Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-69.

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(12) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were determined on a CEC-110 spectrometer. Microanalyses were performed by Galbraith Laboratories. Ir spectra were run on a Perkin-Elmer 700 spectrometer. Uv spectra were obtained on a Beckman DB spectrometer.
(13) See paragraph at end of paper regarding supplementary material.

Condensations of Enol Ethers of β-Dicarbonyl Compounds with Dimethylsulfonium Methylide and Dimethyloxosulfonium Methylide

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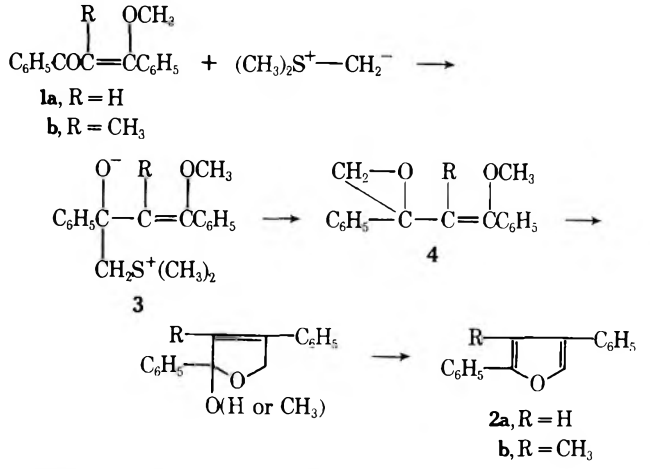
Condensations of dimethylsulfonium methylide with β-alkoxy-α,β-unsaturated ketones have been studied. The reactions of this ylide with the enol ethers of acyclic β diketones gave 2,4-disubstituted furans. Attack by the ylide occurred at the carbonyl carbon atoms. Easily rearranged epoxides are postulated as intermediates in furan formation. With the enol ether of a cyclic β diketone, 1,3-indandione, furanization of the epoxide intermediate was sterically prohibited and the condensation gave 3-(hydroxymethyl)indenone. The enol ethers of β-keto aldehydes reacted with dimethylsulfonium methylide to give two products. In addition to 3-substituted furans, the condensations gave 5-substituted 3,6-dihydro-(2*H*)-pyran-2-ols. Formation of the latter compounds has been rationalized to involve attack by one molecule of the ylide at the β positions of the unsaturated carbonyl compounds followed by a second molecule attacking the carbonyl groups. Rearrangement and hydrolysis of the resulting cyclopropyloxiranes would give the dihydropyran derivatives. β attack by dimethylsulfonium methylide on α,β-unsaturated ketones does not normally occur but is facilitated with the enol ethers of β-keto aldehydes by the reduced steric hindrance at the β positions. The condensations of dimethyloxosulfonium methylide with enol ethers of β diketones were also investigated. Twofold attacks occurred here, as well, but both attacks were by the same ylide molecule. Initial attack by the ylide at the β position, followed by formation of a new ylide by ionization of one of the remaining methyl groups, and finally intramolecular attack of the new ylides on the carbonyl groups, led to 3,5-disubstituted 1-methylthiabenzene 1-oxides.

The reactions of sulfonium ylides with α,β-unsaturated ketones have been employed widely subsequent to the observations by Corey and Chaykovsky that dimethylsulfonium methylide preferentially attacks the carbonyl group to give epoxides, whereas dimethyloxosulfonium methylide attacks the β position to give cyclopropyl ketones.[1,2] The corresponding reactions of β-alkoxy-α,β-unsaturated ketones were of interest to us because both the epoxide and cyclopropane products should be capable of rearrangement to furans or to the related 1,4-dicarbonyl compounds. The reactions of both of the ylides with these enol ethers have now been investigated.[3]

Dimethylsulfonium Methylide (DSM). The initial studies were undertaken with unsaturated methoxy ketone **1a**, which is readily available by methylation of dibenzoylmethane. Treatment of **1a** with 1 equiv of DSM gave 56% of a furanoid product, readily identified as the known[4] 2,4-diphenylfuran (**2a**, Scheme I). A similar con-

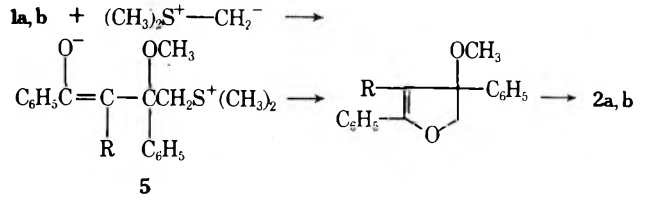
Scheme I



densation of DSM with ketone **1b** gave furan **2b** in 60% yield. No epoxide, cyclopropane, or 1,4 diketone was detected in either case; however, it is possible that small amounts of these were overlooked.

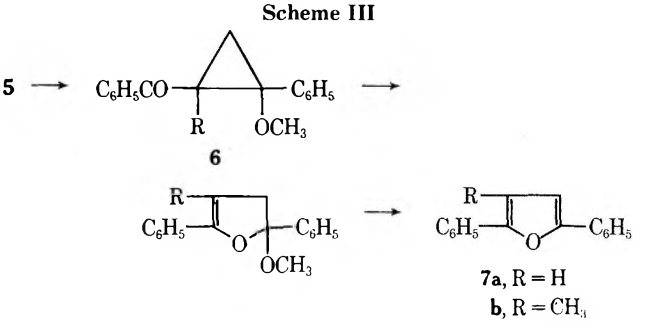
Several reaction pathways can be proposed to account for the formation of **2a** and **2b**. The products could have arisen by attack of the ylide at the carbonyl carbon atoms of **1a** and **1b** followed by cyclization of the resulting zwitterions **3** to epoxides **4**. Rearrangement and loss of methanol during work-up would yield **2a** and **2b** (Scheme I). An alternative is that the ylide attacked at the β positions of **1a** and **1b**; internal displacement of the resulting zwitterions **5** and loss of methanol would have led to **2a** and **2b** (Scheme II). It should be noted that zwitterions **5** might

Scheme II



also have decomposed to give cyclopropyl ketones **6**, which could, in turn, rearrange to diphenylfurans **7a** and **7b** (Scheme III). These, however, are isomeric with the observed products.

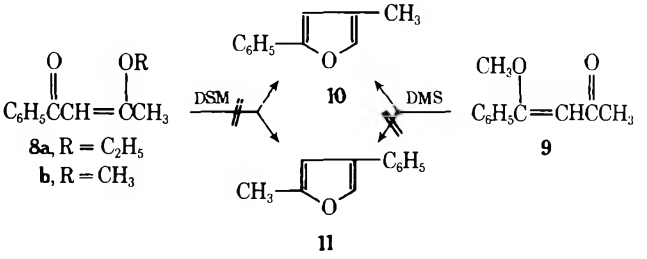
Scheme III



The pathway illustrated in Scheme I is supported by the precedent[2] of the reactions of simple α,β-unsaturated ketones with this ylide. However, it should be noted that starting with **1a** and **1b** Schemes I and II are indistinguishable because both give the same final products and none of the various intermediates have been detected. The two routes become distinguishable when enol ethers of *unsymmetrical* β diketones are employed, since the 1-phenyl groups of **1a** and **1b** become the β-phenyl substituents of **2a** and **2b** by Scheme I but the α substituents by Scheme II.

Appropriate unsymmetrical β-alkoxy-α,β-unsaturated ketones are of limited availability because the most common method for preparation of the enol ethers, O-alkylation of the corresponding β diketones, often gives mixtures with unsymmetrical diketones. One case in which a single enol ether of established structure has been obtained is the ethylation of 1-phenyl-1,3-butanedione with ethyl orthoformate to give enol ether **8a**.[5] Unfortunately, **8a** proved to be insufficiently reactive and was recovered unchanged after treatment with DSM. Treatment of 1-phenyl-1,3-butanedione with diazomethane gave a mixture of the isomeric enol ethers **8b** and **9**.[5b] These were not separable by chromatography but a portion of **8b** was isolated by crystallization, leaving a 1:3 mixture of **8b** and **9**. As with **8a**, **8b** failed to react with DSM. In contrast, the mixture of **8b** and **9** did react with the ylide to give furan **10**. The product can reasonably be assumed to have arisen entirely from **9** and, on this basis, the yield was 42% (Scheme IV). Formation of this product rather than furan

Scheme IV

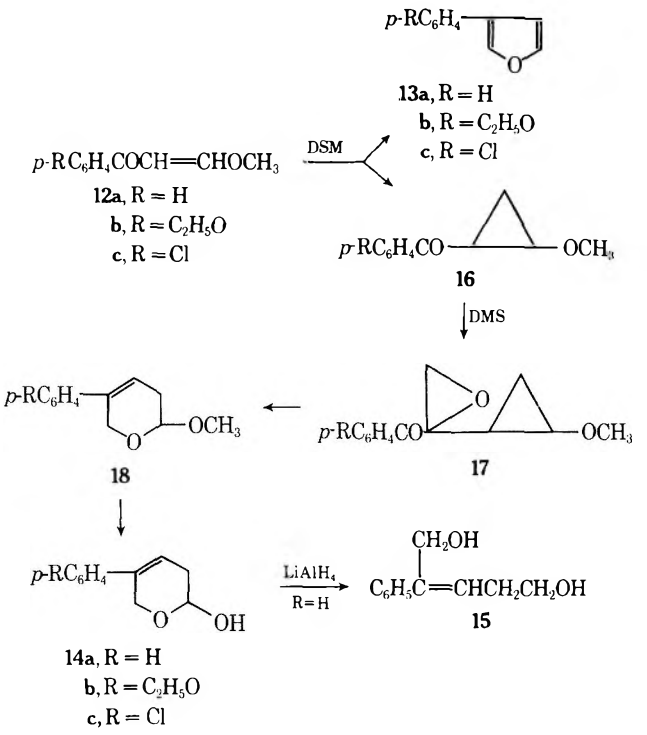


11 supports the exclusive operation of the pathway depicted in Scheme I in which initial attack by the ylide occurs at the carbonyl group.

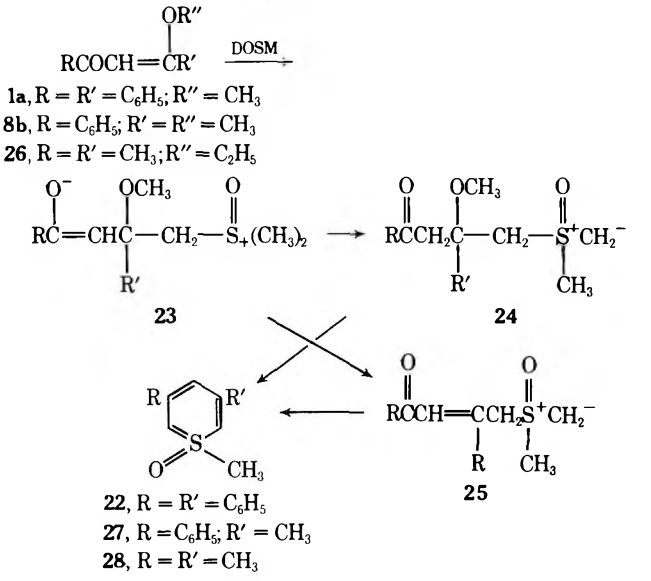
β-Keto aldehydes invariably undergo enol alkylation at the aldehydic oxygen. The resulting enol ethers were employed as the next test of the reaction preference of DSM with β-alkoxy-α,β-unsaturated ketones. With β-methoxyacrylophenone (**12a**), the reaction of DSM gave 18% of furan **13a**, providing further confirmation of the first pathway. In addition, a second product, dihydropyran **14a**, was obtained in 39% yield. The structural assignment for **14a** was based on spectroscopic and chemical evidence. Elemental and mass spectral analyses established the empirical formula as $C_{11}H_{12}O_2$. The presence of the hemiacetal linkage was deduced from the fact that, although no carbonyl group was evident from the infrared spectrum, the compound readily yielded a semicarbazone. Reduction of **14a** to diol **15** confirmed this conclusion and indicated that the hemiacetal linkage was situated in a cyclic structure. The size of the heterocyclic ring and the location of the phenyl group and of the double bond were apparent from the spectra.

The formation of dihydropyran **14a** must involve a twofold attack on unsaturated ketone **12a** by DSM (Scheme V). Probably, initial attack by DSM is at the β position of **12a** leading to cyclopropyl ketone **16**, followed by a second attack at the carbonyl group giving cyclopropyl epoxide **17**. Rearrangement of **17** to acetal **18** and hydrolysis to hemiacetal **14a** can be expected to be extremely facile. The rearrangement process may be promoted by adventitious acidic catalysts or conceivably may involve an uncatalyzed isomerization.

Scheme V

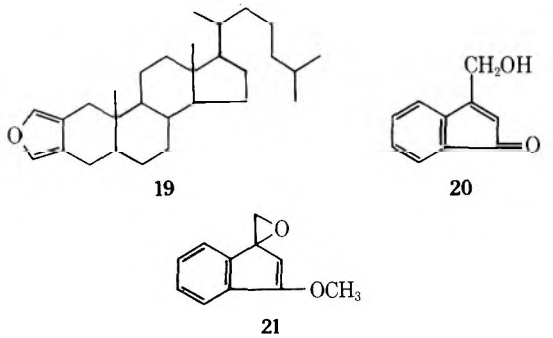


Scheme VI



Similar results were obtained with two other β-methoxyacrylophenones. Ethoxy-substituted **12b** gave mainly (54%) dihydropyran **14b**, although a small amount of furan **13b** was isolated. Chloro-substituted **12c** gave low yields of both **13c** and **14c**.

Two other cases were investigated. 2-Methoxymethylenecholestan-3-one reacted with DSM to give 15% of furan **19**; the related dihydropyran was not observed. 3-Methoxyindenone, which cannot give either a furan or a dihydropyran, yielded 14% of keto alcohol **20**. Spiro epoxide **21** is probably an intermediate in its formation; furanization of **21** is sterically prohibited.



Dimethyloxosulfonium Methylide (DOSM).—This ylide reacted with enol ether **1a** but failed to give any of the expected products. A sulfur-containing crystalline solid was obtained in 68% yield and was identified as thiabenzene oxide **22**.[6] Attack by DOSM occurs at the β position of **1a**. The resulting enolate anion (**23**) might have expelled dimethyl sulfoxide *via* internal displacement by the nucleophilic oxygen to give furan **2a** or by the carbanion to give cyclopropyl ketone **6**. Surprisingly, neither of these was a major course of reaction. Instead, either a direct proton transfer to give new ylide **24** or methoxide loss followed by reionization occurred to give ylide **25**. Both of these ylides are well structured for intramolecular attack on the carbonyl group to give, after elimination, the observed thiabenzene oxide (**22**) (Scheme VI). Similar reactions of **8b** and of enol ether **26** of acetylacetone with DOSM gave thiabenzene oxides **27** and **28** in yields of 46 and 29%, respectively.

Discussion

Although the epoxides (*e.g.*, **4**) that have been postulated as intermediates in the formation of furans by the condensation of DSM with enol ethers of β-dicarbonyl compounds were not isolated or detected, adequate precedents are available to support the contention that such intermediates would rearrange readily to furans. Burness observed that 3,4-epoxy acetals undergo facile rearrangements to 3-substituted furans.[7] Cornforth has also observed this reaction.[8] Equivalent transformations of epoxy ketones[9] and of acetylenic epoxides[10] have been reported. Cyclizations of o-hydroxystyrene oxides to benzofurans also appear to be facile processes.[11]

The introduction of substituents at the β position of furan is generally difficult, the α position being the preferred site of attack by most reagents.[12] The reaction of enol ethers of β diketones with DSM appears to have merit for the synthesis of 2,4-di- and 2,3,4-trisubstituted furans, particularly when the 2 and 4 substituents are identical. However, the usefulness of enol ethers for the synthesis of 3-monosubstituted, and probably 3,4-disubstituted, furans is doubtful on account of the competitive formation of dihydropyran derivatives. Fortunately, Garst and Spencer have recently described a related method which works well for both of the latter classes of furans.[13] Their procedure involves the condensation of DSM with *n*-butylthio ethers of β-keto aldehydes. With the thio ethers β attack is repressed and pyran derivatives are not observed.[14] It is noteworthy that these workers obtained spectral evidence of thio analogs of the intermediates proposed in Scheme I.

Twofold reactions of DSM with unsaturated carbonyl compounds are novel. Normally, initial attack at the carbonyl group blocks further attack at the double bond. With the β-methoxyacrylophenones, steric hindrance at the β position has been minimized, while the susceptibility of the carbonyl group to nucleophilic attack is simultaneously attenuated by electron donation by the β-methoxyl group. It is also likely that the aryl group plays an important part in directing the initial attack of DSM at the β position. Twofold condensations have occasionally been observed with DOSM where the order of reactivity with unsaturated ketones is normally C=C > C=O.[15]

The formation of thiabenzene oxides by the condensation of enol ethers of diketones with DOSM provides an attractive new approach to this interesting class of heterocyclics. The first example of the ring system (22) was prepared by Hortmann by the condensation of DOSM with 1,3-diphenylpropynone.[6] Hortmann and Harris have since demonstrated the generality of the reaction.[16] It is noteworthy that they have isolated allylide intermediates, the cyclizations of which probably involve isomerization to methylides 25. Holt, *et al.*, have obtained thiabenzene oxides by the reaction of DOSM with certain β diketones.[17] 2-Acylcyclohexanones reacted satisfactorily, but the simple diketones, acetylacetone, benzoylacetone, and dibenzoylmethane (the enol ethers of which were used in the present study), gave only C-methylation products. Kishida, *et al.*, have prepared examples having functional substituents on the heterocyclic ring.[18]

Experimental Section

General Procedures. Dimethylsulfonium methylide (DSM) was prepared from trimethylsulfonium iodide and the anion of dimethyl sulfoxide (DMSO) at an approximate concentration of 0.25 *M* in a mixture of DMSO and tetrahydrofuran (THF) following the method of Corey and Chaykovsky.[2] Dimethyloxosulfonium methylide (DOSM) was prepared in DMSO at the same concentration by the reaction of trimethylsulfonium iodide and sodium hydride as described by the same workers.[2] Normal work-up of reaction mixtures involved addition of water and extraction into ether. The ethereal solutions were dried with $MgSO_4$ and concentrated *in vacuo*. Crude products were usually purified by chromatography on silicic acid. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Ultraviolet spectra were determined in 95% ethanol solution and nmr spectra in $CDCl_3$ [60 MHz referenced to internal $(CH_3)_4Si$]. Mass spectra were recorded at 70 eV; sample introduction was by means of the direct inlet.

Enol Ethers of β-Dicarbonyl Compounds. 1,3-Diphenyl-3-methoxy-2-propen-1-one (1a) was prepared by treatment of dibenzoylmethane with diazomethane.[19]

1,3-Diphenyl-2-methyl-3-methoxy-2-propen-1-one (1b). The enol form of 1,1-dibenzoylethane[20,21] was treated with excess ethereal diazomethane to give enol ether **1b** mixed with enol and keto tautomers of the diketone. Chromatography on alumina gave 25% of a mixture of *cis*- and *trans*-**1b** as a pale yellow oil: ν (neat) 2950, 1670, 1650, 1605, 1450, 1325, and 1125 cm^{-1}; nmr (stereoisomer A) δ 1.89 (s, CCH_3), 3.03 (s, OCH_3), 7.1–8.0 (m, C_6H_5), (stereoisomer B) 2.14 (s, CCH_3), 3.45 (s, OCH_3), 7.1–8.0 (m, C_6H_5); mass spectrum *m/e* (rel intensity) 252 (parent, 78), 251 (61), 105 (100), 77 (83).

Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.12; H, 6.33.

3-Ethoxy-1-phenyl-2-buten-1-one (8a) was prepared by treatment of benzoylacetone with ethyl orthoformate.[5] Treatment of benzoylacetone with excess ethereal diazomethane gave a mixture of **3-methoxy-1-phenyl-2-buten-1-one (8b)** and **4-methoxy-4-phenyl-3-buten-2-one (9)**,[5] from which a portion of the cis and trans isomers of **8b** crystallized.[5] The liquid fraction was distilled (88°, 0.25 mm) to give an oil which consisted (nmr) of 25% of **8b** and 75% of **9**. An authentic sample of **9**, needed for the analysis of the mixture of isomers, was prepared by treatment of 4-phenyl-3,4-dibromo-2-butanone with sodium methoxide;[5] the yield was not sufficiently high for the reaction to have preparative value.

3-Methoxy-1-phenyl-2-propen-1-one (β-methoxyacrylophenone, 12a) was prepared by acylation of acetophenone with methyl formate followed by methylation with methanolic HCl.[22]

3-Methoxy-1-(4-ethoxyphenyl)-2-propen-1-one (12b) was prepared by the same general procedure from *p*-ethoxyacetophenone. Distillation (145°, 0.25 mm) of the crude product gave 45% of the enol ether as an oil which solidified: mp 55.5–57.5° after recrystallization from CCl_4–hexane; ν (KBr) 2940, 1650, 1610 (sh), 1570, 1510, 1440, 1398, 1350, 1260, 1200, and 630 cm^{-1}; nmr δ 3.7 (3 H, s, OCH_3), 6.31 (1 H, d, J = 12 Hz, 2-CH), 6.85 (2 H, d, J = 9 Hz, aryl), 7.71 (1 H, d, J = 12 Hz, 3-CH), 7.83 (2 H, d, J = 9 Hz, aryl).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.00; H, 6.92.

3-Methoxy-1-(4-chlorophenyl)-2-propen-1-one (12c) was prepared similarly from *p*-chloroacetophenone.[22] Distillation (122–128°, 0.4 mm) gave 48% of 12c as an oil which solidified: mp 64–65° after recrystallization from hexane; ν (KBr) 1655, 1580, 1265, 1200 cm^{-1}; nmr δ 3.73 (3 H, s, OCH_3), 6.24 (1 H, d, J = 12 Hz, 2-CH), 7.55 (4 H, A_2B_2, aryl), 7.71 (1 H, d, J = 12 Hz, 3-CH).

Anal. Calcd for $C_{10}H_9O_2Cl$: C, 61.07; H, 4.61; Cl, 18.03. Found: C, 61.33; H, 4.59; Cl, 17.77.

2-Methoxymethylenecholestan-3-one was prepared from cholestan-3-one as described by Storm and Spencer.[23]

3-Methoxy-2-inden-1-one. 1,3-Indandione was treated for 12 hr with excess ethereal diazomethane. The solution was washed with aqueous sodium hydroxide and with water, dried, and evaporated to leave 50% of the enol ether as a yellow solid. Recrystallization from hexane gave yellow needles: mp 65.5–67°; ν (KBr) 1710, 1620, 1565, 1430, 1385 cm^{-1}; nmr δ 3.95 (3 H, s, OCH_3), 5.04 (1 H, s, 2-CH), 7.2 (4 H, m, aryl).

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.81; H, 5.12.

4-Ethoxy-3-penten-2-one (26) was prepared by treatment of acetylacetone with ethyl orthoformate.[24]

Reactions of DSM. Preparation of 2,4-Diphenylfuran (2a). Enol ether **1a** (1.19 g, 0.005 mol) in 10 ml of THF was added to a suspension of DSM [prepared from 2.04 g (0.01 mol) of trimethylsulfonium iodide] at −5°. The mixture was warmed to ambient temperature over a 90-min period and poured into water. The THF was partially evaporated under reduced pressure; ether extraction gave 0.946 g of crude product. Chromatography on silica gel (hexane elution) gave 0.622 g (56%) of furan **2a**, mp 107–108.5° and, after recrystallization from ethanol, 109.5–110.5° (lit.[4] mp 109°).

Preparation of 2,4-Diphenyl-3-methylfuran (2b). Enol ether **1b** (1.07 g, 0.0042 mol) in THF (10 ml) was added to DSM [prepared from 2.04 g (0.01 mol) of trimethylsulfonium iodide] at −5°. The mixture was allowed to warm to ambient temperature and, after a 3-hr reaction period, the usual work-up by extraction and chromatography (hexane elution) gave 0.594 g (60%) of **2b**: mp 125–130° and, after sublimation (80°, 0.025 mm), 128–130°;[25] ν (KBr) 1615, 1495, 1440, 1060, 890, 760, 750, 690 cm^{-1}; nmr δ 2.3 (3 H, s, CH_3), 7.13–7.83 (11 H, m, aryl + 5-CH); mass spectrum *m/e* (rel intensity) 234 (parent, 100), 205 (44), 191 (28), 77 (35).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found, 87.26; H, 6.13.

Preparation of 4-Methyl-2-phenylfuran (10). Treatment of enol ethers **8a** and **8b** with DSM failed to give furan **10** or **11**. In both cases the enol ethers were recovered from the reaction mixtures unaltered. Addition of 3.25 g (0.018 mol) of a 3:1 mixture of enol ethers **8b** and **9** to DSM [prepared from 4.08 g (0.02 mol) of trimethylsulfonium iodide] at −5° gave, after 3 hr at room temperature, 2.9 g of crude product, the nmr spectrum of which indicated that it consisted of mainly furan **10** and unaltered enol ether **8b**. Chromatography (elution with hexane–ether 90:10) gave 0.41 g (42%) of furan **10**, mp 38–40° (lit.[26] mp 40°). The chloromercuri derivative melted at 169.5–170.5° (lit.[26] mp 170.5–171°). The yield of furan **10** is calculated with the assumption that the compound had been formed exclusively from enol ether **9**.

Preparation of 3-Phenylfuran (13a) and 3,6-Dihydro-5-phenyl-(2*H*)-pyran-2-ol (14a). Enol ether **12a** (1.62 g, 0.01 mol) was added to DSM [prepared from 4.08 g (0.02 mol) of trimethylsulfonium iodide] at −5°. After 1 hr at ambient temperature, the usual work-up by extraction gave an oily, yellow solid, which was suspended in a small volume of CCl_4 and filtered to give 0.644 g of dihydropyran **14a**: mp 103–103.5° which was not increased by recrystallization from CCl_4 and sublimation (70°, 0.05 mm); ν ($CHCl_3$) 3580, 3400, 2930, 1495, 1450, 1110, 1065, 895 cm^{-1}; ν (KBr) 3360, 3260, 1460, 1140 cm^{-1}; λ_{max} 243 nm (ϵ 12,100); nmr δ 2.30 (2 H, m, 3-CH_2), 3.84 (1 H, d, J = 4.5 Hz, OH), 4.64 (2 H, m, 6-CH_2), 5.25 (1 H, m, 2-H), 6.05 (1 H, m, 4-CH), 7.30 (5 H, m, aryl); mass spectrum *m/e* (rel intensity) 176 (parent, 11), 131 (17), 130 (100), 129 (79), 128 (26), 115 (50), 91 (20).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.91; H, 6.90.

The semicarbazone of **14a** formed readily and quantitatively, mp 179–179.5° after recrystallization from ethanol.

Anal. Calcd for $C_{12}H_{15}N_2O_3$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.86; H, 6.45; N, 18.13.

The filtrate from above was chromatographed on silicic acid. Elution with hexane gave 0.262 g (18%) of furan **13a**: mp 53.5–55° and, after sublimation (30°, 0.05 mm), mp 58.5–59.5° (lit.[27] mp 58.5–59°); ν (KBr) 1570, 1170, 1050, 870, 750, 690 cm^{-1}; nmr δ 6.68 (1 H, m, 4-CH), 7.20–7.60 (6 H, m, aryl + 5-CH), 7.72 (1 H, m, 2-CH). Further elution with ether gave an additional 0.036 g of dihydropyran **14a** (total yield 39%).

Reduction of 14a. Dihydropyran **14a** (0.352 g, 0.002 mol) was treated for 3 hr with 0.200 g (0.0052 mol) of $LiAlH_4$ in 50 ml of anhydrous ether. Water was added and inorganic salts were removed by filtration. The ether layer was separated, dried, and evaporated. The residue was chromatographed on silicic acid (hexane elution followed by ether) to give 0.236 g (66%) of 2-phenyl-2-pentene-1,5-diol (**15**): mp 51–51.5° and, after recrystallization from CCl_4–hexane, 51–52°; ν ($CHCl_3$) 3250 (br), 2880, 1601, 990, 900 cm^{-1}; nmr δ 2.4 (2 H, dt, J_d = 2, J_t = 6 Hz, 4-CH_2), 3.6 (2 H, t, J = 6 Hz, 5-CH_2), 3.9 (2 H, broad, exchangeable with D_2O, 1- and 5-OH), 4.38 (2 H, s, 1-CH_2), 5.82 (1 H, t, J = 2 Hz, 3-CH), 7.24 (5 H, m, aryl).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.88; H, 7.89.

Preparation of 3-(4-Ethoxyphenyl)furan (13b) and 3,6-Dihydro-5-(4-ethoxyphenyl)-(2*H*)-pyran-2-ol (14b). Enol ether **12b** (2.06 g, 0.01 mol) was added to DSM [prepared from 4.08 g (0.02 mol) of trimethylsulfonium iodide] at −5°. After 2 hr at ambient temperature, work-up by extraction gave an ethereal solution, which when concentrated precipitated 1.20 g (54%) of dihydropyran **14b**: mp 115–116.5° and, after recrystallization from CCl_4, 120.5–121°; ν ($CHCl_3$) 3580, 3400, 2980, 2930, 1610, 1510, 1480, 1395, 1280, 1250, 1110, 1045, 900 cm^{-1}; ν (KBr) 3360, 1600, 1510, 1280, 1230, 1040, 900, 790 cm^{-1}; nmr δ 1.38 (3 H, t, J = 7 Hz, CH_2CH_3), 2.42 (2 H, m, 3-CH_2), 3.63 (1 H, d, J = 6 Hz, OH), 4.02 (2 H, q, J = 7 Hz, CH_2CH_3), 4.57 (2 H, m, 6-CH_2), 5.22 (1 H, m, 2-CH), 5.95 (1 H, m, 4-CH), 6.8 (2 H, d, J = 8 Hz, aryl), 7.23 (2 H, d, J = 8 Hz, aryl).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.88; H, 7.21.

The supernatant from above gave on chromatography (hexane elution) 0.155 g (8%) of furan **13b**: mp 80–82° and, after sublimation (50°, 0.05 mm), 81–83°; ν (KBr) 2960, 2910, 1580, 1510, 1490, 1460, 1390, 1230, 1030, 770 cm^{-1}; nmr δ 1.38 (3 H, t, J = 7 Hz, CH_2CH_3), 3.98 (2 H, q, J = 7 Hz, CH_2CH_3), 6.63 (1 H, m, 3-CH), 6.84 (2 H, d, J = 9 Hz, aryl), 7.35 (2 H, d, J = 9 Hz, aryl), 7.44 (1 H, m, 5-CH), 7.63 (1 H, m, 2-CH).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.97; H, 6.56.

Preparation of 3-(4-Chlorophenyl)furan (13c) and 3,6-Dihydro-5-(4-chlorophenyl)-(2*H*)-pyran-2-ol (14c). Enol ether **12c** (1.96 g, 0.01 mol) was added to DSM [prepared from 4.08 g (0.02 mol) of trimethylsulfonium iodide] at −5°. After 90 min at ambient temperature, work-up by extraction and chromatography gave (hexane elution) 0.353 g (20%) of furan **13c**: mp 49–50° and, after sublimation (25°, 0.05 mm), 50–51° (lit.[28] mp 50–51°); ν (Nujol) 2930, 2860, 1515, 1460, 1380, 1170, 1090, 1060, 1020, 870, 830, 780, 720 cm^{-1}; λ_{max} 260 nm (ϵ 12,055) [lit.[28] λ_{max} 262 nm (ϵ 13,200)]; nmr δ 6.6 (1 H, m, 4-CH), 7.30 (4 H, m, aryl), 7.43 (1 H, m, 5-CH), 7.66 (1 H, m, 2-CH). Further elution with ether gave 0.174 g (8%) of dihydropyran **14c**: mp 65–77° and, after sublimation (65°, 0.075 mm), 80.5–82.5°; ν ($CHCl_3$) 3590, 3400, 2940, 1600, 1495, 1405, 1120, 1065, 1010, 900, 820 cm^{-1}; nmr δ 2.57–2.30 (2 H, m, 3-CH_2), 3.58 (1 H, m, OH), 4.57 (2 H, m, 6-CH_2), 5.25 (1 H, m, 2-CH), 6.03 (1 H, m, 4-CH), 7.25 (4 H, m, aryl).

Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.72; H, 5.26. Found: C, 63.02; H, 5.43.

Preparation of Cholestano[2,3-c]furan (19). 2-Methoxymethylene-3-cholestanone (0.80 g, 0.00182 mol) was added to DSM [prepared from 0.816 g (0.004 mol) of trimethylsulfonium iodide] at −5°. After 90 min at ambient temperature, the usual work-up, except that $CHCl_3$ was used for extraction, gave 0.855 g of a yellow gum, chromatography of which (hexane elution) gave 0.110 g (15%) of furan **19**: mp 99.5–102.5° and, after recrystallization from $CHCl_3$–CH_3OH, 105–105.5°; ν (KBr) 2910, 2840, 1455, 1440, 1370, 1030, 885, 765 cm^{-1}; nmr δ 0.7–2.8 (*ca.* 44 H, m, methyl, methylene, and methinyl), 7.0 (2, broad s, vinyls), mass spectrum *m/e* (rel intensity) 410 (parent, 100).

Anal. Calcd for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 85.16; H, 11.03.

Preparation of 3-(Hydroxymethyl)-2-inden-1-one (20). 3-Methoxy-2-inden-1-one (1.04 g, 0.0065 mol) was added to DSM [prepared from 1.42 g (0.007 mol) of trimethylsulfonium iodide] at −5°. After 1 hr at ambient temperature, the usual work-up by extraction and chromatography (ether–hexane elution) gave 0.146 g (14%) of indenone **20**: mp 111–113° and, after recrystallization from benzene and sublimation (87°, 0.05 mm), 114.5–115° (yellow needles); ν (KBr) 3300, 1705, 1610, 1580, 1455, 1430, 1260, 1050, 770 cm^{-1}; nmr (CD_3COCD_3) δ 2.78 (1 H, broad s, OH), 4.57 (2 H, d, J = 2 Hz, CH_2OH), 5.66 (1 H, t, J = 2 Hz, 2-CH), 7.09 (4 H, m, aryl); mass spectrum *m/e* (rel intensity) 160 (parent, 50), 132 (40), 131 (100), 103 (45), 77 (26).

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.19; H, 5.10.

Reactions of DOSM. Preparation of 1-Methyl-3,5-diphenylthiabenzene 1-Oxide (22). Enol ether **1a** (2.0 g, 0.0084 mol) was added to 0.01 mol of DOSM (prepared from 2.2 g of trimethyloxosulfonium iodide). After 2 hr at ambient temperature and 1.5 hr at 50°, work-up by addition to water and extraction into ether gave 1.6 g (68%) of thiabenzene oxide **22**, mp 135–145° and, after recrystallization from methanol, 147.5–149° (lit.[6] mp 148–148.8°).

Preparation of 1,3-Dimethyl-5-phenylthiabenzene 1-Oxide (27). Enol ether **8b** (2.68 g, 0.0152 mol) was added to 0.02 mol of DOSM (prepared from 4.4 g of trimethyloxosulfonium iodide). After 2 hr at ambient temperature and 1 hr at 50°, work-up as with **22** gave 2.64 g of a red oil, which nmr indicated was mainly thiabenzene oxide **27**. Chromatography (ether–hexane elution) of 1.0 g of the oil gave 0.584 g (46%) of **27** as a yellow liquid, which was further purified by molecular distillation (110°, 0.07 mm).[16]

Anal. Calcd for $C_{13}H_{14}SO$: C, 71.52; H, 6.46; S, 14.68. Found: C, 71.38; H, 6.60; S, 14.74.

Preparation of 1,3,5-Trimethylthiabenzene 1-Oxide (28). Enol ether **26** (1.85 g, 0.00144 mol) was added to 0.00145 mol of DOSM (prepared from 3.18 g of trimethyloxosulfonium iodide). After 1 hr at ambient temperature and 2 hr at 50°, work-up by extraction and chromatography (ether elution) gave 0.656 g (29%) of thiabenzene oxide **28**, mp 66.5–68.5° and, after sublimation (60°, 0.03 mm), 69–70° (lit.[16] mp 70.4–71°).

Anal. Calcd for $C_8H_{12}SO$: C, 61.50; H, 7.73; S, 20.52. Found: C, 61.52; H, 7.56; S, 20.27.

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Registry No. *cis*-**1b**, 42392-85-8; *trans*-**1b**, 42392-86-9; **2b**, 42392-87-0; **8b**, 42392-88-1; **12a**, 3617-15-0; **12b**, 42392-90-5; **12c**, 41850-77-5; **13b**, 42392-92-7; **13c**, 20842-12-0; **14a**, 42392-94-9; **14a** semicarbazone, 42392-95-0; **14b**, 42392-96-1; **14c**, 42392-97-2; **15**, 42392-98-3; **19**, 34984-39-9; **20**, 42393-00-0; **26**, 1540-24-5; **27**, 42393-02-2; **28**, 32398-62-2; *p*-ethoxyacetophenone, 1676-63-7; *p*-chloroacetophenone, 99-91-2; 3-methoxy-2-inden-1-one, 42393-04-4; 1,3-indandione, 606-23-5; 2-methoxymethylene-3-cholestanone, 42393-05-5.

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Baeyer–Villiger Oxidation of $\Delta^{1(9)}$-Octalone-2 and $\Delta^{1(8)}$-Indanone-2[1]

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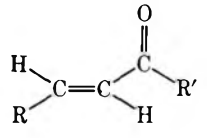
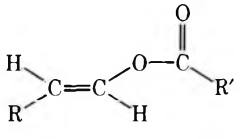
The reactions of $\Delta^{1(9)}$-octalone-2 and $\Delta^{1(8)}$-indanone-2 with trifluoroperacetic acid and *m*-chloroperbenzoic acid have been investigated under a variety of reaction conditions. The reaction conditions which were varied included temperature, reaction time, acidity, and equivalents of oxidizing agent used. Product distributions are reported. Oxidations using trifluoroperacetic acid gave complex product mixtures which resulted from reactions of the initially formed products with more trifluoroperacetic acid or with the trifluoroacetic acid which was produced during the reaction. Varying the above-mentioned variables did not greatly simplify the problem. Oxidation reactions using *m*-chloroperbenzoic acid gave the simplest product mixtures; *e.g.*, $\Delta^{1(9)}$-octalone-2 gave exclusively an epimeric mixture of epoxy lactones when 2 equiv of the peracid was used.

The outcome of the Baeyer–Villiger oxidation of α,β-unsaturated ketones, given by the general formula **1**, seems to be highly dependent upon the nature of the ketone and the reaction conditions used.[2] The primary oxidation products, enol esters (**2**) and epoxy ketones (**4**), are rarely isolated. In general the major product is the epoxy ester (**3**), which is no doubt derived from the enol ester (**2**).[3]



1



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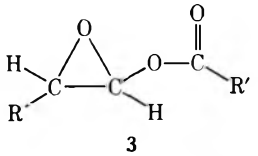

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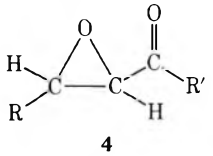
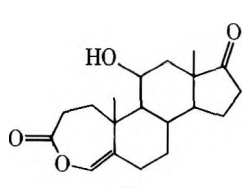


4

Several Δ^4-3-keto steroids have been subjected to Baeyer–Villiger oxidation reactions. The reaction of perbenzoic acid with 11β-hydroxyandrost-4-ene-3,17-dione in the presence of anhydrous perchloric acid in chloroform gave a 60% yield of the enol lactone **5**.[4] In contrast to this, oxidation of cholest-4-en-3-one with trifluoroperacetic acid (TFPAA) gave what was reported as a good yield of **6**.[5] It has been shown that the aldehyde lactone **6** resulted from the acid-catalyzed rearrangement of an intermediate epoxy lactone.[6] This has been confirmed by the oxidation of testosterone acetate with perbenzoic acid, in which all of the intermediates were isolated and characterized.[7]



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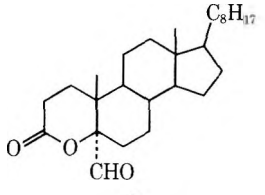

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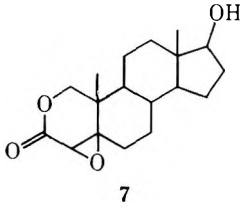
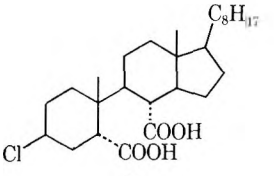


7

Although hydrogen peroxide oxidation of α,β-unsaturated ketones usually leads to the formation of epoxy ketones, it has been found that in the presence of a catalytic amount of selenium dioxide Δ^4-3-keto steroids are converted into enol lactones.[8]

The alkaline hydrogen peroxide oxidation of *A*-nortestosterone leads to the formation of **7**, presumably *via* the epoxy ketone which is subsequently converted to **7**.[9] The oxidation of 3β-chlorocholest-5-en-7-one with TFPAA gave **8**.[10]



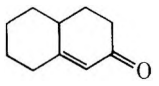
8

In contrast to the data available concerning the above, very few data are available which deal with the Baeyer–Villiger oxidation of simple α,β-unsaturated ketones. Oxidation of 2-cyclohexenone with TFPAA yielded a small amount of 2-hydroxyadipic acid.[11] Reaction of 3-phenyl-2-cyclopentenone with perbenzoic acid gave 4-oxo-4-phenylbutanoic acid.[12]

In view of the lack of information available on the Baeyer–Villiger oxidation of simple α,β-unsaturated cyclic ketones, and, in view of the fact that in most instances a rather complex mixture of products was obtained, this work was carried out to develop processes which would give good yields of intermediates such as **13**, **20**, **21**, and **24** (see Scheme I). In our case these intermediates were always isolated as stereoisomeric pairs. An attempt was made to correlate product distributions with the reaction conditions employed. Also, the use of "buffered" oxidation reaction conditions (TFPAA and disodium hydrogen phosphate) in the oxidation of α,β-unsaturated ketones seems not to have been thoroughly studied. Since it appears that

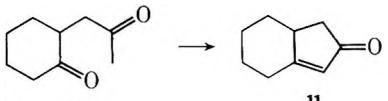
the presence of the trifluoroacetic acid, produced during reactions using TFPAA, may be responsible for the formation of complex reaction product mixtures, the use of *m*-chloroperbenzoic acid (CPBA) could lead to more of the primary oxidation products since the *m*-chlorobenzoic acid which is formed during the reaction is a weaker acid than trifluoroacetic acid, and would probably lead to fewer side reactions.

Two α,β-unsaturated ketones were used in this study. $\Delta^{1(9)}$-Octalone-2 (**9**) was prepared following the procedure



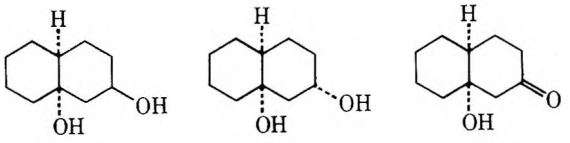
9

of Stork.[13] Details pertaining to the purification of **9** may be found in the Experimental Section. $\Delta^{1(8)}$-Indanone-2 (**11**) was formed by the intramolecular Aldol condensation of the γ-diketone **10**,[14] which was made from cyclohexanone morpholine enamine and bromoacetone.[15]



10 **11**

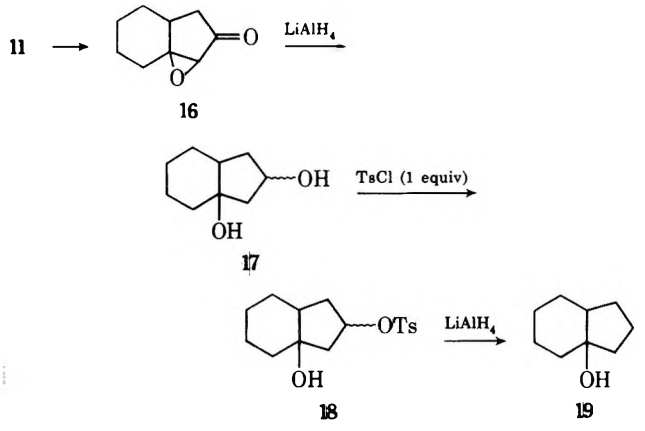
The expected primary oxidation products for the peracid oxidation of **9** were the epoxy ketones **12a** and **12b** and the enol lactone **13** (see Scheme I). An authentic sample of **12a** was readily prepared by the alkaline hydrogen peroxide epoxidation at 20° of the α,β-unsaturated ketone **9**, which produced a single isomer. The stereochemistry of the product was determined by reduction of the epoxy ketone with lithium aluminum hydride to a mixture of diols **14a** and **14b**. The known diol[16] **14a** was isolated in 33% yield. The diol **14a** was oxidized to the known hydroxy ketone **15**.[16] The material remaining after the isolation of **14a** also gave **15** upon oxidation, lending credence to the fact that reduction of **12a** produced both **14a** and **14b**.



14a **14b** **15**

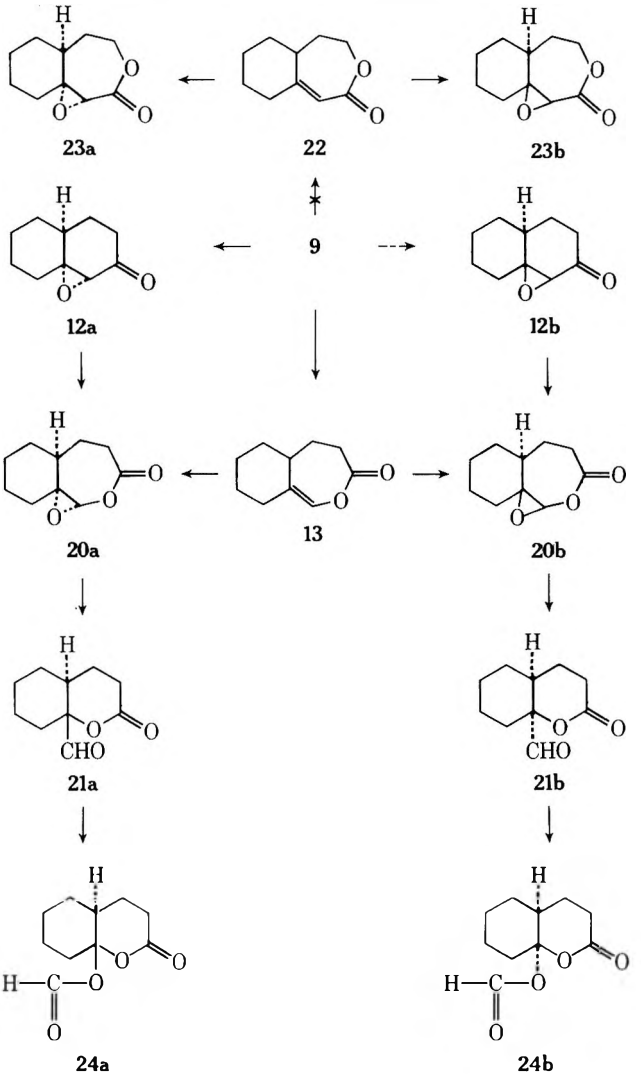
Alkaline hydrogen peroxide oxidation of **9** at 40° resulted in a 9:1 mixture of **12a** and **12b**. The cis:trans ratio was determined from the nmr integral of the oxirane ring proton (δ 2.98 for **12a** and 3.12 for **12b**).

The epoxy ketone **16** was synthesized by the procedure used for the preparation of **12a** and the stereochemistry of **16** was determined by conversion to the known[17] *cis*-3a-indanol (**19**).



16 **17** **18** **19**

Scheme I
The Baeyer-Villiger Oxidation of $\Delta^{1(9)}$-Octalone-2 (9)



Compounds **9** and **11** were oxidized using both 85% CPBA and TFPAA. The reactions were run under various reaction conditions. The variables were temperature, equivalents of oxidizing reagent, reaction times, and, in those cases where TFPAA was used, the presence or absence of disodium hydrogen phosphate. In certain instances, all of the oxidizing reagent was added at one time and in other reactions it was added intermittently. The results and exact experimental conditions employed are indicated in Table I for the oxidation of **9** and Table II for the oxidation of **11**. The product distributions were determined from the nmr spectra of the crude reaction products by measuring the relative areas of signals which were characteristic of the molecules present. Scheme I summarizes the results of the Baeyer-Villiger oxidation of **9**. The relationship indicated by the dashed arrow is only suppositional while those indicated by solid arrows have been observed.

The isolation and characterization of the various intermediates and products in the oxidation of **9** was accomplished as follows. The components of the crude product mixture were separated by elution chromatography. Since an authentic sample of **12a** had already been prepared (*vide supra*), it was readily identified as one of the products. The epoxy ketone **12a** was present only when **9** was treated with 1 equiv of CPBA. For reactions using TFPAA as the oxidizing agent, **12a** was not observed to be present, indicating that **12a** either did not form or it reacted

Table I
The Effect of Type and Amount of Oxidizing Reagent, Reaction Time, Temperature, and Acidity on Product Distributions from the Baeyer–Villiger Oxidation of $\Delta^{1(9)}$-Octalone-2 (9)

Expt	Oxidation reagent	Buffered[a]	Temp, °C	Equiv of oxid reagent used	Reaction time, hr	Product composition, % 9	12a	13	20a	20b	21a	21b	24
1a	TFPAA	+	−6	1	24	77		16	5			2	
1b	TFPAA	+	−6	2[c]	48	54		20	18		1	7	
1c	TFPAA	+	−6	3[c]	72	35		16	29		8	12	
2a	TFPAA	+	10	1	24	59		11	19		4	7	
2b	TFPAA	+	10	2[c]	48	18		6	24		20	14	18
2c	TFPAA	+	10	3[c]	72				24			10	66
3a	TFPAA	+	25	1	24	52		14	16		1	13	4
3b	TFPAA	+	25	2[c]	48	15		6	4		38	26	11
3c	TFPAA	+	25	3[c]	72						41	29	30
4	TFPAA	+	10	3[b]	90	29	*d*	22	37		3	5	4
5a	TFPAA	−	10	1	24	58		11			19	11	1
5b	TFPAA	−	10	2[c]	48	17					44	29	10
5c	TFPAA	−	10	3[c]	72						42	18	40
6	CPBA	−	−7	1	24	30	2	36	16	16			
7	CPBA	−	25	1	24	38	17	7	20	18			
8	CPBA	−	25	2	24				52	48			

[a] + means buffered, − means unbuffered. [b] All of the oxidizing agent was added at one time. [c] One equivalent of the oxidizing agent was added every 24 hr. [d] Trace amounts of **12a** were probably formed, since **12a** was subsequently detected during chromatography (see Experimental Section).

Table II
The Effect of Type and Amount of Oxidizing Reagent, Reaction Time, Temperature, and Acidity on Product Distributions from the Baeyer–Villiger Oxidation of $\Delta^{1(8)}$-Indanone-2 (11)

Expt	Oxidation reagent	Temp, °C	Equiv of oxid reagent used	Reaction time, hr	Buffered	Product composition, % 11	30	31	32
9	TFPAA	10	3[a]	90	+	64	36		
10	TFPAA	25	1	24	+	70	9	20	1
11	CPBA	25	1	24	−	84	16		
12	CPBA	25	2[a]	24	−	57	43		

[a] All of the oxidizing agent was added at one time.

rapidly under the reaction conditions. The trans epoxy ketone **12b** was never detected in any of the product mixtures, indicating that it did not form or that its rate of reaction with acid exceeded its rate of formation.

A second product was identified as having structure **13** on the basis of the following spectral data: ir $\nu_{C=O}$ 1758, $\nu_{C=C}$ 1662 cm^{-1}; nmr δ 6.00 (s, 1, vinyl H). Had oxygen insertion occurred on the other side of the carbonyl group leading to the formation of **22** the ir absorptions would have been at a longer wavelength. Furthermore, as shown by several examples cited earlier, **13** is entirely consistent with the normal mode of the peracid oxidations of α,β-unsaturated ketones.

The epoxy lactone **20a** was prepared by the oxidation of **12a** with CPBA. The nmr spectrum of the product of this oxidation was inconsistent with **23a.** The chemical shift of the oxirane ring proton in **23a** would probably have a value close to that of the oxirane ring proton in **12a,** *i.e.,* δ 2.98. Additionally, the chemical shift of the methylene protons adjacent to the ether type oxygen should have a value of δ 3.5–4.0. In actuality none of the signals expected for **23a** are observed. On the contrary, the signal at δ 4.88 is in good agreement with what is expected for the oxirane ring proton in the epoxy lactone **21a.** The possibility that the trans epoxy lactone **20b** might be formed from **12a** can be eliminated since the stereochemistry of the ring fusion is rigid and not directly involved in the reaction. The epoxy lactone **20a** was observed in product mixtures involving the use of CPBA as the oxidizing agent and also in product mixtures where TFPAA buffered with disodium hydrogen phosphate was used. The epoxy lactone **20a** was not observed in product mixtures where unbuffered TFPAA was used, suggesting that **20a** is unstable under acidic conditions. That **20a** undergoes an acid-catalyzed rearrangement was established (*vide infra*).

When **13** was treated with 1 equiv of CPBA, equal amounts of **20a** and **20b** were formed. The epoxy lactone **20b** was assigned the trans ring juncture on the basis of its synthesis and because it had spectral properties very similar to those of the cis isomer **20a.** Compound **20b** was only observed in reaction mixtures in which **9** had been oxidized with CPBA.

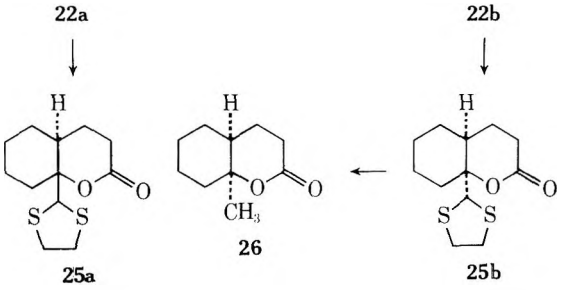
Also, oxidations employing TFPAA yielded products which showed absorptions in the nmr spectrum at δ 9.6 and 9.8. This suggests that the products contain aldehydic protons. By analogy with the already established acid-catalyzed rearrangement for a steroidal system containing a similar functionality,[7] the rearrangement of **20a** and **20b** yields **21a** and **21b.** Evidence supporting this rearrangement was obtained by treatment of **20a** with a catalytic amount of *p*-toluenesulfonic acid which gave a single product (**21a**) having an nmr signal at δ 9.8. Consistent with this structure are selected spectral data: ir ν_{CH} (aldehydic) 2730, $\nu_{C=O}$ (aldehyde and lactone) 1746 cm^{-1}. Additionally, the elemental analysis was consistent with the empirical formula $C_{10}H_{14}O_3$.

Treatment of a 50:50 mixture of **20a** and **20b** with a catalytic amount of *p*-toluenesulfonic acid resulted in a 50:50 mixture of **21a** and **21b.** These data along with the previously established stereospecific rearrangement of the cis isomer **20a** suggest that **20b** undergoes a stereospecific rearrangement to yield **21b.**

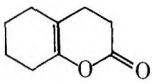
A fifth product (isomeric pair) was detected in product mixtures which resulted when **9** was oxidized with TFPAA. These products were assigned structures **24a** and **24b** on the basis of their nmr spectrum, which showed sin-

glets at δ 8.24 and 8.39 which are attributable to the formate protons. Also, a mixture of **24a** and **24b** could be prepared by TFPAA or CPBA oxidation of a mixture of **21a** and **21b**.

The stereochemistry of **21a** and **21b** was established in the following manner. A mixture of two dithioacetals was obtained upon treatment of a 1:1 mixture of **21a** and **21b** with 1,2-ethanedithiol. The nmr chemical shifts of the methinyl protons (originally the aldehydic protons) of the 1,3-dithiolane rings of the mixture of dithioacetals were at δ 4.7 and 4.9. The dithioacetal **25b** (nmr signal at δ 4.9, *vide infra*) was prepared in pure form by treating the mixture of aldehyde lactones **21a** and **21b** with 1,2-ethanedithiol for a short period of time and then washing the crude product mixture with aqueous Na_2CO_3. The stereochemistry of **25b** was determined by its conversion to the known lactone **26**.[18] In order to determine which aldehyde lactone was derived from **20a** and which one from **20b**, the aldehyde lactone **21a**, prepared from **20a**, was converted into the corresponding dithioacetal **25a** and it indeed gave an nmr signal at δ 4.7. The data imply that the stereochemical relationships are those shown in Scheme I. The mechanism for these rearrangements is analogous to that reported for the rearrangement of the epoxy lactone derived from Δ^4-cholesten-3-one.[6]



Finally, in certain reactions involving oxidation with TFPAA, minor amounts of **27** were isolated. The enol lactone **27** could not be detected by nmr in the product mixtures because it does not give rise to a characteristic nmr absorption. However, it could be isolated by careful chromatography of the reaction products (see Experimental Section).



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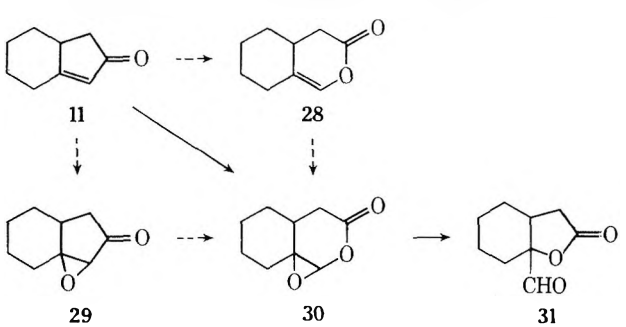
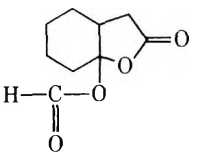
Scheme II outlines the results of the Baeyer–Villiger oxidation of $\Delta^{1(8)}$-indanone-2 (**11**). Oxidation of **11** was not investigated to the same extent as was the oxidation of **9**. The structural assignments were based on analogy with the products obtained from the oxidation of **9**. The primary oxidation products **28** and **29** were not detected in any of the product mixtures, although one or both of them

Scheme II
The Baeyer–Villiger Oxidation of $\Delta^{1(8)}$-Indanone-2



are undoubtedly formed as intermediates in the pathway to the epoxy lactone **30**, which is observed in buffered oxidations using TFPAA as well as in oxidations using CPBA. The aldehyde lactone **31** is observed only for oxidations with unbuffered TFPAA and is undoubtedly the product of an acid-catalyzed rearrangement of **30**. A compound detected in some of the product mixtures using TFPAA as the oxidizing agent may have the structure **32** as suggested by analogy with the oxidation of **9**.



32

The data in Table I are meant to illustrate the complex product mixtures which are obtained when using TFPAA. Several of the experiments have been duplicated but the exact product distribution cannot be predicted with any degree of regularity. This may be due to several factors. First, the thermal instability of the epoxy lactones which restricted us to nmr as our method of analysis and the nmr integral has its limitations. Second, exact reproducibility cannot be expected readily because of the heterogeneous reaction mixtures which were used. The data do, however, permit some conclusions to be drawn. The use of TFPAA with or without added Na_2HPO_4 does not give the intermediates **13**, **20**, or **21** as major products. All cases where TFPAA has been used in this study have resulted in product mixtures in which the components could be separated only by elution chromatography. Also, the use of CPBA gave **20** (epimeric mixture) in good yield. This material could then be used to prepare pure **21**, which in turn could be converted to **24** all in good yield. The only reason **21** and **24** could not be isolated in nearly quantitative yield was because of their sensitivity to the hydrolytic work-up which was used.

Experimental Section[19]

Cyclohexanone Morpholine Enamine. The method of Stork[13] was employed (81% yield), bp 109–111° (12 mm) [lit.[13] bp 104–106° (12 mm)].

$\Delta^{1(9)}$-Octalone-2 (9). The synthesis was performed as described by Stork,[13] bp 66–68° (0.05 mm) [lit.[13] bp 66° (0.05 mm)]. The crude product (74% yield) consisted of approximately 80% of the $\Delta^{1(9)}$ isomer and about 20% of the $\Delta^{9(10)}$ isomer (nmr analysis). Low-temperature (Dry Ice–acetone bath) recrystallization from hexane gave a product which consisted of 94% of the $\Delta^{1(9)}$ isomer and 6% of the $\Delta^{9(10)}$ isomer as indicated by nmr. Ir confirmed the presence of some of the $\Delta^{9(10)}$ isomer.

An attempt to fractionally distil the 80:20 octalone mixture at atmospheric pressure using a 16 × 250 mm column packed with glass helices resulted in extensive decomposition of the octalones. Distillation at 12 mm using the same column resulted in no significant separation of the two isomers.

The 80:20 octalone mixture (0.7 g) was separated by elution chromatography on a 20 × 300 mm column packed with silica gel. The column was successively eluted with 300 ml of hexane, 500 ml of 2% ethyl acetate in hexane, and finally 5% ethyl acetate in hexane. A forerun of 500 ml of solvent was eluted before 16 40-ml fractions were collected. The forerun consisted only of solvent. Fractions 5–7 (0.077 g) were identified as virtually pure $\Delta^{9(10)}$-octalone-2. Fractions 9–16 (0.615 g) were identified as pure $\Delta^{1(9)}$-octalone-2 (**9**) by the absence of saturated carbonyl in the ir and by an aliphatic to vinyl proton ratio of 13:1 ± 5% in the nmr.

The 80:20 octalone mixture apparently contained a third component because of a signal at δ 3.6 in the nmr. A sample of the 80:20 octalone mixture (50 ml) was very slowly distilled and the first 1-ml fraction, bp 103–111° (12 mm), was found to be enriched in the compound responsible for the δ 3.6 nmr signal. This fraction (0.7 g) was placed on a 20 × 300 mm silica gel column and successively eluted with 200 ml of hexane, 200 ml of 2% ethyl

acetate in hexane, 200 ml of 5% ethyl acetate in hexane, and finally 10% ethyl acetate in hexane. A forerun of 400 ml of solvent was eluted before 24 40-ml fractions were collected. The forerun consisted only of solvent. The first two materials to elute from the column were identified as octalones. The third component to elute, fractions 20–24 (0.481 mg), was identified by ir, nmr, and mass spectra as 1-morpholino-3-butanone. The spectra of this material were identical with those of an authentic sample prepared by another route.[20] Removal of this contaminant from the crude 80:20 octalone mixture was accomplished by bubbling HCl into a solution of 40 g of octalone mixture in 50 ml of hexane until no further precipitation occurred. The solid hydrochloride salt was collected by filtration, the filtrate was successively washed with water, 5% aqueous $NaHCO_3$ solution, and water, and the octalones were recovered by distillation. The hydrochloride salt of 1-morpholino-3-butanone was recrystallized from ethanol and had mp 148–149° (lit.[21] mp 149°).

Bromoacetone. The procedure of Catch[22] was used with the exception that both the original aqueous layer and the MgO and water slurry were extracted with ether and the additional material obtained was added to the crude product prior to distillation. The desired product was obtained in 48% yield after distillation: bp 37–45° (12mm) [lit.[22] bp 63–65° (50 mm)]; ir $\nu_{C=O}$ 1720 cm^{-1}; nmr δ 2.28 (s, 3 H), 3.88 (s, 2 H).

1-(2-Oxocyclohexyl)propanone (10). The synthesis was carried out according to the procedure of Baumgarten[15] with the exception that steam distillation was not employed as a means of isolating the crude product. At the end of the heating period the reaction mixture was cooled, the aqueous and organic layers were separated, and the aqueous layer was extracted with ether. The organic extracts were combined and dried, and the solvent was removed on a rotary evaporator. The residue was distilled to yield the product in 21% yield: bp 70–72° (0.04 mm) [lit.[15] bp 91–93° (1.1 mm)]; ir $\nu_{C=O}$ 1712 and 1620 cm^{-1} (doublet); nmr δ 1.1–2.5 (9 H), 2.14 (s, 3 H), 2.90 (m, 2 H).

$\Delta^{1(8)}$-Indanone-2 (11). Cyclization of **10** according to the procedure of Islam and Raphael[14] afforded the desired product in 88% yield after distillation: bp 51–53° (0.02 mm) [lit.[14] bp 88° (4 mm)]; ir ν_{CH} (vinylic) 3070, $\nu_{C=O}$ 1710, $\nu_{C=C}$ 1623 cm^{-1}; uv λ_{max} 230 nm (ϵ17,600); nmr δ 0.8–2.9 (11 H), 5.62 (s, 1 H); mass spectrum *m/e* (rel intensity) 136 (52), 108 (69), 95 (37), 93 (50), 91 (45), 80 (48), 79 (100), 77 (52), 66 (40), 53 (34), 51 (50).

Conversion of $\Delta^{1(9)}$-Octalone-2 (9) to *cis*-1,9-Epoxydecalone-2 (12a). The conversion of 3 g of **9** was performed as outlined by Wasson and House[23] and gave 2.36 g (72%) of **12a**: bp 74–76° (0.03 mm); ir $\nu_{C=O}$ 1710 cm^{-1}; nmr δ 1.1–2.5 (13 H), 2.98 (s, 1 H); mass spectrum *m/e* (rel intensity) 166 (34), 111 (61), 95 (67), 93 (34), 81 (31), 67 (100), 55 (47).

Conversion of *cis*-1,9-Epoxydecalone-2 (12a) to *cis*-2,9-Decalindiol (14a). A solution of 0.6 g (0.0036 mol) of **12a** in 10 ml of THF was added dropwise to an ice bath cooled slurry of 0.205 g (0.0054 mol) of $LiAlH_4$ in 20 ml of THF. The reaction mixture was allowed to come slowly to room temperature and stirring was continued for a total of 18 hr. At the end of this time the reaction mixture was treated successively with 0.2 ml of water, 0.2 ml of 15% aqueous NaOH, and 0.6 ml of water. The salts were removed by filtration and the filtrate was concentrated on a rotary evaporator to give 0.6 g of an oil–solid mixture. Recrystallization from benzene yielded 0.2 g (33%) of **14a**, mp 158–160° (lit.[16] mp 159–160°). Evaporation of the mother liquors gave 0.4 g of an oil suspected to be the epimeric cis diol **14b**. This was confirmed when both **14a** and the oil were oxidized separately with Jones reagent to the same product, *cis*-9-hydroxydecalone-2 (**15**). Spectral data for **14a** are as follows: ir ν_{OH} 3400 cm^{-1}; nmr δ 0.9–2.1 (14 H), 3.30 (m, 1 H), 3.71 (m, 1 H), 3.90 (s, 1 H), 4.20 (d, 1 H); mass spectrum *m/e* (rel intensity) 170 (21), 152 (91), 109 (80), 98 (100), 96 (35), 55 (40), 43 (48), m* 136.0.

Conversion of *cis*-2,9-Decalindiol (14a) to *cis*-9-Hydroxydecalone-2 (15). The conversion of 0.200 g of **14a** was performed according to the procedure of Prelog and Smith[16] to give 0.150 g (75%) of **15**: mp 130–131° (lit.[16] mp 131–132°); ir ν_{OH} 3390, $\nu_{C=O}$ 1710 cm^{-1}; nmr δ 1.1–1.9 (10 H), 2.26 (m, 4 H), 2.41 (ν_{AB} for AB pattern. δ 2.12 ν_A, 2.69 ν_B, J = 14.3 Hz, 2 H); mass spectrum *m/e* (rel intensity) 168 (67), 150 (56), 122 (87), 111 (90), 108 (38), 98 (100), 97 (40), 55 (88), 43 (57), m* 134.0.

Conversion of $\Delta^{1(8)}$-Indanone-2 (11) to *cis*-1,8-Epoxy-1*H*,8*H*-dihydroindanone-2 (16). The conversion was performed in the same manner as the conversion of **9** to **12a**, 2.72 g of **11** giving 1.5 g (60%) of **16**: bp 68–70° (0.05 mm); ir ν_{CH} (epoxy) 3050, $\nu_{C=O}$ 1755 cm^{-1}; nmr δ 0.8–2.7 (11 H), 3.11 (s, 1 H); mass spectrum *m/e* (rel intensity), 142 (9), 95 (100), 67 (55).

Preparation of *cis*-3a-Indanol (19) from *cis*-1,8-Epoxy-1*H*,8*H*-dihydroindanone-2 (16). The epoxy ketone **16** (0.260 g, 0.0017 mol) in 2 ml of THF was added to a slurry of 0.100 g (0.0036 mol) of $LiAlH_4$ in 4 ml of THF at 5°. The reaction mixture was allowed to warm to room temperature and stirred for 17 hr. It was then diluted with ether, and 0.1 ml of H_2O, 0.1 ml of 15% aqueous NaOH, and 0.3 ml of H_2O were added successively. The precipitate was removed by filtration and the filtrate was concentrated to give 0.29 g of crude diol **17**. *p*-Toluenesulfonyl chloride (0.358 g, 0.0019 mol) dissolved in 2 ml of pyridine was added to the crude **17** (0.0018 mol) at 5°. The solution was then poured onto ice and dilute HCl and the product was extracted with ether. The extract was washed successively with dilute HCl, aqueous $NaHCO_3$, and water. After drying and removal of the solvent, 0.43 g of crude monotosylate **18** (oil) was obtained.

The crude tosylate dissolved in 3 ml of THF was added to a slurry of 0.2 g of $LiAlH_4$ in 8 ml of THF at ~0°. The mixture was stirred at room temperature for 1 hr and then under reflux for 20 hr. After the mixture was cooled in an ice bath and diluted with ether, 0.2 ml of H_2O, 0.2 ml of 15% aqueous NaOH, and 0.6 ml of H_2O were successively added. The precipitate was removed by filtration. After removal of the solvent, 0.14 g of **19** was obtained. Sublimation of the crude product gave crystals, mp 51–51.5° (lit.[17] mp 49°). The ir spectrum was identical with that reported.[17]

Trifluoroperacetic Acid. Preparation was according to the method outlined by Lewis.[24]

Oxidation of $\Delta^{1(9)}$-Octalone-2 (9) with TFPAA. Five separate oxidations were performed, each experiment involving a change in one or more of the following parameters: temperature, acidity, reaction time, and equivalents of oxidizing reagent employed. In four of the five experiments the additional equivalents of oxidizing reagent were added at known time intervals during the course of the reaction. In the remaining experiment TFPAA was added at one time.

The composition of the crude product from each of the experiments was determined from an nmr integral by choosing characteristic sharp signals for each of the compounds produced in the reaction and comparing the relative areas of these signals. The crude product compositions for the five reactions are presented in Table I along with the reaction parameters.

Since all five experiments were run in the same fashion, the experimental details of only one will be given.

A solution at 10° of 1 equiv (5.2 g) of TFPAA in 40 ml of CH_2Cl_2 was added slowly to a mixture of 6.0 g (0.04 mol) of **9** and 57 g of anhydrous Na_2HPO_4 in 200 ml of CH_2Cl_2 at 10°. The reaction mixture was kept at 10° and stirring was continued for 24 hr. At the end of this time a 3-ml aliquot was withdrawn from the reaction flask, concentrated, and analyzed by nmr and a second equivalent TFPAA was added. After stirring at 10° for another 24 hr, a second aliquot was withdrawn and a third equivalent of TFPAA was added. After stirring at 10° for an additional 24 hr (total reaction time 72 hr), the salts were removed by filtration, and the filtrate was dried and then concentrated on a rotary evaporator to give 4 g of crude product mixture (for composition see Table I).

The crude product (0.6 g) from expt 1 (see Table I) was placed on a 20 × 300 mm silica gel column and successively eluted with 200 ml of hexane, 200 ml of 2% ethyl acetate in hexane, 500 ml of 5% ethyl acetate in hexane, and finally 10% ethyl acetate in hexane. A forerun of 300 ml of solvent was eluted before 32 40-ml fractions were collected. The forerun consisted only of solvent. Fractions 5–9, 0.097 g (containing some solvent), were identified by ir and nmr as about 90% enol lactone **13** and 10% epoxy ketone **12a**. Fractions 11–14, 0.191 g (containing some solvent), were identified as recovered starting material. Fractions 19–25, 0.166 g (containing some solvent), were sublimed (30°, 0.005 mm) to yield 0.157 g of epoxy lactone **20a**. Fractions 27–31, 0.054 g (containing some solvent), were identified as a mixture of the aldehyde lactones **21a** and **21b** and were distilled, bp 108–11° (0.5 mm).

A chromatography performed after a repetition of the above experiment resulted in the isolation of 0.05 g of material in fractions 3–4. The material was distilled (bp 66°, 0.004 mm) and was identified as the enol lactone **27**: ir $\nu_{C=O}$ 1766, $\nu_{C=C}$ 1713 cm^{-1}; nmr δ 1.64 (m, 4 H), 2.12 (m, 6 H), 2.58 (t, 2 H); mass spectrum *m/e* (rel intensity) 152 (79), 124 (42), 96 (50), 82 (44), 67 (100).

Oxidation of $\Delta^{1(8)}$-Indanone-2 (11) with TFPAA. These oxidations were performed in the same manner as the oxidations of **9** with TFPAA. The crude product distributions were also determined in the same fashion and are tabulated in Table II.

Oxidation of $\Delta^{1(9)}$-Octalone-2 (9) with CPBA. This reaction

was run first using 1 equiv and then 2 equiv of the peracid. The procedure for both experiments was the same and will be given only for the oxidation employing 1 equiv of the peracid.

To a solution at room temperature of 0.2 g (0.00134 mol) of **9** in 50 ml of CH_2Cl_2 was added dropwise with stirring a solution of 0.281 g of 85% CPBA (0.00134 mol of peracid) in 15 ml of CH_2Cl_2 and stirring was continued for a total of 24 hr. The reaction mixture was then extracted with 5% aqueous $NaHCO_3$ solution until the extracts remained basic and washed with water. The organic solution was dried and the solvent was removed on a rotary evaporator to yield 0.180 g of crude product. The crude product composition was determined from the nmr integral in the same manner as it was in the experiments using TFPAA as the oxidizing reagent. The results are listed in Table I.

For the experiment involving 2 equiv of CPBA, 2.0 g of **9** gave 2.03 g (84%) of isomeric epoxy lactones **20a** and **20b** as the only product. In an attempt to separate the mixture of epoxy lactones using a silica gel column and 10% ethyl acetate in hexane as the solvent, the trans isomer **20b** decomposed. The cis isomer **20a** eluted from the column in pure form: ir ν_{CH} (epoxy) 3022, $\nu_{C=O}$ 1748 cm^{-1}; nmr δ 1.1–2.2 (11 H), 2.54 (m, 2 H), 4.88 (s, 1 H).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.07; H, 7.83.

Oxidation of $\Delta^{1(8)}$-Indanone-2 (11) with CPBA. These oxidations were performed and product distributions were determined in the same manner as outlined for the oxidations of **9** with CPBA. All oxidations gave approximately 100% crude yield. The results are listed in Table II.

Conversion of the Epoxy Lactone 20a to the Aldehyde Lactone 21a. *p*-Toluenesulfonic acid monohydrate (0.002 g) was dissolved in 20 ml of benzene. Benzene (4 ml) was removed by distillation to remove water from the solution. The epoxy lactone **20a** (0.150 g) was added and the solution was stirred at room temperature for 10 hr. The reaction mixture was washed with 5% aqueous $NaHCO_3$ and water and dried. After removal of the benzene, the residue was distilled to yield 0.112 g (75%) of **21a:** bp 94–95° (0.005 mm); ir ν_{CH} (aldehydic) 2730, $\nu_{C=O}$ (aldehyde and lactone) 1745 cm^{-1}; nmr δ 1.1–2.3 (11 H), 2.58 (m, 2 H), 9.83 (d, 1 H, J = 1.1 Hz); mass spectrum m/e (rel intensity) 182 (2), 153 (31), 125 (48), 98 (64), 83 (41), 81 (46), 79 (54), 67 (76), 55 (100), 44 (67).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92: H, 7.74. Found: C, 65.73, H, 7.84.

Conversion of the Aldehyde Lactones 21a and 21b to the Formate Lactones 24a and 24b with TFPAA. A solution of TFPAA (0.00055 mol) in 10 ml of CH_2Cl_2 at 5° was added slowly to a cooled, stirred mixture of 0.100 g (0.00055 mol) of a 50:50 mixture of **21a** and **21b** and 0.470 g (0.003 mol) of anhydrous Na_2HPO_4 in 15 ml of CH_2Cl_2. The temperature of the cooling bath was maintained at 12° and the reaction mixture was stirred for 24 hr, after which time a 10-ml aliquot was withdrawn and concentrated and an nmr spectrum was obtained. The nmr spectrum showed the starting material to be 60% converted to a 50:50 isomeric mixture of diesters **24a** and **24b** on the basis of characteristic singlets at δ 8.22 and 8.38. The nmr sample was returned to the reaction vessel and 0.470 g of anhydrous Na_2HPO_4 was added followed by addition of a second equivalent of peracid in 10 ml of CH_2Cl_2. The cooling bath was maintained at 12° and the reaction mixture was stirred for another 24 hr, after which time the nmr spectrum of a second aliquot showed the conversion to be complete. The reaction mixture was filtered and the filtrate was rapidly washed with cold (5°), 10% aqueous $NaHCO_3$ and water and dried. The solvent was removed on a rotary evaporator and the residue was distilled, bp 85–87° (0.005 mm), to yield 0.063 g (60%) of a 50:50 mixture of **24a** and **24b:** ir $\nu_{C=O}$ 1750 (broad, formate and lactone); nmr δ 8.22 (s) and 8.38 (s) (the two peaks integrate to one H), 1.2–2.8 (13 H).

Conversion of *cis*-1,9-Epoxydecalone-2 (12a) to the Epoxy Lactone 20a. To a solution at 25° of 1.0 g (0.006 mol) of **12a** in 100 ml of CH_2Cl_2 was added slowly with stirring a solution at 25° of 1.40 g (0.006 mol of peracid) of 85% CPBA in 50 ml of CH_2Cl_2. The reaction progress was monitored by observing the diminution of the characteristic singlet attributable to the epoxide ring proton of **12a** in the nmr spectrum. After 48 hr, all monitor spectra indicated that the reaction had stopped, so an additional 1.40 g (0.006 mol of peracid) of 85% CPBA was added, and after an additional 24 hr nmr analysis showed the reaction to be complete. The reaction mixture was washed with 100 ml of 10% aqueous $NaHCO_3$ and then with 100 ml of water. After drying, the solvent was removed on a rotary evaporator and the residue was sublimed to yield 0.780 g (71%) of the cis epoxy lactone **20a,** mp 96–97°.

Oxidation of the Enol Lactone 13 with CPBA. To an ice bath cooled solution of 0.150 g (0.0009 mol) of **13** in 20 ml of CH_2Cl_2 was added slowly with stirring a cool (5°) solution of 0.210 g (0.0009 mol of peracid) of 85% CPBA in 20 ml of CH_2Cl_2. The solution was allowed to come to room temperature and stirring was continued for a total of 12 hr, after which time an nmr spectrum indicated that all of **13** had been consumed. The reaction mixture was washed twice with 40 ml of 5% aqueous KOH and once with 40 ml of water. After drying, the solvent was removed on a rotary evaporator and the residue was sublimed to yield 0.145 g (89%) of a 50:50 mixture of the isomeric epoxy lactones **20a** and **20b** as indicated by nmr.

Conversion of 21a and 21b to 24a and 24b with CPBA. To a solution at 12° of 0.100 g (0.00055 mol) of a 50:50 mixture of **21a** and **21b** in 15 ml of CH_2Cl_2 was added a solution at 5° of 0.170 g (0.00066 mol, 1.2 equiv of peracid) of 85% CPBA in 10 ml of CH_2Cl_2. The homogeneous solution was stirred at 12° for 24 hr. The reaction mixture then was washed rapidly with two 20-ml portions of cold 10% aqueous $NaHCO_3$, rinsed with 20 ml of water, and dried. The solvent was removed on a rotary evaporator, and the residue was distilled to yield 0.092 g (85%) of a 50:50 mixture of **24a** and **24b.**

Reaction of the Aldehyde Lactones 21a and 21b with 1,2-Ethanedithiol. A 1:1 mixture (0.1 g, 0.00055 mol) of **21a** and **21b,** 1 ml (excess) of 1,2-ethanedithiol, and a small crystal of *p*-toluenesulfonic acid were added to 2 ml of benzene and this solution was kept at room temperature for 24 hr. An nmr spectrum showed the presence of two singlets (in the ratio of 1:1) at δ 4.7 and 4.9 and these were assigned to the methinyl proton in the 1,3-dithiolane rings of **25a** and **25b,** respectively

On another occasion the reaction mixture was diluted with ether 20 min after mixing the reagents and then washed with aqueous $NaHCO_3$, dried, and concentrated to give **25b.** The fate of the product derived from **21a** was not determined.

Desulfurization of the Dithioacetal 25b. The crude **25b** prepared above was treated with 4 g of Raney Ni (W-2) in 10 ml of dioxane at 85° for 1 hr. The catalyst was removed by filtration, and after removal of the solvent a product was obtained whose ir and nmr spectral properties were identical with those reported for **26.**[18]

Preparation of the Dithioacetal 25a from the Aldehyde Lactone 21a. The procedure used for the preparation of **25a** was identical with that used for the preparation of the mixture **25a** and **25b** above. The chemical shift of the methinyl proton of the 1,3-dithiolane ring of **25a** was δ 4.7.

Registry No. 9, 1196-55-0; **10,** 6126-53-0; **11,** 39163-29-6; **12a,** 42393-90-8; **13,** 42393-91-9; **14a,** 42393-92-0; **15,** 42393-93-1; **16,** 42393-94-2; **19,** 13366-92-2; **20a,** 42393-95-3; **20b,** 42393-64-6; **21a,** 42393-96-4; **21b,** 42393-97-5; **24a,** 42393-98-6; **24b,** 42393-99-7; **25b,** 42394-00-3; **27,** 700-82-3; bromoacetone, 598-31-2

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(19) Microanalyses were performed by Chemalytics Inc., Tempe, Ariz. A Perkin-Elmer grating infrared spectrophotometer, Model 621, and a Beckman spectrophotometer, Model IR-10, were used for the determination of the infrared (ir) spectra. Liquids were run as liquid films between sodium chloride plates, and solids were run as solid dispersions in potassium bromide pellets. A Varian Associates HA-100 spectrometer was used to determine the nuclear magnetic resonance (nmr) spectra; deuteriochloroform or carbon tetrachloride were the solvents, and tetramethylsilane was the internal standard.

The nmr data are reported as chemical shifts in δ units followed by s = singlet, d = doublet, dd = doublet of doublets, t = triplet, or m = multiplet and the relative number of protons attributable to the signal reported. A Beckman DB spectrophotometer was used for the determination of the ultraviolet (uv) spectra. Samples were run as solutions in 95% ethanol in 1-cm quartz cells. Uv data are reported as wavelength of maximum absorption (λ_{max}) followed by the molar absorptivity. Melting points were determined with a Fisher-Johns melting point apparatus and are corrected. Boiling points are uncorrected. Mass spectra were determined with a Varian MAT CH-5 spectrometer. The mass spectral data are reported for $M\cdot^+$ and fragment ions over 30% of the base peak. Important metastable peaks are denoted by m*. Unless otherwise specified, reagents were obtained from regular commercial sources. $MgSO_4$ was the drying agent used.

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Photochemical Reactions of Methyl Phenoxyacetates

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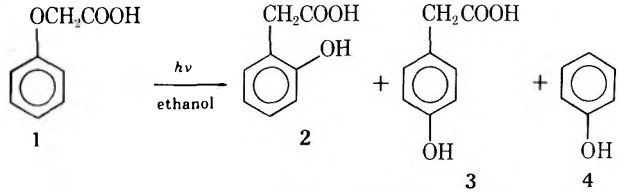
The photochemical reactions of methyl 2,4-dichlorophenoxyacetate (**9**), 4- and 2-chlorophenoxyacetates (**10** and **11**), and phenoxyacetate (**14**) have been investigated. These compounds were found to participate in a photochemical sequence of reactions which begins with **9** and ends with methyl 2- and 4-hydroxyphenylacetates (**12** and **13**). The existence of this reaction sequence when combined with the relative reactivities of its various members and the dependence of reaction on the wavelength of excitation explains the variety of photochemical behaviors which have been observed for phenoxyacetic acids and their derivatives.

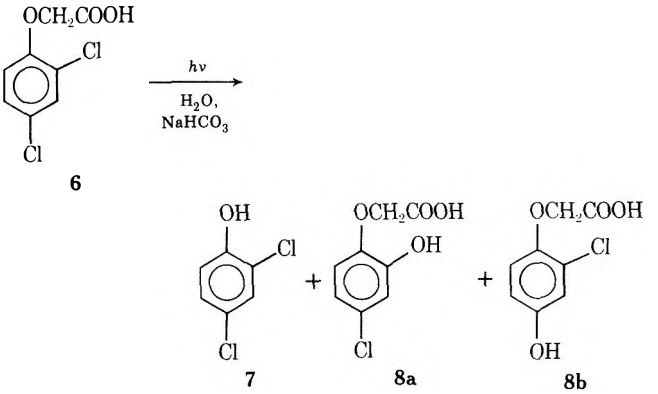
The chlorinated phenoxyacetic acids and esters represent one of the commercially and socially most important groups of organic compounds due to their extensive use in weed control.[1] Stimulated by a desire to understand the natural photochemical decay of these substances, a number of researchers have examined the light-induced reactions of these systems;[2-6] interestingly, the majority of research has been directed toward the parent acids rather than their esters even though the esters are also widely used. Much of the work on the chlorinated phenoxyacetic acids has led to partial identification of photoproducts and to observations of color and pH changes caused by irradiation.[2] Several studies have, however, resulted in more complete product identification; thus, some detailed photochemical understanding of these systems is presently available.

Several years ago Kelly and Pinhey reported that the parent compound in this series, phenoxyacetic acid (**1**), experienced a photochemical rearrangement to yield 2- and 4-hydroxyphenylacetic acids (**2** and **3**) and phenol (**4**).[3] It was further reported that the products **2** and **4**



1 2 3 4

(and a small amount of **1**) were formed when 4-chlorophenoxyacetic acid (**5**) was irradiated; however, 2,4-dichlorophenoxyacetic acid (**6**, the most interesting of these from a herbicidal point of view) produced a complex mixture from which nothing other than phenol (**4**) was detected.[4] Crosby and Tutlass[5] observed that upon irradiation under somewhat different conditions 2,4-dichlorophenoxyacetic acid (**6**) assumed a much different reaction course from the unsubstituted and 4-chloro derivatives (**1** and **5**). No rearrangement took place; instead, substitution and homolysis products **7**, **8a**, and **8b** were formed. These products then experienced further reaction. From the results of these two research groups it was clear that



6 7 8a 8b

some unidentified factor was exercising a deciding influence over the photochemistry of the various phenoxyacetic acids.

More recently it has been shown that photochemical reaction of a series of 2,4-dichlorophenoxyacetic acid esters under conditions simulating those occurring naturally results in replacement of chlorine by hydrogen as the only observable reaction process.[6] Since this result appeared to be still another type of photochemical behavior in the phenoxyacetic acid system, we decided to examine the photochemistry of one of these esters (the methyl) in greater depth in an effort to uncover some of the basic factors responsible for its reactivity.

Results

Vycor-filtered irradiation of 3.00 mmol of methyl 2,4-dichlorophenoxyacetate (**9**) in 350 ml of methanol for 1.5 hr with a 450-W Hanovia mercury vapor lamp under nitrogen caused the reaction of 46% of the starting material to produce, after glc separation, the methyl esters of 4-chlorophenoxyacetic acid (**10**, 16%), 2-chlorophenoxyacetic acid (**11**, 7%), 2-hydroxyphenylacetic acid (**12**, 42%),[7] 4-hydroxyphenylacetic acid (**13**, 18%), and phenoxyacetic acid (**14**, 1%) as well as phenol (**4**, 9%). A dark, insoluble tar presumably accounted for the remaining reacted starting material.[8] The products were each identified by comparison with independently obtained materials.

Irradiation (Vycor filtered) of methyl 4-chlorophenoxyacetate (**10**) under the same conditions as photolysis of **9** resulted in 36% conversion of the starting material in 1 hr. The same isolation procedure yielded the methyl esters of 2-hydroxyphenylacetic[6] (**12**, 40%), 4-hydroxyphenylacetic (**13**, 21%), and phenoxyacetic (**14**, 10%) acids along with phenol (**4**, 10%). A dark material, insoluble in organic solvents, was also formed in this reaction. Irradiation of methyl 2-chlorophenoxyacetate (**11**) under the same conditions as **10** produced the same result.

Similar photolysis (Vycor filtered) of methyl phenoxyacetate (**14**) resulted in complete consumption of **14** in 30 min and the formation of methyl 2-hydroxyphenylacetate (**12**, 58%), methyl 4-hydroxyphenylacetate (**13**, 25%), and phenol (**4**, 12%).

Methyl 2-hydroxyphenylacetate (**12**) did not rearrange to methyl 4-hydroxyphenylacetate (**13**) under the photolysis conditions.

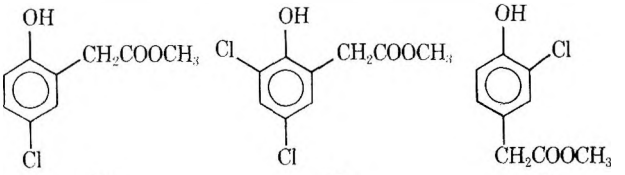
Pyrex-filtered irradiation of methyl 2,4-dichlorophenoxyacetate (**9**) under the conditions described above required 90 hr for a 20% conversion of **9**; however, only the methyl esters of 4- and 2-chlorophenoxyacetic acids (**10** and **11**) were formed in 51 and 39% yields, respectively. The same result was obtained when irradiation of **9** was conducted using water as the solvent. A small amount of hydrolysis of **9** was observed under these conditions. Neither methyl 4-chlorophenoxyacetate (**10**) nor methyl phenoxyacetate (**14**) was reactive when the Pyrex filter was used.

Discussion

The photoproducts arising from irradiation of the various phenoxyacetates (**9**–**11** and **14**) suggest that a sequence of photochemical changes, such as that outlined in Scheme I, is operative. For such a series of transformations to represent correctly the photochemical reactivity of these compounds (**9**–**11** and **14**) it is necessary to demonstrate first that the proposed changes are possible and second that, as well as can be determined, they are the only pathways of reaction. The first is certainly the easier of these two requirements to demonstrate. Photolysis of methyl 2,4-dichlorophenoxyacetate (**9**) and each of the other phenoxyacetates shown in Scheme I produces the succeeding products in the reaction sequence; thus, the postulated pathway (Scheme I) connecting these compounds (**9**–**14**) is a possible one. To show that this sequence is the only one being followed is more difficult to do and requires careful examination of each of the several reaction stages.

Consider the initial step in the reaction sequence in Scheme I (R = CH_3), the conversion of methyl 2,4-dichlorophenoxyacetate (**9**) into methyl 4- and 2-chlorophenoxyacetates (**10** and **11**). The question one must ask concerning this first photochemical process is whether **9** is converted exclusively into **10** and **11**. One way in which this question could be answered would be to prevent the further photochemical reaction of **10** and **11** and then determine whether products **12**–**14** are still capable of forming. With any arbitrary group of compounds such an approach might be impossible or, at least, extremely difficult. In the case of methyl 2,4-dichlorophenoxyacetate (**9**) and methyl 4- and 2-chlorophenoxyacetates (**10** and **11**), however, the fortunate situation exists that the uv absorption of **9** begins at longer wavelength than **10** and **11** (Figure 1); hence, selective absorption of light by **9** is possible. In practice this selective absorption is achieved by use of a Pyrex filter. Pyrex-filtered photolysis of **9** yields only **10** and **11**. This result clearly points to the first step in the reaction sequence shown in Scheme I (R = CH_3) being a required one.

It is, of course, possible that the higher energy radiation incident upon the reaction mixture when the Vycor filter is used causes a new reaction pathway to be operative, perhaps one in which methyl 2,4-dichlorophenoxyacetate (**9**) rearranges to give compounds such as the chlorinated phenols **16**, **17**, or **18**. These systems would then suffer



16 **17** **18**

photochemical chlorine loss to produce methyl 2- and 4-hydroxyphenylacetates (**12** and **13**). Two factors argue against a new reaction pathway. First, no intermediates such as **16**–**18** corresponding to a new rearrangement process were detected in the photolysis mixtures. Second, use of a Corex filter, which allows excitation in the same absorption band as the Pyrex filter but at the somewhat shorter wavelengths necessary to permit methyl 4- and 2-chlorophenoxyacetates (**10** and **11**) and methyl phenoxyacetate (**14**) to absorb light (Figure 1), yielded the same reaction products as with the Vycor filter. Since it seems unlikely that a change in excitation energy within the same absorption band would stimulate a new major reaction pathway and since no new products (*e.g.*, **16**–**18**) indicative of a new pathway were detected, little justification exists for proposing a type of reactivity for methyl 2,4-dichlorophenoxyacetate (**9**) other than that which has been shown to exist (Scheme I). The conclusion reached from consideration of all the evidence pertaining to the photochemical reaction of **9** is that its conversion into **10** and **11** appears to be the only pathway operative.

Turning next to the second transformation in this sequence, the conversion of methyl 4- and 2-chlorophenoxyacetates (**10** and **11**) into methyl phenoxyacetate (**14**), one has greater difficulty in establishing with certainty that **10** and **11** are converted only into **14**. In this case, unfortunately, selective light absorption by either **10** or **11** and not **14** is possible, in theory, but not experimentally feasible (Figure 1). There is ample reason to believe, however, that **14** is the only primary photoproduct from irradiation of **10** or **11**. When either **10** or **11** is irradiated, a small amount of **14** is formed along with the photoproducts

Scheme I
Proposed Reaction Sequences

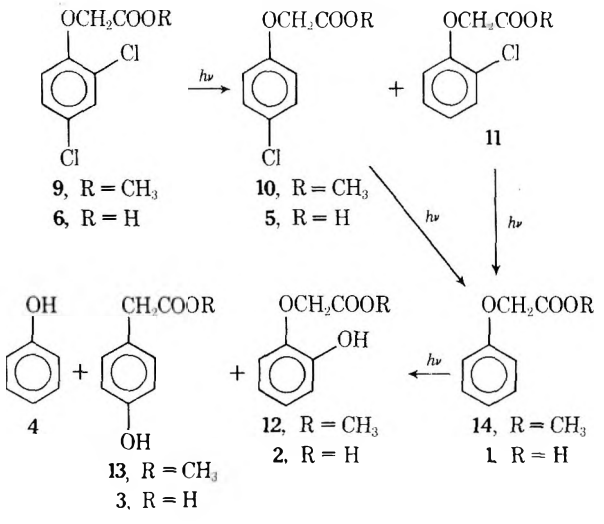


Table I
Photochemical Reactions of Methyl Phenoxyacetates

Compd	Filter	Irradiation time, hr	Per cent conversion	Per cent yield of photoproducts 10	11	14	4	12	13
Methyl 2,4-dichlorophenoxyacetate (**9**)	Vycor	1.5	46	16	7	1	9	42	18
Methyl 2,4-dichlorophenoxyacetate (**9**)	Corex	6.0	32	28	16	10	3	25	12
Methyl 4-chlorophenoxyacetate (**10**)	Vycor	1.0	36			10	10	49	21
Methyl 2-chlorophenoxyacetate (**11**)	Vycor	1.0	36			10	10	50	20
Methyl phenoxyacetate (**14**)	Vycor	0.5	100				12	58	25
Methyl 2,4-dichlorophenoxyacetate (**9**)[a]	Pyrex	90.0	20	51	39				
Methyl 4-chlorophenoxyacetate (**10**)	Pyrex	180.00	0	No reaction					
Methyl phenoxyacetate (**14**)	Pyrex	180.0	0	No reaction					

[a] The same result was obtained with water as a solvent in nitrogen or air atmosphere.

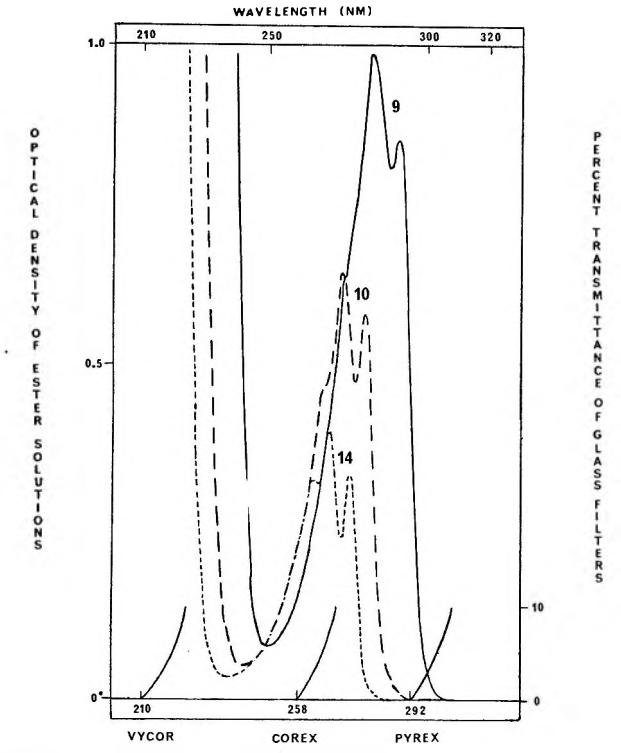


Figure 1. Absorption curves for methyl 2,4-dichlorophenoxyacetate (**9**, —), 4-chlorophenoxyacetate (**10**, --), and phenoxyacetate (**14**, ---) and minimum transmission wavelengths for Vycor, Corex, and Pyrex filters.

methyl 2- and 4-hydroxyphenylacetates (**12** and **13**) and phenol (**4**). The ratio of photoproducts **12**, **13**, and **4** to each other is independent of the choice of **10** or **11** as the starting material. Such behavior certainly suggests a common intermediate in these two reactions. Further strengthening this common intermediate proposal and directly implicating methyl phenoxyacetate (**14**) as the intermediate is the fact that photolysis of **14** produces the photoproducts **12**, **13**, and **4** in the same ratio as obtained from 4- and 2-chlorophenoxyacetates (**10** and **11**).

Recognizing now that the methyl phenoxyacetates (**9**–**11** and **14**) appear to follow a particular sequence of reactions[9] and that the wavelength of light incident upon them determines which compounds are reactive, it is possible for one to return to the variety of photochemical reactivities reported for phenoxyacetic acid derivatives and attempt to understand how these different reactions relate to each other. First, the report by Pinhey and Rigby[4] that 2,4-dichlorophenoxyacetic acid (**6**) produces a complex mixture upon unfiltered irradiation is understandable in light of the findings made here on the photochemistry of methyl 2,4-dichlorophenoxyacetate (**9**), where under similar conditions all members in the reaction sequence (Scheme I) were isolated. A second finding described in the literature, the rearrangement of phenoxyacetic acid (**1**) to 2- and 4-hydroxyphenylacetic acids (**2** and **3**) and phenol (**4**),[3] appears to be the same process as the photoreaction observed in this study for methyl phenoxyacetate (**14**) and represents simply the final step in the sequence shown in Scheme I. This particular process bears a close analogy to the photo-Fries reaction.[10] The fact that photolysis of one intermediate in this sequence, 4-chlorophenoxyacetic acid (**5**),[4] is reported to give only 2-hydroxyphenylacetic acid (**2**) and phenol (**4**) indicates that **1**, like its methyl ester (**14**), is much more reactive than its ring-substituted derivatives; hence, little of the intermediate unsubstituted acid remained after photolysis.[11]

Experimental Section

Synthesis of Reactants and Photoproducts. The starting materials used in this research and the independently obtained samples required for photoproduct identification were either commercially available[12] or were synthesized from commercially available acids by a standard procedure.[13]

General Irradiation and Isolation Procedures. The photochemical reactions conducted in connection with this research were done using a 450-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. A filter (Vycor, Corex, or Pyrex) was placed between the reaction mixture, which was contained in a Model 6515 Ace photochemical reaction vessel, and the light source. The esters (3.00 mmol) were dissolved in 350 ml of methanol and continuously stirred during photolysis. Prepurified nitrogen was passed through the solution prior to irradiation and a slow stream of nitrogen continued during photolysis.

After irradiation, the solvent was removed by fractional distillation *in vacuo* below 35°. Simple distillation allowed some of the more volatile products to be carried over in the distillate. Nmr and ir spectra were taken on the crude reaction mixtures prior to separation and compared with the spectra of the isolated products in an effort to detect any change brought about by the chromatography conditions. With the exception of methyl 2-hydroxyphenylacetate (**12**), which was partially converted into 2-cumaranone (**15**) during separation, all the starting materials and photoproducts were shown to be stable under the isolation conditions.

The reaction mixtures were separated into their individual components and collected for identification using a Varian Aerograph Model 90-P gas chromatograph containing a 0.25 in. × 5 ft column packed with 10% OV-1 on 80–120 mesh Chromosorb W. The column temperature was 170° and the helium flow rate was

40 ml/min. The retention times of the various starting materials and photoproducts under these conditions follow: phenol (4), 3 min; methyl phenoxyacetate (14), 7 min; methyl 2-hydroxyphenylacetate (12), 10 min; methyl 4-hydroxyphenylacetate (13), 13 min; methyl 4-chlorophenoxyacetate (10), 16 min; methyl 2-chlorophenoxyacetate (11), 16 min; and methyl 2,4-dichlorophenoxyacetate (9), 25 min. Each photoproduct was identified by comparison of its nmr and ir spectra with those of an independently obtained sample. The product yields are given in Table I and are determined using only the starting material reacted for calculation. The yields were obtained from integrated recorder curves after response to each compound had been measured and corrections made for varying responses.

Specific Irradiations. The general procedures described in the previous section were followed in each case. The essential information is given in Table I.

Ultraviolet Spectra of Methyl Phenoxyacetates and Transmission Curves for Light Filters. The uv spectra shown in Figure 1 were determined on 0.0022 *M* solutions of the three methyl phenoxyacetates in methanol using a Cary 14 uv spectrometer. The transmission curves for the three light filters shown in Figure 1 were determined on the actual filters used in irradiations by a Beckman Dk 2a uv spectrometer.

Registry No. 9, 1928-38-7; 10, 4841-22-9; 11, 6956-85-0; 14, 2065-23-8.

References and Notes

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(3) D. P. Kelly and J. T. Pinhey, *Tetrahedron Lett.*, 3427 (1964).
(4) J. T. Pinhey and R. D. G. Rigby, *Tetrahedron Lett.*, 1267 (1969).
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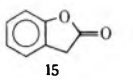
(6) R. W. Binkley and T. R. Oakes, *Chemosphere*, in press.
(7) Methyl 2-hydroxyphenylacetate (12) cyclized to 2-coumaranone (15) to varying extents during glc analysis. The yield reported for 12 has been corrected for this conversion.



15

(8) In the Vycor-filtered reactions even at low conversions color developed in the reaction mixtures and a significant amount of the incident radiation was not being absorbed by the starting material. This situation prevented reliable quantum yield determinations.
(9) A somewhat similar observation has been made by E. A. Caress and I. E. Rosenberg, *J. Org. Chem.*, **36**, 769 (1971).
(10) (a) J. C. Anderson and C. B. Reese, *J. Chem. Soc.*, 1781 (1963). (b) For a recent review, see D. Bellus, *Advan. Photochem.*, **8**, 109 (1971). (c) This similarity has been noted previously by Pinhey, *et al.*, in their complete paper on aromatic ether photochemistry: D. P. Kelly, J. T. Pinhey, and R. D. G. Rigby, *Aust. J. Chem.*, **22**, 977 (1969).
(11) A small but unspecified amount of phenoxyacetic acid (1) was also found (ref 4). 4-Hydroxyphenylacetic acid (3) was not reported (ref 4); however, since only the volatile materials were analyzed, it would not have been detected.
(12) Aldrich Chemical Co., Milwaukee, Wis.
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The Molecular Geometry of β-Pinene as Deduced from the Crystal and Molecular Structure of *cis*-Pinocarvyl *p*-Nitrobenzoate†

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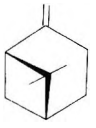
The crystal structure of *cis*-pinocarvyl *p*-nitrobenzoate (abbreviated name, *cis*-PNB), a derivative of β-pinene, has been determined from three-dimensional X-ray data obtained near the temperature of liquid nitrogen. The unit cell was monoclinic with the following dimensions: at approximately −193°, a = 10.583 ± 0.006 Å, b = 6.740 ± 0.003 Å, c = 10.443 ± 0.009 Å, β = 90.46 ± 0.15°; at approximately 22°, a = 10.904 ± 0.012 Å, b = 6.778 ± 0.006 Å, c = 10.906 ± 0.009 Å, β = 91.77 ± 0.27°. Systematic absences occurred for $0k0$ when k was odd, indicating space group $P2_1$. The *p*-nitrobenzoate geometry is similar to that found in other *p*-nitrobenzene derivatives. The cyclobutane ring in the *cis*-pinocarvyl portion of the molecule is normal (internal dihedral angle 141°), leading to severe steric interactions between C-3 and C-7. These interactions are minimized in *cis*-PNB through a decreased puckering in the C-2,C-3,C-4 end of the molecule. The observed C-3···C-7 distance is 2.72 Å. Since the same interactions exist in β-pinene, it is postulated that the *cis*-pinocarvyl grouping and β-pinene have very similar molecular geometries. *cis*-PNB exhibits pseudo-mirror molecular symmetry, C-10 being the only nonhydrogen atom not related to another atom by the mirror plane.

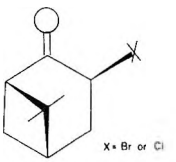
β-Pinene (I) and related bicyclic terpenes undergo cyclobutane ring opening to yield monocyclic or acyclic mol-



I

ecules and cyclobutane ring expansion to form bornane or fenchane compounds.[1-3] Such rearrangements dominate β-pinene chemistry, suggesting that the original bicyclic ring system is relatively unstable.

It has been postulated that the rigid cyclobutane ring leads to severe distortions in the rest of the bicyclic system. Support for this idea is found in the reported crystal structures of chloro-3-nopinone and bromo-3-nopinone (II).[4] In these structures the cyclobutane ring is normal, but the angle between plane C-2,C-3,C-4 and the best

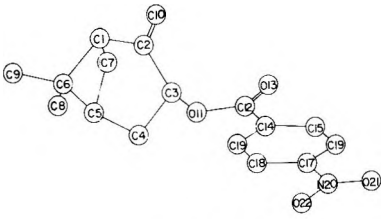


II

† From theses submitted by R. A. M., J. A. H., and W. E. S. in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence University, Appleton, Wis.

plane through C-1, C-2, C-4, and C-5 is only 30°, compared with the 50–60° observed in cyclohexane rings (see Table III). The structural details are not precisely known because the halogen atoms reduced the certainty with which the positions of the other atoms could be determined.

The crystal structure analysis of *cis*-pinocarvyl *p*-nitrobenzoate (abbreviated name, *cis*-PNB) (III) was carried



III

out in order to determine the precise geometry of a β-pinene derivative. *cis*-PNB was suitable for this purpose because the carbon, nitrogen, and oxygen atoms all have approximately equal electron densities. Consequently, it was possible to determine their positions with much higher precision than for the halogenated compounds.

Experimental Section

X-Ray Data. Crystals of *cis*-pinocarvyl *p*-nitrobenzoate (mp 103.0–103.6°, $[\alpha]^{26}D$ −96.0°) suitable for X-ray diffraction analysis were kindly provided by Dr. James Farrand. The unit cell was found to be monoclinic with the following dimensions: at approximately −193°, a = 10.583 ± 0.006 Å, b = 6.740 ± 0.003 Å, c = 10.443 ± 0.009 Å, β = 90.46 ± 0.15°: at approximately 22°, a = 10.904 ± 0.012 Å, b = 6.778 ± 0.006 Å, c = 10.906 ± 0.009 Å, β = 91.77 ± 0.27°. The unit cell parameters were determined by the back-reflection Weissenberg technique. Systematic absences occurred for $0k0$ when k was odd indicating space group $P2_1$. Comparison of measured and calculated crystal densities indicated two molecules of *cis*-PNB per unit cell.

Three-dimensional X-ray data were obtained at approximately −193° using the multiple film equiinclination Weissenberg method and a liquid nitrogen gas flow cryostat.[5] Two crystals were used to obtain layers $0kl$ to $7kl$ and $h0l$ to $h4l$. The reflection intensities were estimated visually by comparison with a calibrated intensity scale. Lorentz and polarization, but no absorption, corrections were made. The data from the two crystal settings were scaled together by the method of Rollett and Sparks.[6] A total of 1361 unique, observed reflections was obtained. An additional 120 reflections were either unobserved or too weak to be measured with confidence. The relative intensities were converted to normalized structure factors, $|E_{hkl}|$, by the K-curve method of Karle and Hauptmann.[7,8]

Structure Determination and Refinement. The unit cell positions of atoms O-11, C-12, O-13, C-14, C-15, C-16, C-17, C-18, C-19, and N-20 were determined by the Patterson search methods of Braun, Hornstra, and Leenhouts.[9-11] Phases calculated from this fragment were used to start the tangent formula refinement procedure.[12] Two cycles were required to determine the positions of the remainder of the nonhydrogen atoms in the molecule. The structure was refined by block-diagonal least-squares methods to an R index[13] of 0.10 using unit weights and anisotropic temperature factors. A three-dimensional difference electron-density map was computed at this point, revealing the positions of all the hydrogen atoms. The least-squares refinement was continued with the hydrogen atoms included. The final R index for all observed reflections was 0.085. Each hydrogen atom was assigned an isotropic temperature factor equal to the final isotropic temperature factor of the atom to which it was bonded, and all hydrogen parameters were held constant during the least-squares refinement.[14] Table I shows the final atomic coordinates and their estimated standard deviations. The anisotropic temperature factors were normal for a structure determined near liquid nitrogen temperature.[15]

Results and Discussion

Figure 1 shows the bond lengths and bond angles in *cis*-PNB.

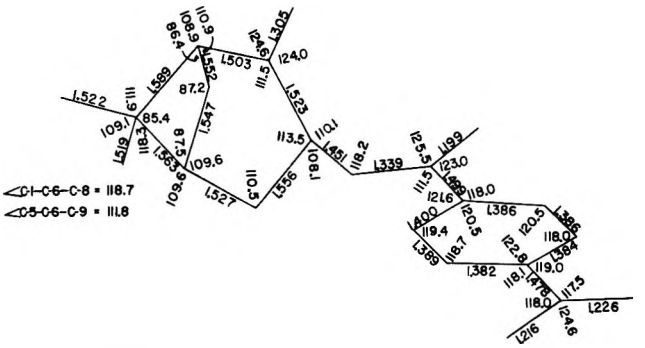


Figure 1. Bond lengths and bond angles in *cis*-PNB. The estimated standard deviation for C–C and C–N bonds is 0.008 Å; for C–O bonds, 0.007 Å; and for the C–N bond, 0.006 Å. The molecule is shown in orthogonal projection in the 010 plane.

Table I
Atomic Parameters

Atom	Fractional coordinates		
	X^a	Y	Z
C-1	0.4411 (6)	0.5260 (9)	−0.2737 (5)
C-2	0.4160 (5)	0.3974 (9)	−0.1591 (5)
C-3	0.2922 (5)	0.4530 (9)	−0.0951 (5)
C-4	0.1910 (5)	0.5352 (9)	−0.1901 (5)
C-5	0.2543 (6)	0.6389 (9)	−0.3027 (5)
C-6	0.3350 (5)	0.4856 (9)	−0.3791 (5)
C-7	0.3801 (6)	0.7338 (10)	−0.2575 (5)
C-8	0.2842 (6)	0.2761 (10)	−0.3945 (5)
C-9	0.3723 (6)	0.5654 (11)	−0.5098 (6)
C-10	0.4893 (6)	0.2533 (10)	−0.1204 (6)
O-11	0.2392 (4)	0.2817 (6)	−0.0309 (3)
C-12	0.2486 (5)	0.2723 (9)	0.0969 (5)
O-13	0.2961 (4)	0.3959 (7)	0.1645 (4)
C-14	0.1933 (5)	0.0834 (9)	0.1476 (5)
C-15	0.1828 (6)	0.0629 (9)	0.2792 (5)
C-16	0.1327 (5)	−0.1085 (9)	0.3316 (5)
C-17	0.0929 (5)	−0.2566 (9)	0.2487 (5)
C-18	0.1001 (5)	−0.2393 (9)	0.1171 (5)
C-19	0.1514 (6)	−0.0675 (10)	0.0655 (5)
N-20	0.0360 (4)	−0.4386 (8)	0.3022 (4)
O-21	0.0375 (4)	−0.4579 (7)	0.4189 (4)
O-22	−0.0077 (4)	−0.5599 (7)	0.2275 (4)
H-1 (C-1)[b]	0.516	0.519	−0.322
H-1 (C-3)	0.316	0.545	−0.030
H-1 (C-4)	0.135	0.426	−0.219
H-2 (C-4)	0.150	0.628	−0.136
H-1 (C-5)	0.200	0.740	−0.340
H-1 (C-7)	0.404	0.821	−0.332
H-2 (C-7)	0.364	0.795	−0.176
H-1 (C-8)	0.200	0.276	−0.445
H-2 (C-8)	0.268	0.246	−0.309
H-3 (C-8)	0.354	0.191	−0.434
H-1 (C-9)	0.315	0.497	−0.550
H-2 (C-9)	0.426	0.461	−0.530
H-3 (C-9)	0.429	0.679	−0.505
H-1 (C-10)	0.468	0.162	−0.057
H-2 (C-10)	0.550	0.197	−0.170
H-1 (C-15)	0.210	0.171	0.330
H-1 (C-16)	0.118	−0.092	0.412
H-1 (C-18)	0.076	−0.368	0.075
H-1 (C-19)	0.176	−0.066	−0.020

[a] Estimated standard deviation times 10^4 in parentheses. [b] H-j (n-k) refers to the jth hydrogen atom bonded to the kth atom of type n.

***p*-Nitrobenzoate Grouping.** The geometry of the *p*-nitrobenzoate portion of *cis*-PNB is similar to that reported for a number of other *p*-nitrobenzene derivatives.[11,23-26] The average C–C bond length within the benzene ring is 1.386 Å and, within experimental error, all the benzene C–C bonds are equivalent. The average distance of the six benzene carbons from the least-squares plane through the ring was 0.004 Å, with the greatest distance being 0.006 Å. The average bond angle within the benzene ring is 120.0°.

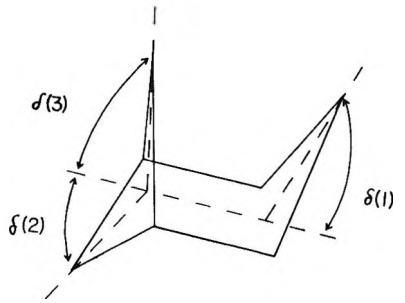


Figure 2. Interplanar angles δ(1), δ(2), and δ(3) formed by the boat and chair conformations of the pinane bicyclic ring system.

Angle C-15–C-16–C-17 is significantly smaller, and angle C-16–C-17–C-18 is significantly larger than the average. The angle between the plane of the nitro group and the best plane through the six benzene carbons is 5°, and the angle between the carboxylate plane and the benzene plane is 7°.

β-Pinene Grouping. The bond lengths and bond angles in the four-membered ring composed of C-1, C-5, C-6, and C-7 agree closely with the values reported for other cyclobutane derivatives.[27-30] The angle between plane C-1,C-7,C-5 and plane C-1,C-6,C-5 is 141°. Values of 149–180° have been reported for other cyclobutane rings. It is likely that the increased pucker aids in relieving severe steric interactions between C-3 and C-7 in *cis*-PNB. Contrary to expectations, bonds C-1–C-2 and C-2–C-3 are not significantly shorter than C-3–C-4 or C-4–C-5, even though the first two bonds involve the trigonal C-2. All four bonds have values close to the normal value of 1.530 Å. The double bond between C-2 and C-10 is shorter than in ethylene (1.334 Å), but close to the length of the exocyclic double bond in *trans*-2,8-dihydroxy-1(7)-*p*-menthene (1.314 Å).[31,32] The (noncyclobutane) ring bond angles at atoms C-1, C-2, C-3, C-4, and C-5 all have values within the range (109–114°) observed in other cyclohexane structures.

Table II contains the values found for the conformation angles within the *cis*-PNB bicyclic ring system.

Ideal cyclohexane boat and chair conformations have conformation angles of 0 and ±60°. The values in Table II indicate that the *cis*-PNB molecule is flatter at the C-3 end and more puckered at the C-6 and C-7 ends than an ideal boat or chair cyclohexane conformation. The greater deviation from ideality exhibited by *cis*-PNB and chloro-3-nopinone compared with some reported cyclohexane derivatives is shown in Table III and Figure 2. Increased ring distortion in β-pinene bicyclic structures appears to be necessary in order to minimize the steric repulsions between C-3 and C-7. For example, in *cis*-PNB a small amount of relief is gained through puckering of the cyclobutane ring, as mentioned earlier. However, the major relief arises from the movement of C-3 toward the C-1,C-2,C-4,C-5 plane and away from C-7, leading to small δ(1) values (*i.e.*, a "flattened" ring). The C-3···C-7 distance observed in *cis*-PNB is 2.72 Å, which is considerably smaller than the sum of the van der Waals radii (3.2 Å).

The ring strain in the molecule could have been partially decreased if the bond angle C-1–C-2–C-3 were near 120°. However, the observed value is 111.5°. The tendency for ring bond angles at carbons involved in exocyclic double bonds to be close to 110° (rather than 120°) has been found previously.[32,33]

In summary, the β-pinene portion of *cis*-PNB lies between a classical bridged chair and a Y-shaped molecule. Previous nmr studies on isopinocampheol[34] and nopinone[35] have been interpreted in terms of the same kind of conformation. Since the ring distortion arises from the need to minimize repulsion between C-3 and C-7, it is very likely that β-pinene itself will closely resemble the β-pinene portion of *cis*-PNB.

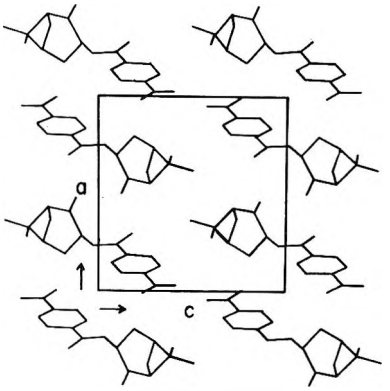


Figure 3. *cis*-PNB crystal packing shown in orthogonal projection in the 010 plane.

Table II
Ring Conformation Angles in the β-Pinene Portion of *cis*-PNB

Atoms $i-1, i, j, j+1$	τ_{ij},[a] deg	Atoms $i-1, i, j, j+1$	τ_{ij},[a] deg
C-6, C-1, C-2, C-3	−64.4	C-7, C-5, C-6, C-1	27.3
C-7, C-1, C-2, C-3	28.7	C-4, C-5, C-7, C-1	83.4
C-1, C-2, C-3, C-4	30.0	C-6, C-5, C-7, C-1	−27.7
C-2, C-3, C-4, C-5	−27.9	C-2, C-1, C-6, C-5	83.7
C-3, C-4, C-5, C-6	61.9	C-7, C-1, C-6, C-5	−26.9
C-3, C-4, C-5, C-7	−33.6	C-2, C-1, C-7, C-5	−81.6
C-4, C-5, C-6, C-1	−82.9	C-6, C-1, C-7, C-5	27.1

[a] Looking down bond $[i-j]$, τ_{ij} is defined as the clockwise angle between bond $[(i-1)-i]$ and bond $[j-(j+1)]$.

Table III[a]
Interplanar Angles δ(1), δ(2), and δ(3) in *cis*-PNB, Chloro-3-nopinone, and Various Cyclohexane Compounds

Compd	δ(1), deg	δ(2), deg	δ(3), deg	Ref
Cyclohexane[b]	60.0	60.0		*d*
Cyclohexane[c]	54.6	54.6		*d*
Cyclohexylammonium chloride	50.0	49.0		*e*
Bicyclohexylidene	49.4	51.1		*f*
cis-PNB	28.2	71.5	69.8	
Chloro-3-nopinone	30.0	75.0	70.0	*g*

[a] See Figure 2. [b] Ideal model. [c] Electron diffraction. [d] R. A. Wohl, *Chimia*, **18**, 219 (1964). [e] S. T. Rao and M. Sundaralingam, *Acta Crystallogr., Sect. B*, **25**, 2509 (1969). [f] K. Sasvari and M. Low, *Acta Crystallogr.*, **19**, 840 (1965). [g] Reference 4.

Molecular Symmetry. The conformation of the benzoate linkage allows a pseudo-mirror plane to be constructed through C-3, C-6, C-7, C-8, C-9, and the nitrobenzoate group. Atoms C-1 and C-2 are approximately related to atoms C-5 and C-4, respectively, by this mirror plane. Of the nonhydrogen atoms, only C-10 is not related by pseudo-mirror symmetry to another atom in the molecule.

Crystal Packing. Figure 3 shows a projection of the unit cell down the *b* axis. The *p*-nitrobenzoate grouping is oriented perpendicular to the 001 plane. Most of the intermolecular distances are much larger than normal van der Waals distances, only 11 distances involving C, N, or O being less than 3.4 Å. The strongest intermolecular interactions occur along the *b* axis, where the molecules are packed so that O-13, C-12, C-14, and C-15 of each molecule lie near O-22, N-20, C-17, and C-18 of another molecule one *b*-axis translation away. In the *c*-axis direction, the closest intermolecular distances occur between each nitro oxygen and either C-16 or C-17 of another *cis*-PNB

molecule. In the a axis direction the packing involved alternating C-10–O-13′ and C-4–O-22″ interactions.

Registry No. β-Pinene, 127-91-3; *cis*-pinocarvyl *p*-nitrobenzoate, 42540-80-7

Supplementary Material Available. A listing of anisotropic temperature factors, observed and calculated structure factors, and distances of atoms in *cis*-PNB from the least-squares plane through the molecule 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 Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $5.00 photocopy or $2.00 for microfiche, referring to code number JOC-74-86.

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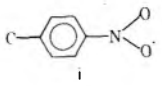

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Acidities of Nitroalkanes in Ammonia. A Warning Concerning the Use of Nuclear Magnetic Resonance as a Method of Analysis

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The deprotonation of nitromethane and of nitroethane by ammonia is readily studied by nmr; the carbon acids and their conjugate bases each show separate signals. At a constant temperature the per cent deprotonation of each acid increases as the concentration of the sample increases. The deprotonation of nitromethane at −33° increases linearly from 34 to 80% as the total concentration of acid plus conjugate base increases from 0.18 to 2.18 *M*. Over this concentration range the chemical shift of the nitromethide ion decreases by 13 Hz. Both carbon acids undergo more deprotonation with decreasing temperature. Significant deprotonation is achieved below −10° for nitromethane and below 5° for nitroethane, the stronger acid. Attempts to express the results at a constant temperature in terms of equilibrium constants were unsuccessful, perhaps because changes in ion aggregation and in solvent polarity accompany variations in sample concentration.

An acidity scale for acids in liquid ammonia solvent is just beginning to be developed. A few pK_a values are available for very weak acids which require amide ion to bring about deprotonation as well as for considerably stronger acids which undergo deprotonation by ammonia itself.[1] For dilute solutions results generally have been obtained by means of potentiometric titration[2] and by using ultraviolet absorption spectroscopy to analyze reaction mixtures.[3] For more concentrated mixtures, nmr has been employed.[4,5]

Nmr is an especially attractive method of analyzing liquid ammonia reaction mixtures. Experimental techniques are relatively simple. Separate signals may be observed for both an acid and its conjugate base, greatly facilitating analysis of mixtures.

We decided to study the deprotonation of nitromethane (I) and nitroethane (II) in ammonia by an nmr method.

CH_3NO_2 $CH_3CH_2NO_2$

I II

We hoped to determine the acidities of these carbon acids in this solvent and to test the suitability of nmr as a method of analysis.

Results

Deprotonation of I and II in ammonia to give III and IV was found to be extensive below room temperature. Studies were carried out using reaction mixtures kept at a constant temperature by means of the variable-temperature nmr probe. All reaction mixtures were clear, colorless, and free of precipitates. Discrete spectra were observed for the acid and its conjugate base under all conditions; no signal averaging of the type found for nitrogen, oxygen, and some carbon acids was evident.[6]

$CH_2{=}NO_2^-$ III $\qquad$ $CH_3CH{=}NO_2^-$ IV

Because the nmr spectra of nitromethane and its conjugate base consist of a pair of singlets, it is necessary to examine signal areas in order to make assignments with structures. For this purpose, mixtures of nitromethane and benzene in ammonia were prepared by weight and the signals for benzene, nitromethane, and nitromethide ion then were integrated. The molar ratio of nitromethane (both forms) to benzene was calculated and compared with the ratio obtained from weighed materials. Consistent agreement between the two ratios was found only when the low-field signal (τ 4.6) was assigned to the anion and the high (τ 5.47) to the acid. Thus, ionization leads to a downfield shift of the signal. The shift of an 0.18 *M* solution is 46 Hz.

Coupling patterns were used to make assignments in the case of nitroethane. This acid shows a quartet (τ 5.35, CH_2, J = 7.5 Hz) and a triplet (τ 8.60, CH_3) while its conjugate base shows a quartet (τ 4.2, CH, J = 6.0 Hz) and a doublet (τ 8.42, CH_3) spectrum. Ionization in ammonia results in downfield shifts of 9 and about 65 Hz for the two types of protons, the acidic center undergoing the larger change. (Similar changes are observed when nitroethane undergoes deprotonation in aqueous solution; the protons are deshielded by 16 and 98 Hz.) Thus, carbon acids I and II both show downfield shifts when they are deprotonated.

The effect of concentration on the degree of deprotonation was examined extensively in the case of I. At −33°, the normal boiling temperature of ammonia, the degree of deprotonation ranges from 34 to 80% as the total concentration of acidic and basic forms ranges from 0.18 to 2.18 *M*, respectively (Table I). Deprotonation is markedly favored by high concentrations at a constant temperature.

A significant change in chemical shift occurs for the protons of the nitromethide ion (III) as concentrations are varied in the above experiments. As the total amount of material in solution increases, the signal of the anion shifts to lower fields. Thus, when the total concentration of I and III is 0.18 *M*, the protons of the anion show a signal 126 Hz upfield from that of benzene. However, when the total concentration is 2.18 *M*, the signal is only 113 Hz away. There is a downfield shift of 13 Hz over the indicated concentration range (Table I). The position of the signal for the methyl group of the acid remains constant (±0.5 Hz) during the variations in total concentration.

The above two changes, per cent ionization of I and shift of the protons of III, are linearly related to the total concentration of acid plus base (Figures 1 and 2, respectively). The linear relationships are described by eq 1 and 2 calculated by the method of least squares. The correlation coefficients for eq 1 and 2 are 0.979 and 0.976, respectively. Indicated uncertainties represent one standard deviation. The shift is given relative to benzene (τ 2.60), which served as the internal standard.

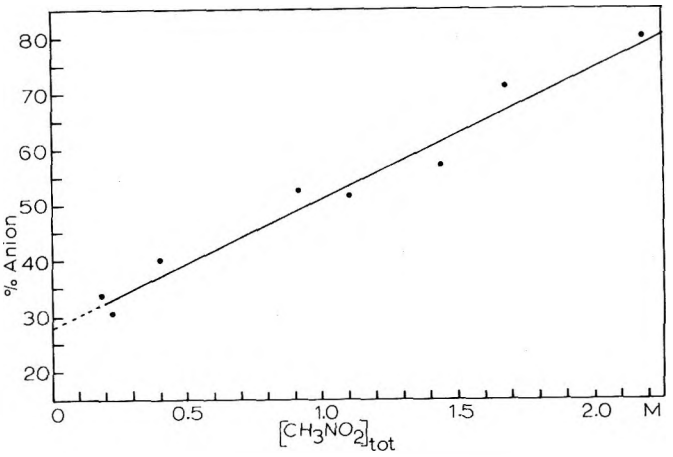

Figure 1. Plot of the percentage of nitromethane which is deprotonated in ammonia at −33° *vs.* the total concentration of the acid and its conjugate base.

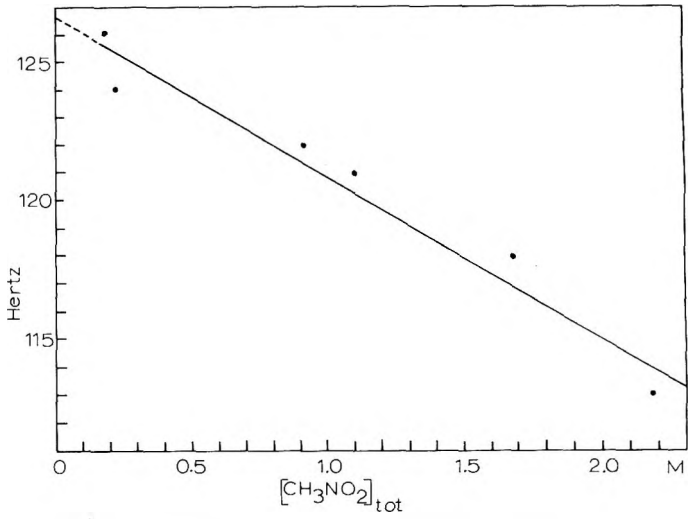

Figure 2. Dependence of the chemical shift of the nitromethide ion in ammonia at −33° on the total concentration of nitromethane and the nitromethide ion. Upfield shifts relative to benzene are indicated.

Table I
Variations in the Per Cent Deprotonation of Nitromethane and in the Chemical Shift of Its Conjugate Base in Ammonia at −33°

Total concn, *M*	% conj base	[Conj base]/[acid]	Hz[a]
0.18	34	0.51	126
0.22	31	0.45	124
0.39	40[b]	0.67	
0.91	53	1.1	122
1.10	52	1.1	121
1.44	57[b]	1.3	
1.68	71	2.5	118
2.18	80	4.0	113

[a] The separation between the signals for $CH_2NO_2^-$ and benzene (τ 2.60) is indicated. [b] Calculated from the data given in Table III.

$$\%\ \text{deprotonation (I)} = 23 \pm 2\,([\text{I}] + [\text{III}]) + 28 \pm 2 \quad (1)$$

$$\text{Shift, Hz (III)} = -5.7 \pm 0.6\,([\text{I}] + [\text{III}]) + 126.6 \pm 0.8 \quad (2)$$

The degree of deprotonation of nitroethane also appears to increase as the total amount of material increases. Only two concentrations (0.43 *M*, 16% deprotonation at 10°, and 0.58 *M*, 23% deprotonation at 11°, Table II) were exam-

Table II
Influence of Temperature on the Degree of Deprotonation of Nitroalkanes in Ammonia

Nitroalkane	Total concn, *M*	Temp, °C[a]	% conj base	[Conj base]/[acid]
CH_3NO_2	0.39	−39	56	1.3
		−30	33	0.50
		−20	14	0.16
		−10	2	0.02
CH_3NO_2	1.44	−45	90	8.4
		−40	80	3.9
		−35	71	2.5
		−30	46	0.87
		−22.5	21	0.26
		−12.5	10	0.11
$CH_3CH_2NO_2$	0.43	−24	87	6.7
		−18.5	78	3.6
		−13.5	66	2.0
		−6.5	53	1.1
		0	29	0.42
		10	16	0.19
$CH_3CH_2NO_2$	0.58	−22.5	92	12.0
		−16	86	6.4
		−7.5	70	2.4
		11	23	0.29

[a] ±1°.

ined. Owing to the small variation in total concentrations, it is not possible to conclude whether changes in chemical shift accompany changes in degree of ionization.

The degree of deprotonation of both nitromethane and nitroethane was determined at temperatures ranging from −45 to −10° for nitromethane and from −24 to 11° for nitroethane. Two samples of each material at two different concentrations were examined. The temperatures ranges for each sample differ slightly (Table II). In the case of both carbon acids an increase in temperature brings about a *decrease* in the degree of deprotonation. In other words, deprotonation of the carbon acid becomes increasingly disfavored as the temperature is increased.

The logarithm of the ratio of the concentrations of conjugate base to carbon acid is related to the inverse of the absolute temperature (eq 3). The slope (A) and intercept (B) values for this equation are given in Table III; these values when used with eq 3 make it possible to calculate acid–base ratios at a variety of temperatures. Lines were calculated by the method of least squares; correlation coefficients are >0.990.

$$\text{Log [conj base]/[acid]} = A/°\text{K} + B \qquad (3)$$

Although the concentration of the nitromethide ion varies with temperature at a fixed total concentration of acid plus base, no change in the chemical shift associated with this ion could be detected. This contrasts with the effect of concentration on the chemical shift at a constant temperature but at a variable total concentration (Table I).

Clearly nitroethane is a stronger acid than nitromethane. For example, at −33°, nitroethane exists 95% in its deprotonated form (0.43 *M* sample) while nitromethane is only 40% deprotonated (0.39 *M* sample). At 25°, both acids are only slightly deprotonated by ammonia. Similarly, it has been found that nitroethane is a stronger carbon acid than nitromethane in water.[7] Replacement of a proton by a methyl group results in a nitroalkane with a greater equilibrium acidity. Of course, deprotonation at ambient temperatures is more extensive in ammonia than water, owing to the greater basicity of the former solvent.

It should be emphasized that measurements were made on systems at equilibrium. That is, the rates of deprotonation of the nitroalkanes and of reprotonation of the conjugate bases are rapid under the conditions employed. This was shown to be the case for deuterated nitromethane. A sample of nitromethane-d_3 in ammonia was prepared in an acetone–Dry Ice bath. Before the sample was placed into the spectrometer probe at −40°, the tube was shaken for 1 min at room temperature to promote mixing. By the time the first nmr spectrum was taken, the sample had undergone complete D–H exchange. At −40° the material exists largely as its conjugate base. Thus, the cycle of dedeuteration, protonation of the conjugate base, and dedeuteration takes place very rapidly. It is likely that such rates are rapid for nitroethane as well.

Table III
Constants to be Used in Calculating the Temperature-Dependent Ratio of Conjugate Base to Acid for Nitroalkane Deprotonation[a,b]

Compd	Total concn, *M*	$10^{-3}A$	B
I	0.39	3.1 (0.2)	−13.1 (0.9)
I	1.44	3.6 (0.2)	−14.8 (0.8)
II	0.43	3.2 (0.1)	−12.0 (0.5)
II	0.58	3.4 (0.1)	−12.6 (0.6)

[a] See eq 3. [b] Sample standard deviations are indicated in parentheses.

Ammonium salts of nitroalkanes have been isolated by removing the solvent from mixtures of the nitroalkane and ammonia. These salts slowly revert to reactants.[8,9] No attempt was made to isolate the ammonium salts in the present study.

Discussion

Many investigations of ionic materials dissolved in liquid ammonia make it clear that ion association is an important phenomenon in this moderately polar solvent (ϵ 23 at −33°[10]), especially in the concentration range employed in the present studies.[1,11-14] Thus, conductance studies of the ammonium and sodium salts of nitromethane in ammonia are consistent with the formation of free ions only at very high dilutions; ion pairs form as concentrations are increased.[8,15] The dissociation constant, K_D, relating the ion pairs and the free ions of ammonium nitromethide, eq 4, is said to have the value 5.3×10^{-5} at −33°.[15] This low value clearly indicates that the ion pairs are considerably more stable than the free ions. Notably, aggregation in ammonia need not stop at the ion pair stage. Triple ions,[16] $(K, NH_2, K)^+$ and $(H_2N, K, NH_2)^-$, are believed to form when the concentration of potassium amide exceeds about 5×10^{-3} *M*.[11]

$$CH_2{=}NO_2^- \; NH_4^+ \overset{K_D}{\rightleftharpoons} CH_2{=}NO_2^- + NH_4^+ \qquad (4)$$

Our results need to be considered in terms of the ion aggregation phenomenon. The observed increases in the degree of deprotonation of nitromethane and nitroethane as the total concentration of material is increased at a constant temperature (Tables I and II) are consistent with the idea that the ionic products do not exist as free ions but as clusters of ions. Association of the ions gives rise to their mutual stabilization, resulting in a shift of the equilibria so as to favor more extensive deprotonation. Also, the observed deshielding of the nitromethide ion as more ions are added to the solvent (Table I) suggests that the environment of this ion is being changed.[13] Perhaps this indicates that the degree of aggregation of the ion is being modified.

Variations in the degree of deprotonation of I with changes in concentration at a constant temperature may also reflect the presence of another phenomenon. This is a medium or solvent polarity or salt effect. As the reaction

medium is made more polar by the addition of ions, the formation of still more ions by deprotonation is facilitated. This type of effect is well known for aqueous solutions,[17] for example. It is likely that medium and ion aggregation effects both are important in the present study.

The present results are too complex to be analyzed solely in terms of equilibria involving ion aggregation. For example, schemes involving deprotonation of I at −33° to give an ion pair or involving deprotonation to give an ion pair which then dissociates into free ions do not quantitatively correlate the observations. It seems likely that activities rather than concentrations are required in order to take medium effects into consideration as well. However, the necessary information about activity coefficients is unavailable.

The observed variations in the anion to acid concentration ratios for I and II may be correlated linearly with the inverse of the absolute temperature (eq 3). The form of this correlation is the same as that for the ionization of an acid to give an ion pair. We do not mean to imply with eq 3 that the ion pair equilibrium scheme, or any other, is favored. Rather, this is the simplest way to deal with the results and to present them in a useful manner.

The temperature dependence of the degree of deprotonation of I and II in ammonia is unusual. Both acids become less acidic as the temperature increases. While both are largely in their acidic forms at 25°, they exist largely as their conjugate bases below about −40° for I and about −10° for II. Although this behavior is unusual, it is not unprecedented for carbon acids.[18]

Curiously, temperature variations bring about changes in the concentration of the nitromethide ion but these are not accompanied by variations in chemical shift. By contrast, the chemical shift of the nitromethide ion is highly dependent on concentration at a constant temperature (Table I). Perhaps the constancy of the shift reflects temperature dependent changes in ion aggregation.

Our new results for I require a comment about the older conductance studies.[8,15] The present results clearly show that the deprotonation of nitromethane is incomplete at −33° when the concentration of acid is >0.1 *M*. The linear plot (Figure 1) relating per cent deprotonation with total concentration implies that at "infinite dilution" (intercept) only 28% of I is converted to its conjugate base. The conductance workers assumed that I was completely deprotonated in dilute solutions at −33°.[15] This assumption has been questioned recently.[1] Unfortunately, our results do not provide the answer. The present per cent deprotonation–concentration relationship is unusual because it is linear; linearity is not likely to result for very dilute solutions.

Clearly, nmr does provide a great deal of useful information about the deprotonation of carbon acids I and II in ammonia. The linear relationships given in Figures 1 and 2 and by eq 3 are useful in that they quantitatively express the acidity of the carbon acids as a function of total concentration and of temperature. However, owing to the necessity of employing high concentrations of material, analysis of the results in terms of p*K* values is made very difficult.

In this study we have been considering charge-forming reactions. Ionic products are produced from neutral reactants in ammonia. The use of high concentrations as required by the nmr method complicates the analysis of the results. It is not possible to describe the deprotonation in terms of equilibrium constants. Problems that we encountered with the analysis of nitroalkane acidity are not likely to be unique. Others who wish to determine p*K* values for similar uncharged acids in ammonia are warned to consider methods other than nmr. Clearly, some method employing more dilute solutions is preferred.

Experimental Section

Benzene (τ 2.60) and nitroalkane were weighed into an nmr tube. Ammonia was condensed into the tube by passing the vapor through a section of constricted glass tubing placed inside the nmr tube. Cooling was achieved with an acetone–Dry Ice bath. After the tube was sealed with a torch the level of ammonia in the tube was measured with a ruler at room temperature. This measurement then was converted to a volume measurement by the use of a calibration curve. The calibration curve was constructed by adding known volumes of water to an nmr tube and by measuring the level of the liquid in the tube. Volume corrections due to thermal expansion of the solvent are small and therefore were not made.

Spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 variable-temperature controller. Temperatures of probe were measured by the chemical shift method using a sample of methanol and a calibration chart provided by Varian Associates.

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Registry No. Nitromethane, 75-52-5; nitroethane, 79-24-3.

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Notes

Acid-Promoted Nucleophilic Aromatic Substitution in Deoxygenation of Nitro and Nitroso Compounds[1]

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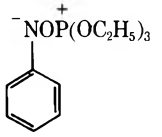
The products of deoxygenation of aryl nitro and nitroso compounds with triethyl phosphite in aprotic media can usually be rationalized in terms of aryl nitrene intermediates.[2-5] We found and reported[1] that the presence of acetic acid led to the formation of products which appeared to arise from nucleophilic atomatic substitution processes. Subsequent studies of deoxygenation reactions in alcohols have further elucidated the nature of nucleophilic aromatic substitution processes which accompany deoxygenation of nitrosobenzene.[6] These reactions have been formulated in terms of an intermediate zwitterion A. Recent studies



A

of other aspects of deoxygenation reactions have also been interpreted in terms of such a nitrenoid intermediate.[7-9]

Yield data were reported[10] in the earlier communication for deoxygenation of nitrobenzene (**1a**), o-nitrotoluene (**1b**), *p*-nitrotoluene (**1c**), 2,4-dimethylnitrobenzene (**1d**), nitrosobenzene (**2a**), o-nitrosotoluene (**2b**), and *p*-nitrosotoluene (**2c**) in solutions containing about 5% by volume acetic acid. We report here the experimental details of the original study and spectral data. Although apparently general in scope, the reaction is characterized by low yields and, because of the difficulties in rapid separation of products, is not conducive to detailed mechanistic study.

The photochemical deoxygenation of nitrobenzene in excess pure triethyl phosphite gives only a trace of triethyl *N*-phenylphosphorimidate.[2] The deoxygenation of nitrosobenzene in excess triethyl phosphite similarly gives no characterizable aromatic product.[4] Polymeric material, presumably derived from phenylnitrene, is formed in both reactions. The presence of acetic acid (5% by volume) in the reaction medium led to the formation of diethyl o-aminophenylphosphonate (**4**), diethyl *p*-aminophenylphosphonate (**5**), aniline (**6**), and o-hydroxyacetanilide (**3**). The latter two compounds were identified by spectral comparison with authentic samples. The structures assigned to **4** and **5** were based on the following data. The composition was deduced from elemental analysis. The solubility of the compounds in aqueous acid and the infrared spectra indicated the presence of primary amine groups in each molecule. The proton nmr, and in particular the P–H coupling pattern,[11] permitted the assignment of the substituent group positions. The nmr signal positions and multiplicity are given in the Experimental Section. The structural assignment of **5** was confirmed by synthesis from *p*-nitrophenylphosphonic acid by esterification and reduction.[12] In **4** a broad singlet assigned to the NH_2 group is present at δ 5.45. A similar signal is observed for the NH_2 group in each of the *o*-aminophenylphosphonates examined in this study and this signal was used to supplement aromatic C–H signals in structural assignments. Hydrogen bonding to the phosphoryl oxygen is probably responsible for the deshielding.

The rapid exothermic reactions of nitroso aromatics with triethyl phosphite[3,4] usually closely parallel the photochemical deoxygenation of nitro aromatics under similar conditions and it has been suggested that the photochemical deoxygenation proceeds through nitroso intermediates.[2] This general similarity was also true for the present TEP–acetic acid reaction system. Deoxygenation of nitrosobenzene gave **4** (3%), **5** (6%), and **3** (11%) as well as diethyl *N*-phenylphosphoramidate (**7**, 3%).

Analogous types of products were obtained for the substituted systems **1b–d** and **2b–c**. The individual reaction products are identified in the Experimental Section and the spectral data which served for structural assignment are also given there. These data permitted straightforward structural assignment, with the exception of **14** and **15**, the two isomeric diethyl aminoarylphosphonates from **1d**. One of these was identified as the ortho substitution product, diethyl 2-amino-3,5-dimethylphenylphosphonate (**14**), on the basis of the nmr spectrum. The amino signal is at δ 5.2 in the region indicative of an ortho disposition of the amino and diethoxyphosphono substituents. The aromatic signals consist of a singlet at δ 6.88 partially overlapping a doublet, $J_{P-H} \cong 14$ Hz, centered at δ 7.0. Neither of the methyl groups shows the fine coupling which characterizes methyl groups ortho to a diethyl phosphono group. The second phosphonate must be diethyl 4-amino-2,5-dimethylphenylphosphonate (**15**). The two aromatic protons do not reveal any mutual splitting. Each shows what must be a PH coupling: a signal at δ 6.90 ($J_{H-P} = 6$ Hz) and at δ 7.23 ($J_{H-P} = 15$ Hz). One of the methyl groups reveals a small ($\sim$1 Hz) splitting. The amino signal is at δ 3.7. The magnitude of the P–H splitting of the aromatic proton signals places the diethyl phosphono substituent ortho to one hydrogen and meta to the other. The upfield aromatic signal reveals the meta P–H coupling favoring the assigned structure over the other possible isomer, diethyl 5-amino-2,4-dimethylphenylphosphonate. Formation of **15** would involve methyl migration in the aromatization step following nucleophilic attack by triethyl phosphite at the 4 position, rather than introduction of the phosphono group at the meta position as indicated originally.[1]

Nitrosobenzene and *o*- and *p*-nitrosotoluene were also deoxygenated in a reaction solution consisting of a 1:1 mixture of TEP–acetic anhydride and which also contained benzene and small amounts of acetic acid. Nucleophilic aromatic substitution was again observed but the principal products were *o*-acetoxyacetanilides. Thus nitrosobenzene gave 2-acetoxyacetanilide (**16**, 6%). *p*-Nitrosotoluene gave 2-acetoxy-4-methylacetanilide (**17**, 46%) and o-nitrosotoluene gave 2-acetoxy-6-methylacetanilide (**18**, 16%). These products were identified by hydrolysis to known hydroxyacetanilides as described in the Experi-

mental Section. The possible involvement of an *O,N*-diacetylphenylhydroxylamine intermediate was investigated, but *O,N*-diacetyl-4-methylphenylhydroxylamine was shown to be stable to the conditions of the deoxygenation reaction, thus excluding it from further consideration as an intermediate.

The salient result of the present investigation is the formation of diethyl aminophenylphosphonates and *o*-hydroxyacetanilides from nitro and nitroso aromatics in the presence of acetic acid. The structures of these products clearly indicate the incursion of aromatic nucleophilic substitution processes when acetic acid is present. Diethyl aminophenylphosphonates have not been reported in previous studies of deoxygenation reactions of nitro or nitroso aromatics[2-5] and we have reexamined the deoxygenation of nitrosobenzene and found that diethyl aminophenylphosphonates are not formed in the absence of acetic acid. Unfortunately, the complexity of the reaction mixture and the attendant difficulty in obtaining precise product yields or mass balance detract from the significance of detailed mechanistic discussion. Although a nitrene might be formed and subsequently protonated, it is perhaps more likely, in view of the results in alcoholic solution,[6] that the deoxygenation intermediate A is diverted by protonation prior to nitrene formation. This comparison is clouded, however, by the possible involvement of strong solvent effects.

Experimental Section[13]

General Procedure for Photochemical Deoxygenation. A solution containing 0.100 mol of the nitro aromatic in triethyl phosphite (190 ml) containing acetic acid (10 ml) was irradiated for 15 hr using a 200-W Type S Hanovia lamp in a water-cooled immersion well under a nitrogen atmosphere. A Pyrex filter was used. Under these conditions the reaction solution temperature remained below 30°. The reaction mixture was then diluted with ether and washed thoroughly with sodium bicarbonate solution. The ether was dried and evaporated and subjected to vacuum distillation below 100° to remove triethyl phosphite, triethyl phosphate, and unreacted nitro aromatic. The composition of the triethyl phosphate–nitro aromatic fraction was estimated by nmr to determine the amount of unreacted nitro compound. The residue was dissolved in ether and partitioned into neutral and acid-soluble fractions by extraction with dilute hydrochloric acid. These mixtures were chromatographed on silicic acid using benzene–ether. Yields quoted are calculated on the basis of the amount of nitro aromatic which reacted.

General Procedure for Deoxygenation of Nitroso Compounds. A solution of the nitroso compound (5.0 g) in 50 ml of benzene was added slowly to a solution of triethyl phosphite (95 ml) and acetic acid (5 ml) maintained at 0°. A nitrogen atmosphere was maintained. Unreacted triethyl phosphite and acetic acid were removed by distillation at 25° (0.1 mm). Triethyl phosphate was distilled at 40–50° (0.1 mm) with gentle heating. The residue was separated into neutral and acid-soluble fractions by extraction with dilute hydrochloric acid and chromatographed as described for the products of the photochemical reaction.

Nitrobenzene (1a). Recovered **1a** accounted for 21% of the starting material. Aniline (4%) was eluted first followed by diethyl o-aminophenylphosphonate[14] (**4**, 8%) as an oil purified by distillation: nmr (CCl_4) δ 7.0–7.5 (m, 2), 6.4–6.8 (m, 2), 5.45 (broad s, 2), 4.03 (quintet, 4), 1.30 (t, 6). The other major product was diethyl *p*-aminophenylphosphonate (**5**, 8%): mp 126–127° (lit.[12] mp 115–119°) after recrystallization from benzene–hexane; nmr (CCl_4) δ 7.60 (d of d, J_{H-H} = 8, J_{H-P} = 13 Hz, 2), 6.70 (d of d, J_{H-H} = 8, J_{H-P} = 4 Hz, 2), 4.08 (quintet overlapping broad signal, 6) 1.30 (t, 6).

From the neutral fraction there was obtained crystalline 2-hydroxyacetanilide (**3**, 6%), identified by spectral comparison with an authentic sample.

Nitrosobenzene (2a). Chromatography of the basic products gave **4** (3%) eluted with 3:1 benzene–ether and **5** (6%), eluted with 1:1 benzene–ether. Chromatography of the neutral fraction on silicic acid gave 2-hydroxyacetanilide (**3**, 11%) and diethyl *N*-phenylphosphoramidate (**7**, 3%). All products were identified by spectral comparison (infrared and/or nmr) with samples from the photochemical deoxygenation or authentic samples.

Synthesis of 5. Reaction of 4-nitrophenylphosphonic[15] acid with ethanol in the presence of cyclohexylcarbodiimide[16] gave diethyl 4-nitrophenylphosphonate[12] having expected spectral features. Reduction in ethanol with Pd/C catalyst gave **5**,[12] having infrared and nmr spectra identical with those of the product from the deoxygenation reactions.

***p*-Nitrotoluene (1b).** Recovery of unreacted **1b** was 26%. The basic product gave *p*-toluidine (10%) and diethyl 2-amino-5-methylphenylphosphonate (**8**, 11%), which was purified by distillation: nmr (CCl_4) δ 6.9–7.3 (m, 2), 6.60 (d of d, J_{H-H} = 8, J_{P-H} = 6 Hz, 1), 5.38 (s, 2) 4.03 (quintet, 4), 2.19 (s, 3), 1.28 (t, 6). The neutral fraction gave 2-hydroxy-4-methylacetanilide (**9**, 27%) and diethyl *N*-(*p*-tolyl)phosphoramidate (**10**, 2%), both of which were identified by spectral comparison with authentic samples. The authentic sample of **9** was prepared from 3-methyl-6-nitrophenol by the procedure of Proskouriakoff and Titherington.[17]

***p*-Nitrosotoluene (2b).** Benzene–ether (3:1) eluted a trace of *p*-toluidine. The major basic product **8** (9%) was eluted by 1:1 ether–benzene and identified by comparison with **8** from the photochemical deoxygenation of *p*-nitrotoluene. A third fraction contained what appeared to be a second aminophenylphosphonate, but conclusive identification of this compound was not accomplished. The neutral product was chromatographed on silicic acid. Benzene–ether (4:1) eluted **9** (23%) and **10** (3%), both of which were identified by spectral comparison with the samples from the photochemical deoxygenation.

***o*-Nitrotoluene (1c).** Unreacted **1c** accounted for 33% of the starting material. Chromatography of the acid-soluble material gave o-toluidine (2%) followed by diethyl 2-amino-3-methylphenylphosphonate (**11**, 2%) purified by bulb-to-bulb distillation: nmr (CCl_4) δ 7.0–7.4 (overlapping doublet and doublet of doublets, 7.05 d, J_{H-H} = 8 Hz, 7.0–7.4, d of d, J_{H-H} = 8, J_{P-H} = 14 Hz, 2), 6.5 (six-line m, J_{H-H} = 8, J_{H-H} = 8, J_{P-H} = 4 Hz, 1), 5.37 (br s, 2), 4.0 (quintet, 4), 2.10 (s, 3), 1.28 (t, 6). There was also eluted diethyl 4-amino-3-methylphenylphosphonate (**12**, 10%): mp 81–83° after recrystallization from ether–hexane; nmr (CCl_4) δ 7.1–7.7 (d at 7.50, J_{P-H} = 13 Hz, overlapping m, 2), 6.72 (d of d, $J_{H-H} \cong 8$, J_{H-P} = 4 Hz, 1), 4.45 (s, 2), 4.08 (quintet, 4), 2.12 (s, 3), 1.30 (t, 6).

From the neutral fraction diethyl *N*-o-tolylphosphoramidate (7%) was isolated and identified by spectral comparison with authentic material.

***o*-Nitrosotoluene (2c).** Chromatographic separation of the basic product gave o-toluidine (1%), diethyl 2-amino-3-methylphenylphosphonate (2%), and diethyl 4-amino-3-methylphenylphosphonate (9%). The only product isolated from the neutral fraction was diethyl *N*-(2-methylphenyl)phosphoramidate (12%). In each case identification was made by spectral comparison with the products from the photochemical reaction.

2,4-Dimethylnitrobenzene (1d). The recovery of **1d** was 13%. The neutral fraction gave 2,4-dimethyl-6-hydroxyacetanilide (**16**, 14%) as crystalline solid, mp 184–185° (lit.[18] mp 186–187°). Chromatography of the remaining neutral fraction gave diethyl *N*-(2,4-dimethylphenyl)phosphoramidate (**17**, 9%). Separation of the basic fraction by chromatography gave **14** (6%) as an oil purified by bulb-to-bulb distillation: nmr (CCl_4) δ 6.8–7.0 (d, $J_{H-P} \cong 14$ Hz, overlapping singlet at 6.88, 2), 5.2 (br s, 2), 4.0 (quintet, 4), 2.19 (s, 3), 2.09 (s, 3), and 1.30 (t, 6). A second aminophosphonate fraction gave **15**: mp 98–99° from benzene–hexane; nmr δ 7.23 (d, J_{H-P} = 15 Hz), 6.90 (d, J_{H-P} = 6 Hz), 4.05 (quintet, 4), 3.65 (broad singlet, 2), 2.40 (d, $J_{H-P} \cong 2$ Hz, 3), 2.13 (s, 3), 1.29 (t, 6).

Deoxygenation of Nitrosobenzene in the Presence of Acetic Anhydride. A solution containing 0.5 mmol of **2a** in benzene (50 ml) was slowly added at 0° to 300 ml of 1:1 TEP–acetic anhydride. Attempts to completely remove acetic acid from commercial acetic anhydride were not successful and the acetic anhydride used contained 1–2% acetic acid on the basis of nmr. When the addition was complete, the benzene was removed using a rotary evaporator and TEP and acetic anhydride were removed at ~0.1 mm. The residue was chromatographed on silicic acid. Benzene–ether eluted 2-acetoxyacetanilide (**18**, 6%), mp 123–124° (lit.[19] mp 124.5–125°).

Ether eluted a substance which was probably diethyl 2-acetamidophenylphosphonate (**19**, 3%): mp 139–140° after recrystallization from benzene; nmr δ 7.6–8.0 (m, 4), 4.12 (quintet, 4), 2.22 (s, 3), 1.34 (t, 6).

Identification of **18** was confirmed by brief hydrolysis with 10% NaOH in 1:1 methanol–water to 2-hydroxacetanilide (**3**). Tlc

comparison with authentic 4-acetoxyacetanilide indicated that no detectable amount of this compound was formed in the reaction.

Deoxygenation of *p*-Nitrosotoluene in the Presence of Acetic Anhydride. The reaction was carried out as described for nitrosobenzene. 2-Acetoxy-4-methylacetanilide (**20**, 46%) crystallized from the crude product, mp 154–155° (lit.[20] mp 153–154°), and was identified by spectral data and hydrolysis to 2-hydroxy-4-methylacetanilide which was identical with an authentic sample.[17] A small amount (2%) of 4-methylacetanilide was isolated from the mother liquors.

Deoxygenation of o-Nitrosotoluene in the Presence of Acetic Anhydride. The reaction was carried out as for nitrosobenzene. Trituration of the crude product with hot hexane gave 2-acetoxy-6-methylacetanilide (**21**, 16%), mp 142–143° (lit.[21] mp 141–143°),[22] after recrystallization from ether–hexane. The identification was accomplished by partial hydrolysis to 2-hydroxy-6-methylacetanilide, mp 161–162° (lit.[17] mp 160–161°), and complete hydrolysis by 2-hr reflux with 15% aqueous sodium hydroxide to 2-hydroxy-6-methylaniline, mp 149–150.5° (lit.[24] mp 150°).

***O,N*-Diacetyl-4-methylphenylhydroxylamine (22).** 4-Methylphenylhydroxylamine[25] (2.0 g, 16 mmol) was dissolved in ether (20 ml) containing pyridine (2 ml) and treated with a solution of acetyl chloride (2.6 g, 32 mmol) in ether (10 ml) at 0°. The solution was washed with water, dried over sodium sulfate, and evaporated to give the product as an oil purified by distillation at diffusion pump vacuum: ir (neat) 1800, 1690 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.6 (m, 4), 2.40 (s, 3), 2.20 (s, 3), 2.05 (s, 3).

Stability of *O,N*-Diacetyl-4-methylphenylhydroxylamine under Deoxygenation Conditions. A solution of **22** (0.30 g, 1.45 mmol), TEP (15 ml), acetic anhydride (15 ml), and benzene (6 ml) was stirred at 0° under nitrogen for 2 hr. The benzene was removed at reduced pressure and TEP and acetic anhydride were removed at 0.1 mm. Chromatography of the residue gave 97% recovery of **22**.

Registry No. 1a, 98-95-3; **1b**, 99-99-0; **1c**, 88-72-2; **1d**, 89-87-2; **2a**, 586-96-9; **2b**, 623-11-0; **2c**, 611-23-4; **4**, 31238-50-3; **5**, 42822-57-1; 8, 42822-58-2; **11**, 42822-59-3; **12**, 42822-60-6; **14**, 42822-61-7; **15**, 42822-62-8; **16**, 42822-63-9; **19**, 42822-64-0; **22**, 27451-20-3; 4-methylphenylhydroxylamine, 623-10-9.

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A General Synthesis of 1,3-Dithiol-2-ones

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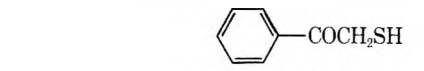
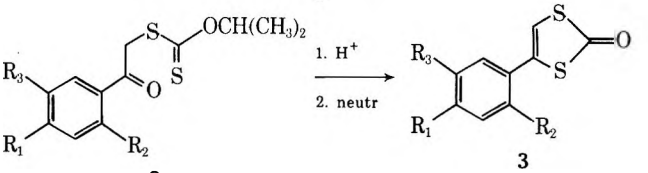
Although specific preparations of 1,3-dithiol-2-one[1] (vinylene dithiocarbonate) and of several substituted analogs[2] have been described, a general synthesis of compounds in this series has never been reported.[3]

In the course of another investigation an attempt was made to prepare ketothiol **1**[4] by heating a solution (CCl_4) of *O*-isopropyl *S*-phenacyl dithiocarbonate (**2a**) in contact with 70% perchloric acid. Upon neutralization and work-up of the reaction mixture, a fair yield of 4-phenyl-1,3-dithiol-2-one (**3a**) was obtained. Further investigation of this reaction led to a general preparation of 1,3-dithiol-2-ones **3a–f** and **5a–d** from the readily accessible β-keto *O*-isopropyl dithiocarbonates **2a–f** and **4a–d**.[5]

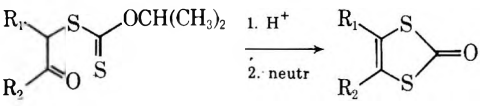


1



2 **3**

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = Ph$; $R_2 = R_3 = H$
c, $R_1 = Br$; $R_2 = R_3 = H$
d, $R_1 = CF_3$; $R_2 = R_3 = H$
e, $R_1 = H$; $R_2 = R_3 = OCH_3$
f, $R_1 = NO_2$; $R_2 = R_3 = H$



4 **5**

a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = R_2 = Ph$
c, $R_1 = CH_3$; $R_2 = C_2H_5$
d, $R_1, R_2 = -(CH_2)_4-$

The 1,3-dithiol-2-ones described herein should also serve as useful precursors of the corresponding 2-hydroxy-1,3-dithiolium cations, which are of some theoretical interest.[3,6]

Experimental Section[7]

***O*-Isopropyl *S*-Phenacyl Dithiocarbonate (2a).** Potassium *O*-isopropyl xanthate[8] (11.3 g) was treated in small quantities during 10 min with a solution of α-bromoacetophenone (12.0 g) in acetone (140 ml). The solvent was removed *in vacuo*. Water was added to the solid residue and the resulting suspension was acidified with dilute HCl and extracted with diethyl ether. The combined extracts were washed with water followed by brine and dried ($MgSO_4$). The solvent was removed *in vacuo*, yielding 14.9 g of crude **2a**: mp 65–67°; purity (pmr assay) *ca.* 90%; pmr ($CDCl_3$) 1.33 (d, 6, J = 6.5 Hz), 4.60 (s, 2), 5.70 (h, 1, J = 6.5 Hz), 7.27–7.63 (m, 3), and 7.88–8.08 (m, 2); ir (CCl_4) 1690, 1240, 1090, 1053, and 686 cm^{-1}. Recrystallization from diethyl ether afforded 12.7 g (83%) of pure **2a**, mp 68–69°. An analytical sample exhibited mp 68–69°. *Anal.* Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.55. Found: C, 56.72; H, 5.46.

***O*-Isopropyl *S*-(*p*-Phenylphenacyl) Dithiocarbonate (2b).** Potassium *O*-isopropyl xanthate (3.0 g) was treated (10 min) in small quantities with a solution of α-bromo(*p*-phenyl)acetophenone (4.0 g) in acetone (40 ml). Work-up as described for **2a** yielded 5.0 g of crude product. Recrystallization from diethyl

ether afforded **2b**: mp 72–74°; pmr ($CDCl_3$) δ 1.35 (d, 6, J = 6.5 Hz), 4.63 (s, 2), 5.73 (h, 1, J = 6.5 Hz), 7.3–7.7 (m, 5), and an A_2B_2 multiplet centered at δ 7.68 and 8.08; ir (CCl_4) 1683, 1606, 1240, 1090, 1050, and 697 cm^{-1}. An analytical sample had mp 74–75°. *Anal.* Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.53; H, 5.55.

***O*-Isopropyl *S*-(*p*-Bromophenacyl) Dithiocarbonate (2c).**[8] Potassium *tert*-butoxide (2.24 g) was dissolved in a solution of 2-propanol (7 ml) in benzene (35 ml). Cooling (ice bath) was followed by slow addition of carbon disulfide (2.25 g) in benzene (5.0 ml) to the sitrred solution. After the solution was stirred for 20 min longer, *p*-bromophenacyl bromide (4.73 g) and benzene (20 ml) were added and the solution was refluxed for 2 hr under N_2. The reaction mixture was cooled and filtered. Removal of the solvent *in vacuo* left 5.1 g (*ca.* 100%) of crude product, mp 89–90°. Recrystallization from diethyl ether afforded **2c**: mp 90–91° (lit.[8] mp 90–91°); pmr ($CDCl_3$) δ 1.38 (d, 6, J = 6.5 Hz), 4.60 (s, 2), 5.76 (h, 1, J = 6.5 Hz), and an A_2B_2 pattern centered at δ 7.81; ir (CCl_4) 1690, 1585, 1240, 1090, and 1045 cm^{-1}; mass spectrum (molecular ion) theoretical 332, found 332.

***O*-Ethyl *S*-(*p*-Bromophenacyl) Dithiocarbonate.**[2d,5] Potassium *O*-ethyl xanthate (2.8 g) was added to a solution of *p*-bromophenacyl bromide (4.17 g) in acetone (50 ml) and the suspension was heated in a water bath at *ca.* 50° for 5 min. The reaction mixture was worked up as described for **2a**, yielding 4.4 g (92%) of crude product, purity *ca.* 84% (pmr assay). Recrystallized product had mp 82–83° (lit.[2d] mp 81–82°); pmr ($CDCl_3$) δ 1.35 (t, 3, J = 7.0 Hz), 4.58 (s, 2), 4.60 (q, 2, J = 7.0 Hz), and an A_2B_2 pattern centered at δ 7.73.

***O*-Isopropyl *S*-(*p*-Trifluoromethylphenacyl) Dithiocarbonate (2d).** Potassium *O*-isopropyl xanthate (1.5 g) was treated in small amounts during 20 min with a solution of *p*-trifluoromethylphenacyl bromide (1.94 g) in acetone (30 ml). The solution was warmed in a water bath (*ca.* 50°) for 15 min and worked up as described for **2a**, yielding 2.17 g (92%) of crude **2d**. Recrystallization from ether afforded pure **2d** (pmr assay): mp 97–99°; pmr ($CDCl_3$) δ 1.35 (d, 6, J = 6.5 Hz), 3.75 (s, 3), 3.88 (s, 3), 4.56 (s, 2), Hz), and an A_2B_2 pattern centered at δ 7.93; ir (CCl_4) 1710, 1692, 1330, 1245, 1090, and 1045 cm^{-1}; mass spectrum (molecular ion) theoretical 322, found 322. An analytical sample had mp 98.5–99.5°. *Anal.* Calcd for $C_{13}H_{13}F_3O_2S_2$: C, 48.44; H, 4.06. Found: C, 48.20; H, 4.05.

***O*-Isopropyl *S*-(2′,5′-Dimethoxyphenacyl) Dithiocarbonate (2e).** Potassium *O*-isopropyl xanthate (7.3 g) was treated in small amounts with a solution of α-bromo-2′,5′-dimethoxyacetophenone (8.0 g) in acetone (125 ml). The solution was allowed to stand at room temperature (40 min). Work-up as described for **2a** yielded 8.7 g (89%) of crude **2e** which was 90% pure by pmr assay: pmr ($CDCl_3$) δ 1.35 (d, 6, J = 6.5 Hz), 3.75 (s, 3), 3.88 (s, 3), 4.56 (s, 2), 5.68 (h, 1, J = 6.5 Hz), and 6.81–7.35 (m, 3); ir (CCl_4) 1670, 1235, 1090, and 1050 cm^{-1}; mass spectrum (molecular ion) theoretical 314, found 314. An analytical sample exhibited mp 49.5–50.5°. *Anal.* Calcd for $C_{14}H_{18}O_4S_2$: C, 53.48; H, 5.77. Found: C, 53.62; H, 5.81.

***O*-Isopropyl *S*-(*p*-Nitrophenacyl) Dithiocarbonate (2f).** Potassium *O*-isopropyl xanthate (6.2 g) was added in small portions to a solution of *p*-nitrophenacyl bromide (9.32 g) in acetone (75 ml) and the mixture was heated on a water bath (*ca.* 50°) for 3 min. The reaction mixture was filtered and washed with acetone (75 ml), and the solvent was removed *in vacuo*. Work-up as described for **2a** afforded 11.2 g (90%) of crude **2f**: mp 68–70°; purity *ca.* 90% (pmr assay); pmr ($CDCl_3$) δ 1.36 (d, 6, J = 6.3 Hz), 4.63 (s, 2), 5.68 (h, 1, J = 6.3 Hz), and an A_2B_2 pattern centered at δ 8.22. An analytical sample exhibited mp 72.5–73.5°. *Anal.* Calcd for $C_{12}H_{13}NO_4S_2$: C, 48.14; H, 4.38. Found: C, 48.37; H, 4.50.

4-Phenyl-1,3-dithiol-2-one (3a). Perchloric acid (70%, 2.0 ml) was slowly added to a solution of dithiocarbonate **2a** (2.5 g, *ca.* 90% pure) in 1:2 ether–$CHCl_3$ (18 ml). The solution was refluxed for 1 hr and poured into ice-water. Extraction with ether followed by a normal work-up yielded 1.8 g (92%) of crude **3a**, purity *ca.* 76% (pmr assay). Recrystallization from ether afforded pure **3a**: mp 96–97.5° (lit.[2b] mp 93–95°); pmr ($CDCl_3$) δ 6.82 (s, 1) and 7.40 (s, 5); ir ($CHCl_3$) 1733, 1690, and 1650 cm^{-1}; mass spectrum (molecular ion) theoretical 194, found 194.

4-(*p*-Phenylphenyl)-1,3-dithiol-2-one (3b). Perchloric acid (70%, 1.5 ml) was slowly added to a solution of the dithiocarbonate **2b** (2.0 g) in 1:2 ether–$CHCl_3$ (15 ml). The solution was refluxed for 15 min, cooled, and poured into ice-water. Extraction with $CHCl_3$ and work-up as described for **3a** afforded 1.6 g of crude **3b**, purity *ca.* 70% (pmr assay). Recrystallization from CH_2Cl_2 afforded pure **3b**: mp 184–186°; pmr ($CDCl_3$–CF_3CO_2D, 2:1) δ 6.95 (s, 1) and 7.36–7.78 (m, 9); ir (CH_2Cl_2) 1642 cm^{-1}; mass spectrum (molecular ion) theoretical 270, found 270. An analytical sample exhibited mp 186–187°. *Anal.* Calcd for $C_{15}H_{10}OS_2$: C, 66.64; H, 3.72; S, 23.71. Found: C, 66.53; H, 3.74; S, 23.53.

4-(*p*-Bromophenyl)-1,3-dithiol-2-one (3c). Method A. Perchloric acid (70%, 1.6 ml) was slowly added to a solution of dithiocarbonate **2c** (0.8 g) in 1:1 ether–CH_2Cl_2 (6.4 ml). After the solution was stirred for 7 hr at room temperature, it was poured into ice-water. Extraction with ether followed by a normal work-up afforded 0.63 g of crude **3c**, purity *ca.* 85% (pmr assay). Recrystallized material had mp 97–98°; pmr ($CDCl_3$) δ 6.90 (s, 1) and an A_2B_2 pattern centered at *ca.* δ 7.43; ir (CCl_4) 1732, 1700, and 1650 cm^{-1}; mass spectrum (molecular ion) theoretical 272, found 272. *Anal.* Calcd for $C_9H_5BrOS_2$: C, 39.57; H, 1.85; S, 23.26. Found: C, 39.72; H, 1.84; S, 23.00.

Method B. *O*-Ethyl *S*-(*p*-bromophenacyl) dithiocarbonate[2d,5] (600 mg) was stirred with cold aqueous H_2SO_4 (80%, 2.0 ml) for 5 min. The solution was then heated for 0.5 hr in an oil bath (77–79°), cooled, diluted with ice-water, and extracted with ether. The combined extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*, yielding 450 mg (87%) of crude **3c**, purity 65% (pmr assay). Recrystallization from ether afforded pure **3c**, mp 97–98°.

4-(*p*-Trifluoromethylphenyl)-1,3-dithiol-2-one (3d). Dithiocarbonate **2d** (480 mg, *ca.* 95% pure) was suspended in cold aqueous H_2SO_4 (0.4 ml) and heated for 15 min at 75°. The mixture was cooled and poured into ice-water. The solid obtained on filtration was washed with water and dried, yielding 460 mg (*ca.* 100%) of crude **3d**, purity *ca.* 60% (pmr assay). Recrystallized product had mp 97–99°; pmr ($CDCl_3$) δ 7.03 (s, 1) and an A_2B_2 pattern centered at δ 7.6; ir (CH_2Cl_2) 1645 and 1330 cm^{-1}; mass spectrum (molecular ion) theoretical 262, found 262. An analytical sample exhibited mp 98–99°. *Anal.* Calcd for $C_{10}H_5F_3OS_2$: C, 45.80; H, 1.92; S, 24.45. Found: C, 45.76; H, 2.06; S, 24.45.

4-(2′,5′-Dimethoxyphenyl)-1,3-dithiol-2-one (3e). Perchloric acid (70%, 2.0 ml) was slowly added to a solution of dithiocarbonate **2e** (1.5 g, *ca.* 90% pure) in 8 ml of ether–CH_2Cl_2 (9:7). The solution was refluxed for 10 hr, cooled, poured into ice-water, and worked up as described for **3a**, yielding 0.9 g (74%) of crude **3e**, purity 82% (pmr assay). Recrystallization from ether afforded pure **3e**: mp 86–87°; pmr ($CDCl_3$) δ 3.76 (s, 3), 3.81 (s, 3), 6.86 (s, 2) and an AB pattern centered at δ 6.91 (J = 7.5 Hz); ir ($CHCl_3$) 1640, 1220, and 1045 cm^{-1}; mass spectrum (molecular ion) theoretical 254, found 254. *Anal.* Calcd for $C_{11}H_{10}O_3S_2$: C, 51.95; H, 3.96; S, 25.21. Found: C, 51.88; H, 3.90; S, 25.04.

4-(*p*-Nitrophenyl)-1,3-dithiol-2-one (3f).[2d,5] A suspension of dithiocarbonate **2f** (340 mg, 90% pure) and cold aqueous sulfuric acid (0.6 ml) was heated for 5 min at 72°, cooled, and poured into ice-water. Extraction with CH_2Cl_2 afforded 260 mg of crude **3f**, purity *ca.* 94% (pmr assay), pmr data identical with those already reported.[2d] The recrystallized product had mp 208–209.5° (lit.[2d] mp 205–208°).

***O*-Isopropyl *S*-Acetonyl Dithiocarbonate (4a).** Potassium *O*-isopropyl xanthate (9.0 g) was treated during 15 min with small portions of 5.0 g of α-chloroacetone in 60 ml of acetone. Work-up as described for **2a** yielded 8.8 g of crude **4a**: purity *ca.* 81% (pmr assay); pmr ($CDCl_3$) δ 1.37 (d, 6, J = 6 Hz), 2.29 (s, 3), 3.97 (s, 2), and 5.70 (h, 1, J = 6 Hz); ir ($CHCl_3$) 1710, 1245, 1085, and 1042 cm^{-1}; mass spectrum (molecular ion) theoretical 192, found 192. An analytical sample was procured by distillation and exhibited bp 42° (0.05 mm). *Anal.* Calcd for $C_7H_{12}O_2S_2$: C, 43.72; H, 6.29. Found: C, 43.63; H, 6.23.

***O*-Isopropyl *S*-(α-Phenylphenacyl) Dithiocarbonate (4b).** Sodium *O*-isopropyl xanthate (5 g) was treated at room temperature during 2 hr with desyl chloride (4.6 g) in acetone (70 ml). Work-up as described for **2a** yielded 6.7 g (100%) of crude **4b**, purity *ca.* 80% (pmr assay). Recrystallization from ether afforded pure **4b**: mp 95–96°; pmr ($CDCl_3$) δ 1.23 (d, 6, J = 6.3 Hz), 5.66 (h, 1, J = 6.3 Hz), 6.65 (s, 1), 7.2–7.6 (m, 8), and 8.0–8.2 (m, 2); ir (CCl_4) 1690, 1235, 1090, 1045, and 695 cm^{-1}; mass spectrum (molecular ion) theoretical 330, found 330. *Anal.* Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.20; H, 5.46.

***O*-Isopropyl *S*-(2-Cyclohexanonyl) Dithiocarbonate (4d).** Potassium *O*-isopropyl xanthate (7.0 g) was added in small amounts to a solution of 5.0 g of 2-chlorocyclohexanone in acetone (100 ml). The suspension was refluxed for 45 min and worked up as described for **2a** to yield 8.5 g (91%) of crude **4d** as a liquid: purity *ca.* 93% (pmr assay); pmr ($CDCl_3$) δ 1.36 (d, 6, J = 6.2 Hz), 1.7–2.8 (m, 8), 4.5 (m, 1), and 5.7 (h, 1, J = 6.2 Hz); ir (CCl_4) 1720, 1235, 1087, and 1045 cm^{-1}. An analytical sample obtained by dis-

tillation exhibited bp 68° (0.04 mm). *Anal.* Calcd for $C_{10}H_{16}O_2S_2$: C, 51.69; H, 6.94. Found: C, 51.63; H, 6.90.

4-Methyl-1,3-dithiol-2-one (5a). Dithiocarbonate **4a** (2.9 g, 81% pure) suspended in cold aqueous H_2SO_4 (80%, 5 ml) was stirred for 4 min and then heated at 67° for 20 min and at 54° for an additional 15 min. The mixture was cooled, poured into ice–water, and worked up as described for **3a** to yield 1.83 g (88%) of crude **5a**, purity *ca.* 77% (pmr assay). Evaporative distillation [40° (0.05 mm)] afforded pure **5a** in 63% yield (based on **4a**): pmr ($CDCl_3$) δ 2.25 (d, 3, J = 1.4 Hz) and 6.32 (q, 1, J = 1.4 Hz); ir ($CHCl_3$) 1725, 1685, and 1640 cm^{-1}; mass spectrum (molecular ion) theoretical 132, found 132. *Anal.* Calcd for $C_4H_4OS_2$: C, 36.34; H, 3.05; S, 48.51. Found: C, 36.50; H, 3.20; S, 48.43.

4,5-Diphenyl-1,3-dithiol-2-one (5b). Dithiocarbonate **4b** (150 mg) suspended in cold aqueous H_2SO_4 (80%, 0.55 ml) was stirred for 5 min and heated for 20 min at 60° (oil bath). The mixture was cooled and diluted with ice and water. Filtration yielded 105 mg (85%) of **5b**: mp 104–106°; pmr ($CDCl_3$) δ 7.2 (m, 10); ir ($CHCl_3$) 1690 and 1635 cm^{-1}. Recrystallization from diethyl ether afforded an analytical sample, mp 109.5–110.5°. *Anal.* Calcd for $C_{15}H_{10}OS_2$: C, 66.64; H, 3.72; S, 23.71. Found: C, 66.90; H, 3.83; S, 23.55.

4-Ethyl-5-methyl-1,3-dithiol-2-one (5c). Potassium *O*-isopropyl xanthate (5.5 g) was treated for 10 min with a solution of 2-bromo-3-pentanone (4.2 g, *ca.* 84% purity) in acetone (50 ml). Work-up as described for **2a** yielded 5.5 g of crude **4c**: purity *ca.* 77% (pmr assay); pmr ($CDCl_3$) δ 1.09 (t, 3, J = 7.0 Hz), 1.38 (d, 6, J = 6.5 Hz), 1.45 (d, 3, J = 7.0 Hz), 2.66 (m, 2), 4.40 (q, 1, J = 7.0 Hz), and 5.71 (h, 1, J = 6.5 Hz); ir (CCl_4) 1720, 1240, 1090, and 1035 cm^{-1}. Perchloric acid (70%, 1.5 ml) was slowly added to a solution of crude **4c** (2.0 g) in 1:1 ether–$CHCl_3$ (16 ml). After the solution was refluxed for 1.5 hr it was worked up as described for **3a**, yielding 1.4 g (96%) of crude **5c**, purity *ca.* 68% (pmr assay). Chromatography on alumina using petroleum ether (bp 66–67°) as eluent afforded pure **5c**: pmr ($CDCl_3$) δ 1.16 (t, 3, J = 7.5 Hz), 2.13 (s, 3), and 2.56 (q, 2, J = 7.5 Hz); ir ($CHCl_3$) 1642 and 1595 cm^{-1}; mass spectrum (molecular ion) theoretical 160, found 160.

4,5-Cyclohexano-1,3-dithiol-2-one (5d). Perchloric acid (70%, 4.0 ml) was slowly added to a solution of dithiocarbonate **4d** (3.0 g, 93% pure) in 1:1 ether–CH_2Cl_2 (30 ml). After the solution was stirred for 10 hr, it was worked up as described for **3a**, yielding 2.1 g (93%) of **5d**, purity 94% (pmr assay). Chromatography on alumina using petroleum ether as eluent afforded pure **5d**: mp 33°; pmr ($CDCl_3$) δ 1.70–1.97 (m, 4) and 2.25–2.53 (m, 4); ir ($CHCl_3$) 1738, 1670, 1635, and 1600 cm^{-1}; mass spectrum (molecular ion) theoretical 172, found 172. *Anal.* Calcd for $C_7H_8OS_2$: C, 48.81; H, 4.68; S, 37.23. Found: C, 49.06; H, 4.76; S, 37.45.

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Registry No. 2a, 42574-08-3; **2b**, 42574-09-4; **2c**, 42588-16-9; **2d**, 42574-10-7; **2e**, 42574-11-8; **2f**, 42574-12-9; **3a**, 939-11-7; **3b**, 42574-13-0; **3c**, 42574-14-1; **3d**, 42573-96-6; **3e**, 42573-97-7; **4a**, 42573-98-8; **4b**, 42573-99-9; **4d**, 42574-00-5; **5a**, 42574-01-6; **5b**, 42574-02-7; **5c**, 42574-03-8; **5d**, 698-41-9; α-bromoacetophenone, 70-11-1; α-bromo(*p*-phenyl)acetophenone, 135-73-9; *p*-bromophenacyl bromide, 99-73-0; *O*-ethyl-*S*-(*p*-bromophenacyl)dithiocarbonate, 1861-48-9; *p*-trifluoromethylphenacyl bromide, 383-53-9: α-bromo-2′,5′-dimethoxyacetophenone, 1204-21-3; *p*-nitrophenacyl bromide, 99-81-0; α-chloroacetone, 78-95-5; desyl chloride, 447-31-4; 2-chlorocyclohexanone, 882-87-7; 2-bromo-3-pentanone, 815-52-1.

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(5) It is noteworthy that Campaigne, *et al.* (ref 2d), found that in the reaction of several *O-ethyl* β-ketodithiocarbonates corresponding to **2** with perchloric acid much decomposition occurred and in most cases (including that of the *O*-ethyl analog of **2c**) no product was isolable, with the exception that **3f** was obtained from the *O*-ethyl analog of **2f**. In our work (see Experimental Section) we have found that the *O*-ethyl analog of **2c** was *also* readily converted at elevated temperature into **3c**, suggesting that under suitable acidic conditions analogs of **3** can indeed be obtained from analogs of **2** having *O*-alkyl groups other than *O*-isopropyl.

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Reaction of a Phosphorus Ylide with Aliphatic Acyl Cyanides

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The phosphorus ylide, dichloromethylenetriphenylphosphorane (II), is most conveniently prepared by the addition of triphenylphosphine to an excess of carbon tetrachloride.[1] The concurrent production of triphenylphosphine dichloride appears to present no problems in the Wittig reactions of II with aldehydes,[1,2] ketones,[1] keto esters,[2] or aroyl cyanides[3] to give substituted 1,1-dichloroethylene derivatives.

In our previous studies of the reactions of II with aroyl cyanides, aliquots of the reaction mixtures were analyzed by an ir spectrophotometer to determine when the reaction was complete. It was found that the aroyl cyanide carbonyl stretching band was absent after 2–4 hr at reflux or 48–72 hr at room temperature. Under these same conditions aliphatic acyl cyanides Ia and Ib appeared to undergo an aldol type side reaction[4] giving only red-colored resinous residues and a strong odor of hydrogen cyanide.

$$\underset{\text{Ia, R = CH}_3}{\underset{\text{b, R = C}_2\text{H}_5}{\underset{\text{c, R = CH(CH}_3)_2}{\underset{\text{d, R = C(CH}_3)_3}{\text{RCCN}}}}} + \underset{\text{II, X = Cl}}{\underset{\text{IV, X = Br}}{(\text{Ph})_3\text{P=CX}_2}} \longrightarrow \underset{\text{IIIa–d, X = Cl}}{\underset{\text{Va, b, X = Br}}{\text{X}_2\text{C=CCN}}} + (\text{Ph})_3\text{PO}$$

It has now been found that deleterious side reactions can be minimized by maintaining the reaction mixture at 0° for 48 hr and then rapidly distilling out the excess carbon tetrachloride and crude products under vacuum. Yields were greatly reduced when the reaction time was changed to 24 or 72 hr at 0°. Higher temperatures invariably produced red, tarry residues and little or no product. In a typical reaction, excess dry carbon tetrachloride and 1.0 equiv of triphenylphosphine were mixed for 30 min at 0° under a nitrogen atmosphere, then 0.5 equiv of the acyl cyanide, Ia–d, was added and the reaction mixture was stirred at 0° for approximately 48 hr. The disappearance of the carbonyl stretching band and the appearance of a strong band in the 920–940-cm^{-1} region (=CCl_2 stretch[5]) was an effective means of determining the reaction end point. After the reaction mixture was quickly warmed, the excess carbon tetrachloride and liquid products were rap-

idly removed by vacuum distillation. With the exception of IIId, the 2-alkyl-3,3-dichloroacrylonitriles were contaminated with by-products which could not be easily separated from the desired products by simple distillation. In two cases, IIIb and IIIc, analytically pure samples were obtained by preparative vpc.

When carbon tetrabromide (0.5 equiv) was added to a cold solution of benzene and 1.0 equiv of triphenylphosphine, an immediate reaction occurred resulting in a precipitate and a bright orange colored solution. Addition of acyl cyanide Ia or Ib to this solution required efficient ice cooling, as a rapid exothermic reaction resulted. An infrared carbonyl absorption was not detectable in this mixture after 5 min. Work-up of these reaction mixtures was carried out in a manner similar to that described above when carbon tetrachloride was used. Purification of the products Va and Vb was simplified owing to the absence of unwanted by-products.

The sensitivity of the acrylonitrile carbon–carbon double bond infrared absorption to substituent effects has been noted previously.[5] A smooth correlation of $+I$ effects and shift of the double bond absorption to lower frequencies were observed for IIIa–d. The dichlorovinylidene stretching frequency (=CCl_2) was also shifted to lower positions as the α substituent in III was changed from methyl to *tert*-butyl. Loss of molecular coplanarity owing to steric interaction by bulkier α groups and the cis β chlorine atom were most likely responsible for a portion of the observed shift.

The dibromovinylidene stretching frequency in Va,b appeared as a very strong absorption in the 840–850-cm^{-1} region.

Experimental Section

All temperatures are uncorrected. Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo. A Beckman IR-8 was used to obtain the infrared spectra, which were calibrated at 2849.9 and 1601.0 cm^{-1} by polystyrene film. All ylide reactions were carried out under dry nitrogen, and maintained at 0° by use of an ice–water bath.

Aliphatic Acyl Cyanides. The following acyl cyanides were prepared by heating a mixture of 1.0 mol of acyl bromide and 1.4 mol of cuprous cyanide in o-dichlorobenzene to approximately 120° for 4 hr and then carefully distilling the reaction mixture:[6] acetyl cyanide (Ia), bp 92–93°, $n^{22}D$ 1.3905 (lit.[7] bp 92–93°, $n^{20}D$ 1.3743); propionyl cyanide (Ib), bp 110–111°, $n^{20}D$ 1.3225 (lit.[7] bp 110°, $n^{20}D$ 1.3225); isobutyryl cyanide (Ic), bp 117–118°, $n^{22}D$ 1.3847 (lit.[7] bp 118°, $n^{20}D$ 1.3790); pivaloyl cyanide (Id), bp 120°, $n^{20}D$ 1.3961 (lit.[8] bp 120°, $n^{20}D$ 1.3961). Three variations of this basic technique[9] were used in the attempted synthesis of trichloroacetyl cyanide. The reaction was run with and without the use of o-dichlorobenzene as solvent, and by substituting potassium cyanide for cuprous cyanide; all attempts to synthesize trichloroacetyl cyanide were unsuccessful.

3,3-Dichloro-2-methylacrylonitrile (IIIa). Into a 250-ml, three-necked flask fitted with nitrogen inlet and drying tube was added 80 ml of dry carbon tetrachloride and 40.0 g (0.152 mol) of triphenylphosphine. The reaction mixture was stirred (magnetic stirrer) for 30 min at 0°, then 5.25 g (0.076 mol) of Ia was added quickly and stirring was continued at 0° for 40 hr. At this time the mixture was heated under vacuum to first remove excess carbon tetrachloride and then the crude product. This crude distillate was then carefully refractionated to yield 6.33 g (61%) of IIIa, bp 68° (28 mm). The ir spectrum of IIIa was identical with that of the known compound.[5]

3,3-Dichloro-2-ethylacrylonitrile (IIIb). In a manner similar to that described above, 80 ml of dry carbon tetrachloride and 40.0 g (0.152 mol) of triphenylphosphine were stirred for 30 min at 0°, then 6.34 g (0.076 mol) of Ib was added and the mixture was stirred at 0° for 44 hr. The reaction mixture was heated to remove the excess carbon tetrachloride and then placed under vacuum to distil out 15.34 g (45%[9]) of crude product. Purification of the crude product by distillation was complicated by closely boiling by-products. An analytically pure sample was obtained by preparative vpc: bp 75–78° (28 mm); $n^{20}D$ 1.4829; ir (neat) 2990, 2890, 2220, 1590, 1460, and 930 cm^{-1} (=CCl_2).

Anal. Calcd for $C_5H_5Cl_2N$: C, 40.04; H, 3.33; N, 9.34; Cl, 47.28. Found: C, 40.38; H, 3.49; N, 9.27; Cl, 46.98.

3,3-Dichloro-2-(isopropyl)acrylonitrile (IIIc). Dry carbon tetrachloride (80 ml) was mixed with 40.0 g (0.152 mol) of triphenylphosphine and the mixture was stirred for 30 min at 0°, then 7.40 g (0.076 mol) of Ic was added quickly. The mixture, stirred at 0° for 40 hr, then was heated under vacuum to distil out the excess carbon tetrachloride and 6.5 g (40%[9]) of crude product. Purification was complicated by the presence of closely boiling by-products. An analytically pure sample was obtained by preparative vpc: bp 85–87° (28 mm); $n^{22}D$ 1.4824; ir (neat) 2980, 2940, 2885, 2230, 1580, 1460, and 935 cm^{-1} (=CCl_2).

Anal. Calcd for $C_6H_7Cl_2N$: C, 43.85; H, 4.26; N, 8.54; Cl, 43.21. Found: C, 43.85; H, 4.39; N, 8.44; Cl, 42.95.

3,3-Dichloro-2-(*tert*-butyl)acrylonitrile (IIId). Dry carbon tetrachloride (80 ml) was mixed with 40.0 g (0.152 mol) of triphenylphosphine, and the mixture was stirred for 15 min at 0°. To this was added 8.47 g (0.076 mol) of Id and the mixture was stirred at 0° for 45 hr. The mixture was then heated under vacuum to first distil the excess carbon tetrachloride and then crude product. The crude product was carefully refractionated to yield 6.55 g (48%) of IIId: bp 102–105° (28 mm); $n^{23}D$ 1.4829; ir (neat), 2980, 2940, 2920, 2880, 2220, 1550, and 920 cm^{-1} (=CCl_2).

Anal. Calcd for $C_7H_9Cl_2N$: C, 47.23; H, 5.05; N, 7.86; Cl, 39.83. Found: C, 47.41; H, 5.04; N, 7.59; Cl, 39.44.

3,3-Dibromo-2-methylacrylonitrile (Va). Into a 250-ml, three-necked flask provided with nitrogen inlet and drying tube was added 80 ml of dry benzene and 40.0 g (0.152 mol) of triphenylphosphine. After all the triphenylphosphine had dissolved, the solution was cooled to 0° and 25.31 g (0.076 mol) of carbon tetrabromide was slowly added. This addition resulted in a highly exothermic reaction which gave a bright orange colored solution and a copious amount of precipitate. The reaction mixture was held at 0° while 5.25 g (0.076 mol) of Ia was added dropwise. This addition produced a second highly exothermic reaction coupled with the complete decolorization of the solution. The mixture was mechanically stirred at 0° for 5 min and then rapidly distilled under vacuum to remove the crude product and solvent. The higher boiling fractions which solidified were washed with cold ligroin to remove unreacted carbon tetrabromide and then refractionated to yield 11.5 g (68%) of Va: bp 94–95° (28 mm); mp 62–63°; ir (KBr pellet), 2230, 1575, 1030, and 850 cm^{-1} (=CBr_2).

Anal. Calcd for $C_4H_3Br_2N$: C, 21.52; H, 1.33; N, 6.23; Br, 71.09. Found: C, 21.82; H, 1.62; N, 6.23; Br, 71.07.

3,3-Dibromo-2-ethylacrylonitrile (Vb). In a manner similar to that described for Va, 40.0 g (0.152 mol) of triphenylphosphine was dissolved in 80 ml of dry benzene and the mixture was cooled to 0°. Carbon tetrabromide (25.31 g, 0.076 mol) was slowly added, yielding an orange-colored solution and a precipitate. The mixture was held at 0° while 6.34 g (0.076 mol) of Ib was added. The mixture was stirred for 5 min and then rapidly heated under vacuum to distil out solvent and crude product. The crude product was refractionated to yield 10.51 g (58%) of Vb: bp 99–102° (28 mm); $n^{24}D$ 1.5430; ir (neat) 2980, 2840, 2885, 2225, 1565, 1455, and 840 cm^{-1} (=CBr_2).

Anal. Calcd for $C_5H_5Br_2N$: C, 25.31; H, 2.11; N, 5.91; Br, 66.66. Found: C, 25.30; H, 2.27; N, 5.87; Br, 66.20.

Acknowledgment. Partial support of this research by the Robert A. Welch Foundation (Grant AF-169) is gratefully acknowledged.

Registry No. Ia, 631-57-2; Ib, 4390-78-7; Ic, 42867-39-0; Id, 42867-40-3; II, 6779-08-4; IIIa, 31413-58-8; IIIb, 42791-06-0; IIIc, 42867-43-6; IIId, 42867-44-7; IV, 42867-45-8; Va, 42867-46-9; **Vb**, 42867-47-0.

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Concerning a Case of Apparent Syn Elimination from *erythro*-1,2-Diphenylpropyltrimethylammonium Salts[1]

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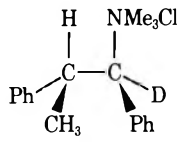
For many years, the E2 transition state was believed to prefer strongly an antiperiplanar orientation of the leaving group and the β hydrogen, except when such an arrangement was sterically prohibited or when the β hydrogen was activated by strongly electron-withdrawing groups.[2] Among the evidence supporting this view was a study by Cram, Greene, and DePuy[3] of eliminations from 1,2-diphenyl-1-propyl derivatives in which the erythro isomer gave *cis*- and the threo isomer *trans*-1,2-diphenylpropene with various bases when the leaving group was chloride, bromide, or trimethylammonium.

One exception was noted: both threo and erythro isomers gave trans olefin when the leaving group was trimethylammonium and the base potassium *tert*-butoxide in *tert*-butyl alcohol. The cis olefin was found to be stable to this base–solvent combination, which means that the erythro isomer formally underwent a syn elimination. The preconception in favor of anti elimination was sufficiently strong at that time, however, that the authors assumed that the reaction involved either epimerization at the α carbon of the reactant, or an ElcB elimination *via* a carbanion which could invert faster than it decomposed to olefin.

To test these hypotheses, we prepared *erythro*-1,2-diphenyl-1-propyl-*1-d*-trimethylammonium chloride (**1**) and *erythro*-1,2-diphenyl-1-propyl-*2-d*-trimethylammonium iodide (**2**). The syntheses were adapted from literature pro-



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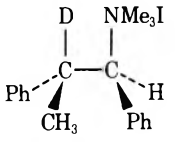

2

cedures for undeuterated compounds in the 1,2-diphenyl-1-propyl series, and are described in the Experimental Section. **1** and **2** were treated with potassium *tert*-butoxide in *tert*-butyl alcohol at 35° for one half-life of the elimination reaction. The unreacted material was recovered as the quaternary ammonium bromide[4] in each case, and the nmr spectra of the recovered salts were compared with those of the starting materials. The results are recorded in Table I.

Within the experimental error of several per cent, neither **1** nor **2** had undergone any change in deuterium content. As a further check on this conclusion, undeuterated *erythro*-1,2-diphenyl-1-propyltrimethylammonium iodide was treated with 0.057 *M* potassium *tert*-butoxide in *tert*-butyl-*O-d* alcohol at 35° for one half-life and the unreacted material was recovered.[4] The mass spectrum at 15 eV showed a "parent" peak at *m/e* 240, corresponding to decomposition of the quaternary salt to 1,2-diphenyl-1-propyldimethylamine. The value of $[(P + 1)/P] \times 100$ was found to be 19.56, compared with 19.34 before reaction and 19.07 calculated from natural abundance. There was evidently no deuterium incorporation within experimental error.

As a final control experiment, we tested the stability of a mixture of *cis*- and *trans*-1,2-diphenylpropene to the reaction conditions. While no isomerization is reported in the presence of potassium *tert*-butoxide,[3] no quaternary ammonium salt was present as it would be in an actual reaction mixture. Since quaternary ammonium salt would convert part of the base into the more reactive quaternary ammonium *tert*-butoxide, we repeated the attempted isomerization in the presence of tetra-*n*-butylammonium bromide. No change in the composition of the olefin mixture was detectable by uv spectroscopy after one half-life of the elimination reaction, and there was still no change after nearly 14 half-lives.

Table I
Nmr Spectra of Deuterium-Labeled *erythro*-1,2-Diphenyl-1-propyltrimethylammonium Salts before and after Subjection to Potassium *tert*-Butoxide in *tert*-Butyl Alcohol at 35°[a,b]

Position of deuterium	Group	Position of absorption, δ	Integration Before	Integration After
1	CH_3	1.0	3.00	3.00
	$N(CH_3)_3$	2.0	9.10	9.12
	1-C-D	4.6	0.04	0.03
	2-C-H	3.85	1.05	1.06
	C_6H_5	7.2	(10.0)[c]	(10.0)[c]
2	CH_3	1.0	3.05	3.05
	$N(CH_3)_3$	2.0	9.10	9.12
	1-C-H	4.6	1.00	1.00
	2-C-D	3.85	0.07	0.08[d]
				0.11[d]
				0.07[d,e]
	C_6H_5	7.1	(10.0)[c]	(10.0)[c]

[a] Reactions carried out for one half-life of the elimination reaction (see ref 3) unless otherwise noted. [b] Solvent for nmr spectra was D_2O, and measurements were made on a JEOLCO C-60HL instrument. [c] The peak area for the phenyl peak was taken as exactly 10.0 and the other areas were calculated relative to it. [d] Each figure represents a separate run. [e] Reaction carried out for two half-lives.

Our data clearly exclude product isomerization, α epimerization of reactant *via* an ylide which can abstract a proton from the bulk solvent, or an ElcB reaction *via* a carbanion which returns appreciably to reactant *via* protonation from the bulk solvent. An ElcB reaction with proton abstraction rate determining still cannot be excluded. Neither can α epimerization, or the reversible ElcB mechanism, if one assumes in each case that reprotonation occurs only from the *tert*-butyl alcohol molecule formed by proton or deuteron abstraction in the first step (internal return[5,6]).

Further narrowing of the possibilities will require additional experimental information. A substantial β-deuterium isotope effect would exclude all possibilities in which cleavage of the β-C–H bond is not rate determining, and appreciable nitrogen isotope effects would exclude all but a concerted elimination or an ElcB process with the second step rate determining. We understand that such studies are under way in another laboratory,[7] and we do not intend to do further work on this system. The data so far are certainly compatible with a syn E2 reaction, a possibility which is rendered still more attractive by numerous recent examples of such eliminations from quaternary ammonium salts.[8-13]

Experimental Section

All melting points and boiling points are uncorrected. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E mass spectrometer and nmr spectra on a JEOLCO C-60HL instrument.

erythro-**1,2-Diphenylpropyltrimethylammonium Chloride.** *threo*-1,2-Diphenylpropyl chloride[14] (0.36 g), trimethylamine (3.7 g), and benzene (5 ml) were heated in a stainless steel reaction tube at 55° for 144 hr. After removal of solvent and excess amine on a rotary evaporator, the crude product was recrystallized three

times from an ethanol–ether mixture to yield 0.19 (33%) of pure product: mp 142° dec; nmr (D_2O) δ 7.1 (multiplet, 10.0 H), 3.85 (quintet, J = 5.0 Hz, 1.08 H), 4.6 (doublet, J = 3.8 Hz, 1.1 H), 2.0 (singlet, 9.0 H), 1.0 (doublet, J = 2.6 Hz, 3.0 H).

erythro-**1,2-Diphenylpropyltrimethylammonium iodide** was prepared by the method of Cram, Greene, and DePuy:[3] mp 212° dec (lit.[3] mp 212–213° dec; nmr (D_2O) δ 7.1 (multiplet, 10.0 H), 3.85 (multiplet, 1.0 H), 4.6 (doublet, J = 3.7 Hz, 1.0 H), 2.0 (singlet, 9.0 H), 1.0 (doublet, J = 2.5 Hz, 3.0 H).

erythro-**1,2-Diphenyl-1-propanol-***1-d* was obtained by reduction of 1,2-diphenylpropanone with lithium aluminum deuteride, following the procedure of Cram and Elhafez[15] for the hydride reduction. After three recrystallizations from ether, 77% of material of mp 49–51° resulted (lit.[15] mp 50–51° for the undeuterated material), 0.93 D atom per molecule by mass spectrometry.

threo-**1,2-Diphenylpropyl-***1-d* **chloride** was prepared from *erythro*-1,2-diphenyl-1-propanol-*1-d* and thionyl chloride as described by Elhafez and Cram.[16]

erythro-**1,2-Diphenylpropyl-***1-d*-**trimethylammonium chloride** was prepared from the reaction of *threo*-1,2-diphenylpropyl-*1-d* chloride with trimethylamine as described above for the undeuterated compound. The product (32% yield) had mp 142–143° dec; nmr (D_2O) δ 7.1 (multiplet, 10.0 H), 3.85 (quartet, J = 5.5 Hz, 1.05 H), 4.6 (doublet, J = 3.7 Hz, 0.04 H), 2.0 (singlet, 9.1 H), 1.0 (doublet, J = 2.5 Hz, 3.0 H).

2-Phenylpropionaldehyde-2-*d* was obtained by refluxing with stirring a mixture of 54 g (0.40 mol) of 2-phenylpropionaldehyde and 40 g (2.0 mol) of deuterium oxide containing a few drops of 40% sodium deuteroxide in deuterium oxide. The aldehyde was recovered and the process was repeated twice. The final product contained 0.97 D atom per molecule by mass spectroscopy.

threo-**1,2-Diphenylpropanol-***2-d* was obtained by the reaction of 2-phenylpropionaldehyde-2-*d* with phenylmagnesium bromide and recrystallization of the *p*-nitrobenzoate of the product 16 times from ethyl acetate [final *p*-nitrobenzoate mp 143–144° (lit.[15] mp 143–144°)], followed by saponification to give a viscous, clear oil: bp 136–137° (1.4 mm); $n^{25}D$ 1.5715 (lit.[15] $n^{25}D$ 1.5718); nmr ($CDCl_3$) δ 1.02 (doublet, J = 5.0 Hz, 3.0 H), 2.25 (broad singlet, 1.1 H), 3.05 (multiplet, 0.9 H), 4.65 (doublet, J = 3.5 Hz, 0.9 H), 7.10 (multiplet, 10.0 H).

threo-**1,2-Diphenylpropyl-***2-d p*-**bromobenzenesulfonate** was obtained as previously described for the undeuterated compound.[17] It was kept in dry benzene because it decomposes in the neat state.[17]

erythro-**1,2-Diphenylpropyl-***2-d*-**dimethylamine** was obtained from *threo*-1,2-diphenylpropyl-2-*d p*-bromobenzenesulfonate and dimethylamine as described for the undeuterated compound.[3] Its mass spectrum indicated 0.97 D atom per molecule; nmr ($CDCl_3$) δ 7.1 (multiplet, 10.0 H), 4.75 (doublet, J = 0.8 Hz, 1.0 H), 3.4 (multiplet, 0.07 H), 2.1 (singlet, 6.0 H), 1.40 (doublet, J = 0.9 Hz, 3.0 H).

erythro-**1,2-Diphenylpropyl-***2-d*-**trimethylammonium iodide** was obtained from *erythro*-1,2-diphenylpropyl-2-*d*-dimethylamine and methyl iodide by the procedure for the undeuterated compound:[3] mp 212–213° dec; nmr (D_2O) δ 7.1 (multiplet, 10.0 H), 3.85 (multiplet, 0.07), 4.6 (doublet, J = 0.8 Hz, 1.0 H), 2.0 (singlet, 9.0 H), 1.0 (doublet, J = 0.9 Hz, 3.0 H).

Recovery of 1,2-Diphenylpropyltrimethylammonium Salts after Partial Reaction. The reactions were carried out with 5.3 × 10^{-4} M *erythro*-1,2-diphenylpropyltrimethylammonium salt, appropriately deuterated, in 0.057 M potassium *tert*-butoxide in *tert*-butyl alcohol at 35° for one half-life (5.8 hr). The mixture was chilled and worked up by the procedure used by Smith and Bourns[4] to recover 2-phenylethyltrimethylammonium bromide. Two recrystallizations of the crude material from ethanol–ether yielded crystals of 1,2-diphenylpropyltrimethylammonium bromide.

Stability of 1,2-Diphenyl-1-propene to Reaction Conditions. A 2.41 × 10^{-3} M solution of α-methylstilbene [Pfaltz and Bauer, Inc., λ_{max} 274 nm (lit.[15] 274 nm for trans isomer)] in *tert*-butyl alcohol was photolyzed for 3 hr in a Kimax test tube with a medium-pressure mercury lamp, using a potassium dichromate filter solution to isolate the 313-nm line. The resulting material was diluted 1:25 with 95% ethanol and the uv spectrum was determined. λ_{max} 264 nm, no shoulder near 255 nm (9-methylphenanthrene). For the cis olefin, λ_{max} 260 nm is reported;[18] so the photoisomerized mixture appears to contain an excess of cis over trans olefin. The photostationary state is reported to have a cis/trans ratio of 2.6 at 313 nm.[19] In contrast, the trans isomer predominates by at least 50:1 at equilibrium.

A solution containing the photoisomerized olefin mixture (4.82 × 10^{-4} M), potassium *tert*-butoxide (0.3 M), and tetra-*n*-butylammonium bromide (8 × 10^{-3} M) was placed in a bath at 30°. Samples were taken after 2 hr and 27 hr and diluted 1:5 with 95% ethanol, and the uv spectra were determined. For both samples λ_{max} 265–266 nm was observed, indistinguishable within experimental error from λ_{max} for the starting material. The half-life of the elimination reaction of 4.82 × 10^{-4} M 1,2-diphenylpropyltrimethylammonium iodide in 0.3 M potassium *tert*-butoxide can be calculated from the reported rate constant[3] at 30° to be 2 hr.

Registry No.—1, 42879-24-3; 2, 42879-25-4; *erythro*-1,2-diphenylpropyltrimethylammonium chloride, 42879-26-5; *threo*-1,2-diphenylpropyl chloride, 7693-88-1; trimethylamine, 75-50-3; *erythro*-1,2-diphenylpropyltrimethylammonium iodide, 42879-28-7; *threo*-1,2-diphenylpropanol-2-*d*, 42879-29-8; *erythro*-1,2-diphenylpropyl-2-*d*-dimethylamine, 42879-30-1; *threo*-1,2-diphenylpropyl-2-*d p*-bromobenzenesulfonate, 42879-31-2.

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Stereospecific Synthesis of D-*threo*-Sphinganine

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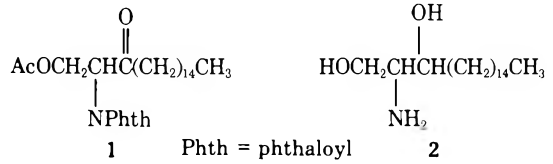
In the course of our studies on the synthesis of sphingolipid bases[1,2] we have uncovered a very interesting case of stereoelectronic control on the course of a reduction, which permits the stereospecific preparation of D-*threo*-sphinganine (2) from the ketone precursor **1**.

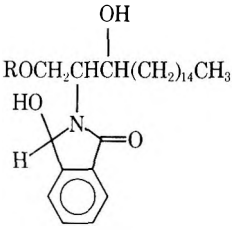


1 Phth = phthaloyl **2**

Heretofore, **2** has been available only by resolution of the DL mixture which was, in turn, obtained by separation

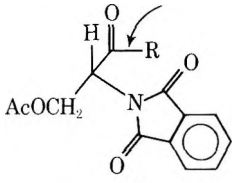
from its DL-erythro isomer with which it is formed in combination.[3,4]

Thus, treatment of chiral D-1 with lithium tri-*tert*-butoxyaluminum hydride resulted in the selective reduction of the ketone carbonyl to give *O*-acetyl-*N*-phthaloyl **2** exclusively, which was then deblocked (see below) to give **2**. Lithium aluminum hydride or sodium borohydride proved unsuitable; both led to concomitant reduction of one of the phthalimido carbonyls to give **3**. The lithium aluminum hydride reduction gave additionally the deacetylated product **4**.



3, R = Ac
4, R = H

The reaction observed is understandable in terms of the unique conformation A for **1** in which the ketone carbonyl

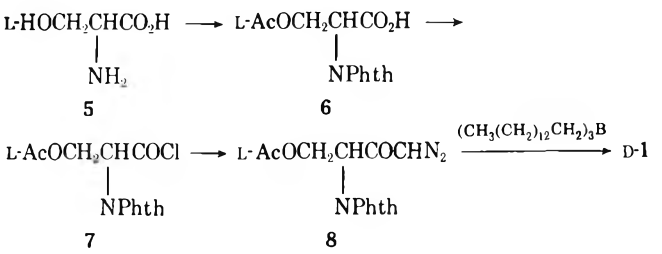


A

group is oriented antiparallel to the phthalimido substituent, thereby minimizing the dipole–dipole interaction between the two moieties.[5]

Exclusive attack of A by hydride from the sterically least hindered top side (see arrow) would then lead to the stereospecific formation of the threo isomer.

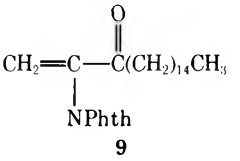
The ketone **1** was prepared according to our previously published method[2] in which a suitably protected serine derivative is elaborated to a diazo ketone and the latter is allowed to react with a trialkylborane. Thus, L-serine **5** was N-phthaloylated and then O-acetylated to give **6**, which was then converted to the acid chloride **7**. Treatment of the latter with diazomethane gave the diazo ketone **8**, which was converted to D-**1** with tritetradecylborane.[6]



Blocking group removal from *O*-acetyl-*N*-phthaloyl **2** was readily accomplished, preferentially in two steps:[7] acid-catalyzed methanolysis to remove the acetyl substituent followed by hydrazinolysis to remove the phthaloyl moiety.

An interesting aspect of the chemistry of **1** is the extreme ease with which it underwent loss of acetic acid to give the unsaturated ketone **9**; thick layer chromatography on silica gel was sufficient to effect this elimination.

In this connection, Weiss and Stiller[8] described a minor product which they obtained admixed with D-1-hydroxy-



9

2-acetamido-3-ketodecane from the chromic oxide–pyridine oxidation of N-acylated sphinganine which became the major product on repeated silicic acid column chromatography. They speculate that this product is a substituted oxazolidine. We would like to suggest the *N*-acetyl analog of the α,β-unsaturated ketone **9** as a likely possibility based on our observations on the chromatographic behavior of **1**.

Experimental Section

General. Evaporations were carried out on a rotary evaporator under reduced pressure. Melting points were taken with a Mel-Temp apparatus and are not corrected. The petroleum ether used boiled at 30–60° and magnesium sulfate was used for drying. Thin layer chromatograms were run on 250-μ silica gel plates (Analtech Inc., Newark, Del.); spots were developed with uv and/or phosphomolybdic acid spray (10% ethanolic phosphomolybdic acid). Nmr spectra were determined on either a Varian A-60 or HA-100 instrument using tetramethylsilane as an internal standard. Mass spectra were run on an AEI-MS-9 spectrometer at 70 eV. The 2-mm silica gel plates used for thick layer chromatography were also obtained from Analtech. Partition chromatographs were run on Celite 545 using heptane–Methyl Cellosolve for development; 1.5 ml of lower phase per gram of Celite was used. The letters w, m, and s following the infrared spectral absorptions denote weak, medium, and strong, respectively.

L-*O*-Acetyl-*N*-phthaloylserine (6). Commercially available L-serine (**5**) was first N-phthaloylated according to the procedure of Nefkin, *et al.*,[9] then O-acetylated. Thus, a mixture of 10.5 g (0.01 mol) of L-serine, 27.5 g (0.014 mol) of *N*-carbethoxyphthalimide (Aldrich), and 28.8 g (0.1 mol) of sodium carbonate decahydrate in 150 ml of water was vigorously stirred at room temperature for 45 min and then filtered to separate the small amount of insoluble material. The clear filtrate was acidified with 6 *N* HCl and the *N*-pathaloyl derivative, which separated as an oil, was extracted into ether. Drying and evaporating the ethereal solution left *ca.* 30 g of *N*-phthaloyl-L-serine as a colorless, viscous oil which was acetylated directly by stirring with 100 ml of acetyl chloride at room temperature for 30 min. Most of the excess acetyl chloride was evaporated with moderate heating and the residue was shaken well with ice–water for 10 min to decompose the remaining acetyl chloride. The water was decanted and the shaking was repeated with a fresh portion of ice–water for 5 min. After the water was decanted, the residue was dissolved in ether and the ethereal solution was dried and evaporated to leave 23 g of a pale yellow, oily solid. Trituration with benzene gave 6.5 g of L-*O*-acetyl-*N*-phthaloylserine, mp 151–153° (lit.[10] mp 151–153), which can be recrystallized from benzene with good recovery.

Dilution of the benzene filtrate with a large volume of petroleum ether caused a thick, opaque oil to separate. The supernatant was decanted, and the oil was washed again with petroleum ether. Removal of the last traces of solvent left 11.7 g of a pasty solid which was indicated by tlc ($CHCl_3$–EtOH–H_2O 40:20:4) to be very largely the desired **6** (R_f 0.55) along with a very minor faster running impurity; total yield 18.2 g (66%). The oily product obtained was of good enough quality to be used for further conversion to the acid chloride and then to the diazo ketone as outlined in the next experiment.

An improved yield of purer product can be obtained by modifying the work-up as follows. After most of the excess acetyl chloride was evaporated, the liquid residue was poured into ice–water and the suspended organic phase was frequently agitated. During the first 6 hr the water was changed at *ca.* 1.5-hr intervals, being separated each time by decantation. After it was kept in the water overnight (room temperature) the now solid, off-white product was collected and air dried. Recrystallization from benzene furnished **6**, mp 154–157°, in overall 40% yield from L-serine.

L-*O*-Acetyl-*N*-phthaloylseryldiazomethane (8). An 11.7-g (0.42 mol) portion of the oily fraction of L-*O*-acetyl-*N*-phthaloylserine (**6**) obtained in the previous experiment in 40 ml of anhydrous benzene was heated under reflux with 7.5 ml of thionyl chloride for 15 min (reaction mixture was inserted into a preheat-

ed bath), then evaporated. Repeating the evaporation twice more with fresh 100-ml portions of benzene gave the acid chloride as a dark orange oil. The crude acid chloride was dissolved in 125 ml of ether and added dropwise with stirring to a cold solution of ethereal diazomethane (from 30 g of *N*-methyl-*N*-nitrosourea) during 25 min. After the solution was stirred in the cold for an additional 1.5 hr, it was evaporated, leaving the diazo ketone **8** as a thick orange oil, λ_{max} (film) 4.73 (s, diazo), 5.70 (s, OAc), and 5.73 (vs) with a weak peak at 5.65 (phthaloyl) and 6.10 μ (s, ketone). The integrated ratio of the phthaloyl at δ 7.8 (multiplet), $-CHN_2$ at δ 5.5, and CH_3CO_2-protons at δ 2.0 in the nmr indicated the product to contain *ca.* 80% diazo ketone.

D-1-Acetoxy-2-phthalimido-3-ketooctadecane (1). A solution of 0.04 mol of tritetradecylborane in tetrahydrofuran was prepared by adding 24 g (0.12 mol) of neat tetradecene (Aldrich) to 40 ml of 1 *M* diborane in THF (Alpha Inorganics) during 5 min with cooling (ice-water) to moderate the strong exotherm accompanying the addition. The cooling bath was removed after the addition was completed and the solution was stirred at room temperature for 2.5 hr [R_f of tritetradecylborane on tlc (PhH–EtOAc 9:1) *ca.* 0.35].

A solution of the diazo ketone **8** in 40 ml of THF (Matheson Coleman and Bell, bp 65.5–66.5°, freshly opened bottle) was then added dropwise during 10 min at room temperature (gas evolution) and the mixture was stirred at room temperature for 2.5 hr. Water (*ca.* 40 ml) was added and the two-phase mixture was heated under vigorous reflux for 30 min. After cooling, ether was added and the aqueous phase (acidic) was separated. Washing, drying, and evaporating the organic phase left 34 g of an opaque yellow residue. After 2 days at room temperature the product was triturated with petroleum ether and filtered to separate insoluble solid. (Although not identified, its infrared spectrum, which showed only weak absorption in the carbonyl region, indicated it not to be any of the desired **1**.) The liquid residue obtained by evaporating the petroleum ether filtrate (*ca.* 23 g) separated into two phases on standing. The lower phase was rich in the desired **1** and the upper phase in unreacted tritetradecylborane (indicated by tlc). The entire residue was partition chromatographed and the desired **1** was eluted after *ca.* two holdback volumes. The product was a pale yellow solid (4.4 g, 22% based on starting acid **6**): mp 52–55° (shrinking 48°); λ_{max} (KBr) 5.7 (OAc). 5.8 μ (ketone + phthaloyl) (a weak 5.6-μ peak associated with the phthaloyl moiety was also present); $[\alpha]^{25}D$ −50.3° (*c* 0.83, EtOH); R_f on tlc (PhH–EtOAc 9:1) *ca.* 0.6.

Anal. Calcd for $C_{28}H_{41}NO_5$ (471.62): C, 71.30; H, 8.76; N, 2.97. Found: C, 71.63; H, 8.85; N, 3.13.

2-Phthalimido-3-ketooctadecene-1 (9). On attempted thick layer chromatography (PhH–EtOAc 9:1) the ketone **1** underwent elimination of acetic acid to give the olefinic ketone **9**: mp 67–70° (after trituration with petroleum ether); λ_{max} (KBr) 5.8 (s) and 5.6 (w, phthaloyl) and 5.9 (w–m, ketone). The nmr spectrum showed two one-proton doublets (J = 1.2 Hz) at δ 6.50 and 6.10 due to the terminal methylene.

Anal. Calcd for $C_{26}H_{37}NO_3$ (411.58): C, 75.87; H, 9.06; N, 3.40. Found: C, 76.19; H, 9.07; N, 3.78.

9 runs slightly faster than **1** on tlc (PhH–EtOAc 9:1).

D-1-Acetoxy-2-phthalimido-3-hydroxyoctadecane (*O*-Ac-*N*-phth-2). Three grams (0.0063 mol) of ketone **1** was added, neat, to a cooled (ice-water), stirred solution of lithium tri-*tert*-butoxyaluminum hydride (Ventron) in 100 ml of THF (Matheson Coleman and Bell, bp 65.5–66.5°) and the solution was stirred in the cold for 35 min, then diluted with ice-water and ether, and acidified with hydrochloric acid. The organic phase was separated, dried, and evaporated to yield 2.9 g of a pasty, ivory-colored solid whose tlc (PhH–EtOAc 9:1) showed very predominantly one spot at R_f 0.35. Purification of a 100-mg sample by thick layer chromatography (PhH–EtOAc 9:1) gave *O*-Ac-*N*-phth-**2**: mp 69–75°; λ_{max} (KBr) 5.72 (s, OAc), 5.86 (vs), 5.6 μ (w, phthaloyl); $[\alpha]^{25}D$ −16.9° (c 0.56, EtOH).

Anal. Calcd for $C_{28}H_{43}NO_5$ (473.63): C, 71.00; H, 9.15; N, 2.96. Found: C, 71.01; H, 9.15; N, 2.95.

The crude material was suitable for conversion to D-*threo*-sphinganine (**2**), as described in the next experiment.

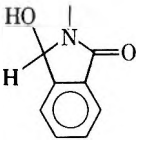
D-*threo*-Sphinganine (1,3-Dihydroxy-2-aminooctadecane) (2). *O*-Ac-*N*-phth-**2** (0.1 g) was heated under reflux in 2 ml of methanol containing 2 drops (Pasteur pipette) of concentrated hydrochloric acid for 30 min. Diluting with ice-water gave *N*-phthaloylsphinganine as a solid which, after drying for 2 hr (probably unnecessary), was heated under reflux with 1.5 ml of 10% ethanolic hydrazine hydrate for 1 hr. The reaction mixture was diluted with ice-water, made strongly basic by adding KOH pellets, and extracted with methylene chloride. Drying and evaporating the methylene chloride extracts left a solid residue which after trituration with ether furnished 25 mg (40%) of colorless, glistening plates: mp 107–109.5°; $[\alpha]^{25}D$ −12.9° (*c* 0.48, $CHCl_3$); R_f on tlc ($CHCl_3$–MeOH–2NNH_4OH 40:10:1)[11] *ca.* 0.35 (I_2 vapor). Grob, *et al.*,[12] report for D-*threo*-sphinganine mp 109°, $[\alpha]^{25}D$ −14.1 ± 2°.

Anal. Calcd for $C_{18}H_{39}NO_2$ (301.50): C, 71.70; H, 13.04; N, 4.65. Found: C, 71.56; H, 13.19; N, 4.60.

***N*-Acetyl Derivative.** Fifty milligrams of analytically pure D-*threo*-sphinganine was dissolved in 5 ml of methanol (with slight warming) and 1 ml of acetic anhydride was added.[13] After 15 hr at room temperature, ice–water was added and the colorless solid which separated was collected, washed with water, and air dried, yield 52 mg, mp 92–96° (shrinking *ca.* 75°). Recrystallization from methylene chloride furnished the analytical sample: mp 97–99.5°; λ_{max} (KBr) 6.05 μ (amide); $[\alpha]^{25}D$ +5.1° (*c* 0.39, $CHCl_3$); R_f on tlc ($CHCl_3$–MeOH 9:1) 0.65 (lit.[11b] mp 98–99°; $[\alpha]^{22.5}D$ +8.5°).

Lithium Aluminum Hydride Reduction of 1. Formation of 1-Acetoxy-2-dihydrophthalimido- 3-hydroxyoctadecane (3) and 1,3-Dihydroxy-2-dihydrophthalimidooctadecane (4). A solution of 180 mg (0.44 mmol) of **1** in 3 ml of anhydrous ether was added during 1 min to a cooled (Dry Ice–methanol), stirred partial solution of 35 mg (0.9 mmol) of $LiAlH_4$ in 3 ml of anhydrous ether. After the solution was stirred in the Dry Ice–methanol bath for another 1 min, ice was added at that temperature followed by water, ether, and dilute hydrochloric acid. The ethereal phase was separated, washed with aqueous bicarbonate, dried, and evaporated to yield 140 mg of a pale yellow syrup which was indicated by tlc (PhH–EtOAc 1:1) to consist very largely of two components with R_f's of 0.55 and 0.25. These were separated by thick layer chromatography (PhH–EtOAc 1:1).

The faster running component (52 mg, yellow syrup) was indicated to be **3** by its infrared [3.1 (moderately broad, OH), 5.75 (OAc), and 6.0 μ (amide carbonyl)], mass [*m/e* 475 (M^+ for **3**), 457 ($M - H_2O$), 397 (M − HOAc)], and nmr spectra [δ 5.9 (bold-faced proton in a) and 3.0 (CH_3CO)].



a

The slower running component (waxy, colorless solid, mp 39–42°, 51 mg) was indicated to be **4** by its infrared [3.1 (moderately broad, OH) and 6.0 μ (amide carbonyl)], mass [*m/e* 433 (M^+ for **4**), 415 ($M - H_2O$)], and nmr spectra [δ 5.9 (bold-faced proton in a)].

Anal. Calcd for $C_{26}H_{43}NO_4$ (433.62) (**4**): C, 72.01; H, 10.00; N, 3.23. Found: C, 71.72; H, 10.05; N, 3.05.

Acknowledgments. Analyses were performed by Mr. L. Brancone and staff, nmr spectra and optical rotations by Messrs. W. Fulmor and G. Morton, partition chromatograms by Mr. J. Baker, and mass spectra by Dr. G. Van Lear.

Registry No. 1, 42806-63-3; **2,** 15639-50-6; *O*-Ac-*N*-phth-**2,** 42806-65-5; *N*-Ac-**2,** 35301-25-8; **3,** 42806-67-7; **4,** 42806-68-8; **6,** 41765-22-4; **8,**42806-70-2; **9,** 42806-71-3.

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(6) The apparent change in configuration of C-2 from L in the serine series to D in the sphinganine series is actually the result of a change in reference origin. In the former series, as with all amino acids, the molecule is, according to convention, oriented in two dimensions with its carboxyl group up. This puts the amino group having the L optical configuration on the left. In the latter series, the terminal OH is oriented upward. This now places the same amino function on the right; therefore, the D optical configuration.
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Photoreaction of 2,6-Diphenyl-4*H*-thiopyran-4-one 1,1-Dioxide with Arylacetylenes

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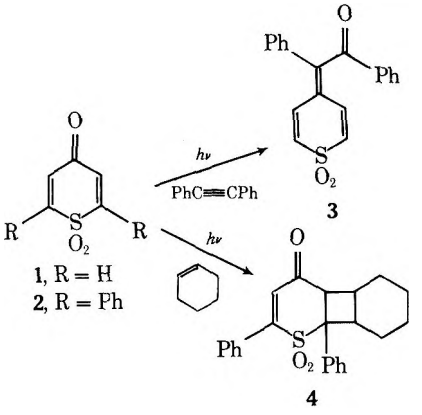
Photoaddition of *p*-quinones to olefins or acetylenes has attracted considerable attention.[2] Two major pathways are cycloaddition of the carbonyl function to the unsaturated carbon–carbon bond to give oxetanes[3] or their rearranged products[4,5] and cycloaddition of the ring double bond of *p*-quinone to a carbon–carbon double or triple bond to yield cyclobutane or cyclobutene derivatives.[6] Even though 4*H*-thiopyran-4-one 1,1-dioxides (**1** and **2**) are structurally similar to *p*-quinones,[7] only few photochemical studies have so far been reported on this project. Ultraviolet irradiation of **1** and diphenylacetylene yields **3**,[8] similar to the photoreaction of *p*-benzoquinone and diphenylacetylene.[4] Also **2** adds photochemically to cyclohexene to form **4**,[9] a reaction identical with the photoaddition of 2-methoxy-*p*-benzoquinone to acetylenes.[6]

The present research, photoaddition of 2,6-diphenyl-4*H*-thiopyran-4-one 1,1-dioxide (**2**) and arylacetylenes, is part of our continued studies on the photoreaction of *p*-quinones and unsaturated hydrocarbons.[5b,10]



A mixture of **2** and an arylacetylene (diphenylacetylene, methylphenylacetylene, or phenylacetylene) in benzene was irradiated with a medium-pressure mercury lamp using a Pyrex filter. Column chromatography of the reaction mixture in each case gave a single product in significant quantity. The infrared spectra of these photoproducts showed strong absorption bands at 1270–1285 and 1110–1125 cm^{-1}, characteristic of antisymmetric and symmetric stretch of the SO_2 group.[11] Absence of a carbonyl band in the infrared rules out structures similar to **3** or **4** as the structure of the photoproduct. The mass spectra obtained at 70 eV for the photoproducts from **2** and diphenylacetylene, methylphenylacetylene, or phenylacetylene displayed the base peak at the highest mass of *m/e* 382, 320, and 306, respectively, their magnitude corresponding to the expulsion of sulfur dioxide from their parent peaks ($M - SO_2$). Lowering the electron energy to 15 eV for the photoproduct of **2** and diphenylacetylene led to the appearance of a weak peak at *m/e* 446, indicative of its mass number. Molecular weights determined by osmometry were 450 and 370 for the products from **2** and diphenylacetylene and **2** and phenylacetylene. These results clearly indicate that the photoproducts are the decarbonylated compounds of the 1:1 adducts of **2** and arylacetylenes. The nmr spectra of the reaction products showed the olefinic and the aromatic protons at δ 6.8–8.0. The ultraviolet spectrum of the photoproduct from **2** and diphenylacetylene exhibited absorptions at 217 nm (ϵ 3.6 × 10^4), 265 (2.6 × 10^4), and 315 (5.4 × 10^3). This spectrum appears to match that of tropone,[12] while the uv spectrum of the parent thiepin 1,1-dioxide[13] is similar to that of cycloheptatriene.[14] Naturally these spectral properties suggest that the photoproducts have the structure of thiepin 1,1-dioxide.[13,15,16]

Confirmation of the thiepin 1,1-dioxide structure was obtained by thermolysis and hydrogenation of the photoproduct from **2** and diphenylacetylene (Scheme I). Heat-

Scheme I

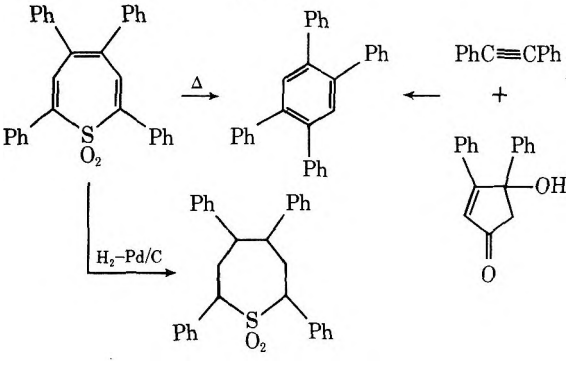
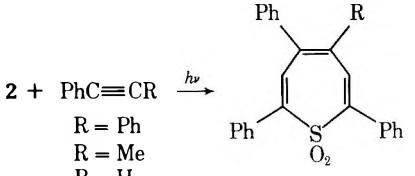


Table I
Spectral and Physical Data for the Photoproducts

Product	Yield, %	Mp, °C	Ir, cm^{-1} (KBr)	Uv (CH_2Cl_2) λ, nm	Uv (CH_2Cl_2) ε	Nmr, δ (acetone-d_6)	Mass spectra, *m/e* (rel intensity) (70 eV)	Mol wt	Anal. Calcd (found), % C	H	O	S
5	60[a]	224–225	1600, 1490, 1285, 1125, 755, 685	217 265 315	36,330 26,000 5,400	7.1–6.2 (m, 10 H) 7.3–7.6 (m, 10 H) 7.9–8.0 (m, 2 H)	496 (M^+, <1)[d], 383 (32), 382 (100), 381 (81), 367 (6), 305 (14), 304 (8), 291 (13), 290 (6), 289 (5)	450	80.54 (80.69)	4.85 (4.96)	7.01 (7.01)	7.07 (7.02)
6	26[b]	88–92	1490, 1445, 1285 1120, 760, 690			1.33 (s, 3 H) 6.87 (s, 1 H) 6.97 (s, 1 H) 7.0–7.8 (m, 15 H)	321 (28), 320 (100), 305 (33), 304 (22), 272 (21)		78.10 (77.92)	5.24 (5.01)		8.34 (8.35)
7	20[c]	172–174	1595, 1485, 1440 1120, 760, 690			7.0–7.3 (m, 11 H) 7.5–7.7 (m, 5 H) 7.9–8.0 (m, 2 H)	307 (25), 306 (100), 305 (20), 290 (20), 288 (21), 102 (33), 91 (20) 77 (29)	370	77.81 (78.07)	4.96 (5.01)		8.44 (8.44)

[a] Recovery of **2** was 11%. [b] Recovery of **2** was 35%. [c] Recovery of **2** was 27%. [d] At 15 eV.

ing of **5** in tetralin yielded 1,2,4,5-tetraphenylbenzene, which is identical (melting point, ir and nmr spectra) with the authentic sample prepared from 3,4-diphenyl-4-hydroxycyclopent-2-en-1-one with diphenylacetylene.[17] Hydrogenation of **5** over Pd/C resulted in the uptake of 3 molar equiv of hydrogen and gave 2,4,5,7-tetraphenylthiacycloheptane 1,1-dioxide. The thermal decomposition to the benzene derivative and sulfur dioxide and ready catalytic hydrogenation to hexahydrothiepin 1,1-dioxide are characteristic with thiepin 1,1-dioxide.[13] These results, in addition to the spectral properties, support the contention that the photoproducts of **2** with diphenylacetylene, methylphenylacetylene, and phenylacetylene are **5**, **6**, and **7**,[18] respectively.



5, R = Ph
6, R = Me
7, R = H

Irradiation of a mixture of **2** and dimethyl acetylenedicarboxylate in benzene resulted in the recovery of the starting materials, whereas photolysis of **2** and 2- or 3-hexyne in benzene gave a polymeric material. Irradiation of a mixture of 3,5-diphenyl-4*H*-thiopyran 1,1-dioxide and diphenylacetylene did not furnish thiepin 1,1-dioxide derivative. The nature of the substituents, both in 4*H*-thiopyran-4-one 1,1-dioxide and acetylenes, seems to be important in the formation of thiepin 1,1-dioxide. Careful study of the ultraviolet spectra of a mixture of **2** and diphenylacetylene in benzene or cyclohexane showed no specific interaction in the ground state, although **2** was expected to function as an electron acceptor in a charge-transfer complex, as has been observed in the case of *p*-quinones.[20]

Experimental Section

Melting points were not corrected. The infrared spectra were recorded on a JASCO DS-402G spectrophotometer. The ultraviolet spectra were obtained with a Hitachi 124 spectrophotometer and the nmr spectra were measured with a JEOL PS-100 spectrometer. The mass spectra were recorded on a Hitachi RMU-6L spectrometer. The molecular weights were determined by a Hitachi 115 molecular weight measuring apparatus.

2,6-Diphenyl-4*H*-thiopyran-4-one 1,1-dioxide[21] was prepared by the oxidation of 2,6-diphenyl-4*H*-thiopyran-4-one with hydrogen peroxide. Arylacetylenes commercially available were used, after purification by distillation or recrystallization.

Irradiation of 2 with Arylacetylenes. A mixture of **2** (0.3 g) and arylacetylene (1.2–3.0 g) in benzene (300 ml) was irradiated under nitrogen for 4 hr using a 300-W medium-pressure mercury lamp equipped with a Pyrex filter. After removal of the solvent, the residual solid was chromatographed on silica gel with cyclohexane–benzene to yield a colorless solid, which was recrystallized from *n*-hexane to give the thiepin 1,1-dioxides. The spectral and physical data of the photoproducts are summarized in Table I.

Thermolysis of 5 in Tetralin. A solution of **5** (0.1 g) in tetralin (3 ml) was refluxed for 3 hr. The reaction mixture was chromatographed on silica gel and eluted with cyclohexane–benzene to give a colorless solid. This solid was recrystallized from ligroin to furnish 1,2,4,5-tetraphenylbenzene in 63% yield: mp 274–275°; mmp 272–275°; nmr ($CDCl_3$) δ 7.25 (s, 20 H), 7.57 (s, 2 H).

Anal. Calcd for $C_{30}H_{22}$: C, 94.13; H, 5.89. Found: C, 94.20; H, 5.80.

Catalytic Hydrogenation of 5. Catalytic hydrogenation of **5** (0.06 g) in ethyl acetate (50 ml) with 10% Pd/C was carried out at room temperature under 15 atm for 50 hr. After removal of the solvent under reduced pressure, preparative thin layer chromatography of the residual solid afforded 2,4,5,7-tetraphenylthiacycloheptane 1,1-dioxide in 60% yield: mp 308–310°; ir (KBr) 1585, 1480, 1435, 1280, 1125, 755, 690 cm^{-1}; nmr ($CDCl_3$) 3 1.2–2.6 (m, 8 H), 7.0–8.0 (m, 20 H).

Anal. Calcd for $C_{30}H_{28}O_2S$: C, 79.61; H, 6.24. Found: C, 79.48; H, 6.28.

Acknowledgment. We thank Dr. R. Mukherjee for his help in preparation of the manuscript.

Registry No. 2, 41068-60-4; **5**, 42867-24-3; **6**, 42867-25-4; **7**, 42867-26-5; diphenylacetylene, 501-65-5; methylphenylacetylene, 673-32-5; phenylacetylene, 536-74-3; 2,6-diphenyl-4*H*-thiopyran-4-one, 1029-96-5; 1,2,4,5-tetraphenylbenzene, 3383-32-2; 2,4,5,7-tetraphenylthiacycloheptane 1,1-dioxide, 42867-28-7.

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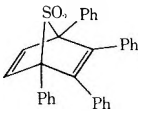
(18) A referee pointed out the possibility **8** for the structure of **5**. It seems, however, unlikely that **8** is stable at room temperature, since the 7-thiabicyclo[2.2.1]hepta-2,5-diene derivative, never isolated, was proposed only as a reaction intermediate.[19] Moreover, cycloaddition of **5** with tetracyanoethylene or dimethyl acetylenedicarboxylate did not occur, while a homo-Diels–Alder reaction of norbornadiene is well established. We believe that the photoproduct has the structure of thiepin 1,1-dioxide, though the structure **8** cannot be ruled out conclusively.



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The Synthesis of 2-Methylproline and 2-Methylornithine

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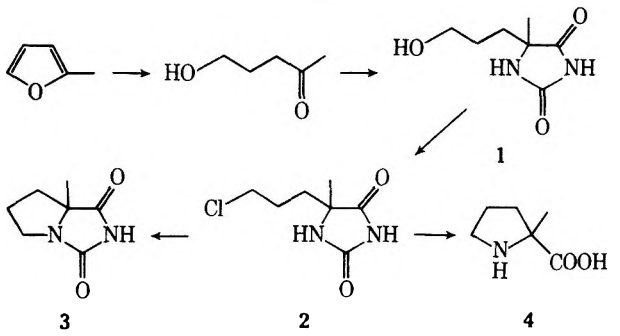
Interest in analogs of the natural amino acids has increased at a rapid rate since du Vigneaud, *et al.*,[1] first re-

ported the synthesis of deaminooxytocin. These amino acid derivatives are substituted into biologically active peptides to modify the activity of the peptide. To this end we have been interested in the synthesis of 2-methylamino acids as substitutes for the naturally occurring amino acids.[2] Our present interest in 2-methylornithine is related to the report by Bodanzky, *et al.*,[3] that a suitably protected ornithine moiety can be readily converted to arginine. This latter amino acid has been shown to be essential in the amino acid sequence of angiotensin and related hypertensive peptides.

The first synthetic route, shown in Scheme I, is based in part on the synthesis of ornithine by Gaudry.[4] Reduc-

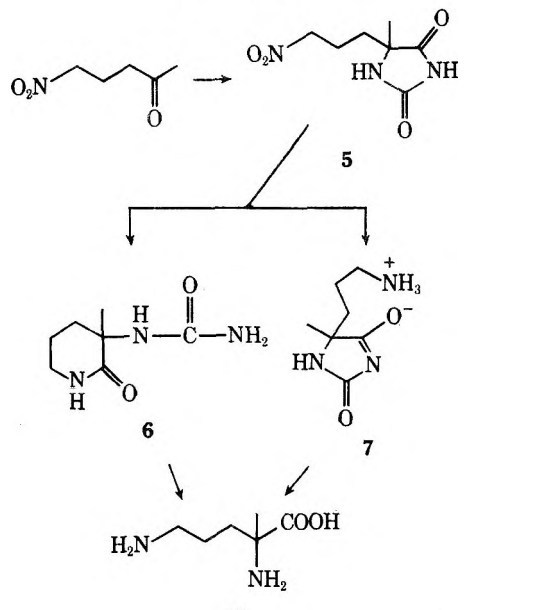
Scheme I



tion of 2-methylfuran[5] and conversion of the 5-hydroxy-2-pentanone to 5-(3-hydroxypropyl)-5-methylhydantoin (1) by the method of Bucherer[6] took place in reasonable yield. Hydantoin 1 was readily converted, in good yield, to the chloro derivative 2 with pyridine–thionyl chloride. Attempts to form 5-(3-aminopropyl)-5-methylhydantoin by amination of 2 resulted in cyclization to 5-methyl-1,5-trimethylenehydantoin (3), a precursor of 2-methylproline (4). Both 2 and 3 were hydrolyzed to 2-methylproline (4).

Failure of the Gaudry route in which the nitrogen is inserted at the hydantoin stage of the synthesis with the resultant cyclization led us to investigate an alternate path to 2-methylornithine as shown in Scheme II. This method

Scheme II



introduced the ornithine ω nitrogen at the ketone level. 5-Nitro-2-pentanone[7] was converted to 5-methyl-5-(3-nitropropyl)hydantoin (5) in reasonable yield. Acid or base hydrolysis of 5 gave 2-methylglutamic acid as the only product.[8] Catalytic reduction of 5 gave two characterizable products, 6 and 7, that had the same elemental analysis. Mass spectra indicated a molecular weight of 171 for both, which is correct for the reduction of the nitro function. Compound 6 (mp 235–236°) was identified as 3-methyl-3-ureidopiperidone. 6 gave a positive test with Ehrlich's reagent (lemon-yellow color) which is characteristic of the ureido moiety. Kurhajec[9] reported formation of 3-ureidopiperidone from the reduction of 5-(2-cyanoethyl)hydantoin. Infrared data for the lactam urea 6 and *N*-methylurea show comparable bands [ν_{max} (KBr) 3660, 3365, 3285, 3191, 1670, and 1575 cm^{-1} for 6 *vs.* 3425, 3330, 1650, and 1575 cm^{-1} for *N*-methylurea]. The nmr data for 6 are also consistent with the lactam urea structure in which the methylene protons on the carbon adjacent to nitrogen are found at δ 3.1, two secondary amide protons at δ 6.1 and 7.3, and two primary amide protons at δ 5.4. Exchangeability of the four amide protons was observed on the addition of D_2O.

Compound 7 (mp 175–177°) was assigned a zwitterionic structure. Schauenstein and Perko[10] report that enolization occurs between N-3 and C-4 of hydantoins while Seth Paul and Demoen[11] prefer a mesomeric structure

for the N–C bond. The nmr spectra of 7 indicated an ammonium ion at δ 4.5 and two of the methylene protons at δ 2.5. Exchangeability of the protons at δ 4.5 was confirmed with D_2O. A sample of 5,5-dimethylhydantoin had characteristic hydantoin carbonyl absorption at 1762 and 1700 cm^{-1}, while the sodium salt had strong absorption at 1575 cm^{-1}, similar to the carbonyl absorption of 7. Phenyl isothiocyanate reacts with 7 to give a single product that has the correct elemental analysis for the phenylthiourea derivative of 7 and has carbonyl absorption at 1760 and 1700 cm^{-1}. Base hydrolysis and acid work-up of 6 and 7 gave 2-methylornithine sulfate (8) as the only product. The resolution of the 2-methylamino acids and their incorporation into peptide analogs will be reported later.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga., and were within ±0.4% of the theoretical values.[12] The ir spectra were recorded with a Perkin-Elmer 237B spectrophotometer and nmr spectra were determined using a Perkin-Elmer R-20A spectrometer with the chemical shifts (δ) given in parts per million downfield from TMS. Mass spectra were obtained with a Du Pont Model 490 mass spectrometer. Thin layer chromatograms were developed on Eastman 6060 silica gel plates with fluorescent indicator. Solvent systems used were (A) 1-butanol–acetic acid–water–pyridine (15:3:12:10); (B) 1-butanol–acetic acid–water (65:15:22); (C) pyridine–isoamyl alcohol–water (35:30:30); (D) ethanol–benzene (2:3); (E) 2-propanol–benzene (1:9). R_f values are reported as solvent system (R_f).

5-(3-Hydroxypropyl)-5-methylhydantoin (1). To 56.5 g (0.55 mol) of 5-hydroxy-2-pentanone dissolved in 1 l. of 60% EtOH was added 163 g (1.7 mol) of wire brushed ammonium carbonate (ACS). The solution was stirred and warmed to 55°, at which time 29.5 g (0.59 mol) of aqueous sodium cyanide was added over a period of 5 min. The mixture was stirred at 55° for 24 hr. The condenser was removed and the temperature was brought to 90° for 3 hr to remove excess ammonium carbonate. After cooling, the pH was adjusted to 5 with concentrated HCl. (Caution! HCN is generated by the acidification.) Reduction in the volume to 300 ml and cooling to 4° overnight gave 50 g of clear crystals, mp 143–145°. Evaporation of the filtrate to dryness and extraction of the solid residue with 75 ml of hot absolute EtOH gave an additional 10 g of hydantoin (yield 73%). An analytical sample was obtained after two crystallizations from absolute ethanol: mp 144–146°; ir

(Nujol) 3375, 3315, 3250, 1762, and 1725 cm^{-1}; nmr (CD_3OD) δ 1.4 (s, 3 H, C-CH_3), 1.7 (m, 4 H, CCH_2CH_2-), 3.5 (t, 2 H, OCH_2-); homogenous in solvent systems B (0.44) and C (0.54). *Anal.* ($C_7H_{12}N_2O_3$) C, H, N.

5-(3-Chloropropyl)-5-methylhydantoin (2). To 5 g (0.029 mol) of 1 and 2.52 g (0.032 mol) of pyridine, cooled to 0° and protected from moisture, was added 2.19 ml (0.03 mol) of thionyl chloride in 10 ml of $CHCl_3$ over a 1-hr period. The solution was stirred for an additional 3 hr, at which time the reaction had warmed to room temperature. The temperature was then raised to 55° for 30 min. After removal of the chloroform *in vacuo* the resulting viscous oil was dissolved in 10 ml of H_2O and extracted with ether (4 × 20 ml). The ether was dried over $MgSO_4$ and evaporated *in vacuo* to yield 4 g of solid (73%). An analytical sample was obtained by crystallization from benzene: mp 127–129°; ir (KBr) 3300–3100 (br), 1750, 1700, and 1425 cm^{-1}; nmr (CD_3OD) δ 1.4 (s, 3 H, CCH_3), 1.8 (m, 4 H, CCH_2CH_2-), 3.5 (t, 2 H, $ClCH_2$-); homogenous in solvents systems B (0.60) and E (0.36). *Anal.* ($C_7H_{11}ClN_2O_2$) C, H, Cl, N.

5-Methyl-1,5-trimethylenehydantoin (3). A 500-ml Parr hydrogenation bottle was charged with 1.7 g (0.009 mol) of 2, 8.6 g (0.09 mol) of ammonium carbonate, and 20 ml of 30% aqueous NH_3. The bottle was securely stoppered and stirred for 16 hr at a temperature of 40°. Solvent was then removed *in vacuo* and the resulting oil was dissolved in dilute HCl and applied to a strong cation exchange resin (Amberlite IRC 120, H^+ form). The column was washed with 4 *N* NH_4OH and the eluent was taken to dryness. The white solid, 0.68 g (50%), was crystallized from H_2O to give an analytical sample: mp 129–131°; ir (KBr) 3175, 3060, 1745, 1700–1675, and 1375 cm^{-1}; nmr (CD_3OD) δ 1.4 (s, 3 H, CCH_3), 2.0 (m, 4 H, CCH_2CH_2C), 3.4 (m, 2 H, NCH_2), 4.9 (s, 1 H, NH); homogenous in solvent systems A (0.64), B (0.58), and C (0.59). *Anal.* ($C_7H_{10}N_2O_2$) C, H, N.

Compound 3 was obtained in 80% yield by refluxing 2 with 2 mol of NaOMe for 3 hr and then neutralizing and extracting the cyclized product from an aqueous solution with ether.

2-Methylproline (4). A glass liner bottle for a high-pressure reaction apparatus was charged with 2 g (0.01 mol) of 2, 6.3 g (0.02 mol) of $Ba(OH)_2 \cdot 8H_2O$, and 50 ml of H_2O. The solution was shaken for 30 min at 160° and then allowed to slowly return to room temperature. The pH was adjusted to 2 with 6 *N* H_2SO_4 and after filtering the $BaSO_4$ the filtrate was applied to a strong cation exchange resin (Amberlite IRC 120, H^+ cycle). Elution with 4 *N* NH_4OH and evaporation of solvent gave 1.2 g (90%) of a white solid, mp 252–258°. Crystallization from MeOH–Et_2O gave an analytical sample: mp 263–264.5°; ir (KBr) 3450, 3200, and 1600 cm^{-1}; nmr (CD_3OD) δ 1.6 (s, 3 H, CCH_3), 1.9 (m, 4 H, CCH_2CH_2C), 3.3 (m, 2 H, $-NCH_2$); homogenous in solvent systems A (0.29), B (0.09), and C (0.14). *Anal.* ($C_6H_{11}NO_2$) C, H, N.

5-Methyl-5-(3-nitropropyl)hydantoin (5). The procedure and equipment were the same as for 1. The quantities used were 30 g (0.23 mol) of 5-nitro-2-pentanone, 96 g (1 mol) of ammonium carbonate, 12.25 g (0.25 mol) of sodium cyanide, and 450 ml of 60% EtOH. Work-up gave a 20-g (43%) crude yield of 5. Two crystallizations from absolute EtOH gave an analytical sample: mp 125–127°; ir (KBr) 3100 (br), 1750, 1700, and 1545 and 1385 cm^{-1} (NO_2); nmr (DMSO-d_6) δ 1.28 (s, 3 H, CH_3), 1.7 (m, 4 H, CCH_2CH_2C), 4.6 (t, 2 H, NCH_2), 8.0 (s, 1 H, NH), and 10.4 (s, 1 H, NH), homogenous in solvent systems A (0.70), B (0.60). *Anal.* ($C_7H_{11}N_3O_4$) C, H, N.

Reduction of 5-Methyl-5-(3-nitropropyl)hydantoin (5). A 500-ml Parr hydrogenation bottle was charged with 4 g (0.02 mol) of 5, 0.25 g of platinum oxide (Adams catalyst), and 75 ml of anhydrous methanol. The solution was shaken for 18 hr at 45 psi and room temperature. Catalyst was removed by filtration and the methanol was evaporated *in vacuo*. The resulting white solid was crystallized from a minimum amount of hot methanol to give 2.45 g (72%) of 5-(3-aminopropyl)-5-methylhydantoin (7), mp 171–174°. Recrystallization gave an analytical sample, mp 175–177°. The filtrate from the first crystallization was reduced in volume and the precipitate 6 collected, 0.32 g (9%), mp 225–227°. Recrystallization of 6 from methanol gave an analytical sample, mp 235–236°. The elemental analysis and molecular weight of 6 and 7 were identical. A reduction time of 2 hr gave 60% of 6 and none of 7. The analytical data for 6 and 7 follow. 6 had mp 235–236°; ir (KBr) 3460, 3365, 3285, 3190, 1670, 1590, and 1230 cm^{-1}; nmr (DMSO-d_6) δ 1.3 (s, 3 H, CCH_3), 1.8 (m, 4 H, $-CCH_2CH_2C$), 3.1 (m, 2 H, NCH_2-), 5.4 (s, 2 H, NH_2), 6.1 (s, 1 H, NH), 7.3 (s, 1 H, NH); mass spectrum molecular ion at *m/e* 171; homogeneous in solvent systems A (0.50), B (0.30), C (0.35). *Anal.* ($C_7H_{13}N_3O_2$) C, H, N. 7 had mp 175–177°; ir (KBr) 3250, 1575 (br), 1390 cm^{-1}; nmr (DMSO-d_6) δ 1.2 (s, 3 H, CCH_3), 1.5 (m, 4 H, CCH_2CH_2C), 2.5 (t, 2 H, NCH_2), 4.1 (br, 3 H, NH_3); mass spectrum molecular ion at *m/e* 171; homogenous in solvent systems A (0.42), B (0.14), C (0.12). *Anal.* ($C_7H_{13}N_3O_2$) C, H, N.

2-Methylornithine Sulfate (8). The hydrolysis procedure was the same as described for 2-methylproline (4). The quantities for a typical hydrolysis were 1 g (0.006 mol) of 6 or 7, 3.78 g (0.012 mol) of $Ba(OH)_2 \cdot 8H_2O$, and 50 ml of H_2O. The pH of the hydrolysis mixture was adjusted to 1.7 with H_2SO_4 and the $BaSO_4$ was removed by filtration and washed with hot H_2O. The combined filtrates were adjusted to pH 6.5 with saturated $Ba(OH)_2$ to remove excess H_2SO_4. Again the $BaSO_4$ was removed by filtration and the combined filtrates were evaporated *in vacuo*. The oily residue was redissolved in hot H_2O and crystallization was facilitated with absolute EtOH and 3 ml of dilute HCl to yield 0.73 g (50%) of product, mp 212–215°. Recrystallization gave an analytical sample: mp 216.5–217.5°; ir (KBr) 3300–2500, 1725, 1580, and 1325 cm^{-1}; nmr (D_2O) δ 1.6 (s, 3 H, $-CCH_3$), 1.95 (m, 4 H, $-CCH_2CH_2C$), 3.1 (t, 2 H, NCH_2); homogenous in solvent systems A (0.18) and C (0.05). *Anal.* ($C_6H_{16}N_2O_6S$) C, H, N, S.

Registry No. 1, 42856-68-8; 2, 42856-69-9; 3, 42856-70-2; 4, 42856-71-3; 5, 42856-72-4; 6, 42856-73-5; 7, 42856-74-6; 8 sulfate, 42856-75-7; 5-hydroxy-2-pentanone, 1071-73-4; 5-nitro-2-pentanone, 22020-87-7.

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(12) Satisfactory analytical data (±0.4%) were reported for compounds 1–8.

Photoinduced Addition of Isopropyl Alcohol to α,β-Unsaturated Lactones[1]

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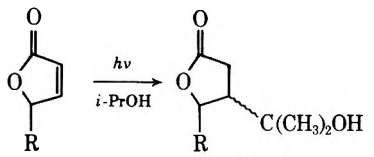
Photoinduced addition of isopropyl alcohol to the double bond adjacent to a carbonyl group has been reported of several ketones[2] and a lactone.[3] The product has been invariably found to be a β adduct. No quantitative study has been made, however, except for the case of 2-cyclopentenone,[2a] where the quantum yield for the photoinduced addition was merely estimated from disappearance of 2-cyclopentenone in dilute solution (0.01 *M*). In the present experiment, the direct excitation of α,β-unsaturated γ-lactones in isopropyl alcohol was found to afford the corresponding adducts with such high quantum yields that the reaction can be used for large-scale preparation.

When 2(5*H*)-furanone (1) in isopropyl alcohol was internally irradiated with a 30-W low-pressure mercury lamp, a single product was obtained after distillation of the



(1)

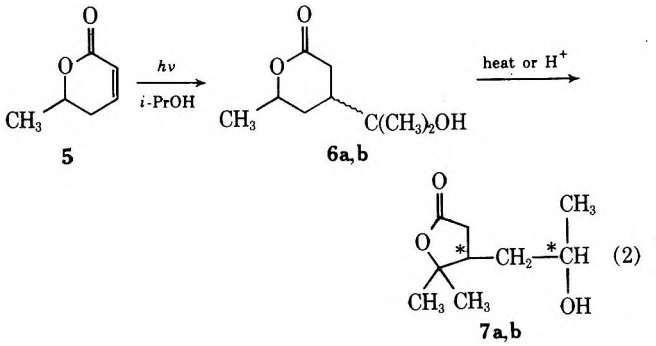
1, R = H
3, R = CH_3

2, R = H
4, R = CH_3

reaction mixture under reduced pressure. The product was identified as **2**, a photoadduct between **1** and isopropyl alcohol. Under irradiation for a few hours, 0.05 mol of **1** was transformed into **2** in 90% yield. The same type of reaction product (**4**) was obtained also on the irradiation of 5-methyl-2(5*H*)-furanone (**3**) under similar conditions.

The quantum yield for the formation of **2** from **1** was measured under the irradiation of deaerated samples with 248-nm light. The quantum yields varied with the concentration of **1** and exceeded unity in all cases. The quantum yield in Table I indicates that the reaction involves a free-radical chain, which may be initiated by the formation of a ketyl radical as a consequence of hydrogen abstraction of the photoexcited carbonyl group from isopropyl alcohol. This is analogous to the case of cyclopentenone.[2] The free-radical chain mechanism is further supported by the fact that the same addition products as above were obtained also on the thermal decomposition (75°, 45 min) of benzoyl peroxide (9×10^{-3} *M*) in isopropyl alcohol solutions of **1** and **3**.

In order to investigate whether the photoinduced addition takes place also with six-membered lactones, the isopropyl alcohol solution of 5,6-dihydro-6-methyl-2*H*-pyran-2-one (**5**) was irradiated. The rate of photochemical conversion of **5** was so low that **5** was hardly consumed even after an irradiation period in which **1** was completely transformed into **2**. At least a ten times longer irradiation period was required to obtain the photoadducts. The photoadducts were so unstable that only one of the stereoisomers (**6a**) was directly isolated (yield 16%); the formation of the other isomer (**6b**) was indicated on the basis of the fact that γ-lactone **7b** was isolated (yield 36%) as a final



(2)

product. The direct product **6a** also was easily converted into the corresponding γ-lactone (**7a**) in the presence of acid catalyst.

The same addition products were easily obtained on the thermal decomposition of benzoyl peroxide in isopropyl alcohol solution of **5** (Table II). In comparison with the thermal reaction, the extremely small yield of the photoadduct of **5** indicates that the quantum yield for hydrogen abstraction of **5** is much less than that for either **1** or **3**.

Experimental Section

Materials. 2(5*H*)-Furanone was prepared as described previously.[4] Thiele, Tischbein, and Lossows' procedure[5] was used to prepare 5-methyl-2(5*H*)-furanone. 5,6-Dihydro-6-methyl-2*H*-pyran-2-one was synthesized according to the method of Kuhn and Jerchel.[6]

Table I
Quantum Yield of 2 under Irradiation of 1 with 248-nm Light

[1] (10^{-1} *M*)	1.40	2.62	5.49	7.96
Quantum yield	30	11	5.7	2.8

Table II
Yield of the Isopropyl Alcohol Adduct of α,β-Unsaturated Lactones

Compd	Photoinduced reaction[a]	Thermal reaction induced by benzoyl peroxide[b]
1	52	59
3	35	27
5	0	12

[a] Irradiation time, 10 min. [b] Reaction time, 45 min.

Irradiation in Preparative Scale. An isopropyl alcohol solution (100–300 ml) of α,β-unsaturated lactone (0.04–0.18 *M*) was internally irradiated under a nitrogen stream with a 30-W low-pressure mercury immersion lamp (Riko-Sha UVL-303Q).

Determination of Quantum Yields. The light source was a Ushio 500-W super-pressure mercury arc lamp (USH-500D). The 248-nm band was isolated with a Hitachi Model EPU-2A spectrometer (quartz prism, half-height width 4 mμ). The beam of the monochromatic light was divided into two portions by the use of an optically flat quartz plate tilted by 45° with respect to the light beam. The transmitted light (3.6×10^{14} quanta/sec) was used to irradiate the sample, and an actinometer cell, containing ferrioxalate solution, was irradiated by the light reflected perpendicular to the transmitted light (approximately 10% of the intensity of the transmitted light). Pure isopropyl alcohol for fluorescence spectroscopy was used to prepare sample solutions, which were degassed by the freeze–thaw technique and were successively transferred into a cylindrical cell (20 × 10 mm) *in vacuo* (less than 10^{-4} mm). Irradiations were carried out at a constant temperature (30.0 ± 0.1°) to less than 5% conversion. The amounts of adducts were determined against an internal reference (benzophenone) by the use of a Shimadzu GC-2C chromatograph equipped with a thermal conductivity detector. Analysis was performed with a column (2.25 m × 3 mm) packed with 10% polyphenyl ether (five rings) on Chamelite CS 60/80. The column temperature was 180°, and the carrier gas was hydrogen.

Determination of Relative Reactivity between the Unsaturated Lactones. Each set of sample tubes containing the appropriate solution (~10^{-1} *M*) was either externally irradiated or kept at 75°, depending on the purpose of the experiment, for a given period of time. Then the amount of isopropyl alcohol adduct in each sample tube was determined by measuring the area under the peak of the corresponding proton signals.

4-(1′-Hydroxy-1′-methylethyl)-4,5-dihydro-2(3*H*)-furanone (2). Distillation of the irradiated sample under reduced pressure afforded pure **2** as a viscous liquid: bp 139–140° (3 mm); ir (neat) 3400 (broad), 1783 (s), 1775 (shoulder), 1180 cm^{-1} (broad); nmr (in benzene) δ 0.96 (s, 6 H), 1.8–2.7 (m, 3 H), 2.92 (s, 1 H), 2.8–4.4 (m, 2 H). The nmr signals of methylene protons adjacent to the ethereal oxygen atom of **2** in KOD–D_2O solution split into an octet, which indicates that the geminal protons are in nonequivalent electromagnetic circumstances ($\Delta\nu_{AB}$ = 9.8, J_{AB} = 11.0 Hz) and both of the protons are coupled to a methine proton (J_{AC} = 5.5 and J_{BC} = 5.0 Hz). On the basis of this evidence, β-adduct structure was assigned to **2**. Treatment of **2** with 3,5-dinitrobenzoyl chloride in pyridine at 70° afforded the 3,5-dinitrobenzoate in 88% yield: mp 135–136° from methanol; ir (KBr) 1775 (shoulder), 1765 (s), 1717 (s), 1545 (s), 1347 (s), 1295 (s), 1178 (s), 1121 cm^{-1} (s); nmr ($CDCl_3$) δ 1.78 (s, 6 H), 2.5–3.5 (m, 3 H), 4.4–4.7 (m, 2 H), 9.0–9.3 (m, 3 H).

Anal. Calcd for $C_{14}H_{14}O_8N_2$: C, 49.71; H, 4.17; N, 8.25. Found: C, 49.89; H, 4.23; N, 8.26.

4-(1′-Hydroxy-1′-methylethyl)-5-methyl-4,5-dihydro-2(3*H*)-furanone (4). The sample was easily purified by distillation under reduced pressure: bp 144–145° (5 mm); ir (neat) 3500 (broad), 1755 (s), 1777 (shoulder), 1190 cm^{-1} (s); nmr (in benzene) δ 0.99 (s, 6 H), 1.19 (d, J = 6.0 Hz, 3 H), 1.4–2.7 (m, 3 H), 2.80 (s, 1 H), 4.55 (dq, $J_1 = J_2$ = 6.0 Hz, 1 H). The nmr signals of

the methine proton adjacent to the oxygen atom of **4** in KOD-D_2O solution was found to be a doublet (J_1 = 1.8 Hz) of quartets (J_2 = 6.5 Hz). As a result of a decoupling experiment, J_1 was found to correspond to the vicinal coupling between the two methine groups in agreement with the assignment of β-adduct structure to **4**. Analogously to the case of **2**, the 3,5-dinitrobenzoate of **4** was obtained in 83% yield: mp 140–143° from methanol; ir (KBr) 1781 (s), 1721 (s), 1550 (s), 1347 (s), 1292 (s), 1179 (s), 1120 cm^{-1} (m); nmr ($CDCl_3$) δ 1.51 (d, 3 H), 1.73 (s, 6 H), 2.3–3.1 (m, 3 H), 4.80 (dq, J_1 = 6.6, J_2 = 2.8 Hz, 1 H), 9.0–9.3 (m, 3 H).

Anal. Calcd for $C_{15}H_{16}O_8N_2$: C, 51.14; H, 4.58; N, 7.95. Found: C, 51.12; H, 4.57; N, 8.09.

Isopropyl Alcohol Adducts of 5,6-Dihydro-6-methyl-2*H*-pyran-2-one. By the use of silica gel chromatography (eluent, benzene–ethyl acetate mixture in 1:1 ratio by v/v), two adducts were separated from the reaction mixture, **7b** (yield 36%) and **6a** (yield 16%). On the basis of both the spectroscopic and chemical evidences described below, **6a** and **7b** were concluded to be δ- and γ-lactone, respectively.

A. γ-Lactone 7b was a viscous liquid: ir (neat) 3440 (broad), 1760 (broad), 1273 cm^{-1} (broad); nmr (in benzene) δ 0.95 (s, 3 H), 1.22 (s, 3 H), 1.10 (d, J = 6.2 Hz, 3 H), 0.8–2.8 (m, 5 H), 2.99 (s, 1 H), 3.2–3.8 (m, 1 H); nmr ($CDCl_3$) δ 1.24 (d, J = 6.2 Hz, 3 H), 1.25 (s, 3 H), 1.45 (s, 3 H), 1.3–1.7 (m, 2 H), 1.7–3.0 (m, 3 H), 2.74 (s, 1 H), 3.5–4.1 (m, 1 H). The frequency of the carbonyl absorption band corresponds to those of saturated γ-lactones. As to the nmr spectra, we observe two singlet signals which correspond to three protons, respectively: the difference in chemical shifts between the two signals is as large as 0.2 ppm in both benzene and deuteriochloroform. It is suggested then that there are two highly nonequivalent methyl groups. In addition, the benzene-induced shifts for these singlets are much larger than that for the doublet (1.10 ppm in benzene) which is assigned to the methyl protons coupled to an adjacent methine proton. These facts are in good agreement with the proposed structure **7b**, but not with **6b**. Finally, the hydroxyl proton signal of **7b** splits into a doublet (J = 4.9 Hz), when the acetone solution is cooled down below −10°. Therefore, a secondary hydroxyl group must be involved in **7b**. The structure of **7b** is thus deduced. The corresponding 3,5-dinitrobenzoate was obtained by the usual method in 93% yield: mp 180–181° from methanol; ir (KBr) 1767 (s), 1756 (shoulder), 1726 (s), 1544 (s), 1347 (s), 1279 (s), 1173 (m), 1133 cm^{-1} (m); nmr ($CDCl_3$) δ 1.31 (s, 3 H), 1.48 (s, 3 H), 1.51 (d, J = 6.0 Hz, 3 H), 1.2–2.9 (m, 5 H), 5.0–5.5 (m, 1 H), 9.0–9.3 (m, 3 H).

Anal. Calcd for $C_{16}H_{18}O_8N_2$: C, 52.47; H, 4.95; N, 7.65. Found: C, 52.52; H, 4.94; N, 7.45.

B. δ-Lactone 6a was a viscous liquid: ir (neat) 3510 (broad), 1729 (s), 1254 cm^{-1} (broad); nmr (in benzene) δ 0.98 (s, 6 H), 1.09 (d, J = 6.2 Hz, 3 H), 0.9–2.5 (m, 5 H), 2.46 (s, 1 H), 3.5–4.2 (m, 1 H). The proton signals of **6a** in $CDCl_3$ gradually disappear and new sets of signals arise in return. Then a benzene solution of **6a** was prepared and a very small amount of dry hydrogen chloride was bubbled into the solution. This treatment completed the transformation from **6a** into the new compound **7a**, which was easily recovered by purging the solvent with a nitrogen stream.

C. γ-Lactone 7a was recrystallized from *n*-hexane–benzene mixture: mp 122.5–123.5°; ir (KBr) 3250 (shoulder), 3400 (broad), 1761 (s), 1747 (shoulder), 1275 (m), 1262 (s), 1122 (s), 1103 cm^{-1} (s); nmr ($CDCl_3$) δ 1.23 (d, J = 6.3 Hz, 3 H), 1.25 (s, 3 H), 1.45 (s, 3 H), 1.3–1.7 (m, 2 H), 1.7–2.9 (m, 3 H), 2.68 (s, 1 H), 3.38 (tq, $J_1 = J_2$ = 6.3 Hz, 1 H). The structure of multiplets with a pair of prominent peaks around 2.5 ppm is clearly different from the corresponding multiplets of **7b** in which a single, sharp peak is observed at 2.5 ppm. The hydroxyl proton signal of **7a** also splits into a doublet (J = 4.8 Hz) when the acetone solution is cooled down. In vpc analyses, there is a small but clear difference in retention time between **7a** and **7b** so that a pair of slightly overlapping peaks are observed when both of the compounds are injected into the column at the same time.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.88; H, 9.66.

Registry No. **1**, 497-23-4; **2**, 42867-48-1; **2** 3,5-dinitrobenzoate, 42867-49-2; **3**, 591-11-7; **4**, 42867-50-5; **4** 3,5-dinitrobenzoate, 42867-51-6; **5**, 108-54-3; **6a**, 42867-52-7; **6b**, 42867-53-8; **7a**, 42867-54-9; **7b**, 42867-55-0; **7** 3,5-dinitrobenzoate, 42867-56-1; isopropyl alcohol, 67-63-0; 3,5-dinitrobenzoyl chloride, 99-33-2.

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Synthesis of Hydroxycitronellal. Hydration and Subsequent Hydrolysis of Imines, Enamines, or Oxazolidines Prepared from Citronellal and Amines

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Hydroxycitronellal (**4**), one of the most widely used synthetic perfumery materials, has been prepared from citronellal (**1**) by the hydration of citronellal bisulfite (**2**) in sulfuric acid and the subsequent hydrolysis with alkali (course A in Scheme I).[1] The process, however, is accompanied by the liberation of **1** from the adduct **2** and the cyclization of **1** to isopulegol (**5**), which is further hydrated to menthoglycol (**6**), as shown in Scheme I (course B).[2] Consequently, the yield of **4** is very poor.

The hydration of olefinic compounds to alcohols generally proceeds very fast in strong acidic media,[3] whereas the hydrolyses of some aldehyde–amine adducts, *i.e.*, imines,[4] oxazolidines,[5] and enamines,[6] have been reported to be relatively slow in strong acidic media and fast in weak alkaline solutions or in water. Imines and enamines have been used for protecting aldehyde grouping in the related citral system where sulfuric acid has been used for generating a carbonium ion to induce cyclization.[7] Thus, these amine adducts should be useful intermediates for protecting the aldehyde group of **1** in strong acid in order to prevent the side reaction shown in Scheme I (course B).

We have found a synthetic route to **4** which is superior in yield as well as in simplicity to the conventional method (Scheme II).[8]

Reactions of **1** with five primary amines gave the imines **7–10** and **18** (Table I). In the crude products prepared from **1** and ethanolamine, the presence of an oxazolidine derivative[9] as well as **8** was noticed from the newly observed νC–O–C band at 1020 cm^{-1} and the decreased absorption at 1060 cm^{-1} attributable to primary OH. The relatively great value (1669 cm^{-1}) of νC=N absorption in **9** suggests that the tautomerism described below does not take place.

$$C_6H_5CH_2N{=}CH{\sim} \rightleftharpoons C_6H_5CH{=}NCH_2{\sim}$$

The isolation of **10** and **18** by means of distillation resulted in the formation of undesirable resinous materials. Therefore, the crude adduct **18** was used for the synthesis of **4**.

Five enamines, **11–15**, were derived from aliphatic secondary amines (Table II). From two aliphatic secondary amines substituted with one or two 2-hydroxyethyl

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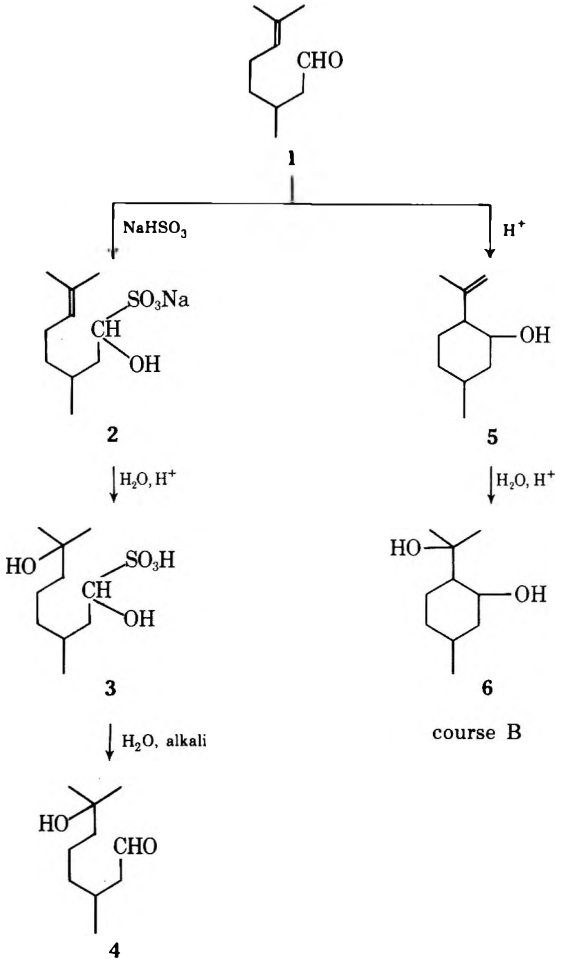
Table I
Imines Derived from Citronellal and Amines

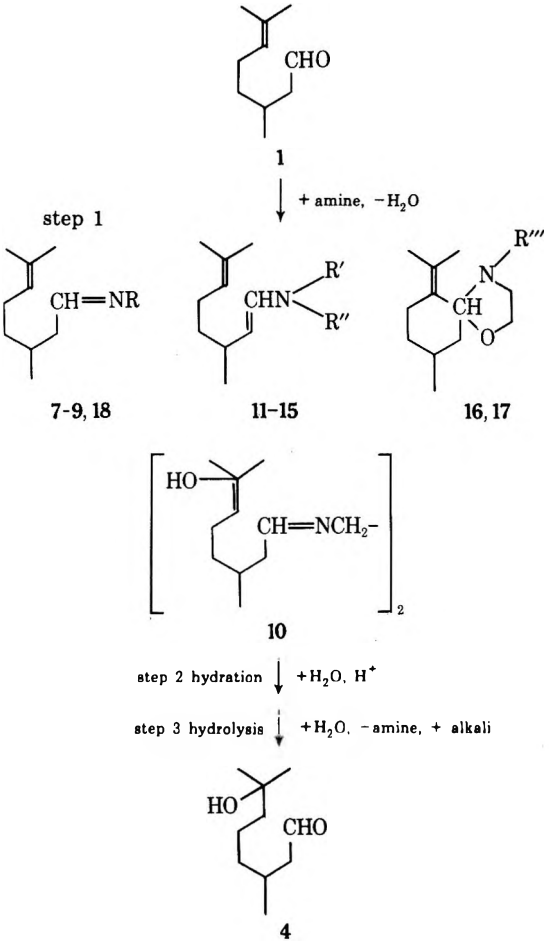
Compd	Applied amine	Yield, %	Bp, °C (mm)	Ir (film), cm⁻¹ C=N	Ir (film), cm⁻¹ Primary OH	Uv (C_6H_{12}), nm (ε)	Mass (80 eV), m/e M⁺	Mass (80 eV), m/e Others[d]
7	Methylamine	93	61 (1.5)	1677		231 (3.9 × 10²) (-CH=NCH₃)[b]	167	
8	Ethanolamine	58	94 (1.5)	1670	3300, 1060		197	166, 87, 69
9	Benzylamine	84	139 (3.0)	1669			243	
10	Ethylenediamine	60	170 (1.5)	1670			332	166, 69
18[a]	Aniline			1650		235 (6.1 × 10³) (-CH=NC₆H₅)[c]		

[a] A mixture of **18** and **1** (*ca.* 90 and *ca.* 10% by glpc) was employed for spectral analyses. [b] R. Bonnett, *J. Chem. Soc.*, 2313 (1965). [c] R. Bonnett in "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Interscience, New York, N. Y., 1970, p 49. [d] $(CH_3)_2C{=}CHCH_2\{CH_2CH(CH_3)CH_2CH{=}NCH_2\{CH_2OH$ (69 / 166).

Scheme I



Scheme II



7, R = CH_3
8, R = $(CH_2)_2OH$
9, R = $CH_2C_6H_5$
18, R = C_6H_5

11, R′ = R″ = CH_3
12, R′ = R″ = $(CH_2)_3CH_3$
13, R′, R″ = $-(CH_2)_5-$
14, R′, R″ = $-(CH_2)_2O(CH_2)_2-$
15, R′ = CH_3; R″ = $-(CH_2)_3NH_2$
16, R‴ = $(CH_2)_2OH$
17, R‴ = CH_3

groups, however, oxazolidines **16** and **17** were obtained (Table III). When *N*-methylaminopropylamine was allowed to react with **1**, not the primary but the secondary amino group was found to react.

The citronellal–amine adducts **7–18**, crude or isolated, were hydrated[10] and the subsequent hydrolysis at neutral pH gave excellent yields of **4** from any of the isolated compounds **11–17**, although accompanied by minor amounts of **5** and **6** (Table IV). This proves that the enamines and oxazolidines are excellent intermediates in protecting the aldehyde group of **1** in strong acidic media. The imines **7–10** are also effective for preventing the cyclization of **1** in the same media; however, only Schiff base **18** gave a large amount of resinous materials. It is noticeable that the yield of **4** from the crude ethanolamine adduct (72%) was found to be greater than that from the isolated **8** (50%). This is attributable to the presence of some oxazolidine derivative as well as **8** in the crude adduct.

From (+)-**1** ($[\alpha]^{20}D$, +8.1°), (+)-**4** ($[\alpha]^{20}D$ +9.8°), which has been recognized as the enantiomer having the desired olfactory properties,[11] was produced by the present practical method.

Experimental Section

Infrared spectra were run with a Nihonbunko ir spectrophotometer, Model IR-S. Nuclear magnetic resonance spectra were taken at 60 MHz with a Nihondenshi nmr spectrometer, JMN C-60, using tetramethylsilane as an internal standard. Ultraviolet spectra were determined at 25° in cyclohexane with a Hitachi spectro-

Table II
Enamines Derived from Citronellal and Amines

Compd	Applied amine	Yield, %	Bp, °C (mm)	Ir (film), cm⁻¹: −CH=CH−, trans	Ir (film), cm⁻¹: C−N	Ir (film), cm⁻¹: −NH₂	Uv (C_6H_{12}), nm (ε) −CH=CHN<[a]	Nmr (CCl_4), δ H_a[b]	Nmr (CCl_4), δ H_c[b]	Mol wt (C_6H_6) (calcd)
11	Dimethylamine	80	117 (27)	1655, 935	1070		229 (6.0 × 10³)	5.77	3.99	188 (181.3)
12	Dibutylamine	66	126 (3.5)	1650, 935	1100			5.75	4.23	
13	Piperidine	90	126 (5.5)	1653, 935	1100		228 (8.3 × 10³)	5.65	4.23	226 (221.4)
14	Morpholine	90	132 (5.5)	1653, 935	1120		225 (7.6 × 10³)	5.88	4.41	207 (223.4)
15	*N*-Methylamino-propylamine	54	110 (2.0)	1655, 935	1100	735				217[c] (224.4)

[a] N. J. Leonard and D. M. Locke, *J. Amer. Chem. Soc.*, **77**, 437 (1955). [b] >CHCH$_b$=CH$_a$N< (trans); signals of H_a and H_b appeared as d, 1, J = 14 Hz, and q, 1, J = 8.3 and 14 Hz, respectively. [c] Solvent was methyl ethyl ketone.

Table III
Oxazolidines Derived from Citronellal and Amines

Compd	Applied amine	Yield, %	Bp, °C (mm)	Ir (film), cm⁻¹: C−O−C	Ir (film), cm⁻¹: Primary OH	Nmr (CCl_4),[a] δ
16[b,d]	Diethanolamine	95	161 (5)	1020	3400, 1050	3.40–2.90 (m, 1, H_a)[c] 2.85–2.40 (m, 3, H_b and H_e)[c] 3.97–3.70 (t, 2, J = 6.8 Hz, H_c) 3.75–3.50 (q, 2, H_f) 4.24–4.05 (t, 1, J = 5 Hz, H_d) 3.04 (21°) or 2.14 (100°) (s, 1, H_g)
17[b]	*N*-Methylethanolamine	95	96 (4)	1020		3.33–2.88 (m, 1, H_a)[c] 2.74–2.33 (m, 1, H_b)[c] 3.95–3.71 (m, 2, H_c) 3.95–3.85 (t, 1, H_d) 2.31 (s, 3, H_h)

[a] R‴ = −CH$_{e2}$CH$_{f2}$OH$_g$ or −CH$_{h3}$. See i. [b] Uv (C_6H_{12}) no absorption at 210–360 nm. [c] J. B. Lambert and R. G. Keske, *J. Amer. Chem. Soc.*, 88, 620 (1966). [d] Mol wt (C_6H_6) 238 (calcd, 241.4).

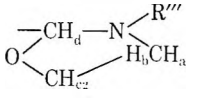


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Table IV
Products of Hydration and Subsequent Hydrolysis of Citronellal–Amine Adducts

Substrate Citronellal–amine adduct	Yield, % (mol/100 mol substrate): Hydroxycitronellal	Citronellal and isopulegol	*cis*- and *trans*-Menthoglycol
7	72	2	10
8	87[a] (72)[b]	2 (3)[b]	3 (8)[b]
9	50	3	10
10	80	6	20
11	85 (77)[b]	2 (2)[b]	5 (14)[b]
12	85	2	5
13	90	2	0
14	95	2	0
15	95	2	0
16	95 (88)[b]	3 (3)[b]	0 (11)[b]
17	85	2	0
18	(0)[b]	(15)[b]	(10)[b]

[a] The yield based upon citronellal employed is 50%. [b] Crude citronellal–amine adducts were used and yields (mol/100 mol citronellal) are listed.

photometer, Model EPS-2. Mass spectra were measured with a Hitachi mass spectrometer, Model RMS-4. Molecular weights were determined in benzene or methyl ethyl ketone with a vapor pressure osmometer, Model 301-A, Mechrolab, Inc. Gas chromatography was carried out with a Kotaki Super Fractioner, Model GU-21, equipped with a column containing 15% Reoplex on Celite 545 SK (40–60 mesh) at 180°.

Materials. Citronellal [bp 64° (5.5 mm)], citronellol [bp 104° (10 mm)], and hydroxycitronellal [bp 110° (5.5 mm)] (given by Ogawa Koryo Co., Ltd.) were more than 99% pure (by glpc). *cis*- and *trans*-Menthoglycols were prepared from citronellal in 5% sulfuric acid according to the method of Zimmerman.[12] All amines (G.R. grade) were used as received.

Preparation of Citronellal–Amine Adducts. An amine (0.1 mol) was added to 1 (15.4 g, 0.1 mol) over a period of 3 min with stirring. The temperature was kept between 15 and 25° on a water–ice bath and additional stirring was continued for 30 min. Centrifuging yielded an oily layer, which was distilled, and the fraction of imine, enamine, or oxazolidine (7–18) was obtained.

Hydration of Citronellal–Amine Adducts and the Subsequent Hydrolysis to Hydroxycitronellal (4). To 50% (v/v) sulfuric acid (34 ml) cooled at 7° on a water–ice bath, a citronellal–amine adduct (0.1 mol) was added drop by drop over a period of 2 min below 30° with vigorous stirring. Further stirring was continued for 2 min at 25–30°. Then the sulfuric acid solution was poured into a mixture of a saturated aqueous NaCl solution (500 ml), benzene (50 ml), NaOH (24 g), and crushed ice (200 g) below 15°. Then the pH of the solution was adjusted to the range 6.5–7.0 with dilute aqueous $NaHCO_3$ or H_2SO_4. The benzene layer was separated and the aqueous portion was extracted twice with benzene (50 ml). The combined benzene extracts were washed with a saturated NaCl solution (3 × 20 ml) and the benzene was distilled off at 40° *in vacuo*. The oil obtained was analyzed by glpc using 1,3-propanediol as an internal standard, and the amounts of hydroxycitronellal (4), citronellal (1), isopulegol (5), and *cis*- and *trans*-menthoglycols (6) were determined.

Acknowledgment. We wish to thank Ogawa Koryo Co., Ltd., for supplying citronellal, hydroxycitronellal, and citronellol and determinations of optical rotation.

Registry No. 1, 106-23-0; **4**, 107-75-5; **5**, 89-79-2; **6**, 42822-86-6; **7**, 42822-87-7; **8**, 42822-88-8; **9**, 42822-89-9; **10**, 42822-90-2; **11**, 42822-91-3; **12**, 42822-92-4; **13**, 1723-79-1; **14**, 42822-94-6; **15**, 42822-95-7; **16**, 42822-96-8; **17**, 42822-97-9; **18**, 42822-98-0.

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(10) Citronellol was utilized to find the optimum conditions for hydration of the C=C bond of **1** in sulfuric acid solution. The maximum yield (95%) of hydroxycitronellol was obtained under the conditions of 50% (v/v) sulfuric acid with a molar ratio (H_2SO_4:citronellol) of 2.5:1 around 27° within 5 min.
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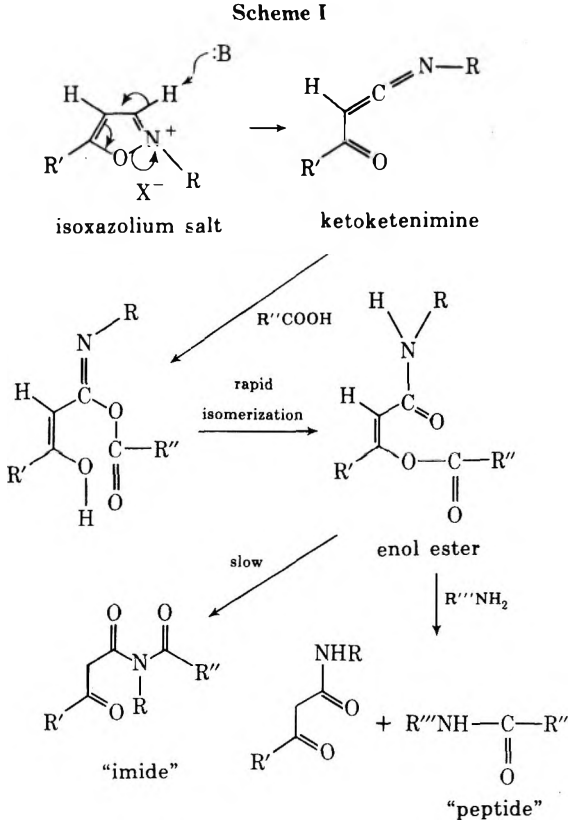
Communications

A Facile Conversion of Carboxylic Acids to Carbinols under Mild Conditions[1]

Summary: Enol ester derivatives, produced upon treatment of carboxylic acids with *N*-ethyl-5-phenylisoxazolium 3′-sulfonate, afford carbinols upon reduction with sodium borohydride in aqueous solution.

Sir: In a reinvestigation of isoxazolium salts, originally reported by Otto Mumm,[2] Woodward and coworkers[3-5] showed that a number of 3-substituted isoxazolium salts react with carboxylic acids in the presence of a base to yield enol ester derivatives which are useful acylating agents, especially in peptide synthesis. The principal features of this chemistry are indicated in Scheme I.

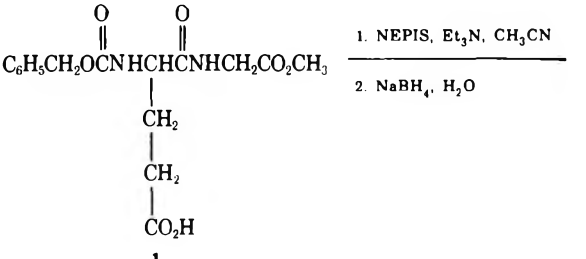
Scheme I



In conjunction with our studies on the catalytic roles of carboxyl groups in the active sites of enzymes, we required a means by which such carboxyl groups could be reduced to carbinol groups. Clearly, the conventional methods employing lithium aluminum hydride or sodium borohydride–aluminum chloride could not be employed for protein modification in aqueous solution. However, recent reports on the use of Woodward's isoxazolium salts in aqueous solution to activate carboxyl groups in enzymes toward attack by various nucleophilic reagents[6-8] suggested that perhaps activation of such carboxyl groups toward reduction by aqueous sodium borohydride might be similarly achieved. The preliminary investigations reported here show that such is indeed the case.

Enol ester derivatives of the acids in Table I were prepared essentially as described by Woodward, *et al.*,[5] using *N*-ethyl-5-phenylisoxazolium 3′-sulfonate[9] (NEPIS) with triethylamine as the derivatizing agent in acetonitrile solution at room temperature. The crude enol esters were then freed of solvent *in vacuo*, dissolved in water, and treated with a 10-fold molar excess of sodium borohydride.[10] Carbinol yields (Table I) varied from 40 to 100%.

The peptide derivative **1** (*O*-methyl *N*-benzyloxycarbonyl-α-L-glutamylglycinate) was prepared as a model substrate to test the applicability of our reduction proce-



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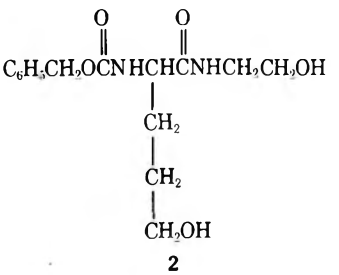

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Table I
Conversion of Carboxylic Acids to Carbinols by NEPIS Activation in Acetonitrile Followed by Sodium Borohydride Reduction in Water

Acid	Carbinol	Method[a]	Yield, %
CH_3COOH	CH_3CH_2OH	A	90[b]
C_6H_5COOH	$C_6H_5CH_2OH$	A	94[b]
$CH_3CH_2CH_2COOH$	$CH_3(CH_2)_3OH$	A	100[b]
$CH_3(CH_2)_{15}COOH$	$CH_3(CH_2)_{16}OH$	B	50[c]
$CH_2{=}CHCOOH$	$CH_3CH_2CH_2OH$	A	100[b]
$HSCH_2COOH$	$HSCH_2CH_2OH$	A	80[b]
$C_2H_5O_2C(CH_2)_4COOH$	$C_2H_5O_2C(CH_2)_5OH$	B	71[d]
$(C_6H_5)_2CHCOOH$	$(C_6H_5)_2CHCH_2OH$[e]	B	40[f]

[a] See Experimental Section for detailed description of the methods employed.[12] [b] Identification and quantitation by comparison of glpc chromatograms of product mixtures with those of standard solutions of authentic carbinols. [c] Isolated yield, mp 48–49° [mp 49°: S. G. Ford and C. S. Marvel, *Org. Syn.*, **10**, 62 (1930)]. Micelle formation made extraction of this carbinol from the aqueous product mixture extremely inefficient and may account in part for the low isolated yield. [d] Isolated yield, $n^{24}D$ 1.4276 [$n^{24}D$ 1.4275: R. Huisgen and J. Reinertshober, *Justus Liebigs Ann. Chem.*, **575**, 174 (1952)]. [e] Accompanied by *N*-ethyl-α,α-diphenylacetamide (35% yield) identified by ir, nmr, and mass spectrum (*m/e* 237) and mp 134–135° [mp 134.5–135.5°: D. B. Limaye and T. B. Pause, *Rasayanam*, **2**, 32 (1950)]. [f] Isolated oil had identical glpc retention time and tlc R_F value as authentic 2,2-diphenylethanol, mp 58–59° [mp 59°: P. S. Hammick, Jr., and C. R. Hawser, *J. Org. Chem.*, **26**, 4199 (1961)], prepared from diphenylacetic acid by the method of N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).

dure to free carboxyl groups in peptides or proteins. Compound **1** was synthesized according to a published procedure for the corresponding ethyl ester.[11] The two-step reduction procedure (method A; see Experimental Section)[12] gave the diol derivative **2**[13] in 50% yield. The free γ-carboxyl function of the glutamyl residue was reduced as expected. The concomitant reduction of the carboxyl-terminal methyl ester linkage of **1** finds ample precedent in the work of Yonemitzu, *et al.*,[14,15] in which it was determined that carboxylic esters having an α-amino function are subject to reduction by sodium borohydride. We in fact confirmed this with our finding that a direct reduction of **1** using aqueous sodium borohydride under the conditions employed to effect the second step in the production of **2** afforded a clean selective reduction of the terminal methyl ester group and was without effect upon the free carboxyl group, the peptide linkage, or the benzyloxycarbonyl moiety of **1**. It should be noted, however, that simple esters which are not activated by the presence of an electron-withdrawing substituent in the α position are not subject to reduction by aqueous sodium borohydride. Thus, treatment of ethyl heptanoate with $NaBH_4$ under the conditions employed in this investigation for the reduction of enol ester derivatives resulted in 96% recovery of the original ester. Also, in the reduction of monoethyl adipate (Table I) the ethyl ester function was not reduced during conversion of the free carboxyl group to the carbinol.

Finally, the low yield of carbinol realized in the reduction of diphenylacetic acid (Table I) and the finding that the 2,2-diphenylethanol produced in this reduction was accompanied by a roughly equivalent yield of *N*-ethyl-α,α-diphenylacetamide suggest that the reduction of NEPIS enol esters may not always be so straightforward as originally envisaged. As shown in Scheme I, the enol esters derived from carboxylic acids by treatment with isoxazolium salts are subject to isomerization *via* an O- to N-acyl shift to give the imide. This isomerization is accelerated by bases[3] and, under the alkaline conditions which accompany aqueous $NaBH_4$, imide formation might be quite rapid. Thus isomerization would be expected to compete to some extent with direct reduction of the enol ester by $NaBH_4$, especially when borohydride attack is sterically hindered as would be the case for the NEPIS enol ester of diphenylacetic acid. The imide products of base-catalyzed isomerization may themselves be subject to reduction by $NaBH_4$. Borohydride reductions of cyclic imides are known,[16-19] with borohydride attack directed preferentially to the less hindered carbonyl group, giving rise to an amide and a carbinol. This would account for the observed amide production which was found to accompany 2,2-diphenylethanol formation in our attempted reduction of diphenylacetic acid.

Experiments directed toward a more definitive elucidation of the chemistry presented in this communication and toward its application in the reduction of carboxyl groups in proteins and carbohydrates are currently in progress. The procedures described here may also find application in general organic synthesis involving the reduction of carboxyl groups in multifunctional compounds which will not tolerate the reagents and conditions conventionally employed in carboxyl group reductions.

Supplementary Material Available. The experimental procedures used in this investigation 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 Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-111.

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(13) Compound **2**: mp 95–96°; ir (KBr pellet) 330 (doublet), 1240, 1650, 1550, 1280, 1180, 1060 cm^{-1}. *Anal.* Calcd for $C_{15}H_{22}N_2O_5$: C, 58.00; H, 7.09; N, 9.03. Found: C, 57.67; H, 7.45; N, 9.02.
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Total Synthesis of a γ-Carboxymethyltetronic Acid. (*S*)-Carlosic Acid

Summary: The first total synthesis of a naturally occurring mold tetronic acid with correct absolute configuration is described, as well as a possible biogenetic precursor for the entire family.

Sir: In recent biosynthetic studies,[1] we demonstrated that carlosic acid (**1**) was the major precursor of (*R*)-carolic acid (**2**) in *Penicillium charlesii*. We noted that no synthetic work had been done on any of the mold tetronic acids bearing the γ-carboxymethyl substituent. Furthermore, the reported total syntheses in the γ-methyl series, *viz.*, (±)-carolic acid[2] and (±)-carolinic acid,[3] were not applicable to either work with chiral compounds or isotopic labeling.[4] This communication describes the first example of a total synthesis of a mold tetronic acid in its correct absolute configuration and incorporates all of the desirable features described above.

The key step in the synthesis involved the cyclization of **3**, which was formed in 80% yield from dimethyl (*S*)-malate and diketene (Et_3N catalyst, PhH). The nmr spectrum of **3** was similar to the starting ester. In addition to the malate moiety [δ 3.67 (3 H, s, ester), 3.72 (3 H, s, ester), 2.90 (2 H, d, J = 6 Hz, methylene), and 5.47 (1 H, t, J = 6 Hz, methine)], new signals appeared at δ 2.25 (3 H, s, acetyl) and 3.50 (2 H, s, methylene) ($CDCl_3$) for the acetoacetyl group. Compound **3** was very thermolabile, and had to be purified by chromatographic means (alumina). The cyclization of **3** to **4** had to be carried out at a low temperature; otherwise mainly dimethyl fumarate was obtained (with concomitant loss of CO_2 and acetone). Treatment of **3** with *t*-BuOK in *t*-BuOH at the freezing point effected a 39% yield of **4** in which the acetoacetyl methylene signal and the ester signal at δ 3.72 were no longer present. In addition to nmr signals at δ 2.38 (3 H, s, acetyl), 3.67 (3 H, s, ester), 2.72 (2 H, m, methylene), and 4.57–4.75 (1 H, m, methine), a new signal appeared at δ 8.42 (1 H, s, enol) ($CDCl_3$). The bromination of **4** to **5** had to be carried out rapidly owing to the sensitivity of the ester function to HBr liberated by the reaction. Compound **5** had a similar nmr spectrum to **4** except for loss of the acetyl signal (δ 2.38) (DMSO-d_6). Its structure was confirmed by conversion to the free carboxylic acid which had been obtained from carlosic acid by degradation.[5] The catalytic reduction of **5** to **6** [which had a nmr similar to **5** except for the appearance of a new signal at δ 4.99 (1 H, s, vinylic) ($CDCl_3$ + 5% DMSO-d_6)] was carried out similarly to that for α-bromo-(*S*)-γ-methyltetronic acid.[6]

Excepting the cyclization, all synthetic yields were in the 70–80% range. Elementary analyses and spectral data for all of the above compounds were in agreement with the assigned structures.

Since our biosynthetic studies[1] seemed to indicate that *P. charlesii* contained a relatively nonspecific biological acylation system, the compound **6** represents a potential intermediate in both the biosynthesis (as the free acid) and synthesis of carlosic acid (**1**), carlic acid (**7**), and viridicatic acid (**8**). In the specific instance of carlosic acid (**1**), treatment of **6** with butyryl chloride, $TiCl_4$, and $PhNO_2$ gave the ester **9**, which was converted by gentle saponification to **1**. The **1** thus obtained was identical in all respects with the natural product. The application of intermediate **6** to the synthesis of **7** and especially **8** should be straightforward. Our present work allows specific isotopic labeling of **9** or **1** *via* use of PrC*OCl, which is available with either ^{14}C or ^{13}C label as shown.

A full account will be given of this work upon completion.

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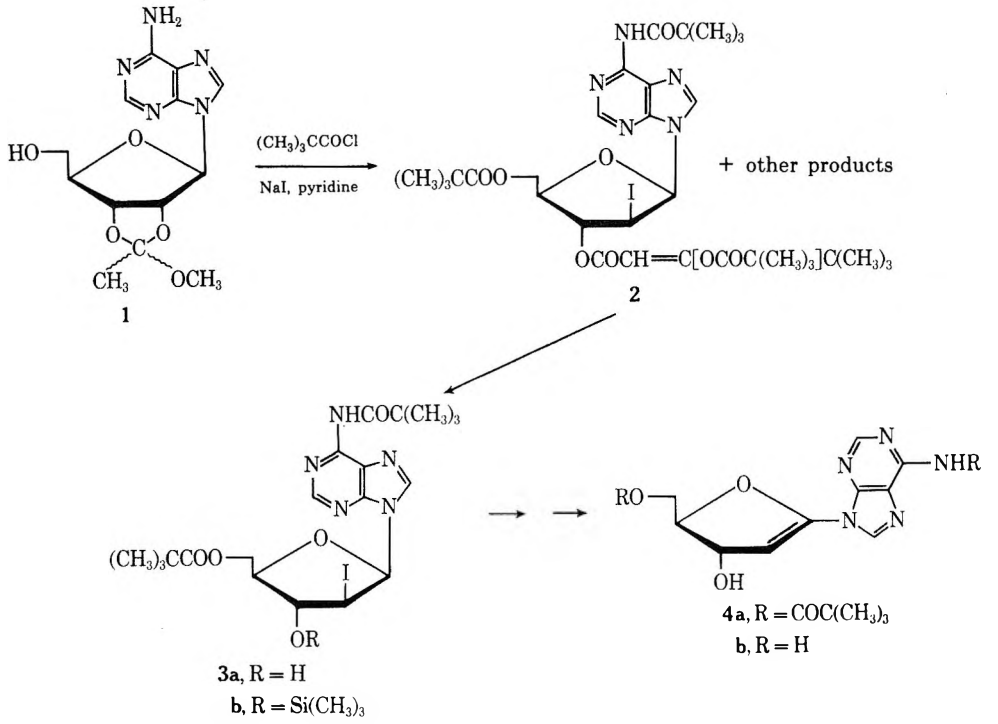
Nucleic Acid Related Compounds. 9. The Synthesis of 6-Amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)-purine, the First 1′,2′-Unsaturated Purine Nucleoside[1,2]

Summary: Adenosine has been transformed into 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine (**4b**) by elimination of hydrogen iodide from a suitably blocked 2′-iodo derivative, and hydrogenation of **4b** completes the conversion to α- and β-2′-deoxyadenosines.

Sir: Access into unsaturated pentofuranosyl nucleosides including the 2′,3′,[3] 3′,4′,[4] and 4′,5′[5] olefinic systems has been reported. However, no authenticated 1′,2′-unsaturated purine nucleoside has been described, although the antibiotic augustmycin A (decoyinine)[6] was originally assigned this structural feature.[7] It has been considered that biological transformation of ribo nucleosides to their 2′-



deoxy counterparts might involve 1′-ene intermediates.[8] The finding that only one deuterium is incorporated completely stereoselectively into the 2′-ribo configuration of the 2′-deoxy nucleotides upon reductase action[9] argues against any unsaturated intermediate unless an unusual abstraction–addition mechanism within a specific, nonexchangable enzymatic cage surrounding the 1′ position occurred. The present example provides access to such a 1′-ene for biochemical evaluation.

It has been reported that treatment of 2′-bromo-2′-deoxyuridine [1-(2-bromo-2-deoxy-β-D-ribofuranosyl)uracil] with reduced hydroxycobalamin gave 1-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)uracil.[10] However, only uv spectral data and qualitative color tests in conjunction with paper chromatography were given as supporting evidence and neither the proposed unsaturated nucleoside nor derived sugar was isolated and characterized.

A refluxing solution of 0.002 mol of 2′,3′-*O*-methoxyethylideneadenosine[11] (**1**) and a 20-fold molar excess of dried NaI in 40 ml of dry pyridine was treated with a 10-fold molar excess of pivalic acid chloride and heating was continued for ~6 min. After cooling, MeOH was added and, after stirring for 2 hr, the mixture was poured into aqueous $NaHCO_3$–$Na_2S_2O_3$ solution and extracted with Et_2O. The washed organic phase was evaporated and the residue chromatographed on activated carbon using EtOAc to elute the 3′-iodo isomer and 3′,4′-unsaturated products.[4a] EtOAc–$CHCl_3$ (1:1) eluted the 2′-iodo isomer (**2**). Rechromatography of intermediate fractions containing 60 mg of both isomers on an analogous smaller column gave effective separation and combination of appropriate fractions gave 6-*N*-pivalamido-9-[2-iodo-2-deoxy-5-*O*-pivalyl-3-*O*-(4,4-dimethyl-3-pivalyloxypent-2-enoyl)-β-D-arabinofuranosyl]purine[12] (**2**) in 15% yield: uv (MeOH) max 272, 213 nm (ε 18,600, 29,100), min 243 nm (ε 9700); uv (0.1 *N* NaOH) 275–295, 216 nm (ε 11,900, 30,600), min 248 nm (ε 7800); uv (0.1 *N* HCl) 282, 218 nm (ε 16,700, 23,500), min 249 nm (ε 7200); nmr ($CDCl_3$, TMS internal) δ 1.18 [s, 9, CH=C[C(CH_3)$_3$](*O*-pivalyl)], 1.26 and 1.34 [s and s, 9 and 9, 5′-OCOC(CH_3)$_3$ and CH=C(*t*-Bu)[OCOC(CH_3)$_3$], 1.41 [s, 9, 6-NHCOC(CH_3)$_3$], 4.17–4.61 (m, 3, $H_{4'}$, $H_{5',5''}$), 4.87 ("q," $J_{2'-1'}$ = 4.5 Hz, $J_{2'-3'}$ = 2.0 Hz, 1, $H_{2'}$), 5.64 ("t," $J_{3'-2'}$ = 2.0 Hz, $J_{3'-4'}$ = 3.0 Hz, 1, $H_{3'}$), 5.75 [s, 1, CH=C(*t*-Bu)(*O*-pivalyl)], 5.95 (d, $J_{1'-2'}$ = 4.5 Hz, 1, $H_{1'}$), 8.31 (s, 1, H_8), 8.60 (br, 1, 6-NH-pivalyl), 8.76 (s, 1, H_2). Treatment of **2** with $KMnO_4$ in pyridine–water (2:1) at 2° effected selective removal of the 3′-enol ester group to give 6-*N*-pivalamido-9-(2-iodo-2-deoxy-5-*O*-pivalyl-β-D-arabinofuranosyl)purine[12] (**3a**) in 75% yield: mp 216–217° dec.; uv (MeOH) max 272, 211 nm (ε 17,400, 19,000), min 231 nm (ε 3600); uv (0.1 *N* NaOH) 280–300, 215 nm (ε 10,600, 16,100), min 244 nm (ε 5700); uv (0.1 *N* HCl) 282, 213 nm (ε 18,900, 17,800), min 238 nm (ε 4100); nmr ($CDCl_3$, TMS internal) δ 1.18 [s, 9, 5′-OCOC(CH_3)$_3$], 1.31 [s, 9, 6-NHCOC(CH_3)$_3$], 3.95 (br m, 1, $H_{4'}$), 4.43 (m, 2, $H_{5',5''}$), 4.78 (m, 2, $H_{2'}$, $H_{3'}$), 6.16 (m, 1, 3′-OH), 6.45 (d, $J_{1'-2'}$ = 4.8 Hz, 1, $H_{1'}$), 8.55 (s, 1, H_8), 8.60 (br, 1, 6-NH-pivalyl), 8.72 (s, 1, H_2).

To avoid the concomitant epoxide formation otherwise observed during the elimination step, **3a** was treated with *N*,*O*-bis(trimethylsilyl)acetamide in pyridine to give the 3′-*O*-trimethylsilyl derivative **3b**: uv (CH_3CN) max 272, 212 nm (ε 272/212 = 0.88), min 237 nm (ε 272/237 = 4.92); nmr ($CDCl_3$, TMS internal) δ 0.24 [s, 9, Si(CH_3)$_3$], 1.27 [s, 9, 5′-OCOC(CH_3)$_3$], 1.41 [s, 9, 6-NHCOC(CH_3)$_3$], 4.11 (m, 1, $H_{4'}$), 4.47 ("d," $J_{apparent}$ = 4.5 Hz, 2, $H_{5',5''}$), 4.66 ("q," $J_{2'-1'}$ = 5.5 Hz, $J_{2'-3'}$ = 4.5 Hz, 1, $H_{2'}$), 4.84 ("t," $J_{3'-2'}$ = $J_{3'-4'}$ = 4.5 Hz, 1, $H_{3'}$), 6.11 (d, $J_{1'-2'}$ = 5.5 Hz, 1, $H_{1'}$), 8.25 (s, 1, H_8), 8.35 (s, 1, 6-NH-pivalyl), 8.78 (s, 1, H_2); mass spectrum calcd for $C_{23}H_{36}IN_5O_5Si$ 617.1531, found 617.1506. To the silylation reaction mixture was added 1,5-diazabicyclo[4.3.0]nonene-5 (DBN) and the solution was stirred for 90 min at room temperature. After methanolysis of the trimethylsilyl blocking group and column chromatographic purification, a 98% yield (overall from **3a**) of 6-*N*-pivalamido-9-(2-deoxy-5-*O*-pivalyl-D-erythro-pent-1-enofuranosyl)purine[12] (**4a**) was obtained: uv (MeOH) max 264, 248 nm (ε 18,600, 19,200), sh 216 nm (ε 15,900), min 257, 227 nm (ε 18,500, 13,200); uv (0.1 *N* NaOH) max 288, 232 nm (ε 12,700, 17,100), min 267 nm (ε 10,700); nmr ($CDCl_3$, TMS internal) δ 1.21 [s, 9, 5′-OCOC(CH_3)$_3$], 1.31 [s, 9, 6-NHCOC(CH_3)$_3$], 4.32 (m, 2, $H_{5',5''}$), 4.69 (m, 1, $H_{4'}$), 4.92 (m, 1, $H_{3'}$), 5.57 (d, *J* = 6.0 Hz, 1, 3′-OH), 5.82 (d,

$J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 8.60 (br, 1, 6-NH-pivalyl), 8.56 and 8.86 (s and s, 1 and 1, H_8 and H_2); mass spectrum (of the 3′-*O*-trimethylsilyl derivative of **4a**) calcd for $C_{23}H_{35}N_5O_5Si$ 489.2407, found 489.2425. Deblocking of **4a** with methanolic sodium methoxide gave (in 84% yield from **3a**) 6-amino-9-(2-deoxy-D-*erythro*-pent-1-enofuranosyl)purine (**4b**): mp 196–198°, resolidifies at ~202–210°, and melts with decomposition at 224–235°; $[\alpha]^{27}D$ 100.5° (c 0.96, DMF); uv (MeOH) max 250 nm (ε 16,500), sh 281, 290 nm (ε 7200, 4700), min 222 nm (ε 10,700); uv (0.1 *N* NaOH) max 251 nm (ε 16,400), sh 279, 290 nm (ε 6200, 3300), min 221 nm (ε 10,600); nmr (DMSO-d_6, TMS internal) δ 3.59 ("t," $J_{apparent}$ = 6 Hz, 2, $H_{5',5''}$), 4.43 ("sextet," $J_{4'-5',5''}$ = 5.0 Hz, $J_{4'-3'}$ = 3.0 Hz, 1, $H_{4'}$), 4.84 ("quintet," $J_{3'-4'}$ = 3.0 Hz, $J_{3'-3'-OH}$ = 6.0 Hz, 1, $H_{3'}$), 5.03 (t, $J_{5'-OH-5',5''}$ = 6.0 Hz, 1, 5′-OH), 5.35 (d, $J_{3'-OH-3'}$ = 6.0 Hz, 1, 3′-OH), 5.69 (d, $J_{2'-3'}$ = 2.8 Hz, 1, $H_{2'}$), 7.47 (s, 2, 6-NH_2), 8.30 and 8.34 (s and s, 1 and 1, H_2 and H_8); mass spectrum calcd for $C_{10}H_9N_5O_2$ ($M^+ - H_2O$) 231.0756, found 231.0752; mass spectrum [of the tris(trimethylsilyl) derivative of **4b**] calcd for $C_{19}H_{35}N_5O_3Si_3$ 465.2047, found 465.2062; spectrophotometrically determined $pK_a \sim 3.31$.

Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.28; H, 4.74; N, 27.92.

It is interesting to note that conjugation of the adenine ring with the 1′–2′ double bond shifts the uv spectrum hypsochromically as found with 9-(5-methyl-2-furyl)adenine.[3a] Heating **4b** gives 9-(5-methyl-2-furyl)adenine[3a] and attempted determination of the uv spectrum at pH 1 results in rapid cleavage to adenine. Blue fluorescence is observed when **4b** is visualized under 2537-Å light, which could be useful if this presumably base-sugar planar 2′-deoxyadenosine derivative can be incorporated into DNA and/or oligonucleotides.

Hydrogenation of **4b** at 3 psi over palladium/charcoal in alcohol-water containing sodium bicarbonate gave 2′-deoxyadenosine and 6-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine[13] in yields of 60 and 12%. It is interesting that the β:α stereoselectivity (5:1) is so high. A preliminary attempt at reduction of **4a** appeared to give no detectable α anomer, although accompanying hydrogenolysis of the glycosidic linkage to give 6-*N*-pivalyladenine made evaluation difficult.

The present study provides a possible route for the conversion of an intact ribo nucleoside to its 2′-deoxy-α anomer. As well, the new nucleoside 1-ene system is now available for biochemical, fluorescence, and synthetic studies.

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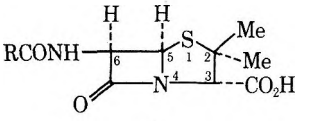
An Exocyclic Thio Analog of the Penicillin System[1]

Summary: A number of 3-arylidene-2-thioalkyl-1-pyrrolines were synthesized from 2-pyrrolidone *via* a three-step sequence and condensation of these thioimidates with phenoxyacetyl chloride in presence of triethylamine led to novel penicillin analogs in which substituents at C-5 have been interchanged to give an exocyclic alkylthio substituent and a carbocyclic five-membered ring; the stereochemistry of these fused β-lactams was established from a study of their nmr spectra.

Sir: An important structural feature of penicillins (**1**) in clinical use is a fused thiazolidine β-lactam system. In the course of research directed toward the synthesis of penicillin and cephalosporin analogs we became interested in the possibility of interchanging the substituents at C-5 to obtain derivatives of a novel fused β-lactam system (**2**) with an exocyclic alkylthio substituent. We describe here the preparation of some derivatives of this previously unknown class of compounds.



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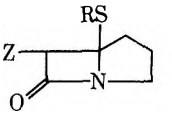

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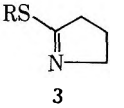
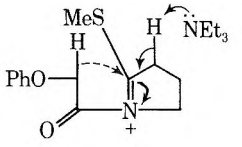


3

In recent years we[2] have synthesized diverse types of mono- and polycyclic β-lactams by the reaction of appropriate acid chlorides with imines in the presence of triethylamine. To take advantage of this approach we sought thioimidates of type **3** as intermediates for **1**. The reaction of phenoxyacetyl chloride and triethylamine with 2-methylthio-1-pyrroline (**3**, R = Me), however, led to the pyrroline derivative **5** instead of the desired β-lactam **6**. Evidently the initial reaction intermediate was **4** which underwent an elimination reaction in preference to cyclization.

To preclude the elimination pathway and thereby favor cyclization to a β-lactam, thioimidates of type **9** were examined next as imine components in the reaction with acid chlorides and triethylamine. Following the method of Zimmer[3] a series of pyrrolidone derivatives of type **7** were prepared by treating *N*-acetylpyrrolidone with aromatic aldehydes in the presence of sodium hydride. A suspen-



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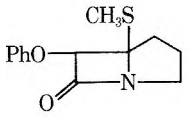

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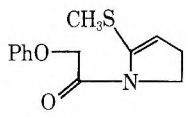
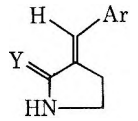


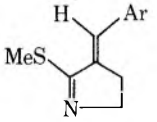
5

sion of 7 (Ar = Ph) and a 0.2 molar equiv of phosphorus pentasulfide was heated under reflux in pyridine for 1 hr and poured through filter paper into a large volume of warm (50°) water.[4] The thioamide 8 (Ar = Ph), mp 163–165°, obtained in quantitative yield, was heated with methyl iodide in tetrahydrofuran solution; the product was neutralized with triethylamine, extracted with dichloromethane, and purified by distillation to give the desired thioimidate (9, Ar = Ph), 68%, mp 94–95°. Several other members of this series were prepared in an analogous manner with yields of 33, 50, and 60% for **9b**, **9c**, and **9d**, respectively.

The reaction of 9a with methoxyacetyl chloride and triethylamine in dichloromethane gave a single product, ir (Nujol) 1780 cm^{-1}, mp 73–74°, in 68% yield, which was shown to be the bicyclic β-lactam **10** on the basis of ir, mass spectral and pmr characteristics.

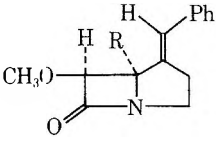


7, Y = O
8, Y = S



9a, phenyl
b, 3,4-dimethoxyphenyl
c, *p*-chlorophenyl
d, *m*-nitrophenyl

The stereochemistry of the β-lactam **10** was established by studying the pmr spectrum of the sulfoxide, **11**, mp 122–123°, and the sulfone **12**, mp 145–146°, obtained by successive oxidations of **10a** with *m*-chloroperoxybenzoic acid.[5] The sulfur was confirmed to be the site of oxidation by the progressive downfield shift of the methylthio group in the pmr spectrum, going from 2.20 ppm in **10a** to 2.45 ppm in **11** to 3.17 ppm in **12**. For this series of compounds



10, R = CH_3S
11, R = $CH_3S\rightarrow O$
12, R = CH_3SO_2

the methoxyl resonance position was virtually unchanged while the C-6 proton shifted from 4.41 ppm in **10** to 4.68 ppm in **11** and 4.60 ppm in **12**.

The 16-Hz anisotropic deshielding effect observed for the C-6 proton upon oxidation of the C-5 methythio substituent is clearly appropriate only for a situation in which the methythio group is oriented cis to the C-6 proton and thus trans to the C-6 methoxy group. In all of these compounds the olefinic proton showed a characteristic trans allylic coupling of 1–2 Hz. On the basis of the pmr data the stereostructure **10a** can be deduced. The trans disposition of the methoxy group in **10a** with respect to the thio function is in agreement with the directive influence and stereospecificity observed earlier by us in forming β-lactams from thioimidates.[6] In view of our earlier studies on the cycloaddition of various acid chlorides—in particular azidoacetyl chloride—to imines, it can be expected that the method described above could be extended to the synthesis of diverse bicyclic β-lactams of type **2**. Further work along these lines is in progress.

Acknowledgment. The authors are grateful to Stevens Institute of Technology for support of this work.

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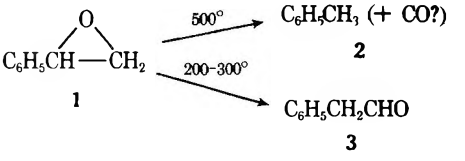
Thermal Rearrangement of 1,2-Epoxyethylbenzene

Summary: Thermolysis of 1,2-epoxyethylbenzene at 500° has been found to produce toluene while thermal rearrangement at 200–300° gives phenylethanal *via* a first-order process; $k = 6.02 \pm 0.12 \times 10^{-2}$ hr^{-1} at 200° in benzene.

Sir: We wish to communicate the results of our investigation of the thermal lability of 1,2-epoxyethylbenzene (**1**). While subjection of **1** to temperatures in the range of 500° leads to a clean thermolysis to toluene (**2**) (Figure 1) and, presumably, carbon monoxide with traces of phenyl acetylene (~1.6%) also being formed, the use of more moderate temperatures gives selective rearrangement of **1** to phenylethanal (**3**) *via* epoxide ring opening and a formal 1,2-hydrogen shift.



1 2 3

Rate data, obtained under liquid phase conditions in benzene solution, show this rearrangement to obey first-order kinetics and to have rate constants as tabulated in Table I. Activation parameters derived from these data are $E_a = 29.2 \pm 0.6$ kcal/mol, $\Delta H^*_{200} = 28.3 \pm 0.6$ kcal/mol, and $\Delta S^*_{200} = +11.0 \pm 1.2$ cal/mol°K. In addition, the rate of rearrangement appears to be somewhat influenced by solvent, being ~35% more rapid in benzene (at 200°) than in toluene.

The dramatic influence of the phenyl substituent on the direction of ring opening of **1** is demonstrated by the absence of acetophenone (**6**) from the product mixture. This contrasts markedly with the complete lack of selectivity in C_1–O *vs.* C_2–O bond breakage reported by Gritter and Sabatino[1] for the photolysis of **1** at 2537 Å. A rather selec-

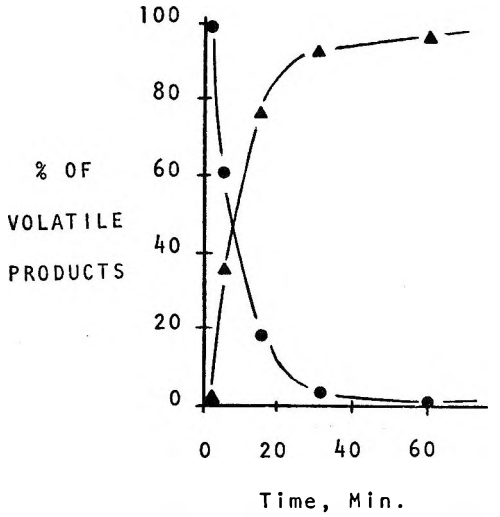
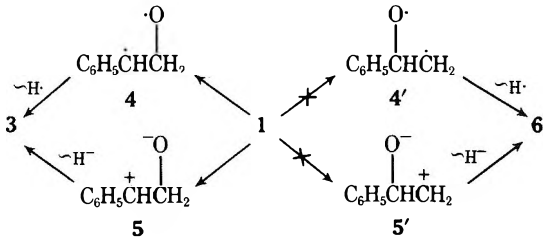


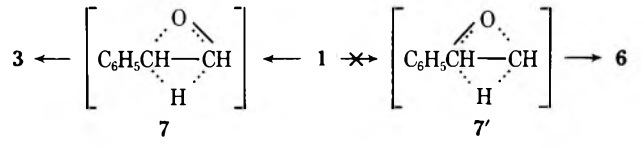
Figure 1. Vapor-phase thermolysis of 1,2-epoxyethylbenzene at 500°: ●, 1,2-epoxyethylbenzene, ▲, toluene.

tive conversion of **1** to **3** (85%) accompanied by **6** (4%) in the presence of sodium iodide–*n*-propyl iodide–dimethyl sulfoxide has been previously reported[2] as has the isomerization of **1** to **3** (no yield given) in the presence of $LiClO_4$,[3] but, to our knowledge, ours is the first report of the thermally induced conversion of **1** to **3**.

The selectivity of aldehyde formation herein and the positive ΔS^* observed constitute evidence for either a diradical or ionic mechanism involving intermediate **4** or **5**, respectively. While both **4** and **5** are benzylically stabilized, neither of the corresponding intermediates, **4′** nor **5′**, leading to acetophenone (**6**) benefit from such stabiliza-



tion. The selectivity to aldehyde could also be rationalized on the basis of a concerted mechanism (**1** → **7** → **3**) as benzylic C–O bond breakage requires less energy than does



cleavage of the bond linking the primary carbon to oxygen,[4] and the transition state for the rearrangement more closely resembles reactant **1** than product **3** owing to the exothermic nature of the reaction. However, any influence of product (**3** and **6**) stability on the transition state would weigh in favor of ketone **6** formation, because, of the transition states (**7** and **7′**, respectively) leading to aldehyde **3** and ketone **6** formation, the latter should be favored owing to the developing conjugation between the carbonyl and phenyl moieties. This fact plus the observed positive ΔS^* lead the authors to favor the stepwise mechanism at this time. Finally, it should be noted that the present evidence does not preclude the possibility of aldehyde formation *via* C_2–O bond scission with phenyl migration as opposed to the above depicted C_1–O bond scission–hydrogen migration sequence.

Table I
First-Order Rate Constants. Rearrangement of 1,2-Epoxyethylbenzene to Phenylethanal

Temp, °C	k, hr^{-1}
180	$1.32 \pm 0.04 \times 10^{-2}$
200	$6.02 \pm 0.12 \times 10^{-2}$
220	$1.86 \pm 0.03 \times 10^{-1}$

Rearrangements at 500° were conducted using 50-μl samples of **1** sealed *in vacuo* in Pyrex tubes; those at the lower temperatures were run using both neat samples of **1** in sealed tubes and benzene or toluene solutions thereof in a stirred stainless steel reactor. Substantial polymerization was observed upon thermolysis in sealed tubes (unseasoned) at 200°, but rearrangements of 8:1 benzene or toluene solutions of **1** consistently provided yields of 91–96% of the aldehyde. Extent of rearrangement was monitored by glc; product identities were confirmed by glc and spectroscopic comparisons with authentic materials. The rates and activation parameters reported were subjected to least-squares optimization; the uncertainties in k are probable errors while those in the values of the activation parameters are statistical errors determined by the method of Purlee.[5]

Experimentation, the purpose of which is to further elucidate the mechanism and scope of this rearrangement, is continuing.

Acknowledgment. Thanks are extended to Professor John C. Gilbert for helpful discussion.

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Structure of the Products Resulting from Photochemically Induced Hydrogen Transfers in the Levopimaric Acid–Cyclopentenedione Adduct

Summary: X-Ray analysis of a derivative of the substance obtained by irradiation of the levopimaric acid–cyclopentenedione adduct confirms that the unusual series of photochemical reactions leading to its formation involves intramolecular energy transfer from enone to isolated double bond and two consecutive transannular hydrogen abstractions, each accompanied by ring closure.

Sir: In attempting to establish the stereochemistry of the levopimaric acid–1-cyclopentene-3,5-dione adduct **1a**,[1] we observed a remarkable example of intramolecular energy transfer which also had important implications for cyclopentenone photochemistry. Irradiation of **1b** afforded not only the expected cage structure, but also, by transfer of excitation energy from triplet cyclopentenone to the isolated double bond, an isomer A which was formulated as

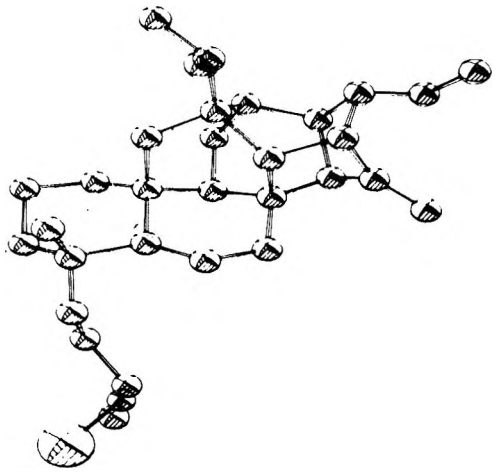
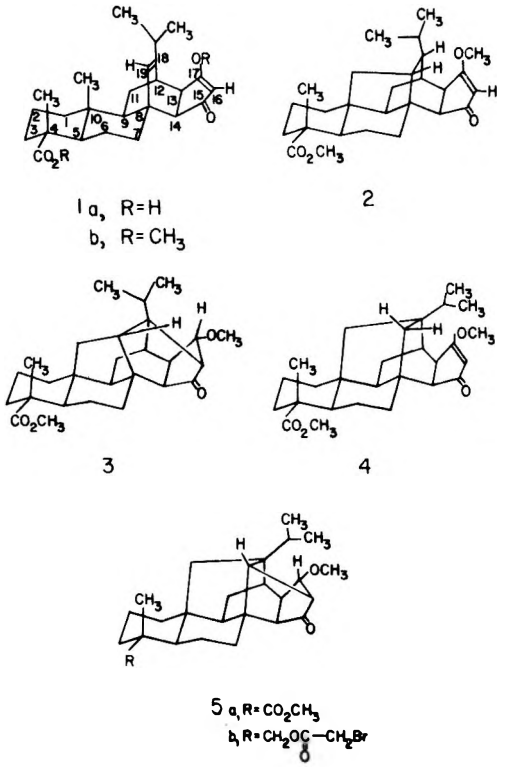


Figure 1. Three-dimensional view of **5b** with spheres of arbitrary radius.

2[2] and was converted on further irradiation to B, presumably 3.[3] Alternative structures 4 for A and hence **5a** for B, formed by a mechanistically similar, though somewhat simpler path not requiring the 1,2-hydrogen shift implicit in the transformation **1b** → **2**, were not discussed in our earlier communication[2] because of the distance between C-17 and C-19 which seemed *a priori* greater than desirable for the observed photochemically induced intramolecular hydrogen transfer in step 2.

To decide between these and other possibilities[2] we considered X-ray analysis of a heavy atom derivative of B. After several preliminary attempts, the bromoacetate of the alcohol formed by reduction of B with a limited amount of $LiAlH_4$ proved suitable and was shown to possess structure **5b**. Hence B is **5a** and A is **4**.[4,6]



Preparation of 5b. A solution of 1 g of **5a**[1] in THF was added to 100 mg of $LiAlH_4$ in 50 ml of THF–ether (8:2) with stirring. The reaction was complete after 1 hr (tlc). Decomposition of excess $LiAlH_4$ with 10% NaOH, filtration, and dilution of the filtrate with ether was followed by the usual work-up. Recrystallization from ether–methanol afforded 0.9 g of **5c** (R = CH_2OH): mp 90°; ir 3480, 1755 cm^{-1} (hydroxyl, cyclopentanone). *Anal.* Calcd for $C_{26}H_{38}O_3$: C, 78.35; H, 9.61; O, 12.04. Found: C, 78.70; H, 9.63; O, 11.76. A solution of 0.2 g of **5c** in 10 ml of dry benzene and a few drops of pyridine was mixed with 0.15 g of bromoacetyl bromide in benzene at 0° with stirring until the reaction was complete (tlc). The usual work-up, trituration of the crude product with methanol, and recrystallization from ethyl acetate–methanol afforded trapezoidally shaped single crystals of **5b**, mp 215°, yield 0.18 g. *Anal.* Calcd for $C_{28}H_{39}O_4Br$: Br, 15.41; mol wt, 520.2012. Found: Br, 15.86; mol wt, 520.2037 (mass spectrum).

Structure Determination. The orthorhombic $P2_12_12_1$ space group was determined unequivocally from Weissenberg photographs of several single crystals of **5b** mounted along different axes. The crystal chosen was ground to a sphere 0.4 mm in diameter and was mounted on a Hilger-Watts Y290 four-circle automatic diffractometer. Unit cell dimensions, obtained by least-squares fitting to angle data of ten high order reflections, were a = 8.507 (2), b = 22.898 (4), c = 12.780 (4) Å. With Z = 4, δ_{calcd} = 1.386 which compares quite favorably with a density of 1.39 measured by flotation in carbon tetrachloride–heptane. Intensity data were collected with Cu Kα radiation out to 2θ = 114° using the $2\theta/\omega$ step-scan technique. From the 2766 measurements made, including periodic measurements of two standard reflections, 1924 independent measurements were obtained; 189 of these fell below the 3σ level as estimated from counting statistics.

All but two atoms of the structure were found by conventional Patterson and Fourier techniques using the XRAY-72 system of programs devised by Stewart.[7] After two cycles of full-matrix isotropic least-squares refinement, R fell to 0.23; a difference map revealed the remaining two atoms. Further cycles of least squares using anisotropic temperature factors resulted in convergence at an R of 0.14. A difference map showed two unequal peaks in the vicinity of the bromine location, which was taken as evidence for disorder in the bromoacetate side chain. Inclusion of these two positions for bromine with appropriate population parameters allowed R to fall to 0.097 after two cycles of least squares. Location of all hydrogen atoms except the two on the disordered part of the side chain, followed by further cycles of least squares, lowered R to its final value of 0.058.

That B does indeed have structure 5 and not 3 can be seen by noting the following observed interatomic distances where C(23) is the former C-10 methyl carbon atom: C(16)–C(19), 1.573 (8) Å; C(16)–C(18), 2.654 (8) Å; C(18)–C(23), 1.539 (8) Å; C(17)–C(23), 2.430 (8) Å. Figure 1 clearly shows these distances and, in addition, gives an indication of the amount of strain involved in the novel cage system. The cyclopentanone rings, in particular, are seen to be highly distorted. Details of the analysis will be published elsewhere.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation (GP-12582).

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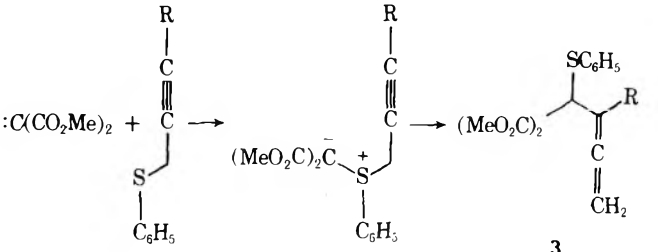
[2,3]-Sigmatropic Rearrangements of Acetylenic and Allenic Sulfonium Ylides. Synthesis of Allenes and Conjugated Dienes

Summary: The [2,3]-sigmatropic rearrangement of acetylenic and allenic sulfonium ylides results in the formation of allenes and conjugated dienes, respectively, in good yield.

Sir: The synthetic utility of the [2,3]-sigmatropic rearrangement of allylic sulfonium ylides and related species (*e.g.*, i → ii) for the construction of β,γ-unsaturated carbonyl compounds,[1] trisubstituted olefinic linkages,[2] and formation of asymmetry at quaternary carbon[3] has been demonstrated in several recent publications. As part of a continuing program aimed at development of the synthetic potential of [2,3]-sigmatropic rearrangements in organic synthesis,[4] we wish to report that acetylenic sulfonium ylides (*e.g.*, **2** and **4**) undergo such a rearrangement providing a route to terminal and internal allenes.[5] The first observation that sp-hybridized bonds participate in the electrocyclic rearrangement of sulfonium ylides with formation of allenes was reported by Baldwin some years ago.[6] In addition, we further report that allenic sulfonium ylides undergo the [2,3]-sigmatropic process providing a new route to conjugated dienes.

i ii

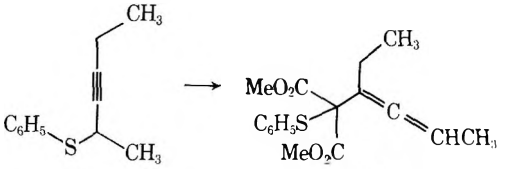
Allylic sulfonium ylides have previously been generated by the addition of the appropriate carbenes to allylic sulfides[7] or by the action of base on allylic sulfonium salts.[8] Employing the former procedure, acetylenic sulfonium ylides (*e.g.*, **2**) can be conveniently prepared *via* the copper salt catalyzed thermal decomposition of diazo compounds in acetylenic sulfides. The rearrangements are conveniently carried out in the absence of solvent at elevated temperatures. Heating a mixture of methyl diazomalonate (1.8 equiv)[9] and the acetylenic sulfide **1** (R = C_2H_5) [prepared by successive treatment of the corresponding acetylenic alcohol in ether–hexamethylphosphoramide (HMPA) (4:1) with methyllithium (1.0 equiv), tosyl chloride (1.05 equiv), and lithium thiophenoxide (1.05 equiv)[10]] in the presence of a catalytic amount of anhydrous cupric sulfate at 95–100° for ~15 hr (no solvent) results in a 71% isolated yield of pure allene **3** (R = C_2H_5) after preparative thin layer chromatography. The assigned structure **3** is in accord with the observed spectral data: ir 1950, 1735, 850 (terminal allene) cm^{-1}; nmr δ 0.85 (t, 3 H), 2.05 (m, 2 H), 3.62 (s, 6 H), 4.70 (t, 2 H, J = 3.5 Hz, $=CH_2$); m/e 306.



1 2 3

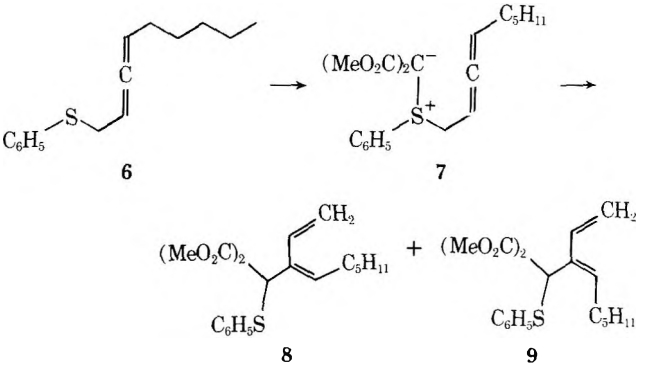
Similarly, reaction of bis(carbomethoxy)carbene with acetylenic sulfide (R = *n*-Bu) results in an 80% isolated yield of pure terminal allene **3** (R = *n*-Bu).

The utility of the procedure is indicated by the construction of internal allenes as well. For example, treatment of the acetylenic sulfide **4** (prepared by treatment of thiophenoxy-2-pentyne at −78° in anhydrous THF with *n*-BuLi, followed by addition of methyl iodide and warming to room temperature) with methyl diazomalonate as described above provides a 60% yield of pure internal allene **5** after preparative thin layer chromatography.



4 5

Finally, the [2,3]-sigmatropic rearrangement is also applicable to allenic sulfonium ylides (*e.g.*, **7**) as was demonstrated by the smooth conversion of allenic sulfide **6** [prepared by successive treatment of nona-2,3-dien-1-ol[11] in ether–HMPA (4:1) with methyllithium, tosyl chloride, and lithium thiophenoxide[10]] into a 4:1 mixture of dienes **8** and **9** (indicated by 250-MHz nmr) employing the procedure described above in 66% isolated yield after purification.



6 7 8 9

The conversion of acetylenic and allenic sulfonium ylides into allenes and conjugated dienes, respectively, further demonstrates the potential of [2,3]-sigmatropic rearrangements in organic synthesis. The extension of our work to the synthesis of naturally occurring allenes is now in progress.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (No. R01 CA 13689-02) from the National Cancer Institute and the National Institutes of Health NMR Facility for Biomedical Studies (Mellon Institute) Grant No. RR-00292-07.

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(11) Nona-2,3-dien-1-ol was synthesized *via* the reductive elimination ($LiAlH_4$)[12] of the tetrahydropyranyloxy group from 4-tetrahydropyranyloxynona-2-yn-1-ol which was prepared by metalation of the tetrahydropyranyl ether of 1-octyn-3-ol with 1.1 equiv of *n*-BuLi in ether at −78°, followed by treatment with excess paraformaldehyde in tetrahydrofuran (25°).[13]

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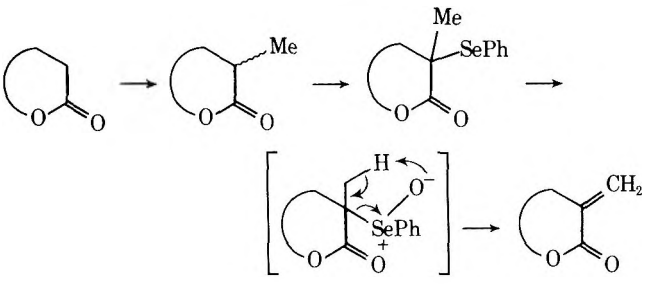
Organoselenium Chemistry. α-Phenylseleno Lactones. A New General Route to the Synthesis of Fused α-Methylene Lactones

Summary: A general high yield "α-methylenation sequence" has been developed for cis- and trans-fused lactone rings employing the reported capabilities of alkylphenyl selenoxides to undergo facile syn elimination at low temperatures.

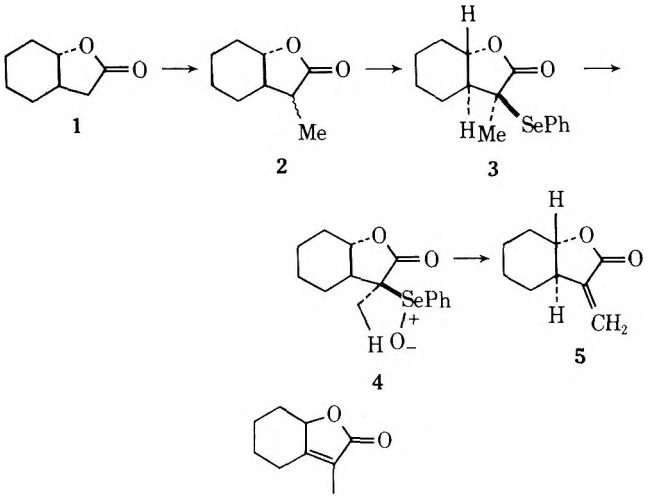
Sir: We report here a general method for the conversion of cis- and trans-fused γ- and δ-lactones into their corresponding α-methylene-γ-butyrolactones and α-methylene-δ-valerolactones which represent structural units found in many naturally occurring cytotoxic sesquiterpenes[1] (*e.g.*, vernolepin[2]). Although the α-methylene lactone structural moiety has been a synthetic objective in several laboratories,[3,4] the number of general approaches[4] remains small.

Our approach requires (a) a method for specific high yield methylation of preformed lactone enolates, (b) a method for stereospecific introduction of an α-phenylseleno substituent (*vide infra*), and (c) a method for specific elimination of the corresponding selenoxide to the exocyclic methylene group (Scheme I). The method is based on the observations by Sharpless[5] and Reich[6] that lithium enolates of ketones, aldehydes, and esters react rapidly and cleanly with phenylselenenyl halides to give α-phenylseleno carbonyl compounds[7] and on the report that alkylphenyl selenoxides readily undergo syn[8] elimination to form olefins.[9]

Scheme I



In the case of the trans-fused γ-butyrolactone **1**, the overall method is illustrated for the conversion of **1** into the *trans*-α-methylene-γ-butyrolactone (**5**), with complete exclusion of the endocyclic isomer **6**. The specific formation of **5** comes about as a result of a stereospecific alkylation of the lactone enolate derived from **2** with diphenyl diselenide[10] which establishes the required anti relationship between the α-phenylseleno substituent and the adjacent methine proton; hence, syn elimination of selenoxide **4** can only lead to **5**.



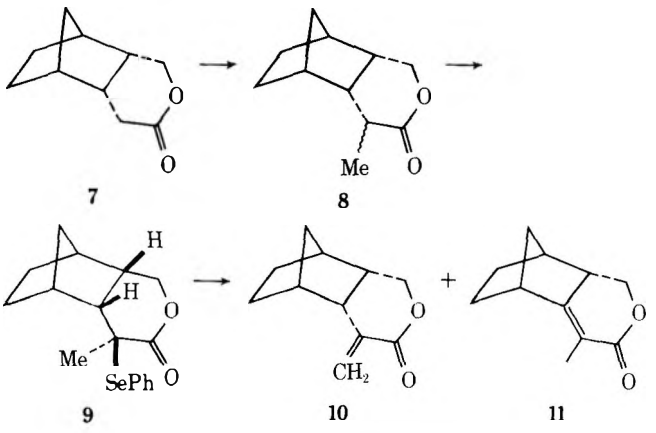
1 2 3 4 5 6

In the conversion of lactones to α-methylene lactones employing the above scheme, the yields of monoalkylated α-methyl lactones are in the range of 90–98%.[12] Similarly, yields for the introduction of the α-phenylseleno group are very high.[11] Formation of the selenoxides is carried out with 30% hydrogen peroxide and results in 90–99% yields of α-methylene lactones. A typical procedure for the conversion of the trans-fused γ-butyrolactone **1** into the trans-fused α-methylene-γ-butyrolactone **5** is as follows. To a solution of 2.4 mmol of lithium diisopropylamide (LDA, prepared from 0.35 ml of diisopropylamine and 1.6 ml of 1.65 *M* butyllithium in hexane under nitrogen at −78°) in 3 ml of anhydrous tetrahydrofuran (THF) was added dropwise over a period of 1 hr, 280 mg (2.0 mmol) of trans-fused lactone **1**[13] in 3 ml of THF. The solution was stirred at −78° for 20 min, 0.15 ml of methyl iodide in 1 ml of THF containing 1 equiv (430 mg) of hexamethylphosphoramide (HMPA) was added rapidly dropwise, and then the mixture was warmed to −40°. The reaction mixture was stirred for 3 hr at −40° and was quenched by the addition of 10% hydrochloric acid. The mixture was diluted with ether and washed with water and saturated sodium chloride solution. There was obtained 310 mg (100%) of crude monoalkylated lactone **2** which was >95% pure by glc analysis.

Introduction of the α-phenylseleno substituent was achieved as follows. The enolate of methylated lactone **2** was prepared as described above by addition of 154 mg (1.0 mmol) of **2** in 1.0 ml of THF to 1.2 mmol of LDA in 3.0 ml of THF. After enolate formation was complete, 377 mg (1.2 mmol) of diphenyl diselenide in 1.0 ml of THF containing 215 mg (1.2 mmol) of HMPA was rapidly added dropwise at −78°. The reaction mixture was stirred at −78° for 40 min, then warmed to −40°, and kept at that temperature for 1.5 hr. The reaction was quenched by the addition of 0.1 *N* HCl solution. Usual work-up afforded yellow crystals which after chromatography on silica gel afforded 264 mg (85%) of the pure α-phenylseleno lactone **3**, mp 124–125°. *Anal.* Calcd for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.86. Found: C, 58.14; H, 5.94.

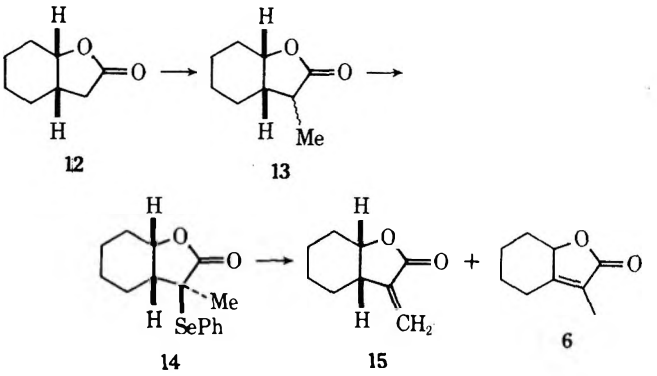
To a solution of the α-phenylseleno lactone **3** (62 mg, 0.2 mmol) in 1.0 ml of THF containing 0.03 ml of acetic acid cooled to 0° was added 0.14 ml of 30% hydrogen peroxide. The reaction was stirred for 30 min at 0°, then poured into cold saturated sodium bicarbonate solution, and extracted with ether. Chromatography of the crude product on silica gel afforded 29 mg (96% yield) of pure trans-fused α-methylene lactone **5**. Its ir [λ_{max} ($CHCl_3$) 5.65 (C=O), 6.00 (C=CH_2) μ] and nmr [δ (CCl_4) 5.95 (d, *J* = 3 Hz, 1 H), 5.30 (d, *J* = 3 Hz, 1 H), 3.9–3.4 (br, 1 H)] were identical with those of a sample of **5** prepared by an alternate procedure.[4a]

The success of the α-methylenation sequence is dependent upon the proper stereochemical relationship between the α-phenylseleno substituent and the proton β to the lactone carbonyl. To achieve the required anti relationship, the introduction of the α substituents must take place with complete stereospecificity. Monoalkylation of the endo δ-lactone **7**[14] proceeded in 95% yield affording lactone **8**. Alkylation of the monomethylated lactone **8** with diphenyl diselenide produced a 62%[12] isolated yield of a pure substance. Spectral data did not allow one to differentiate between the two possible isomeric compounds. However, treatment of **9** with 30% hydrogen peroxide in THF containing a trace of acetic acid resulted in a 3:1 mixture (glc analysis, SE-30) of α-methylene lactone **10**[4c] [λ_{max} ($CHCl_3$) 5.81 (C=O), 6.12 (C=CH_2) μ; nmr (CCl_4) δ 6.11 (t, 1 H), 5.39 (t, 1 H), 4.18 (d, 2 H)] and the corresponding endocyclic double bond isomer **11**, respectively, in 99% isolated yield.



7 8 9 10 11

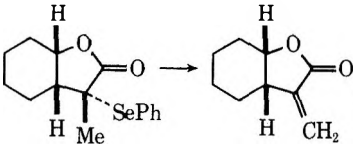
Reaction of the enolate derived from the monomethylated cis-fused lactone **13** (prepared in 90% isolated yield from **12**[15]) with diphenyl diselenide afforded the α-phenylseleno compound **14** (88%) which upon conversion to its selenoxide (30% H_2O_2) produced a 90:10 mixture (glc analysis, SE-30) of endocyclic isomer **6** and cis-fused α-methylene lactone **15**, respectively, in near-quantitative yield.



12 13 14 15 6

In view of the above results, the α-phenylseleno group and the adjacent methine proton in both cases must possess a syn relationship. The obvious way to circumvent formation of the endocyclic isomers (*e.g.*, **6** and **11**) would be to reverse the order of introducing the α-methyl and α-phenylseleno groups maintaining complete stereospecificity during C-alkylation.

α-Phenylselenenylation of cis lactone **12** with diphenyl diselenide employing the general reaction conditions described above, followed by methylation, afforded lactone **16**, free from the isomeric lactone **14**. Employing the usual oxidation procedure, **16** resulted in exclusive formation of the cis-fused α-methylene lactone **15** in very high yield [λ_{max} ($CHCl_3$) 5.69 (C=O), 6.01 (C=CH_2) μ; nmr δ (CCl_4) 5.99 (d, *J* = 2.5 Hz, 1 H), 5.38 (d, *J* = 2.5 Hz, 1 H), 4.40 (q, *J* = 6 Hz, 1 H)].



16 15

This new α-methylenation procedure for the preparation of α-methylene lactones clearly has advantages in terms of yields and mildness of reaction conditions.

Acknowledgment. We thank Professor K. B. Sharpless for helpful suggestions and for informing us of his work prior to publication. We thank Mr. James J. Reap for providing us with lactones **1** and **12**. We thank Eli Lilly and Company and the National Cancer Institute (Public Health Service Research Grant No. R01 CA 13689-02) for generous support of this research.

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(10) The use of PhSeBr in all the cases examined here gave lower yields (50–70%); use of PhSeSePh gave consistently high yields (85–90%) of α-phenylseleno compounds.[11] For example, reactions of the enolate of methylated lactone **2** with PhSeBr resulted in only a 66% isolated yield of pure **3**, whereas use of PhSeSePh afforded an 85% isolated yield of pure **3**.
(11) With the exception of compound **8**, all yields for the introduction of the α-phenylseleno group from monomethylated lactones are in the range of 85–90%. Reaction of monoethylated lactone **8** with PhSeSePh affords α-phenylseleno compound **9** in yields of 60–65%. Use of PhSeBr results in only 20–25% yields of **9**. Introduction of the phenylseleno substituent on the β surface of the molecule forces the methyl group down, thus resulting in severe steric interactions.
(12) A report describing the alkylation of the enolate of γ-butyrolactone with methyl iodide has appeared [G. H. Posner and G. L. Loomis, *Chem. Commun.*, 892 (1972)]; for other studies on enolates derived from lactones, see ref 3m, 4a, and 4c.
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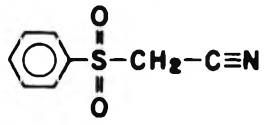
SULFONYL ACTIVATED METHYLENES

UNEXPLORED TERRITORY

Activated methylenes are known to undergo a wide variety of useful and interesting reactions such as: the Aldol, Claisen, Claisen-Schmidt, and Knoevenagel condensations; the Mannich, Thorpe, and Japp-Klingemann reactions; Michael additions; and such standard reactions as halogenation, alkylation and acylation. Activated methylenes have also proven useful in numberless heterocyclic ring closures such as the Hantzsch, and Gattermann-Skita pyridine syntheses; the Hantzsch pyrrole synthesis; the Pfitzinger, and Niementowski quinoline syntheses; and the Timmis synthesis of fused pyrazines. The analogous reactions utilizing sulfonyl activated methylenes are virtually unexplored territory.

A variety of sulfonyl activated methylenes are now commercially available as potential building blocks for novel pharmaceuticals, dyes, herbicides, pesticides, and intermediates. In addition to the practical applications, we think investigators will also discover some plain-ol'-new-fashioned-academically-interesting chemistry along the way.



1023

PHENYLSULFONYLACETONITRILE

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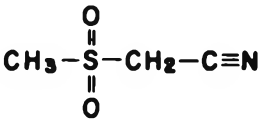
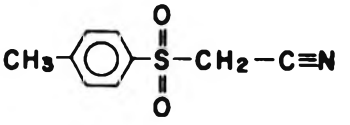


1024

METHYLSULFONYLACETONITRILE

25g $11.60 100g $35.00



1086

p-TOLUENESULFONYLACETONITRILE

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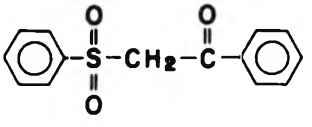
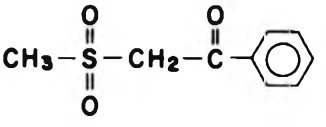


1091

α-PHENYLSULFONYLACETOPHENONE

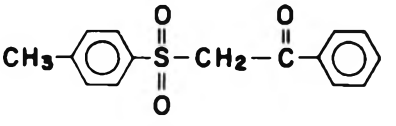
25g $12.50 100g $37.50



1090

α-METHYLSULFONYLACETOPHENONE

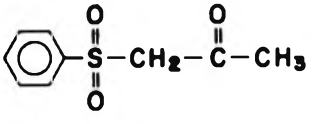
25g $ 8.50 100g $25.50



1092

α-(*p*-TOLUENESULFONYL)ACETOPHENONE

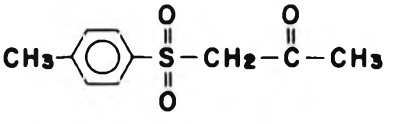
25g $10.00 100g $30.00



1093

PHENYLSULFONYLACETONE

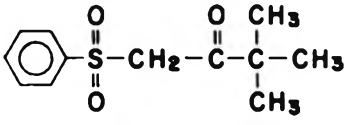
25g $10.00 100g $30.00



1094

p-TOLUENESULFONYLACETONE

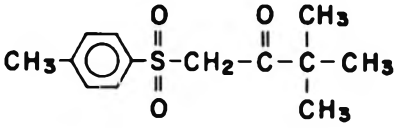
25g $ 8.50 100g $25.50



1097

α-PHENYLSULFONYLPINACOLONE

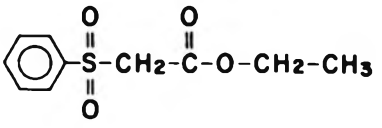
25g $20.00 100g $60.00



1098

α-(*p*-TOLUENESULFONYL) PINACOLONE

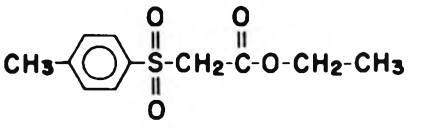
25g $17.50 100g $52.50



1095

ETHYL α-PHENYLSULFONYLACETATE

25g $10.00 100g $30.00



1096

ETHYL α-(*p*-TOLUENESULFONYL) ACETATE

25g $ 8.50 100g $25.50

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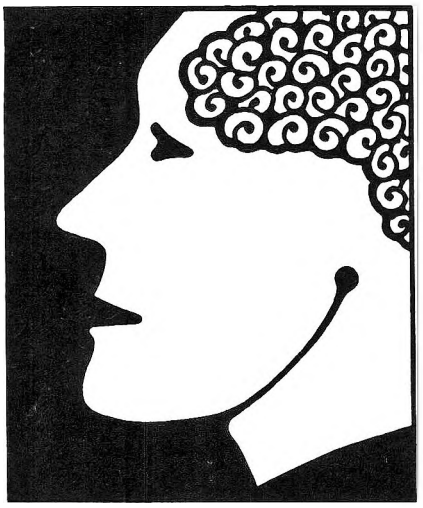

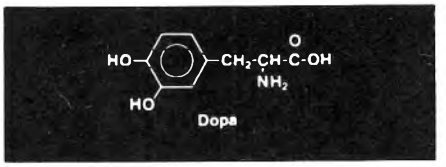

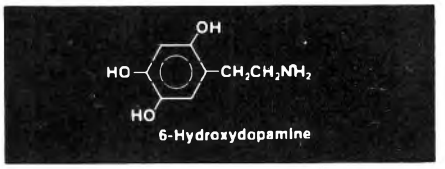

The study of catecholamines, perhaps more than any other pharmacological area,

yields results which rapidly find application in therapy. The treatment of neurologic disorders with **L-dopa** is such a case. A very short time elapsed between the establishment of a role for dopa in central metabolism[1] and its use in the treatment of Parkinsonism.[2] These advances have largely been the result of biochemical studies concerning the conversion of dopa to **dopamine** and the role of dopamine as a neurotransmitter. Thus, dopa decarboxylase inhibitors have been designed to enhance the anti-Parkinsonism action of L-dopa and **α-methyldopa** has recently been shown to be a synergist.[3] Such studies have led to the discovery that dopamine plays the role of a mediator in the discharge of several pituitary hormone releasing factors, increasing growth hormone and decreasing prolactin secretion. The latter observation has resulted in the successful combination of dopa and estrogens in the treatment of breast cancer.[4] Transient effects of dopamine can be prolonged by appropriate derivatization, *e.g.*, amino acid amides of dopamine (we offer the intermediate dibenzyloxydopamine, 16,189-6) are orally effective in greatly increasing renal blood flow.[5] Structural modification of dopamine has led to **6-hydroxydopamine**, a remarkable pharmacological tool for understanding the role and mechanism of neurotransmitters in the sympathetic nervous system.[6] Depletion of catecholamines with this agent is both reversible and irreversible (dose-dependent) and the importance of 6-hydroxydopamine should rival that of reserpine. **5-Hydroxydopamine** also replaces norepinephrine in storage vesicles and its osmiophilic properties enable the replacement to be observed with an electron microscope.[7] The judicial use of enzyme inhibitors and transmitter precursors, *e.g.*, **α-methyltyrosine** to deplete and *threo*-**dihydroxyphenylserine** to selectively increase the concentration of norepinephrine in the brain, will continue to advance the field.

Below is a partial list of catecholamines and amino acid analogs. A complete listing of over 50 enzyme substrates, inhibitors and metabolic products **related to the above** *will be sent on request.*

References:

1) A. Carlsson, M. Lindqvist, T. Magnusson and B. Waldeck, *Science*, **127**, 471 (1958).
2) G. C. Cotzias, M. H. VanWoert and L. M. Schiffer, *New Engl. J. Med.*, **276**, 374 (1967).
3) J. Fermaglich and T. N. Chase, *The Lancet*, 1261 (1972).
4) B. A. Stoll, *The Lancet*, 431 (1972).
5) R. H. Jones, J. H. Biel, W. Ours, I. L. Klundt and R. L. Lenga, 165th National Meeting of the American Chemical Society, Dallas Texas, April 1973, MEDI Abstr. 9.
6) T. Malmfors and H. Thoenen, Eds., "6-Hydroxydopamine and Catecholamine Neurons," North Holland, Amsterdam and Elsevier, N.Y. 1971.
7) J. J. Tranzer and H. Thoenen, *Experientia*, **23**, 473 (1967).

16,189-6	**3,4-(Dibenzyloxy)-phenethylamine hydrochloride**	**1g $7.50; 5g $21.00**
15,431-8	**L-DOPA** [3-(3,4-dihydroxyphenyl)-L-alanine]	**1g $7.50; 5g $28.75; 25g $95.00**
10,216-4	**DL-DOPA** [3-(3,4-dihydroxyphenyl)-DL-alanine]	**5g $8.75; 25g $34.50**
H6025-5	**Dopamine hydrochloride** (3-hydroxytyramine)	**5g $14.65; 10g $19.50**
16,113-6	**Dopamine hydrobromide** (3-hydroxytyramine)	**10g $5.50; 50g $16.00**
14,884-9	**DL-DOPS** [*threo*-3-(3,4-dihydroxyphenyl)-DL-serine]	**100mg $26.00; 500mg $89.50**
15,156-4	**5-Hydroxydopamine hydrochloride**	**100mg $13.20; 500mg $44.00**
14,980-2	**6-Hydroxydopamine hydrochloride**	**100mg $12.00; 500mg $48.00**
16,295-7	**6-Hydroxydopamine hydrobromide**	**250mg $8.00; 1g $20.00**
85,742-4	**DL-α-Methyldopa** [3-(3,4-dihydroxyphenyl)-2-methyl-DL-alanine]	**5g $9.50**
85,741-6	**L-α-Methyldopa monohydrate** [3-(3,4-dihydroxyphenyl)-2-methyl-L-alanine]	**1g $5.00; 5g $20.00**
12,069-3	**DL-α-Methyltyrosine**	**1g $6.55; 5g $22.00; 25g $74.10**
14,888-1	**DL-α-Methyltyrosine methyl ester hydrochloride**	**1g $9.70; 5g $33.30**

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