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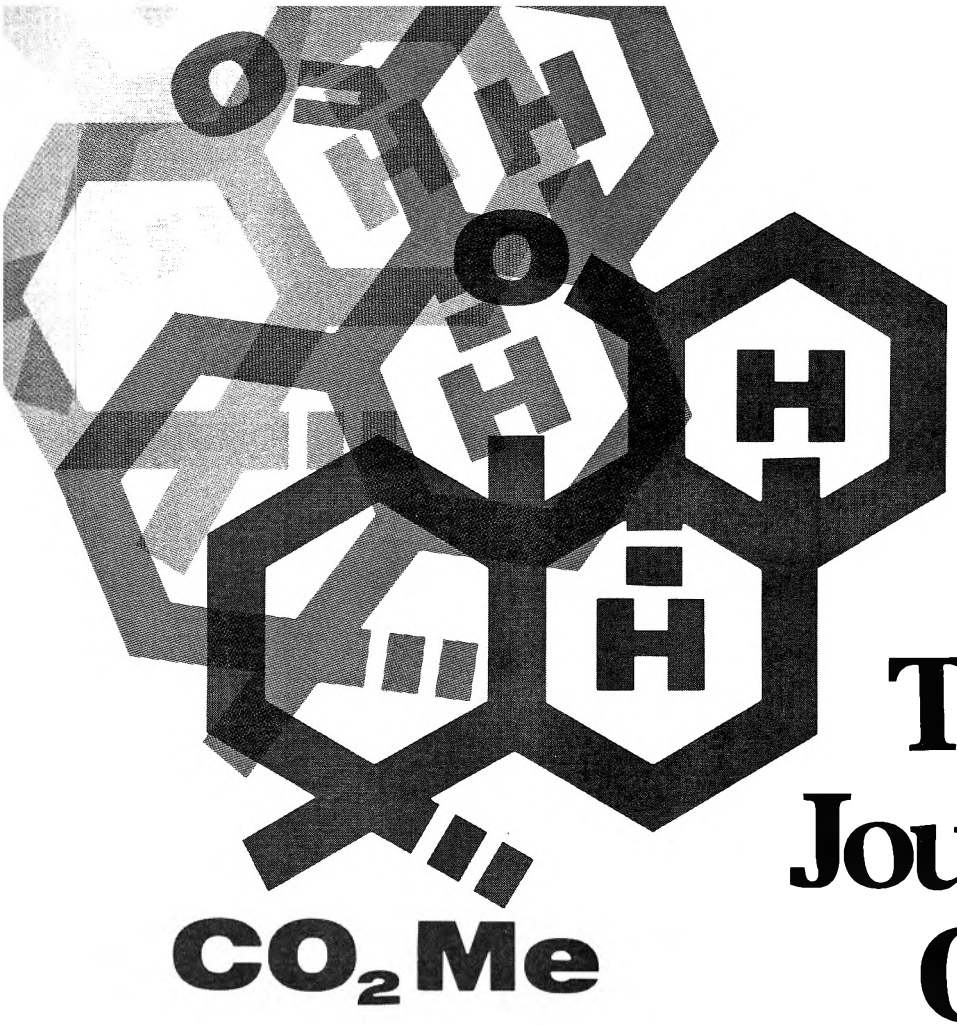

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APRIL 18, 1975

Experiments Directed toward the Total Synthesis of Terpenes. XIX. Synthesis of 8-Methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysen-1(2*H*)-one, a Key Intermediate in the Total Synthesis of (±)-Shionone[1]

Robert E. Ireland,* Marcia I. Dawson, Conrad J. Kowalski,[2] Christopher A. Lipinski,[3] David R. Marshall, Jefferson W. Tilley,[4] Jon Bordner, and Benes L. Trus[2]

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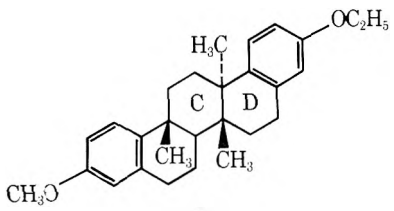
Received October 18, 1974

Three approaches to the synthesis of the tetracyclic ketone **3** (title compound), a key intermediate in the total synthesis of *dl*-shionone, are presented. One approach entails the introduction of the C-8a angular methyl group through the protolysis of the methoxycyclopropane grouping in the bicyclic alcohol **22**. The most efficient approach utilizes the triethylaluminum-catalyzed conjugate addition of hydrogen cyanide to introduce the C-4a angular methyl into the bicyclic enone **28**. The final approach reported entails the cationic cyclization of the polyolefinic aldehyde **47** which results in the direct conversion of an acyclic to a tetracyclic system. Confirmation of the structure and stereochemistry of the tetracyclic ketone **3** was obtained through single-crystal X-ray structure analysis.

Previous reports[5] in this series have discussed the planning and experiments that have led to the total synthesis of the pentacyclic triterpene alnusenone (**2**) through the key intermediate pentacyclic diether **1**. Earlier results[6] from



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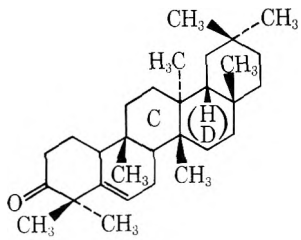

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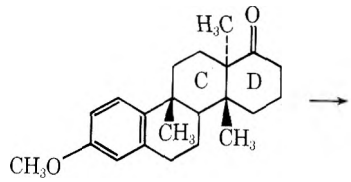
experiments designed to effect the synthesis of the diether **1** showed that the construction of polycyclic systems that contain the trans-fused, diangularly methylated C/D ring system present in alnusenone (**2**) would be a significant synthetic obstacle. As a result, several programs were initiated that were aimed specifically at the development of synthetic procedures for the elaboration of this crucial portion of the molecule. One[5] of these programs (the triethylaluminum-catalyzed conjugate addition of hydrogen cyanide to an appropriate enone) resulted in an efficient means for the synthesis of the diether **1**. The results of the other programs[7] are the subject of this and the following reports. These procedures provide alternate means for the synthesis of the alnusenone class of triterpenes in general and complementary schemes for the construction of trans-fused, diangularly methylated decalin systems in particular.

At the inception of this work two key intermediates for the triterpene syntheses were in mind. In addition to the diether **1**, the tetracyclic ketone **3** was proposed. This substance provides not only the opportunity for elaboration to a pentacyclic structure by the addition of ring E through an annelation procedure, but also the opportunity to develop a total synthesis of the tetracyclic triterpene shionone (**4**).[8] Thus the ketone **3** has functionality appropriately placed in the D ring for the addition of the side chain of shionone (**4**),[8] and the aromatic ring should provide ideal access to



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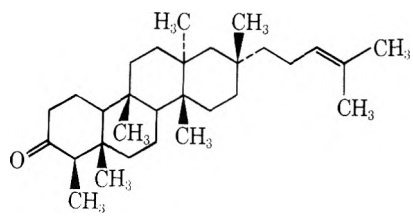

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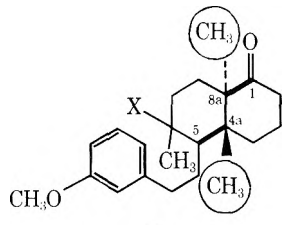
the substitution pattern present in the A ring of the triterpene. An added advantage inherent in the choice of shionone (4)[8] as an objective is that methods developed for the elaboration of the A ring in this molecule should also be applicable for the similar transformation of an aromatic ring in the synthesis of the pentacyclic triterpene friedelin.[9] Therefore, the key intermediate tetracyclic ketone **3** serves as a necessary component of the shionone (4) synthesis, a potentially useful intermediate in the synthesis of the pentacyclic triterpene series and a model for the investigation of the conversion of an aromatic ring to the shionone–friedelin A ring. As well, the ketone **3** retains the principal synthetic challenge of this series of triterpenes, namely, the trans-fused, diangularly methylated C/D ring system.

Since prior experience[10] in model systems had demonstrated the utility—both stereochemical and practical—of the Friedel–Crafts-type cyclialkylation for the formation of similar tetracyclic ketones, the intermediate objective became the construction of a functional derivative of the ketone **5.** Three approaches were taken to the problem: (1)



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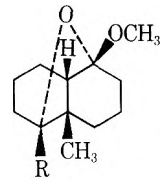
the stereoselective introduction of the C-8a angular methyl group into a dicyclic system that already contained the C-4a methyl group;[7a] (2) the reverse mode that entailed the stereoselective introduction of the C-4a angular methyl group into a dicyclic that already contained the C-8a methyl group;[7b] and (3) the stereoselective formation of the diangularly methylated, dicyclic system through the formation of the C-1 (8a) and C-4a (5) bonds in an acid-catalyzed cyclization of the appropriate polyene.[7c] Each of these approaches successfully led to the desired intermediate ketone **5** and thence to the tetracyclic ketone **3;** the unique features of each approach are discussed below.

1. Stereoselective Introduction of the C-8a Methyl Group. The starting material envisaged for this approach was the methoxyenone **10** (Chart I); this material was prepared in 24% overall yield on large scale from 2-methyldihydroresorcinol and 1,4-dimethoxy-2-butanone[11] through a five-step procedure (see Experimental Section) that involved annelation[12] and then reductive removal[13] of the allylic oxygen function. The location of the functionality in this ketone **10** is ideal for the introduction of both the C-8a methyl group and the β-arylethyl side chain. For the former transformation the protolysis of the derived cyclopropyl ether after a procedure suggested by the work of Wenkert and Berges[12] appeared well suited. In this work an efficient, stereoselective route to the 4a,8a-dimethyl-*cis*-1-decalone system was developed through protolysis of the cyclopropyl ether derived from the corresponding β-methoxyallylic alcohol. The stereochemical control results from the directive effect[14] of the alcohol function in the Simmons–Smith methylenation reaction,[15] and thus the overall stereochemical result is a function of the original configuration of this alcohol.

For the present purposes the desired *trans*-1-decalone series proscribed the use of a similar β-methoxy*allylic* alcohol in the methylenation reaction by virtue of the relative inaccessibility of the required axially oriented alcohol function. The disposition of the functionality in the ketone **10,** however, suggested that the desired outcome might be realized through the methylenation of the corresponding axial *homoallylic* alcohol system and that the latter arrangement might be attainable through condensation and/or reduction reactions of the starting ketone **10.** Two such series were investigated (Chart I).

Condensation of the ketone **10** with dimethyloxosulfonium methylide[16] resulted in equatorial attack by the ylide and the subsequent formation of the α-oxirane **15,** which on reduction with lithium aluminum hydride afforded the α (axial) alcohol **16** (R = H) in 77% overall yield. This alcohol **16** (R = H) was quite labile in contrast to the epimer formed by the direct addition of methyllithium to the ketone **10,** and was not purified sufficiently for combustion analysis. Indeed, the lability of the epimer **16** (R = H) served to prove its stereochemistry, for on standing at room temperature in chloroform solution or on treatment with mild anhydrous acid, the hydroxy enol ether cyclized to form the stable ketal **24** (R = CH_3). The epimeric alcohol was stable to these and even harsher acid conditions.



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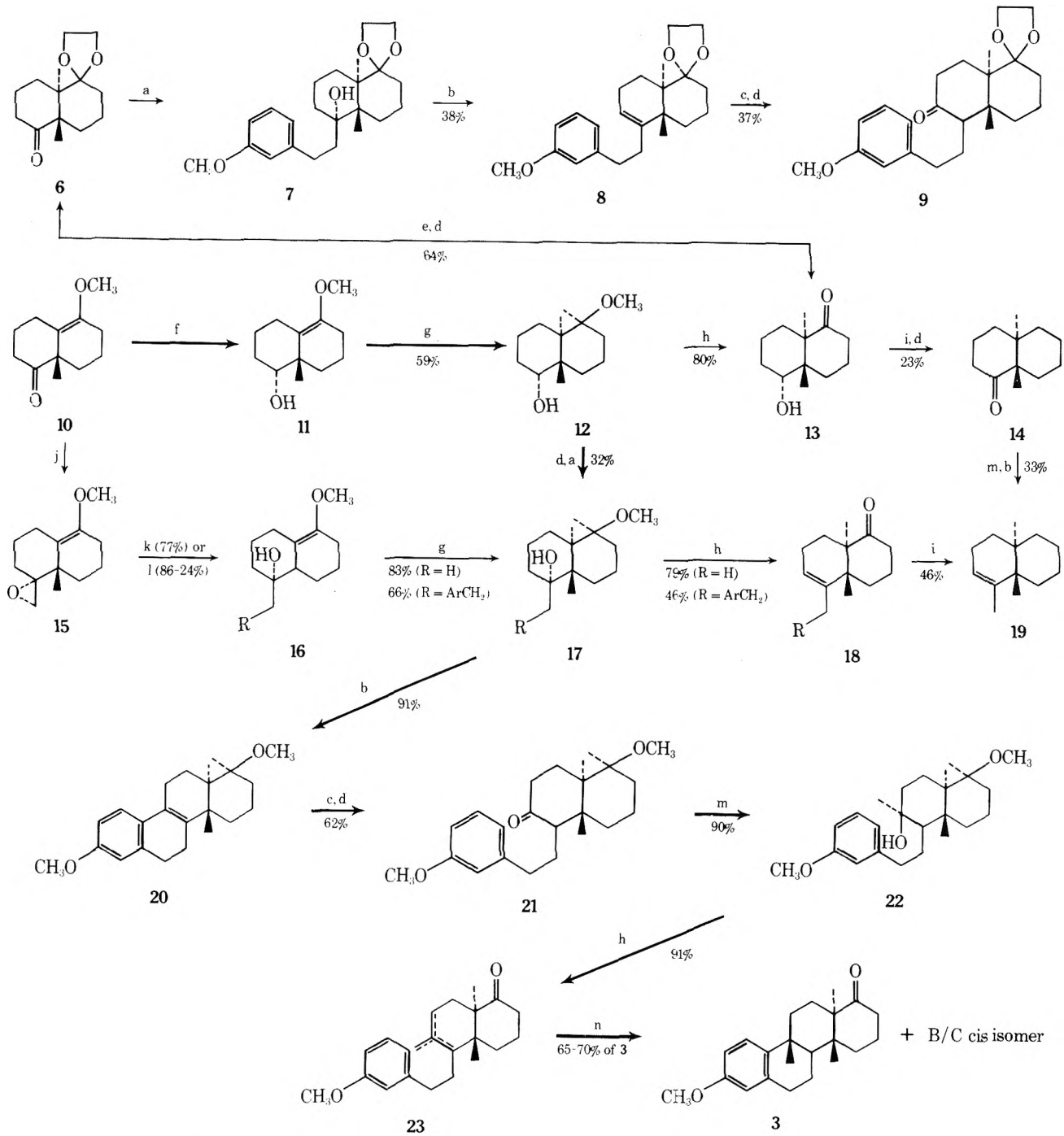
The lower homolog **11** of the axial alcohol **16** (R = H) also became available with the introduction of lithium 9b-boraperhydrophenalyl hydride[17] as a selective reducing agent. Thus, reduction of the ketone **10** with this reagent afforded a quantitative yield of a 70:30 mixture (NMR analysis) of the axial alcohol **11** and its epimeric equatorial isomer in contrast to the results with lithium aluminum hydride or sodium borohydride, which both gave >80% yields of only the equatorial alcohol. Again the axial alcohol **11** was quite labile and was readily converted to the ketal **24** (R = H) on standing in chloroform solution. For this reason both mixtures containing this axial alcohol **16** (R = H) and its higher homolog **16** (R = CH_3) were used in the methylenation reaction without further purification.

Methylenation[15] of both of these alcohol mixtures proceeded smoothly, and the methoxycyclopropane **12** was isolated in 59% overall yield from the ketone **10,** while the higher homolog **17** (R = H) was available in 64% overall yield. In each case the crucial stereochemical question was answered by conversion of these methoxycyclopropane derivatives to the corresponding diangularly methylated dicyclic compounds **14** and **19.** Thus, protolysis[12] of the methoxycyclopropane **12** afforded the keto alcohol **13,** while under similar protolytic conditions the tertiary alcohol in the higher homolog **17** (R = H) suffered dehydration during the cleavage, and the keto olefin **18** (R = H) resulted. Wolff–Kishner reduction and then oxidation of the keto alcohol **13** afforded the decalone **14,** the structure of which was unambiguously established through X-ray single-crystal structural analysis of a derivative (vide infra). Interrelation of this series with the materials prepared from the higher homolog was achieved through the olefin **19.**

With the preparative and stereochemical success of this sequence for the formation of a trans-fused, diangularly methylated 1-decalone derivative assured, attention was turned to the conversion of these intermediates to the desired tetracyclic ketone **3.** While this objective was ultimately achieved as outlined in Chart I (boldface arrows), this scheme was not possible until several unexpected characteristics of these decalone systems were uncovered.

Chart I
Synthesis of the Tetracyclic Ketone 3 via the Stereoselective Introduction of the C-8a Methyl Group[a]



[a] a, m-$CH_3OC_6H_4C{\equiv}CLi$, H_3O^+; 10% Pd/Cl, H_2, EtOAc; b, Py, $SOCl_2$, 0°; c, BH_3·THF; OH^-, H_2O_2; d, 8 N H_2CrO_4, acetone; e, $(HOCH_2)_2$, H^+, C_6M_6; f, $LiBR_3H$, THF; g, CH_2I_2, Zn(Cu), Et_2O, DME; h, 7% aq CH_3OH-HCl; i, N_2H_4-H_2O, KOH, DEG; j, $(CH_3)_2S^+OCH^-{}_2$, DMSO; k, $LiAlH_4$, Py; l, $(m\text{-}CH_3OC_6H_4CH_2)_2Mg$, dioxane; m, CH_3Li, Et_2O; n, p-TsOH, $C_6H_5CH_3$, Δ.

The initial plan entailed the conversion of the ketone **18** (R = H) to the corresponding α-methylene ketone[18] through a series of reactions in which sensitized photooxygenation[19] of the derived ketal **25** was a central feature. A variety of reaction conditions failed to generate any oxidation product, and only when the reaction was carried out in pyridine with hematophorphyrin[19] as the sensitizer for 132 hr was it possible to realize a meager 32% yield of the intermediate allylic alcohol **26.** The photooxygenation reaction is known[19] to be very sensitive to steric hindrance, and apparently the presence of angular methyl groups on both sides of this rigid olefin **25** sufficiently shields the rather remote double bond from attack by singlet oxygen. The α orientation of the hydroxyl group in the product **26** is proposed on the basis that the C-4a angular methyl group will

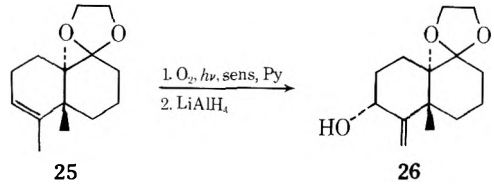


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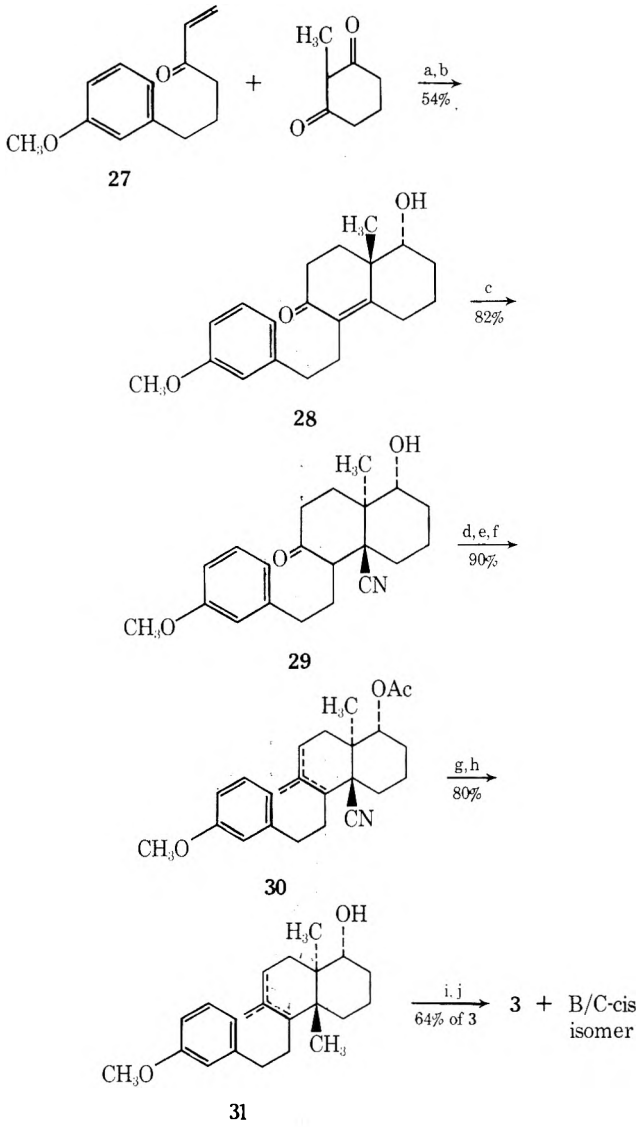
Chart II
Synthesis of the Tetracyclic Ketone 3 via the Stereoselective Introduction of the C-4a Methyl Group[a]



[a] a, Et_3N, CH_3OH; $C_6H_5CO_2H$, Et_3N; b, $NaBH_4$, EtOH; c, Et_2AlCN, C_6H_6 or Et_3Al, HCN, THF; d, CH_3MgI, C_6H_6–Et_2O; e, $(CH_3CO)_2O$, Py; f, $SOCl_2$, Py; g, $(i\text{-}Bu)_2AlH$, C_6H_6; h, N_2H_4, $N_2H_4 \cdot 2HCl$, TEG, KOH; i, 8 *N* H_2CrO_4, acetone; j, CF_3CO_2H, reflux.

offer more steric hindrance to the photooxygenation than the more distant C-8a methyl group.

Steric congestion was again shown to be an insurmountable factor in the preparation and reactions of the ketone **9** from the hydroxy ketone **13** (Chart I). Thus, the reaction of lithium (*m*-methoxyphenyl)acetylide with the ketone ketal **6** occurred in poor yield, and significant amounts of starting ketone ketal **6** were recovered. In spite of this it was possible to realize a 38% overall yield of the olefin **8** through dehydration of the saturated alcohol **7.** Again steric hindrance played a significant role, for hydroboration of this olefin **8** went slowly and even under optimized conditions led to only a 38% yield of the desired secondary alcohol. Chromic acid oxidation of this alcohol afforded the ketone **9** in excellent yield, but this ketone proved completely resistant toward the action of methyllithium, methylmagnesium bromide, and dimethylmagnesium. Thus, the steric hindrance toward reactions at C-5 and C-6 offered by the two angular methyl groups and buttressed by the C-1 ketal precluded further investigation of this already low-yield approach.

Inasmuch as the steric problems encountered above seemed to be associated with the tetrahedral substitution at positions 1 and 8a, attention was turned to an approach that avoided tetrahedral character at these positions until the remainder of the ring substitutions had been made. A means for accomplishing this goal became apparent when it was realized through handling experience that the methoxycyclopropane moiety was quite stable to all but relatively vigorous (refluxing 7% aqueous methanolic hydrochloric acid) protolytic conditions.

The first approach investigated stemmed from the α-oxirane **15** and led through the α (axial) alcohol **16** (R = $CH_2C_6H_5OCH_3$-*m*), formed by cleavage of the oxirane with di-*m*-methoxybenzylmagnesium bromide, to the methoxycyclopropane **17** (R = $CH_2C_6H_5OCH_3$-*m*). In one case this approach led to a 57% overall yield of the desired methoxycyclopropane, but these results proved unreproducible. Despite considerable experimentation the cleavage of the oxirane system by the magnesium derivative was very capricious (yields from 24 to 57%) and could not be standardized.

Finally, an acceptable, though far from ideal, route to the methoxycyclopropane **17** (R = $CH_2C_6H_5)OCH_3$-*m*) was realized through the alcohol **12.** Treatment of the ketone, formed in 73% yield by chromic acid oxidation of the alcohol **12,** with lithium *m*-methoxyphenylacetylide and catalytic hydrogenation of the product afforded a 44% overall yield of the α (axial) alcohol **17** (R = $CH_2C_6H_5OCH_3$-*m*), together with a 46% overall yield of the epimeric β (equatorial) alcohol. This unfortunate ratio of alcohol isomers severely reduced the attractiveness of this approach, for while dehydration of the α (axial) isomer **17** (R = $CH_2C_6H_5OCH_3$-*m*) with thionyl chloride–pyridine led to a 91% yield of the desired endocyclic olefin **20,** the same treatment of the β (equatorial) alcohol isomer resulted in a 43% yield of the corresponding exocyclic olefin as the only pure, isolable product.[20]

Despite these lackluster yields the olefin **20** was carried through the remainder of the proposed transformations, which resulted in the generation of the first samples of the tetracyclic ketone **3.** The final acid-catalyzed cyclization of the olefinic ketone **23** behaved as expected from the model series,[10] and while the B/C-trans isomer **3** was the predominant product, the cyclization also produced the B/C-cis isomer. The fact that these latter transformations can be realized at all adds credence to the hypothesis that the methoxycyclopropane moiety in the 1 and 8a positions reduces significantly the steric hindrance toward reaction at C-5 and C-6 over those cases cited earlier where the 1 and 8a positions were tetrahedrally substituted. Unfortunately, the overall yield of this successful approach to the tetracyclic ketone **3** was only 3.3% in 15 steps and further work on more viable approaches was warranted.

2. Stereoselective Introduction of the C-4a Methyl Group. Another sequence[7b] investigated for the preparation of the tetracyclic ketone **3** entailed the introduction of the C-4a angular methyl group through the initial conjugate addition of cyanide[21] to the enone **27** (Chart II). This sequence, which ultimately proved by far the most practical, closely parallels that used in the total synthesis of *dl*-alnusenone,[5] and some of the results reported in that series stemmed from observations made in the present case. Since these two experiences are so similar, only the unique features of the synthesis of the tetracyclic ketone **3** will be mentioned here.

An interesting feature of the present series was that, unlike the results found in the *dl*-alnusenone work,[5] the hy-

drocyanation of the enone **28** led to the same trans-fused cyano ketone **29** no matter whether preformed diethylaluminum cyanide[21c] or the mixture of triethylaluminum–hydrogen cyanide[21c] were used as the reagent. In both the triterpene synthesis and the extensive investigations of this method by its originator,[21b] these two conditions for the Nagata hydrocyanation led to mixtures of isomers that in the first case were considered to reflect thermodynamic control of the reaction, while in the second kinetic control was judged to predominate under the protic conditions. Indeed the protic character inherent in the hydroxy enone **28** may be the answer, and reaction under *both conditions* may reflect the protonation of the initially formed cyano diethylaluminum enolate[21a] by the ever-present hydroxyl group. In accord with this rationalization the hydrocyanation of the acetate or trimethylsilyl ether of the hydroxy enone **28** with diethylaluminum cyanide[21c] led to a mixture of products in which the trans cyano ketone was accompanied by at least one other isomer as judged by the NMR spectrum of the crude product. Unfortunately, after hydrolysis the only pure crystalline material that could be isolated from these mixtures in low yield was the familiar trans isomer **29**, and the hypothesis remains to be conclusively established by isolation of the cis cyano ketone.

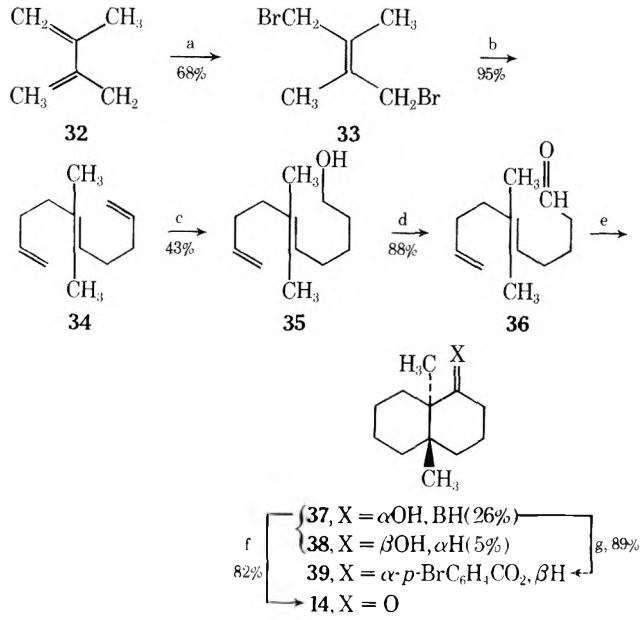
In view of the apparent efficiency of this sequence for the synthesis of the tetracyclic ketone **3**, an effort was made to optimize and streamline the synthesis so as to produce significant quantities of the ketone for further experimentation. This effort resulted in the procedures reported here (see Experimental Section) and the isolations outlined in Chart II. The overall yield of the ketone **3** from 2-methyldihydroresorcinol was 20.4% in ten steps and 10% from the *m*-methoxycinnamic acid used to prepare the vinyl ketone **27**.

Single-crystal X-ray structure analysis established that the structure of the tetracyclic ketone **3** was indeed that inferred from the chemical and spectroscopic data. The ketone **3** crystallized from ether as colorless plates elongated along the c axis, and the crystals were shown to belong to the $P_{na}2_1$ space group (Table I). The stereoscopic view (Figure 1) of the molecule shows that the conformations of the B, C, and D rings are half-boat, chair, and flattened chair, and the desired trans fusion between the C and D rings is apparent.

3. Polyene Cyclization Approach. An alternate approach to the synthesis of polycyclic systems with terpenoid stereochemistry and substitution is through the acid-catalyzed cyclization of polyolefinic substrates. The elegant work[22] of Johnson, Corey, and van Tamelen has reduced this biochemically patterned route[23] to laboratory practice for the construction of steroids and certain terpenes. Before these principles could be applied to the synthesis of the tetracyclic ketone **3** it seemed wise to test certain aspects of the approach in model systems.

Consideration of the disposition of the angular methyl groups in the target ketone **3** suggests that cyclization of the aldehyde **46** (Chart IV) or a derivative would lead to an alcohol which could easily be transformed into the desired product. Even at the outset of this work there was ample precedent[24] for the utility of the anisyl ring in the termination of a cationic cyclization process, although in most cases both ortho and para substitution products were observed. Of preliminary concern, therefore, was the lack of prior evidence for the compatibility of a tetrasubstituted double bond with the cationic cyclization process.[25] Two problems were considered, namely, the greater basicity of the tetrasubstituted double bond might interfere in the acidic conditions necessary for cyclization through initial complexation with the catalyst, and the symmetrical substitution of the tetrasubstituted double bond could result[26] in the formation of *either* five- or six-membered rings during the cyclization process. Rather than deferring the answers to these questions until the complex olefinic aldehyde **46** was prepared, it was decided that they could best be determined in the less complex model system[7c] that represented the C/D ring system of the ketone **3**. This approach also provided experience with the stereoselective synthesis of polyolefinic materials that contain such tetrasubstituted double bonds—an ancillary question of no minor concern.

Chart III
Formation of 4aβ,8aα-Dimethyl-1-decalone via Polyene Cyclization[a]



[a] a, Br_2, $HCCl_3$; b, $CH_2{=}CHCH_2MgBr$, Et_2O–THF; c, Sia_2BH, OH^-, M_2O_2; d, $CrO_3 \cdot 2Py$, CH_2Cl_2; e, 5 equiv $SnCl_4$, CH_3NO_2; Pt, EtOH, H_2; f, 8 *N* H_2CrO_4, acetone; g, *p*-BrC_6H_4COCl, Py.

The desired substrate for this model study was the aldehyde **36**, which was conveniently prepared from 2,3-dimethylbutadiene (**32**) as outlined in Chart III. Indeed this synthetic scheme, and particularly the trans dibromide **33**,[27] served the dual role of providing the compounds for the model series, as well as a viable approach and the key starting material for the ultimate synthesis of the aldehyde **46**. Particularly important were the ease of generating stereochemically homogeneous materials that contained the tetrasubstituted double bond, and the functional symmetry of the initial intermediates that obviated tedious, yield-consuming selective reactions early in the scheme.

The cationic cyclization[22] of the aldehyde and the derived ethylene acetal were investigated in several solvent systems with stannic chloride, boron trifluoride, or trifluoroacetic acid catalysts. The yields of cyclic material were rather low in all systems but appeared best when the aldehyde **36** itself in nitromethane at 0° was treated with 5 equiv of stannic chloride. The initial product mixture from such treatment was subjected to catalytic hydrogenation without purification, and the saturated alcohols **37** and **38** were isolated by a combination of direct crystallization and preparative thin layer chromatography. Oxidation of these alcohols **37** and **38** afforded the same saturated ketone **14**, the infrared spectrum of which confirmed the formation of a six-membered ring ketone. In addition the NMR spectrum of the major alcohol **37** showed resonances at δ 0.96 and 1.0 which were assigned to angular methyl groups in the bicyclic system. Further, Wolff–Kishner reduction of

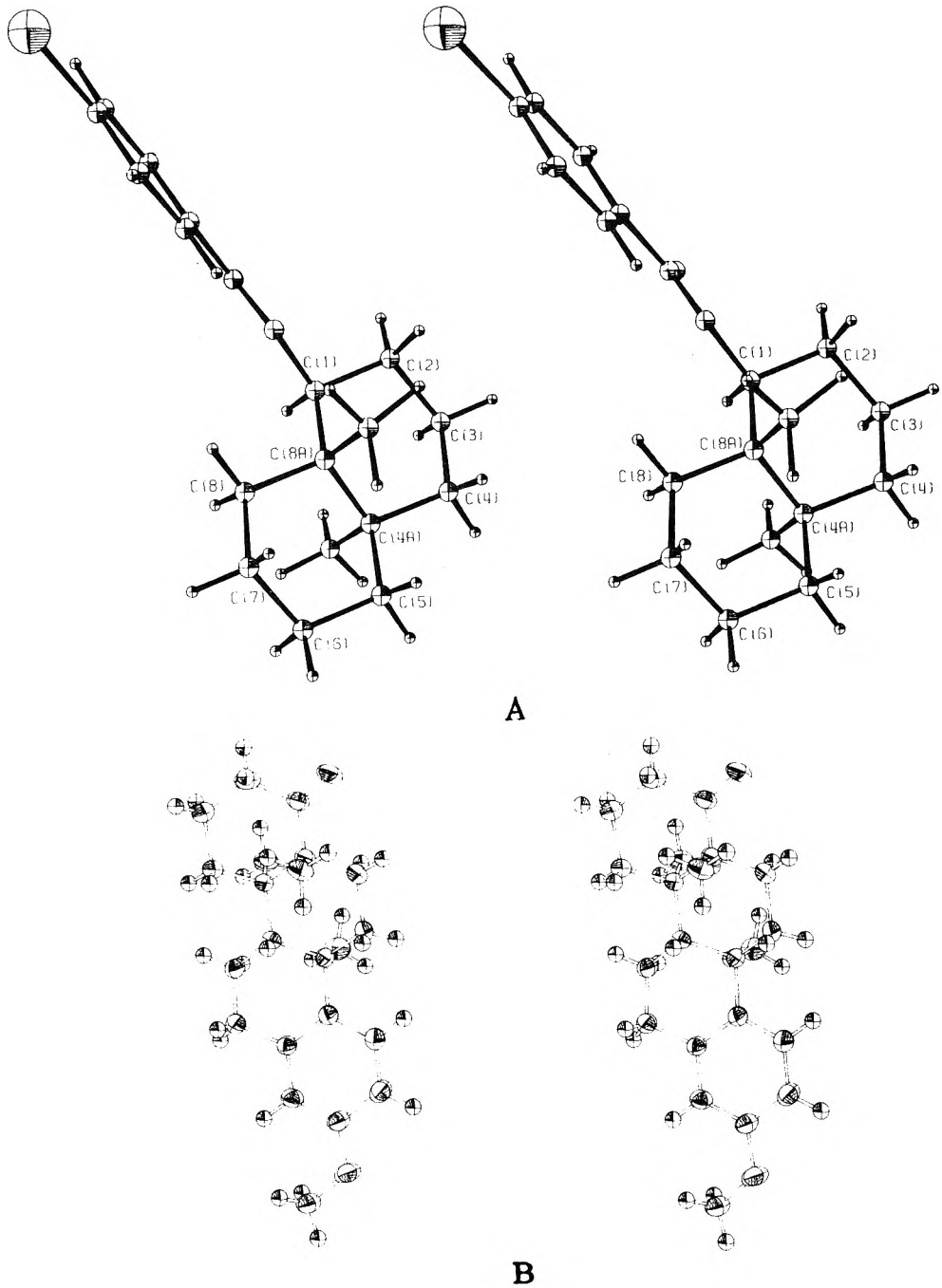


Figure 1. Stereoplot of (A) *p*-bromobenzoate **39** and (B) tetracyclic ketone **3.**

the ketone **14** afforded a hydrocarbon (mp 97–98°) that was *different* from the corresponding 4aβ,8aβ-dimethyldecalin (mp 88–91°) obtained by the similar reduction of the known[28] 4aβ,8aβ-dimethyl-2-decalone. Thus, on the assumption that a decalin system has been formed by this cyclization, it was reasonable to propose the trans-fused, diangularly methylated structures **37** and **38** on the basis of the above evidence. Confirmatory proof that this hypothesis was correct was found in the single-crystal X-ray structure analysis of the *p*-bromobenzoate **39,** prepared from the major alcohol **37.** The stereoplot of the structure that resulted from this analysis (Figure 1) shows the trans-fused decalin system, the equatorial *p*-bromobenzoate, and the chair conformation of each six-membered ring. The dramatic steric congestion at the ring positions adjacent to the fusion experienced in the chemistry described in the first approach above is not obvious from this molecular picture. However, the important questions for the approach at hand have been satisfactorily answered, and a trans-fused, diangularly methylated bicyclic system does result from the cationic cyclization of a system that contains a tetrasubstituted double bond. The low yield (31% total of alcohols **37** and **38**) may be result of several factors, one of which may indeed be the presence of the basic tetrasubstituted double bond.

Despite the discouraging yields in the model series, the investigation was pressed further to the tetracyclic cyclization. For the synthesis of the aldehyde **46** for cyclization to the tetracyclic ketone **3,** it was necessary to modify the scheme used in the model series so as to incorporate differentiatable functionality in the branches (Chart IV). The convenient stereochemical control provided by the dibromide **33** dictated its use as the starting material, and the plan entailed the dienyne **42** as a crucial intermediate. Several attempts to convert the triene **34** to the dienyne **42** by selective additions to one terminal double bond were unsuccessful, and the coupling of the dibromide **33** with 1 equiv of allylmagnesium bromide gave only polymeric materials

and none of the desired monocoupling product. In an attempt to form the enediyne **41** the coupling reaction between the dibromide **33** and propyne derivatives was investigated. Application of the lithio-1-trimethylsilylpropyne coupling procedure[29] afforded less than 5% (GLC analysis) of the expected disilyl derivative **42**, but direct coupling[7d] of the dibromide **33** with propargylmagnesium bromide and then trimethylsilylation of the crude product to derivatize the acetylenic portion in the presence of any allenes formed afforded the desired disilyl enediyne **42** in good yield. In this manner the symmetrical enediyne **41** became readily available after cleavage[30] of the trimethylsilyl groups, and monoreduction[31] of one acetylenic group through protolysis of the derived organoborane provided a viable route to the crucial dienyne **42**. The plan for this molecule entailed the use of the remaining acetylenic unit for the incorporation of the trisubstituted double bond and its appended aromatic substituent while the terminal double bond was used to mask the aldehyde function throughout these operations. These transformations, which were accomplished as outlined in Chart IV, led to the desired aldehyde **46** in good yield. Central to this scheme was the application of the Corey trisubstituted olefin synthesis[32] for the stereoselective generation of the last double bond.

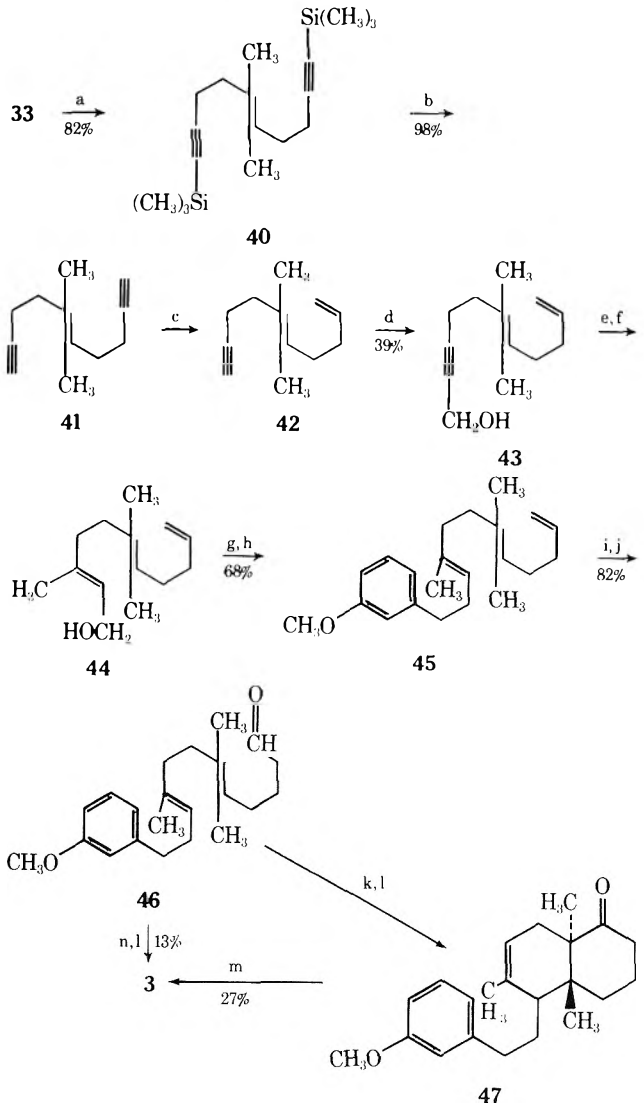
The cationic cyclization of the aldehyde **46** was again investigated under several sets of conditions suggested by the work of Johnson and coworkers.[22] While the corresponding acetal of the aldehyde **46** was investigated as well, again there seemed to be no advantage in using this more stable derivative. None of these cyclizations were clean, and in addition to polymeric material, the product mixture always contained four or more components. Three of these were rigorously identified after preparative thin layer and gas–liquid chromatography of the mixture formed by treatment of the aldehyde **46** with 0.5 equiv of stannic chloride in benzene at 25° for 75 sec and then oxidation to form ketonic products. The nonpolymeric portion of this mixture, obtained in a 58% yield, consisted of 12% of what was judged by NMR and infrared spectroscopy to be a mixture of monocyclic five- and six-membered ring, unsaturated ketones, 44% of the octalinone **47**, 23% of the desired tetracyclic ketone **3**, and 15% of the isomeric 1-methoxytetracyclic ketone that results from cationic attack of the anisyl ring in the poition ortho to the methoxyl group. At best this represents only a 13% yield of the ketone **3** from direct cyclization of the aldehyde **46**. The major product was the octalinone **47** that results from deprotonation of the intermediate cation rather than attack of the aromatic ring. Concurrent work referred to above indicated that strong protonic acid catalyzed cyclization of the octalinone **47** should complete the formation of the ketone **3**, and this proved to be the case. Interestingly, in this latter experiment none of the isomeric ortho-substituted tetracyclic ketone was formed but, as experienced earlier, significant quantities of the epimeric B/C cis-fused tetracyclic ketone were formed. As expected from the extensive work of the Johnson group,[22] none of the latter epimer was observed from the polyolefin cyclization.

Since an efficient method was available for the subsequent conversion of the octalinone **47** to the desired tetracyclic ketone **3**, an effort was made to optimize the formation of this bicyclic derivative at the expense of the tetracyclic substances. Even this ploy met with only limited success, and after considerable experimentation, the best yield of the tetracyclic ketone **3** that could be realized from the aldehyde **46** by a combination of stannic chloride and, after oxidation, *p*-toluenesulfonic acid catalyzed cyclization was 27%.

While in our hands this polyolefin cyclization route is not competitive with the preceding conjugate cyanide addition sequence for the preparative formation of the tetracyclic ketone **3**, these experiments do offer some insight about both the process and this system. The success of the laboratory polyene cyclization scheme for the synthesis[22] of steroids and terpenes from acyclic substrates that bear the squalene-like disposition of methyl substituents is well documented. The polyene used here deviates from this pattern substantially, and yet cyclization to a tetracyclic system does indeed occur in significant amounts. Unfortunately, inherent in these deviations of more normal polyisoprenoids is the introduction of a more labile tetrasubstituted double bond and a less nucleophilic aromatic ring. It seems probable that these components of the substrate coupled with the apparent necessity that the cyclization be initiated from the sensitive aldehyde function account for the relatively low overall yields observed.

In spite of the difficulties encountered in the cyclization of the aldehyde **46**, this polyolefin approach to the synthe-

Chart IV
Synthesis of the Tetracyclic Ketone 3 via Polyene Cyclization[a]



[a] a, $CH_2{=}C{=}CHMgBr$, THF; EtMgBr, THF, $(CH_3)_3SiCl$; b, $AgNO_3$, KCN, aq EtOH; c, Sia_2BH, HOAc; d, EtMgBr, HCHO, THF; e, $LiAlH_4$, $NaOCH_3$, THF; I_2, THF, −78°; f, $LiCu(CH_3)_2$, Et_2O; g, $(C_6H_5)_3P$, CCl_4; h, *m*-$CH_3OC_6H_4CH_2MgCl$, 20% HMPA–THF; i, Sia_2BH, OH^-, H_2O_2; j, $CrO_3 \cdot 2Py$, CH_2Cl_2; k, 0.5 equiv $SnCl_4$, C_6H_6, 25°, 65 sec; l, 8 *N* H_2CrO_4, acetone; m, *p*-TsOH, $CH_3C_6H_5$, Δ; n, 0.5 equiv $SnCl_4$, C_6H_6, 25°, 75 sec.

sis of the tetracyclic ketone **3** was competitive with the more classical approach through protolysis of the methoxycyclopropane **22**. The aldehyde **46** was available in 17% overall yield from the dibromide **33** in ten operations, and this yield, coupled with the 27% observed for the two-stage cationic cyclization, amounts to a 4.5% overall yield of the tetracyclic ketone **3** in 12 steps. The ease and efficiency of the formation of the aldehyde **46** developed in this work prompted a further investigation[33] of its use for the preparation of alternate substrates for related cationic cyclizations to pentacyclic intermediates in the synthesis of the friedelin–alnusenone family of triterpenes.

Experimental Section[34]

5-Methoxy-8aβ-methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione. To a 2-l. flask containing 70.0 g (0.555 mol) of 2-methyldihydroresorcinol was added a solution of 69.2 g (0.522 mol) of 1,4-dimethoxy-2-butanone[11] and 16.0 ml of triethylamine in 100 ml of triethylamine in 100 ml of xylene. The atmosphere was replaced with nitrogen, and the mixture was heated to reflux. After 1.5 hr, 50 ml of solvent was removed by distillation, and 23.6 g of benzoic acid and 23 ml of triethylamine were added. Reflux was continued for 15 hr while the water formed was removed through a Dean-Stark apparatus. Upon cooling, the solution was washed with three 250-ml portions of 5% aqueous potassium hydroxide and dried (Na_2SO_4). After filtration, removal of the solvent at reduced pressure afforded 51.3 g (47%) of a yellow, crystalline solid, mp 66–71°. Extraction of the aqueous washings with chloroform yielded an additional 5.30 g (5%) of the same material (overall yield based on 1,4-dimethoxy-2-butanone, 52%). The analytical sample obtained after two crystallizations of a sample of this material from ether–hexane melted at 78–80°: ir ($CHCl_3$) 1715 (C=O), 1680 (unsaturated C=O), and 1615 cm^{-1} (conjugated C=C); NMR ($CDCl_3$) δ 1.43 (s, 3, C-8a CH_3), 3.67 (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.10; H, 7.81.

5-Methoxy-8aβ-methyl-3,4,6,7,8,8a-hexahydro-1(2*H*)-naphthalenone (10). A solution of 37.70 g (0.181 mol) of the above diketone in 250 ml of ether was added to a stirred solution of 15.70 g (0.413 mol) of lithium aluminum hydride in 2 l. of dry ether over the course of 1 hr. After decomposition of the excess hydride with ethyl acetate and 10% aqueous sodium hydroxide and then filtration of the solids, followed by evaporation of the ether, 35.8 g (95%) of a white, crystalline solid, mp 88–92° (part melt) and 134–140°, was isolated that consisted of a 2:1 mixture of the 6β and 6α alcohol isomers by NMR integration of the C-8a angular methyl resonances. An analytical pure sample of the 6β isomer obtained from another experiment under the same conditions, prepared after two crystallizations of this mixture from ethyl acetate, melted at 147–150°: ir ($CHCl_3$) 3600 (OH) and 1665 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.22 (s, 3, C-8a CH_3) and 3.70 (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.98; H, 9.59.

A solution of 35.8 g (0.169 mol) of the crude diol above in 600 ml of dry pyridine was treated with 62.5 ml (0.85 mol) of acetic anhydride, and the reaction mixture was stirred at room temperature for 17 hr. After dilution with 500 ml of saturated aqueous sodium bicarbonate, the product was isolated by ether extraction.[35] The residue amounted to 50.1 g (quantitative) of the corresponding diacetates as an oil. Purification by preparative TLC (40% ether–petroleum ether, double elution) and evaporative distillation (100°, 0.025 mm) of a portion of this material afforded an analytically pure sample of a mixture of C-6 isomers: ir ($CHCl_3$) 1725 (C=O) and 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.08 (s, 1, C-8a CH_3 of 6αa isomer), 1.15 (5, 2, C-8a CH_3 of 6β isomer), 2.03 and 2.05 (pair of s, 6, acetate CH_3), and 3.48 (s, 3, OCH_3).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.88; H, 8.24.

To a solution of 23.7 g (0.08 mol) of the above diacetate mixture and 60 ml (0.63 mol) of dry *tert*-butyl alcohol in 1 l. of ethylamine was added 5.5 g (0.80 mol) of lithium wire in small pieces over 5 min with rapid stirring. After stirring for 20 min, excess lithium was destroyed with solid ammonium chloride, and the ethylamine was removed by evaporation in a stream of nitrogen. The product was isolated by ether extraction[35] and chromatographed on 920 g of neutral alumina I. Elution with 17 l. of ether afforded 15.78 g (58%) of the methoxyoctalol, mp 83.5–86.5°. The analytical sample, obtained after three crystallizations from ether–hexane, melted at 85.5–865°: ir ($CHCl_3$) 3610 (OH) and 1645 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.02 (s, 3, C-8a CH_3)and 3.47 (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.50; H, 10.23.

A solution of 6.10 g (31.1 mmol) of the above alcohol in 50 ml of dry dichloromethane was oxidized with 900 ml (0.175 mol) of a 5% solution of chromium trioxide–dipyridine complex[36] in dry dichloromethane, and the product was isolated by suction filtration of the reaction mixture through 375 g of grade II alumina, which was followed by a washing with 1 l. of ether. After evaporation of the solvents at reduced pressure, the residue (5.86 g) was adsorbed on 150 g of grade II alumina, and then 5.02 g (82%) of the ketone **10** as a water-white oil was eluted with 700 ml of 10% ether–petroleum ether. The analytical sample was obtained after evaporative distillation of a sample at 50° and 0.025 mm: ir ($CHCl_3$) 1705 (C=O) and 1670 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.35 (s, 3, C-8a CH_3) and 3.40 (s, 3, OCH_3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.01; H, 9.49.

Spiro-1α-oxiranyl-5-methoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (15). A solution of dimethyloxosulfonium methylide[16] from 798 mg (19.0 mmol) of 57% sodium hydride dispersion and 4.25 g (19.3 mmol) of dry trimethyloxosulfonium iodide in 40 ml of dry dimethyl sulfoxide was transferred by syringe to a 50-ml flask that contained a solution of 361 mg (1.86 mmol) of ketone **10** in 4 ml of dry dimethyl sulfoxide under a nitrogen atmosphere. The course of the reaction was monitored by GLPC,[35] and after 7 hr at 23° when the peak representing starting material had disappeared, the excess reagent was carefully decomposed with 1.0 ml of water. An additional 15 ml of water was then added, and the product was isolated by ether extraction.[35] The residue, purified by preparative TLC (20% ether–petroleum ether, double elution), afforded 315 mg (81%) of the α-oxirane **15** (R_f 0.7) which crystallized on standing at −10°: ir ($CHCl_3$) 1670 (C=C), 1130 (C–O), and 1055 cm^{-1} (C–O); NMR ($CDCl_3$) δ 1.20 (, 3, C-8a CH_3), 2.33 and 2.70 (2 d, 1 each, J = 5.5 Hz, oxirane CH_2), and 3.42 (s, 3, OCH_3). This material was sensitive to storage and was not purified further for additional analysis but used directly.

1β,8aβ-Dimethyl-5-methoxy-1,2,3,4,6,7,8,8a-octahydro-1α-naphthol (16, RH = H). To a solution of 740 mg (3.55 mmol) of the above oxirane in 25 ml of dry pyridine at 0° (ice bath) was added 440 mg (11.6 mmol) of lithium aluminum hydride. The mixture was stirred 10 min at 0°, then 1 hr at room temperature. The muddy-green solution was diluted with 25 ml of ether; the excess hydride was destroyed by the consecutive addition of 0.45 ml of water, 0.45 ml of 10% aqueous potassium hydroxide solution, and 1.35 ml water, and then the mixture was filtered. The filtrate was washed with water (2 × 20 ml), saturated aqueous copper(II) sulfate (2 × 20 ml), and saturated brine (2 × 20 ml) and then dried ($MgSO_4$). Filtration of this mixture through 30 g of grade II alumina with the aid of 200 ml of 50% ether–petroleum ether and evaporation of the solvents at reduced pressure afforded 690 mg (94%) of the alcohol **16** (R = H) as an oil, which was contaminated with less than 5% of the equatorial alcohol isomer by comparative NMR integration of the C-1 and C-8a methyl groups. This alcohol was quite labile and was used without further purification: ir ($CHCl_3$) 3500 (OH) and 1665 cm^{-1} (C=C); NMR ($CDCl_3$ + 1 drop pyridine) δ 1.11 (s, 3, C-8a CH_3), 1.13 (s, 3, C-1 CH_3), and 3.47 (s, 3, OCH_3).

1α,8β-Dimethyl-5-methoxy-1,2,3,4,6,7,8,8a-octahydro-1β-naphthol. To a solution of 2 ml (4 mmol) of a 2 *M* ethereal solution of methyllithium in 5 ml of dry ether was added dropwise 109 mg (0.52 mmol) of the ketone **10** in 1.0 ml of dry ether under a nitrogen atmosphere. After 1 min the mixture was cooled in an ice bath, and the remaining reagent was decomposed with 0.50 ml of water. Isolation of the product by ether extraction[35] afforded 118 mg of a colorless oil. The analytical sample was prepared by preparative TLC (20% ether–petroleum ether) and evaporative distillation (60°, 0.005 mm) of a sample of this material: ir ($CHCl_3$) 3600 (OH) and 1665 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.15 (s, 3, C-8a CH_3), 1.20 (s, 3, C-1 CH_3), and 3.45 (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.33; H, 10.51.

1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β,8aβ-dimethyl-5β-methoxy-1α-naphthol Ketal (24, R = CH_3). A solution of 79 mg (0.38 mmol) of the alcohol **16** (R = H) in 1 ml of chloroform-*d* was stored in an NMR tube, and after 5 days at 25° the NMR spectrum indicated that the starting alcohol had disappeared and that

a single product was formed. Evaporation of the solvent gave 63 mg (80%) of an oil which afforded 43 mg (55%) of the pure ketal **24** (R = CH_3) after preparative TLC (15% ether–benzene) and evaporative distillation at 55° and 0.05 mm: ir ($CHCl_3$) 1085 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.92 (s, 3, C-8a CH_3) and 3.37 (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.26; H, 10.56.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1β,8aβ-dimethyl-5α,4a-methano-5β-methoxy-1α-naphthol (17, R = H). To a solution of the Simmons–Smith reagent[15] prepared from 12.8 g (0.183 mol) of zinc–copper couple[37] and 14.7 ml (0.183 mol) of dry diiodomethane in 250 ml of dry ether was added a solution of 4.04 g (0.019 mol) of the alcohol **16** (R = H) in 20 ml of dry ether and 15 ml (0.17 mol) of dry 1,2-dimethoxyethane over a period of 10 min. After 40 min at room temperature the flask was cooled in an ice bath, and the excess reagent was decomposed with 3.0 ml of 10% aqueous ammonium chloride. The product was isolated by ether extraction including a base wash[35] and the residue was chromatographed on 300 g of grade II alumina. Elution with 1200 ml of 50% ether–petroleum ether gave 3.54 g (83%) of crystalline methoxycyclopropane **17** (R = H), mp 58–60°. The analytical sample, obtained by crystallization of a sample from ether–heptane, then from ethanol–water, melted at 60–61.5°: ir ($CHCl_3$) 3600 (OH) and 1075 and 1060 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.52 and 0.82 (2 d, 1 each, J = 5.5 Hz, cyclopropyl CH_2), 1.03 (s, 3, C-8a CH_3), 1.15 (s, 3, C-1 CH_3), and 3.23 (s, 3, OCH_3).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.01; H, 10.78.

3,4,4a,7,8,8a-Hexahydro-1,4aα,8aβ-trimethyl-5(6*H*)-naphthalenone (18, R = H). A solution of 595 mg (2.65 mmol) of the methoxycyclopropane **17** (R = H) in 20 ml of methanol and 2.0 ml of 37–38% hydrochloric acid was refluxed for 4 hr, cooled, and then neutralized with saturated aqueous sodium bicarbonate. After most of the methanol was removed at reduced pressure, the product was isolated by ether extraction, including a base wash,[35] and then the residual yellow oil (510 mg) was chromatographed on 20 g of grade II alumina. Petroleum ether (150 ml) eluted 376 mg (74%) of the ketone **18** (R = H), mp 67–68°, the analytical sample of which was prepared by crystallization of a portion from ethanol–water and sublimation (50°, 0.025 mm) and melted at 68–69°: ir ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.00 (s, 3, C-8a CH_3), 1.22 (s, 3, C-4a CH_3), 1.65 (d, 3, J = 1.5 Hz, C-1 CH_3), and 5.20 (m, 1, vinyl).

3,4,4a,5,6,7,8,8a-Octahydrol-1,4aα,8aβ-trimethylnaphthalene (19). A. From Ketone 18 (R = H). A solution of 141 mg (0.735 mmol) of the ketone **18** (R = H), 500 mg of crushed potassium hydroxide, and 0.40 ml of 85% hydrazine hydrate in 5 ml of diethylene glycol was heated under nitrogen to 100–105° for 30 min and then to 200–205° for 120 min while the volatile products distilled. The apparatus was cooled, and the contents of the pot and receiver were combined and extracted with ether. The ether solution was dried ($MgSO_4$), and the solvent was distilled at atmospheric pressure; sublimation of the crude product at 40° and 0.025 mm afforded 60 mg (46%) of white crystals. The analytical sample, obtained after preparative TLC (petroleum ether) and resublimation (40°, 0.025 mm), melted at 52–55°: ir ($CHCl_3$) 1640 cm^{-1} (weak); NMR ($CDCl_3$) δ 0.90 (s, 3, C-4a CH_3), 1.03 (s, 3, C-8a CH_3), 1.58 (d, 3, J = 1.5 Hz, C-1 CH_3), and 5.03–5.23 (m, 1, vinyl).

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.36; H, 12.48.

B. From Ketone 14. The corresponding tertiary alcohol was prepared from 59 mg (0.33 mmol) of the ketone **14** in 12 ml of ether by the addition of 2 ml of a 2 *M* ethereal solution of methyllithium under a nitrogen atmosphere. The product (59 mg) from this treatment was shown to contain 25% of the ketone **14** and 75% of the desired alcohol by GLC (150°),[35] and this mixture was retreated with methyllithium as above. After preparative TLC (benzene) of the crude product and then evaporative distillation (60–70°, 0.25 mm) of the tertiary alcohol band, the analytical pure alcohol (40 mg) was obtained as crystals that melted at 40–41°: ir ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.03 (s, 3, C-8a CH_3), 1.08 (s, 3, C-1 CH_3), and 1.30 (s, 3, C-4a CH_3).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.33. Found: C, 79.41; H, 12.33.

Dehydration of the alcohol (50 mg, 0.25 mmol) in 5 ml of dry pyridine was accomplished at −10° in 45 min with 0.30 ml (4.1 mmol) of thionyl chloride. After dilution of the reaction with water, the product was isolated by ether extraction[35] and then chromatographed on 5 g of grade I alumina. Elution with 15 ml of pentane afforded the olefin **19**, mp 50–54°, as a crystalline solid. The infrared and NMR spectra of this sample were identical with those of the material prepared in part A, and the melting point of a mixture of the material from part A, mp 45–50°, and part B, mp 50–54°, was 45–50°.

5-Methoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydro-1,5-naphthol (11). To a solution of 448 mg (2.30 mmol) of the ketone **10** in 5 ml of dry tetrahydrofuran was added 4.20 ml (3.20 mmol) of a 0.77 *M* tetrahydrofuran solution of lithium perhydro-9b-boraphenalylhydride[17] at −10° (ice–salt bath) under a nitrogen atmosphere. After 30 min, the excess reagent was destroyed by the careful, dropwise addition of 2.0 ml of 3 *N* aqueous sodium hydroxide, followed by 1.0 ml of 30% hydrogen peroxide. The mixture was poured onto 30 ml of 20% aqueous potassium carbonate, and the product was isolated by ether extraction.[35] There remained a residue of 483 mg of a colorless oil that comparative NMR integration of the angular methyl resonances showed was a 70:30 mixture of the axial alcohol **11** and its equatorial epimer. The axial alcohol was quite labile, and therefore this mixture was used without further purification: ir ($CHCl_3$) 3600 (OH), 1670 cm^{-1} (C=C); NMR (CCl_4) δ 0.95 (s, 0.9, C-8a CH_3, equatorial alcohol), 1.05 (s, 2.1, C-8a CH_3, axial alcohol), 3.40 (s, 0.9, OCH_3, equatorial alcohol), and 3.43 (s, 2.1, OCH_3, axial alcohol).

1,2,3,4,4a,β,5,6,7,8,8a-Decahydro-5β-methoxy-8aβ-methyl-1α-naphthol Ketal (24, R = H). A solution of 154 mg (0.785 mmol) of the above crude mixture of alcohols in 3 ml of chloroform-*d* that contained 1–2 mg of *p*-tolulenesulfonic acid was allowed to stand for 12 hr at room temperature. After removal of the solvent, preparative TLC (30% ether–petroleum ether) gave two bands, the first of which (R_f 0.1, 64 mg) was shown to be a mixture of starting alcohols and their hydrolysis products by NMR. The faster moving band (R_f 0.3) contained 43 mg (28% from the ketone **10**) of the pure ketal **24** (R = H). The analytical sample was obtained by evaporative distillation of this sample at 45° and 0.15 mm: ir ($CHCl_3$) 1055 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.97 (s, 3, C-8a CH_3), 3.30 (s, 3, OCH_3), and 3.77–3.90 (m, 1, CH–O–C).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.54; H, 10.23.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-5α,4a-methano-5β-methoxy-8aβ-methyl-1α-naphthol (12). In a manner similar to that described above for the formation of the methoxycyclopropane **17** (R = H), the Simmons–Smith reagent[15] prepared from 2.10 g (30.0 mmol) of zinc–copper couple[37] and 2.40 ml (30.0 mmol) of diiodomethane in 30 ml of dry ether was added to a solution of 483 mg (2.30 mmol) of the above 70:30 mixture of alcohols in 3.2 ml (30 mmol) of dry 1,2-dimethoxyethane under a nitrogen atmosphere. After 1 hr the reaction was quenched with 1.0 ml of 10% aqueous ammonium chloride, and the product was isolated by ether extraction including a base wash.[35] After preparative TLC (30% ether–petroleum ether) of the crude product, there was obtained 278 mg (59% from the ketone **10**) of the methoxycyclopropane **12**. Rechromatography and then evaporative distillation (120°, 0.65 mm) of a sample gave analytically pure material: ir ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.38 and 0.78 (2 d, 1 each, J = 5 Hz, cyclopropyl CH_2), 1.11 (s, 3, C-8a CH_3), 3.17 (s, 3, OCH_3), and 3.17–3.37 (m, 1, CHOH).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.32; H, 10.63.

4aα,8aβ-Dimethyl-1α-hydroxy-1,2,3,4,4a,7,8,8a-octahydro-5(6*H*)-naphthalenone (13). In a manner similar to that described above for the formation of the ketone **18** (R = H), a solution of 114.2 mg (0.545 mmol) of the methoxycyclopropane **12**, 0.5 ml of water, and 2.0 ml of 38–39% hydrochloric acid in 8 ml of methanol was refluxed for 1.5 hr. The product was isolated by ether extraction including a base wash[35] and tituration of the crude crystalline solid with ether afforded 78 mg (80%) of the ketone **13**, mp 125–130°. The analytical sample, obtained after crystallization (ether–heptane) and sublimation (150°, 0.025 mm) of a portion of this material, melted at 158–159°: ir ($CHCl_3$) 3615 (OH) and 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.83 (s, 3, C-8a CH_3), 1.46 (s, 3, C-4a CH_3), and 3.50–3.65 (m, 1, HCOH).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.17.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-4aα,8aβ-dimethyl-1α-naphthol (38). The Huang-Minlon modification[38] of the Wolff–Kischner reduction was carried out on 73 mg (0.38 mmol) of keto alcohol **13** in 1.0 ml of ethanol and 2.5 ml of diethylene glycol with 0.20 ml of 85% hydrazine hydrate and 250 mg of crushed potassium hydroxide. The reaction mixture was heated to 100–105° for 0.5 hr

and then to 200–205° for 2 hr. After cooling, the contents of the pot and the distillate were combined, and the product was isolated by ether extraction.[35] After two successive preparative TLC (30% ether–petroleum ether) of the crude product, 15 mg (23%) of the pure alcohol **38**, mp 70.5–72°, was isolated as white crystals: ir ($CHCl_3$) 3615 (OH) and 1260 cm^{-1} (COH); NMR ($CDCl_3$) δ 0.98 (s, 3, C-8a CH_3), 1.23 (s, 3, C-4a CH_3), and 3.33–3.50 (m, 1, CHOH).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.93; H, 12.05.

The infrared and NMR spectra of this material were identical with those of the minor alcohol formed during stannic chloride catalyzed cyclization of the aldehyde **36** (vide infra). Oxidation of this material with 8 *N* chromic acid in acetone[39] afforded the ketone **14**, which on crystallization from heptane and then petroleum ether melted at 108–110° (sealed capillary), alone and in admixture with a sample, mp 108–110° (sealed capillary), obtained by a similar oxidation[39] of the alcohol **37** from cyclization of the aldehyde **36** (vide infra). The infrared and NMR spectra of the two samples of the ketone **40** were indistinguishable.

4aα,8aβ-Dimethyl-5,5-ethylenedioxo-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-naphthalenone (6). A solution of 117 mg (0.596 mmol) of the ketone **13** and 2.5 ml of ethylene glycol and 11 mg of *p*-toluenesulfonic acid in 35 ml of benzene was heated at reflux under a Dean-Stark water separator for 7.5 hr. The cooled solution was poured onto 30 ml of water, and the product was isolated by ether extraction, including a base wash.[35] After preparative TLC (50% ether–petroleum ether) of the crude product, there was obtained 66 mg (64%) of the hydroxy ketal, mp 89–91°. The analytical sample, obtained after two crystallizations of a portion of this material from ether–heptane, melted at 92–94°: ir ($CHCl_3$) 3615 cm^{-1} (OH); NMR ($CDCl_3$) δ 1.12 (s, 3, C-8a CH_3), 1.40 (s, 3, C-4a CH_3), 3.37–3.50 (m, 1, CHOH), and 3.67–4.1 (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.99; H, 9.99.

The oxidation of 133 mg (0.554 mmol) of the hydroxy ketal in 20 ml of acetone was carried out with 0.25 ml (1.0 mequiv) of 8 *N* chromic acid.[39] After 1 min, 0.10 ml of isopropyl alcohol was added; the mixture was diluted with 20 ml of saturated aqueous sodium bicarbonate, and isolation of the product by ether extraction[35] gave 32 mg (quantitative) of the ketal **6**, mp 78–82°, as yellow crystals. The analytical sample, prepared by two crystallizations of a portion of this material from ether–hexane and then sublimation at 80° and 0.05 mm, melted at 88–89°: ir ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.00 (s, 3, C-4a CH_3), 1.35 (s, 3, C-8a CH_3), and 3.70–4.17 (m, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.61; H, 9.44.

4aα,8aβ-Dimethyl-5,5-ethylenedioxo-1-(2′-*m*-methoxyphenylethyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene (8). After lithium *m*-methoxyphenylacetylide was prepared from 931 mg (7.05 mmol) of *m*-methoxyphenylacetylene in 15 ml of dry ether under a nitrogen atmosphere by the addition of 2.0 ml of a 2.5 *M* hexane solution of *n*-butyllithium, a solution of 76 mg (0.32 mmol) of the ketone ketal **6** in 3 ml of dry ether was added, and the mixture was stirred at −78° for 4 hr. The reaction was quenched with 0.5 ml of 10% aqueous ammonium chloride solution followed by 15 ml of water, and the product wa isolated by ether extraction.[35] After preparative TLC (40% ether–petroleum ether) there was obtained 102 mg of an oil which was judged to consist of 50% of the addition product and 50% of the starting ketone by integration of the methoxyl region of the NMR spectrum. This crude mixture was dissolved in 5 ml of ethyl acetate, and the solution was stirred under a hydrogen atmosphere for 1 hr in the presence of 30 mg of 10% palladium on carbon. After removal of the catalyst and evaporation of the solvent at reduced pressure, 78 mg of an inseparable mixture of the tertiary-alcohol **7** and the starting ketone **6** remained.

A solution of 150 mg (0.52 mmol) of this crude reduction product from two experiments in 5 ml of dry pyridine was cooled in an ice bath, and 0.20 ml (2.8 mmol) of thionyl chloride was added. The yellow solution was stirred for 50 min at 0° and then poured into 25 ml of ice and water, and the product was isolated by ether extraction including an acid wash.[35] On preparative TLC (30% ether–petroleum ether) of the residue there were obtained two bands which consisted of 45 mg (28%) of starting ketone **6** (R_f 0.5) and 68 mg (38% based on the ketone **6** used) of the desired olefin **8** (R_f 0.7). The analytical sample of this olefin was obtained after another preparative TLC (30% ether–petroleum ether) and evaporative distillation at 120° and 0.005 mm: ir ($CHCl_3$) 1600, 1585 cm^{-1} (Ph); NMR ($CDCl_3$) δ 1.10 (s, 3, C-4a CH_3), 1.25 (s, 3, C-8a CH_3), 3.78–4.08 (m, 7, $-OCH_2CH_2O-$ and OCH_3), 5.15–5.35 (m, 1, –C=CH–), and 6.62–7.37 (m, 4, ArH).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.35; H, 9.15.

4aα,8aβ-Dimethyl-5,5-ethylenedioxo-1β-(2′-*m*-methoxyphenylethyl)-1α,4,4a,5,6,7,8,8a-octahydro-2(3*H*)-naphthalenone (9). The hydroboration[40] of 165 mg (0.464 mmol) of the olefin **8** in 4 ml of dry tetrahydrofuran was accomplished through the addition of 3.0 ml (3 mmol) of a 1 *M* tetrahydrofuran solution of borane under a nitrogen atmosphere. The reaction mixture was stirred for 50 min, cooled to 0°, and then treated with 0.20 ml of water, followed by 2.0 ml of 3 *N* aqueous sodium hydroxide and 2.0 ml of 30% hydrogen peroxide. After an additional 45 min, the resultant mixture was diluted with 25 ml of 10% aqueous potassium carbonate, and the product was isolated by ether extraction.[35] The residue amounted to 107 mg of an oil which was fractionated by preparative TLC (40% ether–petroleum ether). The desired alcohol (63 mg, 37%) was obtained in the band with R_f 0.2 as an oil: ir ($CHCl_3$) 3600 (OH) and 1600, 1585 cm^{-1} (ArH); NMR ($CDCl_3$) δ 1.07 (s, 3, C-4a CH_3), 1.42 (s, 3, C-8a CH_3), 3.67–4.07 (m, 8, $-OCH_2CH_2O-$, OCH_3, CHOH), and 6.60–7.37 (m, 4, ArH).

The oxidation of this alcohol (63 mg, 0.168 mmol) in 5 ml of acetone was accomplished with 0.06 ml (0.24 mequiv) of 8 *N* chromic acid solution,[39] and the ketone **9** (62 mg, 37% from the olefin **8**) was isolated by ether extraction[35] after dilution of the oxidation mixture with 20 ml of water. The analytical sample was obtained by preparative TLC (50% ether–petroleum ether) and then flame flash distillation (0.15 mm) of this sample: ir ($CHCl_3$) 1695 (C=O), 1600, 1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 1.05 (s, 3, C-4a CH_3), 1.23 (s, 3, C-8a CH_3), 3.60–3.97 (m, 7, $-OCH_2CH_2O-$ and OCH_3), and 6.60–7.40 (m, 4, ArH).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.17; H, 8.79.

4a,5α-Methano-5β-methoxy-8aβ-methyl-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-naphthalenone. An ice-cooled solution of 240 mg (1.22 mmol) of the alcohol **12** in 45 ml of acetone was oxidized with 0.40 ml (1.60 mequiv) of 8 *N* chromic acid solution[39] over a period of 3 min. After the addition of 0.20 ml of isopropyl alcohol and 5 ml of saturated aqueous sodium bicarbonate solution, the acetone was removed at reduced pressure; 30 ml of water was added, and the product was isolated by ether extraction.[35] After preparative TLC (30% ether–petroleum ether) of the residue, 174 mg (73%) of the ketone, mp 60.5–2°, was obtained. Crystallization of a portion of this material from hexane and then sublimation at 55° and 0.005 mm provided the analytical sample: mp 61–62°; ir ($CHCl_3$) 3075 (cyclopropyl CH), 1705 (C=O), and 1055 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.38 and 0.60 (2 d, 1 each, J = 5.5 Hz, cyclopropyl CH_2), 1.38 (s, 3, C-8a H_3), and 3.27 (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 76.70; H, 9.36. Found: C, 76.64; H, 9.47.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-4a,5α-methano-5β-methoxy-1β-(2′-*m*-methoxyphenylethyl)-8aβ-methyl-1α-naphthol (17, R = CH_2Ar). A. From Grignard Cleavage of Oxirane 15. To a suspension of 313 mg (12.9 mg-atoms) of magnesium shavings in 5 ml of dry ether was added a solution of 1.867 g (11.9 mmol) of *m*-methoxybenzyl chloride in 5 ml of dry ether over the course of 15 min while the mixture refluxed spontaneously. After an additional 30-min reflux, 10 ml of dry tetrahydrofuran was introduced and then 10 ml (11.7 mmol) of dry dioxane.[41] After 2 min, stirring was stopped, and the precipitate was permitted to settle for 10 min. Titration of an aliquot of this solution was *sec*-butyl alcohol in xylene using 1,10-phenanthrolene as indicator[42] showed that the solution was 0.26 *M* in dialkylmagnesium. The supernatant, 13 ml (3.4 mmol), was transferred with a syringe to a flask that contained a solution of 200 mg (0.96 mmol) of the oxirane **15** in 1 ml of dry dioxane under a nitrogen atmosphere. The reaction mixture was refluxed for 65 min, cooled, and quenched with 1 ml of water, and the resulting mixture was poured into 50 ml of water. Isolation of the product by ether extraction[35] gave 411 mg of an oil which was adsorbed on 20 g of alumina. Elution with 60 ml of petroleum ether gave 119 mg of 3,3′-dimethoxybibenzyl, and then 60 ml of 10% ether–petroleum ether gave 74 mg (37%) of recovered starting oxirane **15**. Further elution with 80 ml of ether afforded 181 mg of a mixture which consisted of 65% of the desired alcohol **16** (R = CH_2Ar) by integration of the methoxyl region of the NMR spectrum: ir ($CHCl_3$) 3550–3500 (broad, w, OH), 1665 (C=C), and 1600, 1585 cm^{-1} (Ar); NMR ($CDCl_3$ + 1 drop of pyridine) δ 1.13 (s, 3, C-8a CH_3), 3.50 (s, 3, OCH_3), and 3.82 (s, 3, $ArOCH_3$). The product was extremely labile and was used directly in the methylenation reaction. The yields of the alcohol **16** (R = CH_2Ar) from other

similar experiments were highly variable and ranged from 29 to 86% based on consumed starting material. In one experiment the alcohol **16** (R = CH_2Ar) was obtained free of impurities; in this case the methylenation proceeded well. In other instances poor yields were realized.

To a solution of the Simmons–Smith reagent[15] prepared from 1.168 g (16.7 mmol) of zinc–copper couple[37] in 17 ml of dry ether and 1.30 ml (16.2 mmol) of diiodomethane was added a solution of 520 mg (1.57 mmol) of the alcohol **16** (R = CH_2Ar) (obtained free of impurities from one cleavage experiment) in 1.75 ml (16.7 mmol) of dry 1,2-dimethoxyethane and 5 ml of dry ether under a nitrogen atmosphere. After 50 min at room temperature the excess reagent was destroyed with 0.5 ml of water, and the mixture was poured into 35 ml of saturated aqueous potassium carbonate solution. Isolation of the crude product by ether extraction[35] and then preparative TLC (20% ether–petroleum ether) gave two products. The first band at R_f 0.2 amounted to 352 mg (66%) of the desired methoxycyclopropane **17** (R = CH_2Ar). A portion of this material was further purified by preparative TLC (20% ether–petroleum ether), and the resulting oil was flame flash distilled (0.01 mm) to give the analytical sample: ir ($CHCl_3$) 3600 (OH) and 1600 1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.50 and 0.80 (2 d, 1 each, J = 5 Hz, cyclopropyl CH_2), 1.13 (s, 3, C-8a CH_3), 3.22 (s, 3, OCH_3), 3.77 (s, 3, $ArOCH_3$), and 6.57–7.37 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 76.70; H, 9.36. Found: C, 76.62; H, 9.22.

The second band at R_f 0.7 amounted to 42 mg (8%) of the ketal **24** (R = CH_2CH_2Ar), which was further purified by preparative TLC (20% ether–petroleum ether) and also flame flash distilled (0.01 mm) to afford the analytical sample: ir ($CHCl_3$) 1600, 1585 (Ar), and 1155, 1085 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.95 (s, 3, C-8a CH_3), 3.37 (s, 3, OCH_3), 3.77 (s, 3, $ArOCH_3$), and 6.53–7.25 (m, 4, ArH).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 76.33; H, 9.15. Found: C, 76.36; H, 9.20.

B. From the Methoxycyclopropyl Ketone. Lithium *m*-methoxyphenylacetylide was prepared in a nitrogen atmosphere from 3.2 g (10 mmol) of *m*-methoxyphenylacetylene in 27 ml of dry ether by the addition of 3.0 ml of 2.5 *M* hexane solution of *n*-butyllithium, and then a solution of 287 mg (1.38 mmol) of the methoxycyclopropyl ketone in 4 ml of dry ether was added. The resulting mixture was stirred at room temperature for 1 hr and then the excess acetylide was decomposed by the addition of 0.5 ml of 10% aqueous ammonium chloride solution. The resulting mixture was poured into 50 ml of water, and the product was isolated by ether extraction.[35] After preparative TLC (50% ether–petroleum ether) there was obtained 455 mg (96%) of a yellow oil.

This crude product was hydrogenated as described above in the formation of the hydroxy ketal **7** by stirring in 10 ml of ethyl acetate with a suspension of 200 mg of 10% palladium on carbon in a hydrogen atmosphere. After filtration of the catalyst and removal of the solvent from the filtrate at reduced pressure, fractionation of the residue by preparative TLC (50% ether–petroleum ether) gave two products. The more polar band at R_f 0.3 contained 204 mg (46%) of the equatorial alcohol, mp 95–98°. Crystallization of a portion of this material from ether–heptane gave the analytically pure sample: mp 100.5–101.5°; ir ($CHCl_3$) 3610 (OH) and 1600, 1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.53 (m, 2, cyclopropyl CH_2), 1.25 (s, 3, C-8a CH_3), 3.23 (s, 3, OCH_3), 3.80 (s, 3, $ArOCH_3$), and 6.57–7.37 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.64; H, 9.17.

The less polar band, at R_f 0.4, contained 192 mg (44%) of the desired axial alcohol **17** (R = CH_2Ar), which was identical with that obtained in part A above.

4aα,8aβ-Dimethyl-3,4,4a,7,8,8a-hexahydro-1-(2′-*m*-methoxyphenyethyl)-5(6*H*)-naphthalenone (18, R = CH_2Ar). A solution of 181 mg (0.525 mmol) of the cyclopropyl alcohol **17** (R = CH_2Ar) in 15 ml of methanol containing 1.5 ml of 37–38% hydrochloric acid was refluxed for 4 hr. The solution was poured into 25 ml of saturated aqueous sodium bicarbonate solution, and the product was isolated by ether extraction.[35] Purification of the residue (159 mg) by preparative TLC (20% ether–petroleum ether) gave a band at R_f 0.3 that contained 89 mg (46%) of the ketone **18** (R = CH_2Ar), as a colorless oil that was contaminated with about 20% of the exocyclic olefin by NMR analysis. A portion of this material was further purified by preparative TLC (20% ether–petroleum ether) and then flame flash distillation (0.01 mm) for the analytically pure sample: ir ($CHCl_3$) 1695 (C=O) and 1600, 1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 1.02 (s, 3, C-8a CH_3), 1.20 (s, 3, C-4a CH_3), 3.80 (s, 3, $ArOCH_3$), 5.22–5.37 (m, 1, –C=CH–), and 6.58–7.42 (m, 4, ArH).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.65; H, 9.11.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1-(2′-*m*-methoxyphenylethylidene)-4a,5α-methano-5β-methoxy-8aβ-methylnaphthalene. To a solution of 204 mg (0.594 mmol) of the above equatorial alcohol in 5 ml of dry pyridine at −10° (ice–salt bath) was added 0.25 ml (3.44 mmol) of thionyl chloride. The reaction mixture was stirred in the cold for 45 min and then poured into ice and water, from which the product was isolated by ether extraction.[35] After preparative TLC (20% ether–petroleum ether) of the residue, there was obtained 82 mg (43%) of an olefin that was different from that prepared below from the axial alcohol **17** (R = CH_2Ar). Rechromatography and then flame flash distillation (0.1 mm) gave the analytical sample: ir ($CHCl_3$) 1665 (C=C), 1600, 1585 (Ar), and 1055 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.37 (m, 2, cyclopropyl CH_2), 1.28 (s, 3, C-8a CH_3(= 3/23 (s, 3, OCH_3), 3.77 (s, 3, $ArOCH_3$), 5.00–5.33 (m, 1, –C=CH–), and 6.57–7.33 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.82; H, 9.20.

4a,5α-Methano-5β-methoxy-1-(2′-*m*-methoxyphenylethyl)-8aβ-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene (20). To a solution of 317 mg (0.92 mmol) of the axial alcohol **17** (R = CH_2Ar) in 7 ml of dry pyridine cooled to −10° was added 0.35 ml (4.5 mmol) of thionyl chloride. After 45 min the reaction mixture was diluted with 300 ml of ether, and the product was isolated by ether extraction.[35] Purification of the residue by preparative TLC (20% ether–petroleum ether) gave 241 mg (91%) of the endocyclic olefin **20** as an oil. Rechromatography of a sample of this material and then flame flash distillation at 0.01 mm gave analytically pure material: ir ($CHCl_3$) 1600, 1585 (Ar), and 1155 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.35 and 0.62 (2 d, 1 each, J = 5 Hz, cyclopropyl CH_2), 1.27 (s, 3, C-8a CH_3), 3.23 (s, 3, OCH_3), 3.77 (s, 3, $ArOCH_3$), 5.30–5.50 (m, 1, –C=CH–), and 6.57–7.37 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.17; H, 9.13.

4a,5αa-Methano-5β-methoxy-1β-(2′-*m*-methoxyphenylethyl)-8aβ-methyl-1α,2,3,4,4a,7,8,8a-octahydro-5(6*H*)-naphthalenone (21). The hydroboration of 210 mg (0.645 mmol) of the olefin **20** in 6 ml of dry tetrahydrofuran was carried out under a nitrogen atmosphere by the addition of 2.0 ml of a 1 *M* tetrahydrofuran solution of borane. After 1 hr at 25° the reaction mixture was cooled to 0° and treated successively with 0.5 ml of water, 3 ml of 3 *N* aqueous sodium hydroxide, and 3 ml of 30% hydrogen peroxide. After an additional 45 min, the mixture was poured into 30 ml of 10% aqueous potassium carbonate, and the product was isolated by ether extraction.[35] Purification of the residue by preparative TLC (50% ether–petroleum ether) gave 185 mg (84%) of the secondary alcohol (R_f 0.2), isolated as an oil which crystallized on standing, mp 90–97°. A portion of this material was crystallized from ether–hexane and then further purified by rechromatography to give analytically pure material: mp 100–102° (amorphous solid); ir ($CHCl_3$) 3600 (OH), 1602, 1585 (Ar), and 1155 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.35 and 0.58 (2 d, 1 each, J = 5 Hz, cyclopropyl CH_2), 0.98 (s, 3, C-8a CH_3), 3.20 (s, 3, OCH_3), 3.75 (s, 3, $ArOCH_3$), and 6.57–7.18 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.87; H, 9.37.

Oxidation of the above alcohol was accomplished through the addition of 0.15 ml (0.60 mequiv) of 8 *N* chromic acid solution[39] to 164 mg (0.476 mmol) of the alcohol in 15 ml of acetone, followed by the same work-up described above for similar oxidations. Purification of the crude product by preparative TLC (50% ether–petroleum ether) gave 130 mg (74%) of the ketone **21** (R_f 0.3), which formed waxy crystals on standing. Two crystallizations of a portion of this material from ether–heptane gave the analytical sample: mp 108–110°; ir ($CHCl_3$) 1700 (C=O), 1600, 1585 (Ar), and 1155 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.67 (m, 2, cyclopropyl CH_2), 0.90 (s, 3, C-8a CH_3), 3.23 (s, 3, OCH_3), 3.77 (s, 3, $ArOCH_3$), and 6.57–7.27 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.23; H, 8.87.

1α,2,3,4,4a,5,6,7,8,8a-Decahydro-2α,8aβ-dimethyl-4a,5α-methano-5β-methoxy-1β-(2′-*m*-methoxyphenylethyl)-2β-naphthol (22). To 1.4 ml (3.3 mmol) of a 2.4 *M* ethereal solution of methyllithium in 10 ml of dry ether at 0° under a nitrogen atmosphere was added a solution of 109 mg (0.318 mmol) of the ketone **21** in 4 ml of dry ether. After 10 min the excess reagent was quenched with 0.5 ml of water and the product was isolated by

ether extraction.[35] Fractionation of the residue by preparative TLC (50% ether–petroleum ether) gave 102 mg (90%) of white crystals, mp 87–101°. Two crystallizations of a portion of this material from ether–hexane gave the analytical sample: mp 106.5–107.5; ir ($CHCl_3$) 3605 (OH), 1600, 1585 (Ar), and 1155 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.30 and 0.63 (2 d, 1 each, J = 5 Hz, cyclopropyl CH_2), 1.40 (s, 6, C-4a and C-8a methyls), 3.25 (s, 3, OCH_3), 3.78 (s, 3, $ArOCH_3$), and 6.57–7.37 (m, 4, ArH).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.19; H, 9.63.

1α-Hydroxy-5β-(2′-*m*-mehoxyphenylethyl)-8aα-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-4aβ-carbonitrile (29). According to the general procedure of Nagata and coworkers,[21a,c] 140 ml (210 mmol) of a 1.5 *M* benzene solution of diethylaluminum cyanide was added in a slow stream over several minutes to a stirred, ice-cooled solution of 21.9 g (69.8 mmol) of the enone **28** in 230 ml of dry benzene. After stirring for 2.5 hr without cooling, the mixture was poured with vigorous stirring onto 1 l. of 10% aqueous sodium hydroxide solution and 1 kg of ice, and the product was isolated by dichloromethane extraction with a base wash.[35] Crystallization of the resulting gum from ether–hexane afforded 19.04 g (80%) of trans cyanide **29** as white crystals, mp 115–121°. The analytical sample, obtained after two further crystallizations of a portion of this material from ether–hexane, melted at 122–125°; ir ($CHCl_3$) 3615, 3480 (OH), 2225 (C≡N), 1720 (C=O), 1600, 1585, 1490 (aromatic), and 1260, 1150, 1050 cm^{-1} (ArOMe); NMR ($CDCl_3$) δ 1.12 (s, 3, C-8a CH_3), 3.70 (m, 1, C-1 H), 3.80 (s, 3, $ArOCH_3$), and 6.6–7.3 (m, 4, ArH).

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.96; H, 7.96; N, 4.06.

The mother liquors from the first crystallization were chromatographed on 1 kg of silica gel. After elution with 4.5 l. of ether, continued elution with 1.5 l. of ether gave 0.610 g of an oil which on crystallization from ether–hexane afforded an additional 0.361 g of crystalline cyanide **29**, mp 119–122°. The total yield of the trans cyano ketone **29** was thus 19.4 g (82%).

1α-Acetoxy-5β-(2′-*m*-methoxyphenylethyl)-6-8aα-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4aβ-carbonitrile (30). A solution of methylmagnesium iodide from 88 ml (200 g, 1.41 mol) of iodomethane and 40.5 g (1.67 mol) of magnesium turnings in 930 ml of dry ether was cooled in an ice bath, and then a solution of 51 g (0.15 mol) of the cyano ketone **29** in 900 ml of benzene was added over a 50-min period. Stirring and cooling were continued for an additional 45 min, and the solution was then carefully treated with 40 ml of saturated aqueous ammonium chloride solution. This mixture was poured onto 2.0 l. of ice and saturated aqueous ammonium chloride solution, and after the product was isolated by dichloromethane extraction,[35] 51.6 g of the crude cyanodiol, mp 170–173°, remained. The analytical sample, obtained after three crystallizations of similar material from another experiment from ether–acetone, melted at 175–178°: ir ($CHCl_3$) 3610, 3460 (OH), 2220 (–C≡N), 1600, 1585, 1485 (aromatic), and 1150, 1040 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.93 (s, 3, C-8a CH_3), 1.13 (s, 3, C-6 CH_3), 3.80 (s, 3, $ArOCH_3$), 3.82 (m, 1, C-1 H), and 6.6–7.3 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 73.82; H, 8.69; N, 3.81.

A solution of 51.6 g of this crude diol in 1 l. of dry pyridine was treated with 385 ml of acetic anhydride and stirred at room temperature for 22 hr. The mixture was diluted with 2.0 l. of ethyl acetate, and then isolation of the product by ether extraction, including a base wash,[35] gave 57 g of solid hydroxy acetate. The analytical sample, obtained after three crystallizations of similar material from another experiment from ethyl acetate–chloroform, melted at 163–165°: ir ($CHCl_3$) 3600 (OH), 2225 (C≡N), 1725 (CH_3C=O), 1600, 1585, 1485 (aromatic), and 1150, 1035 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 1.02 (s, 3, C-8a CH_3), 1.12 (s, 3, C-6 CH_3), 2.03 (s, 3, $COCH_3$), 3.80 (s, 3, $ArOCH_3$), 5.1 (m, 1, C-1 H), and 6.7–7.4 (m, 4, ArH).

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.22; H, 8.22; N, 3.48.

This crude alcohol (57 g) was dissolved in 1.1 l. of dry pyridine, and the solution was chilled with a ice bath. To this solution 61 ml (102 g, 0.856 mol) of thionyl chloride was then added dropwise with stirring over a 30-min period. The solution was stirred at 0° for an additional 75 min, and then without cooling for 45 min. This mixture was poured into 500 ml of ice and water and then isolation of the product by benzene–ether–ethyl acetate (1:1:1) extraction, including an acid and a base wash,[35] gave 55.6 g of brown oil which on crystallization from ethanol afforded 42.2 g (74%) of cyano olefin mixture **30**, mp 85–105°, as slightly brown crystals. The mother liquors from this crystallization were concentrated and then chromatographed on 2 kg of silica gel, and after 4 l. of 70% ether–petroleum ether eluent was discarded, continued elution with 3 l. of the same solvent system afforded an additional 8.83 g (16.2%) of the cyano olefin mixture **30** as an oil. The combined yield of the cyano olefin mixture **30** from crystallization and chromatography was 51.03 g (90%). The analytical sample, obtained after preparative TLC (50% ether–petroleum ether) and then crystallization from ethanol of a portion of this material, melted over the range 89–108°: ir ($CHCl_3$) 2220 (C≡N(= [735 (acetate C=O), 1600, 1585, 1490 (aromatic), and 1150, 1035 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.95, 1.08 (two singlets, 3 each, C-8a CH_3, ratio ca. 4:1), 1.62 (s, 3, C-6 CH_3), 2.04 (s, 3, $COCH_3$), 3.80 (s, 3, $ArOCH_3$), 5.0 (m, 1, C-1 H), 5.41 (m, ca. 0.2, C-7 H of Δ^6 olefin component), and 6.7–7.4 (m, 4, ArH). The bulk material obtained above also had the same spectral properties.

Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.64; H, 8.21; N, 3.66.

5β-(2′-*m*-Methoxyphenylethyl)-4aβ,6,8aα-trimethyl-1,2,3,4,-4a,7,8,8a-octahydronaphth-1α-ol (31). To a stirred solution of 14.0 g (36.7 mmol) of cyano olefin mixture **30** in 560 ml of dry benzene at room temperature was added 92 ml (0.147 mol) of a 1.6 *M* benzene solution of diisobutylaluminum hydride. After stirring for 2.5 hr, the mixture was poured into 1 l. of 10% aqueous potassium hydroxide solution and ice, and on isolation of the crude product by ether extraction[35] there remained 12.9 g of crude hydroxy imine as a white foam: ir ($CHCl_3$) 3620 (OH), 1612 (HC=NH), 1600, 1585, 1485 (aromatic), and 1260, 1150, 1040 cm^{-1} ($ArOCH_3$).

This entire crude product was treated[43] with 60 ml of 99% hydrazine hydrate and 17.6 g of hydrazine dihydrochloride in 540 ml of triethylene glycol. This mixture was heated under an argon atmosphere with stirring for 5 hr at an internal temperature of 135°, and then 116 g of 85% potassium hydroxide pellets was added portionwise. The internal temperature was raised to 155° and for 1.5 hr volatile mixture was allowed to distil in an argon flow. The argon flow was then stopped, and stirring and heating were continued for 5 hr. The mixture was then allowed to cool to room temperature over a 7-hr period, and after the resulting solid white mass was dissolved in 1.4 l. of water, the product was isolated by ether extraction.[35] The residue amounted to 10.2 g of a white solid which on crystallization from ether–hexane gave 9.57 g (80%) of crystalline olefin mixture **31**, mp 92–103°. Two subsequent crystallizations of a portion of this olefin mixture from ether–hexane afforded the analytical sample: mp 98–105°; ir ($CHCl_3$) 3610, 3450 (OH), 1600, 1585, 1485 (aromatic), 1370 (CH_3), and 1150 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.75, 0.90 (two singlets, 3 each, C-8a CH_3, ratio ca. 1:3), 0.82, 1.00 (two singlets, 3 each, C-4a CH_3, ratio ca. 1:3), 1.61 (s, C-6 CH_3), 37 (m, 1 C-1 H), 3.76 (s, 3, $ArOCH_3$), 5.38 (m, ca. 0.25, C-7 H of Δ^6 olefin component), and 6.6–7.3 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.82.

5β-(2′-*m*-Methoxyphenylethyl)-4aβ,6,8aα-trimethyl-3,4,4a,-7,8,8a-hexahydro-1(2*H*)-naphthalenone (23). A solution of 60.5 mg (0.169 mmol) of the alcohol **22** in 8 ml of methanol and 2.0 ml of 37–38% hydrochloric acid was refluxed under an argon atmosphere for 2 hr. The course of the reaction was followed by TLC (30% ether–petroleum ether); over the 2-hr period the spot for the alcohol **22** (R_f 0.3) was quickly replaced by one (R_f 0.7) corresponding to an intermediate olefin, which in turn was replaced by a spot (R_f 0.6) that represented the ketone **23.** The reaction mixture was diluted to 150 ml with water. The product was isolated by ether extraction, including a base wash.[35] Purification of the residue by preparative TLC (30% ether–petroleum ether) afforded 50 mg (91%) of a colorless oil. This material, which consisted of a 71:29 mixture of Δ^5 and Δ^6 isomeric olefins by comparative integration of the angular methyl region of the NMR spectrum, slowly crystallized on standing and melted over the range 60–87°. The analtyical sample, prepared by crystallization of this material from ether, melted at 68–93°: ir ($CHCl_3$) 1700 (C=O) 1600, 1585, 1485 (aromatic), and 1260, 1150, 1040 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.68 (s, 0.85, C-8a CH_3, Δ^6 isomer), 0.97 (s, 2.15, C-8a CH_3, Δ^5 isomer), 1.08 (s, 0.85, C-4a CH_3, Δ^6 isomer), 1.17 (s, 2.15, C-4a CH_3, Δ^5 isomer), 1.65 (s, 3, C-6 CH_3), 3.80 (s, 3, OCH_3), and 6.60–7.40 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.02; H, 9.38.

8-Methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,-11,12,12a-decahydro-1(2*H*)-chrysenone (3). A. From Cycliza-

tion of the Keto Olefin 23. A solution of 67 mg (0.20 mmol) of the keto olefin mixture **23** and 100 mg of *p*-toluenesulfonic acid monohydrate in 7 ml of toluene was heated at reflux in an argon atmosphere under a Dean-Stark water separator for 2 hr. After the reaction mixture was cooled the product was isolated by ether extraction, including a base wash.[35] After preparative TLC (30% ether–petroleum ether) of the residue, there was obtained 53 mg (81%) of a white solid that consisted of an 80:20 mixture of the trans-anti-trans ketone **3** and its cis-anti-trans isomer by comparative integration of the angular methyl region in the NMR spectrum. Three crystallizations of this material from ether gave 42 mg (65%) of the ketone **3**, mp 150–152° (vacuum), which was of sufficient purity for analysis: ir ($CHCl_3$) 1700 (C=O), 1605, 1575, 1500 (3,4-disubstituted anisole ring), and 1030 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.90 (s, 3, C-4a CH_3), 1.19 (s, 3, C-12a CH_3), 1.22 (s, 3, C-10b CH_3), 3.77 (s, 3, OCH_3), and 6.6–7.3 (m, 3, ArH).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.89; H, 9.34.

A mixture of a sample of this material, mp 150–152° (vacuum), with material obtained from the hydrocyanation route, mp 150–152° (vacuum) as well as with that obtained from the polyene cyclization route, mp 150–152° (vacuum), melted at 150–152° (vacuum). The infrared and NMR spectra of all three samples were also identical.

A sample of the ketone **3** which was crystallized from ether–heptane, twice from ethyl alcohol, and finally from ether formed clear needles, mp 153–154° (vacuum), which were used for single-crystal X-ray structure analysis (vide infra).

B. From the Hydroxy Olefin Mixture 31. A stirred and ice-cooled solution of 12.49 g (38 mmol) of the hydroxy olefin mixture **31** in 850 ml of acetone was treated portionwise over a 5-min period with 19.0 ml (152 mequiv) of 8 *N* chromic acid solution.[39] After stirring for 10 min with cooling, the solution was treated with 12 ml of isopropyl alcohol and poured into 1.8 l. of water. After isolation of the product by ether extraction,[35] there was obtained 12.0 g of ketone **23** as a light brown solid. An 11.5-g portion of the above crude keto olefin **23** was dissolved in 115 ml of trifluoroacetic acid, and the solution was heated at reflux with stirring for 3.5 hr. The black mixture was cooled with an ice bath and the product (12 g) was isolated by ether–benzene (1:1) extraction, including a base wash.[35] Two crystallizations of this material from ethanol afforded 7.6 g (64% from alcohol **31**) of tetracyclic ketone **3**, mp 149–151° (vacuum), as light tan crystals.

The mother liquors from these crystallizations were purified by preparative GLC on a 10 ft × 0.25 in. 20% SE-30 on 60–80 Chromosorb W at 290° with a helium flow of 70 ml/min. The compounds with retention times of 16 and 20 min were collected by passing the effluent gases through glass tubes packed with alumina. The product with retention time of 20 min had a NMR spectrum which was identical with that of the ketone **3** obtained above.

The compound with a retention time of 16 min was freed from SE-30 by preparative TLC (50% ether–petroleum ether) and then crystallized by scratching, mp 125–134° (vacuum). Crystallization from ethanol and then flame flash sublimation at 0.1 mm gave the analytical sample of the cis-anti-trans tetracyclic ketone isomer: mp 136–138° (vacuum); ir ($CHCl_3$) 1700 (C=O) and 1605, 1500 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 0.35 (s, 3, C-4aβ CH_3), 1.17 (s, 3, C-10bα CH_3), 1.30 (s, 3, C-12aα CH_3), 3.75 (s, 3, OCH_3), and 6.50–7.40 (m, 3, ArH).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 0.94; H, 9.26. Found: C, 80.98; H, 9.20.

5,6-Dimethyl-(*E*)-1,5,9-decatriene (34). To 650 ml (0.715 mol) of a 1.1 *M* ethereal solution of allylmagnesium bromide diluted with 450 ml of dry tetrahydrofuran was added at reflux over a 3-hr period 39 g (0.161 mol) of 1,4-dibromo-2,3-dimethyl-(*E*)-2-butene[27] in 100 ml of dry tetrahydrofuran. After stirring for 1 hr at 25°, the reaction mixture was cooled to 0° and then quenched with 20 ml of saturated ammonium chloride solution, and the product was isolated by ether extraction[35] except that the solvent was removed by distillation through a 1-ft Vigreux column at atmospheric pressure. Distillation of the colorless liquid residue through a 2-ft Teflon spinning band column gave 25 g (95%) of the triene **34**, bp 86–87° (15 mm). Gas–liquid chromatography (130°, 7.5 ft × 0.125 in., 5% SE-30 on Diatoport S) of this material showed a single volatile component that amounted to 99% of the effluent at a retention time of 1.3 min. Redistillation of a sample of this material in the same apparatus afforded the analytical sample: bp 100–105° (25 mm); ir (film) 1650 (C=C) and 990, 910 cm^{-1} (-CH=CH_2); NMR ($CDCl_3$) δ 1.65 (s, 6, C-5 and C-6 CH_3), 4.8–5.25 (m, 4, C=CH_2), and 5.6–6.15 (m, 2, -CH=C).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.56; H, 12.29.

5,6-Dimethyl-(*E*)-5,9-decadienol-1 (35). To a solution of 36.5 g (0.225 mol) of the triene **34** in 200 ml of dry tetrahydrofuran under a nitrogen atmosphere at 0° was added 400 ml (0.292 mol) of 0.77 *M* tetrahydrofuran solution of disiamylborane[31] over a 2-hr period. After stirring for 1 hr, the mixture was treated with 120 ml of 6 *N* sodium hydroxide solution and then 90 ml of 30% hydrogen peroxide. The aqueous layer was saturated with potassium carbonate, and then the organic phase was decanted and dried ($MgSO_4$). After filtration to remove the drying agent, the solvent was removed by distillation through a 1-ft Vigreux column at atmospheric pressure, and the residue was then chromatographed on 1.5 kg of grade III alumina. Elution with 3 l. of 10% ether–petroleum ether gave 8.2 g (22%) of unreacted triene **34**, bp 92–95° (20 mm). Further elution with 6 l. of 75% ether–petroleum ether afforded a mixture of alcohols which was separated by distillation through a 2-ft Teflon spinning band column at reduced pressure. After a forerun of 3-methyl-2-butanol, bp 40–42° (20 mm), there was obtained 17.2 g (43%) of the dienol **35**, bp 94–95% (0.25 mm), the GLC (200°, 6 ft × 0.125 in. 10% SE-30 on Diatoport S) of which showed >99% of a single volatile component with a retention time of 1.5 min. The analytical sample was obtained by evaporative distillation of a portion of this material at 120° and 0.25 mm: ir (film) 3300 (OH), 1640 (C=C), and 980, 905 cm^{-1} (-CH=CH_2); NMR ($CDCl_3$) δ 1.6 (s, 6, C-5 and C-6 CH_3), 3.45–3.8 (m, 2, -CH_2O), 4.8–5.2 (m, 2, C=CH_2), and 5.4–6.15 (m, 1, -CH=C-).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.06. Found: C, 78.91; H, 12.09.

5,6-Dimethyl-5,9-decadienal (36). A solution of 1.0 g (5.5 mmol) of the alcohol **35** in 60 ml of dry dichloromethane was added to a stirred suspension of 8.6 g (33.1 mmol) of chromic anhydride–dipyridine complex[36] in 60 ml of dry dichloromethane, and the mixture was stirred at room temperature for 15 min. The entire reaction mixture was then filtered though 100 g of Merck acid-washed alumina with the aid of an additional 600 ml of dichloromethane. After the solution was concentrated at reduced pressure, the crude aldehyde, which contained some pyridine, was taken up in 300 ml of ether, and the ethereal solution was washed successively with saturated aqueous copper sulfate (2 × 70 ml), water (50 ml), and saturated brine (50 ml), and then dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded 0.886 g (88%) of the aldehyde **36** as a colorless liquid which was >95% a single volatile component on GLC (200°, 6 ft × 0.125 in., 10% SE-30 on Diatoport S, retention time 1.2 min). The analytical sample was obtained by evaporative distillation of a portion of this material at 70° (0.08 mm): ir (film) 2710 (CHO), 1725 (>C=O), and 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.80; H, 11.15.

The **2,4-dinitrophenylhydrazone** of the aldehyde **36** melted at 88–90° after two crystallizations from ethanol.

Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.18; H, 6.78; N, 15.70.

Cyclization of the Aldehyde 36. To a solution of 9.8 g (37.6 mmol) of stannic chloride in 155 ml of nitromethane cooled in an ice bath was added a solution of 1.36 g (7.55 mmol) of the aldehyde **36** in 100 ml of nitromethane. The mixture was stirred for 9 min at the bath temperature and then partitioned between 150 ml of 1 *N* hydrochloric acid and 150 ml of ether. Isolation of the product by ether extraction including an acid wash[35] afforded 1.40 g of brown oil which on evaporative distillation (90–100°, 0.15 mm) gave 1.05 g (77%) of a volatile, yellow oil, the GLC (220°) of which showed in addition to numerous minor volatile components major peaks with retention times of 0.6 (20%), 0.8 (70%), and 1.1 min (3%).

A solution of the above mixture in 25 ml of ethyl alcohol in which was suspended 150 mg of platinum oxide was stirred in a hydrogen atmosphere at room temperature for 24 hr. After removal of the catalyst by filtration and then the solvent at reduced pressure, the residual oil was evaporatively distilled at 90–100° and 0.15 mm. Crystallization of the semisolid distillate (940 mg) from hexane afforded 82 mg (6%), mp 115–117°, of the equatorial alcohol **37**, and an additional 274 mg (20%), mp 115–117°, of the same alcohol **37** was obtained by preparative TLC (30% ether–petroleum ether, R_f 0.3). The analytical sample, obtained after one further crystallization of a portion of this material from hexane, also melted at 115–117°: ir ($CHCl_3$) 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.96 and 1.00 (2 s, 3 each, C-4a and C-8a CH_3) and 3.33–3.83 (m, 1, C-1 H).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.16; H, 12.03.

Extraction of the band at R_f 0.4 in the above chromatogram afforded 69 mg (5%) of the axial alcohol **38** as a viscous oil which crystallized on trituration with petroleum ether and melted at 69–71° alone or in admixture with material prepared above from the methoxycyclopropane route (vide supra).

The *p*-bromobenzoate **39**, mp 76–78°, was formed in 89% yield (95 mg) from 53 mg (0.29 mmol) of the equatorial alcohol **37** and 128 mg (0.58 mmol) of *p*-bromobenzoyl chloride in 3 ml of pyridine. After crystallization of this material from petroleum ether, material was obtained which was suitable for single-crystal X-ray structure analysis and melted at 77–78°: NMR ($CDCl_3$) δ 1.12 and 1.16 (2 s, 3 each, C-4a and C-8a CH_3) and 7.73 (m, 4, ArH).

Anal. Calcd for $C_{19}H_{25}BrO_2$: C, 62.47; H, 6.90; Br, 21.88. Found: C, 62.28; H, 6.80; Br, 21.80.

4aβ,8aα-Dimethyl-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-naphthalenone (14). A solution of 100 g (0.55 mmol) of the alcohol **37** in 20 ml of acetone was oxidized with 0.25 ml of 8 *N* chromic acid solution,[39] and the product was isolated by ether extraction[35] except that the solvent was removed by distillation through a 1-ft Vigreux column at atmospheric pressure. Evaporative distillation of the pale yellow residue at 95° and 0.5 mm gave 82 mg (82%) of the ketone **14** as a viscous liquid which crystallized on trituration with ether and melted at 101–103°. The analytical sample, obtained after two crystallizations of this material from petroleum ether, melted at 108–110° (sealed capillary): ir (CCl_4) 1710 cm^{-1} (>C=O); NMR ($CDCl_3$) δ 0.90 and 1.23 (2 s, 3 each, C-4a and C-8a CH_3).

Anal. Calcd for $C_{12}H_{20}$: C, 79.94; H, 11.18. Found: C, 80.07; H, 11.23.

4aβ,8aα-Dimethyldecalin. Application of the Huang-Minlon modification[38] of the Wolff–Kishner reduction to 50 mg (0.28 mmol) of the ketone **14** in 3 ml of triethylene glycol with 0.2 ml of 98% hydrazine and 88 mg of potassium hydroxide afforded 22 mg (48%) of 4aβ,8aα-dimethyldecalin, mp 97–98°, after chromatography of the crude product on 2 g of Merck acid-washed alumina (elution with 6 ml of hexane) and then evaporative distillation at 100–120° (30 mm): ir (CCl_4) 1370, 1210, 1160, 1020, 970, 926 cm^{-1}; NMR ($CDCl_3$) δ 1.01 (s, 6, C-4a and C-8a CH_3) and 1.55 (CH_2 envelope).

Anal. Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.76; H, 13.32.

A similar reduction[38] performed on 248 mg (1.38 mmol) of 4aβ,8aβ-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone[28] with 1.46 ml of 97% hydrazine and 785 mg of potassium hydroxide in 10 ml of triethylene glycol afforded 138 mg (60%) of 4aβ,8aβ-dimethyldecalin, mp 88–91°: ir (CCl_4) 1380, 1370, 1180, 1003, and 926 cm^{-1} (all strong); NMR ($CDCl_3$) δ 88 (s, 6, C-4a and C-8a CH_3) and 1.46 (CH_2 envelope).

Anal. Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.71; H, 13.40.

The melting point of a mixture of this material, mp 88–91°, and the trans isomer prepared above, mp 97–98°, was 55–70°.

5,6-Dimethyl-1,10-bis(trimethylsilyl)-(*E*)-5-decene-1,9-diyne (40). To a solution of propargylmagnesium bromide prepared in 450 ml of dry ether from 143 g (1.2 mol) of propargyl bromide and 28.8 g (1.2 g-atoms) of magnesium turnings was added 72.6 g (0.3 mol) of the dibromide **33**[27] in 100 ml of dry tetrahydrofuran over a 10-min period, while the temperature was maintained between 10 and 15°. After the addition was complete, the mixture was allowed to warm to 25°, and stirring was continued for 2 hr. The mixture was then treated with 120 ml of saturated aqueous ammonium chloride solution, and the product was isolated by ether extraction.[35] A solution of the resulting crude coupling product (ca. 60 g) in 50 ml of dry tetrahydrofuran was added dropwise over 45 min to 400 ml (0.8 mol) of a 2 *M* tetrahydrofuran solution of ethylmagnesium bromide, and then the mixture was refluxed for 1 hr. After cooling to 40°, the gelatinous mixture was treated with a solution of 94 g (0.86 mol) of trimethylchlorosilane in 100 ml of dry tetrahydrofuran and then refluxed for 1 hr. After cooling to room temperature, the reaction mixture was treated with a mixture of 100 ml of saturated aqueous ammonium chloride solution and 10 ml of concentrated ammonium hydroxide, and then the product was isolated by ether extraction.[35] Crystallization of the residue from ethanol gave 75.1 g (82%) of the disilane **40**, mp 65–67°, in two crops of 71.5 and 3.6 g each. The analytical sample, obtained after an additional crystallization of a sample of this material from pentane–ethanol, also melted at 65–67°: ir (film 2170 (C≡C) and 835–875 cm^{-1} (CH_3Si); NMR ($CDCl_3$) δ 0.11 (s, 2 × 9, 2 $(CH_3)_3Si$), 1.68 (s, 2 × 3, C-5 and C-6 CH_3), and 2.26 (m, 2 × 4, $-CH_2-$).

Anal. Calcd for $C_{18}H_{32}Si_2$: C, 70.97; H, 10.59; Si, 18.44. Found: C, 70.96; H, 10.51; Si, 18.39.

5,6-Dimethyl-(*E*)-5-decene-1,9-diyne (41). To a solution of 58.7 g (0.192 mol) of disilane **40** in 600 ml of absolute ethanol at 30° was added dropwise over 0.5 hr a solution of 81.5 g (0.480 mol) of silver nitrate in 180 ml of water and 180 ml of 95% ethanol. After stirring for 2 hr, the mixture was treated with a solution of 62.5 g (0.960 mol) of potassium cyanide in 500 ml of water. When the addition was complete, the mixture was stirred until it had cooled to room temperature and then poured into 1 l. of water. The product was isolated from this aqueous mixture by petroleum ether extraction,[35] and then distillation of the residue afforded 30.2 g (98%) of the enediyne **41** as a colorless liquid, bp 85.5–86.0° (4.3 mm). The analytical sample was obtained by evaporative distillation of a portion of this material at 110° (2 mm): ir (neat 3290 (C≡CH) and 2120 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 1.70 (s, 2 × 3, C-5 and C-6 CH_3), 1.93 (m, 2 × 1, C≡CH), and 2.26 (br s, 2 × 4, CH_2).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.08; H, 10.14.

6,7-Dimethyl-(*E*)-6,10-undecadien-2-ynol (43). A solution of 30.2 g (0.189 mol) of the enediyne **41** in 300 ml of dry tetrahydrofuran was cooled to 0°, and then 190 ml (0.19 mol) of a tetrahydrofuran solution of disiamylborane[31] (prepared from 190 ml of a 1 *M* tetrahydrofuran solution of diborane and excess 2-methyl-2-butene) was added dropwise over 2 hr. The mixture was stirred at room temperature for 4 hr, and then 45 ml of glacial acetic acid was added dropwise over 0.5 hr. The mixture was stirred for an additional 2 hr, and then poured into 1.5 l. of cold water, from which mixture the product was isolated by ether extraction including a base wash[35] except that the solvent was removed by distillation through a 1-ft Vigreux column at atmospheric pressure. The resulting opaque liquid residue was distilled through a 6-in. Vigreux column at 3 mm and the following fractions were obtained.

Fraction	Bp, °C (3 mm)	Wt, g	Composition (GLC, 90°)[35]
A	65–69	12.4 g	**34:42** (1:1)
B	69–73	19.0 g	**34:42:41** (1:5:2)
Residue		22.6 g	**42:41** (1:8)

In addition to the expected components, each fraction contained a substantial amount of boronic impurities. Each fraction was subjected to filtration through silica gel (10 g/g product) with petroleum ether. The fractions thus obtained were then subjected to medium-pressure chromatography (petroleum ether). From these purifications, 7.4 g of pure enediyne **41** was recovered, and 13.2 g of a 1:8 mixture of triene **34** and dienyne **42** were obtained.

The latter mixture was dissolved in 50 ml of dry tetrahydrofuran and added dropwise over 0.5 hr to a solution of 200 ml (0.164 mol) of a 0.82 *M* tetrahydrofuran solution of ethylmagnesium bromide. After the mixture was added, the reaction was maintained at reflux for 1 hr, then cooled to 20°, and dry paraformaldehyde was depolymerized at 160–180° and bubbled through the solution for 30 min in a stream of dry nitrogen. A cooling bath was used to keep the temperature between 25° during the formaldehyde addition. After the mixture was cooled to 0°, 75 ml of a saturated aqueous ammonium chloride solution was added, and the product was then isolated by ether extraction.[35] The crude product (16.3 g) was chromatographed on 140 g of silica gel. Elution with 500 ml of petroleum ether afforded 1.3 g of the triene **34**, and continued elution with 1.5 l. of 40% ether–petroleum ether gave 10.7 g (39% based on recovered enediyne **41**) of the alcohol **43** as a colorless liquid which was used in subsequent experiments without further purification. The analytical sample, obtained by distillation and then evaporation distillation of a portion of this material, boiled at 109–110° (0.15 mm): ir (neat) 3700 (OH), 2290, 2230 (C≡C), 1640, 1000, and 910 cm^{-1} (-CH=CH_2); NMR (CCl_4) δ 1.70 (s, 2 × 3, C-6 and C-7 CH_3), 2.11 (d, 4, J = 3 Hz, C-8 and C-9 CH_2), 4.14 (broad s, 2, CH_2OH), 4.83 (d, 1, J = 4 Hz, C-11 H), 5.08 (d of d, 1, J = 9 and 3 Hz, C-11 H), and 5.75 (m, 1, C-10 H).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.06; H, 10.39.

6,7-Dimethyl-3-iodo-(*E,E*)-2,6,10-undecatrienol. The procedure of Corey, Katzenellenbogen, and Posner[32] was followed. To a suspension of 30.45 g (0.564 mol) of sodium methoxide in 625 ml of dry tetrahydrofuran was added 137 ml (0.282 mol) of a 2.06 *M* tetrahydrofuran solution of lithium aluminum hydride over a 10-min period. The mixture was stirred at room temperature for 30 min, and then a solution of 27.1 g (0.141 mol) of the propargylic alcohol

43 in 100 ml of dry tetrahydrofuran was added over 20 min. After heating the mixture at reflux for 1.5 hr it was cooled to −5°, and then 26.3 ml (23.6 g, 0.282 mol) of dry ethyl acetate was added to destroy the excess hydride. The resulting mixture was cooled to −78°, and 178 g (0.701 mol) of iodine in 310 ml of dry tetrahydrofuran was added dropwise over a 40-min period. The reaction mixture was quickly warmed to 0° with an ice bath and then allowed to stir at room temperature until the internal temperature reached 25°. The reaction was quenched by the addition of 18 ml of water, followed by 600 ml of ether, and then the product was isolated by ether extraction.[35] The residue amounted to 43.85 g (97%) of the 3-iodo alcohol, which was not further purifie but used in the following experiment. The analytical sample was obtained by evaporative distillation at 85° and 0.12 mm of a sample of similar purity from another experiment: ir (neat) 3700–3650 (OH), 1640, 1000, and 910 cm^{-1} (-CH=CH_2); NMR ($CDCl_3$) 1.68 (s, 2 × 3, C-6 and C-7 CH_3), 4.18 (d, 2, J = 5 Hz, CH_2OH), 4.85 (d, 1, J = 3 Hz, C-11 H), 5.09 (d of d, 1, J = 9 and 3 Hz, C-11 H), 5.7 (m, 1, C-10 H), and 5.80 (t, 1, J = 5 Hz, C-2 H).

Anal. Calcd for $C_{13}H_{21}OI$: C, 48.76; H, 6.61; I, 39.63. Found: C, 48.96; H, 6.57; I, 39.56.

3,6,7-Trimethyl-(*E,E*)-2,6,10-undecadienol (44). A solution of the above crude iodo alcohol (43.85 g, 0.137 mol) in 100 ml of dry hexane was added over a 0.5-hr period at 0° to 1 l. (0.705 mol) of a 0.705 *M* ethereal solution of lithium dimethylcuprate,[44] and the mixture was stirred overnight at 0°. The mixture was then treated with 190 ml of methyl iodide, and after stirring for 0.5 hr at 0°, the reaction was quenched by the addition of 300 ml of saturated aqueous ammonium chloride solution. The product was isolated by ether extraction,[35] and the residue amounted to 28.9 g (98%) of the alcohol **44**, as a clear, colorless oil. Since GLC analysis (190°) indicated that this material consisted of a 95:5 mixture of the desired alcohol **44** and the corresponding C-2-methylated isomer, no further purification was done before use in the following work. An analytical sample was obtained by evaporative distillation at 70° and 0.5 mm of a sample of similar purity for another experiment: ir (neat) 3650–3100 (OH), 1670 (C=C), 1645, 995, and 910 cm^{-1} (-CH=CH_2); NMR ($CDCl_3$) δ 1.65 (s, 2 × 3, C-6 and C-7 CH_3), 1.70 (d, 3, J = 1.5 Hz, C-3 CH_3), 4.11 (d, 2, J = 7 Hz, CH_2OH), 4.81 (d, 1, J = 3 Hz, C-11 H0, 5.05 (d of d, 1, J = 9 and 3 Hz, C-11 H), 5.38 (t, 1, J = 7 Hz, C-2 H), and 5.6 (m, 1, C-10 H).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.74; H, 11.50.

12-*m*-Methoxyphenyl-5,6,9-trimethyl-(*E,E*)-1,5,9-dodecatriene (45). The crude allylic alcohol (52.8 g, 0.254 mol) from two experiments as described above in 300 ml of dry carbon tetrachloride was converted into the corresponding allylic chloride by the addition of 79.7 g (0.304 mol) of triphenylphosphine.[45] After a 3-hr reflux, the excess triphenylphosphine was decomposed with 2.5 ml of methanol, and the precipitated triphenylphosphine oxide was removed by filtration. After the solvent was removed at reduced pressure, distillation of the residue afforded 43.5 g (76%) of the allylic chloride, bp 87–92° (0.2 mm), as a pale yellow liquid. This material was not stored but used directly in the coupling reaction:[46] ir (neat) 1662 (C=C) and 1637 cm^{-1} (-CH=CH_2); NMR ($CDCl_3$) δ 1.65 (s, 2 × 3, C-6 and C-7 CH_3), 1.76 (s, 3, C-3 CH_3), 4.07 (d, 2, J = 8 Hz, CH_2OH), 4.81 (d, 1, J = 3 Hz, C-11 H), 5.08 (d of d, 1, J = 9 and 3 Hz, C-11 H), 5.46 (t, 1, J = 8 Hz, C-2 H), and 5.6 (m, 1, C-10 H).

To a solution of 43.5 g (0.192 mol) of the above chloride in 200 ml of dry tetrahydrofuran and 200 ml of dry hexamethylphosphoramide was added over a 4-hr period a solution of *m*-methoxybenzylmagnesium chloride prepared from 134.9 g (0.862 mol) of *m*-methoxybenzyl chloride and 82.8 g (3.45 g-atoms) of magnesium turnings in 800 ml of dry tetrahydrofuran, and the mixture was stirred at room temperature overnight. The reaction mixture was then cooled to 0°; 100 ml of saturated aqueous ammonium chloride solution was carefully added, and the product was isolated by ether extraction.[35] Distillation of the resulting residue (80.5 g) afforded 38.0 g (63%) of the triene **45**, bp 148–152° (0.001 mm), which consisted of >98% of a single volatile component on GLC (210° on the column described;[34] 230°, 6 ft × 0.125 in., 2.5% SE-30 on Chromosorb W AW DMCS, retention time 5.51 min; and 140°, 6 ft × 0.125 in. 10% Carbowax 20M on Diatoport S, retention time 4.98 min). The medium boiling range forerun [25.9 g, bp 131–148° (0.001 mm)] from this distillation was chromatographed on 600 g of silica gel, and elution with 2.5 l. of 4% ether–petroleum ether afforded an additional 15.8 g (26%) of the triene **45** of the same purity as above. The analytical sample was obtained by evaporative distillation of a portion of this material at 125° and 0.01 mm: ir (film) 1640, 995, and 910 (CH=CH_2), and 1615–1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 1.62 (s, 3, C-9 CH_3), 1.66 (s, 2 × 3, C-5 and C-6 CH_3), 3.83 (s, 3, OCH_3), 4.94 (d, 1, J = 3 Hz, C-1 H), 5.16 (d of d, 1, J = 9 and 3 Hz, C-1 H), 5.27 (t, 1, J = 8 Hz, C-10 H), 5.8 (m, 1, C-2 H) and 7.45–6.70 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.82; H, 10.34.

12-*m*-Methoxyphenyl-5,6,9-trimethyl-(*E,E*)-5,9-dodecadienal (46). A solution of 10.1 g (32.3 mmol) of the triene **45** in 10 ml of dry tetrahydrofuran was cooled to 0°, and 52.9 ml (35.7 mmol) of a 6.76 *M* tetrahydrofuran solution of disiamylborane[31] was added. After stirring for 3 hr at 0°, the mixture was treated with 1 ml of water, followed by 40 ml of 3 *N* aqueous sodium hydroxide solution and then 15 ml of 30% hydrogen peroxide. After the addition was complete, the mixture was heated to 40–45° and maintained at that temperature for 2 hr. The mixture was then poured into 200 ml of water and the product isolated by ether extraction.[35] Chromatography of the residue (10.8 g) on 176 g of Florisil afforded 9.05 g (85%) of the corresponding primary alcohol as a colorless liquid which was eluted with 2 l. of 20% ether–petroleum ether. This material consisted of >98% of a single volatile component on GLC (280°). The analytical sample was obtained by evaporative distillation of a sample of this material at 140–160° and 0.06 mm: ir ($CHCl_3$) 3620 (OH), 1665 (C=C), and 1615–1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 1.59 (s, 3, C-9 CH_3), 1.63 (s, 2 × 3, C-5 and C-6 CH_3), 3.60 (m, 2, CH_2OH), 3.77 (s, 3, OCH_3), 5.18 (t, 1 J = 6 Hz, C-10 H), and 7.4–7.6 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.82; H, 10.40.

To a solution of chromium trioxide–dipyridine complex[36] prepared from 6 g (60 mmol) of chromium trioxide and 9.62 ml (9.48 g, 120 mmol) of dry pyridine in 150 ml of dichloromethane was added a solution of 3.3 g (10 mmol) of the dienol above in 5 ml of dichloromethane. After 40 min the mixture was filtered through a bed of 50 g of Florisil with the aid of ether washes. After concentration of the filtrate at reduced pressure, the concentrate was taken up in 200 ml of ether, and the ethereal solution was washed successively with 5% aqueous sodium hydroxide solution (100 ml), 5% hydrochloric acid (2 × 100 ml), saturated aqueous sodium bicarbonate solution (100 ml), and saturated brine (100 ml) and dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded 3.15 g (90%) of the aldehyde **46** as a clear, colorless liquid which consisted of >97% of one volatile component on GLC analysis (240°, retention time 2.12 min). Material of this purity was used in the cyclization studies described below. An analytical sample was obtained by evaporative distillation of a portion of this material at 150° and 0.05 mm: ir ($CHCl_3$) 2730 (CHO), 1720 (CO), and 1615–1585 cm^{-1} (Ar); NMR ($CDCl_3$) δ 1.57 (s, 3, C-9 CH_3), 1.61 (s, 2 × 3, C-5 and C-6 CH_3), 3.73 (s, 3, OCH_3), 5.15 (t, 1, J = 6 Hz, C-10 H), and 7.3–6.5 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.41; H, 9.87.

Cyclization of Aldehyde 46. A solution of 657 mg (2.0 mmol) of the aldehyde **46** in 40 ml of dry benzene was stirred at room temperature under a nitrogen atmosphere and 117.0 μl (0.5 mequiv) of dry stannic chloride was rapidly injected. After exactly 75 sec the reaction mixture was poured into iced 0.05 *N* aqueous sodium hydroxide solution layered with ether in a separatory funnel, and the product was isolated by ether extraction.[35] The resulting residue was oxidized by titration of an acetone solution with 8 *N* chromic acid.[39] The crude product from this treatment amounted to 636 mg, which on preparative TLC (15% ether–petroleum ether) gave 384 mg of clear, colorless oil. The remaining 252 mg consisted of tarry nonvolatile material. GLC examination (240°) of the product showed four clearly resolved peaks at 1.88, 2.43, 3.25, and 4.08 min, which were separated (poor recovery owing to aerosoling) by preparative GLC (20°, 6 ft × 0.25 in. SE-52 on Diatoport S, He flow 60 ml/min).

Three of the main components of this mixture was identified. The peak at 1.88 min (12% of the crude mixture) showed only one unsplit methyl resonance at δ 1.13 in the NMR spectrum and two absorptions at 1710 and 1735 cm^{-1} in the ir spectrum. This suggests monocyclic material consisting of a mixture of the five- and six-membered ketone rings.

5β-(2′-*m*-Methoxyphenylethyl)-4aβ,6,8aα-trimethyl-3,4,4a,-5,8,8a-hexahydro-1(2*H*)-naphthalenone (47) (retention time 2.43 min at 240° on analytical GLC, 44% of the crude mixture) was isolated as a clear, colorless oil which after evaporative distillation

at 100° and 0.1 mm solidified and melted at 58.5–65°: ir (CCl_4) 1708 (C=O) and 1600 cm^{-1} (Ar); NMR (CCl_4) δ 0.70 (s, 3, C-8a CH_3), 1.05 (s, 3, C-4a CH_3), 1.82 (broad d, 3, C-6 CH_3, irradiation at 5.42 results in d, J = 2 Hz), 3.77 (s, 3, OCH_3), 5.42 (m, 1, C-7 H), and 7.3–6.5 (m, 4, ArH).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.07; H, 9.40.

3,4,4a,4b,5,6,10b,11,12,12a-Decahydro-10-methoxy-4aβ,-10bβ,12aα-trimethyl-1(2*H*)-chrysenone (retention time 3.25 min at 250° on analytical GLC,[35] 15% of the crude mixture) was isolated as an oil which soon solidified. Three crystallizations of this material from ether gave material of 90% purity as determined by GLC (240°) on analytical GLC: ir (CCl_4) 1710 (C=O), 1595, and 1575 cm^{-1} (Ar); NMR (CCl_4) δ 0.90 (s, 3, C-4aβ CH_3), 1.30 and 1.23 (s, 2 × 3, C-10β and C-12aα CH_3), 3.93 (s, 3, OCH_3), and 6.48, 6.52, 6.64, 6.85, 6.95, 6.98, 7.09 (m, 3, ArH). The analytical sample prepared by two crystallizations of this material from aqueous acetone and then sublimation at 100° (0.1 mm) melted at 129–132°.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.79; H, 9.37.

3,4,4a,4b,5,6,10b,11,12,12a-Decahydro-8-methoxy-4aβ,-10bβ,12aα-trimethyl-1(2*M*)-chrysenone (3) (retention time 4.08 min on analytical GLC at 240°, 23% of the crude mixture) was isolated as an oil which soon crystallized. After two crystallizations from ether, this material melted at 150–152° alone or in admixture with the material prepared above. The spectral comparison (ir and NMR) of the two samples also revealed their identity.

Two-Stage Cyclization of the Aldehyde 46. The yield of the bicyclic ketone **47** was maximized by treatment of 190 mg (0.58 mmol) of the aldehyde **46** in 11.6 ml of dry benzene (0.05 *M* solution) with 33.8 μl of dry stannic chloride for exactly 65 sec. The reaction was run as described above, and after work-up and oxidation, there resulted 174 mg of ketonic material. A solution of this crude material in 10 ml of dry toluene containing 300 mg of *p*-toluenesulfonic acid was heated at reflux for 48 hr, and then the product was isolated by ether extraction.[35] Purification of the residue (167 mg) by preparative TLC (20% ether–petroleum ether) gave 78 mg of an oil which on GLC (240°) consisted of two volatile components at 4.08 (86%) and 3.30 min (12%). An ether solution of this oil deposited needle-shaped crystals which after two crystallizations from ether amounted to 58 mg (27%) of the tetracyclic ketone **3**, mp 150–152°, alone or in admixture with authentic material, mp 150–152°, prepared above. The infrared and NMR spectra of the two samples were also identical.

X-Ray Analysis of Decalyl *p*-Bromobenzoate 39 and Tetracyclic Ketone 3. Suitable crystals of the *p*-bromobenzoate **39** were grown from petroleum ether by slow evaporation. The large, prismatic crystals were surveyed with a precession camera, and the photographs indicated the monoclinic space group $P2_1/c$. The cell dimensions were established by NaCl-calibrated precession photographs. Crystals of the tetracyclic ketone **3** in the form of colorless plates elongated along C were prepared from an ether solution by evaporation. The space group $Pna2_1$ and approximate cell constants were obtained from Weissenberg photographs; more accurate cell constants were obtained by a least-squares fit to 20 values measured on a diffractometer. The densit was measured in a zinc chloride solution by flotation. Crystal data are given in Table I.

Intensity data to a resolution of 1 Å (max $\sin\theta/\lambda = 0.5$) were collected on a Datex automated General Electric diffractometer using θ–2θ scanning. A single check reflection (130) was monitored every 30 reflections for the *p*-bromobenzoate **39** and two check reflections were monitored every 40 reflections for the tetracyclic ketone **3**. The crystals showed no sign of decomposition in the course of the data collection.

Each reflection was assigned a variance $\sigma^2(I)$ based on counting statistics plus an empirical term $(0.02s)^2$, where s is the scan count. Values of F_o^2 and $\sigma(F_o^2)$ were derived from the net intensities by application of Lorentz and polarization factors. Any reflection for which the net value of $|F_o|^2$ was less than or equal to zero was assigned an intensity and a weight of zero. The data were scaled by Wilson's[47] method, and values of $|E|$ and $|F|$ calculated.

Determination and Refinement of Structure of *p*-Bromobenzoate 39. The trial structure was derived by the usual Patterson and Fourier techniques in three dimensions. Full-matrix least-squares refinement of coordinates, isotropic temperature factors (bromine anisotropic), and scale factor reduced the R index to 10.6%. A difference Fourier indicated no misplaced or missing Br, C, or O atoms. The difference Fourier was also utilized to locate the hydrogen atoms. The addition of the hydrogen atoms to the structure factor calculation and the application of anisotropic temperature factors and second extinction factor[48] to the refinement reduced the R index to its final value of 0.056.

Table I
Crystal Data

Molecule	Tetracyclic ketone **3**	Decalyl *p*-bromobenzoate **39**
Formula	$C_{22}H_{30}O_2$	$C_{19}H_{25}BrO_2$
Formula weight	326.5	365.4
Approximate crystal size, mm	0.12 × 0.22 × 0.33	0.3 × 0.3 × 0.2
Space group	$Pna2_1$	$P2_1/c$
Systematic absences	$0kl$: $k + l = 2n + 1$	$h0l$: l odd
	$h0l$, $h = 2n + 1$	$0k0$: k odd
a, Å	29.922 (4)	7.075 ± 0.001
b, Å	7.752 (1)	25.062 ± 0.005
c, Å	7.630 (4)	10.312 ± 0.002
β		106.08 ± 0.08°
Z	4	4
F_{000}	712	760
λ	Cu Kα = 1.5418Å	1.5418 Å
D_c	1.225 g cm^{-3}	1.381 g cm^{-3}
D_m	1.23	1.38 g cm^{-3}
μ	6.0 cm^{-1}	35.
V	1770 Å	1757 $Å^3$
Diffractometer background time	30 sec	10 sec
Diffractomer scan rate	2°/min	2°/min
Number of reflections	1970	1831
Nonzero reflections	1834	1721
Final R index[a]	0.048	0.056
Standard deviations in C, O bond lengths	0.005 Å	0.005 Å
Standard deviations in C, O bond angles	0.3°	0.5°

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.

Determination and Refinement of Structure of Tetracyclic Ketone 3. The structure was solved by the symbolic addition method[49,50,51] applied to 73 reflections with $E > 2.0$. Table II lists the origin choice and symbols. There were no $00l$ reflections with high E which could be used to fix the origin. The results which led to the correct solution had the higher consistency (0.69). These 73 phases were tangent refined[48] and expanded to 241 reflections with $E > 1.3$.

Table II
Data from Symbolic Addition

	h	k	l	E	Fixed phases	Assigned phase
Origin	22	2	3	3.532	45°	
	4	1	7	3.314	90°	
	3	2	0	2.049	0°	
From σ_2's	0	2	0	1.819	180°	
Symbol	24	1	3	3.061		135°

An E map based on phases from the tangent refinement showed a continuum of hexagons. The best model gave the best fit to the $h00$ data, though other models fit the E map better. The resulting structure factor calculation based on the best model gave an R of 0.367. A series of difference-map calculations, model adjustments, and structure-factor calculations was begun reducing R to 0.247 for all nonhydrogen atoms. Full-matrix least-squares adjustment of the coordinates and isotropic temperature factors lowered R to 0.163. Difference maps clearly indicated the location of all the hydrogen atoms. Hydrogen atoms were included in subsequent structure-factor calculations in idealized positions 0.95 Å from the neighboring carbon atom. Anisotropic and positional refinement

for all heavy atoms, a scale factor, and a secondary-extinction factor[52] decreased R to 0.048.

We observed that the best model was not exactly the correct solution In fact, they differ by about 0.6 Å along a. One explanation is the difficult application of direct methods for this data set. The phases with low and high h from the original 73 phases were determined correctly. However, the middle phases ($h \sim 20$) were essentially off by 180°. One reason for this is the poor distribution of high E reflections; there are no $E > 2.0$ with $8 < h < 18$ or $28 < h < 33$.

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Registry No.—**3,** 53311-24-3; **3** cis-anti-trans isomer, 54163-13-2; **6,** 54099-89-7; **8,** 54143-28-1; **9,** 54099-88-6; **10,** 54099-90-0; **11,** 54099-91-1; **11** equatorial alcohol epimer, 54099-92-2; **12,** 54163-14-3; **13,** 54099-93-3; **14,** 54099-94-4; **15,** 54099-95-5; **16** (R = H), 54099-96-6; **16** (R = CH_2Ar), 54099-97-7; **17** (R = H), 54163-15-4; **17** (R = CH_2Ar), 54099-98-8; **17** (R = CH_2Ar) equatorial OH epimer, 54163-16-5; **18** (R = H), 54099-99-9; **18** (R = CH_2Ar), 54100-00-4; **19,** 54100-01-5; **20,** 54100-02-6; **21,** 54100-03-7; **22,** 54100-04-8; Δ^5-**23,** 53311-23-2; Δ^6-**23,** 53311-20-9; **24** (R = CH_3), 54163-17-6; **24** (R = H), 54163-18-7; **24** (R = CH_2CH_2Ar), 54143-29-2; **28,** 54100-05-9; **29,** 54100-06-0; Δ^5-**30,** 53311-22-1; Δ^6-**30,** 54100-07-1; Δ^5-**31,** 54100-08-2; Δ^6-**31,** 54100-09-3; **33,** 6044-73-1; **34,** 52713-77-6; **35,** 54100-10-6; **36,** 29023-69-6; **36** 2,4-DNP, 54100-11-7; **37,** 54100-12-8; **38,** 54100-13-9; **39,** 54100-14-0; **40,** 54100-15-1; **41,** 53311-29-8; **42,** 54100-16-2; **43,** 54100-17-3; **44,** 54100-18-4; **45,** 54100-19-5; **46,** 53311-19-6; **47,** 53311-20-9; methoxy-8aβ-methyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)naphthalenedione, 54100-20-8; 2-methyldehydroresorcinol, 1193-55-1; 1,4-dimethoxy-2-butanone, 25680-86-8; 5-methoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydro-1α,6β-naphthalenediol, 54100-21-9; 5-methoxy-8aβ-methyl-1,2,3,-4,6,7,8,8a-octahydro-1α,6α-naphthalenediol, 54100-22-0; 5-methoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydro-1α,6β-naphthalenediol diacetate, 54100-23-1; 5-methoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydro-1α,6α-naphthalenediol diacetate, 54100-24-2; 5-methoxy-8aβ-methyl-1,2,3,4,6,7,8,8a-octahydro-1α-naphthenol, 54099-91-1; 1,2,3,4,4a,5,6,7,8,8a-decahydro-1β,4aα,8aβ-trimethyl-1α-naphthalenol, 54100-25-3; 1,2,3,4,4a,5,6,7,8,8a-decahydro-4aα,8aβ-dimethyl-5,5-ethylenedioxo-1α-naphthenol, 54100-26-4; 1,2,3,4,4a,5,6,7,8,8a-decahydro-4a,8a-dimethyl-5,5-ethylenedioxo-1-(2′-*m*-methoxyphenylethyl)-2-naphthalenol, 54100-27-5; 4a,5α-methano-5β-methoxy-8aβ-methyl-3,4,4a,5,6,7,8,8a-octahydro-1(2*H*)-naphthalenone, 54100-28-6; *m*-methoxybenzyl chloride, 824-98-6; 1,2,3,4,4a,5,6,7,8,8a-decahydro-1-(2-*m*-methoxyphenylethylidene)-4a,5α-methano-5β-methoxy-8aβ-methylnaphthalene, 54100-29-7; 1,2,3,4,4a,5,6,7,8,8a-decahydro-1-(2′-*m*-methoxyphenylethyl)-4a,5-methano-5-methoxy-8a-methyl-2-naphthalenol, 54100-30-0; 1,2,3,4,4a,5,6,7,8,8a-decahydro-1,6-dehydroxy-6,8a-dimethyl-5-(2′-*m*-methoxyphenylethyl)-4a-naphthalenecarbonitrile, 54100-31-1; 1,2,3,4,4a,5,6,7,8,8a-decahydro-1-acetoxy-6-hydroxy-6,8a-dimethyl-5-(2′-*m*-methoxyphenylethyl)-4a-naphthalenecarbonitrile, 54100-32-2; 5-(2′-*m*-methoxyphenylethyl)-6,8aα-dimethyl-1α-hydroxy-4aβ-(iminomethyl)-1,2,3,4,4a,-7,8,8a-octahydronaphthalene, 54100-33-3; 5β-(2′-*m*-methoxyphenylethyl)-6,8aα-dimethyl-1α-hydroxy-4aβ-(iminomethyl)-1,2,3,4,-4a,5,8,8a-octahydronaphthalene, 54100-34-4; 4aβ,8aα-dimethyldecalin, 28831-72-3; 4aβ,8aβ-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-naphthalenone, 54100-35-5; 4aα,8aβ-dimethyldecalin, 13950-38-4; 6,7-dimethyl-3-iodo-(*E*,*E*)-2,6,10-undecatrienol, 54100-36-6; 1-chloro-3,6,7-trimethyl-(*E*,*E*)-2,6,10-undecatriene, 53311-18-5; 12-(*m*-methoxyphenyl)-5,6,9-trimethyl-(*E*,*E*)-5,9-dodecadienol, 54062-61-2; 3,4,4a,4b,5,6,10b,11,12,12a-decahydro-10-methoxy-4aβ,10bβ,12aα-trimethyl-1(2*H*)-chrysenone, 54100-37-7.

Supplementary Material Available. Structure factor tables and the final parameters and their standard deviations for the structural analyses of both the *p*-bromobenzoate **39** and the tetracyclic ketone **3** are listed in Tables III–X, which 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 Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-973.

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(1) The structural formulas containing one or more asymmetric carbon atoms depict one enantiomer but refer to racemic compounds throughout. In the text the (±) prefix will be omitted and intermediates are to be assumed to be racemic. In this discussion, naphthalene nomenclature and numbering will be used to describe dicyclic compounds, and each racemate is arbitrarily represented by that enantiomer that has the C-8a methyl group in the α configuration. The tetracyclic compounds will be described by the chrysene nomenclature, and each racemate is arbitrarily represented by that enantiomer that has the C-12a methyl group in the α configuration.
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(3) Postdoctoral Fellow (GM 39806) of the National Institute of General Medical Sciences, 1968–1970.
(4) National Science Foundation Predoctoral Fellow, 1968–1972.
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Gas–liquid phase chromatographic (GLC) analyses were determined on either a Hewlett-Packard 5750 or F & M 810 research chromatograph using helium carrier gas at a flow rate of 60 ml/min. Unless otherwise noted, all analytical GLC was conducted on a 6 ft × 0.125 in. column packed with 4% SE-30 on 60–80 mesh Chromosorb W AW DMCS.

Preparative thin layer chromatography (preparative TLC) was carried out on 20 × 20 × 0.2 cm glass plates coated with silica gel $PF_{254+266}$ (Brinkman Instruments Co.). Analytical thin layer chromatography (TLC) was conducted on 1 × 3 in. microscope slides coated with a 0.5-mm layer of silica gel G or $PF_{254+266}$.

Alumina used for column chromatography refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany and made up to grade II or III as indicated by the addition of 3% or 6% water prior to use. Silica gel columns used the 0.05–0.2 mm silica gel manufactured "for column chromatography" by E. Merck & Co., Darmstadt, Germany. Preparative medium-pressure column chromatography was performed using 0.5 × 20 in. or 2 × 20 in. glass columns with fittings supplied by Chromatronix, Inc., Berkeley, Calif., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

"Dry" solvents were dried immediately prior to use. Ether, benzene, tetrahydrofuran, and dimethoxyethane were distilled from lithium aluminum hydride; *tert*-butyl alcohol, dimethyl sulfoxide, pyridine, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride; dichloromethane, carbon tetrachloride, diiodomethane, and methyl iodide were distilled from phosphorus pentoxide; ammonia was distilled from the tank and then from a blue lithium or sodium solution. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30–60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Reactions described as run under nitrogen or argon employed a mercury bubbler arranged so that the system could be alternately evacuated and filled with the inert gas and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(35) In cases where products were isolated "by solvent extraction", the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water, followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.
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Experiments Directed toward the Total Synthesis of Terpenes. XX. Total Synthesis of (±)-Shionone, a Tetracyclic Triterpene[1]

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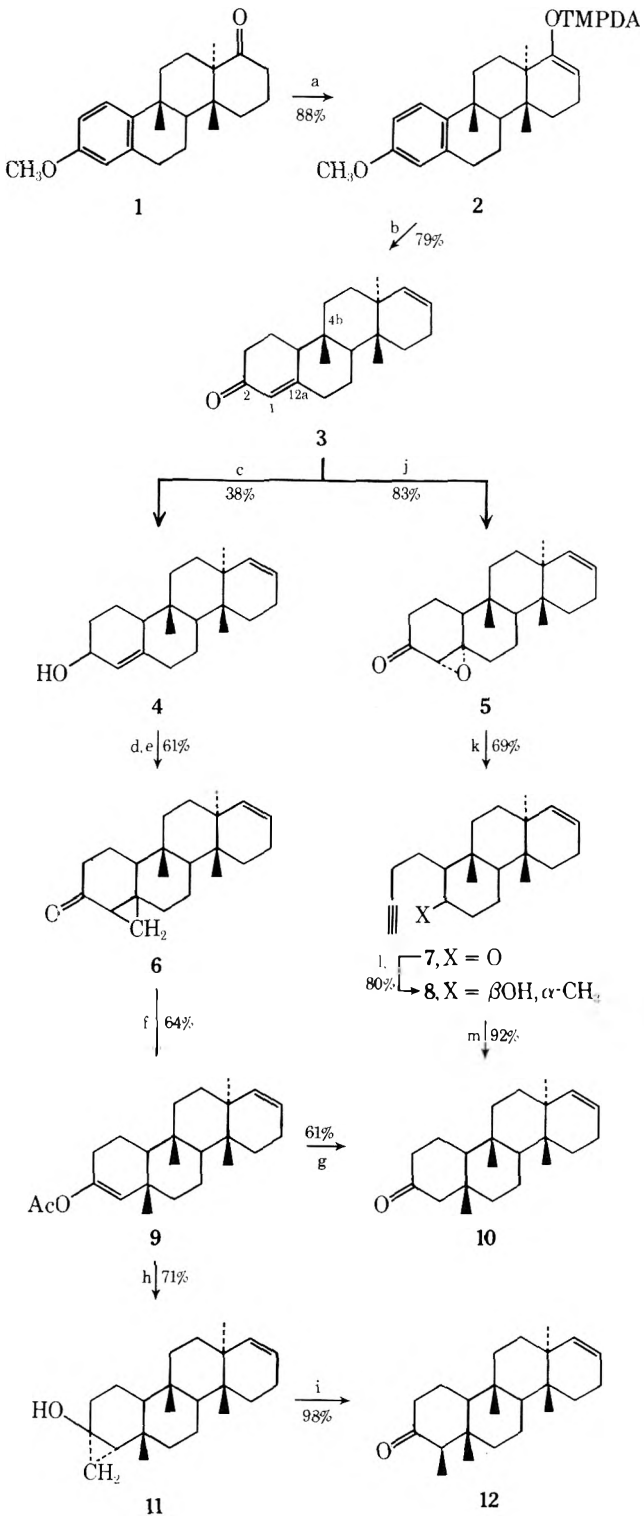
The conversion of the tetracyclic ketone **1** to the triterpene shionone (**23**) is explored by two alternative sequences. Both approaches rely on the introduction of the more or less completely formed side chain and then modification of the aromatic A ring. One unsuccessful approach entails incorporation of the intact side chain and then cleavage and recyclization of the enone **18**. Acid-catalyzed recyclization of the A ring results in hydration of the side-chain double bond. This problem was overcome and the synthesis of (±)-shionone achieved through postponement of the introduction of the side-chain unsaturation until the A ring sequence was complete.

In the preceding paper[5] in this series the development of a practical and efficient synthesis of the tetracyclic ketone **1** is described. This material, as well as some of the intermediates used in its synthesis, were envisaged as key intermediates for synthesis of both penta- and tetracyclic triterpenes. In this report the successful conversion of the ketone **1** to the tetracyclic triterpene shionone (**23**)[6] is described.[7] For this synthesis it was necessary to devise two mutually compatible schemes for the remaining operations, namely, the introduction of the side chain in ring D and the modification of the aromatic A ring to that of the natural product. The investigation of the latter problem was undertaken first (Chart I).

A convenient system—the enone **3**—with which to explore means for the A ring conversion was obtained by first transformation of the tetracyclic ketone **1** to the enol phosphorodiamidate (TMPDA) **2**[8] and then Birch reduction to remove the TMPDA as well as reduce the aromatic ring. This two-stage transformation afforded the enone **3** in 70% overall yield; during the course of optimizing this yield, it was observed that if a proton source, such as alcohol, was omitted from the Birch reduction step, the TMPDA grouping was still reductively removed in high yield, but the aromatic ring remained intact. Of course, the corresponding aromatic olefin could be subsequently reduced to the enone **3** under standard Birch reduction conditions, and this two-step reduction sequence primarily serves to demonstrate the functional selectivity possible during the reductive removal[8] of the TMPDA grouping.

The α,β-unsaturated ketone system of the enone **3** offers an ideal substrate for the regioselective introduction of the two remaining methyl groups at C-12a and C-1 through conjugate addition and then α-methylation. The stereochemical situation is, however, somewhat less satisfactory.

Chart I
Ring A Modification of Tetracyclic Ketone 1[a]



[a] a, $LiN[CH(CH_3)_2]_2$, THF; $ClPO[N(CH_3)_2]_2$; b, Li, NH_3, THF, t-BuOH; 5 *N* HCl, ETOH; c, LiR_3BH, THF; d, Zn–Cu. CH_2I_2, Et_2O; e. $CrO_3 \cdot 2Py$, CH_2Cl_2; f, Li, NH_3, THF; Ac_2O; g, KOH, EtOH; h, CH_3Li, DME; Zn–Cu, CH_2I_2, Et_2O; i, HCl, H_2O, EtOH; j, H_2O_2, aq NaOH, CH_3OH; k, *p*-$TsNHNH_2$, HOAc. CH_2Cl_2; l, CH_3Li, Et_2O; m, CF_3CO_2H-$(CF_3CO)_2O$, CH_3COCH_3, CH_3OH, aq HCl.

The C-4bβ angular methyl group severely shields the C-12a carbon from attack by a reagent from the desired β face of the molecule. Thus, while conjugate addition of a methyl group per se $[LiCu(CH_3)_2]$ to this enone system would be expected to lead to a cis-fused product, even a reagent known to produce trans-fused rings systems in other molecules[9] ($AlEt_3$–HCN[10]) gave no reaction or predominantly a low yield of cis-fused product here.[11] To overcome this stereochemical situation a method was sought that relied on the *intra*molecular orientation of carbon–carbon bond formation at C-12a, and two such schemes were investigated.

One method relies on the orientation[12] of the Simmons–Smith methylenation reaction[13] by the alcohol function in an allylic alcohol system, and here requires the generation of a C-2β (axial) hydroxyl group. The formation of the desired allylic alcohol **4** proved itself to be a thorny problem, for standard hydride reductions ($LiAlH_4$, $NaBH_4$) produced little, if any, of the β (axial) alcohol. The only satisfactory method for reduction of this enone system was through the use of lithium perhydro-9b-boraphenalylhydride recently developed by Brown and Dickason[14] and utilized effectively in an earlier stage[5] in the synthesis. Unfortunately, probably owing to the flat, unhindered character of the enone system, the yield of the desired β (axial) alcohol **4** was not as high as the yields experienced elsewhere when saturated ketones were reduced.[14] It was possible, however, after a rather tedious and inefficient chromatographic sequence, to realize a fair yield of the desired allylic alcohol **4** and pursue the sequence further, as shown in Chart I.

These remaining stages resulted in quite satisfactory yields of the respective intermediate products. A useful consequence, of course, of the methylenation process for the formation of the C-12a bond in the β (axial) orientation is that lithium–ammonia reduction[15] of the cyclopropyl ketone **6** generates the enolate anion necessary for the introduction of the C-1 methyl group by methylation. In spite of the fact that this methylation would be expected to take place through the unhindered, α (axial) approach to the tetracyclic enolate, direct methylation[16] of the enolate generated during reduction of the cyclopropyl ketone **6** or methylation[17] of the enolate regenerated in dimethoxyethane from the intermediate enol acetate **9** were singularly unsuccessful. The desired monomethylated ketone in low yield was always accompanied by unmethylated material in much higher yield. While the reasons for this behavior are unclear, a convenient solution to the problem was found in the Simmons–Smith methylenation[13] of this same enolate—a procedure suggested by the work of Whitlock and Overman.[18] While it was possible to achieve the desired end result by removal of the ammonia and then addition of the Simmons–Smith reagent directly to the enolate formed from reduction of the cyclopropyl ketone **6**, a cleaner product was obtained in more reproducible yields if this enolate was regenerated in dimethoxyethane with methyllithium from the initially trapped enol acetate **9**. Contrary to the results reported by Whitlock and Overman,[18] there is no question but that the expected cyclopropyl alcohol is the primary product of this process. By rapid and careful chromatography of the crude product, it is possible to remove all the iodide–iodine formed and isolate the cyclopropyl alcohol **11** in good yield. This material is quite labile to traces of iodide ion in hydroxylic solvents and is rapidly cleaved to the corresponding methylated ketone. This lability and the failure to remove these by-products probably accounts for the fact that Whitlock and Overman[18] did not observe the formation of a cyclopropyl alcohol in their investigations. For preparative purposes a more convenient means of cyclopropyl alcohol cleavage is the use of mineral acid, which not only provides for the cleavage but also isomerizes the initially α (axial) methyl group.

The overall yield of the ketone **12** from the enone **3** by this sequence is only 10.3%, and the route suffers primarily

from the only fair yield of the allylic alcohol 4 and the tedious procedure necessary to achieve even that result. As a consequence of this experience another sequence was investigated in which the stereochemical outcome of the formation of a carbon–carbon bond at C-12a is controlled *in a desirable fashion* by the C-4bβ methyl group. For this result to pertain it is necessary to plan for the formation of the C-1–C-12a ring bond which is α (equatorial) to the B ring. Such a plan implies the prior introduction of the potential C-12a methyl group, as well as the cleavage and reformation of the C-1–C-12a bond which already exists in the enone **3.** A sequence which involved just such a process is outlined in Chart I, and in spite of what at first sight seems inefficiency owing to the necessity of ring cleavage, this route is significantly more efficient than that just described.

Utilization of the sequence developed by Eschenmoser and coworkers[19] provided an excellent means for cleavage of the A ring of the enone **3** without the loss of any carbon atoms. Owing to the diversity of the functionality that results from the Eschenmoser cleavage, it was now possible to incorporate the potential C-12a angular methyl group through the direct addition of methyllithium to the acetylenic ketone **7** without the necessity of incorporating blocking groups in the sequence. With the acetylenic alcohol **8** in hand the stage was set for the re-formation of the C-1–C-12a ring bond through cyclization. The pioneering work of Peterson[20] and the extensive work of Johnson and Lansbury and their coworkers[21] provided the basis for the selection of the reaction conditions. Confidence that the stereochemistry of the molecule that would result from this cyclization would be that with the C-12a methyl group in the desired β (axial) orientation stemmed from the extensive previous experience[22] in these laboratories that demonstrated the stereochemical control provided by the axial C-4bβ methyl group during similar cationic ring closures. It was nevertheless gratifying to find that cyclization of the acetylenic alcohol **8** in trifluoroacetic acid led to an enol trifluoroacetate in excellent yield and that hydrolysis of this intermediate provided the same saturated ketone **10** that was obtained on saponification of the corresponding enol acetate **9** from the previously described route. The convergence of these two routes at this point serves to confirm the β (axial) orientation of the C-12a methyl group, for the β (quasi-axial) assignment of the configuration of the C-2 hydroxyl group in the allylic alcohol **4**—and hence the orientation of the Simmons–Smith methylenation reaction—rests on firm ground. In view of the ease with which the enol trifluoroacetate could be isolated from this cyclization and the already proven utility of the enol acetate **9** for the incorporation of the remaining methyl group at C-1, the present route seemed well suited to the construction of the shionone A ring, and attention was turned to the introduction of the side chain in ring D.

Since the general plan for the total synthesis of shionone (**23**) entailed the incorporation of the ring D side chain and then modification of the aromatic A ring by the process discussed above, the tetracyclic ketone **1** again became the starting point. While the ketone functionality in the D ring of this material would obviously serve to introduce the two required alkyl groups in the adjacent α position, the efficiency and stereochemical outcome of these alkylation reactions were circumspect. In addition such a plan incorporates the potential difficulties that would be associated with the ultimate necessary removal of what would then be a very hindered ketone function. In order to circumvent these anticipated chemical problems, as well as have a sound basis for the stereochemical results, means were sought to remove the existing ring D ketone and at the same time introduce activating functionality external to the ring system. This plan was effectively accomplished (Chart II) by a two-step process that led from the tetracyclic ketone **1** through the chloro aldehyde **13** from the Vilsmeier reaction[23] and then by lithium–ammonia reduction–methylation[16] to the aldehyde **14.** The yields in this process were quite satisfactory, and the efficiency of the structural changes that attend the reduction–methylation step is noteworthy. The stereochemical outcome of the methylation of the enolate from the lithium–ammonia reduction of the chloro aldehyde **13** is well precedented[24] in similar systems, but the preparative use of α,β-unsaturated aldehydes in such reductions to generate useful aldehyde enolates appears[25] to be novel. As might be expected, the conditions for the reduction stage had to be carefully controlled (see Experimental Section) in order to prevent dimerization and overreduction.

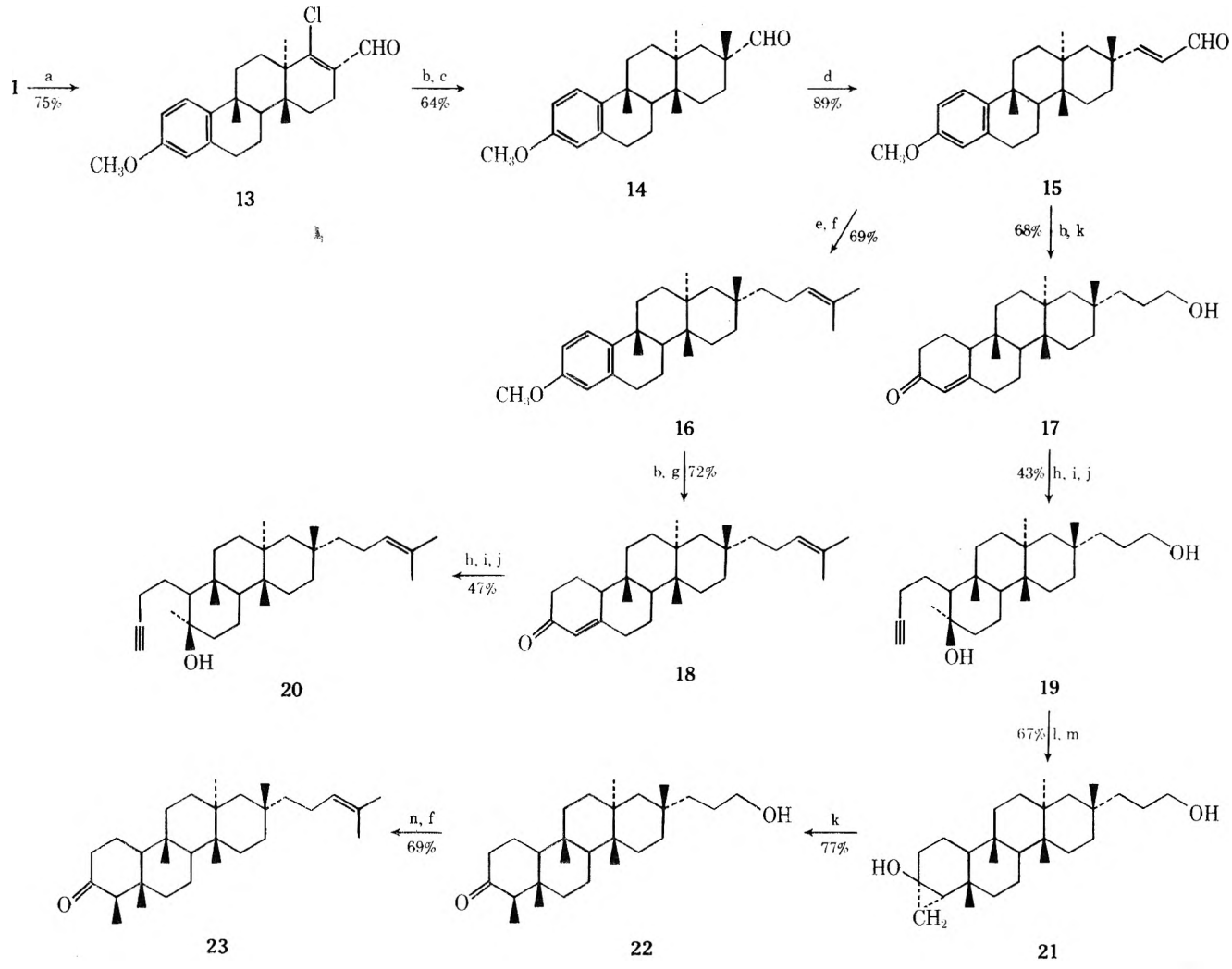
With an eye toward the rapid completion of the side chain, the aldehyde **14** was quantitatively reduced to the corresponding primary alcohol with lithium aluminum hydride and efforts were made to convert this alcohol to the iodide preparative to a coupling reaction[26] with π-(1,1-dimethylallyl)–nickel bromide complex. Unfortunately, both the neopentyl character and the severe steric congestion about this axial hydroxymethyl grouping thwarted all attempts to prepare the iodide or other halides. Reactions of the alcohol with triphenyl phosphite–methyl iodide,[27] triphenylphosphine, carbon tetrabromide, and carbon tetrachloride,[28] and thionyl chloride–quinoline led either to recovered alcohol after no reaction or a plethora of products that resulted from the intervention of cationic species that led to backbone rearrangements.

To overcome these difficulties an alternate scheme was developed for the addition of the remainder of the side chain through the use of two successive Wittig-type condensations. The aldehyde **14** was first converted to the unsaturated aldehyde **15** by the efficient formylolefination procedure of Nagata and Hayase,[29] and after reduction[30] of the unsaturated aldehyde **15** with triethylsilane in the presence of tris(triphenylphosphine)rhodium chloride, the process was completed in 30% overall yield from the tetracyclic ketone **1** by the condensation of the saturated aldehyde with isopropylidenephosphorane.

With the aromatic olefin **16** thus in hand, modification of the A ring by the method developed above was projected to complete the synthesis. Indeed this process proceeded well (Chart II) up to the stage of final reformation of the A ring from the acetylenic alcohol **20.** This approach irreversibly broke down at this point, for the acidic conditions necessary to effect the cyclization invariably resulted in acid-catalyzed hydration of the side-chain trisubstituted double bond. When modifications were made in the reaction conditions in order to avoid this addition reaction by reducing the acidity, lowering the temperature, and/or changing the acid catalyst, it was found that the sequence of events involved initial rapid addition to the side-chain double bond. In experiments where the conditions were vigorous enough, cyclization of the acetylenic alcohol was a subsequent step. Indeed, it was possible to hydrate the side-chain double bond without affecting the acetylenic alcohol system. The lability of this side-chain unsaturation was a surprise, particularly when the model system used to explore this sequence—the acetylenic alcohol **8**—was specifically chosen with this side chain in mind and itself contains an isolated (albeit disubstituted) double bond.

The solution to this last problem dictated a change in methodology for either the A ring modifications or the

Chart II
Conversion of Tetracyclic Ketone 1 to (±)-Shionone (23)[a]



[a] a, $POCl_3$, DMF; b, Li, NH_3, THF, *t*-BuOH; c, $NaO_2CC_6H_5$, CH_3I; d, NaH, $(EtO)_2POCH_2CH{=}NC_6H_{11}$, THF, aq $(CO_2H)_2$, C_6H_6; e, Et_3SiH, $[(C_6H_5)_3P]_3RhCl$, C_6H_6, CH_3COCH_3, aq HCl; f, $(C_6H_5)_3PCH(CH_3)_2{}^+I^-$, C_6H_5Li, THF; g, $(CO_2H)_2$, aq EtOH, NaOH, aq EtOH; h, H_2O_2, aq NaOH, CH_3OH-CH_2Cl_2; i, *p*-$TsNHNH_2$, HOAc-CH_2Cl_2; j, CH_3Li, THF; k, aq HCl, EtOH; l, CF_3CO_2H-$(CF_3CO)_2O$; m, $LiN[CH(CH_3)_2]$, THF, Zn-Ag, CH_2I_2, Et_2O; n, $CrO_3 \cdot 2Py$, CH_2Cl_2.

side-chain construction. Rather than tamper with the more intricate procedures in the former process, a reshuffling of the steps in the side-chain construction seemed advisable. Since the offending functionality in the side chain was the double bond that resulted from the last stage in the process, this reaction was deferred until the completion of the A ring. Thus, complete reduction of the unsaturated aldehyde **15** led in good yield to the hydroxyenone **17**, which could be carried through the A ring synthesis without major incident (Chart II). The result of the trifluoroacetic acid catalyzed cyclization of the acetylenic alcohol **19** was the expected bis trifluoroacetate, but this posed no significant experimental problem in the subsequent stages that completed the shionone (23) synthesis.

A noteworthy point did come to light when the bis trifluoroacetate was used to generate the enolate in ring A. Under the conditions used earlier for the generation and methylenation of the enolate from the enol acetate **9**, none of the expected cyclopropyl alcohol was observed, and the product was the C-1 demethyl keto alcohol. Model studies showed that this was not the result of hydrolysis or protonation of the enolate by traces of moisture, nor was it the result of the failure of the methylenation reaction. Reasoning that the enolate generated by methyllithium addition[17] was being rapidly protonated by the initially formed 1,1,1-trifluoroacetone, an aminolysis reaction was substituted for the Grignard reaction with salutory results. The enol trifluoroacetate was readily cleaved by lithium diisopropylamide, and the resulting enolate behaved as expected in the methylenation reaction. This observation should render enol trifluoroacetates generally useful for the formation of ketone enolates, and coupled with the addition of trifluoroacetic acid to acetylenes, the overall process is an interesting ketone synthesis.

Experimental Section[31]

8-Methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,-11,12,12a-decahydrochrysen-1-yl Tetramethylphosphorodiamidate (2). To a solution of lithium diisopropylamide prepared from 8 ml (57 mmol) of diisopropylamine and 13 ml of a 2.84 *M* hexane solution of *n*-butyllithium in 150 ml of dry ether under an argon atmosphere was added over a 10-min period a solution of 2.27 g (7 mmol) of the ketone **1** in 20 ml of dry tetrahydrofuran and 8 ml of *N,N,N',N'*-tetramethylethylenediamine. The mixture was then cooled in an ice bath, and 15 ml (81 mmol) of tetramethyldiamidophosphorochloridate[32] was added dropwise. After the resulting yellow solution was allowed to warm to room temperature and then stirred for 1.5 hr, the mixture was poured into ice and 400 ml of 10% aqueous hydrochloric acid, and the product was isolated by ether extraction[33] including a base wash. On chromatography of

the crude product on 200 g of silica gel, 2.81 g (88%) of the phosphorodiamidate **2**, mp 108–111° (vacuum), was eluted with 1800 ml of 10% acetone–ethyl acetate after an initial wash with 800 ml of ethyl acetate and then 600 ml of 5% acetone–ethyl acetate. The analytical sample, obtained after cystallization of a portion of this material from ether–heptane, also melted at 108–111° (vacuum): ir ($CHCl_3$) 1670 (C=C), 1605, 1500 (Ar), 1305 (P–N), and 980 cm^{-1} (P–O–C); NMR ($CDCl_3$) δ 1.02 (s, 3, C-4a CH_3), 1.22 (s, 2 × 3, C-10b and C-12a CH_3), 2.70 (d, 12, J = 10 Hz, NCH_3), 3.75 (s, 3, OCH_3), and 5.20 (m, 1, C=CH).

Anal. Calcd for $C_{26}H_{41}O_3N_2P$: C, 67.80; H, 8.97; N, 6.08; P, 6.73. Found: C, 67.96; H, 8.86; N, 6.16; P, 6.64.

8-Methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,-11,12,12a-decahydrochrysene. To a solution of 37 mg (5.3 mg-atoms) of lithium in 50 ml of dry ammonia and 10 ml of dry tetrahydrofuran under an argon atmosphere was added a solution of 210 mg (0.45 mmol) of the phosphorodiamidate **2** in 6 ml of dry tetrahydrofuran. After 1.5 hr the blue color faded, and an additional 37 mg (5.3 mg-atoms) of lithium was added. After stirring for 3.5 hr longer, the reaction mixture was treated with 400 mg of sodium benzoate and then 200 mg of solid ammonium chloride. After the ammonia was evaporated in a stream of argon, the residue was dissolved in 50 ml of water, and the product was isolated by ether extraction[33] including an acid and base wash. On preparative TLC (30% ether–petroleum ether) of the crude product there was obtained 115 mg (82%) of the tetracyclic olefin (R_f 0.7) as a colorless oil. The analytical sample was obtained after further preparative TLC (30% ether–petroleum ether) and then evaporative distillation (120°, 0.01 mm) of a portion of this material: ir ($CHCl_3$) 1605 and 1500 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.82 (s, 3, C-4a CH_3), 1.00 (s, 3, C-12a CH_3), 1.22 (s, 3, C-10b CH_3), 3.77 (s, 3, $ArOCH_3$), 5.52 (m, 2, CH=CH), and 6.50–7.17 (m, 3, ArH).

Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 84.96; H, 9.64.

4bβ,6aα,10aβ-Trimethyl-4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12-dodecahydro-2(3*H*)-chrysenone (3). A. From the Phosphorodiamidate 2. A solution of 370 mg (53 mmol) of lithium wire in 550 ml of dry ammonia and 140 ml of dry tetrahydrofuran was stirred for 30 min, and then a solution of 1.53 g (3.32 mmol) of the phosphorodiamidate **2** in 30 ml of dry tetrahydrofuran was injected all at once with a syringe. After 5 hr an additional 960 mg (139 mmol) of lithium and 85 ml of dry *tert*-butyl alcohol were added. After the reaction had stirred for an additional 2 hr, the excess lithium was decomposed with 20 ml of methanol, and the ammonia was allowed to evaporate overnight. The gray residue was treated with 500 ml of water, and the product was isolated by ether extraction.[33] A solution of the resulting residue in 200 ml of ethanol and 130 ml of 5 N aqueous hydrochloric acid was heated at 65–70° for 40 min in an argon atmosphere. The cooled reaction mixture was then poured into 500 ml of water, and the product was isolated by ether extraction,[33] including a base wash. On chromatography of the dark yellow, oily residue on 100 g of silica gel there was obtained 782 mg (79%) of the enone **3**, mp 88–92°, by elution with 600 ml of 50% ether–petroleum ether. Crystallization (ethanol–water) and then sublimation (120°, 0.01 mm) of a portion of this material gave the analytical sample: mp 94–97°; ir ($CHCl_3$) 1665 (C=O) and 1620 cm^{-1} (C=C); NMR ($CDCl_3$), δ 0.87 (s, 2 × 3, C-4b and C-10a CH_3), 1.07 (s, 3, C-6a CH_3), 5.47 (m, 2, CH=CH), and 5.92 (s, 1, O=C–CH=C).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.54; H, 10.13. Found: C, 84.51; H, 10.22.

B. From Tetracyclic Olefin. A stirred solution of 182 mg (0.58 mmol) of the above olefin in 60 ml of dry ammonia, 20 ml of dry tetrahydrofuran, and 10 ml of dry *tert*-butyl alcohol under an argon atmosphere was treated with 111 mg (16 mg-atoms) of lithium. After 2 hr the excess lithium was decomposed with 3 ml of methanol, and the ammonia was evaporated in a stream of argon. The gray residue was dissolved in 150 ml of water, and the product was isolated by ether extraction.[33] A solution of the crude product in 30 ml of ethanol and 20 ml of 5 N aqueous hydrochloric acid was heated at 65–70° for 40 min under an argon atmosphere, and after dilution of the cooled reaction mixture with 100 ml of water, the product was isolated by ether extraction,[33] including a base wash. The crude product was chromatographed on 22 g of silica gel, and elution with 175 ml of 50% ether–petroleum ether afforded 153 mg (78%) of the enone **3**, mp 91–94°, that was identical (mixture melting point, ir, NMR) with the material prepared above in part A.

2β-Hydroxy-4bβ,6aα,10aβ-trimethyl-2α,3,4,4aα,4b,5,6,6a,9,-10,10a,10bα,11,12-tetradecahydrochrysene (4). Following the general procedure of Brown and Dickason,[14] an ice-cold solution of 781 mg (2.62 mmol) of the enone **3** in 15 ml of dry tetrahydrofuran under an argon atmosphere was treated with 6.0 ml (5.1 mmol) of a 0.85 M tetrahydrofuran solution of the trialkylborohydride. After 30 min the organoborane was decomposed by the sequential addition of 1.0 ml of 3 N aqueous sodium hydroxide solution and 2.0 ml of 30% hydrogen peroxide. The reaction mixture was immediately poured into 50 ml of saturated aqueous sodium carbonate solution and the product isolated by ether–benzene (4:1) extraction. The crude product was chromatographed on 100 g of Florisil which was eluted with 59% ether–petroleum ether. The first 300 ml eluted 75 mg of a mixture of nonpolar products that was discarded. The next 200 ml afforded 183 mg (23%) of the axial alcohol **4**, mp 130–133°. Further elution with 400 ml of the same solvent gave 316 mg of a mixture of the two alcohols which on further separation by preparative TLC (10% ether–chloroform) gave 188 mg (24%) of the equatorial alcohol (R_f 0.4) and 114 mg (15%) of the axial alcohol **4** (R_f 0.5). Finally, washing the column with 500 ml of ether gave 206 mg (26%) of the equatorial alcohol, mp 119–120° (vacuum). The total yield of axial alcohol **4** was 296 mg (38%) and that of the equatorial alcohol was 394 mg (50%).

The analytical sample of the axial alcohol **4**, prepared by crystallization of a portion of similar material from another reduction experiment from ethyl acetate–heptane and then ethanol–water, melted at 131–134° (vacuum): ir 3600, 3450 (OH), and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.85 (s, 2 × 3, C-4b and C-10a CH_3), and 1.05 (s, 3, C-6a CH_3), 4.00–4.20 (m, 1, CHO), 5.48 (m, 2, CH=CH), and 5.50–5.77 (m, 1, OCCH=C).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.87; H, 10.78.

The analytical sample of the equatorial alcohol was prepared in the same fashion and melted at 114–116° (vacuum): ir ($CHCl_3$) 3605, 3450 (OH), and 1655 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.77, 0.82, and 1.05 (s, 3 each, C-4b, C-6a, and C-10a CH_3), 3.95–4.30 (m, 1, CHO), and 5.37–5.53 (m, 3, CH=C).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.93; H, 10.87.

1β,12aβ-Methano-4bβ,6aα,10aβ-trimethyl-1α,4,4aα,4b,5,6,-6a,9,10,10a,10bα,11,12,12a-tetradecahydro-2(3*H*)-chrysenone (6). To a suspension of 4.0 g (57 mmol) of zinc–copper couple[34] in 4.6 ml (57 mmol) of diiodomethane and 60 ml of dry ether was added a solution of 638 mg (2.21 mmol) of the axial alcohol **4** in 10 ml of dry ether, and the resulting mixture was heated at reflux under an argon atmosphere for 4 hr. After cooling, the reaction mixture was poured into 100 ml of saturated aqueous sodium carbonate, and the product was isolated by ether–benzene (4:1) extraction.[33] On chromatography of the product on 250 g of grade III alumina, elution with 600 ml of 3% methanol–ether gave 512 mg (80%) of the corresponding cyclopropyl alcohol, mp 135–139° (vacuum): ir ($CHCl_3$) 3600, 3450 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.85, 0.95, 1.05 (3 s, 3 each, C-4b, C-6a, and C-10a CH_3), 4.07–4.43 (m, 1, CHO), and 5.47 (s, 2–CH=CH–)

After the procedure of Radcliffe and Rodehorst,[35] a solution of 512 mg (1.69 mmol) of the above cyclopropyl alcohol in 8 ml of dry dichloromethane was added under an argon atmosphere to a solution of 1.62 ml (20 mmol) of dry pyridine and 1.00 g (10 mmol) of anhydrous chromium trioxide in 50 ml of dry dichloromethane, and the red solution was stirred for 10 min. The dark mixture was then filtered through a pad of grade III alumina with the aid of 200 ml of ether. Evaporation of the solvents from the filtrate at reduced pressure afforded 490 mg (77%, 61% overall) of the ketone **6**, mp 149–152° (vacuum). The analytical sample, prepared from a portion of this material by preparative TLC (50% ether–petroleum ether) and then crystallization from ether–hexane, melted at 150–153° (vacuum): ir ($CHCl_3$) 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90, 1.02, 107 (3 s, 3 each, C-4b, C-6a, and C-10a CH_3), and 5.47 (s, 2, CH=CH).

Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.49; H, 10.39.

2-Acetoxy-4bβ,6aα,10aβ,12aβ-tetramethyl-3,4,4aα,4b,5,6,6a,-9,10,10a,10bα,11,12,12a-tetradecahydrochrysene (9). To an argon-protected solution of 18 mg (2.6 mg-atoms) of lithium in 60 ml of dry ammonia and 20 ml of dry tetrahydrofuran was added a solution of 203 mg (0.65 mmol) of the cyclopropyl ketone **6** in 5 ml of dry tetrahydrofuran. After stirring for 1.5 hr, the blue color faded; an additional 18 mg (2.6 mg-atoms) of lithium was then added, and the mixture was stirred for 2.5 hr. Most of the ammonia was then removed by evaporation in a stream of argon through a mercury bubbler, and the resulting gray suspension was treated

with 5 ml (53 mmol) of dry acetic anhydride at room temperature. After stirring for 6 hr, the reaction mixture was poured into a mixture of ice and 70 ml of 10% aqueous potassium hydroxide solution, and the product was isolated by ether–benzene (1:1) extraction.[33] On chromatography of the crude product (285 mg) on 30 g of silica gel, elution with 150 ml of 20% ether–petroleum ether gave 146 mg (64%) of the enol acetate **9**, mp 119–121° (vacuum). The analytical sample, prepared from a portion of this material by preparative TLC (20% ether–petroleum ether) and crystallization from ether–hexane, melted at 121–123° (vacuum): ir ($CHCl_3$) 1755 (C=O), 1690 (C=C), and 1220 cm^{-1} (C–O–C); NMR (CCl_4) δ 0.78, 0.88 (2 s, 3 each, C-4b, and C-10b CH_3), 1.02 (s, 2 × 3, C-6a and C-12a CH_3), 2.00 (s, 3, CH_3CO), 4.97 (s, 1, C-1 H), and 5.40 (s, 2, CH=CH).

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 81.05; H, 10.23.

Further elution of the column with 25 ml of the same solvent mixture gave 37 mg of a mixture that consisted of approximately equal parts of the enol acetate **9** and the Δ^2-enol acetate of the starting ketone **6** (**2-acetoxy-1β,12aβ-methano-4bβ,6aα,10aβ-trimethyl-1,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-tetradecahydrochrysene**) on the basis of the comparative integration of the acetyl methyl signals at δ 2.00 and 2.03 in the NMR spectrum. An analytically pure sample of the latter Δ^2-enol acetate was obtained from another similar experiment after preparative TLC (20% ether–petroleum ether) and then crystallization of the material with R_f 0.4 from hexane and melted at 110–112° (vacuum): ir (CCl_4) 1755 (C=O), 1685 (C=C), and 1220 cm^{-1} (C–O–C); NMR (CCl_4) δ 0.85, 0.98, and 1.03 (3 s, 3 each, C-4b, C-6a, and C-10a CH_3), 2.03 (s, 3, CH_3CO), 4.80–5.05 (m, 1, C-3 H), and 5.40 (s, 2, CH=CH).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.46; H, 9.75.

Saponification of this Δ^2-enol acetate in aqueous, alcoholic potassium hydroxide solution afforded a 70% yield of the cyclopropyl ketone **6**, mp 123–126°, alone or in admixture with authentic material of the same melting range.

Finally, continued elution of the column with 100 ml of the same solvent mixture afforded 10 mg (5%) of the ketone **10**, mp 150–158°. Further purification of this material by preparative TLC (40% ether–petroleum ether) and then crystallization from hexane–dichloromethane gave material that melted at 172–176°, alone or in admixture with authentic ketone **10**, mp 172–176°, prepared below by hydrolysis of the enol acetate **9**.

4bβ,6aα,10aβ,12aβ-Tetramethyl-3,4,4aα,4b,5,6,6a,9,10,10a,-10bα,11,12,12a-tetradecahydro-2(1*H*)-chrysenone (10). A. From Enol Acetate 9. A solution of 90 mg (0.25 mmol) of the enol acetate **9** and 180 mg (2.7 mmol) of potassium hydroxide in 5 ml of ethanol was stirred at room temperature for 14 hr under argon atmosphere. The mixture was then diluted with water, and the product was isolated by ether–benzene (1:1) extraction.[33] Purification of the crude product by preparative TLC (40% ether–petroleum), then crystallization from hexane–dichloromethane, and finally sublimation at 160–170° and 0.025 mm gave 46 mg (61%) of analytically pure ketone **10**: mp 172–176° (vacuum); ir ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.82 (s, 3), 0.90 (s, 6), and 1.06 (s, 3) (C-4b, C-6a, C-10a, and C-12a CH_3), and 5.48 (s, 2, CH=CH).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 83.90; H, 10.99.

B. From Acetylenic Alcohol 8. A mixture of 2.0 ml of trifluoroacetic acid and 0.6 ml of trifluoroacetic anhydride was cooled in a −18° bath; 1.6 ml of this cold solution was then added to 16.0 mg (0.051 mmol) of the acetylenic alcohol **8** at −18°, and the mixture was stirred at this temperature for 20 min. The pressure in the system was then reduced with a vacuum pump, and the cooling bath was then removed to facilitate evaporation of the solvents. Most of the liquid was gone within 5 min, but the residual oil was dried at room temperature for 20 min at ca. 0.05 mm pressure. This oil was handled so as to avoid prolonged contact with moist air and appeared to be the desired enol trifluoroacetate: ir ($CHCl_3$) 1790 (CF_3CO), 1695 (–OC=C–), 1385 (CH_3), and 1220, 1170, 1140 cm^{-1} (C–O–C and CF_3); no remaining 3300 cm^{-1} (–C≡CH); NMR ($CDCl_3$) δ 0.81, 0.90, 1.04 (3 s, 3, 3, and 6, respectively, C-4a, C-6a, C-10a, and C-12a CH_3), 5.28 (m, 1, CF_3CO_2C=CH), and 5.44 (s, 2, HC=CH); analysis by GLC (250°) showed only one peak at retention time 1.2 min.

A solution of this crude enol trifluoroacetate in 1 ml of acetone and 1 ml of methanol was treated with 5 drops of water and 5 drops of 10% aqueous hydrochloric acid and then stirred at room temperature for 75 min. After neutralization of this solution with solid sodium bicarbonate, the product was isolated by ether extraction.[33] Purification of the crude product (17.5 mg) by preparative TLC (40% ether–petroleum ether) afforded 14.7 mg (92%) of the tetracyclic ketone **10** as a white solid, mp 166–172° (vacuum); the ir and NMR spectra of this material were identical with those of purified ketone **10** prepared in part A above. Crystallization of this solid from dichloromethane–hexane afforded white crystals, mp 170–174° (vacuum), alone or in admixture with material prepared above, mp 172–176° (vacuum), in part A.

2β-Hydroxy-1α,2α-methano-4bβ,6aα,10aβ,12aβ-tetramethyl-1β,2,3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-hexadecahydrochrysene (11). A solution of 153 mg (0.43 mmol) of the enol acetate **9** in 5 ml of dry dimethoxyethane was added to an argon-protected solution of methyllithium (0.7 ml, 1.2 mmol), and the mixture was stirred at room temperature for 30 min. To this solution was added by syringe the supernatant solution from the preparation of the Simmons–Smith reagent from 1.20 g (17 mmol) of zinc–copper couple[34] and 1.40 ml (1.20 mmol) of diiodomethane in 17 ml of dry ether. After stirring in an ice bath for 1 hr, the reaction mixture was poured into 50 ml of saturated aqueous sodium carbonate solution, and the product was isolated by ether–benzene (1:1) extraction[33] including a base and 10% aqueous sodium thiosulfate solution wash. On chromatography of the crude material on 70 g of grade III alumina, elution with 200 ml of ether gave 100 mg (71%) of the cyclopropyl alcohol **11**, mp 161–165° (vacuum). The analytical sample, obtained after crystallization of a portion of this material from dichloromethane–hexane, melted at 166–168° (vacuum): ir ($CHCl_3$) 3600, 3450 (OH), and 1180 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.80, 0.87, 1.02, and 1.15 (4 s, 3 each, C-4b, C-6a, C-10a, and C-12a CH_3), and 5.42 (s, 2, CH=CH).

Anal. Calcd for $C_{23}H_{36}O$: C, 84.09; H, 11.04. Found: C, 83.85; H, 11.13.

1β,4bβ,6aα,10aβ,12aβ-Pentamethyl-3,4,4aα,4b,5,6,6a,9,10,-10a,10bα,11,12,12a-tetradecahydro-2(1*H*)-chrysenone (12). A solution of 161 mg (0.49 mmol) of the cyclopropyl alcohol **11** and 1 ml of concentrated hydrochloric acid in 12 ml of ethanol was heated under reflux in an argon atmosphere for 1 hr. After cooling, the solution was diluted with 50 ml of water, and the product was isolated by ether extraction,[33] including a base wash. The resulting material amounted to 157 mg (98%) of the ketone **12**, mp 169–176° (vacuum), from which the analytical sample, mp 178–182° (vacuum), was prepared by preparative TLC (40% ether–petroleum ether) and then sublimation at 150–155° and 0.7 mm: ir ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.73 (s, 3), 0.83 (s, 4.5), 0.95, (s, 4.5), and 1.05 (s, 3) (C-1, C-4b, C-6a, C-10a, and C-12a CH_3), and 5.47 (s, 2, CH=CH).

Anal. Calcd for $C_{23}H_{36}O$: C, 84.09; H, 11.04. Found: C, 84.16; H, 11.16.

1α,12aα-Epoxy-4bβ,6aα,10aβ-trimethyl-3,4,4aα,4b,5,6,6a,9,-10,10a,10bα,11,12,12a-tetradecahydro-2(1*H*)-chrysenone (5). To a stirred solution of 125 mg (0.42 mmol) of the enone **3** in 10 ml of methanol at room temperature was added 1 ml (*ca.* 300 mg, 16 mmol) of 30% aqueous hydrogen peroxide solution and 0.5 ml of 10% aqueous sodium hydroxide solution, and the mixture was stirred at room temperature for 1 hr. The solution was then diluted with ether and water, and the product was isolated by ether extraction.[33] Purification of the resulting semicrystalline solid (126 mg) by preparative TLC (30% ether–petroleum ether) afforded 109 mg (83%) of the epoxy ketone **5** (R_f 0.45), mp 98–100° (vacuum). The analytical sample, mp 102.5–103.5° (vacuum), was obtained after two crystallizations of this material from methanol–dichloromethane: ir ($CHCl_3$) 1700 (C=O), 1450 (CH_2), and 1385 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.82, 0.87, and 1.05 (3 s, 3 each, C-4b, C-6a, and C-10a CH_3), 3.16 (s, 1, C-1 H), and 5.49 (s, 2, CH=CH).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.44; H, 9.69.

1β-(3′-Butynyl)-4bβ,8aα,10aβ-trimethyl-3,4,4aα,4b,5,6,8a,9,-10,10a-decahydrophenanthren-2(1*H*)-one (7). A slight modification of the general procedure of Eschenmoser and coworkers[19] was employed. To a dry mixture of 77.0 mg (0.244 mmol) of the epoxy ketone **5** and 48.8 mg (0.261 mmol) of *p*-toluenesulfonylhydrazine at −20° was added with stirring and swirling 1.5 ml of −20° acetic acid–dichloromethane (1:1). After stirring for 5 min at −20°, the solution was stored at −20° for 15 hr. The mixture was then stirred at room temperature for an additional 4 hr (during which time it turned red) and then the product was isolated by ether extraction,[33] including a base wash. Purification of the crude product (81 mg) by preparative TLC (30% ether–petroleum ether)

afforded 50.5 mg (69%) of the acetylenic ketone **7** as a yellow oil (R_f 0.48) which was suitable for analysis: ir ($CHCl_3$) 3300 (-C≡CH), 2120 (-C≡C-), 1700 (C=O), and 1390 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.77, 0.85, 1.13 (3 s, 3 each, C-4b, C-8a, and C-10a CH_3), and 5.49 (s, 2, HC=CH).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.25; H, 10.02.

1β-(3′-Butynyl)-2α,4bβ,8aα,10aβ-tetramethyl-1,2,3,4,4aα,4b,-5,6,8a,9,10,10a-dodecahydro-2β-phenanthrol (8). To a stirred and ice-cooled mixture of 0.36 ml (0.68 mmol) of 1.9 *M* ethereal methyllithium solution and 2.0 ml of dry ether was added over a 2-min period a solution of 19.0 mg (0.064 mmol) of the acetylenic ketone **7** in 1.2 ml of dry ether. After stirring for 10 min longer at 0°, and for 5 min without cooling, the reaction mixture was cautiously quenched with 0.5 ml of water and then the product was isolated by ether extraction.[33] Purification of the crude product (18.8 mg) by preparative TLC (50% ether–petroleum ether) afforded 16.0 mg (80%) of the alcohol **8** as a white solid, mp 84–88° (vacuum). The analytical sample, obtained after two crystallizations of a portion of this material from ether–hexane, melted at 91.0–92.5° (vacuum): ir ($CHCl_3$) 3600 (OH), 3300 (-C≡CH), 2115 (-C≡C-), and 1385, 1370 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.81, 1.00, 1.03, 1.17 (4 s, 3 each, C-2, C-4b, C-8a, and C-10a CH_3), and 5.45 (s, 2, HC=CH).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 84.01; H, 11.04.

1-Chloro-2-formyl-8-methoxy-4aβ,10bβ,12aα-trimethyl-3,-4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysene (13). Following a modification of the procedure of Moersch and Neuklis,[23] ice-cooled phosphoryl chloride (12 ml, 20.1 g, 0.131 mmol) was stirred and treated over a 1-min period with 13.6 ml (12.8 g, 0.176 mmol) of dimethylformamide. After stirring for 30 min without cooling, the viscous solution of reagent was added at room temperature to a stirred solution of 1.158 g (3.54 mmol) of the tetracyclic ketone **1** in 24 ml of dimethylformamide. The stirred reaction mixture was then heated with a preheated, 60° oil bath for 6 hr so that the internal temperature rose to a constant 55–56°. After cooling with an ice bath, the solution was poured onto 350 g of ice and 40 ml of 40% aqueous sodium hydroxide solution, and the product was isolated by dichloromethane extraction.[33] The crude residue (1.310 g) was chromatographed on 200 g of silica gel in a medium-pressure column with dichloromethane. After the first 400 ml of eluent was discarded, evaporation of the next 600 ml of eluent at reduced pressure provided 854 mg (65%) of the chloroaldehyde **13** as a white solid, mp 196–198° (vacuum). The analytical sample, obtained after crystallization of a portion of this material from acetone–dichloromethane–water, melted at 198.5–199° (vacuum): ir ($CHCl_3$) 2750 (-CHO), 1665 (C=C-CHO) 1605, 1575, 1500 (ArH), 1385 (CH_3), and 1150, 1040 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.92, 1.21 (2 s, 3 and 6, C-4a, C-10b, and C-12a CH_3), 3.77 (s, 3, $ArOCH_3$), 6.6–7.3 (m, 3, ArH), and 10.30 (s, 1, CHO).

Anal. Calcd for $C_{23}H_{29}O_2Cl$: C, 74.08; H, 7.84; Cl, 9.51. Found: C, 74.12; H, 7.96; Cl, 9.49.

No material was eluted from the column by additional 350 ml of dichloromethane, but evaporation of the following 600 ml of eluent afforded 154 mg (13%) of starting ketone as a white solid; ir and NMR spectra are the same as those of a purified sample of ketone **1**.

Further elution with 500 ml of 5% methanol–ether gave 147 mg of a white solid, which on crystallization from acetone–dichloromethane–water afforded **2,9-bisformyl-1-chloro-8-methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysene:** mp 265–266° dec (vacuum); ir ($CHCl_3$) 2770 (CHO), 1670 (C=O), 1605, 1570, 1495 (ArH), and 1150, 1055 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.92, 1.21 (2 s, 3 and 6, C-4a, C-10b, and C-12a CH_3), 3.90 (s, 3, $ArOCH_3$), 6.70 (s, 1, C-7 H), 7.80 (s, 1, C-10 H), 10.30 (s, 1, C-2 CHO), and 10.50 (s, 1, C-9 CHO).

Anal. Calcd for $C_{24}H_{29}O_3Cl$: C, 71.90; H, 7.29; Cl, 8.84. Found: C, 71.82; H, 7.24; Cl, 8.90.

The yield of the desired chloro aldehyde **13** based upon recovered starting material was 75%. In a similar experiment, in which the reaction mixture was heated with a 69° bath for 4.5 hr, the yield of purified aldehyde **13** (without recovery of starting material) was 71%.

2α-Formyl-8-methoxy-2β,4aβ,10bβ,12aα-tetramethyl-1,2,3,4,-4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (14). To an argon-protected solution of 260 mg (38 mg-atoms) of lithium in 120 ml of dry ammonia and 50 ml of dry tetrahydrofuran was slowly added over a 50-min period with vigorous stirring a solution of 253 mg (0.68 mmol) of the chloro aldehyde **13** and 128 μl (100 mg, 1.36 mmol) of dry *tert*-butyl alcohol in 60 ml of dry tetrahydrofuran. After stirring for an additional 15 min the blue color of the reaction mixture was discharged by the portionwise addition of dry, powdered sodium benzoate, and the ammonia was evaporated through a mercury bubbler by heating the mixture with a hot air gun. After the addition of 40 ml of dry tetrahydrofuran, the reaction mixture was stirred with ice cooling and treated with 5 ml (11.4 g, 80 mmol) of iodomethane. After stirring without cooling for 2 hr, the resulting white suspension was diluted with 200 ml of ether and the product was isolated by ether extraction,[33] including both an acid and a base wash. Purification of the crude product (281 mg) by preparative TLC (15% ether–petroleum ether, double development) afforded 154 mg (64%) of the aldehyde **14** (R_f 0.45): mp 111–116° dec (vacuum); ir ($CHCl_3$) 2805, 2705 (CHO), 1720 (C=O), 1605, 1575, 1500 (ArH), 1385 (CH_3), and 1245, 1040 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.76 (s, 3, C-12a CH_3), 0.93, 1.00 (2 s, 3 each, C-2 and C-4a CH_3), 1.21 (s, 3, C-10b CH_3), 3.76 (s, 3, $ArOCH_3$), 6.6–7.3 (m, 3, ArH), and 9.45 (s, 1, CHO). The same spectral properties were observed for the analytical sample which was prepared by crystallization of a portion of this material from ether–hexane and also melted over the range 111–116° dec (vacuum).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.43; H, 9.67.

Reduction of 143 mg (0.403 mmol) of this aldehyde **14** in 10 ml of dry tetrahydrofuran with 110 mg (2.9 mmol) of lithium aluminum hydride afforded 139 mg (97%) of the corresponding primary alcohol as a white foam: ir ($CHCl_3$) 3625, 3470 (OH), 1608, 1575, 1495 (ArH), and 1385 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.97, 1.00 (2 s, 6 and 3, C-2, C-4a, and C-12a CH_3), 1.21 (s, 3, C-10b CH_3), 3.43, 3.55 (2 s, 1 each, $-CH_2O-$), 3.67 (s, 3, $ArOCH_3$), and 6.6–7.3 (m, 3, ArH). The same spectral properties were observed for the analytical sample which was prepared by crystallization of a portion of this material from methanol and melted at 123.5–125.5° (vacuum).

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.73; H, 10.25.

Attempts to convert this primary alcohol to the corresponding primary halide with triphenyl phosphite–iodomethane,[27] thionyl chloride–quinoline, and triphenylphosphine–carbon tetrachloride[28] led either to no observable reaction or a mixture of numerous products, judged to be the result of deep-seated rearrangements by the ir and NMR spectra.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(3′-oxo-1′-propenyl)-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (15). Following an adaptation of the general procedure of Nagata and Hayase,[29] a stirred suspension of 880 mg (21 mmol) of 57% sodium hydride–mineral oil dispersion in 13.5 ml of dry tetrahydrofuran was cooled with an ice bath and treated over a 5-min period with a solution of 5.46 g (21 mmol) of diethyl 2-(cyclohexylimino)ethylphosphonate in 25 ml of dry tetrahydrofuran. After 15 min, a solution of 1.100 g (3.10 mmol) of the aldehyde **14** in 20 ml of dry tetrahydrofuran was then added over a 1-min period. This stirred mixture was heated with a preheated 60° oil bath for 80 min, cooled with an ice bath, and then poured onto 150 ml of ice and water. After isolation of the crude product by ether extraction[33] there was obtained 6.3 g of a yellow-brown oil that contained the corresponding aldimine.

Hydrolysis of the aldimine was accomplished by treatment of this crude product in 150 ml of benzene with 500 ml of 1% aqueous oxalic acid solution. This two-phase system was stirred at room temperature for 19 hr. The organic layer was separated and the aqueous layer was then extracted with three 200-ml portions of ether. The combined organic phases were washed with 2% aqueous hydrochloric acid (200 ml), 2% aqueous sodium hydroxide solution (two 200-ml portions), and saturated brine (200 ml), and then dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent at reduced pressure, 1.64 g of a yellow oil was obtained. Purification of this oil on 200 g of silica gel in a medium-pressure column was accomplished by elution with 40% ether–petroleum ether. When the second 200 ml of eluent from the column was evaporated at reduced pressure, there was obtained 1.066 g (89%) of unsaturated aldehyde **15** as a white solid. Crystallization of a portion of this material from ether–petroleum ether afforded analytically pure material that melted at 131–133° (vacuum): ir ($CHCl_3$) 2735 (CHO), 1675 (C=O), 1625 (C=C), 1605, 1575, 1495 (ArH), 1385 (CH_3), and 1035 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.87, 1.04 (2 s, 3 and 6, C-2, C-4a, and C-12a CH_3), 1.21 (s, 3, C-10b CH_3), 3.76 (s, 3, $ArOCH_3$), 6.05 (dd, 1, J = 16 and 7.5 Hz, C-2′ C=CH, 6.6–7.3 (m, 4, ArH and C-1′ C=CH), and 9.52 (d, 1, J = 8 Hz, CHO).

Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.06; H, 9.53. Found: C, 82.07; H, 11.41.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(3′-oxopropyl)-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene. After the procedure of Nagai and coworkers,[30] a solution of 135 mg (0.355 mmol) of the unsaturated aldehyde **15** and 1.25 ml of triethylsilane in 1 ml of benzene was treated with 4.5 mg (4.9 μmol) of tris(triphenylphosphine) rhodium chloride, and the mixture was heated at 50° for 1.25 hr. While heating was continued for an additional 1.50 hr, two 2-mg (2.2 μmol) portions of the rhodium catalyst were added at 0.5-hr intervals. After dilution with 25 ml of ether and then filtration, evaporation of the solvents from the filtrate at reduced pressure afforded a yellow oil that contained the corresponding silyl enol ether.

A solution of this oil in 5 ml of acetone was treated with 0.5 ml of 5% aqueous hydrochloric acid, and the mixture was stirred at room temperature for 20 min. Isolation of the product by ether extraction,[33] including a base wash, afforded 200 mg of a yellow, semicrystalline solid which on purification by preparative TLC (35% ether–petroleum ether) gave 113 mg (83%) of the saturated aldehyde (R_f 0.42) as a white, amorphous solid: ir ($CHCl_3$) 2735 (CHO), 1720 (C=O), 1605, 1575, 1495 (ArH), 1380 (CH_3), and 1035 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.90, 1.00, 1.05 (3 s, 3 each, C-2, C-4a, and C-12a CH_3), 1.22 (s, 3, C-10b CH_3), 3.77 (s, 3, $ArOCH_3$), 6.6–7.3 (m, 3, $ArOCH_3$), and 9.80 (m, 1, CHO). This material was not further purified but used directly in the following experiment.

8-Methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(4′-methyl-3′-pentenyl)-1,2,3,4,4a,4bα,5,6,10b,11,12,12a-dodecahydrochrysene (16). A stirred suspension of 4.62 g (10.7 mmol) of isopropyltriphenylphosphonium iodide in 30 ml of dry tetrahydrofuran at room temperature was treated dropwise over a 3-min period with 4.03 ml (8.55 mmol) of a 2.12 *M* solution of phenyllithium in 30% ether–benzene. The red suspension was stirred for 2.25 hr, and then a solution of 819 mg (2.14 mmol) of the above saturated aldehyde in 13 ml of dry tetrahydrofuran was added over a 5-min period. After stirring at room temperature for 50 min longer the product was isolated by ether extraction,[33] including a 10% hydrogen peroxide wash and a 10% sodium thiosulfate wash. After removal of the desiccant and evaporation of the solvent at reduced pressure, a semisolid mixture was obtained. This material was filtered through a glass wool plug with the aid of 100 ml of petroleum ether to remove most of the relatively insoluble triphenylphosphine oxide. Concentration of the filtrate at reduced pressure afforded 1.2 g of a yellow oil which was purified by chromatography on 120 g of silica gel with 4% ether–petroleum ether. After the first 150 ml of eluent was discarded, the next 25 ml contained 101 mg of a mixture which on preparative TLC (4% ether–petroleum ether) afforded 69 mg (8%) of the olefin **16** which was combined with the bulk of the product obtained later. Concentration of the following 250 ml at reduced pressure afforded 651 mg (75%) of the olefin **16** as a white solid: ir ($CHCl_3$) 1605, 1575, 1495 (ArH), 1385 (CH_3), and 1035 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.92, 0.98, 1.05 (3, s, 3 each, C-2, C-4a, and C-12a CH_3), 1.21 (s, 3, C-10b CH_3), 1.59, 1.66 [2 s, C=C(CH_3)$_2$], 3.76 (s, 3, $ArOCH_3$), 4.85–5.35 (m, 1, C=CH), and 6.6–7.3 (m, 3, ArH). The combined yield of the olefin **16** was thus 720 mg (83%). Crystallization of a portion of this material from methanol with a trace of methylene chloride afforded the analytical sample as fluffy, white crystals, mp 78–80° (vacuum), and with the same ir and NMR spectra as those recorded above.

Anal. Calcd for $C_{29}H_{44}O$: C, 85.23; H, 10.85. Found: C, 85.06; H, 10.66.

4bβ,6aα,8β,10aβ-Tetramethyl-8α-(4′-methyl-3′-pentenyl)-4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12-tetradecahydro-2(3*H*)-chrysenone (18). To a solution of 50 mg (0.127 mmol) of the olefin **16** and 2.1 ml (1.66 g, 22.5 mmol) of dry *tert*-butyl alcohol in 5 ml of dry tetrahydrofuran and 15 ml of dry ammonia under an argon atmosphere was added with stirring 24 mg (3.5 g-atoms) of lithium, and the mixture was allowed to reflux for 2 hr. The excess lithium was then quenched with 0.6 ml of methanol, and after evaporation of the ammonia, the crude product (56 mg) was isolated by ether extraction.[33]

To a stirred solution of this crude dihydroaromatic system in 1 ml of dichloromethane at room temperature was added sequentially 2 ml of ethanol, 0.5 ml of water, and 50 mg of oxalic acid. After stirring for 2 hr, the reaction mixture was diluted with 100 ml of ether, and the product (50 mg) was isolated by ether extraction,[33] including a base wash.

Conjugation of the double bond of this β,γ-unsaturated ketone [ir ($CHCl_3$) 1710 cm^{-1} (C=O)] was effected by stirring at room temperature a solution of the crude material with 1 ml of ethanol, 0.15 ml of water, and 0.30 ml of 10% aqueous sodium hydroxide in 5 ml of dichloromethane. After isolation of the crude product (50 mg) by ether extraction[33] and purification of that material by preparative TLC (40% ether–petroleum ether), there was obtained 35 mg (72%) of the desired enone **18** as a pale yellow solid: ir ($CHCl_3$) 1655 (C=O), 1625 (C=C), and 1390, 1375 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.88, 0.90, 0.93, 1.15 (4 s, 3 each, C-4b, C-6a, C-8, and C-10a CH_3), 1.61, 1.67 [2 s, 3 each, C=C(CH_3)$_2$], 5.08 (m, 1, RCH=CR_2'), and 5.87 (br s, 1, O=C–CH=C); analysis by GLC (300°)[31] indicated the presence of a single volatile component to the extent of >99% with retention time of 3.8 min. This material was used directly in subsequent experiments without further purification.

1,12a-Epoxy-4bβ,6aα,8β,10aβ-tetramethyl-8α-(4′-methyl-3′-pentenyl)-1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-hexadecahydro-2(3*H*)-chrysenone. To a stirred solution of 392 mg (1.0 mmol) of the enone **18** in 9 ml of dichloromethane at room temperature was added sequentially 20 ml of methanol, 5.3 ml of 30% aqueous hydrogen peroxide solution, and 1.2 ml of 10% aqueous sodium hydroxide solution. After stirring in a closed flask for 21 hr, the crude product was isolated by ether extraction[33] and on crystallization from methanol–dichloromethane afforded 310 mg (76%) of the epoxy ketone: mp 103.5–105.5° dec (vacuum); ir ($CHCl_3$) 1700 (C=O) and 1375 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.90, 1.12 (2 s, 9 and 3, C-4b, C-6a, C-8, and C-10a CH_3), 1.59, 1.67, [2 s, 3 each, C=C(CH_3)$_2$], 3.11 (s, 1, epoxy H), and 5.07 (m, 1, C=CH). The analytical sample, obtained after two further crystallizations of a portion of this material from methanol–dichloromethane, had the same spectral properties and melted at 107–108.5° (vacuum).

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.49; H, 10.73.

1β-(3′-Butynyl)-4bβ,7β,8aα,10aβ-tetramethyl-7α-(4′-methyl-3′-pentenyl)-3,4,4aα,4b,5,6,7,8,8a,9,10,10a-dodecahydro-2(1*H*)-phenanthrenone. According to the procedure described above for the cleavage[19] of the epoxy ketone **5**, a solution of 51 mg (0.124 mmol) of the epoxy ketone above and 24.5 mg (0.131 mmol) of *p*-toluenesulfonylhydrazine in 2.5 ml of 1:2 acetic acid–dichloromethane was stored for 30 hr at −20° and then stirred for 13 hr at room temperature. After isolation of the product by ether extraction,[33] including a base wash, and then purification of the residue by preparative TLC (15% ether–petroleum ether), 31 mg (63%) of the acetylenic ketone (R_f 0.32) was obtained as a white solid: ir ($CHCl_3$) 3300 (C≡CH), 2120 (C≡C), 1700 (C=O), and 1390, 1380 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.76 (s, 3), 0.91 (s, 6), 1.21 (s, 3) (C-4b, C-7, C-8a, and C-10a CH_3), 1.62 and 1.68 [2 br s, 3 each, C=C(CH_3)$_2$], and 5.1 (m, 1, RCH=C). The analytical sample, obtained after two crystallizations of this material from methanol, had the same spectral properties and melted at 90.5–91.5° (vacuum).

Anal. Calcd for $C_{28}H_{44}O$: C, 84.79; H, 11.18. Found: C, 84.72; H, 11.21.

1β-(3′-Butynyl)-2α,4bβ,7β,8aα,10aβ-pentamethyl-7α-(4′-methyl-3′-pentenyl)-1,2,3,4,4aα,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-2β-phenanthrol (20). To a stirred and ice-cooled solution of 1.1 ml (1.81 mmol) of 1.65 *M* ethereal methyllithium in 2.2 ml of dry tetrahydrofuran was added over a 7-min period a solution of 55 mg (0.139 mmol) of the acetylenic ketone above in 4.5 ml of dry tetrahydrofuran, and the mixture was allowed to stir at room temperature for an additional 25 min. After the reaction was quenched with 1 ml of water, the product was isolated by ether extraction[33] and amounted to 56 mg (99%) of a white foam: ir ($CHCl_3$) 3600 (OH), 3300 (C≡CH), 2115 (C≡C), and 1385, 1375 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.89 (s, 6), 0.97, 1.06, 1.13 (3 s, 3 each) (C-2, C-4b, C-7, C-8a, and C-10a CH_3), 1.62 and 1.68 [2 br s, 3 each, C=C(CH_3)$_2$], and 5.1 (m, 1, RCH=C); analytical TLC (50% ether–petroleum ether) showed a one-component system with R_f 0.50. This material was not further purified but used directly in numerous acid-catalyzed cyclization reactions, all of which resulted in hydration of the terminal double bond with or without cyclization of the acetylenic side chain.

8α-(3′-Hydroxypropyl)-4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12-tetradecahydro-4bβ,6aα,8β,10aβ-tetramethyl-2(3*H*)-chrysenone (17). To a solution of 19 ml of dry dimethoxyethane and 2.33 ml of ethanol in 65 ml of dry ammonia containing 56 mg (8 mg-atoms) of lithium was added dropwise with stirring a solution of 76 mg (0.2 mmol) of the aldehyde **15** in 19 ml of dry dimethoxyethane and 2.3 ml of ethanol. The blue color of the solution was maintained over a 2-hr period by the portionwise addition of 497 mg (71 mg-atoms) of lithium, and then the excess lithium was destroyed by the addition of 3 ml of methanol. After evaporation of

the ammonia in a stream of argon and then treatment of the residue with 150 ml of 5% aqueous hydrochloric acid, the product was isolated by ether extraction,[33] including a base wash. The residual, light yellow oil was dissolved in a mixture of 9 ml of ethanol and 6 ml of 5 *N* aqueous hydrochloric acid, and the resulting solution was refluxed under an argon atmosphere for 1 hr. After dilution of the solution with 50 ml of water, the product was isolated by ether extraction,[33] including a base wash, and then purified by preparative TLC (ether). The resulting clear, colorless oil amounted to 51 mg (68%) of the hydroxyenone **17**. Crystallization of a portion of this oil from *n*-hexane–dichloromethane afforded analytically pure material: mp 144–146.5° (vacuum); ir ($CHCl_3$) 3610, 3400 (OH), 1655 (C=O), and 1610 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.90 (s, 6) 0.95, 1.15 (2 s, 3 each) (C-4b, C-6a, C-8, and C-10a CH_3), and 3.62 (t, 2, J = 6 Hz, $-CH_2OH$).

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.86; H, 10.80.

1,12a-Epoxy-1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-hexadecahydro-8α-(3′-hydroxypropyl)-4bβ,6aα,8β,10aβ-tetramethyl-2(3*H*)-chrysenone. To a stirred solution of 52 mg (0.15 mmol) of the hydroxyenone **17** in 3.6 ml of dichloromethane were added 5.4 ml of methanol, 0.9 ml of 30% aqueous hydrogen peroxide, and 0.44 ml of 10% aqueous sodium hydroxide solution. After stirring under argon for 8 hr, the reaction mixture was poured into 50 ml of brine, and the product was isolated by ether extraction.[33] Purification by medium-pressure chromatography (ether) afforded 34 mg (64%) of the epoxy ketone and 13 mg (25%) of recovered hydroxyenone **17**. Crystallization of a portion of the epoxy ketone from ether afforded analytically pure material: mp 165–166° (vacuum); ir ($CHCl_3$) 3620 (OH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) *δ 0.88 (s, 9), 1.10 (s, 3) (C-4b, C-6a, C-8, and C-10a CH_3), 3.13 (s, 1,* epoxy H), and 3.62 (t, 2, J = 6 Hz, CH_2OH).

Anal. Calcd for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 77.33; H, 10.44.

1β-(3′-Butynyl)-3,4,4aα,4b,5,6,7,8,8a,9,10,10a-dodecahydro-7α-(3′-hydroxypropyl)-4bβ,7β,8aα,10aβ-tetramethyl-2(1*H*)-phenanthrone. To a dry mixture of 112 mg (0.29 mmol) of the epoxy ketone above and 59 mg (0.32 mmol) of *p*-toluenesulfonylhydrazine cooled to −20° under an argon atmosphere was added 4 ml of a −20° solution of 1:2 glacial acetic acid–dichloromethane which had been previously degassed by alternate evacuation and ebullition with argon. After 25 hr at −15 to −25°, followed by 12 hr at room temperature, the reaction mixture was poured into 100 ml of water, and the product was isolated by ether extraction,[33] including a base wash. Purification by chromatography on Florisil *(1:1 chloroform–ether) gave 82 mg (77%) of the acetylenic ketone* as a slightly yellow oil that was a single-component system by tlc (1:1 chloroform–ether, R_f 0.39): ir ($CHCl_3$) 3610 (OH), 3300 (C≡CH), 2120 (C≡C), and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.77 (s, 3), 0.90 (s, 6), 1.18 (s, 3) (C-4b, C-7, C-8a, and C-10a CH_3), and 3.60 (t, 2, J = 6 Hz, CH_2OH). A portion of this oil was crystallized from ethanol–water, mp 99.5–101° (vacuum). However, the resulting solid did not give a satisfactory combustion analysis. Satisfactory results were obtained from a sample prepared by flash distillation of a portion of the original oil at 10^{-4} mm.

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.60; H, 10.85.

1β-(3′-Butynyl)-7α-(3′-hydroxypropyl)-2α,4bβ,7β,8aα,10aβ-pentamethyl-1,2,3,4,4aα,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-2β-phenanthrol (19). To a stirred and ice-cooled mixture of 4.8 ml (8.5 mmol) of 1.7 *M* ethereal methyllithium solution and 7.5 ml of dry tetrahydrofuran under an argon atmosphere was added dropwise a solution of 82 mg (0.22 mmol) of the acetylenic ketone above in 8 ml of tetrahydrofuran. After 10 min of stirring without cooling the excess methyllithium was destroyed with water, and the solution was diluted with 100 ml of brine. Isolation of the product by ether extraction,[33] followed by purification by chromatography on Florisil (10% ether–chloroform), afforded 75 mg (88%) of acetylenic alcohol **19** as a white, crystalline solid. Crystallization of a portion of this material from *n*-hexane–ether afforded analytically pure material that melted at 153–155° (vacuum): ir ($CHCl_3$) 3610 (OH), 3300 (C≡CH), and 2120 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 0.88 (s, 6), 1.0, 1.07, 1.15 (3 s, 3 each) (C-2, C-4b, C-7, C-8a, and C-10a CH_3), and 3.62 (t, 2, J = 6 Hz, CH_2OH).

Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.32; H, 11.41.

8α-(3′-Hydroxypropyl)-1α,2α-methano-1,2,3,4,4aα,4b,5,6,-6a,7,8,9,10,10a,10bα,11,12,12a-octadecahydro-4bβ,6aα,8β,10a-β,12aβ-pentamethyl-2β-chrysenol (21). A. Preparation of the Enol Bis Trifluoroacetate. To 85 mg (0.22 mmol) of the acetylenic diol **19** *cooled to* −25° under an argon atmosphere was added 14.5 ml of a −25° solution of 30% trifluoroacetic anhydride in trifluoroacetic acid. After 45 min of stirring at −25°, the solvents were removed at reduced pressure (~1 mm), and the dark residue was taken up in ether and washed with water and saturated aqueous sodium bicarbonate solution. The resulting oil, which amounted to 136 mg, was used directly in the next experiment: ir ($CHCl_3$) 1780 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.87 (s, 9), 1.0, 1.03 (2 s, 3 each) (C-4b, C-6a, C-8, C-10a, and C-12a CH_3), 4.33 (t, 2, J = 6 Hz, CH_2–OTFA), and 5.30 (s, 1, C-1 H).

B. Cleavage of the Trifluoroacetate and Methylenation. To a stirred solution of lithium diisopropylamide prepared from 5.1 ml (10.9 mmol) of 2.13 *M* hexane solution of *n*-butyllithium and 1.82 ml (12.0 mmol) of diisopropylamine in 12 ml of dry tetrahydrofuran at 0° under an argon atmosphere was added a solution of *136 mg of the crude bis trifluoroacetate from above in* 5 ml of dry tetrahydrofuran. To the cloudy, red-brown solution which resulted after 15 min of stirring were added all at once 43.6 ml (43.6 mmol) of the Simmons–Smith reagent prepared from the zinc–silver couple[36] [4.9 g (75 mmol) of granular zinc, 38 mg of silver acetate, and 38 ml of glacial acetic acid] and 5.78 ml (72 mmol) of diiodomethane in 66 ml of dry ether in the presence of a few strands of silver wool after the procedure of Conia.[36]

After stirring at room temperature for 50 min, the solution was diluted with 200 ml of ice cold, saturated sodium carbonate solution and 30 ml of 40% aqueous ammonium sulfate solution. Isolation of the product by ether extraction[33] including saturated aqueous sodium carbonate and 10% aqueous sodium thiosulfate solution washes afforded a dark red oil which was immediately chromatographed on 130 g of Florisil. Elution with 300 ml of petroleum *ether removed diiodomethane, and continued* elution with 250 ml of 1:1 ether–petroleum ether and then 350 ml of ether afforded 59 mg (67%) of the cyclopropanol **21** as a yellow, crystalline solid. Crystallization of this material from $CHCl_3$ or hexane–dichloromethane gave colorless crystals, mp ~200° dec (vacuum): ir ($CHCl_3$) 3580 cm^{-1} (OH); NMR (DMSO-d_6) δ 0.449 (m, 2, cyclopropyl CH_2), 0.915 (s, 9), 1.12, 1.17 (2 s, 3 each) (C-4b, C-6a, C-8, C-10a, and C-12a CH_3), and 4.16 (t, 2, J = 6 Hz, CH_2OH); high-resolution, mass measured molecular ion 402.3497 ± 0.0008 (calcd for $C_{27}H_{46}O_2$, 402.34976).

1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-Hexadecahydro-1β,4bβ,6aα,8β,10aβ,12aβ-hexamethyl-8α-(3′-hydroxypropyl)-2(3*H*)-chrysenone (22). To a solution of 54 mg (0.13 mmol) of the cyclopropanol **21** in 25 ml of ethanol was added 30 drops of concentrated hydrochloric acid solution, and the mixture was refluxed *in an argon atmosphere for 40 min. After* dilution of the solution with 175 ml of water, the product was isolated by ether extraction,[33] including base wash, and then purified by chromatography on 20 g of Florisil. Elution with 120 ml of ether gave 41 mg (77%) of tetracyclic hydroxy ketone **22**. Crystallization of a portion of this material from *n*-hexane afforded analytically pure material: mp 158–160° (vacuum); ir ($CHCl_3$) 3610 (OH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.72 (s, 3, C-12a CH_3), 0.80, 0.90, 0.93, 1.13 (s, 15, C-1, C-4b, C-6a, C-8, and C-10a CH_3), and 3.62 (t, 2, J = 7 Hz, CH_2OH).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.43; H, 11.43.

1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-Hexadecahydro-1β,4bβ,6aα,8β,10aβ,12aβ-hexamethyl-8α-(3′-oxopropyl)-2(3*H*)-chrysenone. To a suspension of 300 mg (3 mmol) of chromic anhydride in 15 ml of dry dichloromethane under an argon atmosphere was added dropwise 0.48 ml (6 mmol) of pyridine. After 20 min of stirring at room temperature, 2.39 ml (0.48 mmol) of this deep burgundy solution was added to 19 mg (0.048 mmol) of the hydroxy ketone **22**, and the mixture was stirred for 10 min. The red and black mixture was then filtered with the aid of suction through alumina (III), and the alumina was washed with 150 ml of dichloromethane. Removal of the solvent at reduced pressure afforded 16 mg (84%) of the keto aldehyde as a slightly yellow crystalline solid. Crystallization of a portion of this material from *n*-hexane afforded analytically pure material as colorless crystals: mp 177–179° (vacuum); ir ($CHCl_3$) 2775 (CHO), 1720 (C=O), and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.71 (s, 3, C-12a CH_3), 0.88, 0.89, 0.92, 1.11 (4 s, 3 each, C-4b, C-6a, C-8, and C-10a CH_3), 0.88 (d, 3, J = 7 Hz, C-1 CH_3), and 9.8 (s, 1, CHO).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.93; H, 11.11.

(±)-Shionone. To a solution of 62 mg (1.3 mmol) of triphenylisopropylphosphonium iodide in 4.5 ml of dry tetrahydrofuran under an argon atmosphere was added dropwise 0.50 ml (1 mmol)

of a 2 *M* *n*-hexane–phenyllithium solution. After stirring for 2 hr at room temperature, 3.7 ml (0.74 mmol) of this reagent was added to a solution of 19.6 mg (0.049 mmol) of the above keto aldehyde in 2 ml of dry tetrahydrofuran. After stirring for 20 min at room temperature the product was isolated by ether extraction,[33] including a 10% aqueous hydrogen peroxide wash, and purified by chromatography on 20 g of silica gel. Elution with 100 ml of 10% ether–petroleum ether afforded 17 mg (82%) of (±)-shionone. Analytically pure material was obtained upon crystallization from methanol as small needles: mp 161.5–163° (vacuum); ir ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.71 (s, 3, C-12a CH_3), 0.88, 0.90, 0.92, 1.13 (4 s, 3 each, C-4b, C-6a, C-8, and C-10a CH_3), 0.88 (d, 3, J = 7 Hz, C-1 CH_3), 1.61, 1.69 [2 s, 3 each, C=C(CH_3)$_2$], and 5.10 (t, 1, J = 8 Hz, RCH=CR_2).

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.38; H, 11.90.

The ir, NMR, GLC, and TLC of this material were identical with those found for an authentic sample of natural shionone provided by Professor G. Ourisson.

Registry No.—**1**, 53311-24-3; **2**, 54141-74-1; **3**, 54036-92-9; 4 axial alcohol, 54036-93-0; 4 equatorial alcohol, 54036-94-1; **5**, 54036-95-2; **6**, 54036-96-3; **7**, 54036-97-4; **8**, 54036-98-5; **9**, 54036-99-6; **10**, 54037-00-2; **11**, 54037-01-3; **12**, 54037-02-4; **13**, 54062-79-2; **14**, 53311-25-4; **15**, 54037-03-5; **16**, 54054-05-6; **17**, 53311-26-5; **18**, 54054-06-7; **19**, 54037-04-6; **20**, 54054-07-8; **21**, 54082-41-6; **22**, 54037-05-7; **23**, 53402-15-6; tetramethyldiamidophosphorochloridate, 1605-65-8; 8-methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysene, 54141-75-2; 1β,12aβ-methano-4bβ,6aα,10aβ-trimethyl-1α,2,3,4,4aα,4b,5,6,6a,-9,10,10a,10bα,11,12,12a-hexadecahydro-2β-chrysenol, 54037-06-8; 2-acetoxy-1β,12aβ-methano-4bβ,6aα,10aβ-trimethyl-1,4,4aα,4b,5,-6,6a,9,10,10a,10bα,11,12,12a-tetradecahydrochrysene, 54062-80-5; 2-trifluoroacetoxy-4bβ,6aα,10aβ,12aβ-tetramethyl-3,4,4aα,4b,-5,6,6a,9,10,10a,10bα,11,12,12a-tetradecahydrochrysene, 54037-07-9; 2,9-bisformyl-1-chloro-8-methoxy-4aβ,10bβ,12aα-trimethyl-3,4,4a,4bα,5,6,10b,11,12,12a-decahydrochrysene, 54037-08-0; 8-methoxy-2β,4aβ,10bβ,12aα-tetramethyl-1,2,3,4,4a,4bα,5,6,10b,11,-12,12a-dodecahydrochrysen-2α-methanol, 54037-09-1; 8-methoxy-2β,4aβ,10bβ,12aα-tetramethyl-2α-(3′-oxopropyl)-1,2,3,4,4a,4bα,5,-6,10b,11,12,12a-dodecahydrochrysene, 54037-10-4; 1,12a-epoxy-4bβ,6aα,8β,10aβ-tetramethyl-8α-(4′-methyl-3′-pentenyl)-1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-hexadecahydro-2(3*H*)-chrysenone, 54054-08-9; 1β-(3-butynyl)-4bβ,7β,8aα,10aβ-tetramethyl-7α-(4′-methyl-3′-pentenyl)-3,4,4aα,4b,5,6,7,8,8a,9,-10,10a-dodecahydro-2(1*H*)-phenanthrone, 54054-09-0; 1,12a-epoxy-1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-hexadecahydro-8α-(3′-hydroxypropyl)-4bβ,6aα,8β,10aβ-tetramethyl-2(3*H*)-chrysenone, 54037-11-5; 1β-(3′-butynyl)-3,4,4aα,4b,5,6,7,8,8a,-9,10,10a-dodecahydro-7α-(3′-hydroxypropyl)-4bβ,7β,8aα,10aβ-tetramethyl-2(1*H*)-phenanthrone, 53311-27-6; 2-trifluoroacetoxy-8α-(3′-trifluoroacetoxypropyl)-4bβ,6aα,8β,10aβ,12aβ-pentamethyl-3,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-hexadecahydrochrysene, 54037-12-6; 1,4,4aα,4b,5,6,6a,7,8,9,10,10a,10bα,11,12,12a-hexadecahydro-1β,4bβ,6aα,8β,10aβ,12aβ-hexamethyl-8α-(3′-oxopropyl)-2(3*H*)-chrysenone, 54037-13-7.

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References and Notes

(1) The structural formulas containing one or more asymmetric carbon atoms depict one enantiomer but refer to racemic compounds unless otherwise designated. In the text the (±) prefix will be omitted, and intermediates are to be assumed to be racemic. The tetracyclic compounds will be described by the chrysene nomenclature and each racemate is arbitrarily represented by that enantiomer that has the C-6a (C-12a) methyl group in the α configuration.
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(3) National Science Foundation Predoctoral Fellow, 1968–1972.
(4) National Defense Education Act Trainee, 1971–1974.
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Gas–liquid phase chromatographic (GLC) analyses were determined on either a Hewlett-Packard 5750 or F & M 810 research chromatograph using helium carrier gas at a flow rate of 60 ml/min. Unless otherwise noted, all analytical GLC was conducted on a 6 ft × 0.125 in. column packed with 4% SE-30 on 60–80 mesh Chromosorb W AW DMCS.

Preparative thin layer chromatography (preparative TLC) was carried out on 20 × 20 × 0.2 cm glass plates coated with silica gel $PF_{254+266}$ (Brinkman Instruments Co). Analytical thin layer chromatography (TLC) was conducted on 1 × 3 in. microscope slides coated with a 0.5-mm layer of silica gel G or $PF_{254+266}$.

Alumina used for column chromatography refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany, and made up to grade II or III as indicated by the addition of 3% or 6% water prior to use. Silica gel columns used the 0.05–0.2 mm silica gel manufactured "for column chromatography" by E. Merck & Co., Darmstadt, Germany. Preparative medium-pressure column chromatography was performed using ½ × 20 in. or 2 × 20 in. glass columns with fittings supplied by Chromatronix, Inc., Berkeley, Calif., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck and Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

"Dry" solvents were dried immediately prior to use. Ether, benzene, tetrahydrofuran, and dimethoxyethane were distilled from lithium aluminum hydride; *tert*-butyl alcohol, trimethyl sulfoxide, pyridine, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride; dichloromethane, carbon tetrachloride, diodomethane, and methyl iodide were distilled from phosphorus pentoxide; ammonia was distilled from the tank and then from a blue lithium or sodium solution. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30–60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Reactions described as run under nitrogen or argon employed a mercury bubbler arranged so that the system could be alternately evacuated and filled with the inert gas and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
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was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.

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Experiments Directed toward the Total Synthesis of Terpenes. XXI. An Alternate Total Synthesis of *dl*-Alnusenone *via* Polyene Cyclization[1]

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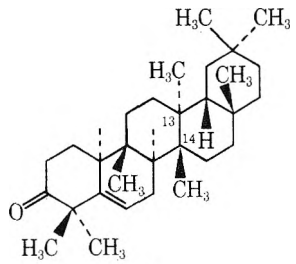
Using the aldehyde **2** as a model for the alnusenone (**1**) precursor **15**, a method based on acid-catalyzed polyene cyclization procedures was developed for the synthesis and cyclization of the 3-methyl-2-cyclopentenol **5** that gave the tricyclics **6**, **7**, and **8**. Oxidative ring enlargement of the alcohol **8** led to the tricyclic enone **11**, a model of the C, D, and E rings of the key pentacyclic alnusenone intermediate **19**. The structure of this enone **11** was proven by its independent synthesis from the ketonitrile **13** of known structure and stereochemistry. Application of the methods developed in this model study to the aldehyde **15** leads through the 3-methyl-2-cyclopentenone **16** to both the ortho- (**18**) and para- (**17**) substituted pentacyclic olefins. Conversion of the latter to the enone **19** by the oxidative ring enlargement procedure completes the second total synthesis of *dl*-alnusenone (**1**), by virtue of the use of this enone **19** in an earlier study. Confirmation of the structure and stereochemistry of the ortho-substituted pentacyclic olefin **18** was obtained by the formation of the hydrocarbon **20** from demethoxylation of both olefinic isomers **17** and **18**.

In earlier work[4] on the total synthesis of the pentacyclic triterpenes of the alnusenone (**1**) class, it became apparent that, in addition to the obvious logistic problems, the synthetic difficulties that attended the introduction of the two trans-disposed angular methyl groups at C-13 and C-14 were not trivial. Several approaches[5] aimed specifically at



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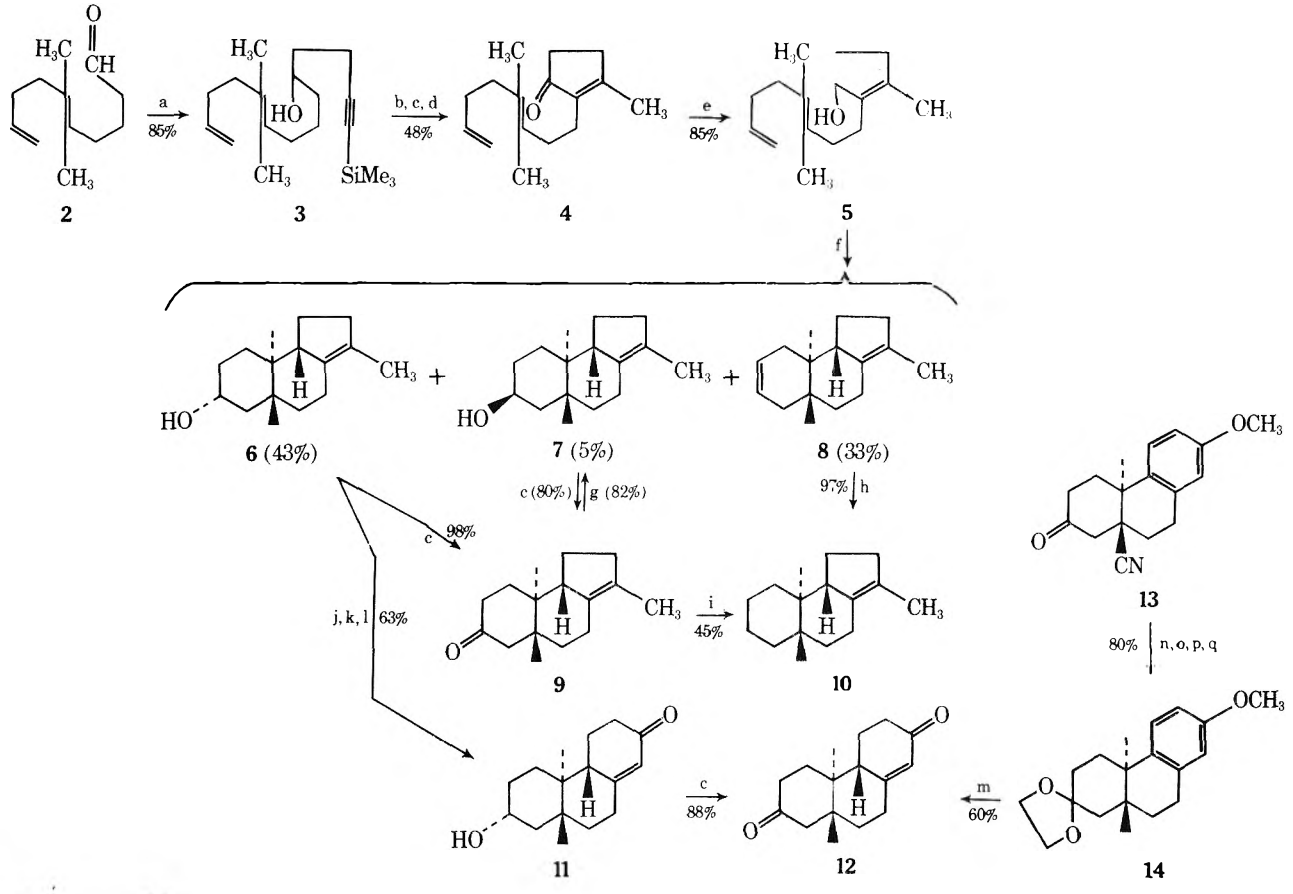
accomplishing this task were investigated, and a particularly efficient scheme[6] was developed through the use of the Nagata procedure[7] for the conjugate hydrocyanation of enones. Another approach that was demonstrated[5a] to be of value for this situation was the acid-catalyzed cyclization of polyolefinic substrates[8] that incorporated a tetrasubstituted double bond. Thus, from a two-stage, acid-catalyzed cyclization of the aldehyde **15**,[9] it was possible to prepare the corresponding tetracyclic, A ring aromatic ketone. While this ketone was used in the total synthesis of the tetracyclic triterpene shionone[10] and has potential as an intermediate in schemes for the synthesis of pentacyclic triterpenes, the low overall yield of the two-stage, acid-catalyzed cyclization and the desire to incorporate the rudiments of the E ring in the polyolefinic substrate prompted a further investigation of other related systems.

The aim of this phase of the work was threefold. First, systems were sought that could be prepared from the aldehyde **15**, such that the efficient synthesis[9] of this material could form the backbone of the approach. Secondly, on the assumption that the low yields experienced from the cyclization of the aldehyde **15** were in part the result of the utilization of the labile aldehyde function to initiate the cyclization process, a less sensitive, yet still effective, source of cationic character in this position was sought. Finally, in view of the potential difficulties associated with the selective reduction of the two dissimilar A and E aromatic rings in the intermediates from the conjugate hydrocyanation route,[6] systems were sought that would result directly in the formation of a nonaromatic E ring after the cyclization process. From a synthetic design standpoint, the polyolefinic cyclization approach[8] offers a particularly elegant solution to the latter situation.

From the extensive work of Johnson and coworkers,[11] the systems that appear to meet the above criteria are the cyclic allylic alcohols. Such systems offer the advantage of lower sensitivity to the acidic conditions than the aldehydes, and the potential for the incorporation of larger carbon residues at the cationic site. Particularly suited to the present situation is the 3-methyl-2-cyclopentenol unit, as Johnson has shown[11c] that this system is an excellent precursor of a fused 2-cyclohexenone ring system after cyclization and then oxidative ring enlargement. The present report describes the results of an investigation into the synthesis and subsequent cyclization of such a system that leads ultimately to the construction of the pentacyclic enone **19**, an intermediate previously converted to *dl*-alnusenone (**1**) in earlier work.[6]

Before utilization of the aldehyde **15** for any studies, a model system was investigated to develop means for the conversion of the aldehyde function to the 3-methyl-2-cyclopentenol system and to study the compatibility of the central, tetrasubstituted double bond in this type of cationic cyclization. The starting material for this work was the aldehyde **2** (Chart I), prepared previously[5a] for the initial polyene cyclization studies with a tetrasubstituted double bond. After some experimentation with other schemes, the utility of 4-trimethylsilylhomopropargylmagnesium chloride as a masked 2-butanone synthon evolved, and the scheme outlined in Chart I for the construction of the desired cyclopentenol **5** was developed. The carbonyl addition of this fragment went in excellent yield, and after hydration with concomitant desilylation, oxidation of the result-

Chart I
Synthesis and Cyclization of the Model 3-Methyl-2-cyclopentenol 5[a]



[a] a, $(CH_3)_3SiC{\equiv}CCH_2CH_2MgCl$, Et_2O; b, $HgSO_4$, aq H_2SO_4, THF; c, 8 *N* H_2CrO_4, acetone; d, 2% aq NaOH, EtOH; e, $LiAlH_4$, Et_2O; f, HCO_2H, 9°; g, $LiAl(O\text{-}t\text{-}Bu)_3H$, THF; h, $(Ph_3P)_3RhCl$, C_6H_6, H_2; i, $N_2H_4 \cdot 2HCl, N_2H_4 \cdot H_2O$, KOH, DEG; j, OsO_4, dioxane, H_2S, CH_2Cl_2; k, $Pb(OAc)_4$, THF; l, 2.5% aq KOH; m, Li, NH_3, *t*-BuOH, 5 *N* aq HCl, C_6H_6–EtOH; n, $(CH_2OH)_2$, *p*-TsOH, C_6H_6; o, $(i\text{-}Bu)_2AlH$, C_6H_6; p, NaOAc, aq HOAc; q, $N_2H_4EG \cdot H_2O$, KOH, DEG.

ing hydroxy ketone led to the corresponding dione. While intramolecular aldol condensation of this dione could lead to two different cyclopentenone derivatives, only the enone **4** related to methylene condensation was observed. Reduction of the enone **4** with lithium aluminun hydride completed a successful route for the transformation of the aldehyde function to the desired 3-methyl-2-cyclopentenol system **5**.

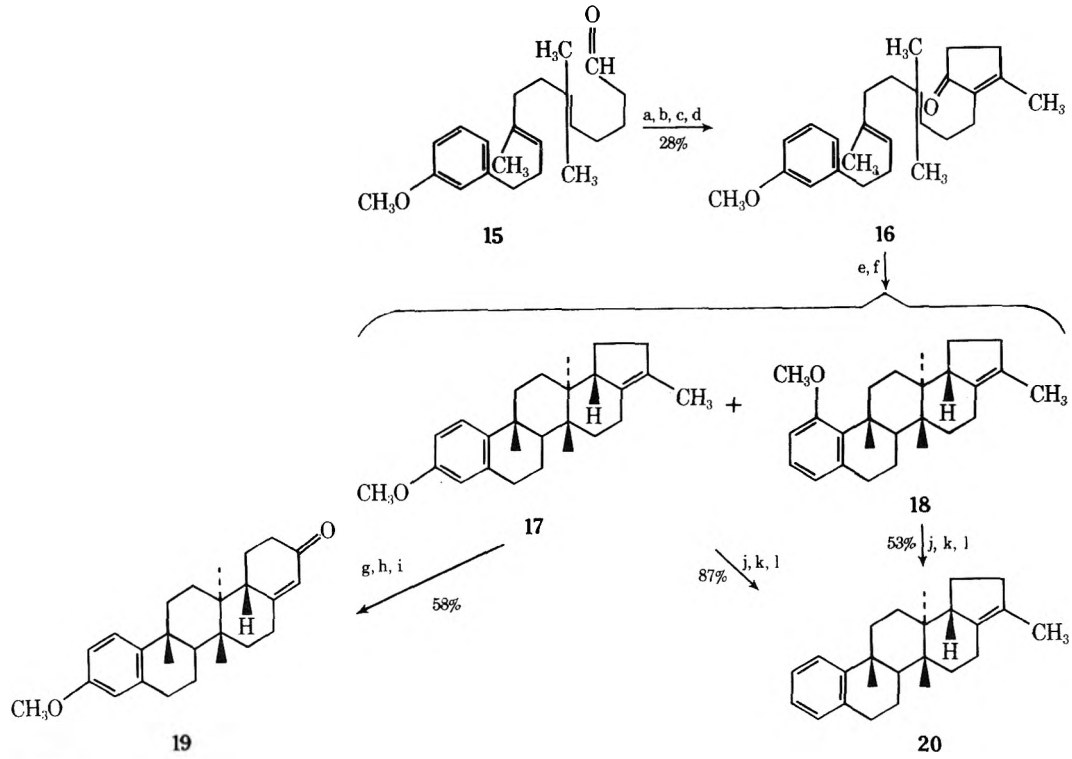
Cyclization of this alcohol **5** in formic acid at 9° resulted in the formation of tricyclic material in high (81%) yield. Separation of the product mixture by silica gel chromatography afforded the alcohols **6** and **7** and the hydrocarbon **8**. The efficiency of this cyclization was quite encouraging in spite of the formation of these three individual products. The observed mixture of products from this cyclization was a result of the mode in which the final tricyclic cation was quenched, and in the triterpene synthesis, an internal nucleophile (the anisole ring) would be present to carry such a tricyclic cation on to the desired pentacyclic stage.

The correlation of the three products isolated from the formic acid cyclization of the alcohol **5** was accomplished as shown in Chart I, and the major alcoholic product **6** was transformed into the enone **11** by oxidative ring enlargement.[11c] Not only did this process substantiate the utility of this scheme[11] for the formation of the C, D, and E rings of the alnusenone (**1**) molecule, but it also provided material which was readily amenable to correlation with compounds of known[6] structure and stereochemistry (Chart I). With these results in hand the construction of material suitable for the formation of the corresponding pentacyclic analogs was pursued.

Conversion of the aldehyde **15** to the required cyclopentenone **16** (Chart II) was accomplished in good overall yield by the procedures developed in the model series. After reduction of this enone **16** with lithium aluminum hydride, cyclization of the resulting cyclopentonol under the same conditions used in the model series led to an inseparable mixture of products. After some experimentation, it was found that stannic chloride in dichloromethane[11a] at −78° provided the most readily separable mixture of products, although simple silica gel chromatography of the cyclopentenol also led to cyclized material. From a combination of these procedures, it was possible to isolate the olefins **17** and **18**, as pure compounds, albeit in low yield. The lack of correlation between the cyclization results realized in the model series (Chart I) and those observed in this case, as well as the formation[12] of *both* the para and ortho isomers **17** and **18**, seems to be a function of the incorporation of the anisole ring in the system as a trap for the tricyclic cation. A similar result was observed[9] in the cyclization experiments performed on the aldehyde **15**. Unfortunately, the system **16** required for this synthesis does not adequately test this point, as the sensitivity of the tetrasubstituted double bond to protonation under harsher acidic conditions (trifluoroacetic acid with or without dichloromethane as a diluent) and the insolubility of the substrate 3-methyl-2-cyclopentenol in certain media (formic acid) limit severely the range of experimentation.

Despite the unsatisfying yields observed in this cyclization, sufficient quantities of each pentacyclic isomer **17** and **18** were obtained to allow further investigations. Oxidative ring enlargement[11c] of the major isomer **17** resulted in the

Chart II
Pentacyclic Olefin Synthesis by Polyene Cyclization[a]



[a] a, $(CH_3)_3SiC{\equiv}CCH_2CH_2MgCl$, Et_2O; b, $HgSO_4$, aq H_2SO_4, THF; c, 8 *N* H_2CrO_4, acetone; d, 2% aq NaOH, EtOH; e, $LiAlH_4$, Et_2O; f, $SnCl_4$, CH_2Cl_2, −78° or silica gel chromatography; g, OsO_4, dioxane, H_2S, CH_2Cl_2; h, $Pb(OAc)_4$, THF; i, 10% aq NaOH, CH_3OH; j, $LiPPh_2$, TMEDA, THF; k, $ClPO(NMe_2)_2$, HMPA, Et_3N, THF; l, $LiNH_3$, THF, EtOH.

formation of the target enone **19**[6] and thus completed an alternate total synthesis of alnusenone (**1**). This transformation also served to confirm the structure and stereochemistry assigned to the pentacyclic olefin **17** from the polyene cyclization. Finally, in order to provide similar confirmation of the structural assignment made for the minor pentacyclic olefin **18**, samples of both isomers **17** and **18** were demethoxylated[13] through reductive removal of the intermediate phosphorodiamidate.[14] In both cases the same pentacyclic hydrocarbon **20** resulted from these experiments, and the identity of the two samples established beyond reasonable doubt the structure assigned the minor pentacyclic isomer **18**.

This work, then, establishes another route, albeit less efficient owing to the problem of the acid-catalyzed cyclization stage,[15] for the synthesis of pentacyclic intermediates suitable for conversion to the alnusenone class of triterpenes. Not to be overlooked in this connection is the efficiency of the polyene cyclization scheme for the synthesis of the *tricyclic* systems **6**, **7**, and **8**, used here as model compounds, but potentially interesting intermediates themselves.

Experimental Section[16]

1-Trimethylsilyl-4-chloro-1-butyne. To a solution of ethylmagnesium bromide prepared from 36.6 g (1.5 g-atoms) of magnesium and 114 ml (1.5 mol) of ethyl bromide in 300 ml of dry tetrahydrofuran under a nitrogen atmosphere was added with stirring over a 0.5-hr period a solution of 42 g (0.6 mol) of 4-hydroxy-1-butyne in 360 ml of dry tetrahydrofuran, and after stirring for 20 min the mixture was treated with 190 ml (1.5 mol) of trimethylchlorosilane in 400 ml of dry tetrahydrofuran. After stirring for an additional 1.5 hr the reaction mixture was hydrolyzed with an aqueous (500 ml) solution of 132 g of ammonium chloride, and then the organic phase was decanted from the resulting thick, white aqueous suspension. The organic extract was concentrated to 400 ml and then stirred overnight at room temperature with a solution of 132 g of ammonium chloride in 500 ml of water. The residue obtained after ether extraction[17] was dissolved in 140 ml of freshly distilled thionyl chloride containing 10 ml of dry pyridine, and the mixture was refluxed under a nitrogen atmosphere for 7 hr. After cooling, the reaction mixture was poured into ice and water, and the product was isolated by ether extraction,[17] including an acid wash. Distillation of the dark brown residue through a 1.5-ft spinning band column afforded 40 g (42%) of 1-trimethylsilyl-4-chloro-1-butyne, bp 74° (30 mm), as a clear, colorless liquid. Redistillation of a portion of this material in the same apparatus afforded the analytical sample which boiled at 72° (28 mm) and consisted of a single volatile component on GLC (100°): ir (neat) 2190 (C≡C), 850, and 760 cm^{-1}; NMR ($CDCl_3$) δ 0.16 [s, 9, $Si(CH_3)_3$], 2.66 (t, 2, J = 7 Hz, $C{\equiv}CCH_2$), and 3.63 (t, 2, J = 7 Hz, $-CH_2Cl$).

Anal. Calcd for $C_7H_{13}SiCl$: C, 52.35; H, 8.10. Found: 52.16; H, 8.30.

1-Trimethylsilyl-9,10-dimethyl-(*E*)-9,13-tetradecadien-1-yn-5-ol (3). A nitrogen-protected solution of the Grignard reagent prepared from 8.3 g (0.052 mol) of 1-trimethylsilyl-4-chloro-1-butyne and 2 g (0.082 g-atom) of magnesium in 25 ml of dry ether was separated from excess magnesium by syringe, and after the solution was cooled to −5°, a solution of 4.0 g (0.022 mol) of the aldehyde **2** in 20 ml of dry ether was added over a 1-hr period under a nitrogen atmosphere. The reaction mixture was then quenched with 80 ml of a 10% aqueous ammonium chloride solution, and the product was isolated by ether extraction.[17] Chromatography of the crude product (9.06 g) on 400 g of silica gel afforded 4.9 g (85%) of the alcohol **3** as a mobile, colorless liquid which was eluted with 3 l. of 20% ether–petroleum ether and represented 93% of the volatile components on GLC (215°). The analytical sample was prepared by evaporative distillation of a portion of this material at 120° and 0.1 mm: ir (neat) 3600–3150 (OH), 2190 (C≡C), and 1645 cm^{-1} (C=CH_2); NMR ($CDCl_3$) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.64 (s, 2 × 3, $CH_3C{=}C{-}CH_3$), 3.50–4.00 (m, 1, CHO), 4.76–5.23 (m, 2, C=CH_2), and 5.50–5.90 (m, 1, CH=C).

Anal. Calcd for $C_{19}H_{34}SiO$: C, 74.44; H, 11.18; Si, 9.16. Found: C? 74.33; H, 11.01; Si, 9.05.

9,10-Dimethyl-(*E*)-9,13-tetradecadiene-2,5-dione. To a solution of 5.9 g (0.019 mol) of the alcohol **3** in 400 ml of tetrahydrofuran and 160 ml of water under a nitrogen atmosphere was added 40

ml of a saturated solution of mercuric sulfate in 1% aqueous sulfuric acid. After stirring for 4 hr at room temperature, the cloudy mixture was saturated with salt, and the product was isolated by ether extraction.[17] This crude material (4.65 g of a colorless oil) was dissolved in 60 ml of dry acetone, and the solution was cooled to 0° and then treated with 4.6 ml of a 2.7 *M* aqueous chromic acid solution.[18] After stirring for 5 min the reaction mixture was quenched with a few drops of isopropyl alcohol and diluted with water, and then the product was isolated by ether extraction,[17] including a base wash. On chromatography of the crude product (4.2 g of colorless oil) on 300 g of silica gel, 2.45 g (54%) of the corresponding diketone was eluted with 2 l. of 30% ether–petroleum ether. This material consisted of 93% of a single volatile component on GLC (210°). The analytical sample was obtained by evaporative distillation of a portion of this material at 110° (0.1 mm): ir (neat) 1720 and 1715 (C=O), 1645 (C=C), and 910 cm^{-1} (C=CH_2); NMR ($CDCl_3$) δ 1.63 (s, 2 × 3, CH_3C=CCH_3), 2.66 (s, 4, $COCH_2CH_2CO$), 4.76–5.23 (m, 2, C=CH_2), and 5.50–5.90 (m, 1, CH=C).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.85; H, 10.51.

2-(3′,4′-Dimethyl-(*E*)-3′,7′-octadienyl)-3-methyl-2-cyclopentenone. A solution of 2.45 g (9.8 mmol) of the above diketone in 300 ml of ethanol and 70 ml of a 2% aqueous sodium hydroxide solution was refluxed under a nitrogen atmosphere for 4 hr. After a solution of 2.8 ml of concentrated hydrochloric acid in 100 ml of water was added, most of the ethanol was removed at the rotary evaporator, and then the product was isolated by ether extraction,[17] including a base wash. On chromatography of the crude material (2.25 g of colorless oil) on 150 g of silica gel, 2.01 g (88%) of the cyclopentenone as a colorless oil was eluted with 2 l. of 30% ether–petroleum ether. This material consisted of >97% of a single volatile component on GLC (180°), and the analytical sample was prepared by evaporative distillation of a portion of this product at 110° (0.5 mm): ir (neat) 1705 (conjugated C=O), 1650 (conjugated C=C), and 910 cm^{-1} (C=CH_2); NMR ($CDCl_3$) δ 1.62, 1.66 (2 s, 3 each, CH_3C=C–CH_3), 2.2 (s, 3, C_3CH_3), 4.76–5.23 (m, 2, C=CH_2), and 5.50–5.90 (m, 1, CH=C).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.65; H, 10.41.

2-(3′,4′-Dimethyl-(*E*)-3′,7′-octadienyl)-1-methylcyclopenten-3-ol (5). To a solution of 118 mg (0.51 mmol) of the above cyclopentenone in 10 ml of dry ether cooled to 0° was added 20 mg (0.53 mmol) of lithium aluminum hydride, and then the mixture was stirred at 0° for 1 hr. After the addition of 0.08 ml of water and then magnesium sulfate, the heterogeneous mixture was stirred at room temperature for 1 hr and then filtered. After evaporation of the ether at reduced pressure and then preparative TLC (50% ether–petroleum ether) of the residue, there was obtained 98 mg (85%) of the cyclopentenol **5** (R_f 0.4–0.5) as a colorless liquid. The analytical sample was obtained by evaporative distillation of this material at 90–100° and 0.5 mm: ir (neat) 3600 (OH), 1645 (C=C), and 910 cm^{-1} (C=CH_2); NMR ($CDCl_3$) δ 1.66 (s, 2 × 3, CH_3C=CCH_3), 2.10 (s, 3, C-1 CH_3), 4.75 (m, 1, C-1 H), 4.8–5.1 (m, 2, C=CH_2), and 5.5–6.1 (m, 1, CH=C).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.09; H, 11.11.

Cyclization of 2-(3′,4′-Dimethyl-(*E*)-3′,7′-octadienyl)-1-methylcyclopenten-3-ol (5). To 500 mg (2.14 mmol) of the cyclopentenol **5**, precooled in an ice bath, was added under a nitrogen atmosphere 50 ml of dry formic acid, precooled to 9°. After the cloudy reaction mixture had stirred in the ice bath for 4 min, it was poured into a mixture of 200 g of ice and 400 ml of water that contained 70 g of sodium hydroxide. After isolation by ether extraction,[17] the crude product (510 mg) was reduced with 55 mg (1.45 mmol) of lithium aluminum hydride in 50 ml of dry ether. After stirring for 1 hr at room temperature, this mixture was treated with 0.2 ml of water and then solid magnesium sulfate, and the resulting suspension was stirred for an additional 1 hr. After filtration and then removal of the solvent at reduced pressure, the semicrystalline residue (490 mg) was chromatographed on 55 g of silica gel. Elution with 100 ml of 20% ether–petroleum ether afforded 185 mg of a hydrocarbon mixture which consisted of 85% of a major volatile component on GLC (170°). Rechromatography of this material on 30 g of alumina impregnated with 10% silver nitrate gave 152 mg (33%) of the diene **8**, as a colorless oil which was eluted with 30 ml of 50% benzene–ether and consisted of a single volatile component by GLC (175°). The analytical sample was obtained by evaporative distillation of a portion of this material at 80° and 0.5 mm: ir (neat) 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.66 and 1.00 (2 s, 3 each, C-5a and C-9a CH_3), 1.63 (s, 3, C-3 CH_3), and 5.63 (s, 2, CH=CH).

Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.64; H, 11.21.

Continued elution of the silica gel column with 200 ml of 40% ether–petroleum ether afforded a mixture of alcohols shown by comparison NMR spectra (vide infra) to contain ~50% (5%) of the axial tricyclic alcohol **7** which after two crystallizations from hexane at −20° and then sublimation at 70° and 0.2 mm gave 15 mg of the crystalline alcohol **7**, mp 74–78°. This material, which consisted of 85% of a major component on GLC (175°), was not further purified, as comparison ir and NMR spectra with the authentic alcohol **7** were identical.

Continued elution of the column with 300 ml of 50% ether–petroleum ether afforded 217 mg (43%) of the equatorial alcohol **6**, mp 125–127°. The analytical sample, obtained after crystallization of a portion of this material from hexane, melted at 124–126°: ir ($CHCl_3$) 3610 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.77 and 1.07 (2 s, 3 each, C-5a and C-9a CH_3), 1.63 (br s, 3, C-3 CH_3), and 3.83 (br m, 1, C-7 H).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.99; H, 11.21.

3,5aβ,9aα-Trimethyl-2,4,5,5a,8,9,9a,9bβ-octahydro-7(6*H*)-1*H*-benz[*e*]indenone (9). A. From the Alcohol 6. To a solution of 300 mg (1.28 mmol) of the tricyclic alcohol **6** in 12 ml of dry acetone was added at room temperature 0.3 ml of 2.7 *M* aqueous chromic acid solution,[18] and the mixture was stirred for 5 min. After dilution with water and isolation of the product by ether extraction,[17] including a base wash, chromatography of the crude material on 10 g of silica gel with 1 ether–petroleum ether afforded 300 mg (98%) of the ketone **9**, mp 54–56°, which consisted of a single volatile component on GLC (170°). The analytical sample was obtained by sublimation of a portion of this material at 40° and 0.1 mm: ir ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.97 and 1.03 (2 s, 3 each, C-5a and C-9a CH_3) and 1.62 (br s, 3, C-3 CH_3).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.59; H, 10.42.

B. From the Alcohol 7. In a manner similar to that described above, 15 mg of 85% pure alcohol **7** from the cyclization reaction was oxidized with 0.1 ml of 2.672 *M* aqueous chromic acid solution[18] in 5 ml of dry acetone. After isolation of the product by ether extraction[17] and filtration of the crude material through 5 g of silica gel with 10% ether–petroleum ether, there was isolated 10 mg (80%) of the ketone **9**, mp 54–56°, alone or in admixture with a sample of the material prepared above.

7β-Hydroxy-3,5aβ,9aα-trimethyl-2,4,5,5a,6,7α,8,9,9a,9bβ-decahydro-1*H*-benz[*e*]indene (7). To a solution of 58 mg (0.25 mmol) of the ketone **9** in 8 ml of dry tetrahydrofuran was added 167 mg (1.55 mmol) of lithium tri-*tert*-butoxyaluminum hydride, and then the reaction mixture was stirred at room temperature for 2 hr. After the reaction was quenched with 0.2 ml of 2 *N* aqueous hydrochloric acid and then dried over 1 g of magnesium sulfate, filtration and then removal of the solvent at reduced pressure afforded 58 mg of semicrystalline residue. On purification of this material by preparative TLC (50% ether–petroleum ether) 48 mg (82%) of the alcohol **7**, mp 78–80°, was obtained at R_f 0.4. The analytical sample, prepared by sublimation of this material at 70° and 0.1 mm, also melted at 78–80° with softening at 55°: ir ($CHCl_3$) 3610 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.71 and 1.27 (2 s, 3 each, C-5a and C-9a CH_3), 1.62 (br s, 3, C-3 CH_3), and 4.10 (br s, 1, C-7 H).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.95; H, 11.02.

The solution ir and NMR of this material were identical with those of the minor alcohol obtained above on cyclization of the cyclopentenol **5** and distinctly different from the spectra of the major alcohol **6** from this cyclization.

3,5aβ,9aα-Trimethyl-2,4,5,5a,6,7,8,9,9a,9bβ-decahydro-1*H*-benz[*e*]indene (10). A. By Reduction of the Ketone 9. To a solution of 100 mg (0.43 mmol) of the ketone **9** in 5 ml of diethylene glycol under a nitrogen atmospehre was added 0.5 ml of 100% hydrazine hydrate and 0.166 g of hydrazine dihydrochloride. The reaction mixture was heated at 110° for 21 hr, and then 0.85 g of potassium hydroxide was added. The temperature was raised to 165°, and a stream of nitrogen was passed over the solution for 1.5 hr to remove volatile material. The temperature was maintained at 165° for 3.5 hr; then the mixture was cooled and poured into water, and the product was isolated by ether extraction.[17] Filtration of the residue through 5 g of silica gel in 2% ether–petroleum ether afforded 47 mg of a colorless oil which gave 41 mg (45%) of analytically pure olefin **10** on evaporative distillation at 80–90° and 0.3

mm: ir ($CHCl_3$) 1375, 1155, 1055, and 912 cm^{-1}; NMR ($CDCl_3$) δ 0.73 and 1.07 (2 s, 3 each, C-5a and C-9a CH_3), and 1.60 (br s, 3, C-3 CH_3).

Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 88.02; H, 12.14.

B. By Hydrogenation of the Diene 8. A solution of 70 mg (0.32 mmol) of the diene **8** and 20 mg of tris(triphenylphosphine)-rhodium chloride[19] in 4 ml of benzene was stirred at room temperature under a hydrogen atmosphere for 20 hr. After filtration of the reaction mixture through 5 g of Florisil with ether eluent, there was obtained 68 mg (97%) of the olefin **10** as a colorless oil. The solution ir and NMR spectra of this material were identical with those reported above for the olefin **10** obtained from reduction of the ketone **9**.

4bα,8aβ-Dimethyl-7α-hydroxy-4,4aβ,4b,5,6,7β,8,8a,9,10-decahydro-2(3*H*)-phenanthrenone (11). A solution of 170 mg (0.73 mmol) of the alcohol **6** and 400 mg (1.57 mmol) of osmium tetroxide in 40 ml of dry dioxane was allowed to stand at room temperature under a nitrogen atmosphere for 3 days. After 5 ml of pyridine was added, the black reaction mixture was allowed to stand for an additional 3 days, and then the solvent was removed at reduced pressure. The black residue was dissolved in 40 ml of dry dichloromethane, and a stream of hydrogen sulfide was bubbled through the black solution for 20 min. The resulting black precipitate was removed by filtration, and the crystalline residue obtained after removal of the solvent from the filtrate at reduced pressure was dissolved in 40 ml of dry tetrahydrofuran. This solution was cooled to 0° and then treated with 1 g (2.26 mmol) of lead tetraacetate. After this mixture had stirred at 0° for 15 min, 1 ml of ethylene glycol was added, and the resulting brown precipitate was removed by filtration. The filtrate was diluted with water, and the product was isolated by ether extraction.[17] The resulting residue (170 mg of a colorless oil) was then heated at 65° with 40 ml of a 2.5% aqueous potassium hydroxide solution under a nitrogen atmosphere for 14 hr. After neutralization with 2*N* aqueous hydrochloric acid and isolation of the product by ether extraction,[17] purification of the residue (140 mg of colorless oil) by preparative TLC (5% methanol–ether) gave 118 mg (63%) of the enone **11**, mp 144–146°, at R_f 1.5–2.0. This material was not further purified for combustion analysis: ir ($CHCl_3$) 3610 (OH), 1660 (conjugated C=O) and 1615 cm^{-1} (conjugated C=C); NMR ($CDCl_3$) δ 0.91 and 1.15 (2 s, 3 each, C-4b and C-8a CH_3), 4.00 (m, 1, C-7 H), and 5.98 (s, 1, C-1 H).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.34; H, 9.74. Found: C, 77.24; H, 9.71.

4bα,8aβ-Dimethyl-4,4aβ,4b,5,6,8a,9,10-octahydro-2(3*H*),7-(8*H*)-phenanthrenedione (12). A. By Reduction of the Aromatic Ketal 14. To a solution of 650 mg (0.093 g-atom) of lithium in 210 ml of dry liquid ammonia was added with stirring over a 10-min period a solution of 1.080 g (3.58 mmol) of the aromatic ketal **14** in 68 ml of dry tetrahydrofuran. After 10 min 63 ml of *tert*-butyl alcohol was added dropwise, and the reaction mixture was stirred for an additional 1 hr. During this period two 210-mg (0.03 g-atom) batches of lithium were added after 10 min and again after 35 min when the blue color discharged. Finally, the blue color was discharged by the addition of 3 ml of methanol; the ammonia was removed in a stream of nitrogen, and after the addition of 100 ml of water, the product was isolated by ether extraction.[17] A solution of the crude residue in 26 ml of benzene and 130 ml of ethanol was stirred and heated at reflux for 30 min with 70 ml of 5 *N* aqueous hydrochloric acid. Isolation of the product by ether extraction[17] including a base wash afforded 840 mg of a crystalline residue which after repeated washing with ether gave 518 mg (60%) of the enedione **12**, mp 187–192°. The analytical sample, obtained after two crystallizations of a portion of this material from dichloromethane–hexane, melted at 190–193°: ir ($CHCl_3$) 1710 (C=O), 1660 (conjugated C=O), and 1615 cm^{-1} (conjugated C=C); NMR ($CDCl_3$) δ 1.13 (s, 2 × 3, C-4b and C-8a CH_3) and 6.00 (br s, 1, C-1 H).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.82; H, 8.92.

B. By Oxidation of Keto Alcohol 11. To a solution of 54 mg (0.22 mmol) of the keto alcohol **11** in 3 ml of dry acetone at 0° was added 0.055 ml of 2.7 *M* aqueous chromic acid solution.[18] The mixture was stirred for 2 min and then quenched with a few drops of isopropyl alcohol. After dilution with water and isolation of the product by ether extraction,[17] including a base wash, there resulted 51 mg (95%) of the enedione **12**, mp 181–189°. After two crystallizations of this material from dichloromethane–hexane there was obtained 48 mg (88%) that melted at 190–193° alone or in admixture with the authentic material prepared above. The ir and NMR spectra of the two samples were also identical.

10aβ-Cyano-2,2-ethylenedioxy-7-methoxy-4aα-methyl-1,2,-3,4,4a,9,10,10a-octahydrophenanthrene. In a flask fitted with a Dean-Stark water separator was placed 2.30 g (8.65 mmol) of trans cyano ketone **13**, 10 ml of ethylene glycol, 150 mg of *p*-toluenesulfonic acid monohydrate, and 200 ml of dry benzene. The mixture was stirred vigorously at reflux overnight in an atmosphere of argon. After the mixture was cooled, it was poured into 500 ml of water and the ketal [2.63 g (98%), mp 161–162°] was isolated by ether extraction, including a base wash. The analytical sample, prepared by one crystallization of a portion of this material from methanol, also melted at 161–162°: ir ($CHCl_3$) 2250 (C≡N), 1610, 1580, 1500 (ArH), and 1250 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 1.20 (s, 3, C-4a CH_3), 3.77 (s, 3, $ArOCH_3$), 4.3–6.2 (m, 4, OCH_2CH_2O), and 7.3–6.5 (m, 3, ArH).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.92; H, 7.38; N, 4.36.

4aα,10aβ-Dimethyl-2,2-ethylenedioxy-7-methoxy-1,2,3,4,-4a,9,10,10a-octahydrophenanthrene (14). In a dry flask was placed 9.42 g (0.030 mol) of the above cyano ketal, 450 ml of dry benzene, and 24 ml (0.036 mol) of a 1.5 *M* benzene solution of diisobutylaluminum hydride in an atmosphere of argon. The resulting solution was stirred at room temperature for 2 hr and then poured into 1 l. of a well-stirred, ice-cold, aqueous 5% sodium hydroxide solution. Isolation of the product by ether extraction, including a base wash, gave 9.49 g (100%) of a white foam, the solution ($CHCl_3$) infrared spectrum of which showed imine absorption at 1630 cm^{-1}, but no nitrile absorption at 2250 cm^{-1}.

A solution of this crude imine in 270 ml of tetrahydrofuran and 270 ml of methanol was heated to reflux in an atmosphere of argon, and then a solution of 4.2 g (0.051 mol) of anhydrous sodium acetate and 11.5 ml (12 g, 0.20 mol) of glacial acetic acid in 34 ml of water was added. After the resulting solution was heated at reflux for 10 min, the mixture was cooled to 40°, concentrated to approximately 150 ml at reduced pressure, and then poured into 1 l. of a well-stirred, ice-cold 5% aqueous sodium carbonate solution. Isolation of the crude product by ether extraction afforded 9.48 g (100%) of a white, crystalline solid, mp 117–120°, the solution ($CHCl_3$) infrared spectrum of which showed aldehyde absorption at 1710 cm^{-1}. Similar material from another experiment was crystallized twice from ether–hexane for combustion analysis, and this sample melted at 117–120° also: ir ($CHCl_3$) 2770 (CHO), 1710 (C=O), 1610, 1575, 1495 (ArH), and 1245 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 1.20 (s, 3, C-4a CH_3), 4.1–3.5 (m, 4, OCH_2CH_2O), 3.75 (s, 3, $ArOCH_3$), 7.3–6.5 (m, 3, ArH), and 9.45 (s, 1, CHO).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.05; H, 7.60.

The crude aldehyde, 72 ml (72 g, 1.44 mol) of 99% hydrazine hydrate, and 500 ml of diethylene glycol were heated at 140–145° (internal) for 23 hr in an atmosphere of argon. After the solution was cooled to approximately 110° (internal), 81 g of 85% potassium hydroxide was added. The reaction mixture was then stirred at 170–175° (internal) in a stream of argon for 2 hr, and finally at 165–170° (internal) for 3 hr under an atmosphere of argon. The pale yellow solution was cooled, poured into 2 l. of water and the product was isolated by extraction with 3:1 ether–dichloromethane. The residue amounted to 8.00 g (88%) of a crystalline solid which consisted of 99% of a single volatile component on GLC (225°). One crystallization of this material from ether–hexane afforded 7.45 g (82%) of the ketal **14** as white crystals, mp 111.5–112.5°, which was sufficiently pure for analytical purposes: ir ($CHCl_3$) 1605, 1575, 1495 (ArH), 1240 ($ArOCH_3$), 1150, and 1145 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 0.93 (s, 3, C-10a CH_3), 1.13 (s, 3, C-4a CH_3), 3.57 (s, 3, $ArOCH_3$), 4.1–3.5 (m, 4, OCH_2CH_2O), and 7.5–6.5 (m, 3, ArH).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.46; H, 8.76.

1-Trimethylsilyl-9,10,13-trimethyl-16-(*m*-methoxyphenyl)-(*E,E*)-9,13-hexadecadien-1-yn-5-ol. In a manner similar to that described for the preparation of the alcohol **3** a solution of the Grignard reagent from 2.43 g (0.1 g-atom) of magnesium and 10.75 g (67.2 mmol) of 1-trimethylsilyl-4-chloro-1-butyne in 45 ml of dry ether was cooled to −15° and added over a 1-hr period under an argon atmosphere to a cooled (−15°) solution of 7.355 g (22.4 mmol) of the aldehyde **15**[9] in 20 ml of dry ether. After stirring at room temperature for an additional 1 hr, the reaction mixture was worked up as described above, and the crude product (11.94 g) was purified on 410 g of silica gel in a medium-pressure chromatography apparatus[16] using 20% ether–petroleum ether as eluent. Elu-

tion with 2.5 l. of solvent afforded 7.084 g (70%) of the desired alcohol as an oil in the fractions from 1–2 l. The analytical sample was obtained by evaporative distillation of a portion of this material at 190° and 0.01 mm: ir ($CHCl_3$) 3650–3500 (OH), 2180 (C≡C), and 1610, 1605 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.15 [s, 9, $Si(CH_3)_3$], 1.61 (br s, 3, C-13 CH_3), 1.63 (s, 2 × 3, C-9 and C-10 CH_3), 3.80 (m, 1, C-5 H), 3.82 (s, 3, $ArOCH_3$), 5.20 (br t, 1, C-14 H), and 6.5–7.3 (m, 4, ArH).

Anal. Calcd for $C_{29}H_{46}O_2Si$: C, 76.59; H, 10.20. Found: C, 76.35; H, 10.00.

9,10,13-Trimethyl-16-(*m*-methoxyphenyl)-(*E,E*)-9,13-hexadecadiene-2,5-dione. In a manner similar to that described above for the formation of the model dione a solution of 6.98 g (15.37 mmol) of the above silyl alcohol in 320 ml of tetrahydrofuran and 130 ml of water was treated with 32 ml of a saturated solution of mercuric sulfate in 1% aqueous sulfuric acid. After stirring at room temperature for 1.5 hr, the mixture was saturated with sodium chloride, and the product was isolated by ether extraction,[17] including a base wash.

A solution of the crude product (6.85 g) from the above hydrolysis in 60 ml of dry acetone was treated with 4.5 ml of 8 *N* aqueous chromic acid solution,[18] and the mixture was stirred at 0° for 20 min. After dilution of the mixture with water and isolation of the product by ether extraction,[17] including a base wash, the crude diketone (5.374 g) was purified by medium-pressure chromatography[16] on 410 g of silica gel. Elution with 1.4 l. of 40% ether–petroleum ether afforded 3.083 g (50%) of the diketone as an oil in the fractions from 750–1100 ml. The analytical sample was prepared by evaporative distillation of a portion of this material at 160–165° and 0.001 mm: ir (CCl_4) 1720 and 1715 (C=O) and 1640, 1620 cm^{-1} (C=C); NMR (CCl_4) δ 1.58 (br s, 3, C-13 CH_3), 1.60 (s, 2 × 3, C-9 and C-10 CH_3), 2.07 (s, 3, C-1 CH_3), 3.88 (s, 3, $ArOCH_3$), 5.02 (br t, 1, C-14 H), and 6.4–7.2 (m, 4, ArH).

Anal. Calcd for $C_{26}H_{38}O_3$: C, 78.35; H, 9.61. Found: C, 78.35; H, 9.59.

2-(3′,4′,7′-Trimethyl-10′-(*m*-methoxyphenyl)-(*E,E*)-3′,7′-decadienyl)-3-methyl-2-cyclopentenone (16). In a manner similar to that described above for the formation of the cyclopentenone **4** a solution of 2.93 g (7.36 mmol) of the above diketone in 225 ml of ethanol and 53 ml of aqueous sodium hydroxide solution was heated at reflux under an argon atmosphere for 4 hr. After the reaction was cooled and neutralized with 10% aqueous hydrochloric acid, most of the ethanol was removed at reduced pressure, and then the product was isolated by ether extraction.[17] The crude product (2.793 g) was purified by medium-pressure chromatography[16] on 200 g of silica gel, and elution with 750 ml of 40% ether–petroleum ether afforded 2.236 g (80%) of the cyclopentenone **16** as an oil in the fractions from 300–600 ml. The analytical sample was prepared by evaporative distillation of a portion of this material at 145° and 0.003 mm: ir (CCl_4) 1705 (C=O) and 1650 cm^{-1} (C=C); NMR (CCl_4) δ 1.5–1.7 (m, 9, C-3′, C-4′, and C-7′ CH_3), 2.00 (s, 3, C-3 CH_3), 3.75 (s, 3, $ArOCH_3$), 5.16 (br t, 1, C-8′ H), and 6.5–7.35 (m, 4, ArH).

Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.06; H, 9.53. Found: C, 81.83; H, 9.24.

2-(3′,4′,7′-Trimethyl-10′-(*m*-methoxyphenyl)-(*E,E*)-3′,7′-decadienyl)-1-methylcyclopenten-3-ol. Reduction of 668 mg (1.76 mmol) of the cyclopentenone **16** was accomplished in a manner similar to that described above for the formation of the alcohol **5** with 100 mg (2.63 mmol) of lithium aluminum hydride in 30 ml of dry ether. After a similar work-up there resulted 661 mg of a colorless oil that on purification by preparative TLC (33% ether–petroleum ether) afforded 595 mg (90%) of the desired cyclopentenol (R_f 0.21) as an oil, 90% of which consisted of a single volatile component on GLC (280°). This material was not further purified but used directly in the cyclization experiments described below: ir (CCl_4) 3600, 3500 cm^{-1} (OH); NMR (CCl_4) δ 1.60 (br s, 3, C-1 CH_3), 1.65 (s, 3 × 3, C-3′, C-4′, and C-7′ CH_3), 3.73 (s, 3, $ArOCH_3$), 4.7 (br m, 1, C-3 H), 5.17 (br t, 1, C-8′ H), and 6.5–7.3 (m, 4, ArH).

Cyclization of 2-(3′,4′,7′-Trimethyl-10′-(*m*-methoxyphenyl)-(*E,E*)-3′,7′-decadienyl-1-methylcyclopenten-3-ol. A. With Stannic Chloride in Dichloromethane. A solution of 38.2 mg (0.1 mmol) of the above cyclopentenol in 3 ml of dry dichloromethane was cooled to −78°, and then 1.2 ml of a 0.1 *M* dichloromethane solution of stannic chloride was added. After 5 min 3 ml of a 20% aqueous potassium carbonate solution and then 5 ml of ether were added, and the mixture was poured into 50 ml of water. Analysis by GLC (280°) of the crude product (40 mg) isolated by ether extraction[17] showed a mixture that consisted of three major components (D, E, and F) with retention times of 4.0, 5.05, and 6.1 min, respectively, and in a ratio of 1:3:12. In addition there were several unresolvable peaks from 2.8–4.4 min.

This crude product was combined with 309 mg of identical material obtained from the cyclization of 264 mg of the cyclopentenol under identical conditions, and this mixture was chromatographed on 45 g of silica gel impregnated with 10% silver nitrate. Elution was accomplished with 50% ether–petroleum ether; 10-ml fractions were collected and the residues were analyzed by GLC (280°).

Fraction	Wt, mg	Composition
14, 15	18	E (90%)
16	3	E:F (1:3)
17–22	157	D:E:F (5:4:90)
23	3	D:F (1:1)
24–28	23	D + others (1:1)
29–45	17	Eleven side products

Trituration of the material from fractions 17–22 with petroleum ether at −78° afforded 96 mg (33%; estimated by GLC 108 mg, 3) of the olefin **17** (component F), mp 149–151°, 96% of which was a single volatile component on GLC (280°). The analytical sample, prepared by crystallization of this material from ether–hexane, melted at 150–151.5°: ir ($CHCl_3$) 1610 cm^{-1} (1,2,4-trisubstituted aromatic); NMR ($CDCl_3$) 0.72, 1.03, 1.21 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.61 (s, 3, C-3 CH_3), 3.76 (s, 3, $ArOCH_3$), 6.60 (d, 1, $J_{8,10}$ = 2 Hz, C-8 H), 6.70 (d of d, 1, $J_{8,10}$ = 2, $J_{10,11}$ = 8 Hz, C-10 H), and 7.20 (d, 1, $J_{10,11}$ = 8 Hz, C-11 H).

Anal. Calcd for $C_{26}H_{36}O$: C, 85.66; H, 9.95. Found: C, 85.65; H, 9.99.

Components D and E from this experiment could not be further purified but were obtained in part B.

B. With Silica Gel. On attempted purification of 1.36 g (3.56 mmol) of the above cyclopentenol by chromatography on 95 g of silica gel, 890 mg (69%) of cyclized material, the major components of which were D, E, and F (17) in a ratio of 13:3:4 by GLC (280°), was obtained on elution with 300 ml of 30% ether–petroleum ether. After rechromatography of this material on 40 g of silica gel impregnated with 2% silver nitrate and then preparative TLC (petroleum ether) of the residues from the major fractions, both components D and E were obtained pure.

Component D, isolated in 14% yield (184 mg) as a colorless oil, was shown to be 6-(2′-*m*-methoxyphenylethyl)-3,5aβ,7,9aα-tetramethyl-2,4,5,5a,6α,9,9a,9bβ-octahydro-1*H*-benz[*e*]indene and was evaporatively distilled for analysis at 110° and 0.075 mm: ir ($CHCl_3$) 1605, 1585 cm^{-1} (C=C, Ar); NMR ($CDCl_3$) δ 0.62, 0.85 (2 s, 3 each, C-5a and C-9a CH_3), 1.60 1.80 (2 br s, 3 each, C-3 and C-7 CH_3), 3.75 (s, 3, $ArOCH_3$), 5.36 (m, 1, C-8 H), and 6.48–7.35 (m, 4, ArH).

Anal. Calcd for $C_{26}H_{36}O$: C, 85.66; H, 9.95. Found: C, 85.76; H, 10.01.

Component E, isolated in 3% yield (45 mg), was crystallized from ether–hexane and shown to be the isomeric pentacyclic ether **18**: mp 157.5–161°; ir ($CHCl_3$) 1575 cm^{-1} (C=C, Ar); NMR ($CDCl_3$) δ 0.72, 1.01, 1.33 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.60 (br s, 3, C-3 CH_3), 3.75 (s, 3, $ArOCH_3$), 6.67 (d of d, 1, $J_{9,10}$ = 8, $J_{8,10}$ = 1.5 Hz, C-10 H), 6.73 (s, 1, C-8 H), and 7.05 (d of d, 1, $J_{8,9}$ = 7, $J_{9,10}$ = 8 Hz, C-9 H).

Anal. Calcd for $C_{26}H_{36}O$: C, 85.66; H, 9.95. Found: C, 85.57; H, 9.97.

3,5aβ,11bβ,13aα-Tetramethyl-2,4,5,5a,5bα,6,7,11b,12,13,13a,-13bβ-dodecahydro-1*H*-cyclopenta[*a*]chrysene (20). To a solution of 0.6 mmol of lithium diphenylphosphide[20] [prepared from 111.6 mg (0.6 mmol) of a 2.2 *M* hexane solution of *n*-butyllithium in 1 ml of dry tetrahydrofuran under an argon atmosphere] was added 80 μl of *N,N,N′,N′*-tetramethylethylenediamine and 36.4 mg (0.1 mmol) of the olefin **17**, and then the mixture was refluxed for 19 hr. After the addition of 1 ml of water and then isolation of the product by ether extraction,[17] including both an acid and base wash, purification of the crude product (110 mg) by preparative TLC (20% ether–petroleum ether) afforded 32 mg (9) of the corresponding phenolic olefin (R_f 0.25), mp 188–191° dec. The analytical sample, prepared by crystallization of this material from ether–hexane, also melted at 188–191°: ir ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.70, 1.01, 1.20 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.61 (br s, 3, C-3 CH_3), 4.58 (br s, 1, C-9 OH), and 6.43–7.43 (m, 3, ArH).

Anal. Calcd for $C_{25}H_{34}O$: C, 85.66; H, 9.78. Found: C, 85.57; H, 9.74.

To a solution of 17.5 mg (0.05 mmol) of the 9-hydroxy olefin

above and a few crystals of 1,10-phenanthroline in 1 ml of dry tetrahydrofuran was added enough ethereal methyllithium to impart a brown color to the solution. This mixture was treated sequentially with 35 μl of triethylamine, 35 μl of hexamethylphosphoramide, and 50 μl of the *N,N,N′,N′*-tetramethyldiamidophosphorochloridate,[20] and after stirring at room temperature for 17 hr, the mixture was poured into 15 ml of water. Isolation of the product by ether extraction,[17] including an acid wash, afforded 24 mg (99%) of white crystals of the corresponding phosphorodiamidate as the only volatile component by GLC (300°): ir ($CHCl_3$) 1610 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.70, 1.03, 1.20 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.61 (br s, 3, C-3 CH_3), 2.58 (d, 12, J = 12 Hz, NCH_3), and 6.80–7.33 (m, 3, ArH).

This crude phosphorodiamidate was dissolved in 15 ml of ammonia and 2 ml of dry tetrahydrofuran, and ca. 3 mg of lithium was added. The blue solution was stirred for 15 min at reflux, and then 0.5 ml of ethanol was added. The ammonia was evaporated under a stream of dry nitrogen, and the residue was dissolved in 20 ml of water and extracted with 3 × 15 ml of ether. The combined ethereal extracts were washed with 2 × 15 ml of water and dried ($MgSO_4$). Evaporation of the solvent at reduced pressure afforded 21 mg of an oil which contained one volatile component by GLC (300°), and on preparative TLC (benzene) afforded 16 mg (96%) of the pentacyclic hydrocarbon **20.** Crystallization of this material from methanol and then bulb-to-bulb distillation (167° at 0.0015 mm) gave analytically pure material: mp 99–101.5°; NMR ($CDCl_3$) δ 0.70, 1.03, 1.23 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.61 (br s, 3, C-3 CH_3, ArH); ir ($CHCl_3$) 3060 (ArH) and 1490, 1455, 1445, and 1385 cm^{-1}.

Anal. Calcd for $C_{25}H_{34}$: C, 89.76; H, 10.24. Found: C, 89.85; H, 10.19.

B. From the 11-Methoxy Olefin 18. Demethylation of 36.4 mg (0.1 mmol) of the 11-methoxy olefin was accomplished in 71% (25 mg) yield in the same manner as that described above for the 9-methoxy olefin **17** except that 0.3 mmol of lithium diphenylphosphide[20] [prepared from 56 mg (0.30 mmol) of diphenylphosphine and 150 μl (0.33 mol) of a 2.2 *M* hexane solution of *n*-butyllithium], 40 μl of *N,N,N′,N′*-tetramethylethylenediamine, and 200 μl of dry tetrahydrofuran were used. This material, which was not further purified for combustion analysis but used directly in subsequent experiments, melted at 192–196° dec: ir ($CHCl_3$) 3590 (OH) and 1580 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.71, 1.01, 1.36 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.60 (br s, 3, C-3 CH_3), and 6.35–7.53 (m, 3, ArH); TLC (benzene) R_f 0.6.

The phosphorodiamidate [26 mg crude, >99% single volatile component on GLC (300°)] was prepared from 14 mg (0.04 mmol) of the above phenol as described above in part A with 40 μl of *N,N,N′,N′*-tetramethyldiamidophosphorochloridate,[21] 30 μl of triethylamine, and 30 μl of hexamethylphosphoramide in 1 ml of dry tetrahydrofuran: ir ($CHCl_3$) 3150 cm^{-1} (ArH); nmr ($CDCl_3$) δ 0.73, 1.03, 1.40 (3 s, 3 each, C-5a, C-11b, and C-13a CH_3), 1.60 (br s, 3, C-3 CH_3), 2.73 (d, 12, J = 13 Hz, NCH_3), and 6.70–7.36 (m, 3, ArH).

On reduction of this material by the same procedure as described in part A in 15 ml of dry ammonia and 2 ml of dry tetrahydrofuran with ca. 3 mg of lithium and 0.5 ml of ethanol, 10 mg (74%) of the hydrocarbon **20,** mp 97.5–99.5°, was obtained after preparative TLC (benzene, R_f 0.7) and then crystallization (methanol) of the crude product. The melting point of a mixture of this material and that, mp 99–101.5°, prepared from the 9-methoxy olefin **17** was 98.5–101.5° and quantitative peak enhancement of GLC[17] (300°) indicate only one volatile component.

1-(3-Oxobutyl)-8-methoxy-4aβ,10bβ,12aα-trimethyl-3,4,-4a,4bα,5,6,10b,11,12,12a-decahydro-2(1*H*)-chrysenone. The methoxy olefin **17** (52.4 mg, 0.144 mmol) was hydroxylated and then cleaved with 119.7 mg (0.432 mmol) of osmium tetroxide in 12 ml of dry dioxane and 0.75 ml of dry pyridine (62 hr at room temperature; osmate ester cleaved with hydrogen sulfide in 12 ml of dichloromethane), followed by treatment with 1.0 g of lead tetraacetate in 12 ml of dry tetrahydrofuran. On purification of the crude product (60 mg) by preparative TLC (40% ether–chloroform), 49 mg (88%) of the desired diketone, mp 148–150.5°, was obtained. An analytical sample, obtained after crystallization of this material from ether–hexane, was a polymorph of the original material (identical solution ir and NMR) and melted at 134–135°: ir ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 (s, 3, C-4a CH_3), 1.25 (s, 2 × 3, C-10b and C-12a CH_3), 2.15 (s, 3, CH_3CO), 3.80 (s, 3, $ArOCH_3$), and 6.53–7.38 (m, 3, ArH).

Anal. Calcd for $C_{26}H_{36}O_3$: C, 78.75; H, 9.15. Found: C, 78.68; H, 9.14.

10-Methoxy-6aβ,12bβ,14aα-trimethyl,1,5,6,6a,6bα,7,8,12b,-13,14,14a,14bβ-dodecahydro-3(2*H*)-picenone (19). A solution of 19 mg (0.048 mmol) of the diketone above in 10 ml of methanol and 1 ml of 10% aqueous sodium hydroxide solution was heated at reflux for 10 hr, and then the product was isolated by benzene extraction.[17] After preparative TLC (9:2 chloroform–ether) of the crude product (22 mg) and then crystallization (hexane–dichloromethane) of the material in the band at R_f 0.45, there was obtained 12 g (66%) of the enone **19,** mp 196–198.5°. Recrystallization of this material from the same solvent mixture afforded material which melted at 197–199°, and on admixture with authentic enone,[6] mp 197–200.5°, the mix melted at 196–198.5°. The ir and NMR spectra of this material were identical with those recorded[6] previously, and the mobility of samples from the two different sequences on TLC (9:2 chloroform–ether) and GLC (300°) were indistinguishable.

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Registry No.—**1,** 50676-11-4; **2,** 29023-69-6; **3,** 54181-98-5; **4,** 54191-90-1; **5,** 54181-99-6; **6,** 54182-00-2; **7,** 54182-01-3; **8,** 54182-02-4; **9,** 54182-03-5; **10,** 54182-04-6; **11,** 54182-05-7; **12,** 54182-06-8; **13,** 54191-89-8; **14,** 54182-07-9; **15,** 53311-19-6; **16,** 54182-09-1; **17,** 54182-10-4; **17** OH analog, 54182-11-5; **17** OH analog *N,N,N′,N′*-tetramethylphosphorodiamidate, 54182-12-6; **18,** 54191-68-3; **18** OH analog, 54182-13-7; **18** OH analog *N,N,N′,N′*-tetramethylphosphorodiamidate, 54182-14-8; **19,** 30454-41-2; **20,** 54182-15-9; 1-trimethylsilyl-4-chloro-1-butyne, 54182-16-0; 4-hydroxy-1-butyne, 927-74-2; trimethylchlorosilane, 75-77-4; 9,10-dimethyl-(*E*)-9,13-tetradecadiene-2,5-dione, 54182-17-1; 10aβ-cyano-2,2-ethylenedioxy-7-methoxy-4aα-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, 54182-18-2; 10aβ-formyl-2,2-ethylendioxy-7-methoxy-4aα-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, 54182-19-3; 1-trimethylsilyl-9,10,13-trimethyl-16-(*m*-methoxyphenyl)-(*E,E*)-9,13-hexadecadien-1-yn-5-ol, 54182-20-6; 9,10,13-trimethyl-16-(*m*-methoxyphenyl)-(*E,E*)-9,13-hexadecadiene-2,5-dione, 54182-21-7; 2-(3′,4′,7′-trimethyl-10′-(*m*-methoxyphenyl)-(*E,E*)-3′,7′-decadienyl)-1-methylcyclopenten-3-ol, 54182-22-8; 6-(2′-*m*-methoxyphenylethyl)-3,5aβ,7,9aα-tetramethyl-2,4,5,5a,6α,-9,9a,9bβ-octahydro-1*H*-benz[e]indene, 54182-23-9; *N,N,N′,N′*-tetramethyldiamidophosphorochloridate, 1605-65-8; diketone (mp 148–150.5°), 54182-24-0.

References and Notes

(1) The structural formulas containing one or more asymmetric carbon atoms depict one enantiomer, but refer to racemic compounds unless otherwise designated. In the text, the (±) prefix will be omitted, and intermediates are assumed to be racemic. The tricyclic compounds will be described by the 1*H*-benz[e]indene or phenanthrene nomenclature, and each racemate is arbitrarily represented by that enantiomer that has the C-9a or C-4b methyl group, respectively, in the α configuration. The pentacyclic compounds will be described by the 1*H*-cyclopenta-[*a*]chrysene or picene nomenclature, and each racemate is arbitrarily represented by that enantiomer that has the C-13a or C-14a methyl group, respectively, in the α configuration.
(2) On study leave from the Centre National de la Recherche Scientifique, France.
(3) Trainee of the National Institute of General Medical Sciences, National Institutes of Health.
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(15) Since completion of this work the results of the work of Johnson and coworkers[12] became available. This evidence suggests the possibility that the yield of the isomer **17** in the cyclization stage of the present scheme could be improved.
(16) Melting points labeled (vacuum) were taken in evacuated capillaries on a Hoover capillary melting point apparatus, while all others were determined on a Kofler micro hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded using either a Varian A-60A or T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ_{TMS} 0.0 ppm) as an internal standard.

Gas–liquid phase chromatographic (GLC) analyses were determined on either a Hewlett-Packard 5750 or F & M 810 research chromatograph using helium carrier gas at a flow rate of 60 ml/min. Unless otherwise noted, all analytical GLC was conducted on a 6 ft × 0.125 in. column packed with 4% SE-30 on 60–80 mesh Chromosorb W-DMCS.

Preparative thin layer chromatography (preparative TLC) was carried out on 20 × 20 × 0.2 cm glass plates coated with silica gel $PF_{254+266}$ (Brinkman Instruments Co.). Analytical thin layer chromatography (TLC) was conducted on 1 × 3 in. microscope slides coated with a 0.5-mm layer of silica gel G or $PF_{254+266}$.

Alumina used for column chromatography refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany, and made up to grade II or III as indicated by the addition of 3 or 6% water prior to use. Silica gel columns used the 0.05–0.2-mm silica gel manufactured "for column chromatography" by E. Merck & Co., Darmstadt, Germany. Preparative medium-pressure column chromatography was performed using 0.5 × 20 in. or 2 × 20 in. glass columns with fittings supplied by Chromatronix, Inc., Berkeley, Calif., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ manufactured by E. Merck & Co., Darmstadt, Germany). Solvents were degassed under water aspirator vacuum prior to use.

"Dry" solvents were dried immediately prior to use. Ether, benzene, tetrahydrofuran, dioxane, and dimethoxyethane were distilled from lithium aluminum hydride; *tert*-butyl alcohol, dimethyl sulfoxide, pyridine, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride; dichloromethane, carbon tetrachloride, diodomethane, and methyl iodide were distilled from phosphorus pentoxide; ammonia was distilled from the tank and then from a blue lithium or sodium solution; acetone was analytical reagent grade distilled from potassium permanganate; formic acid was distilled from boric anhydride. "Petroleum ether" refers to the "Analyzed Reagent" grade hydrocarbon fraction, bp 30–60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Reactions described as run under nitrogen or argon employed a mercury bubbler arranged so that the system could be alternately evacuated and filled with the inert gas and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(17) In cases where products were isolated "by solvent extraction," the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water, followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.
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Experiments Directed toward the Total Synthesis of Terpenes. XXII. A Polyene Cyclization Approach to Tetradecahydropicene Derivatives for Pentacyclic Triterpene Synthesis[1]

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The syntheses of two trienols through the ketones **8** and **9** are described, and the results of the stannic chloride catalyzed cyclizations of these materials is presented. The product variation as a result of solvent changes in the cyclization of the trienol from the ketone **8** revealed the formation of significant amounts of solvent-trapped products. The synthesis of the trienol from the ketone **25** follows the same pattern as the above models, but the yield of the olefin **26** in the stannic chloride cyclization is significantly lower than in the model series. Attempts to convert the olefin **26** to a known intermediate in a previous alnusenone (**1**) total synthesis were unsuccessful. The X-ray structural analysis of the ketone **27** is presented.

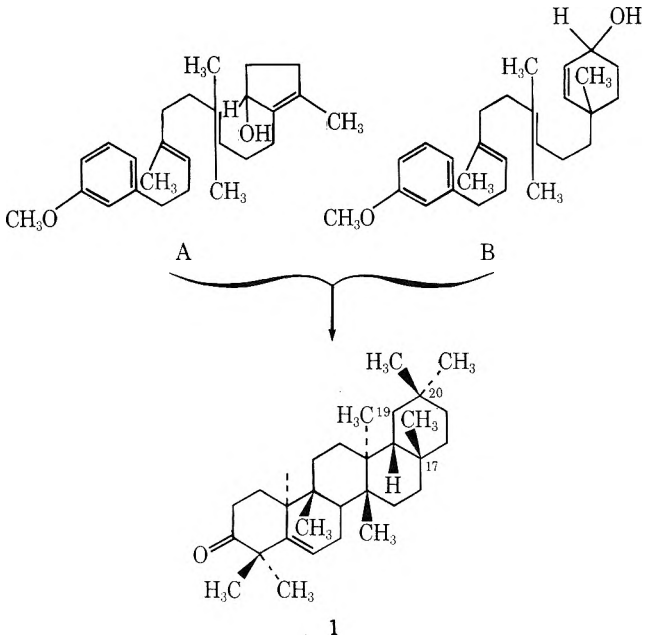
In the preceding paper[4] in this series the results of a program designed to construct intermediates for the total synthesis of alnusenone (**1**) via the acid-catalyzed cyclization of the 3-methyl-2-cyclopentenol A were discussed. At the inception of this synthetic scheme two possible cyclic allylic alcohol systems were considered useful candidates for the initiation of the cyclization step.[5] In addition to the 3-methyl-2-cyclopentenol system A, the 4-methyl-2-cyclohexenol system B has significant potential. In principle cyclization of this molecule will establish a pentacyclic intermediate in which the E ring is already six-membered and bears the desired C-17[1] methyl group at a cis D/E ring fusion. Addition of the *gem*-dimethyl grouping at C-20[1] through the agency of the C-19–C-20[1] double bond that results from cyclization would then complete the construction of the triterpenoid E ring. The advantages of this concept are apparent, for it avoids not only the selective lithium–ammonia reduction of the A,E-diaromatic pentacyclic intermediate used in the initial approach[6] but also the necessity for the subsequent incorporation of the C-17[1] angular methyl group that is inherent in both preceding syntheses.[4,6] While these two operations did not pose significant problems in fact, the advantages of this proposed scheme were great enough to warrant a concurrent investigation. The results of both a model study and the cyclization of the alcohol B are presented here.

Of initial concern in this work was the development of procedures for the conversion of the dienol **24** (Chart III) to the desired cyclization substrate B. The efficient synthesis already described[7] for the dienol **24** dictated its use in the synthesis of both allylic alcohols A[4] and B, but different subsequent schemes were required in each case. In addition a model series designed to test the efficiency of the cyclization step was deemed advisable. Even though this stage of the scheme is based on the principles that have been developed in the Johnson laboratories,[5,8] the presently proposed

Table I
Variation in Product Composition with Solvent on Cyclization of 4-Methyl-4-(3′-methyl-(*E*)-3,7-octadienyl)-2-cyclohexenol

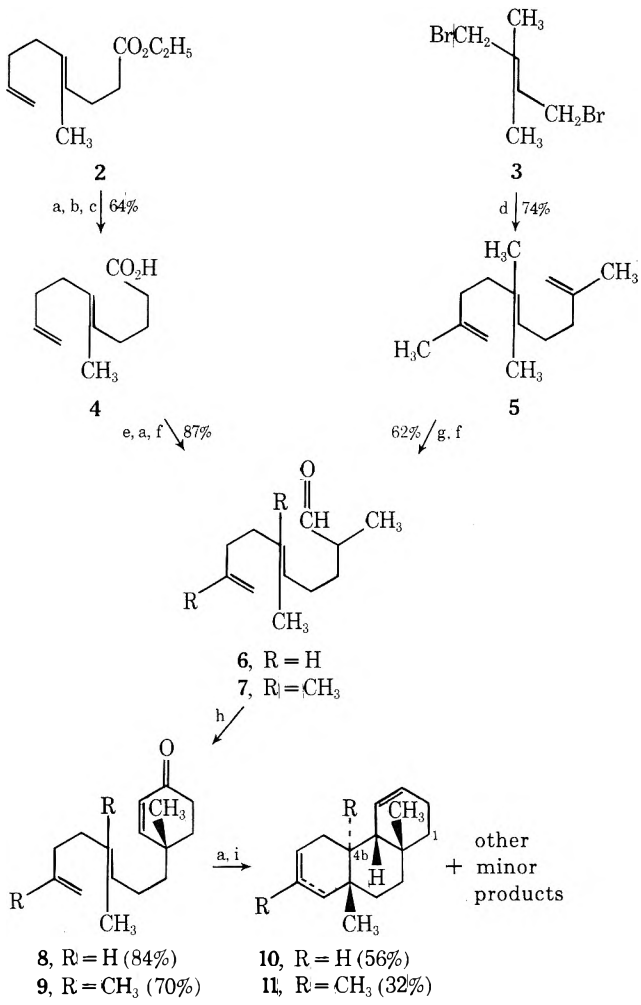
Expt	Solvent	Molar ratio SnCl/alc	Temp, °C	Reaction time	Products (% isolated yield)
1	CH_3NO_2	1.5	−28	1.5 min	**10** (25%)
2	CH_2Cl_2–$CO(OCH_3)_2$	6	25	1 hr	**10** (56%), **20** (4%)
3	C_6H_6	6	5	1.5 hr	**10** (22%), **19** (28%)
4	CH_2Cl_2	1.5	25	4 min	**10** (14%), **19** (35%)
5	CF_3CH_2OH	3	0	3 hr	**10** (20%), **21** (16%)
6	$C_6H_5OCH_3$	3	−10	15 min	**10** (12%), **20** (25%), **22** (20%), **23** (28%)
7	$C_6H_5CO_2CH_3$	3	then 25	5 hr	**10** (35%), **20** (3%)

substrate B differs in subtle but significant ways from those employed by Johnson. Thus, a 4-methyl-2-cyclohexenol is proposed here in contrast to the 1- and 3-methyl-2-cyclohexenols[8a,b] used by Johnson, and it seemed reasonable to test the stereochemical outcome of the cyclization with this system in a less complex model series before the dienol **24** was used. The synthesis and cyclization of two such model systems—the alcohols derived from the ketones **8** and **9**—were investigated.



An obvious route for the formation of the required allylic alcohols was through hydride reduction of the enones **8** and **9** (Chart I). Annelation of the enamines[9] derived from the aldehydes **6** and **7** with methyl vinyl ketone provided ready access to these enones **8** and **9**. For the construction of the aldehyde **7** in the series with the tetrasubstituted double bond, it was a simple matter to hydroborate[10] and then oxidize[11] the symmetrical diene **5** obtained from the coupling reaction[12] between methallylmagnesium bromide and the dibromide **3**.[13] However, since a polyene system like **5** was *not* intermediate in the established synthesis of the dienol **24**, another route to a 2-methylaldehyde similar to **7** was sought that required the introduction of the methyl group at this site. Such a system was the aldehyde **6**, which was available through direct methylation of the acid **4** and then a reduction–oxidation[11] sequence. The choice of this system **6** that contained the trisubstituted rather than the tetrasubstituted double bond was predicated on its ease of access through the ester **2**,[14] and the expectation that cyclization of the alcohol derived from the resulting enone **8** would be efficient.[8] That the structure and stereochemistry of the resulting tricyclic products would be more readily amenable to definition than in the tetrasubstituted double bond series was also considered.

Chart I
Hydrophenanthrene Formation via Polyene Cyclization[a]

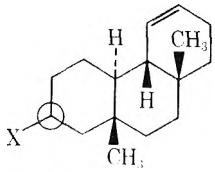


[a] a, $LiAlH_4$, Et_2O; b, Ph_3P, CCl_4; c, Mg, THF, CO_2; d, $CH_2{=}C(CH_3)CH_2MgBr$, THF; e, $LiN(i\text{-}Pr)_2$, THF, CH_3I; f, $CrO_3 \cdot 2Py$, CH_2Cl_2; g, Sia_2BH, THF, H_2O_2, aq NaOH; h, C_4H_9N,C_6H_6, $CH_3COCH{=}CH_2$, NaOAc, aq HOAc; i, $SnCl_4$, $(CH_2O)_2CO$, CH_2Cl_2.

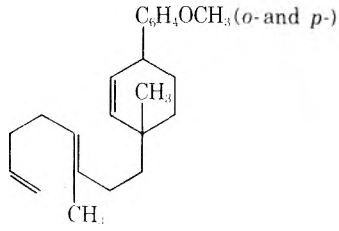
In fact, cyclization of the alcohol derived from the ketone **8** wth stannic chloride in dichloromethane–ethylene carbonate solution[15] led to a mixture of the dienes **10** in 56% yield. In addition it was possible to identify a minor component of the product mixture as the cholorocarbon **20** that resulted from solvent trapping of the tricyclic cation. This interesting observation led to the consideration of the effect of the solvent on the product distribution from the cy-

clization (Table I). It is interesting to note that in benzene, a common solvent for such reactions,[5] the *major* isolated product arises from attack of the tricyclic cation by the benzene solvent. Even the poorly nucleophilic solvent trifluoroethanol[16] successfully competed with proton abstraction and produced significant amounts of the ether **21**. Comparison of experiments 2 and 4 reveals the effect of the addition of ethylene carbonate to the reaction mixture. This reagent has been used[15] to trap the vinyl cation generated during cyclizations that terminate at an acetylenic linkage. In the present case, where a saturated cationic center is generated by cyclization, ethylene carbonate behaves as a base and promotes proton abstraction.

Particularly interesting, in view of the past[4] and proposed use of the anisole ring in the cyclization substrates, is the result (expt 6) when the cyclization was conducted in anisole. Even though the anisole solvent was quite nucleophilic and trapped both the initial **23** and tricyclic **22** cations effectively, it was not nucleophilic enough to prevent the formation of the dienes **10** and even allowed the tricyclic cation to be trapped by chloride from the catalyst. In addition the observed formation of *both* the ortho- and para-substitution products **22** and **23** corroborates previous experience[4,8c,17] in which both substitution patterns resulted when substrates that contained the anisole ring were used.



19. X = C_6H_5
20. X = Cl
21. X = CF_3CH_2O
22. X = *o*- and *p*-$CH_3OC_6H_4$



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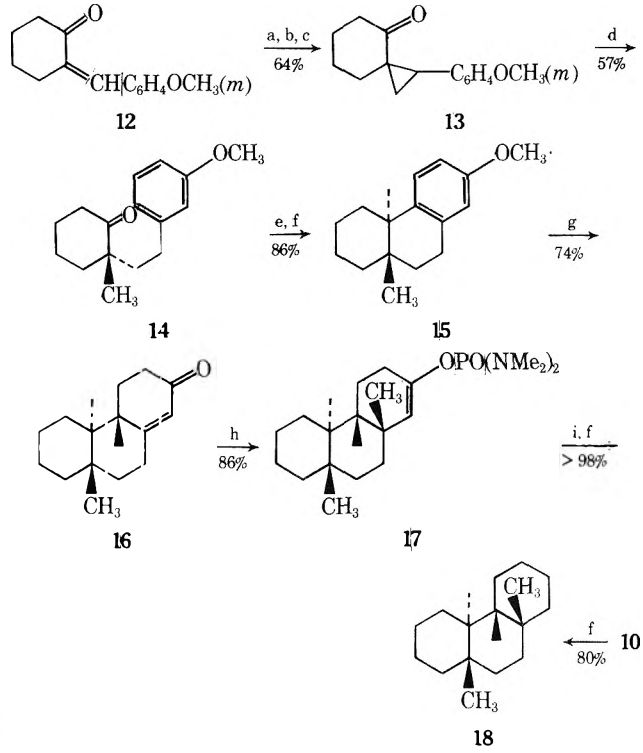
In order to provide the structure and stereochemistry of the tricyclic products from this cyclization, an alternate, stereorational synthesis of the system was developed (Chart II). A new route to the key substance in this sequence—the ketone **14**—was developed from *m*-methoxybenzylidenecyclohexanone (**12**)[18] via methylenation[19,20] to the cyclopropyl ketone **13** and then reductive methylation[21] to form the desired intermediate **14**. This sequence avoids the low yield anticipated from the more obvious alkylation of 2-methylcyclohexanone with β-(*m*-methoxyphenyl)ethyl bromide and should prove to be of general utility for the construction of systems such as the ketone **14**.

For comparison purposes the hydrocarbon **18** was prepared from the ketone **14** as outlined in Chart II. Strong precedence[22] as well as experimental evidence[23] exists for the stereochemical outcome at each stage, and the identity of the samples of the hydrocarbon **18** prepared by this route and by hydrogenation of the dienes **10** was established by spectra and GLC comparison. At least for a trisubstituted central double bond, this identity establishes that the cyclization of the 4-methyl-2-cyclohexenol bearing system gives the same trans-anti-trans stereochemical result as that observed by Johnson[8] in the 1- and 3-methyl cases.

Attention was now turned to the cyclization of the alcohol derived from the ketone **9** in order to test the effect of the central tetrasubstituted double bond on the outcome. Cyclization of this material with stannic chloride in dichloromethane again resulted in the formation of a complex mixture of products from which the major isolated component was taken to be the diene **11**. Although no detailed structure proof was undertaken, the spectral properties of this material as well as the analogy to the preceding cyclization serve to substantiate this structural assignment. The significant difference between the present cyclization experiment and the preceding one is the lower yield and more complex product mixture. Under the conditions used the more basic tetrasubstituted double bond may interfere through competitive interaction with the catalyst, but probably more significant is the severe congestion that develops during cyclization between the C-1[1] methylene and the C-4bα[1] angular methyl group. This interaction was lacking in the preceding trisubstituted double bond case and may add sufficient energy to the cyclization transition state to allow alternative reaction pathways to compete more effectively.

Chart II
Synthesis of the Hydrocarbon 18[a]



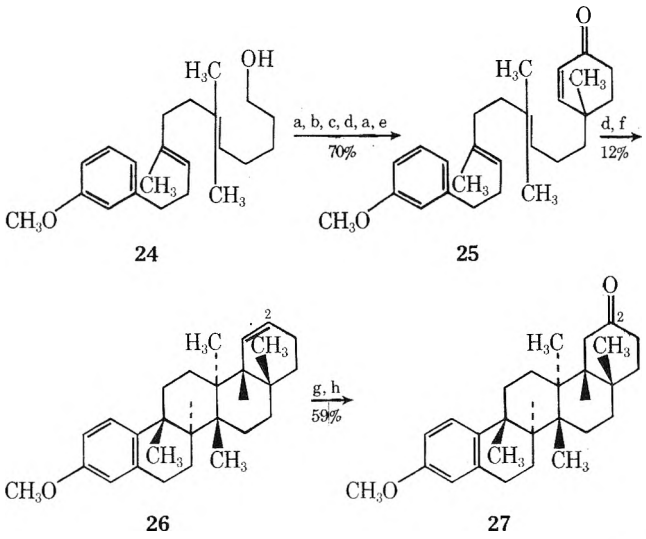
[a] a, $NaBH_4$, CH_3OH; b, Zn(Cu), CH_2I_2, Et_2O; c, 8 *N* aq H_2CrO_4, acetone; d, Li, NH_3, $(CH_3OCH_2)_2$, *t*-BuOH, HMPA, CH_3I; e, PPA; f, 10% Pd/C, EtOH or C_6H_{14},H_2; g, Li, NH_3, THF, *t*-BuOH; 5 *N* aq HCl, CH_3OH; h, $LiCu(CH_3)_2$, Et_2O, HMPA, $ClPO(NMe_2)_2$; i, Li, $EtNH_2$, THF, *t*-BuOH.

In spite of this nascent trend toward lower yields in the cyclization step as the system becomes more similar to the desired substrate B for the pentacyclic synthesis, the advantages of this approach in terms of structural and stereochemical control encouraged the continuation of the effort toward its desired conclusion.

Conversion of the dienol **24**[7] to the enone **25** (Chart III) followed the procedure already tested in the formation of the enone **8** from the acid **4** (Chart I), and the overall yield was equally as satisfactory. Cyclization of the alcohol obtained on hydride reduction of the enone **25** was accomplished with stannic chloride in dichloromethane–ethylene carbonate.[15] Again a complex mixture of products resulted, but one product predominated enough to permit its isolation and purification after repeated chromatography. The spectral properties of this material were consistent with those expected of the desired olefin **26**. Unfortunately, the unsatisfactorily low yield in which the olefin **26** was formed

in this cyclization could not be increased by experimentation with several alternate reaction conditions.

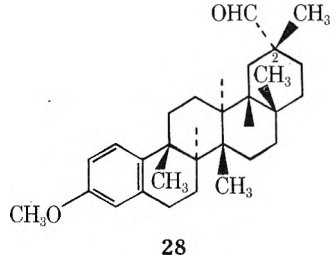
Chart III
Formation of Pentacyclic Olefin 26 via Polyene Cyclization[a]



[a] a, $CrO_3 \cdot 2Py$, CH_2Cl_2; b, $AgNO_3$, aq NaOH, EtOH; c, LiN(*i*-Pr)$_2$, THF, HMPA, CH_3I; d, $LiAlH_4$, Et_2O; e, C_4H_9N,C_6H_6, $CH_3COCH{=}CH_2$, NAOAc, aq HOAc; f, $SnCl_4$, $(CH_2O)_2CO$, CH_2Cl_2; g, $BH_3 \cdot THF$, THF, H_2O_2, aq NaOH; h, 8 *N* aq H_2CrO_4, acetone.

All that remained to connect the thread of the present synthetic scheme with that of the previously successful total synthesis[6] of alnusenone (**1**) was the conversion of the olefin **26** to the pentacyclic system that had a *gem*-dimethyl grouping at C-2.[1]

As a first step in this operation, hydroboration[10] and then oxidation[24] of the olefin **26** gave the ketone **27**, the point at which the synthetic effort came to a halt. The steric congestion about substituents at C-2[1] as a result of the cis D/E ring fusion and the subsequent proximity of the C-14aα[1] methyl group thwarted several attempts to develop means for this transformation. While the severely limited supply of the olefin **26** did not allow extensive experimentation, treatment with trimethylaluminum–benzene at 200°[25] and methylenetriphenylphosphorane in dimethyl sulfoxide[26] were found to be ineffectual. Formation of the C-2 oxirane by the method of Coates and Johnson[27] was possible and subsequent rearrangement of this oxirane to the C-2 aldehyde and then methylation led to material which had spectral properties (ir and NMR) consistent with the aldehyde **28**. Again limited supplies owing to low



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yields did not allow complete purification of this material, and it could not be freed from minor components that resulted from side reactions at each stage. Material of sufficient purity for combustion analysis was therefore not obtained. As might be expected, reduction of this aldehyde **28** to the desired C-2 *gem*-dimethyl system was not possible. Even after reduction with hydride to what was presumed to be the primary alcohol, the severe steric hindrance thwarted the formation of a phosphorodiamidate[28] derivative. These observations, as well as the bulk of precedence,[29] suggest the stereochemistry shown at C-2[1] in the aldehyde **28**. The aldehyde function in this configuration is effectively blocked toward intermolecular reactions by the C-14aα methyl group. This same steric situation exists in alnusenone (**1**) itself and is in part responsible for the ease of the acid-catalyzed rearrangement[30] of that carbon skeleton to the more familiar B-amyrin structure.

Table II
Crystal Data

Molecule trans-anti-trans-anti-cis ketone **27**
Formula $C_{27}H_{38}O_2$
Formula wt 394.6
Space group $C2/c$
Systematic absences
hkl, $h + k = 2n + 1$
no $l\ l = 2n + 1$
a 50.1255 (16)
b 7.5886 (3)
c 11.4010 (4)
β 90.504 (2)
Z 8
F_{000} 1728
λ Co Kα 1.7902 Å
D_c 1.21 g cm^{-3}
D_m 1.23 ± 0.02 g cm^{-3}
μ 8.8 cm^{-1}
V 4336 Å^3
Background time 30 sec
Scan rate 2°/min
No. of reflections 2505
Nonzero reflections 2319
Final R index [a] 0.168
Standard deviation in C,O bond lengths 0.01 Å
Standard deviation in C,O bond angle 0.7°

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.

In view of these observations and the very limited supplies of the olefin **26**, no further efforts were undertaken to effect the introduction of the *gem*-dimethyl grouping at C-2. In order to confirm the proposed structures and thereby establish that the formation of the olefin **26** in the cyclization reaction had taken the expected course, a single-crystal X-ray structural analysis was undertaken on the ketone **27**. The X-ray data were collected with iron-filtered Co Kα radiation to a spacing of 0.97 Å. The structure was solved by direct methods and refined by full-matrix least-squares refinement with isotropic temperature factors of all heavier atoms. The R index is 0.168 (Table II). A stereoplot of the molecule (Figure 1) confirms the structure assigned on the earlier spectral data and graphically illustrates the steric situation in the C/D/E rings that prevented the conversion of this ketone **27** to the desired hexamethyl system.

This work and that reported in the preceding paper demonstrate that the polyene cyclization sequence[5] is a valid means for the construction of polycyclic systems from polyolefinic substrates that make no attempt to simulate natural intermediates. The results of the cyclizations in anisole (Table I) and with those systems that incorporate the anisole ring in the polyene leave much to be desired in our hands.[8c] This should not, however, detract from the efficiency of the scheme, as demonstrated by the good yields obtained in the model aliphatic systems investigated. The

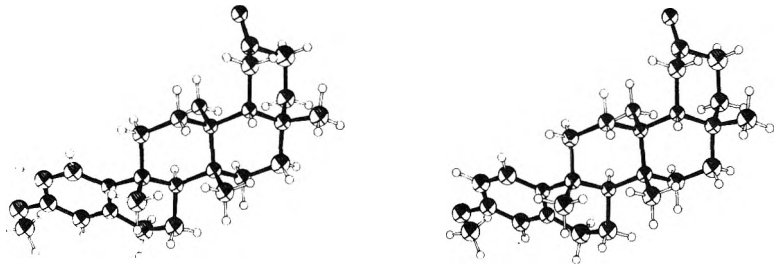

Figure 1. Stereoplot of the ketone 27.

present work serves to underscore the effect of steric congestion on both the cyclization stage and the subsequent, more standard transformations.

Experimental Section[31]

4-Methyl-(*E*)-4,8-nonadienol. A solution of 4.63 g (23.6 mmol) of the ester **2**[14] in 30 ml of dry ether was added over 1 hr to a mixture of 0.90 g (23.6 mmol) of lithium aluminum hydride in 30 ml of dry ether, and the mixture was stirred at room temperature for 12 hr. After decomposition of the excess hydride with water and aqueous base, 3.58 g (99%) of the corresponding alcohol was isolated by ether extraction.[32] Bulb-to-bulb distillation (72°, 0.5 mm) of a portion of this material afforded analytically pure material: ir ($CHCl_3$) 3630 (OH), 1673 (C-4 C=C), 1645, 1010, and 920 cm^{-1} (C-8 C=C); NMR ($CDCl_3$) δ 1.56 (s, 1, OH), 1.63 (s, 3, C-4 CH_3), 3.63 (t, 2, J = 6 Hz, C-1 H_2), 4.8–5.3 (m, 3, C-5 H and C-9 H_2), and 5.6–6.3 (m, 1, C-8 H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.96; H, 11.79.

1-Chloro-4-methyl-(*E*)-4,8-nonadiene. A solution of 2.038 g (13.2 mmol) of the alcohol above and 3.80 g (14.5 mmol) of triphenylphosphine in 10 ml of dry carbon tetrachloride was heated at reflux for 33 hr, during which time approximately 10 ml of volatile distillate was removed. After cooling, the mixture was diluted with 20 ml of petroleum ether, and filtered to remove precipitated triphenylphosphine oxide, and then the crude chloride (2.7 g) was isolated by evaporation of the filtrate at atmospheric pressure. Purification of this material by chromatography on 75 g of silica gel (580 ml of petroleum ether eluent) and then bulb-to-bulb distillation at 75° and 1.75 mm gave 1.688 g (74%) of the corresponding chloride as a colorless liquid which showed one volatile component on GLC (100°): ir ($CHCl_3$) 1670 [CH=C(CH_3)], 1640, 995, and 920 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 1.61 (s, 3, C-4 CH_3), 3.56 (t, 2, J = 6 Hz, C-1 H_2), 4.8–5.3 (m, 3, C-5 H and C-9 H_2), and 5.6–6.3 (m, 1, C-8 H).

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.55; H, 9.92; Cl, 20.52. Found: C, 69.63; H, 9.94; Cl, 20.47.

5-Methyl-(*E*)-5,9-decadienoic Acid (4). The Grignard reagent prepared from 7.55 g (43.7 mmol) of the above chloride and 7.2 g (0.3 g-atom) of magnesium in 60 ml of dry tetrahydrofuran was poured into a slurry of 300 g of Dry Ice in 100 ml of ether, and then the mixture was acidified to pH 2 with 6 *N* aqueous hydrochloric acid. The mixture was extracted with 2 × 10 ml of ether, and the combined ethereal extracts in turn were extracted with 3 × 100 ml of 10% aqueous sodium hydroxide solution. After acidification of the basic extracts to pH 2 and isolation of the crude product by ether extraction,[32] bulb-to-bulb distillation of the residue at 98–101° and 0.15 mm gave 6.96 g (88%) of the acid **4** as a colorless oil that consisted of a single volatile component on GLC (160°): ir ($CHCl_3$) 3400–2750 (bonded OH and CH), 1702 (C=O), 1635, 990, and 910 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 1.60 (s, 3, C-5 CH_3), 4.8–5.3 (m, 3, C-6 H and C-10 H_2), 5.6–6.3 (m, 1, C-9 H), and 10.81 (br s, 1, CO_2H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.57, H, 10.00.

2,5-Dimethyl-(*E*)-5,9-decadienoic Acid. To a solution of lithium diisopropylamide, prepared from 13.4 ml (9.64 g, 0.095 mol) of diisopropylamine and 28 ml (0.088 mol) of a 3.13 *M* hexane solution of *n*-butyllithium in 63 ml of dry tetrahydrofuran, was added with stirring under an argon atmosphere at 0° a solution of 6.94 g (0.038 mol) of the acid **4** in 30 ml of dry tetrahydrofuran. After the reaction solution had stirred for 15 min, 17.2 ml (17.09 g, 0.096 mol) of hexamethylphosphoramide, followed by 3.57 ml (8.16 g, 0.057 mol) of methyl iodide, were added at 0°, and then the mixture was stirred for 2 hr at room temperature. After acidification to pH 2, the organic layer was separated and washed with 5 × 75 ml of 10% aqueous hydrochloric acid solution and then extracted with 4 × 50 ml of 1:1 10% aqueous sodium hydroxide solution and saturated brine. After acidification of the basic extracts and isolation of the product by petroleum ether extraction,[32] purification of the crude product by bulb-to-bulb distillation at 111° and 0.18 mm afforded 7.06 g (95%) of the methylated acid which consisted of a single volatile component on GLC (160°): ir ($CHCl_3$) 3400–2750 (OH and CH), 1700 (C=O), 1640, 990, and 915 cm^{-1} (C=C and CH=CH_2); NMR ($CDCl_3$) δ 1.18 (d, 3, J = 6.5 Hz, C-2 CH_3), 1.61 (s, 3, C-5 CH_3), 4.8–5.3 (m, 3, C-6 H and C-10 H_2), 5.5–6.2 (m, 1, C-9 H), and 11.30 (br s, 1, CO_2H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.26.

2,5-Dimethyl-(*E*)-5,9-decadienal (6). Reduction of 11.68 g (0.06 mol) of the above methylated acid was accomplished with 3.42 g (0.09 mol) of lithium aluminum hydride in 190 ml of dry ether at room temperature for 10 hr. After decomposition of the excess hydride with 8.5 ml of water, followed by the addition of 5 g of magnesium sulfate, filtration of the suspension, and then evaporation of the ether from the filtrate at reduced pressure afforded a colorless liquid which on bulb-to-bulb distillation at 84° and 0.3 mm gave 10.63 g (98%) of the corresponding alcohol: ir ($CHCl_3$) 3620 (OH), 1665 (C=C), 1635, 995, 910 (CH=CH_2), and 1025 cm^{-1} (C–O); NMR ($CDCl_3$) δ 0.92 (d, 3, J = 7 Hz, C-2 CH_3), 160 (s, 3, C-5 CH_3), 3.48 (br d, 2, J = 5 Hz, C-1 H_2), 4.8–5.3 (m, 3, C-6 H and C-10 H_2), and 5.5–6.2 (m, 1, C-9 H).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.15; H, 12.26.

Oxidation[11] of 1.83 g (0.01 mol) of the above alcohol was accomplished with a suspension formed from 6.00 g (0.06 mol) of chromium trioxide and 9.49 g (0.12 mol) of pyridine in 50 ml of dry dichloromethane. After 20 min at room temperature, the mixture was filtered through 25 g of Florisil with the aid of 75 ml of ether, and then the filtrate was concentrated by distillation of most of the solvents through a 12-in. Vigreux column on the steam bath. The aldehyde **6**, isolated from this concentrate by ether extraction[32] and then bulb-to-bulb distillation of the crude product at 80° and 0.75 mm, amounted to 1.68 g (93%) of a colorless liquid which consisted of a single volatile component on GLC (120°): ir ($CHCl_3$) 2720 (CHO), 1720 (C=O), 1655 (C=C), 1640, 995, and 915 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 1.09 (d, 3, J = 7 Hz, C-2 CH_3), 1.61 (s, 3, C-5 CH_3), 4.8–5.4 (m, 3, C-6 H and C-10 H_2), 5.5–6.3 (m, 1, C-9 H), and 9.63 (d, 1, J = 2 Hz, C-1 H).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.93; H, 11.04.

The aldehyde **6** was further characterized as the 2,4-dinitrophenylhydrazone, mp 64–65.5° (from ethanol).

Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.98; H, 6.70; N, 15.62.

2,5,6,9-Tetramethyl-1,(*E*)-5,9-decatriene (5). To a filtered solution of α-methallylmagnesium bromide, prepared from 39 ml (36.2 g, 0.4 mol) of α-methallyl bromide and 38.4 g (1.6 g-atoms) of magnesium in 340 ml of dry tetrahydrofuran, was added over a 5-hr period a solution of 24.2 g (0.1 mol) of the dibromide **3**[13] in 75 ml of dry tetrahydrofuran while the temperature was maintained at 30–35°, and then the mixture was allowed to stir at room temperature for an additional 4 hr. After the addition of 125 ml of a saturated aqueous ammonium chloride solution and then 125 ml of saturated brine, isolation of the crude product by ether extraction[32] afforded a yellow liquid which consisted of two volatile components in a ratio 15:85 by GLC (100°). Distillation of this material through a 6-in. Vigreux column afforded 14.2 g (74%) of the triene **5**, bp 40–46° (0.15 mm), which consisted of >91% of a single volatile component on GLC (100°). The analytical sample, obtained by redistillation of this material through an 18-in. spinning

column, boiled at 64° at 0.85 mm [99% one volatile component on GLC (100°)]: ir ($CHCl_3$) 1645 and 885 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 1.67 (s, 3, C-5 and C-6 CH_3), 1.77 (s, 3, C-2 and C-9 CH_3), 2.10 (s, 4, C-3 and C-4 H_2), 4.72 (br S, 2, C-1 and C-10 H_2).

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.52; H, 12.49.

2,5,6,9-Tetramethyl-(*E*)-5,9-decadienal (7). To a solution of 35 g (0.183 mol) of the triene **5** in 100 ml of dry tetrahydrofuran cooled to 0° was added 0.09 mol of a tetrahydrofuran solution of disiamylborane,[10] and then the mixture was allowed to warm to room temperature and stir for 15 hr. After the mixture was cooled at 0°, it was treated with a solution of 12 g of sodium hydroxide in 40 ml of water, and then with 35 ml of 30% aqueous hydrogen peroxide. Isolation of the crude product by ether extraction[32] and then purification of this material by chromatography on 1200 g of Florisil gave first 20 g (57% recovery) of the triene **5** with 500 ml of petroleum ether. Distillation of the material eluted with 2.5 l. of 40% ether–petroleum ether afforded 10.83 g (28%, 65% based on recovered triene **5**) of the corresponding monoalcohol, bp 111–114° (1.5 mm), which consisted of >95% of a single volatile component on GLC (140°). Evaporative distillation of a portion of this material at 100° and 2.0 mm gave the analytical sample: ir ($CHCl_3$) 3620, 3450, (OH), 1650, and 890 cm^{-1} ($CHCH_2$); NMR ($CDCl_3$) δ 0.93 (d, 3, J = 6 Hz, C-2 CH_3), 1.43 (s, 1, OH), 1.67 (s, 2 × 3, C-5 and C-6 CH_3), 1.75 (br s, 3, C-9 CH_3), 3.48 (d, 2, J = 5.5 Hz, C-1 H_2), and 4.72 (br s, 2, C-10 H_2).

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 80.04; H, 12.51.

To a suspension[11] of 15.04 g (0.04 mol) of pyridinium dichromate in 200 ml of dry dichloromethane was added 1.05 g (0.005 mol) of the above alcohol in 20 ml of dry dichloromethane. After removal of the salts by filtration of the reaction mixture through 10 g of Florisil and concentration of the filtrate by distillation at atmospheric pressure on the steam bath, bulb-to-bulb distillation of the residue at 72–76° and 025 mm afforded 0.98 g (94%) of the aldehyde **7** as a colorless liquid that was >90% of a single volatile component on GLC[31] (140°). The analytical sample was obtained from material of similar purity from another experiment by evaporative distillation at 85° and 0.5 mm: ir ($CHCl_3$) 2720 (CHO), 1720 (C=O), 1650, and 890 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 1.11 (d, 3, J = 6.5 Hz, C-2 CH_3), 1.67 (s, 2 × 3, C-5 and C-6 CH_3), 1.75 (s, 3, C-9 CH_3), 4.72 (br s, 2, C-10 H_2), and 9.67 (d, 1, J = 2 Hz, C-1 H); GLC (140°) >98% single volatile component.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.70; H, 11.62. Found: C, 80.65; H, 11.76.

The aldehyde **7** was further characterized as the 2,4-dinitrophenylhydrazone, mp 102–105° (from ethanol).

Anal. Calcd for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.92; H, 7.11; N, 14.49.

4-Methyl-4-(3′-methyl-(*E*)-3′,7′-octadienyl)-2-cyclohexenone (8). A solution of 4.6 g (0.026 mol) of the aldehyde **6** and 4.4 g (0.06 mol) of pyrrolidine in 175 ml of dry benzene was refluxed under an argon atmosphere under a Dean-Stark water separator for 4 hr, and then the benzene and excess pyrrolidine were removed at reduced pressure. The residue was dissolved in 200 ml of dry benzene under an argon atmosphere, and then 3.57 g (0.05 mol) of methyl vinyl ketone was added. After stirring at room temperature for 2 hr and then at reflux for 17 hr, the mixture was treated with a solution of 1.55 g of sodium acetate in 4.2 ml of glacial acetic acid and 5 ml of water. After 4 hr at reflux, this mixture was diluted with water, and the product was isolated by ether extraction.[32] Evaporative distillation of the residue at 112–115° and 0.15 mm afforded 4.97 g (84%) of the enone **8**. The analytical sample was obtained by a second evaporative distillation of a portion of this material under the same conditions: ir ($CHCl_3$) 1665 (C=O), 1610 (C=C), 995, and 910 cm^{-1} (CH=CH_2); uv (95% ethanol) 226 nm (ϵ 11,200); NMR ($CDCl_3$) δ 1.15 (s, 3, C-4 CH_3), 1.61 (s, 3, C-3 CH_3), 2.46 (t, 2, J = 6.5 Hz, C-6 H), 4.8–5.3 (m, 3, C-4′ H and C-8′ H_2), 5.5–6.2 (m, 1, C-7′ H), 5,86 (d, 1, J = 10 Hz, C-2 H), and 6.68 (d, 1, J = 10 Hz, C-3 H).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.68; H, 10.43. Found: C, 82.59; H, 10.19.

4-Methyl-4-(3′,4′,7′-trimethyl-(*E*)-3′,7′-octadienyl)-2-cyclohexenone (9). By a similar procedure to that described above for the formation of the enone **8**, 1.40 g (7.7 mmol) of the aldehyde **7** was converted first to its enamine with 0.72 g (10 mmol) of pyrrolidine in 55 ml of benzene, and this enamine was then condensed with 0.91 g (13 mmol) of methyl vinyl ketone in 40 ml of dry benzene. After hydrolysis of the reaction mixture with 0.37 g of sodium acetate in 0.75 ml of glacial acetic acid and 0.75 ml of water and then ether extraction,[32] purification of the product was effected by chromatography of the residue on 100 g of silica gel. Elution with 2 l. of benzene afforded 1.36 g of material that consisted of >95% of a single volatile component on GLC (180°) and which on bulb-to-bulb distillation at 116–124° and 0.1 mm afforded 1.16 g (70%) of the enone **9** as a colorless liquid [>98% of a single volatile component on glpc (180°)]: ir ($CHCl_3$) 1665 (C=O), 1610 (C=C), and 885 cm^{-1} (C=CH_2); uv (CH_3OH) 224 nm (ϵ 10,900); NMR ($CDCl_3$), δ1.20 (s, 3, C-4 CH_3), 1.68 (s, 2 × 3, C-3′ and C-4′ CH_3), 1.77 (s, 3, C-7′ CH_3), 4.73 (br s, 2, C-8′ H_2), 5.91 (d, 1, J = 10 Hz, C-2 H), and 6.75 (d, 1, J = 10 Hz, C-3 H).

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.95; H, 10.94.

The enone **9** was further characterized by formation of the semicarbazone, mp 136.5–138° (from 50% ethanol–water).

Anal. Calcd for $C_{19}H_{31}N_3O$: C, 71.88; H, 9.84; N, 13.24. Found: C, 71.85; H, 9.65; N, 13.26.

4-Methyl-4-(3′-methyl-(*E*)-3′,7′-octadienyl)-2-cyclohexenol. The reduction of 3.87 g (16.5 mmol) of the enone **8** was accomplished with 0.314 g (8.2 mmol) of lithium aluminum hydride in 60 ml of dry ether at 0°. After decomposition of the excess hydride with 1.5 ml of water and then addition of 2 g of magnesium sulfate, the mixture was filtered and then the ether was removed from the filtrate at reduced pressure. Evaporative distillation of the residue at 110–112° and 0.1 mm afforded 3.82 g (98%) of the corresponding alcohol as a colorless liquid that consisted of two volatile components (epimeric at C-1) in the ratio of 2:1 on GLC (160°): ir ($CHCl_3$) 3600 (OH), 1640 (C=C), 990, 915 (CH=CH_2), and 1040 cm^{-1} (C–O); NMR ($CDCl_3$) δ 0.96 [s, 1, C-4 CH_3 (C-1 αOH)], 1.01 [s, 2, C-4 CH_3 (C-1 βOH)], 4.0–4.2 (br m, 1, C-1 H), and 4.8–6.4 (m, 6, olefinic H).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.82; H, 11.20.

4-Methyl-4-(3′,4′,7′-trimethyl-(*E*)-3′,7′-octadienyl)-2-cyclohexenol. By the same procedure as that described above for the reduction of the enone **8**, 2.56 g (9.8 mmol) of the enone **9** was reduced at 0° with 190 mg (5 mmol) of lithium aluminum hydride in 55 ml of dry ether. After the same work-up and evaporative distillation of the residue at 110° and 0.1 mm, there was obtained 2.55 (99%) of the corresponding alcohol as a colorless liquid that also consisted of two volatile components in a ratio of 2:1 by GLC (180°): ir ($CHCl_3$) 3600 (OH), 1648, and 885 cm^{-1} (C=C and C=CH_2); NMR ($CDCl_3$) δ 0.96 [s, 1, C-4 CH_3 (C-1 αOH)], 1.01 [s, 2, C-4 CH_3 (C-1 βOH)], 1.63 (s, 2 × 3, C-3′ and C-4′ CH_3), 1.75 (s, 3, C-7′ CH_3), 4.10 (m, 1, $W_{1/2}$ = 12 Hz, C-1 H), 4.70 (s, 2, C-8′ H_2), and 5.63 (m, 2, C-2 H, C-3 H).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 83.20; H, 11.48.

Cyclization of 4-Methyl-4-(3′-methyl-(*E*)-3′,7′-octadienyl)-2-cyclohexenol. A. 8aβ,10aβ-Dimethyl-1,4,4aα,4bβ,7,8,8a,9,-10,10a-decahydrophenanthrene and 8aβ,10aβ-Dimethyl-3,4,4aα,4bβ,7,8,8a,9,10,10a-decahydrophenanthrene (10). To a solution of 117 mg (0.5 mmol) of the alcohol from ketone **8** and 6 ml of ethylene carbonate in 2 ml of dry dichloromethane was added 350 μl of stannic chloride, and the red mixture was stirred for 1 hr at 25°. The mixture was then poured into a solution of 25 g of potassium carbonate in 50 ml of methanol. After the color disappeared, sufficient methanol was added to form one phase, and then the solution was stirred at room temperature for 10 hr. After isolation of the product by ether extraction,[32] there was obtained 117 mg of a yellow oil, the GLC (150°) of which consisted of two overlapping peaks (corresponding to the tricyclic dienes **10**) that comprised ca. 75% of the volatile material. In addition to several less volatile components in minor amounts, a more volatile series of peaks that comprised ca. 15% of the volatile material corresponded to the chlorocarbon mixture **20**.

Purification of this crude mixture by chromatography on 25 g of silica gel afforded 61 mg (56%) of a mixture of the dienes **10** with 60 ml of petroleum ether eluent as a colorless oil that consisted of >99% of these two partially resolved components on GLC (150°). The analytical sample was obtained by evaporative distillation of this material at 60–64° and 0.3 mm: ir ($CHCl_3$) 1655 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.81, 0.91 (2 × s, 3 each, C-8a and C-10a CH_3), and 5.33–5.95 (m, 4, vinyl H).

Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.76; H, 11.17.

Continued elution of the column with 20 ml of petroleum ether gave 5 mg (4%) of the epimeric chlorocarbons **20**. This material was identified by comparison of the ir, NMR, and GLC (150°) spectral data of this sample with those of an authentic sample prepared in

an alternate experiment (see Table I). Material from the latter procedure was used for analytical purposes after bulb-to-bulb distillation at 75° and 0.075 mm; ir ($CHCl_3$) 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.85, 0.90 (2 s, experiment (see Table I). Material from the latter procedure was used for analytical purposes after bulb-to-bulb distillation at 75° and 0.075 mm; ir ($CHCl_3$) 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.85, 0.90 (2 s, 3 each, C-8a and C-10a CH_3), 3.75–4.75 (br m, 1, CHCl), and 5.33–6.00 (m, 2, CH=CH).

Anal. Calcd for $C_{16}H_{25}Cl$: C, 76.00; H, 9.96; Cl, 14.02. Found: C, 75.84; H, 9.74; Cl, 13.96.

B. Variation of Product Composition with Solvent. In Table I are compiled the results of the cyclization of the alcohol from the ketone 8 in various solvents and conditions. The general procedure used was identical with that described in part A except for the variations noted in Table I. Identification of the solvent-trapped compounds isolated is presented below.

8aβ,10aβ-Dimethyl-7-phenyl-1,2,4aβ,4bα5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene (19): oil, evaporative distillation at 121–124° (0.1 mm); ir ($CHCl_3$) 1601 and 1495 cm^{-1} (C_6H_5); NMR (CCl_4) δ 0.90, 0.96 (2 s, 3 each, C-8a and C-10a CH_3), 2.46–2.93 (m, 1, C-7 H), 5.16–5.83 (m, 2, C-3 and C-4 H), and 7.08 (s, 5, ArH); MS (70 eV) *m/e* 294 (M^+).

Anal. Calcd for $C_{22}H_{30}$: C, 89.73; H, 10.27. Found: C, 89.97; H, 10.20

8aβ,10aβ-Dimethyl-7-(2′,2′,2′-trifluoroethoxy)-1,2,4aβ,4bα,-5,6,7,3,8a,9,10,10a-dodecahydrophenanthrene (21): oil, evaporative distillation at 107° (0.075 mm); ir ($CHCl_3$) 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.83, 1.01 (2 s, 3 each, C-8a and C-10a CH_3), 3.83 (q, 2, J = 9 Hz, CH_2CF_3), 3.65 (m, 1, C-7 H), and 5.36–5.80 (m, 2, C-3 and C-4 H).

Anal. Calcd for $C_{18}H_{27}F_3O$: C, 68.32; H, 8.60; F, 18.01. Found: C, 68.45; H, 8.70; F, 18.09.

8aβ,10aβ-Dimethyl-7-(2′- and 4′-methoxyphenyl)-1,2,4aβ,-4bα,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene (22): oil, evaporative distillation at 145° (0.05 mm); ir ($CHCl_3$) 1580–1610 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.80–1.13 (br s, 6, angular CH_3), 3.76, 3.80 (2 s, 3, OCH_3), 5.36–6.03 (m, 2, C-3 and C-4 H), and 6.73–7.36 (m, 4, ArH); MS (70 eV) *m/e* 324 (M^+).

Anal. Calcd for $C_{23}H_{32}O$: C, 85.13; H, 9.94. Found: C, 85.11; H, 9.97.

The dienes **23** were analyzed as their perhydro derivatives formed by hydrogenation of the mixture in hexane over 10% palladium on carbon. On preparative TLC (1:1 ether–benzene) of the saturated products, the mixture could be separated into two components that consisted of the *o*-methoxyphenyl derivatives (R_f 0.7) and the *p*-methoxyphenyl isomers (R_f 0.6).

***cis*- and *trans*-4-(2′-Methoxyphenyl)-1-methyl-1-(3′-methylloctyl)cyclohexane:** oil, evaporative distillation at 160° (0.06 mm); ir ($CHCl_3$) 1612 and 1585 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.80–1.13 (br s, 6, methyl groups), 3.83 (s, 3, OCH_3), and 6.73–7.06 (m, 4, ArH).

Anal. Calcd for $C_{23}H_{38}O$: C, 83.59; H, 11.59. Found: C, 83.56; H, 11.70.

***cis*- and *trans*-4-(4′-Methoxyphenyl)-1-methyl-1-(3′-methyloctyl)cyclohexane:** oil, evaporative distillation at 160° (0.06 mm); ir ($CHCl_3$) 1612 and 1585 cm^{-1} ($ArOCH_3$); NMR ($CDCl_3$) δ 0.80–1.13 (br s, 6, methyl groups), 3.80 (s, 3, OCH_3), 7.12 (d, 2, J = 8 Hz, C-3′ and C-5′ H), and 7.33 (d, 2, J = 8 Hz, C-2′ and C-6′ H).

Anal. Calcd for $C_{23}H_{38}O$: C, 83.59; H, 11.59. Found: C, 83.57; H, 11.62.

1-*m*-Methoxyphenyl-*trans*-spiro[2.5]octan-4-one (13). Reduction of 4.03 g (0.019 mol) of the unsaturated ketone **12**[18] was accomplished with 7.07 g (0.019 mol) of sodium borohydride in 175 ml of methanol, and after bulb-to-bulb distillation of the crude product at 123° and 0.1 mm, there was obtained 3.65 (90%) of the corresponding allylic alcohol as a colorless oil which was homogeneous by TLC ($CHCl_3$, R_f 0.08): ir (CCl_4) 3620 (OH) and 1665 cm^{-1} (C=C); NMR (CCl_4) δ 3.71 (s, 3, OCH_3), 410 (br m, 1, C-1 H), and 6.31–7.43 (m, 5, C=CH– and ArH).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.99; H, 8.22.

A solution of 3.75 g (0.017 mol) of the above allylic alcohol in 25 ml of dry ether was added to 250 ml of an ethereal solution of iodomethylzinc iodide[20] prepared from 22.3 ml (73.7 g, 0.275 mol) of diiodomethane and 18 g of zinc–copper couple,[20] and the mixture was stirred under an argon atmosphere for 4 hr. After the addition of 25 ml of saturated aqueous ammonium chloride solution, the product was isolated by ether extraction[32] and then chromatographed on 300 g of neutral alumina (activity III). After elution with 100 ml each of 2, 5, 10, 25, and 50% ether–petroleum ether, 500 ml of ether eluted 3.92 g (98%) of the cyclopropyl alcohol as a colorless oil which consisted of a single volatile component on GLC (200°). The analytical sample was obtained by evaporative distillation of a portion of this material at 110–114° and 0.1 mm: ir ($CHCl_3$) 3600 (OH) and 3050 cm^{-1} (cyclopropyl CH); NMR (CCl_4) δ 0.53–0.95 (m, 2, cyclopropyl CH_2), 1.91–2.25 (m, 1, cyclopropyl, benzyl CH), 3.21–3.48 (m, 1, CHOH), 3.75 (s, 3, OCH_3), and 6.45–7.31 (m, 4, ArH).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.80.

Oxidation of this cyclopropyl alcohol was accomplished routinely on a small scale by titration of an acetone solution with 8 *N* aqueous chromic acid solution.[24] Thus, oxidation of 2.61 mg (1.12 mmol) of the alcohol in 15 ml of acetone afforded 186 mg (72%) of the ketone **13** as a colorless liquid [evaporative distillation at 104–108° (0.1 mm)] that consisted of a single volatile component on GLC (200°): ir (CCl_4) 3050 (cyclopropyl CH) and 1685 Cm^{-1} (C=O); NMR (CCl_4) δ 0.72–1.06 (m, 2, cyclopropyl CH_2), 2.16–2.76 (m, 3, cyclopropyl, benzyl CH, and CH_2CO), 3.76 (s, 3, OCH_3), and 6.51–7.35 (m, 4, ArH).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.37; H, 7.94.

2-(2′-*m*-Methoxyphenylethyl)-2-methylcyclohexanone (14). To a solution of 40 mg (5.7 mg-atom) of lithium in 15 ml of dry ammonia was added a solution of 178 mg (0.77 mmol) of the cyclopropyl ketone **13** and 94 μl (74 mg, 1 mmol) of dry *tert*-butyl alcohol in 5 ml of glyme. The mixture was stirred under a nitrogen atmosphere for 45 min and then 180 μl (179 mg, 1 mmol) of hexamethylphosphoramide was added. The ammonia was then evaporated in a stream of nitrogen, and then a solution of 1 ml of methyl iodide in 18 ml of dry glyme was added all at once with vigorous stirring. After stirring at room temperature for 1 hr, the mixture was treated with 80 ml of water, and the product was isolated by ether extraction,[32] including both an acid and base wash. Purification of the crude product (179 mg) by chromatography on 20 g of silica gel afforded 109 mg (57%) of the ketone **14** as a colorless oil by elution with 850 ml of 50% ether–benzene. The analytical sample was obtained by evaporative distillation of this material at 115–116° and 0.1 mm: ir (CCl_4) 1700 cm^{-1} (C=O); NMR (CCl_4) δ 1.08 (s, 3, C-2 CH_3), 3.73 (s, 3, OCH_3), and 6.46–7.26 (m, 4, ArH).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.11; H, 9.00.

2-Methoxy-8a-methyl-6,7,8,8a,9,10-hexahydrophenanthrene. To a solution of 246 mg (1 mmol) of the ketone **14** in 2.5 ml of dry benzene was added 75 ml of freshly prepared polyphosphoric acid,[33] and the mixture was heated at 50° for 1 hr. The reaction mixture was then poured onto 450 g of ice in water with stirring, and the product was isolated by benzene extraction,[32] including a base wash. Chromatography of the crude product on 25 g of silica gel afforded 208 mg (91%) of the tricyclic olefin, mp 63–65°, by elution with 500 ml of 1% ether–petroleum ether. The analytical sample, obtained by crystallization of a portion of this material from methanol, melted at 69–69.5°: ir ($CHCl_3$) 1635 cm^{-1} (C=C); NMR (CCl_4) δ 1.00 (s, 3, C-8a CH_3), 3.75 (s, 3, CH_3), 5.91 (br t, 1, J = 3.5 Hz, C-5 H), 6.16 (d, 1, $J_{1,3}$ = 2 Hz, C-1 H), 6.70 (d of d, 1, $J_{3,4}$ = $J_{1,3}$ = 2 Hz, C-3 H), 7.43 (d, 1, $J_{3,4}$ = 7 Hz, C-4 H).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.01; H, 8.80.

2-Methoxy-8aβ-methyl-4bα,5,6,7,8,8a,9,10-octahydrophenanthrene (15). A solution of 173 mg (0.75 mmol) of the tricyclic olefin above in 32 ml of hexane containing 50 mg of 10% palladium on carbon as stirred in a hydrogen atmosphere at room temperature and atmospheric pressure for 22 hr. After the catalyst was removed by filtration and the solvent was removed from the filtrate at reduced pressure, bulb-to-bulb distillation of the residue at 98° and 0.08 mm afforded 167 mg (96%) of a colorless liquid which consisted of two volatile components on GLC (200°) in a ratio of 92:8. A sample of the major component—the tricyclic ether **15**—was obtained by preparative GLC (200°) and analytical GLC (200°) showed a single volatile component in >99% yield: ir (CCl_4) 1610 and 1575 cm^{-1} (C=C, Ar); NMR (CCl_4) δ 0.71 (s, 3, C-8a CH_3), 3.70 (s, 3, OCH_3), 6.50 (d, 1, $J_{1,3}$ = 2 Hz, C-1 H), 6.55 (d of d, 1, $J_{1,3}$ = 2, $J_{3,4}$ = 9 Hz, C-3 H), and 6.98 (d, 1, $J_{3,4}$ = 9 Hz, C-4 H); $\Delta_{1,4}$ = 0.54 ppm (trans isomer).[23]

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.35; H, 9.52.

8aβ-Methyl-4,4aβ,4bα,5,6,7,8,8a,9,10-decahydro-2(3*H*)-phenanthrenone (16). A solution of 167 mg (0.73 mmol) of a 92:8 mixture of the trans/cis isomers of the tricyclic ether **15** and 20 ml of dry *tert*-butyl alcohol in 25 ml of dry tetrahydrofuran was

added over 10 min to a solution of 240 mg (34 mg-atoms) of lithium in 62 ml of dry ammonia under a nitrogen atmosphere. The blue mixture was stirred for 3.5 hr, and then 25 ml of methanol was added to discharge the blue color. After the ammonia was removed in a stream of nitrogen on the steam bath, the residue was diluted with water, and the product was isolated by benzene extraction.[32] The resulting crude product was dissolved in 130 ml of methanol; 55 ml of 5 *N* hydrochloric acid solution was added, and then the mixture was heated under reflux for 2 hr. After dilution of the mixture with 200 ml of saturated brine, the product was isolated by benzene extraction,[32] including a base wash. Crystallization of the residue from ether–hexane afforded 105 mg (74%) of the enone **16** in two crops of 91 mg (mp 125–128°) and 14 mg (mp 120–123°), both of which consisted of a single volatile component on GLC (200°). The analytical sample, obtained after one further crystallization of a portion of the first crop material from ether–hexane, melted at 126–128° (lit.[22] mp 125–127°): ir ($CHCl_3$) 1660 (C=O) and 1615 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.98 (s, 3, C-8a CH_3) and 5.86 (br s, 1, C-1 H); uv (CH_3OH) 243 nm (ϵ 14,400).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.58, H, 10.07.

8aβ,10aβ-Dimethyl-3,4,4aβ,4bα,5,6,7,8,8a,9,10,10a-dodecahydro-2-phenanthryl *N,N,N′N′*-Tetramethyldiamidophosphorodiamidate (17). A solution of 55 mg (0.25 mmol) of the enone **16** in 4 ml of dry ether was added dropwise over 15 min to a solution of lithium dimethylcuprate, prepared from 625 μl (1.25 mmol) of a 2 *M* ethereal methyllithium solution and 119 mg (0.625 mmol) of copper(I) iodide in 6 ml of dry ether. After the mixture was stirred under a nitrogen atmosphere for 2 hr at 0°, 0.2 ml of hexamethylphosphoramide was added, and then a solution[28] of 0.4 ml of *N,N,N′,N′*-tetramethyldiamidophosphorochloridate in 1 ml of dry ether was added dropwise over 5 min. After stirring for 2.5 hr at room temperature, the mixture was diluted with 50 ml of dilute aqueous ammonium hydroxide solution, and the product was isolated by ether extraction, including both an acid and base wash. Chromatography of the residue (87 mg) on 10 g of silica gel (ether, 100 ml, followed by 3:2 ether–ethyl acetate, 150 ml) afforded a colorless oil which on evaporative distillation at 117° and 0.06 mm gave 76 mg (86%) of the phosphoradiamidate **17** which consisted of >97% of a single volatile component on GLC (230°): ir ($CHCl_3$) 1675 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.81 (s, 3, C-8a CH_3), 1.06 (s, 3, C-10a CH_3), 2.68 (d, 12, J = 10 Hz, NCH_3), and 5.03 (br s, 1, C-1 H).

Anal. Calcd for $C_{20}H_{37}N_2O_2P$: C, 65.18; H, 10.12; N, 7.60; P, 8.40. Found: C, 65.05; H, 10.06; N, 7.52; P, 8.31.

8aβ,10aβ-Dimethyl-3,4,4aβ,4bα,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene. To a solution of 25 mg (3.6 g-atoms) of lithium in 40 ml of dry ethylamine was added a solution of 69 mg (0.19 mmol) of the phosphorodiamidate **17** and 0.1 ml of dry *tert*-butyl alcohol in 6 ml of dry tetrahydrofuran, and the reaction mixture was stirred under a nitrogen atmosphere for 2.5 hr. After the addition of 10 ml of ethanol, the ethylamine was removed in a stream of nitrogen, and the mixture was then diluted with 50 ml of water. After isolation of the product by petroleum ether extraction,[32] including an acid and base wash, and then filtration of the residue through 2 g of silica gel with petroleum ether, bulb-to-bulb distillation of the resulting oil at 74° and 0.55 mm afforded 35 mg (83%) of colorless liquid which consisted of a single volatile component on GLC (170°): ir ($CHCl_3$) 1645 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.83 (s, 3, C-8a CH_3), 1.05 (s, 3, C-10a CH_3), 5.26 (d, 1, $J_{1,2}$ = 7 Hz, C-1 H), and 5.63 (d of m, 1, $J_{1,2}$ = 7 Hz, C-2 H).

Anal. Calcd for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 87.96; H, 11.90.

8aβ,10aβ-Dimethyl-4aβ,4bα-perhydrophenanthrene (18). A. From the Tricyclic Dienes 10. A solution of 49 mg (0.23 mmol) of the dienes **10** in 5 ml of ethanol in which was suspended 10 mg of 10% palladium on carbon was stirred in an atmosphere of hydrogen at room temperature and atmospheric pressure for 1 hr. After removal of the catalyst and then evaporation of the ethanol at reduced pressure, the residue (48 mg) was chromatographed on 1.5 g of silica gel impregnated with 10% silver nitrate. Elution with 15 ml of petroleum ether and then bulb-to-bulb distillation (73–75° at 0.35 mm) of the residue remaining after solvent evaporation afforded 40 mg (80%) of the hydrocarbon **18** as a colorless oil: ir (neat) 2950, 1450 (CH), and 1375 cm^{-1} (CH_3); NMR ($CDCl_3$) δ 0.73 and 1.00 (2 s, 3 each, C-8a and C-10a CH_3).

Anal. Calcd for $C_{16}H_{28}$: C, 87.19; H, 12.81. Found: C, 87.22; H, 13.00.

The properties [TLC, GLC (170°), ir, NMR] of this material were identical with those of the authentic sample prepared below.

B. From the Tricyclic Olefin. A solution of 30 mg (0.14 mmol) of the tricyclic olefin prepared above in 8 ml of hexane in which was suspended 10 mg of 10% plladium on carbon was stirred in an atmosphere of hydrogen as above in part A for 5 hr. After the same work-up there resulted 30 mg (100%) of the hydrocarbon **18** which showed idntical ir (neat), TLC (petroleum ether), and NMR ($CDCl_3$) with the material prepared in part A and on GLC (170°) the two samples were indistinguishable by peak enhancement.[35]

Cyclization of 4-Methyl-4-(3′,4′,7′-trimethyl-(*E*)3′,7′-octadienyl)-2-cyclohexenol. A solution of 198 mg (0.76 mmol) of the alcohol from the ketone **9** in 85 ml of dry dichloromethane was cooled to −78°, and then 150 μl of stannic chloride was added. After stirring at −78° for 1 hr, the mixture was warmed to −6° in an ice–salt bath, and stirring was continued for 0.5 hr. The mixture was then poured into 50 ml of water and 15 g of potassium carbonate, and after stirring for 0.5 hr, the layers were separated and the aqueous layer was extracted twice with 30-ml portions of dichloromethane. After the combined organic layers were washed with water and then dried ($MgSO_4$), evaporation of the solvent at reduced pressure afforded 199 mg of a colorless oil. On GLC (180°) this oil consisted of seven volatile components, one of which comprised ca. 75% of the material. On chromatography of this product on 55 g of silica gel, the first 50 ml of petroleum ether eluted 41 mg of material judged to contain >75% of the major component on GLC (180°), and then 35 mg (19%) of material that consisted of >98% of the single major volatile component on GLC (180°) was eluted with an additional 155 ml of the same eluent. Rechromatography on neutral alumina (activity I) (petroleum ether) or preparative[34b] GLC (200°, retention time 17.6 min) of the first 41-mg fraction afforded additional quantities of the major component in >99% homogeneity by GLC (180°). The total isolated yield of this major component, **2,4aα,8aβ,10aβ-tetramethyl-1,4,4a,4bβ,7,8,-8a,9,10,10a-decahydrophenanthrene (11),** by these procedures was 58 mg (32%).

The analytical sample, prepared by evaporative distillation of the material at 102° and 0.6 mm, solidified on storage at −20° and melted at 44–47°: ir ($CHCl_3$) 1670–1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.83 (s, 3) and 0.91 (s, 2 × 3) (C-4a, C-8a, and C-10a CH_3), 1.67 (br d, 3, J = 3 Hz, C-2 CH_3), 5.28 (m, 1, $W_{1/2}$ = 7.5 Hz, C-3 H), and 5.56–5.96 (m, 2, C-5 and C-6 H).

Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.55; H, 11.42.

12-*m*-Methoxyphenyl-2,5,6,9-tetramethyl-(*E,E*)-5,9-dodecadienoic Acid. To a solution of lithium diisopropylamide [prepared from 1.44 ml (1.045 g, 10.35 mmol) of dry diisopropylamine and 4.31 ml (9.28 mmol) of a 2.13 *M* hexane solution of *n*-butyllithium] in 6 ml of dry tetrahydrofuran under an argon atmosphere was added at −5 to 2° 1.424 g (4.14 mmol) of **12-*m*-methoxyphenyl-5,6,9-trimethyl-(*E,E*)-5,9-dodecadienoic acid,** which was obtained in 88% overall yield by Collins[11] and then silver oxide oxidation of the alcohol **24**, and was an oil [evaporative distillation at 184° (0.0005 mm)]: ir ($CHCl_3$) 3400–2800 (CH and bonded OH) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.60 (masked d, 3, C-9 CH_3), 1.63 (s, 2 × 3, C-5 and C-6 CH_3), 3.80 (s, 3, OCH_3), 5.21 (br t, 1, J = 9 Hz, C-10 H), and 6.61–7.41 (m, 4, ArH). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.79; H, 9.38. After 15 min 1.04 ml of hexamethylphosphoramide and then 0.37 ml (0.85 g, 6 mmol) of dry methyl iodide were added, and the resulting mixture was stirred at 23° for 1.5 hr. Isolation of the product by ether extraction,[32] including an acid wash, afforded 1.43 g (97%) of the methylated acid as an oil that was not further purified but used directly in the following experiment. An analytical sample was obtained by evaporative distillation of a portion of this material at 178° and 0.0005 mm: ir ($CHCl_3$) 3450–2620 (CH and bonded OH) and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.21 (d, 3, J = 7 Hz, C-2 CH_3), 1.60 (masked d, 3, C-9 CH_3), 1.63 (s, 2 × 3, C-5 and C-6 CH_3), 3.80 (s, 3, OCH_3), 5.20 (br t, 1, J = 6.5 Hz, C-10 H), and 6.61–7.41 (m, 4, ArH).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.16; M, 9.61.

12-*m*-Methoxyphenyl-2,5,6,9-tetramethyl-(*E,E*)-5,9-dodecadienal. The reduction and oxidation of the above methylated acid was accomplished in the same manner as that described above for the formation of the aldehyde **6**. Thus, reduction of 1.41 g (3.96 mmol) of the above carboxylic acid with 228 mg (6 mmol) of lithium aluminum hydride in 25 ml of dry ether afforded 1.27 g (94%) of the corresponding alcohol which consisted of >93% of a single volatile component on GLC (280°) after chromatography on 100 g of Florisil with 1.1 l. of 20% ether–petroleum ether. The analytical sample was obtained by bulb-to-bulb distillation of a portion of

this material at 160° and 0.0008 mm: ir ($CHCl_3$) 3620 (OH) and 1670 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.95 (d, 3, J = 6 Hz, C-2 CH_3), 1.38 (s, 1, OH), 1.60 (d, 3, J = 1.5 Hz, C-9 CH_3), 1.65 (s, 2 × 3, C-5 and C-6 CH_3), 3.52 (d, 2, J = 5 Hz, C-1 H_2), 3.83 (s, 3, OCH_3), 5.23 (t, 1, J = 6 Hz, C-10 H), and 6.61–7.41 (m, 4, ArH).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.05; H, 10.62.

Oxidation of 250 mg (0.73 mmol) of this alcohol with a solution of chromium trioxide–dipyridine complex[11] [prepared from 500 mg (5 mmol) of chromium trioxide and 796 μl (791 mg, 10 mmol) of pyridine] in 14.5 ml of dry dichloromethane afforded 227 mg (92%) of the methylated aldehyde as an oil which consisted of >97% of a single volatile component on GLC (280°) after evaporative distillation at 153° and 0.001 mm: ir ($CHCl_3$) 2720 (CHO), 1725 (C=O), and 1370 cm^{-1} (C=C); NMR ($CHCl_3$) δ 1.11 (d, 3, J = 6 Hz, C-2 CH_3), 1.60 (d, 3, J = 1.5 Hz, C-9 CH_3), 1.63 (s, 2 × 3, C-5 and C-6 CH_3), 3.80 (s, 3, OCH_3), 5.20 (t, 1, J = 5.5 Hz, C-10 H), 6.61–7.41 (m, 4, ArH), and 9.65 (d, 1, J = 2 Hz, C-1 H).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.67; H, 10.10.

4-Methyl-4-(10′-*m*-methoxyphenyl-3′,4′,7′-trimethyl-(*E,E*)-3′,7′-decadienyl)-2-cyclohexenone (25). By a similar procedure to that described above for the formation of the enone **8**, the enamine of the above aldehyde [prepared from 1.40 g (4.1 mmol) of the aldehyde and 453 μl (386 mg, 5.44 mmol) of dry pyrrolidine by heating for 2.5 hr in 50 ml of dry benzene under a Dean-Stark water separator] and 622 μl (538 mg, 7.68 mmol) of methyl vinyl ketone in 50 ml of dry benzene was heated under reflux for 17 hr, and then a solution of 0.25 g of sodium acetate and 0.5 ml of water in 0.5 ml of glacial acetic acid was added, whereupon heating was continued for an additional 4 hr. Chromatography of the crude product on 160 g of silica gel afforded 1.48 g (92%) of the enone **25** with 1 l. of 16% ether–petroleum ether after forefractions of 1 (100 ml), 2 (100 ml), 4 (100 ml), 8 (1800 ml), and 12 (750 ml) of ether–petroleum ether. This material consisted of >94% of a single volatile component on GLC (290°). The analytical sample was obtained by evaporative distillation at 194° and 0.0025 mm: ir ($CHCl_3$) 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.16 (s, 3, C-4 CH_3), 1.60 (d, 3, J = 1.5 Hz, C-7′ CH_3), 1.63 (s, 2 × 3, C-3′ and C-4′ CH_3), 3.80 (s, 3, OCH_3), 5.21 (t, 1, J = 6 Hz, C-8′ H), 5.90 (d, 1, J = 10 Hz, C-2 H), 6.73 (d, 1, J = 10 Hz, C-3 H), and 6.63–7.50 (m, 4, ArH).

Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 82.25; H, 9.69.

4-Methyl-4-(10′-*m*-methoxyphenyl-3′,4′,7′-trimethyl-(*E,E*)-3′,7′-decadienyl)-2-cyclohexenol. Reduction of 2.10 g (5.3 mmol) of the enone **25** with 103 mg 2.7 mmol) of lithium aluminum hydride in 45 ml of dry ether at 0° afforded 2.09 g (99%) of the corresponding allylic alcohol as an oil that decomposed on GLC, but showed one spot on TLC (50% ether–petroleum ether). The analytic sample was prepared by evaporative distillation of a porton of this material at 205° and 0.001 mm: ir ($CHCl_3$) 3590 (OH), 1670, and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.96 (s, 0.4 × 3, C-4 CH_3 in αC-1 OH), 1.01 (s, 0.6 × 3, C-4 CH_3 in βC-1 OH), 1.60 (d, 3, J = 1.5 Hz, C-7′ CH_3), 1.63 (s, 2 × 3, C-3′ and C-4′ CH_3), 3.80 (s, 3, OCH_3), 4.16 (m, 1, C-1 H), 5.20 (t, 1, J = 5 Hz, C-8′ H), 5.60 (m, 2, C-2 and C-3 H), and 6.61–7.40 (m, 4, ArH).

Anal. Calcd for$C_{22}H_{40}O_2$: C, 81.77; H, 10.17. Found: C, 81.68; H, 10.16

3-Methoxy-6bβ,8aβ,12bα,14aβ-tetramethyl-5,6,6aα,6b,7,8,-8a,9,10,12aβ,12b,13,14,14a-tetradecahydropicene (26). To a solution of 240 mg (0.61 mmol) of the above allylic alcohol in 24 ml of dry dichloromethane cooled to −63.5° (cryostatic chloroform bath) was added 13.5 ml of a 0.1 M dichloromethane solution of stannic chloride precooled to −63.5°, followed 30 sec later by 40 μl of dimethyl carbonate. After stirring for 15 min, the mixture was poured into 75 ml of 20% aqueous potassium hydroxide solution, and then the product was isolated by ether extraction.[32] Chromatography of the crude product (240 mg) on 20 g of silica gel afforded 112 mg of a mixture [GLC (300°) showed four major volatile components in a ratio of 2:1:2:6] with 150 ml of 10% ether–petroleum ether. Rechromatography (25% benzene–petroleum ether, 40 ml) of this material on 14 g of silica gel impregnated with 10% silver nitrate gave 38 mg in which the last major volatile component represented 85% of the mixture on GLC (300°). Trituration of this mixture in ether at −20° gave 28 mg (12%) of the pentacyclic olefin **26**, mp 185–188°, which consisted of >98% of a single volatile component on GLC (300°). The analytical sample, obtained after crystallization of this material from ether–dichloromethane and then ether–hexane, melted at 186–190°: ir ($CHCl_3$) 1655 (w, C=C), 1602, and 1575 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.90. 0.93, 1.05, 1.21 (4 s, 3 each, C-6b, C-8a, C-12b, and C-14a CH_3), 2.66–3.13 (m, 2, C-5 H_2), 3.75 (s, 3, OCH_3), 5.60–5.80 (m, 2, C-11 and C-12 H), and 6.50–7.30 (m, 3, ArH).

Anal. Calcd for $C_{27}H_{38}O$: C, 85.66; H, 10.12. Found: C, 85.66; H, 10.25.

3-Methoxy-6bβ,8aβ,12bα,14aβ-tetramethyl-5,6,6aα,6b,7,8,-8a,9,10,11,12,12aβ,12b,13,14,14a-hexadecahydro-11β-picenol. To a solution of 59 mg (0.16 mmol) of the pentacyclic olefin **26** in 1.5 ml of dry tetrahydrofuran cooled to 0° under an argon atmosphere was added 1.5 ml of an 0.85 M tetrahydrofuran solution of diborane, and the mixture was stirred for 9 hr. After decomposition of the excess diborane with 0.75 ml of water, the mixture was treated with 3 ml of 20% aqueous sodium hydroxide solution and 3 ml of 30% hydrogen peroxide, and the resulting solution was allowed to stir at room temperature for 4 hr. After isolation of the product by ether extraction,[32] the residue (75 mg) was separated into two components by preparative TLC (40% ether–petroleum ether): band A (R_f 0.3, 18 mg, 22%) and band B (R_f 0.2, 48 mg, 77%).

Crystallization of the material from band B from acetone afforded 40 mg (64%) of the 11β-alcohol: mp 190–192.5°; ir ($CHCl_3$) 3600 (OH), 1602, and 1575 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.96, 1.00, 1.11, 1.20 (4 s, 3 each, C-6b, C-8a, C-12b, and C-14a CH_3), 2.66–3.16 (m, 2, C-5 H_2), 3.75 (s, 3, OCH_3), 3.93 (m, 1, $W_{1/2}$ = 22 Hz, C-11 H), and 6.46–7.30 (m, 3, ArH).

Anal. Calcd for $C_{27}H_{40}O_2$: C, 81.77; H, 10.17. Found: C, 81.78; H, 9.97.

The material in band A was not further purified but was judged to be the corresponding 12β (axial) alcohol from the regeneration of the olefin **26** by treatment with phosphorus oxychloride in pyridine and the spectra: ir ($CHCl_3$) 3600 (OH), 1602, and 1575 cm^{-1} (Ar); NMR ($CDCl_3$) δ 0.98, 1.00, 1.20, 1.25 (4 s, 3 each, C-6b, C-8a, C-12b, and C-14a CH_3), 2.66–3.16 (m, 2, C-5 H_2), 3.76 (s, 3, OCH_3), 4.23 (m, 1, $W_{1/2}$ = 7 Hz, C-12 H), and 6.46–7.44 (m, 3, ArH).

10-Methoxy-4aβ,6bα,12bβ,14aα-tetramethyl-3,4,4a,5,6,6a,-6bα,7,8,12b,13,14,14a,14bβ-tetradecahydro-2(1*H*)-picenone (27). A solution of 75 mg (0.19 mmol) of the 11β-alcohol above in 8 ml of dry acetone cooled to 0° was treated with excess 8 N aqueous chromic acid solution[24] (persistent brown-yellow coloration) and then stirred for 15 min. After decomposition of the excess oxidant with isopropyl alcohol, the product was isolated by ether extraction.[32] On crystallization of the residue from acetone there resulted 68 mg (92%) of the ketone **27**, mp 200.5–204.5°, which showed one spot on TLC (20% ether–petroleum ether, R_f 0.2). The analytical sample, obtained after one further crystallization from acetone, also melted over the same range: ir ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.83, 1.00, 1.20, 1.26 (4 s, 3 each, C-4a, C-6a, C-12b, and C-14a CH_3), 2.20–2.56 (m, 4, C-1 and C-3 H_2), 2.66–3.20 (m, 2, C-8 H_2), 3.73 (s, 3, OCH_3), and 6.46–7.26 (m, 3, ArH).

Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 82.03; H, 9.68.

X-Ray Structure of 3,4,4a,5,6,6a,6bβ,7,8,12b,13,14,14a,-14bα Tetradecahydro-10-methoxy-4bα,6aα,12bα,14aβ-tetramethyl-2(1*H*)-picenone (1). Unit cell dimensions were obtained from least-squares refinement of the 2θ angles of 36 reflections measured on a Datex automated General Electric diffractometer. Unit cell parameters are a = 50.1255 ± 0.0016 Å; b = 7.5886 ± 0.0003 Å; c = 11.4010 ± 0.0004 Å; β = 90.504 ± 0.002°.

The absence of hkl reflections for $h + k$ odd and hl for h odd indicated that the space group is $C2/C$. The crystal density was found to be 1.23 ± 0.02 g cm^{-3}. The calculated density is 1.21 g cm^{-3} for eight molecules of molecular weight 394.603 per unit cell.

Intensity data were collected by the θ–2θ scan method with iron-filtered Co Kα radiation (λ 1.79021 Å). Reflections were collected to a maximum value of 2θ = 135° with a scan rate in 2θ of 2° min^{-1}. Three reflections monitored at regular intervals during the data collection showed no significant variation in intensity.

The intensities of 2505 reflections were measured. The intensities of 186 of thee were found to be less than one standard deviation above background and were assigned a value of zero with zero weight throughout the refinement. The data were corrected for Lorentz–polarization effects but not for absorption (μ = 8.8 cm^{-1}). The data were placed on an absolute scale by Wilson's method.[36] A Howells, Phillips, and Rogers' plot[37] confirmed that the crystal is centrosymmetric.

The phases of 253 reflections with an E value greater than 1.50 were assigned by the CRYM[38] symbolic addition[39] program. The phase assignment with the smallest conflict ratio gave an E map in

which 27 of the heavier atoms were located. Least-squares refinement of the coordinates and isotropic temperature factors converged at an R index of 0.168%. In the last cycle of refinement the average shift of a refined parameter, except for atom C(2), was 0.56 of the estimated standard deviation of that parameter. The weighted R index was 12.4%, and the goodness-of-fit was 7.2. The average standard deviation in atomic position is 0.008 Å, the average standard deviation in bond length is 0.011 Å, and the average standard deviation in bond angle is 0.7°.[40]

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Registry No.—**1,** 50676-11-4; **2,** 53359-96-9; **3,** 6044-73-1; **4,** 54062-32-7; **5,** 54062-33-8; **5** mono-OH analog, 54062-34-9; **6,** 54062-35-0; **6** 2,4-DNP, 54062-36-1; **7,** 54062-37-2; **7** 2,4-DNP, 54062-38-3; **8,** 54062-39-4; **8** *cis*-OH analog, 54062-40-7; **8** *trans*-OH analog, 54141-80-9; **9,** 54062-41-8; **9** semicarbazone, 54062-42-9; **9** *cis*-OH analog, 54062-43-0; **9** *trans*-OH analog, 54141-81-0; **10** Δ^2 isomer, 54062-44-1; **10** Δ^1 isomer, 54062-45-2; **11,** 54062-46-3; **12,** 54062-47-4; **12** OH analog, 54062-48-5; **13,** 54062-49-6; **13** OH analog, 54062-50-9; **14,** 54062-51-0; *trans*-**15,** 54062-52-1; *cis*-**15,** 54062-53-2; **16,** 54141-82-1; **17,** 54062-54-3; **18,** 54062-55-4; **19,** 54062-56-5; **20** α epimer, 54062-57-6; **20** β epimer, 54141-83-2; **21,** 54062-58-7; **22** ortho isomer, 54062-59-8; **22** para isomer, 54062-60-1; **24,** 54062-61-2; **25,** 54062-62-3; **25** OH analog, 54062-63-4; **26,** 54062-64-5; **27,** 54062-65-6; 4-methyl-(*E*)-4,8-nonadienol 54062-66-7; 1-chloro-4-methyl-(*E*)-4,8-nonadiene, 54062-67-8; 2,5-dimethyl-(*E*)-5,9-decadienoic acid, 54062-68-9; *cis*-4-(2′-methoxyphenyl)-1-methyl-1-(3′-methyloctyl)cyclohexane, 54062-69-0; *trans*-4-(2′-methoxyphenyl)-1-methyl-1-(3′-methyloctyl)cyclohexane, 54062-70-3; *cis*-4-(4′-methoxyphenyl)-1-methyl-1-(3′-methyloctyl)cyclohexane, 54062-71-4; *trans*-4-(4′-methoxyphenyl)-1-methyl-1-(3′-methyloctyl)cyclohexane, 54062-72-5; 2-methoxy-8a-methyl-6,7,8,8a,9,10-hexahydrophenanthrene, 54062-73-6; *N,N,N′,N′*-tetramethyldiamidophosphorochloridate, 1605-65-8; 8aβ,10aβ-dimethyl-3,4,4aβ,4bα,5,6,7,8,8a,9,10,10a-dodecahydrophenanthrene, 54062-74-7; 12-*m*-methoxyphenyl-2,5,6,9-tetramethyl-(*E,E*)-5,9-dodecadienoic acid, 54119-84-5; 12-*m*-methoxyphenyl-5,6,9-trimethyl-(*E,E*)-5,9-dodecadienoic acid, 54062-75-8; 12-*m*-methoxyphenyl-2,5,6,9-tetramethyl-(*E,E*)-5,9-dodecadienol, 54083-29-3; 12-*m*-methoxyphenyl-2,5,6,9-tetramethyl-(*E,E*)-5,9-dodecadienal, 54083-30-6; 3-methoxy-6bβ,8aβ,12bα,14aβ-tetramethyl-5,6,6aα,6b,7,8,8a,9,10,11,12,12aβ,12b,13,14,14a-hexadecahydro-11β-picenol, 54062-76-9; 3-methoxy-6bβ,8aβ,12bα,14aβ-tetramethyl-5,6,6aα,6b,7,8,8a,9,10,11,12,12aβ,12b,13,14,14a-hexadecahydro-12β-picenol, 54062-77-0; 2,5-dimethyl-(*E*)-5,9-decadienol, 54062-78-1.

Supplementary Material Available. Tables III–VII containing the observed and calculated structure factors, the heavier atom parameters, the hydrogen atom coordinates, the bond distances and angles, and the least-squares plane of the aromatic ring, respectively, 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 $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1007.

References and Notes

(1) The structural formulas containing one or more asymmetric carbon atoms depict one enantiomer, but refer to racemic compounds unless otherwise designated. In the text the (±) prefix will be omitted, and intermediates are assumed to be racemic. The tricyclic compounds will be described by the phenanthrene nomenclature, and each racemate is arbitrarily represented by that enantiomer that has the C-4b methyl group in the α configuration. The pentacyclic compounds will be described by the picene nomenclature, and each racemate is arbitrarily represented by that enantiomer that has the C-14a methyl group, respectively, in the α configuration. In discussions, where naturally occurring triterpenes are involved, the nomenclature and numbering suggested by S. Allred and G. Ourisson [*Tetrahedron,* **1,** 277 (1957)] will be used as necessary.

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(30) H. Dutler, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta,* **38,** 1268 (1955); G. Brownlie, F. S. Spring, R. Stevenson, and W. S. Strachan, *Chem. Ind. (London),* 656 (1955); E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.,* **77,** 3667 (1955); R. M. Coates, *Tetrahedron Lett.,* 4143 (1967).

(31) Melting points labeled (vacuum) were taken in evacuated capillaries on a Hoover capillary melting point apparatus, while all others were determined on a Kofler micro hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded using either a Varian H-60A or T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ_{TMS} 0.0 ppm) as an internal standard.

Gas–liquid phase chromatographic (GLC) analyses were determined on either a Hewlett-Packard 5750 or F & M 810 research chromatograph using helium carrier gas at a flow rate of 60 ml/min. Unless otherwise noted, all analytical GLC was conducted on a 6 ft × 0.125 in. column packed with 4% SE-30 on 60–80 mesh Chromosorb W AW-DMCS.

Preparative thin layer chromatography (preparative TLC) was carried out on 20 × 20 × 0.2 cm glass plates coated with silica gel $PF_{254+266}$ (Brinkman Instruments Co.). Analytical thin layer chromatography (TLC) was conducted on 1 × 3 in. microscope slides coated with a 0.5 mm layer of silica gel G or $PF_{254+266}$.

Alumina used for column chromatography refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany, and made up to grade II or III as indicated by the addition of 3 or 6% water prior to use. Silica gel columns used the 0.05–0.2-mm silica gel manufactured "for column chromatography" by E. Merck & Co., Darmstadt, Germany. Preparative medium-pressure column chromatography was performed using 0.5 × 20 in. or 2 × 20 in. glass columns with fittings supplied by Chromatronix, Inc., Berkeley, Calif., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

"Dry" solvents were dried immediately prior to use. Ether, benzene, tetrahydrofuran, dioxane, and dimethoxyethane were distilled frm lithium

aluminum hydride; *tert*-butyl alcohol, dimethyl sulfoxide, pyridine, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride; cichloromethane, carbon tetrachloride, diodomethane, and methyl iodide were distilled from phosphorus pentoxide; ammonia was distilled from the tank and then from a blue lithium or sodium solution; acetone was analytical reagent grade distilled from potassium permanganate; formic acid was distilled from boric anhydride. 'Petroleum ether" refers to the 'Analyzed Reagent" grade hydrocarbon fraction, bp 30–60°, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Reactions described as run under nitrogen or argon employed a mercury bubbler arranged so that the system could be alternately evacuated and filled with the inert gas and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(32) In cases where products were isolated 'by solvent extraction", the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water, followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned washing with water.

(33) F. Uhlig and H. R. Snyder, *Adv. Org. Chem.*, **1**, 35 (1960).

(34) Preparative GLC under the same conditions described above[31] except that the following columns were used: (a) 5% SE-30 on Chromosorb W AW-DMCS (6 ft × 0.125 in); (b) 10% Carbowax 20M on Chromosorb W AW-DMCS (10 ft × 0.25 in).

(35) For spectra, see R. I. Trust, Ph.D. Thesis, California Institute of Technology, 1974.

(36) A. J. C. Wilson, *Nature (London)*, **150**, 152 (1942).

(37) E. R. Howells, D. C. Phillips, and D. Rogers, *Acta Crystallogr.*, **3**, 210 (1950).

(38) D. J. Duchamp, Program and Abstracts, ACA Meeting, Bozeman, Mont., 1964, Paper E-14, p 29.

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(40) See paragraph at end of paper regarding supplementary material.

Rearrangements in the Photolevopimaric Acid Series. A Paradigm of Bicyclo[2.2.0]- and Bicyclo[2.1.1]hexane Chemistry[1,2]

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Unexpected rearrangements of photolevopimaric acid derivatives are described. Hydroboration–oxidation of methyl levopimarate (**3c**) gave the previously reported *exo*-bicyclo[2.2.0]hexanol **7a** and a new tertiary alcohol **12a** which was prepared independently from the epoxide **5**. Treatment of **5** with Lewis acids resulted in rearrangement to **6**. Mercuric acetate oxidation of **3c** resulted in conversion to **13**. Contrary to an earlier report, Jones oxidation of **7a** proceeded with rearrangement to the bicyclo[2.1.1]hexanone **20**, whose structure was established by degradation to the cyclopentanone **30**, acid cleavage to **35**, base-catalyzed cleavage to **36**, and degradation of the latter to the drimane derivative **38**. Treatment of the *endo*-bicyclo[2.1.1]hexyl tosylate **23a** with tosyl chloride resulted in rearrangement to a bicyclo[3.1.0]hexane derivative, the new resin acid isomer methyl isophotolevopimarate (**39**). An unusual oxidation of the *exo*-bicyclo[2.2.0]hexanol **7a** to the lactone **14a** and **14b** with Fétizon's reagent was observed. Solvolytic reactions of the *exo*-bicyclo[2.2.0]hexyl tosylate **7c** resulted in rearrangement to the bicyclo[2.1.1]hexane derivatives **44** and **45**.

The observations which are described in the present report are the result of work originally aimed at the synthesis of 14-deuteriolevopimaric acid (**1b**). This substance was desired to help clarify the nature of the intramolecular hydrogen transfer which occurs on irradiation of the levopimaric acid–cyclopentenedione adduct **2**,[3,4] a problem which was eventually solved by X-ray analysis of one of the photolysis products.[5]

The simplest path to **1b** appeared to be introduction of deuterium in some fashion at C-14 of the photolevopimaric acid skeleton **3a**, since thermal reversion of the valence isomerization **1a** → **3a**[6,7] has been described.[7] The rearrangements which negated this approach and will be described in this report constitute not only an instructive paradigm of bicyclo[2.2.0]- and bicyclo[2.1.1]hexane chemistry, but illustrate several other unusual reactions which presumably occur because these strained systems are part of a relatively rigid diterpene skeleton. See Scheme I.

Attempts to Prepare Bicyclo[2.2.0]hexanone 8. Our failure to effect direct introduction of deuterium into **3c**[8a] forced us to investigate more circuitous routes to **3d** by way of **8**, which are outlined in Scheme II. The preparation of **8** from **7a** has been reported previously[7]; although Dauben and Coates did not discuss the stereochemistry of **7a** and **8**, it seemed likely that these substances possessed the configurations indicated in Scheme II, thus necessitating further reduction of **8** to **9**, which has the correct stereochemistry for bimolecular elimination to **3d**. However, as the reported[7] overall yield of **8** was rather low, we first explored its preparation from the epoxide **5**.

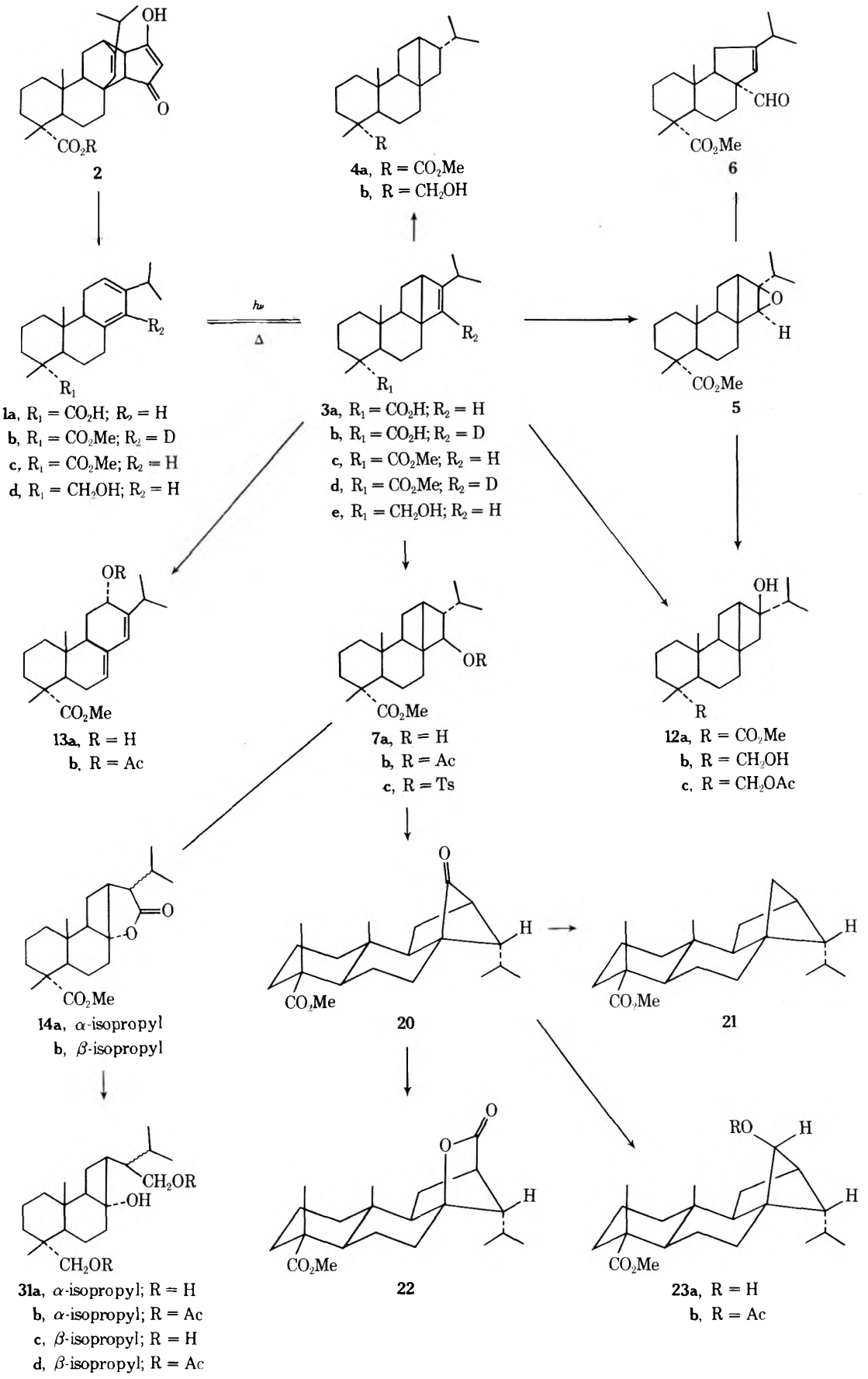
This substance, isolated in 81% yield, was assigned the exo configuration depicted in Scheme II because of the appearance of H-14 as a narrowly split doublet (J = 2.5 Hz) at 3.82 ppm. The W arrangement for such long-range coupling of H-14 to H-12 is achieved only if H-14 is α; this is also consonant with the deduction, from models, that the least hindered side of **3c** is the β face.

Treatment of **5** with acidic reagents generally produced complex mixtures which resisted attempts at separation, but contained no fraction corresponding to **8**. On the other hand, use of boron trifluoride etherate under carefully defined conditions resulted in rearrangement (64% yield) to an unsaturated aldehyde (sharp singlet at 9.3 ppm, broadened vinylic singlet, $W_{1/2}$ = 6.6 Hz, at 5.83 ppm). This substance was assigned structure **6**, formally derivable by the shifts depicted in Scheme III, rather than **10** for the following reason.

By sweeping the methylene region of the ^{1}H NMR spectrum, the center of the H-15 signal was found at 2.07 ppm. Irradiation at this frequency collapsed the isopropyl methyl doublets at 0.90 and 1.06 ppm to singlets and sharpened the vinyl proton signal ($W_{1/2}$ = 2.5 Hz). The existence of allylic coupling between the vinyl proton and H-15 was thus established, an observation which excludes structure **10**. The α configuration of the aldehyde is deduced on mechanistic grounds; an upfield shift of the C-10 methyl resonance to 0.86 ppm may be attributed to the shielding effect of the 12,13 double bond.

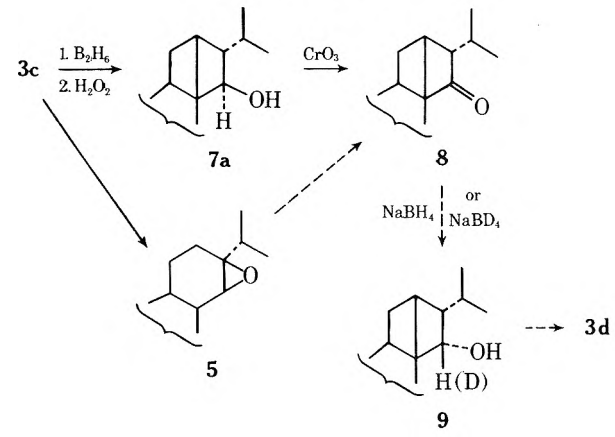
As a result of this rearrangement we returned to Dauben and Coates' method of preparing **8**. Slight modifications in

Scheme I

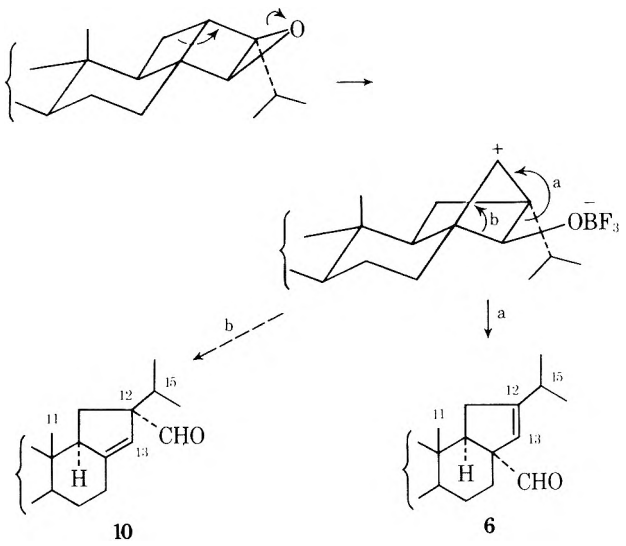


the isolation procedure resulted in an improved yield (67%) of alcohol **7a**, whose stereochemical assignment was based not only on the assumption that cis addition of the reagent takes place from the least hindered, β face of **3c**, but also on the appearance of the H-14 resonance (doublet, J = 7 Hz, at 4.06 ppm in **7a** and at 5.16 ppm in **7b**) which indicated that H-13 and H-14 were trans. Contrary to the literature report,[7] however, there was also formed an appreciable

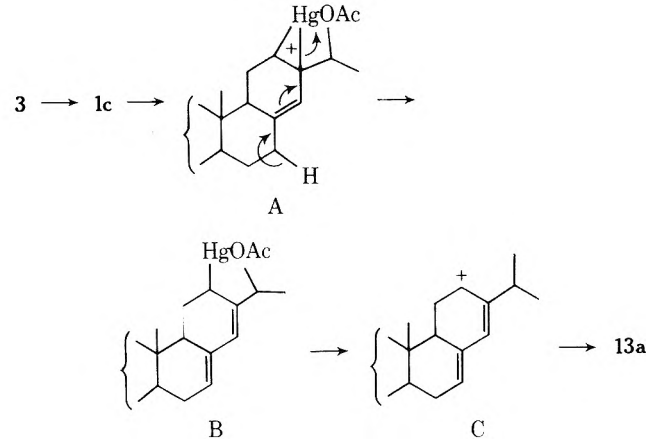
Scheme II



Scheme III



Scheme IV



amount (27%) of a tertiary alcohol **12a,** whose structure was confirmed by $LiAlH_4$ reduction to **12b,** the same substance being formed by $LiAlH_4$ reduction of **5.**

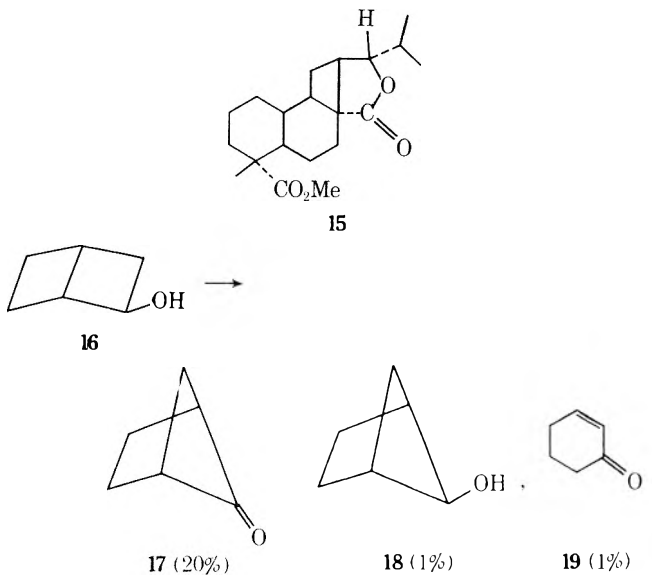
The surprising formation of a tertiary alcohol in appreciable quantity during the normally much more regioselective hydroboration reaction may be attributed to the high reactivity of the bicyclo[2.2.0]hexene system of **3c** as the result of excessive strain which "decreases the activation energy of the addition process, thereby making the transition state more reactant-like and, hence, less sensitive to steric and polar factors" as has been claimed[10] in a somewhat similar situation, i.e., the hydroboration of bicyclo[3.3.1]nonene, which also furnishes a mixture of isomeric alcohols.

An attempt to prepare **12a** independently from **3c** by the oxymercuration–demercuration reaction did not result in the formation of the expected alcohol, but gave a mixture of **13** (62%)[11] and methyl levopimarate (**1c,** 22%). Since omission of $NaBH_4$ or treatment of methyl levopimarate with mercuric acetate gave the same mixture of **1c** and **13,** the reaction probably proceeds as outlined in Scheme IV. Such a scheme was proposed earlier[12] to account for the products obtained on treatment of cholesta-6,8(9)-dien-3-ol *p*-nitrobenzoate with mercuric acetate.

Repetition of the literature oxidation of **7** to **8** with Jones reagent gave a single substance in 90% yield which had properties identical with those described by Dauben and Coates[7] and whose previously unreported ^1H NMR spectrum was, on the whole, consonant with structure **8** assigned by them (Scheme II) except for an inexplicable upfield shift of the C-10 methyl resonance (from 1.02 ppm in **7** to 0.78 ppm in **8**). Hydride reduction of the ketone led to a new alcohol which was initially presumed to be alcohol **9.**

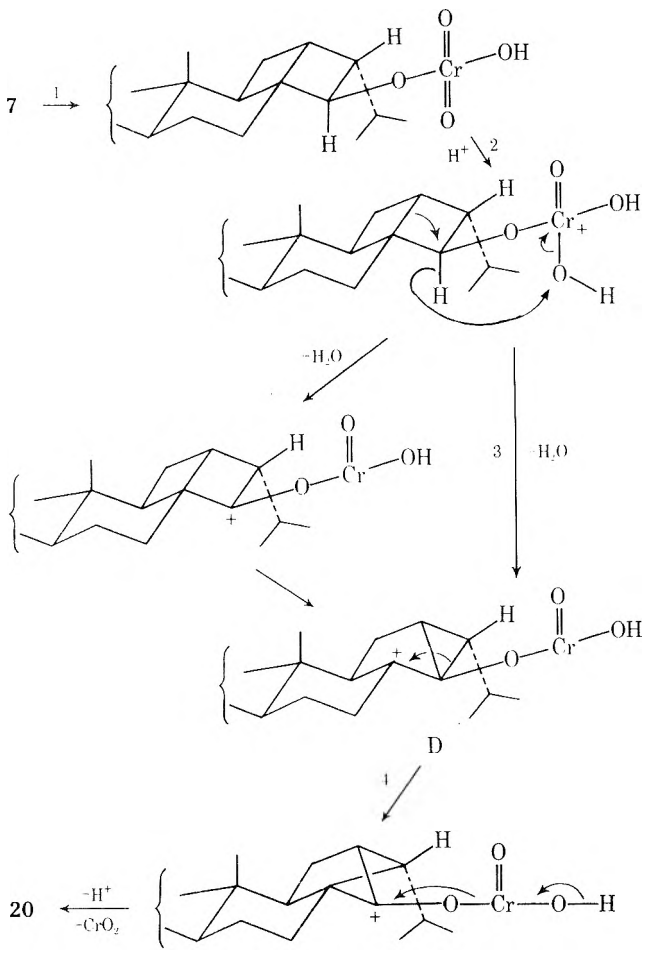
Subsequent transformations of these two substances, however, did not yield products to be expected on the basis of the postulated structures. Of special importance was the observation that the lactone obtained by Baeyer–Villiger oxidation of the ketone was not identical with either of the authentic lactones **14a** and **14b** (vide infra) nor was the ^1H NMR spectrum of this lactone compatible with formula **15.** Moreover, conversion of the ketone to a thioketal followed by nickel desulfurization gave a gummy but homogeneous saturated ester different in all respects from authentic crystalline methyl dihydrophotolevopimarate (**4a**). It was clear, therefore, that the structures of **8** and **9** required revision and that an entirely unexpected rearrangement had taken place during the oxidation of **7.**

A clue to the situation was provided by a recent observation[13] that *exo*-bicyclo[2.2.0]hexan-2-ol (**16**) undergoes oxidative rearrangement under Oppenauer conditions, albeit in low yield, to a mixture of **17, 18,** and **19,** the driving force

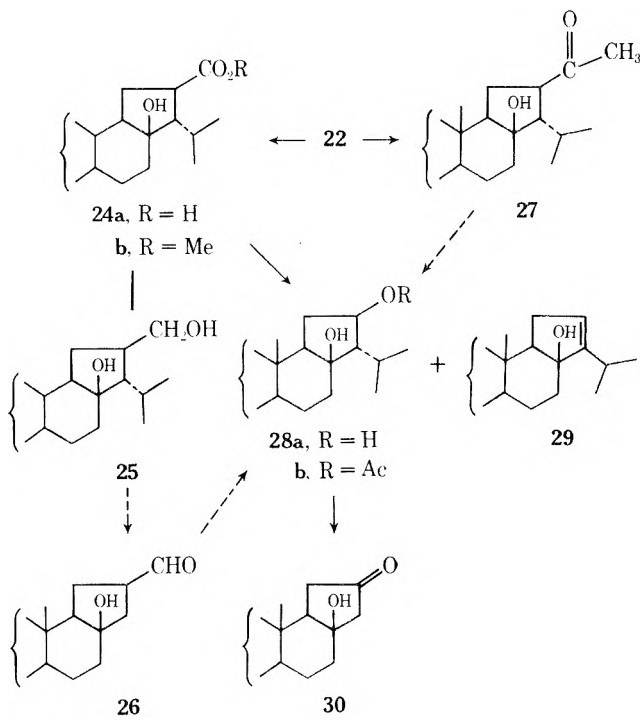


of the rearrangement being attributed to the greater strain in the bicyclo[2.2.0] system as compared with the strain in the bicyclo[2.1.1] system. If **7** undergoes a similar oxidative rearrangement under the influence of the Jones reagent, the structure of the resulting ketone reagent should be **20.** The thioketal desulfurization product would be **21,** the Baeyer–Villiger product would be **22,** and the alcohol produced by hydride reduction of the ketone would be **23** be-

Scheme V



Scheme VI



cause approach of the reagent from the side of the C-10 methyl group would be severely hindered.

A possible mechanism for the formation of **20** (Scheme V) involves transfer of hydride ion to reagent accompanied, for stereoelectronic reasons, by migration of the 8,12, not the 8,9, bond, the driving force for this being the formation of the more stable bicyclo[3.1.0]hexyl cation D.[14] Concomitant or subsequent migration of the 13,14 bond, necessarily from the bottom face of the molecule, would give **20.** Alternatively, initial transfer of hydride ion without 8,12-bond migration might first lead to the bicyclo[2.2.0]hexyl cation E, which could undergo a series of Wagner–Meerwein shifts; however, even here some degree of participation by the 8,12 σ bond to maintain maximum overlap with the developing p orbital on C-8 will probably have to be invoked.[19]

Formula **20** also provides a ready explanation for the upfield shift of the C-10 methyl group to which allusion has been made earlier, since it is now shielded by a one-carbon bridge.[20] Oxidation to **22** produces a downfield shift to 0.90 ppm and reduction to **23** a downfield shift to 1.08 ppm, both understandable if lactone and hydroxyl groups were situated on the β face as required by the formulas.

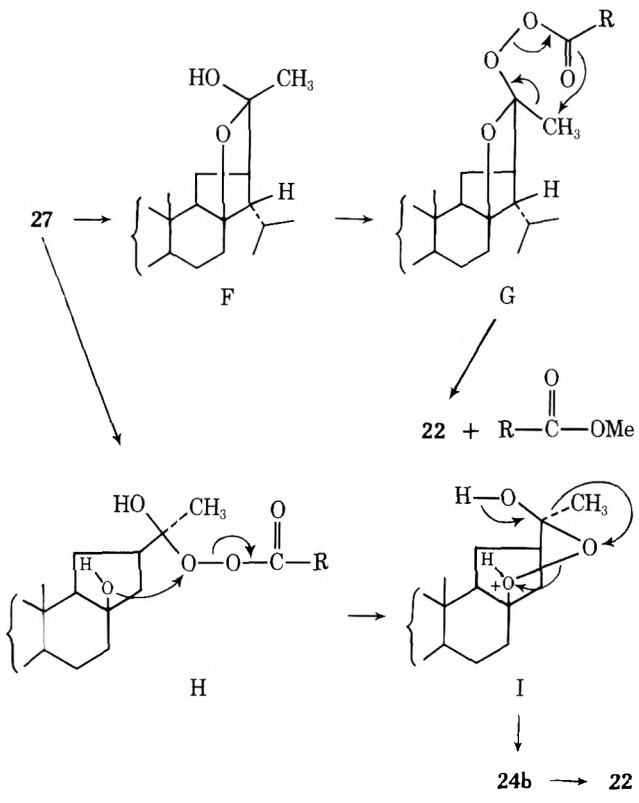
Structure Proof of Bicyclo[2.1.1]hexanone 20. To confirm the presence of a bicyclo[2.1.1]hexanone system in **20,** degradation of lactone **22** to a product exhibiting the spectral characteristics of a cyclopentanone was undertaken as outlined in Scheme VI. Reduction of **24a** with B_2H_6–THF complex[21] gave diol **25** in 72% yield, but treatment of the latter with various oxidizing agents merely resulted in regeneration of **22** instead of formation of the hoped-for **26,** possibly by way of a transitory hemiacetal (but see discussion in the next paragraph).

In exploration of an alternative route to **28b,** reaction of **22** with 1.5 equiv of methyllithium gave the methyl ketone **27** (56%).[22a] However, exposure of the latter to *m*-chloroperbenzoic acid resulted, very surprisingly, again in isolation of lactone **22.** This might conceivably be rationalized by assuming that **27** is in equilibrium with the hemiketal F (Scheme VII) and that esterification of the latter by peracid to G and decomposition by way of a cyclic transition state leads to the observed product. However, the ir spectrum shows that **27** is entirely in the ketone form as might be expected, since molecular models indicate that in the preferred conformation of **24b** and **27** the hydroxyl group at C-8 and the substituent at C-12 are oriented away from each other. "Flipping" of the five-membered ring to a less stable conformation which brings the substituents at C-8 and C-12 closer would not be expected to occur except at higher temperatures or in a situation where the equilibrium **27** $\rightleftarrows$ F, normally unfavorable to F, is displaced toward the right by further reaction.[22b]

A situation somewhat more favorable to participation by the hydroxyl group is pictured in the second row of Scheme VII. Approach of the bulky peracid molecule to the carbonyl group from the least hindered side of **27** would give rise to intermediate H. The tertiary hydroxyl group may now participate in decomposition of H to give species I. Molecular models of I indicate that the bond linking the methyl group to C-14 is trans-antiparallel to the –O–O– bond; thus collapse of I with preferential methyl migration, rather than 12,14 σ bond migration, could occur to give **24b.** The latter might undergo transesterification to give lactone **22,** although this would again require prior "flipping" to an unfavorable conformation. That this is a possibility is shown by the formation of **22** from **24b** at elevated temperatures.

Finally, oxidative decarboxylation of **24a** with lead tetraacetate in benzene afforded a mixture of **22** (27%), **29** (10%), and **28b** (3%), the acetate group in **28b** being assigned the β orientation because of the coupling constants exhibited by the H-12 signal at 5.01 ppm.[22] Repeated recycling of lactone **22** permitted accumulation of a sufficient quantity of **28b** for hydrolysis to **28a** (H-12 signal at 4.21 ppm) and subsequent oxidation ($CrO_3 \cdot 2Py$) to hydroxycy-

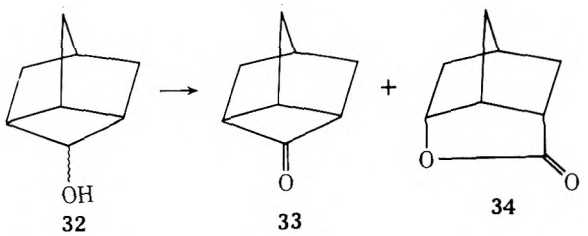
Scheme VII



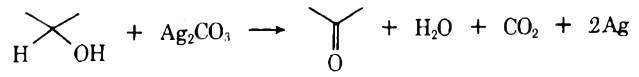
clopentanone **30,** which had ir bands at 3615 (hydroxyl), 1739 (cyclopentanone), and 1728 cm^{-1} (carbomethoxy group). Thus, the structure of ketone **20** was securely established.

To avoid the rearrangement encountered during the chromic acid oxidation of **7a,** the action on **7a** of dimethyl sulfoxide in combination with various other reagents[23] was also investigated; however, this invariably led to recovery of starting material. Treatment of **7a** with silver carbonate on Celite[24] again did not yield the desired 8 but resulted in formation of a lactone **14a** (Scheme I, 73% yield, new ir band at 1772 cm^{-1}), which was converted to an epimer **14b** on treatment with base. This is in accord with stability relationships deduced from Dreiding models. These indicate that **14a** contains an interaction between H-11α and one of the methyls of the isopropyl group which is relieved in **14b.** The isomeric lactones were reduced to the triols **31a** and **31c,** which were characterized as the isomeric diacetates **31b** and **31d.**

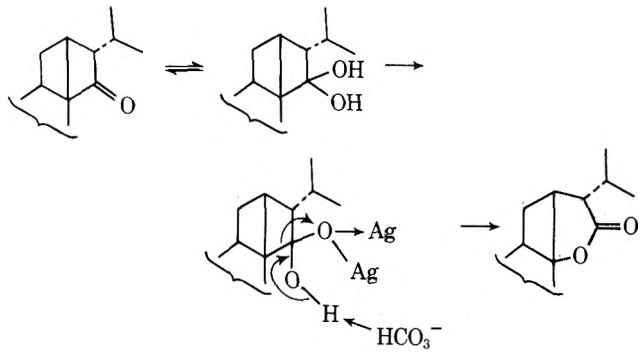
The unusual oxidation of a secondary alcohol to a γ-lactone with silver carbonate–Celite has one precedent.[25] Oxidation of the *exo*- and *endo*-tricyclo[3.2.1.0^{36}]octan-4-ols **32** with this reagent under anhydrous conditions afforded a mixture of ketone **33** and lactone **34** in yields of 69 and 31%,



respectively. It was proposed that lactone **25** was formed via the hydrated form of ketone **33,** since treatment of the ketone with moist reagent gave an 11% yield of the lactone. Presumably, the water required for the hydration of **33** under anhydrous conditions was that liberated in the overall equation[26] below.

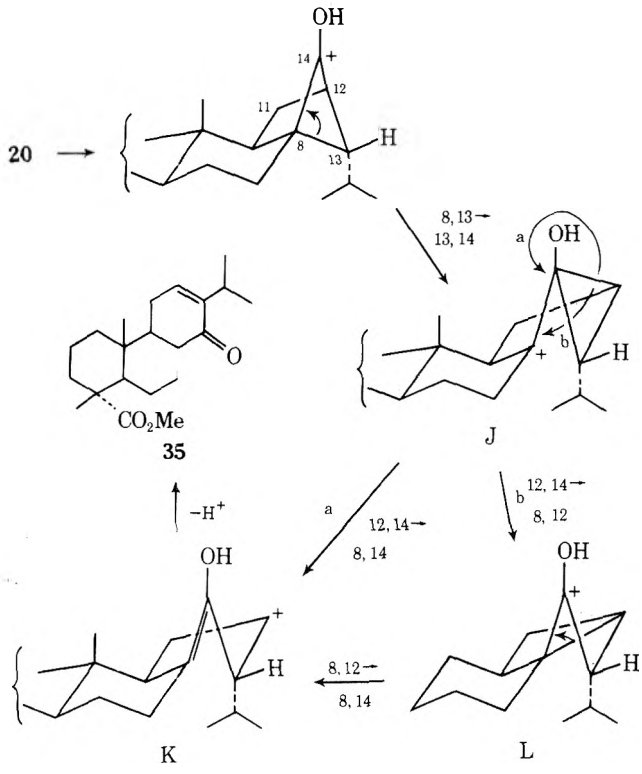


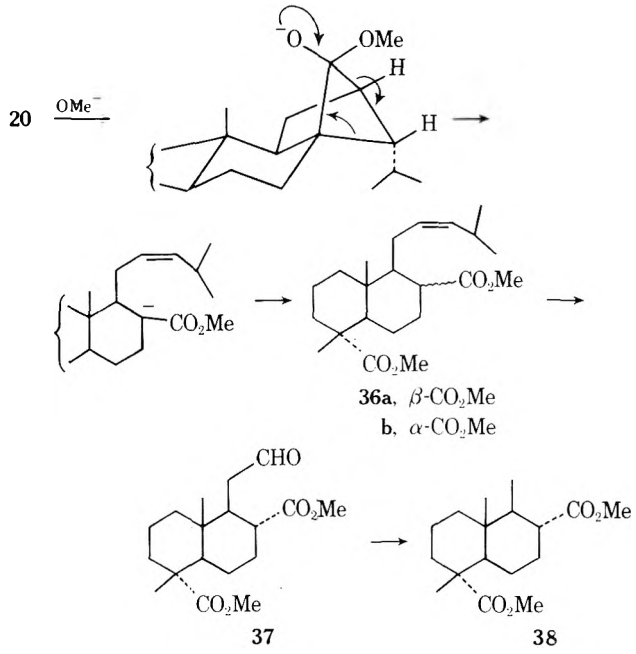
In the present instance, the complete conversion of **7a** to lactone **14a** may perhaps be due to the high reactivity of the intermediate bicyclo[2.2.0]hexanone **8,** which is in equilibrium with its hydrated form and undergoes further oxidation as illustrated.[26]



Rearrangement of Bicyclo[2.1.1]hexanone 20. Additional reactions of ketone **20** which are in agreement with its formulation as a bicyclo[2.1.1]hexan-5-one will now be described. Solution of **20** in chloroform saturated with HCl resulted in formation of an α,β-unsaturated ketone which was identified as **35,** a substance previously prepared in our laboratory.[27] Its formation from **20** can be rationalized in terms of a series of Wagner–Meerwein shifts (Scheme VIII) similar to those postulated for the acid-induced rearrangement of some simpler cyclobutanones.[28] The cyclopropyl carbinyl cation J, formed by initial migration of the 8,13 bond, could be converted to homoallylic ion K, and thence to **35,** either directly (path a) or by way of the protonated bicyclo[2.2.0]hexanone L which, because of its high reactivity (vide supra), undergoes further rearrangement (path b).

Scheme VIII





36a, β-CO_2Me
b, α-CO_2Me

37 38

Treatment of the nonenolizable ketone **20** with sodium methoxide resulted in cleavage to a mixture of epimeric unsaturated esters **36a** and **36b** which could be separated by preparative TLC. Hydrogenation of the mixture afforded a mixture of two saturated esters, an observation which demonstrated that the two products were not cis–trans or double-bond isomers. Equilibration with base converted **36a** (carbomethoxy group axial) quantitatively to **36b** (carbomethoxy group equatorial).

Haller–Bauer cleavage of a nonenolizable ketone normally results in cleavage of one of the bonds adjacent to the carbonyl group, the resultant carbanion being discharged by reaction with a proton donor.[29] In the present instance, the driving force leading to formation of **36** may be attributed to stabilization of the final anion by the carbomethoxy group after additional cleavage of the five-membered ring, the composition of the final product being due at least partially to kinetic control.[30]

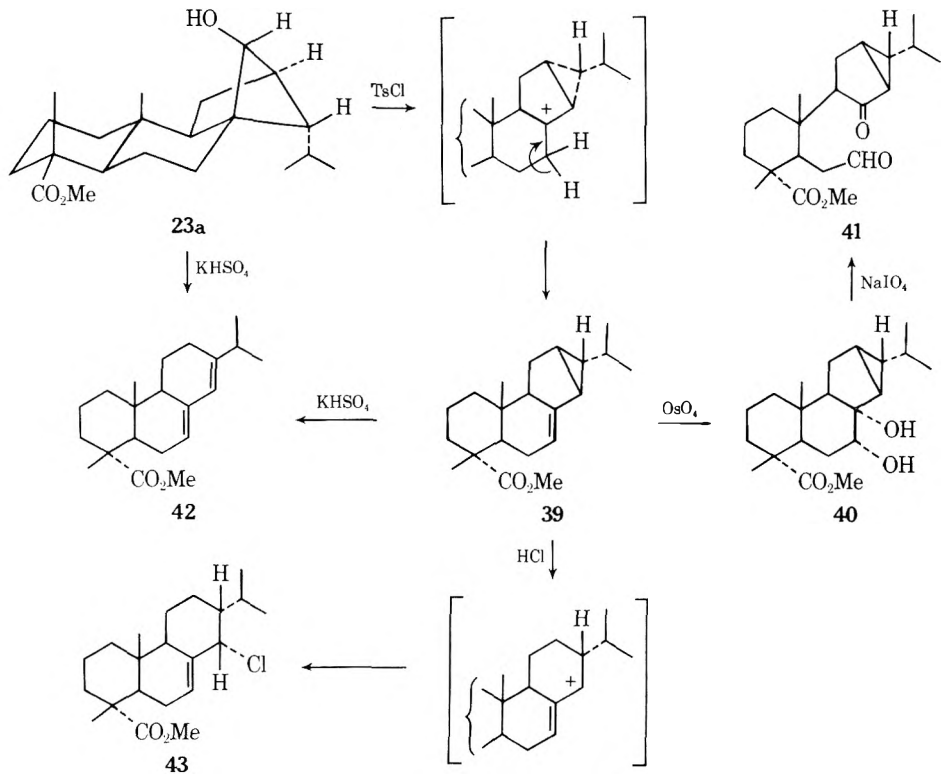
Proof for the nature of the unsaturated side chain was obtained by further degradation. Ozonolysis of **36b** gave a saturated aldehyde **37** containing the partial structure $-CH_2CHO$ (aldehyde triplet at 9.4 ppm). Decarbonylation of this substance with tris(triphenylphosphine)rhodium chloride yielded the drimane derivative **38** whose ^1H NMR spectrum, in addition to the C-4 and C-10 methyl resonances, exhibited a doublet at 1.21 ppm (J = 6 Hz) for the methyl group attached to C-9.[30] Thus, the double bond of **36b** is two carbon atoms removed from ring B, a situation which requires attachment of a five-membered ring to C-8 and C-9 of the precursor ketone **20.**

Solvolytic Rearrangement of Bicyclo[2.1.1]hexanol 23. The endo configuration of alcohol **23a** was deduced on steric grounds and is supported by analysis of the ^1H NMR spectrum of **23a** and its derived acetate. The appearance of the H-14 signal (sharp doublet, J = 3 Hz) is in accordance with the H-12, H-14 dihedral angle measured on models (45–50°) as is the absence of long-range coupling to H-13 which would be expected in an endo alcohol. Additional chemical evidence was provided by its solvolysis.

Treatment of **23a** with p-toluenesulfonyl chloride–pyridine did not result in formation of a tosylate; instead, there was isolated a new isomer **39** of methyl photolevopimarate which was named methyl isophotolevopimarate. The presence of a double bond in **39** was evident from the ^1H NMR spectrum, which exhibited a broadened singlet at 5.3 ppm, different from that of H-14 in the ^1H NMR spectrum of **3b** and similar in appearance and chemical shift to the H-7 signal of 7-abietenes, hence obviously coupled to two other protons. The isopropyl signals had remained unaffected by this transformation; thus, an obvious possibility for the new compound was the cyclopropane derivative **39,** a more complex relative of the bicyclo[3.1.0]hexane derivatives which are found among the solvolysis products of *endo*-bicyclo[2.1.1]hexyl 5-tosylate.[31]

Further spectroscopic evidence for formula **39** was diffi-

Scheme IX



23a 41 42 39 40 43

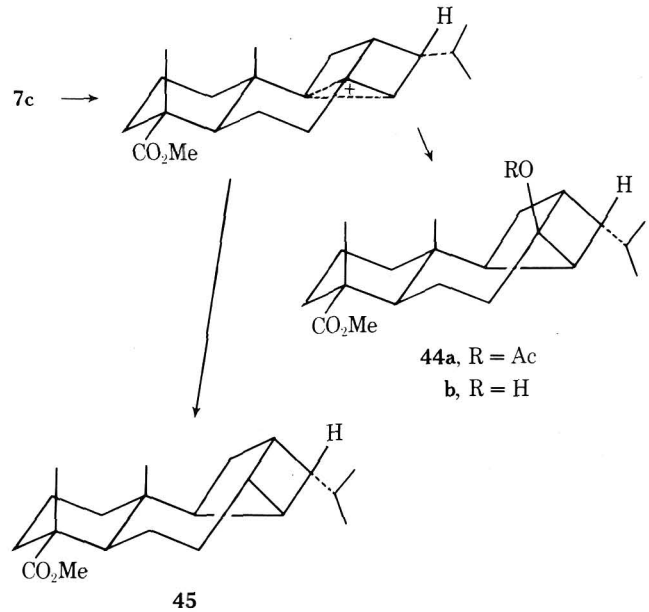
cult to adduce, since signals of the cyclopropyl protons were obscured by the methylene envelope and the uv spectrum displayed only end absorption. However, the transformations outlined in Scheme IX provided adequate proof.

Osmylation of **39** furnished a diol which was assigned stereochemistry **40**. Earlier work on osmylation of abietenes[32-34] resulted in osmylation from the α or the β face depending on the conformation of starting material; models of **39** suggested that α-osmylation would be preferred. This was borne out by the ^{1}H NMR spectrum, which displayed the H-7 signal as a triplet (J = 8 Hz), compatible only with α orientation of the 7-hydroxyl, and the C-10 methyl signal at 0.86 ppm, appropriate for an α-oriented 8-hydroxyl group.[34] Periodate cleavage of **40** gave **41** (aldehyde triplet at 9.6 ppm); unfortunately, no firm conclusions could be drawn from the uv spectrum, which exhibited little evidence of conjugation.

Acid-catalyzed cleavage, however, provided conclusive proof for the presence of a cyclopropane ring. Treatment with HCl gave a substance $C_{21}H_{33}O_2Cl$ (**43**) (mass spectrum) which displayed a one-proton peak in the vinyl region similar to that of **39** itself and a broadened one-proton singlet at 4.46 ppm ($W_{1/2}$ = 6 Hz) assignable to H-14. This is the result of cyclopropane ring cleavage in such a manner so as to form the most stable carbonium ion, in this instance an allylic carbonium ion. Inversion at the point of attack of the nucleophile should result in α orientation of the halogen, a supposition confirmed by the half-height width of the H-14 signal characteristic of an equatorial proton. Lastly, the negative Cotton effect exhibited by **43** is typical of 7-abietenes.[35]

Dehydration of **23** with $KHSO_4$ in refluxing dioxane resulted in conversion to methyl abietate (**42**). It is probable that methyl isophotolevopimarate is an intermediate, since it is also transformed into **42** under these conditions.

Solvolytic Rearrangements of Bicyclo[2.2.0]hexanol 7c. The observation that hydride abstraction during the chromic acid oxidation of **7a** resulted in rearrangement due to migration of the 8,12 σ bond made it of interest to study the solvolysis of **7c** since, in analogy with earlier work[36] on the solvolysis of simpler bicyclo[2.2.0]hexan-2-ol tosylates,



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Experimental Section[41]

Methyl Photolevopimarate (3c).--Modification of the procedure of Dauben and Coates[7] resulted in improvement of the yield to 70%. A solution of 10 g of levopimaric acid in 200 ml of methanol was irradiated in a quartz cell with unfiltered light from a Hanovia high pressure mercury vapor arc lamp for 7 hr under a slow stream of nitrogen. Part of the solvent was evaporated; the crystals of 3a which separated were recrystallized from methanol, yield 7.0 g, mp 115-116°, $[\alpha]_D^{25}$ + 79.2°, pmr signals at 5.50br (H-14), 1.25 (C-4 methyl), 1.08 (C-10 methyl), 1.00d (J=7, C-15 methyls). Esterification with diazomethane and purification of the product by passage through an alumina column (activity III) gave the gummy ester 3c, $[\alpha]_D^{25}$ + 57°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.11. Found: C, 79.71; H, 10.01; O, 9.84.

One g of 3c was pyrolyzed by heating in a nitrogen atmosphere at 120° for 6 hr. The crude product was recrystallized from methanol, yield 0.78 g (78%) of 1c, identical in all respects with an authentic sample.

Preparation of 4a and 4b.--Methyl dihydrophotolevopimarate (4a) was prepared by the literature method.[7] The previously unreported pmr spectrum exhibited signals at 1.22 (C-4 methyl), 1.05 (C-10 methyl), 0.74d and 0.63d (J=7, C-15 methyls).

To a stirred suspension of 0.1 g of $LiAlH_4$ in 15 ml of tetrahydrofuran was added a solution of 0.1 g of 4a in 6 ml of tetrahydrofuran. Stirring was continued for 4 hr, at which time excess reagent was decomposed by wet ether. Dilution with water, filtration and evaporation of the ether layer gave (4b) which was recrystallized from methanol and then melted at 64-65°, yield quantitative, pmr signals at 3.23 (center of AB system of -CH OH), 1.11 (C-4 methyl), 0.87 (C-10 methyl), 0.81d and 0.70d (J=7, C-15 methyls).

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.29; H, 11.90; O, 5.30.

Epoxidation of Methyl Photolevopimarate.--To a solution of 2.0 g of m-chloroperbenzoic acid in 25 ml of $CHCl_3$ was added dropwise 2.0 g of 3c in 10 ml of $CHCl_3$. The reaction was followed by tlc and was complete after 2 hr. The mixture was evaporated at reduced pressure and taken up in ether. Washing with aqueous Na_2CO_3, KI and sodium thiosulfate solution and evaporation furnished 2 g of gum which crystallized on addition of methanol. Recrystallization from hexane gave 1.7 g (87%) of 5, mp 111-112°, pmr signals at 3.72d (J=3, H-14), 1.20 (C-4 methyl), 1.02 (C-10 methyl), 1.01d and 0.78d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{32}O$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.61; H, 9.92; O, 14.70.

The substance was not affected by treatment with silver perchlorate or lithium diethylamide.

Rearrangement of Methyl 13β,14β-epoxydihydrophotolevopimarate to 6.--To a solution of 1 g of 5 in 10 ml of ether was added 0.5 ml of BF_3- etherate, the progress of the reaction which was complete after 15 min being monitored by tlc. Addition of water, separation of the organic layer, washing, drying and evaporation gave a gum which was recrystallized from hexane, yield of 6 0.64 g, mp 62-63°,

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ir bands at 2780 (aldehyde C-H), 1735 (aldehyde C=O), 1721 cm^{-1} (ester), pmr signals at 5.83br ($W_{1/2}$=6.5 Hz, H-14), 3.73 (methoxyl), 1.20 (C-4 methyl), 1.10d and 0.95d (J=7 Hz, C-15 methyls), 0.81 (C-10 methyl).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.70; H, 9.40; O, 14.14.

The dinitrophenylhydrazone was prepared in the usual fashion, mp 132-133° after recrystallization from methanol.

Anal. Calcd. for $C_{27}H_{36}O_6N_4$: C, 63.26; H, 7.08; O, 18.73. Found: C, 63.56; H, 7.00; O, 19.12.

Hydroboration-Oxidation of Methyl Photolevopimarate.--To a solution of 4.3 g of 3c in 45 ml of dimethoxyethane was added 1 g of $NaBH_4$ at 0° with stirring, followed by dropwise addition of 3.75 g of freshly distilled BF_3-etherate. The solution was allowed to warm up to room temperature, stirring being continued for 4.5 hr. Two drops of water were added followed by cautious addition of 25 ml of 10% NaOH solution and 30 ml of 30% H_2O_2. The mixture was stirred overnight and thoroughly extracted with ether. The ether extracts were washed, dried and evaporated to give 4.0 g of gum from which alcohol 7a crystallized on addition of methanol, yield 3.0 g (70%), mp 126-130°, lit.[7] 129-131°, pmr signals at 4.06d (J=7, H-14), 3.70 (methoxyl), 1.20 (C-4 methyl), 1.02 (C-10 methyl), 0.96d and 0.78d (J=7, C-15 methyls).

The mother liquor was evaporated and the residue chromatographed over alumina (activity III). Elution with benzene gave 0.8 g (26%) of 12a, mp 171°, ir bands at 3610 (-OH), 1723 cm^{-1} (ester), pmr signals 1.21 (C-4 methyl), 1.10 (C-10 methyl), 0.92d and 0.80d (J=7.0, C-15 methyls). This substance was prepared independently as described in the next section.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.40, H, 9.89; O, 14.69.

Acetylation of 0.1 g of 7a with pyridine-acetic anhydride and recrystallization from hexane gave 0.09 g of 7b, mp 118-119°, ir bands at 1730 (acetate) and 1723 (ester), pmr signals identical to those of 7a except for a shift of the H-14 signal to 5.16d (J=7) and an acetate resonance at 2.00 ppm.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 73.37; H, 9.64; O, 17.00. Found: C, 73.19; H, 9.44; O, 16.86.

$LiAlH_4$ Reduction of Methyl 13β,14β-epoxydihydrolevopimarate.--Reduction of 1.0 g of 5 in 6 ml of THF with 0.6 g of $LiAlH_4$ in 20 ml of THF at reflux temperature followed by the usual work-up and recrystallization from methanol gave 0.8 g of 12b, mp 140-142°, pmr signals at 3.7 (center of AB system of -CH_2OH), 1.06 (C-4 methyl), 0.81 (C-10 methyl), 0.78d and 0.70d (J=7, C-15 methyls).

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76; O, 10.37. Found: C, 77.59; H, 11.46; O, 10.27.

Acetylation of 0.100 g of acetic anhydride-pyridine at room temperature for 16 hr followed by the usual work-up gave 0.098 g of 12c, mp 132-133° (from hexane), ir bands at 3615 and 1723 cm^{-1}, pmr signals similar to those of 12b except for a shift of -CH_2O- to 4.7 and an acetate resonance at 2.00 ppm.

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Anal. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93; O, 13.69. Found: C, 75.45; H, 10.43; O, 14.00.

To a solution of 0.2 g of 12b in 10 ml of acetone at 0° was added 3 ml of Jones reagent dropwise with stirring. After 1 hr, acetone was removed at reduced pressure. The remaining mixture was diluted with water and extracted with ether. The washed and dried ether extracts were evaporated and the residue was esterfied with diazomethane. After recrystallization from hexane, the product melted at 170-171° and was identical in all respects with 12a from the hydroboration reaction.

Reaction of Methyl Levopimarate and Methyl Photolevopimarate with Mercuric Acetate.--A solution of 1.06 g of mercuric acetate and 1 g of 3c in 30 ml of 50% aqueous THF was stirred overnight, filtered and evaporated at reduced pressure. The residue was taken up in ether. Evaporation of the washed and dried ether extract gave a gum which was chromatographed over alumina (acitivty III). Elution with hexane gave 0.22 g (22%) of methyl levopimarate (1c). Further elution with benzene gave 0.66 g (66%) of 13a, mp 88-89° (from hexane), $[\alpha]_D^{25}$ -117°; pmr signals at 5.58br (H-14), 5.50c (H-7), 4.28c (H-12), 3.76 (methoxyl), 1.24 (C-4 methyl), 1.10d and 1.07d (J=7, C-15 methyls), 0.77 (C-10 methyl).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.71; O, 14.44. Found: C, 75.71; H, 9.59; O, 14.18.

Acetylation of 0.1 g of 13a with pyridine-acetic anhydride in the usual fashion and recrystallization of the crude product from hexane gave 0.08 g of 13b, mp 77-78°, ir bands at 1728 (acetate) and 1720 cm^{-1}(methyl ester), pmr signals at 5.58c (H-14, H-12 superimposed), 5.50c (H-7), 3.76 (methoxyl), 2.0 (acetate), 1.20 (C-4 methyl), 1.07d and 1.00d (J=7, C-15 methyls), 0.79 (C-10 methyl).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.36; H, 9.15; O, 17.09. Found: C, 73.19; H, 9.01; O, 16.86.

Reaction of 1.06 g of 1c with mercuric acetate in the manner described above gave the same ratio of 13a and recovered 1c.

Silver Carbonate-Celite Oxidation of Methyl 14β-hydroxydihydrophotolevopimarate.--A mixture of 1 g of 7a and 7 g of freshly prepared silver carbonate-Celite reagent was refluxed for 18 hr, filtered and evaporated. The solid residue (14a) was recrystallized from hexane, yield 0.74 g, mp 205-206°, $[\alpha]_D^{27}$ -2.5°; ir bands at 1772 (γ-lactone), 1723 cm^{-1} (ester); pmr signals at 3.72 (methoxyl), 1.23 (C-4 methyl), 1.10 (C-10 methyl), 1.16d and 0.85d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36; MW, 348. Found: C, 72.80; H, 9.29; O, 17.94; MW (MS), 348.

A solution of 0.075 g of 14a in 10 ml methanol was mixed with 10 ml of 5% methanolic sodium hydroxide solution, allowed to stand with stirring at room temperature for 16 hr, acidified and evaporated. The residue was taken up in ether, washed, dried and evaporated. The residual solid (14b) was recrystallized from hexane, yield 0.064 g, mp 131-132°, $[\alpha]_{Hg}^{25}$ +32.5°; ir bands at 1770 and 1723 cm^{-1}; pmr signals at 3.74 (methoxyl), 1.20 (C-4 methyl), 0.98 (C-10 methyl), 0.92d and 0.81d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36; MW, 348. Found: C, 72.32; H, 9.55; O, 18.43; MW (MS), 348.

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tered and evaporated. The residual gum (21) was purified by chromatography, but could not be induced to crystallize; pmr signals at 3.76 (methoxyl), 1.11 (C-4 methyl), 0.94d and 0.73d (J=6, C-15 methyls), 0.74 (C-10 methyl).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 78.98; H, 10.66; O, 9.89.

Baeyer-Villiger Oxidation of 20.--A mixture of 1 g of 20 and 400 mg of 30% H_2O_2 and 2 ml of 9 M sodium hydroxide solution in 10 ml of methanol was stirred at room temperature for 2 hr, acidified with 25 ml of 10% HCl and extracted with ether. The washed and dried ether solution was evaporated and the residue recrystallized from hexane, yield of 22 0.65 g (65%), mp 177-178°, $[\alpha]_{Hg}^{25}$ -3.1°, ir bands at 1785 cm^{-1}(strained γ-lactone), 1723 cm^{-1} (ester), pmr signals at 2.73c (H-13), 1.20 (C-4 methyl), 0.97d and 0.90d (J=7, C-15 methyls), 0.90 (C-10 methyl).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36; MW, 348. Found: C, 72.61; H, 9.17; O, 18.18; MW (MS), 348.

Oxidation of 20 to 22 with m-chloroperbenzoic acid was very slow at room temperature, but could be accomplished satisfactorily in about the same yield as above by refluxing the $CHCl_3$ solution.

$NaBH_4$ Reduction of 20 to 23a.--A mixture of 1 g of 20, 0.8 g of $NaBH_4$ and 15 ml of ethanol was stirred at room temperature for 3 days, evaporated at reduced pressure, diluted with water, heated on the steam bath for one half hour, cooled and extracted with ether. Evaporation of the washed and dried ether layer gave solid 23a which was recrystallized from methanol, yield 0.8 g, mp 161°, ir bands at 3615br (-OH) and 1721 cm^{-1} (ester); pmr signals at 3.71 (methoxyl), 3.0d (J=2.8, H-14), 1.21 (C-4 methyl), 1.08 (C-10 methyl), 0.88d and 0.78d (C-15 methyls).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.19; H, 10.21; O, 14.50.

The acetate 23b was recrystallized from methanol and melted at 119°; the pmr spectrum which contained an acetate singlet at 2.00 ppm was similar to that of 23b except for a downfield shift of the H-14 resonance to 4.2 ppm.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64; O, 17.00. Found: C, 72.98; H, 9.90; O, 16.88.

Degradation of 20 to 30.--A mixture of 0.2 g of 22 in 5 ml of methanol and 20 ml of 6% sodium hydroxide solution was refluxed for 2 hr, cooled, neutralized with 10% HCl and extracted with ether. The washed and dried ether extract was evaporated. The residue (24a) was recrystallized from methanol, yield 0.19 g, mp 164-165°, pmr signals at 7.21br (-COOH), 3.76 (methoxyl), 1.20 (C-4 methyl), 1.06 (C-10 methyl), 0.96d and 0.83d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35; O, 20.81. Found: C, 68.87; H, 9.48; O, 21.12.

Treatment of 24a with acetic anhydride-pyridine resulted in quantitative reconversion to 22. The methyl ester 24b was obtained in quantitative yield by treatment with diazomethane and recrystallized from hexane, mp 169-170°, pmr signals similar to that of 24a except

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Reduction of 0.2 g of 14a with 0.18 g of $LiAlH_4$ in refluxing THF solution followed by the usual work up gave the triol 31a, yield 0.17 g, mp 146-148° (from hexane).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 74.03; H, 11.18; O, 14.79. Found: C, 74.05; H, 11.10; O, 14.89.

The gummy acetate 31b exhibited pmr signals at 4.1dbr (2 protons, center of AB part of ABX system, H-14), 3.70 (center of AB system, $-CH_2OAc$), 2.00 (two acetates), 0.99 (C-4 methyl), 0.94 (C-10 methyl); 0.85d (J=7, C-15 methyls).

Anal. Calcd. for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87; O, 19.58. Found: C, 70.37; H, 9.90; O, 19.52.

$LiAlH_4$ reduction of 0.2 g of 14b in refluxing THF and recrystallization of the crude product from methanol gave 0.164 g of triol 31c, mp 177-178°.

Anal. Calcd. for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18; O, 14.79. Found: C, 73.76; H, 10.99; O, 15.01.

The diacetate 31d was recrystallized from hexane, mp 106-107°, pmr signals 4.0 (2 protons, center of AB system, $-CH_2OAc$), 2.00 (two acetates), 1.00 (C-4 methyl), 0.90 (C-10 methyl), 0.80d (J= 6.0, C-15 methyls).

Anal. Calcd. for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87; O, 19.58. Found: C, 70.70; H, 10.00; O, 19.02.

Oxidative rearrangement of Methyl 14β-Hydroxydihydrophotolevopimarate.--To a solution of 5 g of 7a in 15 ml of acetone cooled to 0° was added dropwise with stirring 8 ml of Jones reagent. The reaction was monitored by tlc and was complete in 20 min. The solvent was evaporated and the residue taken up in ether, washed and dried. Removal of solvent gave 4.9 g of gum which crystallized on addition of hexane. Recrystallization from aqueous methanol gave 4.7 g (97%) of 20, mp 102-104° (lit. 103.5-104.5°)[7], $[\alpha]_{Hg}^{25}$ -1.2° (lit. $[\alpha]_D^{28}$ -2.6°)[7], ir bands as reported[7], pmr signals at 3.70 (methyl ester), 2.7c (H-13), 1.16 (C-4 methyl), 0.98d and 0.90d (J=7, C-15 methyls), 0.78 (C-10 methyl), CD curve (methanol, C 3 mg/5 ml) $[\theta]_{278}$ -23.40 (min).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.71; H, 9.60; O, 11.19.

Oxidation of 7a with excess chromic acid-pyridine reagent for two days and chromatography of the crude product resulted in a 15% yield of 20 and 82% recovery of unreacted starting material.

Conversion of 20 to 21.--Treatment of 0.5 g of 20 with 2 ml ethanedithiol and 0.4 ml of BF_3-etherate for 18 hr at room temperature, precipitation of the crude product by addition of methanol, and chromatography over Florosil after thorough washing with methanol and drying in vacuo afforded, after elution with benzene-chloroform (1:1), a solid thioketal which was recrystallized from methanol, yield 0.24 g (49%), mp 192-193°, pmr signals at 3.70 (methoxyl), 3.20br ($W_{1/2}$=3 Hz, thioketal methylenes), 1.10 (C-4 methyl), 0.98d and 0.90d (J=7, C-15 methyls), 0.82 (C-10 methyl).

A mixture of 0.1 g of the preceding compound, 2 g of Raney nickel and 25 ml of absolute methanol was refluxed for 18 hr, fil-

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for replacement of the carboxylic OH resonance by an additional methoxyl signal; H-13 also became visible as 2.74 dt (J=8.0, 2.4).

Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54; O, 21.02. Found: C, 69.50; H, 9.77; O, 20.97.

To a solution of 0.2 g of 24a in 40 ml of dry benzene was added 0.16 g of lead tetraacetate. The solution turned brown immediately and was refluxed under a slow stream of nitrogen, the exit gas being bubbled through a $Ca(OH)_2$ solution. After evolution of CO_2 had ceased (6 hr), the mixture was refluxed for an additional 30 min, cooled, filtered and the precipitate washed with hot benzene. The combined filtrate and washings were washed (1 M NaOH, water, and brine), dried and evaporated; recrystallization of the residue from hexane gave 54 mg (27%) of lactone 22. The mother liquor was chromatographed over Florosil. Elution with hexane-benzene (1:1) gave 20 mg of olefin 29 as a gum, pmr signals at 5.21c (H-12), 3.70 (methoxyl), 1.20 (C-10 methyl), 1.06 (C-4 methyl), 0.90d (J=7, C-15 methyls). Further elution with benzene gave 5 mg (2.5% yield) of acetate 28b, mp 156-158° (from hexane), pmr signals at 5.01dt (J= 7.5, 2.4, H-12), 2.70 (methoxyl), 2.01 (acetate), 1.15 (C-4 methyl), 1.03 (C-10 methyl), 0.90d and 0.87d (J=7, C-15 methyls).

Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.16; H, 9.25; O, 21.38. Found: C, 69.44; H, 9.54; O, 21.02.

A solution of 0.1 g of 28b in 15 ml of 2% methanolic sodium hydroxide was refluxed for one hr, concentrated at reduced pressure, diluted with water and extracted with ether. The washed and dried ether extract was evaporated; recrystallization of the residue from hexane furnished 0.08 g of 28a, mp 136-137°, pmr signals at 4.21c (H-12), 3.70 (methoxyl), 1.20 (C-10 methyl), 1.07 (C-4 methyl), 1.00d and 0.87d (J=7, C-15 methyls).

Anal. Calcd. for $C_{20}H_{34}O_4$: C, 71.48; H, 9.57; O, 19.20. Found: C, 71.27; H, 9.51; O, 18.21.

A suspension of 0.4 g of freshly prepared chromium trioxide-pyridine complex in 10 ml of CH_2Cl_2 was mixed with 0.028 g of 28a in 10 ml of CH_2Cl_2 and stirred at room temperature for 25 min. The entire mixture was added to the top of a silica gel column and eluted with benzene-$CHCl_3$ (1:1). Evaporation of solvent and recrystallization from hexane gave 18 mg of 30, mp 130-131°, $[\alpha]_{Hg}^{27}$ +78.3°, ir bands at 3615 (3° hydroxyl), 1739 (cyclopentanone) and 1728 cm^{-1} (ester); pmr signals at 3.70 (methoxyl), 1.21 (C-10 methyl), 1.06 (C-4 methyl), 1.03d and 0.85d (C-15 methyls).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 70.64; H, 9.35; O, 19.38. Found: C, 70.39; H, 9.59; O, 19.02.

Diborane Reduction of 24a.--To a solution of 0.15 g of 24a in 3 ml THF kept at -16°C was added 8 drops of a 0.9 M solution of diborane over a period of 5 min. The solution was allowed to warm up to room temperature and allowed to stand until tlc indicated complete disappearance of starting material (5 hr). The mixture was cooled to 0° and hydrolyzed with 15 ml of water. After addition of 4 g of K_2CO_3 the aqueous layer was extracted thoroughly with ether. Evaporation of the washed and dried ether extracts and recrystallization of the residue from methanol furnished 0.085 g (70%) of 25, mp 141-142°; pmr signals at 3.70 (methoxyl), 3.0c (center of AB part of ABX system, H-14), 1.20 (C-4 methyl), 1.03 (C-10 methyl), 0.88d and 0.83d (J=7, C-15 methyls).

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Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29; O, 18.15. Found: C, 71.90; H, 10.11; O, 18.50

Oxidation of the above with chromic trioxide-pyridine in methylene chloride solution gave a 90% yield of 22.

Reaction of 22 with Methyl Lithium.--Addition of 1 ml of a 1.5 M solution of methyl lithium in ether to an ice cold solution of 0.5 g of 22 in 30 ml of anhydrous ether, stirring for 4 hr was followed by addition of a saturated solution of NH_4Cl°. The washed and dried ether layer was evaporated and the residue (27) was recrystallized from hexane, yield 0.57 g, mp 144-145°, $[\alpha]_{Hg}^{25}$ -2.08°; ir bands at 3615, 1725 and 1707 cm^{-1}, pmr signals at 3.70 (methoxyl), 2.81dt (J=8.8, 2.8, H-13), 2.27 (methyl ketone), 1.20 (C-4 methyl), 1.05 (C-10 methyl), 0.89d and 0.87d (J=7, C-15 methyls).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; O, 17.65. Found: C, 72.61; H, 9.80; O, 17.27.

Oxidation of 0.08 g of 27 with 0.1 g of m-chloroperbenzoic acid in refluxing $CHCl_3$ gave 54 mg (68%) of lactone 22. Under identical conditions, 24b was converted to 22 in 55% yield.

Acid-Catalyzed Cleavage of 20.--A solution of 0.2 g of 20 in 20 ml of $CHCl_3$ saturated with hydrogen chloride was stirred at room temperature for 4 hr and evaporated at reduced pressure. The residue was taken up in ether; evaporation of the washed and dried ether solution and recrystallization from hexane at -76° gave 0.174 g of 35, mp 62-63°, ir bands at 1730 (ester), 1680 and 1660 (α,β-unsaturated ketone); λ_{max} 237 nm (ε=7160); pmr signals at 6.72t (J=4, H-12), 3.66 (methoxyl), 2.85m (H-15), 1.20 (C-4 methyl), 0.98 (C-10 methyl), and 1.00d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.70; H, 9.41; O, 14.30

Base-Catalyzed Cleavage of 20.--A solution of 1 g of 20 in 4% methanolic sodium methoxide was refluxed for 12 hr, cooled, evaporated at reduced pressure, diluted with water and extracted with ether. Evaporation of the washed and dried extract gave a gum which was subject to preparative tlc ($CHCl_3$-2% methanol). The less polar fraction was 36a (0.37 g) which could not be induced to crystallize, pmr signals at 5.25c (H-11 and H-12), 3.74 and 3.72 (methoxyls), 1.05 (C-4 methyl), 1.00 (C-10 methyl), 0.83d (J=6.5, C-15 methyls).

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95; O, 17.56. Found: C, 72.88; H, 9.95; O, 16.96.

The more polar product 36b (0.37 g) was also a gum and had pmr signals at 5.10c (H-11 and H-12), 3.74 and 3.72 (methoxyls), 1.05 (C-4 methyl), 0.90d (J=7, C-15 methyls), and 0.86 (C-10 methyl).

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95; O, 17.56. Found: C, 72.79; H, 10.09; O, 17.18.

A solution of 0.1 g of 36a in 3% methanolic sodium hydroxide was refluxed for 12 hr and acidified. The usual work-up gave 36b in almost quantitative yield.

Catalytic hydrogenation of the mixture of 36a and 36b obtained prior to separation by tlc (Pd-C, ethyl acetate solution) and work-up in the usual fashion gave a gummy residue which was a mixture of

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two saturated diesters (tlc, pmr spectrum). No attempt was made to resolve the mixture.

A solution of 0.5 g of 36b in 25 ml of CH_2Cl_2 was ozonized at -70° until excess ozone was detected in the KI trap. The solution was flushed with dry nitrogen and decomposed by being stirred with one ml of dimethyl sulfide overnight. The solvent was removed at reduced pressure and the residue taken up in ether. Evaporation of the washed and dried ether extract, chromatography of the residue over silica gel and elution with $CHCl_3$ gave 0.25 g of 37 as a gum which could not be induced to crystallize, ir bands at 2735, 1730 (sh) and 1725 cm^{-1}, pmr signals at 9.4t (J=3, -CHO), 3.74 and 3.72 (methoxyls), 1.13 (C-4 methyl) and 0.85 (C-10 methyl).

Anal. Calcd. for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70; O, 24.66. Found: C, 67.04; H, 8.79; O, 24.14.

A solution of 0.1 g of 37 in 30 ml of benzene was refluxed with 1 g of tris-triphenylphosphine rhodium chloride until the orange color of the solution had changed to yellow. Addition of 15 ml of ethanol to the cooled solution to precipitate the complex, filtration and evaporation of the filtrate gave a gum which was chromatographed over Florosil. Elution with $CHCl_3$ gave 38 (0.032 g) as a gum which could not be induced to crystallize, pmr signals at 3.74, 3.72 (methoxyls), 1.21d (J=6, C-9 methyl), 1.21 (C-4 methyl), 0.88 (C-10 methyl).

Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52; O, 21.59. Found: C, 68.60; H, 9.61; O, 21.40.

Methyl Isophotolevopimarate (39).--A mixture of 0.500 g of 23a and 0.512 g of p-toluenesulfonyl chloride in 6 ml of pyridine was kept at 0° for 20 hr, poured over crushed ice and extracted with ether. The washed and dried ether layer was evaporated at reduced pressure to give a gum which showed a major spot on tlc. Chromatography over Florosil and elution with benzene furnished 0.365 g of 39 which could not be induced to crystallize, $[\alpha]_D^{27}$ +9°, ir band at 1721 cm^{-1}(ester), pmr signals at 4.3br (H-7), 3.73 (methoxyl), 1.25 (C-4 methyl), 1.01d and 0.98d (J=7, C-15 methyls), 0.76 (C-10 methyl).

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

A mixture of 0.08 g of 39 in 15 ml of dioxane and 1.5 g of $KHSO_4$ was refluxed for 10 hr. The solvent was removed at reduced pressure, the residue extracted with ether and the washed and dried extract was evaporated. The residue was methyl abietate (42), yield essentially quantitative. The same result was obtained when 23a was refluxed with $KHSO_4$ in dioxane.

Cleavage of 39 to 41.--A solution of 1 g of 39 in 30 ml of benzene was oxidized with 1 g of OsO_4 in 10 ml of pyridine by stirring at room temperature for 72 hr. The osmate ester was decomposed by bubbling H_2S through the solution of 1.5 hr. The mixture was allowed to stand at room temperature for an additional 5 hr, filtered and the precipitate washed with hot $CHCl_3$. The combined filtrate and washings were washed, dried and evaporated. Chromatography of the residue over silicic acid and elution with $CHCl_3$ furnished 40 which was recrystallized from hexane, yield 0.35 g (36%), mp 105-106°, pmr signals 4.21t (J=6, H-7), 3.71 (methoxyl), 1.26 (C-4 methyl), 1.13d and 1.00d (J=7, C-15 methyls) and 0.88 (C-10 methyl).

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Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71.57; H, 9.92; O, 18.60.

A solution of 0.2 g of 40 in 10 ml of methanol and 10 drops of water was oxidized with 0.5 g of $NaIO_4$ by stirring at room temperature for 2 hr at the end of which period all starting material had been replaced by a less polar product (tlc). The solution was diluted with ether, filtered and the precipitate washed with ether. The combined solvents were washed, dried and evaporated; the residue (41) was recrystallized from hexane, yield 0.09 g, mp 136-137°, $[\alpha]_D^{25}$ +69.1°, ir bands at 2710 and 1735 sh (aldehyde), 1720 (ester) and 1700 cm^{-1}(ketone); uv λ_{max} 281 nm, pmr signals at 9.6t (J=2.5, CHO), 3.74 (methoxyl), 1.22 (C-4 methyl), 1.21 (C-10 methyl) and 1.03d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.19; H, 9.42; O, 18.66.

Conversion of 39 to 43.--A solution of 0.25 g of 39 in 10 ml of $CHCl_3$ saturated with hydrogen chloride was allowed to stand at room temperature for 6 hr, evaporated and the residue was taken up in ether. The washed and dried ether extract was evaporated and the residual red gum was chromatographed over Florosil. Elution with benzene furnished 43 which was recrystallized from hexane, yield 0.187 g, mp 99°, pmr signals at 5.36br (H-7), 4.46br (H-14), 3.73 (methoxyl), 1.2 (C-4 methyl), 1.00d and 0.98d (J=6.5, C-15 methyls), and 0.81 (C-10 methyl), ord curve (hexane, C 5.6 mg/ml) Φ_{223} = -2500 (min).

Anal. Calcd. for $C_{21}H_{33}O_2Cl$: C, 71.59; H, 9.36; O, 9.09; Cl, 9.94; MW 354, 352. Found: C, 71.19; H, 9.49; O, 8.86; Cl, 9.99; MW(MS), 354 (32%), 352.

Solvolytic Rearrangements of 7c.-- a) Tosylation of 1 g of 7a with p-toluenesulfonyl chloride in pyridine in the usual fashion and

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recrystallization of the crude product from hexane gave 0.86 g of 7c, mp 111-112°, pmr signals at 7.2-7.6c (4 aromatic protons), 4.7d (J=6.5, H-14), 3.74 (methoxyl), 3.1 (aromatic methyl), 1.16 (C-4 methyl), 0.98 (C-10 methyl), 0.81d and 0.66d (J=7, C-15 methyls).

A solution of 0.5 g of 7c and 0.3 g of sodium acetate in 25 ml of acetic acid was refluxed for 12 hr, evaporated at reduced pressure, diluted with water and extracted with ether. Evaporation of the washed and dried ether extract, chromatography of the residue over alumina (activity III) gave 44a which was recrystallized from hexane, yield 0.418 g, mp 118-119°, ir bands at 1728 and 1720 cm^{-1}, pmr signals at 3.76 (methoxyl), 2.00 (acetate), 1.13 (C-4 methyl), 0.98 (C-10 methyl), 0.79d and 0.72d (J=7, C-15 methyls).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64; O, 17.00. Found: C, 73.58; H, 9.70; O, 16.90.

Hydrolysis of 0.1 g of 44a with refluxing 2% methanolic sodium hydroxide, concentration to small volume, extraction with ether and evaporation of the washed and dried ether extract gave a homogeneous product (44b) which could not be induced to crystallize, ir bands at 3615 and 1720 cm^{-1}, pmr signals at 3.74 (methoxyl), 1.22 (C-4 methyl), 1.05 (C-10 methyl), 0.85d and 0.65d (J=7, C-15 methyls).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.50; H, 10.19; O, 14.47.

b) Reduction of 0.1 g of 7c with 0.1 g of $LiAlH_4$ in THF at room temperature for 4 hr followed by the usual work-up gave 45 in quantitative yield as a gum which could not be induced to crystallize and had pmr signals at 3.21 (center of AB system of $-CH_2OH$), 1.02 (C-4 methyl), 0.73 (C-10 methyl), 0.73d and 0.70d (J=7, C-15 methyls).

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80; O, 5.51. Found: C, 82.21; H, 11.57; O, 5.31.

at least partial migration of the 8,9 bond which is trans-antiparallel to the departing tosylate was to be expected. In fact, acetolysis of **7c** yielded a single acetate in 90% yield whose ^1H NMR spectrum did not exhibit a signal characteristic of hydrogen geminal to an acetoxy group. Hydrolysis yielded an alcohol which resisted oxidation and acetylation under ordinary conditions. Consequently, the acetate and the alcohol derived from it were formulated as **44a** and **44b**. Similarly, $LiAlH_4$ reduction of **7c** gave an alcohol whose physical properties differentiated it from alcohol **4b**, obviously as the result of solvolytic rearrangement to **45**.

These rearrangements are similar in type to the biosynthetic pathway postulated for the atisane–aconane conversion[37] which has been duplicated in several diterpenoid bicyclo[2.2.2]octane model systems[38,39] and utilized in the recent synthesis of the delphinine-type alkaloid talatisamine.[40]

Registry No.—**1c**, 3513-69-7; **3a**, 5947-57-9; **3c**, 54003-59-7; **4a**, 54003-60-0; **4b**, 54003-61-1; **5**, 54003-62-2; **6**, 54003-63-3; **6** dinitrophenylhydrazone, 54003-64-4; **7a**, 54003-65-5; **7b**, 54003-66-6; **7c**, 54003-67-7; **12a**, 54003-68-8; **12b**, 54003-69-9; **12c**, 54003-70-2; **13a**, 3484-53-5; **13b**, 6821-61-0; **14a**, 54003-71-3; **14b**, 54081-34-4; **20**, 54003-72-4; **20** thioketal, 54003-73-5; **21**, 54003-74-6; **22**, 54003-75-7; **23a**, 54003-76-8; **23b**, 54003-77-9; **24a**, 54003-78-0; **24b**, 54003-

79-1; **25,** 54003-80-4; **27,** 54003-81-5; **28a,** 54003-82-6; **28b,** 54019-71-5; **29,** 54003-83-7; **30,** 54036-74-7; **31a,** 54003-84-8; **31b,** 54003-85-9; **31c,** 54081-35-5; **31d,** 54053-75-7; **35,** 54003-86-0; **36a,** 54003-87-1; **36b,** 54003-88-2; **37,** 54003-89-3; **38,** 54003-90-6; **39,** 54003-91-7; **40,** 54003-92-8; **41,** 54003-93-9; **43,** 54003-94-0; **44a,** 54003-96-2; **44b,** 54003-95-1; **45,** 54003-58-6.

Supplementary and Miniprint Material Available. The Experimental Section will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material and full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and 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 $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1017.

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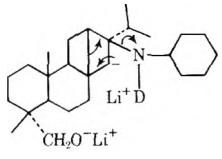
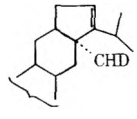
(8) The reported[7] low yield (18%) of **1a** from the pyrolysis of **3a,** which would have interfered with the feasibility of the proposed scheme, could be raised to 80% by operating on **3c.** This avoids the self-induced acid-catalyzed isomerization of **1a** to abietic acid and other resin acid isomers. However, an attempt at a shortcut to **3d** through direct exchange of sp^2-bound H-14 in **3e** (to avoid complications due to reaction of butyllithium with the ester function) with lithium deuteriocyclohexylamide–*N,N*-dideuteriocyclohexylamine gave only **1d,** presumably by the mechanism depicted below. As there was no deuterium incorporation either at C-12 or C-14, the rearrangement must have taken place prior to capture of D^+ from the medium by the anion.



(9) A third possibility, **11,** resulting from formal consecutive shifts of the 8,12 and 13,14 bonds, was unlikely on mechanistic grounds in a β-oriented epoxide and is excluded by the ^{1}H NMR data, since H-12 should exhibit vicinal couplings of ~2 and ~6 Hz.



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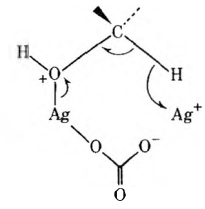

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Preparation of Bicyclo[3.2.1]octan-6-ones from Substituted Cyclohexyl Diazo Ketones

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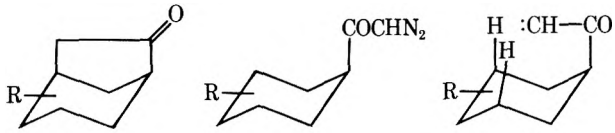
The copper or silver ion catalyzed decomposition of diazo ketones **4b–9b** has been examined with reference to formation of bicyclooctanones through carbon–hydrogen bond insertion at C(3). The course of the reaction is sensitive to the nature of alkyl substitution in the cyclohexane ring, and the results are analyzed in terms of both conformational effects and the degree of substitution at the site of insertion.

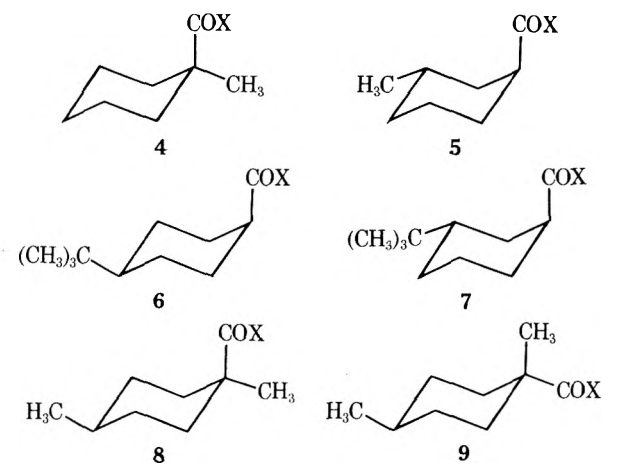
In the course of other investigations we required a number of bicyclo[3.2.1]octan-6-ones (**1**) bearing various substituents of known stereochemistry at different positions on the six-membered ring. An attractive route to several of the desired compounds involved metal ion catalyzed decomposition of the appropriately substituted cyclohexyl diazo ketones **2**. There are several known examples of this transformation in which bicyclooctanones are formed through insertion of the intermediate carbene or carbenoid species (formally **3**) into an axial carbon–hydrogen bond at



1 **2** **3**

C(3).[1-3] We describe here our experiments in preparing six new bicyclooctanones using this procedure. Points of general interest include the variable effectiveness of both silver and copper in catalyzing the reaction, and substituent effects which may be interpreted as involving both the degree of substitution at C(3) and also the preferred conformations of the side chain and the cyclohexane ring.

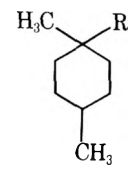
The carboxylic acids **4a–8a**, all of which have been previously described,[4,5] were prepared as precursors of the desired diazo ketones. The configuration of **8a** and its epimer **9a** has been assigned[5b] on the basis of retention times of



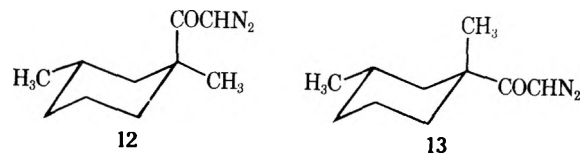
4 **5** **6** **7** **8** **9**

a, X = OH; b, X = CHN_2

the methyl esters on vapor phase chromatography (VPC), NMR spectral data, and comparisons of refractive indices. Our present work provides corroboration for this stereochemical conclusion. We have prepared a mixture of these acids (**10**) by Koch carbonylation of 1,4-dimethylcyclohexanol (**11**) in sulfuric acid and formic acid.[5a] VPC of the de-



10, R = COOH
11, R = OH



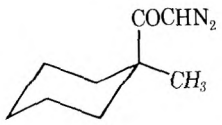
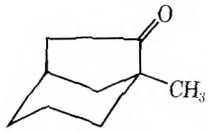
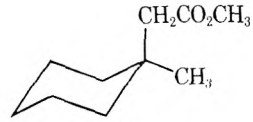
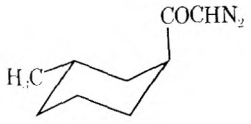
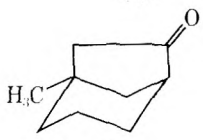
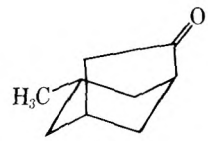
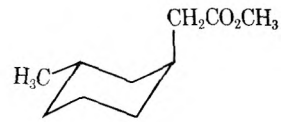
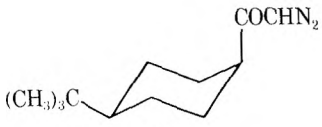
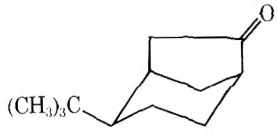
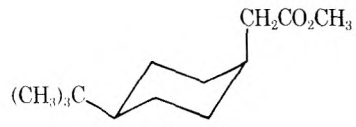
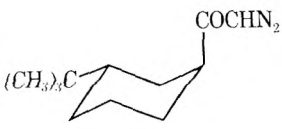
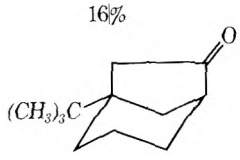
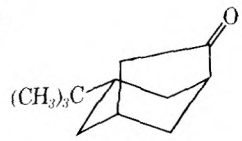
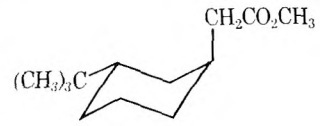
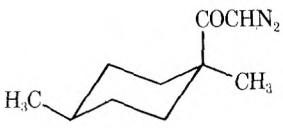
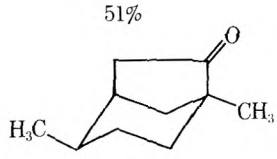
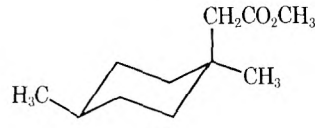
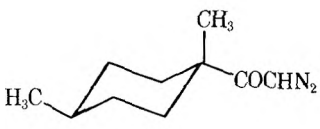
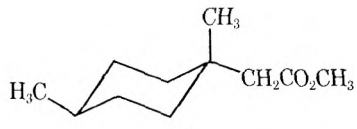
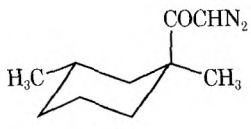
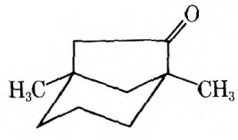
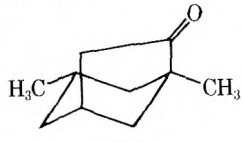
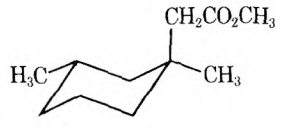
12 **13**

rived methyl esters indicated that the two isomers **8a** and **9a** were formed in the ratio 86:14. Since exposure of minor isomer **9a** to the reaction conditions did not lead to its epimerization, the carbonylation reaction is under kinetic control. Such Koch reactions are expected[6] to proceed by preferential introduction of an axial carboxyl group, and this implies that the major isomer formed is **8a**, in line with the original assignment.[5b] Furthermore, this stereochemistry is in keeping with subsequent transformations of **8a** and **9a** described below.[7]

Each of these carboxylic acids was converted through the acyl chloride to the diazo ketone in the usual manner,[8] and these diazo ketones were then decomposed in one of two known ways. In the first procedure[9] a methanolic solution of diazo ketone (~0.25 *M*) was treated with silver benzoate in triethylamine at room temperature with subsequent heating at reflux for 1 hr. The second method[1] involved very slow addition (~4 drops/min) of a dilute solution of diazo ketone in cyclohexane (~300 ml, ≤0.1 *M*) to a refluxing suspension of $CuSO_4$ in ~1.25 l. of the same solvent, followed by 5-hr reflux after addition was complete.

Products were isolated and purified by preparative VPC, and the results are gathered in Chart I. Yields are based on relative VPC areas and are referred to the carboxylic acid used. Those given for the reactions of **4b** include data from the original study by Wenkert and his coworkers, wherein other products also were isolated. Data for **12**, partly from work which we reported earlier,[2] are also included. The difference in behavior between **8b** and **9b**, with only **8b** undergoing the insertion reaction to yield a ketone, is parallel to earlier results[2] with **12** and its stereoisomer **13**. The present observation is in accord with the stereochemical assignment noted above for acids **8a** and **9a**. The structures of the products from **5b–9b** rest on ir and 220-MHz NMR spectroscopic properties recorded in the Experimental Section, as well as general previous experience[1-3] with the transformation. In particular the two isomeric ketones **16** and **17** obtained from **5b**, as well as **21** and **22** from **7b**, could be

Chart I
Decomposition of Diazo Ketones

Diazo ketone	Metal ion	Products and yields		
 **4b**	Ag	 **14** 8%		 **15** 58%
	Ag[a]	6%		51%
	Cu	48%		
	Cu[a]	62%		
 **5b**	Ag	 **16** <1%	 **17** <1%	 **18** 41%
	Cu	26%	2%	
 **6b**	Ag[b]			
	Cu	16%		
 **19**			 **20** 80%[b]	
 **7b**	Ag	 **21** <1%	 **22** <1%	 **23** 62%
	Cu	51%	7%	
 **8b**	Ag	 **24** 40%		 **25** 36%
	Cu	67%		
 **9b**	Ag	No ketone found		 **26** 53%
 **12**	Ag[c]	 **27** 35%	 **28** 15%	 **29** 29%
	Cu	58%	22%	

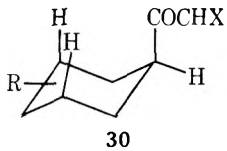
[a] From ref 1; Ag reaction using silver oxide in methanol. [b] H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *J. Am. Chem. Soc.*, **92**, 2800 (1970); yield based on recrystallized **6b**. [c] From ref 2.

distinguished from each other by the multiplicity of the signals for the exo C(7) methylene protons (α to the carbonyl group). Vicinal coupling of this proton to the bridgehead was absent in **16** and **21**, but present in **17** and **22**. In this regard it was profitable to make comparisons with the NMR spectra of **27** and **28**, for which the structural distinction is firmly based on chemical degradation of **27**.[2,10]

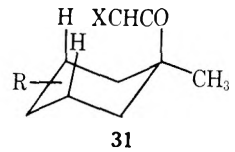
From Chart I it is clear that for preparation of these bicyclooctanones, copper catalysis is invariably superior to silver, and indeed it is well known[1,11,12] that copper favors external reactions in decomposition of diazo ketones, while silver is particularly effective in promoting Wolff rearrangement. While the use of silver is then of no preparative value for the desired ketones, the results provide an in-

structive comparison with the copper-catalyzed process in evaluation of structural effects on the transformation.

These structural effects appear to be of three types from the product distributions observed, and we consider each of these individually. First, the degree of substitution of the carbon–hydrogen bond at C(3) into which insertion may occur plays a role. Thus in the copper decomposition of both **5b** and **7b** the intramolecular competition in each case strongly favors insertion into the tertiary bond (leading to **16** and **21**) rather than the secondary one (leading to **17** and **22**). Such regioselectivity in intermolecular insertion is well documented[13] for a variety of other types of stabilized carbene species, including carboalkoxy and cyano carbenes. A second discernible effect is the conformational behavior of the cyclohexane ring. This is obvious in rather strongly biased systems such as **8b** and **9b,** in which essentially all reaction occurs from the stable conformations shown, but, more interestingly, the effect is also apparent when **8b** is compared with the conformationally more mobile **4b.** The latter system, lacking the anchoring effect of the 4-methyl substituent, presumably reacts from both chair conformers. Only the one shown can lead to ketone, however, and the result with silver catalysis is more ester and less ketone from **4b** than from **8b.** It is noteworthy that this effect is much less significant with copper catalysis, where Wolff rearrangement is inherently less favored. Finally, the success of these reactions depends importantly on the presence of substitution at C(1) in the diazo ketone. Without this substitution the silver reactions fail to give ketones at all, as seen with **5b** and **7b,** and the copper reactions are adversely affected. Thus, although there is little conformational difference between **4b** and **5b,** and despite the availability only in **5b** of a tertiary carbon–hydrogen bond for insertion, it is **4b** with a 1-methyl substituent that furnishes more ketone. Previous examples[1,2] of the formation of bicyclooctanones by this process from diazo ketones all have involved only cyclohexanes bearing a methyl group at C(1), and the particular significance of this substitution, therefore, could not be appraised. We suggest that this behavior may be ascribed to a rotational conformation effect on the axial side chain when there is geminal substitution at C(1). In the absence of such C(1) substitution, the axial group will be preferentially rotated away from the ring (see **30**) to avoid nonbonded interactions with the C(3) and C(5) axial hydrogens. When a substituent is present at C(1), however, this orientation of the axial group is somewhat less favorable. The result is that the orientation toward the ring (see **31**), which is necessary for insertion at C(3) or



30



31

C(5), is then relatively more favorable. It is reasonable that this effect be more pronounced in the silver reactions, since, as noted with the ring conformational effect above, Wolff rearrangement provides better competition to insertion under these conditions.

Despite the sensitivity of yield to the specific substitution pattern involved, this cyclization clearly offers convenient access to a variety of alkylated bicyclo[3.2.1]octan-6-ones.

Experimental Section

Materials and Equipment. All VPC was carried out using a Varian Aerograph Model A-90-P3 gas chromatograph with one of the following columns: A, 25% DEGS, 20 ft × 0.25 in.; B, 25% DEGS, 25 ft × 0.375 in.; C, 30% DEGS, 10 ft × 0.375 in.; D, 25% PDEAS, 48 ft × 0.25 in.; E, 30% Carbowax 20M, 10 ft × 0.375 in.; F, 30% SE-30, 10 ft × 0.375 in. All columns were prepared using 45/60 Chromosorb W in aluminum tubing. Ir and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian HR-220 (220 MHz) spectrometer. Mass spectra were obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4, and results were processed with an AEI DS-30 data system. Boiling points are uncorrected; melting points are corrected. Solutions were dried over $MgSO_4$. Unless otherwise noted, products were obtained as colorless oils.

Preparation of Diazo Ketones. The pure carboxylic acids were converted to acyl chlorides with thionyl chloride according to the procedure of Eliel.[14] heating at the end of the reaction was omitted in the case of epimerizable acid chlorides. Excess thionyl chloride was removed in vacuo, and the residue was added immediately to an excess (>3 equiv) of distilled ethereal diazomethane cooled in an ice bath. The reaction mixture was allowed to warm to room temperature overnight. Excess diazomethane and solvent were removed by evaporation in a steam bath and then in vacuo. The diazo ketones thus prepared showed strong absorption at 2110 and 1640 cm^{-1} in their ir spectra (other carbonyl absorptions were absent) and were used in subsequent steps without further purification.

General Procedure for Silver(I)-Catalyzed Decomposition of Diazo Ketones. The method of Newman and Beal[9]—addition of a triethylamine solution of silver benzoate to the diazo ketone dissolved in alcoholic solvent—was employed without modification. The prescribed work-up yielded a residue which was distilled bulb-to-bulb to give a colorless distillate. Analysis of the reaction mixture and further purification were accomplished with VPC using the column indicated in each case. Products are described in order of their elution.

General Procedure for Copper(II)-Catalyzed Decomposition of Diazo Ketones. The crude diazo ketone (12–30 mmol) was taken up in cyclohexane (200–300 ml), filtered through Celite, and added at a very slow rate (<4 drops/min) through a constant addition funnel to a suspension of anhydrous $CuSO_4$ (2 equiv) in cyclohexane (800–1250 ml) heated to reflux; the reaction was mechanically stirred and protected from atmospheric moisture with a drying tube. Three to five days were usually necessary to complete the addition. To ensure complete decomposition of the diazo ketone, the reaction mixture was heated at reflux for at least another 5 hr after addition was complete. About ⅓ of the solvent was removed by distillation through a 35-cm Vigreux column. After cooling, water (250 ml) was added and the organic phase was washed with 10% Na_2CO_3 (100 ml) and brine (100 ml), and then dried. The remainder of the cyclohexane was removed by careful distillation (Vigreux column) and the residue was distilled under reduced pressure. The yellow distillate obtained was further purified by VPC using the column indicated in each case. Products are described in order of their elution.

Silver(I)-Catalyzed Decomposition of 4b. Products were analyzed on column A. 1-Methyl-1-cyclohexaneacetic acid methyl ester (**15,** 58%): ir 2945 (s), 2870 (m), 1738 (s), 1455 (m), 1225 (m), 1190 (m), 1165 (m), 1023 cm^{-1} (m); NMR δ 3.57 (s, 3 H), 2.16 (s, 2 H), 1.54–1.21 (br m, 10 H), 0.98 (s, 3 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.49; H, 10.73.

5-Methylbicyclo[3.2.1]octan-6-one (**14,** 8%):[1] ir 2960 (s), 2890 (m), 1745 (s), 1450 (m), 1400 (w), 1038 cm^{-1} (w); NMR δ 2.50 (br, 1 H), 2.19 (dd, J = 7, 18 Hz, 1 H), 2.00 (dd, J = 3.5, 18 Hz, 1 H), 1.93–1.24 (br m, 8 H), 0.936 (s, 3 H).

Copper(II)-Catalyzed Decomposition of 4b. Products were analyzed on column B. In addition to **14** (48%), there was obtained a small amount of a cyclobutanone (ir 1775 cm^{-1}).[1]

Silver(I)-Catalyzed Decomposition of 5b. Product analysis on column B indicated essentially one component. This was collected and identified as *trans*-3-methylcyclohexaneacetic acid methyl ester (**18,** 41%): ir 2920 (s), 1740 (s), 1455 (m), 1430 (m), 1165 (s), 1020 cm^{-1} (m); NMR δ 3.59 (s, 3 H), 2.21–2.03 (m, 2 H), 1.82–1.02 (br m, 10 H), 0.925 (d, J = 7 Hz, 3 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.55; H, 10.69.

Copper(II)-Catalyzed Decomposition of 5b. Product analysis on column B afforded two products. 1-Methylbicyclo[3.2.1]octan-6-one (**16,** 26%): ir 2945 (s), 2860 (m), 1745 (s), 1455 (m), 1377 (w), 1345 (w), 1255 (w), 1165 (m), 1122 (w), 1080 (m), 1028 cm^{-1} (w); NMR δ 2.33 (br, 1 H), 1.98 (dd, J = 3, 18 Hz, 1 H), 1.83 (dd, J =

0.5, 18 Hz, 1 H), 1.90–1.38 (br m, 8 H), 1.13 (s, 3 H); mass spectrum 138.1047 (M^+, calcd for $C_9H_{14}O$, 138.1044).

exo-3-Methylbicyclo[3.2.1]octan-6-one (**17**, 2%): ir 2945 (s), 2860 (m), 2845 (m), 1745 (s), 1455 (m), 1407 (m), 1155 (m), 1052 cm^{-1} (m); NMR δ 2.54 (br, 1 H), 2.23 (br, 1 H), 2.12 (ddd, J = 0.5, 7, 18 Hz, 1 H), 1.95 (dd, J = 3, 18 Hz, 1 H), 2.04–1.05 (br m, 7 H), 0.90 (d, J = 6 Hz, 3 H); mass spectrum 138.1051 (M^+, calcd for $C_9H_{14}O$, 138.1044).

Copper(II)-Catalyzed Decomposition of 6b. Product analysis on column C yielded *endo*-2-*tert*-butylbicyclo[3.2.1]octan-6-one (**19**, 16%): ir 2980 (s), 2900 (m), 1747 (s), 1445 (m), 1360 (m), 1162 cm^{-1} (m); NMR δ 2.63 (br, 1 H), 2.19 (br, 1 H), 2.16 (dd, J = 3, 18 Hz, 1 H), 2.02 (dd, J = 6, 18 Hz, 1 H), 1.86–1.23 (br m, 7 H), 0.89 (s, 9 H); mass spectrum 180.1512 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

Silver(I)-Catalyzed Decomposition of 7b. Product analysis on column C indicated a single major component which was identified as *trans*-3-*tert*-butylcyclohexaneacetic acid methyl ester (**23**, 62%): ir 2965 (s), 2900 (m), 1742 (s), 1470 (m), 1448 (m), 1428 (m), 1360 (m), 1148 (m), 1022 cm^{-1} (w); NMR δ 3.56 (s, 3 H), 2.38–2.22 (m, 2 H), 1.78–1.04 (br m, 10 H), 0.81 (s, 9 H).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.44; H, 11.38.

Copper(II)-Catalyzed Decomposition of 7b. Products analysis on column C yielded *exo*-3-*tert*-butylbicyclo[3.2.1]octan-6-one (**22**, 7%): ir 2970 (s), 2895 (m), 1747 (s), 1460 (m), 1360 (m), 1140 cm^{-1} (w); NMR δ 2.58 (br, 1 H), 2.26 (br, 1 H), 2.11 (dd, J = 6.5, 18 Hz, 1 H), 1.94 (dd, J = 3.5, 18 Hz, 1 H), 1.95–1.20 (br m, 7 H), 0.84 (s, 9 H); mass spectrum 180.1510 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

1-*tert*-Butylbicyclo[3.2.1]octan-6-one (**21**, 51%): ir 2980 (s), 2900 (m), 1747 (s), 1470 (br, m), 1365 (m), 1150 (m), 1088 cm^{-1} (m); NMR δ 2.34 (br, 1 H), 2.09 (dd, J = 0.5, 18 Hz, 1 H), 1.80 (dd, J = 3, 18 Hz, 1 H), 1.99–1.06 (br m, 8 H), 0.91 (s, 9 H); mass spectrum 180.1519 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

Silver(I)-Catalyzed Decomposition of 8b. Product analysis on column D indicated two major components which were collected and identified as 1,*c*-4-dimethyl-*r*-1-cyclohexaneacetic acid methyl ester (**25**, 36%): ir 2950 (s), 2925 (s), 2870 (m), 2850 (m), 1740 (s), 1450 (m), 1430 (m), 1375 (m), 1195 (m), 1150 (m), 1095 cm^{-1} (m); NMR δ 3.55 (s, 3 H), 2.20 (s, 2 H), 1.92–1.02 (br m, 9 H), 0.96 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.72; H, 11.02.

endo-2,5-Dimethylbicyclo[3.2.1]octan-6-one (**24**, 40%); ir 2965 (s), 2940 (s), 2875 (m), 1745 (s), 1448 (m), 1400 (w), 1375 (w), 1130 (w), 1042 (w), 980 cm^{-1} (w); NMR δ 2.19 (br, 1 H), 2.09 (dd, J = 4, 18 Hz, 1 H), 1.98 (dd, J = 7, 18 Hz, 1 H), 1.98–1.00 (br m, 7 H), 0.93 (s, 3 H), 0.89 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.66; H, 10.70.

Copper(II)-Catalyzed Decomposition of 8b. Distillation of the crude product (98–108°, 16 mm) yielded **24** (67%), identical with material described above.

Silver(I)-Catalyzed Decomposition of 9b. Product analysis on column C gave a single product identified as 1,*t*-4-dimethyl-*r*-1-cyclohexaneacetic acid methyl ester (**26**, 53%): ir 2950 (s), 2930 (s), 2860 (m), 2850 (m), 1740 (s), 1438 (m), 1250 (m), 1190 (m), 1140 (m), 1023 (w), 995 cm^{-1} (w); NMR δ 3.55 (s, 3 H), 2.07 (s, 2 H), 1.88–1.02 (br m, 9 H), 0.97 (s, 3 H), 0.89 (d, J = 6 Hz, 3 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.75; H, 11.13.

Copper(II)-Catalyzed Decomposition of 12. Product analysis on column A gave ketones **27** (58%) and **28** (22%), identical with previously described material.[2]

1,*t*-3-Dimethyl-*r*-1-cyclohexanecarboxylic Acid. Addition of a solution of 3,5-dimethylcyclohexanol (32.1 g, 0.25 mol) in 97+% formic acid to 96% sulfuric acid[15] gave 31.0 g (80%) of white, crystalline material, mp 76.5–81.5°. Two recrystallizations from aqueous methanol gave 1,*t*-3-dimethyl-*r*-1-cyclohexanecarboxylic acid, mp 88.5–89.5° (lit. mp 88.5–89.5° [2] and 92° [5a]). Esterification of the crude acid with diazomethane and analysis by VPC on column E indicated two components in the ratio 19:1. The isomeric minor acid (also independently available[2]) was submitted to the reaction conditions; the recovery of material was quantitative, and VPC analysis after diazomethane esterification indicated formation of ≤1% of the major acid under these conditions.

1,*c*-4- and 1,*t*-4-Dimethyl-*r*-1-cyclohexanecarboxylic Acids (8a and 9a). Treatment of 1,4-dimethylcyclohexanol (9.45 g, 0.074 mol) with sulfuric and formic acid as described above gave 7.30 g (64%) of a colorless oil. After diazomethane esterification VPC analysis on column F showed the presence of two components in the ratio 86:14. Each of these compounds was collected and hydrolyzed with methanolic alkali to regenerate the acid. The major ester yielded an acid, mp 44.5–45.5° (lit.[5b] mp 46.5–47°), and amide, mp 82–83° (lit.[5a] mp 82°); the second ester yielded an acid, mp 41–42°, and amide, mp 129.5–130.5° (lit.[5a] mp 134°). Submission of the minor acid (34.6 mg) to the reaction conditions described above again gave a quantitative recovery of material with essentially no isomerization.

Acknowledgments. We thank Miss Luz Catan for expert technical assistance and The Rockefeller University Mass Spectrometry Laboratory for mass spectra. NMR spectra were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant No. GB-29946.

Registry No.—**4b**, 20609-36-3; **5b**, 54277-24-6; **6b**, 28125-14-6; **7b**, 54277-25-7; **8a**, 24097-70-9; **8b**, 54277-26-8; **9a**, 24097-71-0; **9b**, 54277-27-9; **12**, 38864-05-0; **14**, 20608-68-8; **15**, 20608-66-6; **16**, 54277-28-0; **17**, 54277-29-1; **18**, 54277-30-4; **19**, 54277-31-5; **21**, 54277-32-6; **22**, 54277-33-7; **23**, 54277-34-8; **24**, 54277-35-9; **25**, 54277-36-0; **26**, 54277-37-1; silver, 7440-22-4; copper, 7440-50-8; 1,*t*-3-dimethyl-*r*-1-cyclohexanecarboxylic acid, 38864-02-7; 3,5-dimethylcyclohexanol, 5441-52-1; 1,4-dimethylcyclohexanol, 5402-28-8; 1,*c*-4-dimethyl-*r*-1-cyclohexanecarboxamide, 54277-38-2; 1,*t*-4-dimethyl-*r*-1-cyclohexanecarboxamide, 54277-39-3.

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Preparation and Favorskii Reaction of Equatorial and Axial 2-Bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one[1]

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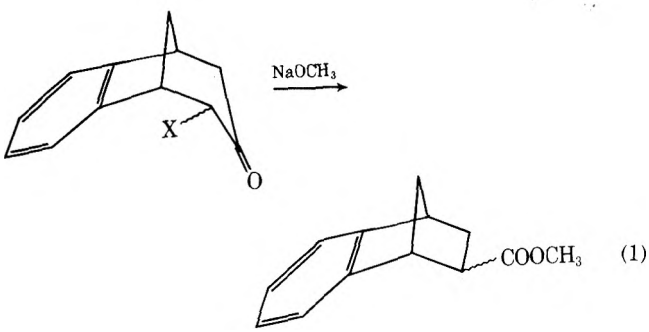
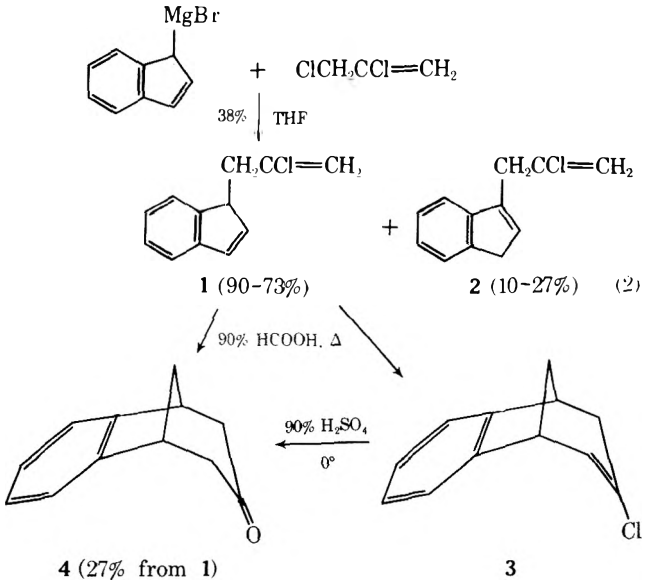
The title ketone was brominated to afford equatorial and axial 2-bromo ketones **6** and **7**, respectively, as well as the axial,axial 2,4-dibromo ketone **8**. Chlorination results were similar. Preparative routes to the individual brominated products were developed. The spectral characteristics of **6**, **7**, and **8** were quite like those of the nonbenzo analogs. The Favorskii reaction of either bromo ketone led to ring contraction and to the formation of the epimeric methyl benzonorbornene-2-carboxylates in good yield. The composition of the ester product did not depend significantly upon the reactant used but it did depend upon the solvent employed. The more polar solvent methanol (sodium methoxide was the base) largely favored the exo ester (exo:endo 80:20), whereas the less polar solvent glyme (same base) allowed an increase in the endo ester (exo:endo 58.5:41.5). The results are rationalized in terms of a cyclopropanone-mediated pathway from the bromo ketones to the esters. Subsequent base-catalyzed epimerization of the esters (solvent dependent) to the observed mixtures limited definitive conclusions about the Favorskii process.

Although monocyclic ring contraction by means of the Favorskii reaction is well known, such contraction in bicyclic molecules is less common.[2] In particular, this conversion in common bicyclic systems seems limited to bridgehead bromo ketones.[3] As part of a general program in benzonorbornene chemistry, it was of interest to investigate the reaction shown in eq 1.[4] Aside from the immediate



(1)

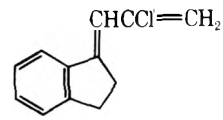
question about the feasibility of reaction 1, two other specific points seemed worthwhile for investigation. First, would epimeric halo ketones yield epimerically related products, i.e., is reaction (1) stereospecific?[5] Second, could the solvent effect noted in earlier Favorskii reactions[7] be used to enhance the production of the endo 2-substituted product in eq 1—a type of compound generally less available than its exo counterpart?



(2)

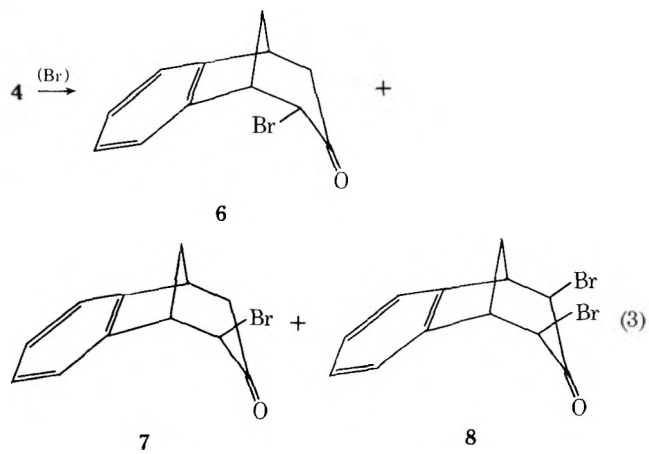
Results

Benzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (**4**) was prepared by the method of Lansbury and Nienhouse,[8] as shown in eq 2. The yields for the sequence were considerably below those reported. Moreover, in our preparations, the (chloroallyl)indene **2** accompanied the reported product **1**, making the separation of these isomers an additional complication.[9] Another isomeric possibility, compound **5**, was absent on the basis of both NMR and uv data.



5

Bromination of **4** under most conditions tried led to product mixtures of the equatorial 2-bromo ketone **6**, the axial 2-bromo ketone **7**, and the axial,axial 2,4-dibromo ketone **8**, shown in eq 3. *N*-Bromosuccinimide (NBS) was more selective, however, and its use constituted a good route to **7**. Some results are given in Table I.



(3)

Chlorination of **4** was less satisfactory but quite analogous to bromination. When sulfuryl chloride was used, the axial,axial dichloro ketone (**8**-Cl) was isolable. Only crude samples of the axial chloro ketone **7**-Cl were obtained, and evidence for the equatorial isomer **6**-Cl was indirect. Use of *N*-chlorosuccinimide appeared to favor **7**-Cl.

The structure proofs for the bromo ketones **6**–**8** rest entirely upon their spectra. As may be seen in Table II, these bromo ketones were easily identified, nonetheless, because

Table I
Bromination of Benzobicyclooctenone 4

Study	Reactants	Conditions	Products, % 6	7	8
a	4 + Br_2	HOAc, 20°	10–20	30–40	30–40
b	4 + Br_2	HOAc, NaOAc, 20°	Trace	40–50	40–50
c	4 + $PhN(CH_3)_3^+Br_3^-$	THF, 20°	Trace	Trace	40–50
d	4 + NBS + Bz_2O_2	CCl_4, 76°	Trace	90–98	Trace

Table II
Selected Spectral Characteristics of Bromo Ketones[a]

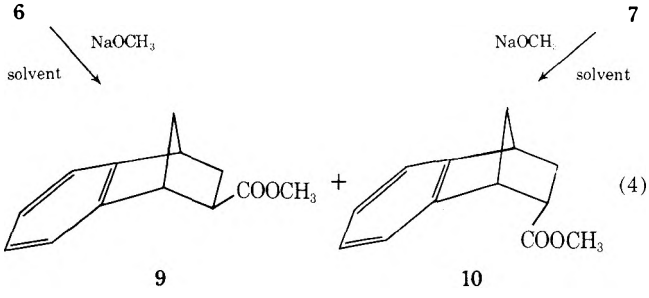
Ketones	λ_{max} (n,π*), nm (ε) c-C_6H_{12}	CH_3CN	$\nu C=O$,[b] cm^{-1} $CHCl_3$	CH_3CN	δH-2[c]	J, Hz 1,2	2, anti-8
4	288 (30)		1704		2.38 (m)		
4a	280 (19)		1711				
6	285 (29)	283 (32)	1727	1728	4.93 (d)	3.6	0
6a		284 (33)	1733		(4.93)	3.6	0
7	315 (188)	308 (172)	1720	1718	4.23 (m)	3.2	1.6
7a	315 (105)	313 (96)	1715	1715	(4.22)	3.0	2.0
8	335 (105)	332 (236)	1722	1722	4.28 (dd)	3.2	2.2
8a	342 (195)	341 (190)	1725	1722	(4.28)	3.0	1.8

[a] Ketone 4a is bicyclo[3.2.1]octan-3-one. Ketones 6a–8a are its bromo derivatives related to 6–8. Data for the ketones 4a and 6a–8a are taken from ref 10b. [b] Ca. 3% solutions in the given solvent. [c] $CDCl_3$ solvent. The values in parentheses are the observed values (ref 10b) + 0.25, an increment added to adjust these values taken in CCl_4 solvent to the $CDCl_3$ values.

their spectra closely resembled those of their nonbenzo analogs.[10]

As Table I indicates, the axial bromo ketone **7** was best synthesized using NBS. The dibromo ketone **8** was best obtained using phenyltrimethylammonium tribromide. The equatorial bromo ketone **6** was not easily producible from ketone **4**, however. Rather, epimerization of **7** with hydrogen bromide in acetic acid was employed. A mixture of **6** and **7** in a ca. 1:2 ratio was produced in this way. Separation by chromatography on silica gel then gave pure **6**. Epimerization of **7** to **6** with lithium bromide in acetone was unsuccessful. Characterization of **6** and **7** by their 2,4-DNP derivatives was complicated. Bromo ketone **6** afforded a product containing bromine, λ_{max} ($CHCl_3$) 357 nm (log ε 4.35), which analyzed correctly for **6** 2,4-DNP. Thin layer chromatography showed that it was a mixture of two major and a number of minor components, however. Bromo ketone **7** produced an axial 2-ethoxy ketone 2,4-DNP derivative, λ_{max} ($CHCl_3$) 359 nm (log ε 4.36).

Application of the Favorskii reaction on pure **6** or **7**, using sodium methoxide as the base, gave benzonorbornene products, as shown in eq 4. Moreover, the yields of esters **9**



9 **10**

and **10** were good (70–94%) and the esters were separable. Two solvents were employed, methanol and 1,2-dimethoxyethane (glyme). Choice of solvent affected the reaction, as shown in Table III. Studies indicated, however, that this solvent effect involved *epimerization*. Placement of pure ester **9** in the basic medium used in each case gave comparable product mixtures of esters **9** and **10** as did the Favorskii reactions themselves.

Table III
Favorskii Reaction on Bromo Ketones

Bromo ketone	Solvent[a]	Ester yield, %	Composition by GLC[b] % 9	% 10
6	CH_3OH	82	83.3 (90)	16.7 (10)
7	CH_3OH	70	79.9	20.1
6	Glyme	94	58.5 (58)	41.5 (42)
7	Glyme	75	58.5	41.5

[a] Excess sodium methoxide was present in all cases. See Experimental Section. [b] Values in parentheses are the percentage compositions obtained by epimerization of pure ester **9** in the given solvent–base system.

The exo ester **9** and its corresponding acid obtained by saponification were identical with samples available by another route.[11] Unreported at the outset of this study,[12a] endo ester **10** and its acid were initially characterized structurally only by spectra (see Discussion). In response to a referee's challenge on its structure, however, ester **10** (and its acid) were independently synthesized[12b] for comparison.

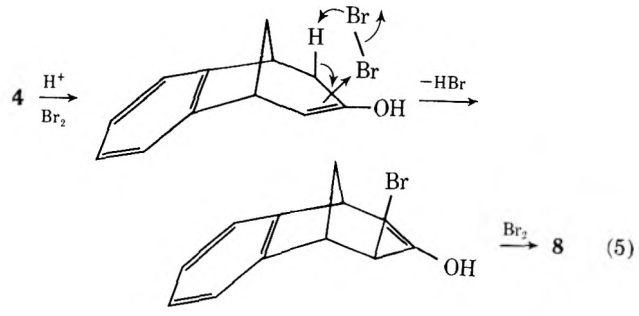
Discussion

The structural evidence for and the origin of (chloroallyl)indene **2** in the sequence of eq 2 deserve comment. While there were slight differences between **1** and **2** in their ir and uv spectra, substantial structural evidence was best obtained from their NMR spectra. In **1**, the chloroallylic methylene protons were clearly nonequivalent because of the adjacent asymmetric center. An AB multiplet centered at δ 2.53 was evident.[13] In **2**, however, these methylene protons were equivalent as expected and a broad singlet resonance at δ 3.63 was observed. Additionally, **2** possessed another pair of methylene protons (benzylic), seen as a narrow doublet at δ 3.40. Finally, **1** exhibited four vinyl protons whereas **2** exhibited three. The origin of **2** probably was a base-promoted isomerization of **1** by excess indenyl Grignard reagent. The recommended procedure[8] utilized inverse addition (the Grignard reagent was *slowly added to* the dichloropropene). Such a procedure should minimize such an isomerization because locally high base (Grignard

reagent) concentrations are avoided. Nonetheless, as **1** builds in concentration, opportunity for contact with the entering Grignard reagent increases. While not thoroughly investigated, the *rate of addition* of the Grignard reagent seemed important. Slow (ca. 10 min) addition gave 10% of **2**, while addition in toto gave 27% of **2**. In none of our tries, however, was the formation of some **2** avoided.[14]

The possibility that the by-product was **5** seems remote. The NMR spectrum of **5** should present an AA'BB' pattern for the methylene protons and its uv spectrum should resemble that of 3-chloro-1-phenylbutadiene [lit.[16] λ_{max} 283 nm (ϵ 20,400)]. However, the by-product showed no such NMR pattern and had λ_{max} 250 nm (ϵ 6712).

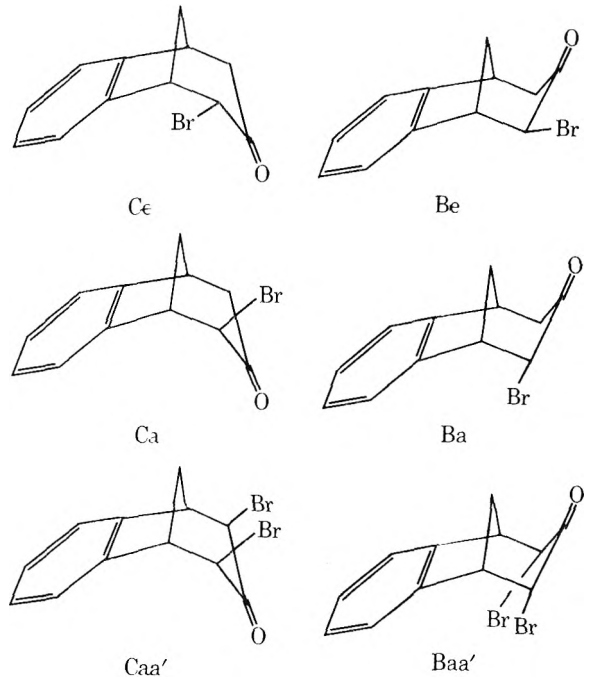
The bromination of ketone **4** proceeded largely as anticipated. Axial bromination via enol intermediates is well documented[10] in **4a** and the preponderance of **7** over **6** is unexceptional. Comparison of studies a and b in Table I indicates that **6** is not a kinetic product. In the presence of a hydrogen bromide scavenger (sodium acetate), the formation of **6** was suppressed. Most likely, therefore, it formed in study a by an acid-catalyzed epimerization of **7**. Studies a–c do show one interesting feature: α,α'-dibromination to **8** is a serious side reaction in all cases, but particularly in tetrahydrofuran. The recent report[17] that dibromination follows a different mechanistic pathway than monobromination may find further exemplification here. If **8** had resulted from a *second* bromination of **7** (as has been customarily believed for such dibromo products), then about half of **7** was so changed in a and b. However, this same fate should have befallen **6**, and 5–10% of an equatorial, axial 2,4-dibromo ketone should have resulted. The absence of this product lends support to the idea that **4** is itself the source of **8** via a bromo enol as in eq 5. The improved formation of **8** in tetrahydrofuran in study c is in accord with the contention[17] that aprotic nonpolar media should assist dibromination relative to monobromination. Study d employed a radical bromination pathway. In the absence of benzoyl peroxide no reaction took place. The absence of **8** as a product is explicable because enols do not mediate such pathways. The formation of **7** must result from the lack of other easy reaction sites and the known exo (axial here) preference for chain transfer in related bicyclic systems.[18]



The structures for **6**–**8** that are based upon spectra seem secure.[19] In brief, equatorial α-bromo substituents in ketones are known to cause little change in the n,π^* absorption in the uv, either in λ_{max} or in ϵ, compared to the parent ketone. In contrast, a significant shift to higher frequency in the ir carbonyl stretch is observed. Bromo ketones **6** and **6a** show such behavior relative to **4** and **4a**. Essentially the reverse effects are caused by axial α-bromo substituents, as illustrated by **7**, **7a**, **8**, and **8a** relative to the parent ketones. One point deserves more comment. The ir shift for the carbonyl stretch between **4** and **7** is greater than that between **4a** and **7a** (16 vs. 4 cm^{-1}) even though the bromo substituent is axial in both **7** and **7a**. This results from the more skewed axial position of the bromine in **7** caused by the [6,7]benzo ring. This skewing decreases the axial character at C-2 somewhat and increases the shift in the ir. The close similarity of the spectra of the benzo and nonbenzo ketones in Table II demonstrates that in these cases the aromatic π system does not seriously perturb the situation, a point that had been a concern to others.[10c]

From the spectral data just discussed, an axial or an equatorial position for the bromide in the bromo ketones may be assigned. So **6** is either Ce or Be, **7** is either Ca or Ba, and **8** is either Caa' or Baa', as shown in Chart I, provided that only extreme chair or boat conformers are considered. Various data indicate that the chair conformers in Chart I predominate. The carbonyl stretching frequencies

Chart I

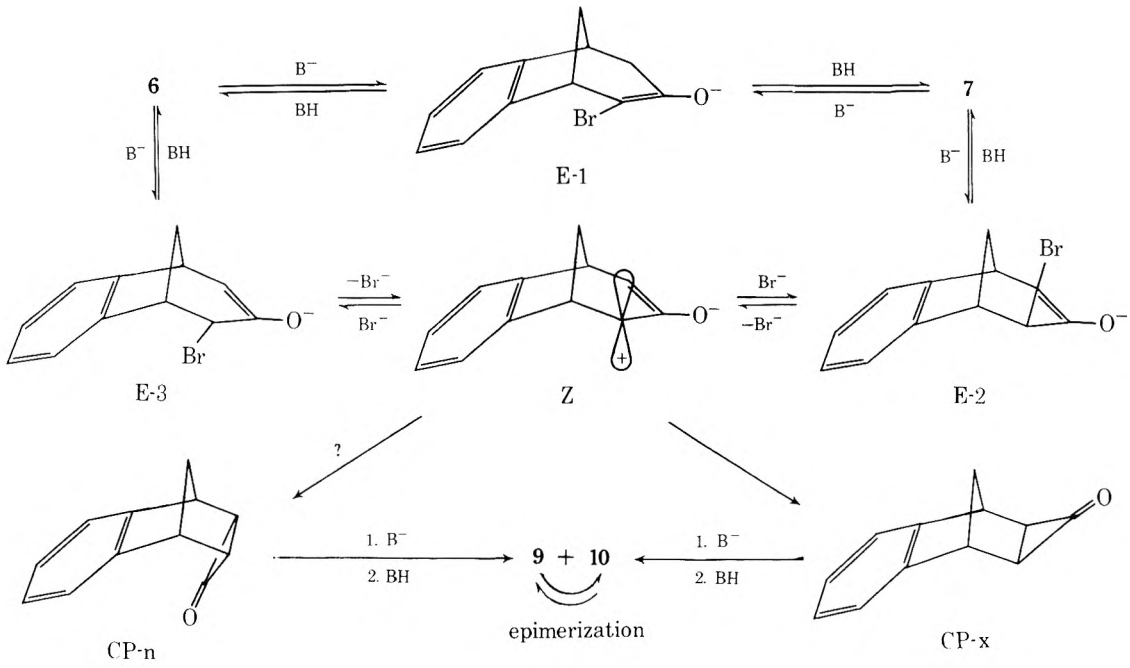


of these compounds remained essentially constant in either cyclohexane or acetonitrile, as did the molar absorptivities of the n,π^* uv transition. Both of these features imply a high degree of conformational rigidity.[19] The symmetrical structure given for **8** (Caa') was assigned from its revealing NMR spectrum. The bromomethine protons were identical and exhibited a doubled doublet at δ 4.28, with vicinal and long-range coupling constants in accord only with a chair conformer.[10] The similarity in those selected spectral characteristics presented in Table II between **8** and **7** clearly establish the chair conformation Ca for **7** as well. The bromomethine proton in **6** appeared as a sharp doublet at δ 4.93. Spin-decoupling experiments[20] showed that vicinal coupling alone was present. The value of $J_{1,2}$ here (3.6 Hz) was in better accord with the vicinal dihedral angle of 60° present in Ce than with one of 100° present in Be. The latter would be expected to have $J_{1,2} \simeq 0$ Hz, especially so because the bromine atom would nearly eclipse H-1 and contribute to the vanishing of the coupling.[21]

The formation of an ethoxy ketone 2,4-DNP derivative from **7** is not unexpected.[22] Bromo ketone **7** was itself stable in acidic alcohol; so the derivative was probably formed from solvolysis of the **7** 2,4-DNP first formed. The mixture of derivatives formed from **6** may be *E,Z* isomers or skeletally rearranged products.[23] No work was done on this point, however.

Favorskii product **9** was identified by comparison with a

Chart II[a]



[a] $B^- = CH_3O^-$; BH = CH_3OH.

known sample.[11] The structure of ester **10** was most convincingly evidenced by comparison with **9**. In particular, three spectral features were sought and found that helped to distinguish the two. First, the exo methine proton H-2 in **10** was deshielded relative to the endo H-2 in **9** (δ 3.17 vs. 2.38, respectively). Second, the cis coupling for exo H-2 and the adjacent exo H-3 in **10** was greater[24] than the trans coupling for endo H-2 and the adjacent exo H-3 in **9** (10 vs. 5 Hz, respectively). Third, the methoxy protons in **10**, being closer to the aromatic ring, were upfield relative to those in **9**[25] (δ 3.49 vs. 3.72, respectively). Additionally, however, ester **10** was shown to be identical with a sample prepared by an unambiguous path.[12b]

The literature on the Favorskii reaction is voluminous. The current "normal" mechanism is a cyclopropanone-mediated pathway with intervening dipolar ion species.[26] "Abnormal" Favorskii reactions have been rationalized via a semibenzilic acid rearrangement mechanism.[27] The scheme given in Chart II is based on the more common "normal" mechanism as a guide. Because our studies do not bear significantly on the Favorskii pathway itself, particularly as kinetic control was absent owing to the ready epimerization of ester **9**,[28] it seems best to accommodate our results to the generally accepted mechanism. In dilute base (0.1 *M* sodium methoxide in methanol) **6** and **7** equilibrated rapidly, presumably via enolate E-1. The bromo ketones were additionally slowly consumed in the Favorskii process. The alternative enolates E-2 and E-3 formed from **7** and **6** should afford the zwitterion Z easily because the bromine in each is similarly positioned for departure. The disrotatory closure of Z to the exo cyclopropanone CP-x can then readily occur. Though symmetry-allowed, such analogous closure of Z to the endo cyclopropanone CP-n appears from molecular models to be somewhat unfavorable for steric reasons, although our data cannot exclude it. The carbonyl and ring π systems are severely close and the transition state leading to CP-n should be disfavored for this reason. Also, some torsional strain between the bridgehead hydrogens and H-2,4 would develop as they pass by one another in the formation of CP-n. Nonetheless, either CP-x and CP-n would yield the esters **9** and **10** via base-promoted ring opening and subsequent epimerization. Finally, the different compositions of esters found in the two solvents used may reflect different solvation effects on the equilibria involved, but no further studies were made on this point.

Experimental Section

Melting points and boiling points are uncorrected. The former were taken in capillaries in a Thomas-Hoover oil bath apparatus. All thin layer chromatography (TLC) was performed on Silicar-7GF coated plates or on commercial Analtech S. G. F. plates. Spectra were determined on the following instruments: NMR, Varian A-60, T-60, or HA-100 spectrometers; ir, Perkin-Elmer 421 or 521 spectrophotometers; and uv, Cary 11 or Beckman Octa V spectrophotometers. Gas chromatography (GLC) was conducted on a Varian Aerograph 1520 instrument with helium carrier gas. Microanalyses were done by Abbott Laboratories, North Chicago, Ill.

Benzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (4). This ketone was obtained as reported, mp 66–67° (lit.[8b] mp 64–66°). Selected spectral features are given in Table II.[29]

3-(2-Chloroallyl)indene (2). In the preparation of **4**, reaction of indenylmagnesium bromide with 2,3-dichloropropene in tetrahydrofuran gave the reported product 1[8] and varying amounts of **2**, depending upon the time of addition of the Grignard reagent (see Discussion). Indene **2** was isolated in one preparation by GLC on a column of fluorosilicone oil (QF-1, 15% on Chromosorb W) at 140°: ν (CCl_4) 1394 cm^{-1} (trisubstituted alkene); δ (CCl_4) 7.40 (m, ArH), 6.43 (m, H-2), 5.33, 5.23 (m, $=CH_2$), 3.63 (broad s, allylic CH_2), 3.40 (narrow d, 1-CH_2); λ_{max} (hexane) 250 nm (ϵ 6712).[30]

Anal. Calcd for $C_{12}H_{11}Cl$: C, 75.59; H, 5.82. Found: C, 75.45; H, 5.98.

(a)-2-Bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (7). Ketone **4** (12 g, 70 mmol), *N*-bromosuccinimide (freshly recrystallized from water, 12.4 g, 70 mmol), benzoyl peroxide (0.96 g), and carbon tetrachloride (60 ml) were heated under reflux for 8 hr. The material was chilled and separated from the precipitate of succinimide. Evaporation under reduced pressure left a yellow oil (17.5 g, ca. 100%) which was indicated by TLC to be mainly **7**. The pure product was obtained by chromatography on silica gel using chloroform hexane mixtures as eluents as a colorless oil: 17.1 g (97%); ν ($CHCl_3$) 1720 cm^{-1} (C=O); δ ($CDCl_3$) 7.22 (m, ArH), 4.23 (m, H-2), 3.31 (m, H-1, axial 4, 5), 2.48 (m, 8-CH_2, equatorial H-4); λ_{max} (cyclohexane) 315 nm (ϵ 188). Other spectral data are in Table II.[29] The bromo ketone should be stored below 0°.

Anal. Calcd for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42. Found: C, 57.58; H, 4.53.

Reaction of **7** (0.4 g) with 2,4-DNP reagent in alcohol–sulfuric acid slowly gave an orange precipitate (0.46 g, mp 74–84° dec). Re-

crystallization from acetone–water (no exchange to an acetone derivative occurred) gave a bromine-free pure product, mp 172.5–174.5° dec, 87 mg (14%), λ_{max} ($CHCl_3$) 359 nm (ϵ 22,912). The presence of an ethoxy group was clear in the NMR spectrum, δ ($CDCl_3$) 3.58 (q), 1.26 (t). The derivative was presumably the 2,4-DNP derivative of the axial 2-ethoxybenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one.

Anal. Calcd for $C_{20}H_{20}O_5N_4$: C, 60.60; H, 5.09; N, 14.13. Found: C, 60.73; H, 5.11; N, 14.32.

Bromo ketone **7** did not solvolyze in acidic alcohol under these conditions. Therefore the ethoxy derivative is believed to form from **7** 2,4-DNP by ethanolysis.

(e)-2-Bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (6). Hydrogen bromide (8.75 g) was gently bubbled into bromo ketone **7** (17.5 g, 70 mmol) dissolved in acetic acid (875 ml). The solution was allowed to stand at room temperature. Analysis by TLC after 1.5 days indicated an epimeric mixture of **6** and **7**, together with small amounts of the parent ketone **4** and dibromo ketone **8**. No further change was observed in the time period 1.5–5 days. The mixture was poured into water and extracted with ether. Upon removal of the solvent from the dried extracts, a crude mixture of mostly **6** and **7** was obtained as a brown oil (16.1 g, 92%). Analysis by NMR indicated ca. two parts of **7** to one part of **6**. In chromatography on silica gel with chloroform–hexane, the elution order was **8**, **7**, **6**, and lastly **4**. In this way was isolated pure **6**, 3.77 g (21%), mp 108–109° from hexane: ν ($CHCl_3$) 1727 cm^{-1} (C=O); δ ($CDCl_3$) 7.27 (m, ArH), 4.93 (d, H-2), 3.75 (m, H-1), 3.45 (m, H-5), 2.78 (finely structured m, 4-CH_2), 2.38 (m, 8-CH_2); λ_{max} (cyclohexane) 285 nm (ϵ 28.8). Other spectral data are in Table II.[29]

Anal. Calcd for $C_{12}H_{11}OBr$: C, 57.39; H, 4.42. Found: C, 57.37; H, 4.48.

Use of catalytic amounts of hydrogen bromide in acetic acid, or formic acid, or carbon tetrachloride under various conditions was less effective in the epimerization. Pyridine failed to promote the reaction after 1 week at 25°. Under these last conditions lithium bromide in acetone was similarly ineffective. Sodium methoxide in methanol (0.1 *M*) at 25° rapidly isomerized **7** to **6** and vice versa. The process was complicated by loss of reactant to the Favorskii reaction, however.

Reaction of **6** (100 mg) with 2,4-DNP reagent in alcohol–sulfuric acid gave a precipitate, 160 mg, mp 138–143°. The orange solid was recrystallized from acetone (no exchange), mp 169–173° dec, λ_{max} ($CHCl_3$) 357 nm (ϵ 22,514). Analysis by TLC indicated two major and several minor components. While no definite structures were assigned to these components, it is clear that no bromine loss occurred in this derivatization (cf. **7** above).

Anal. Calcd for $C_{18}H_{15}O_4BrN_4$: C, 50.13; H, 3.51; N, 12.99. Found: C, 50.18; H, 3.54; N, 13.04.

(a,a)-2-4-Dibromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (8). To a solution of ketone **4** (0.5 g, 2.9 mmol) in anhydrous tetrahydrofuran (20 ml) held at 20° there was added phenyltrimethylammonium tribromide (Aldrich, 1.6 g, 4 mmol). After 1 hr the solution was added to a saturated solution of sodium bicarbonate (12.5 ml) combined with sodium thiosulfate (0.1 *N*, 25 ml). The product was extracted with ethyl acetate. The extracts were dried and evaporated to afford crystalline **8**. Recrystallization from ether gave pure **8**, 0.44 g (46%), mp 166–169°: ν ($CHCl_3$) 1723 cm^{-1} (C=O); δ ($CDCl_3$) 7.27 (s, ArH), 4.28 (dd, H-2, 4), 3.63 (m, H-1, 5), 3.27 (d, J = 13 Hz, H-8 anti to aromatic ring), 2.42 (m, H-8 syn to aromatic ring); λ_{max} (cyclohexane) 335 nm (ϵ 233). Other spectral data are given in Table II.[29]

Anal. Calcd for $C_{12}H_{10}OBr_2$: C, 43.67; H, 3.05. Found: C, 43.65; H, 3.21.

Other Bromination Studies. (1) Bromination of ketone **4** in glacial acetic acid (equimolar reactants at 20° with illumination from a 275-W sun lamp) gave a mixture of **6**, **7**, and **8**. See Table I. Analysis was by TLC, although crystalline **8**, which settled out upon completion of the reaction, could be isolated directly. This represented the fastest method to obtain **8**, but the yield was somewhat lower than the method described above. (2) Ketone **4** (0.5 g, 3 mmol) in glacial acetic acid (15 ml) containing 1 drop of acetic acid saturated with hydrogen bromide was treated dropwise with bromine (0.53 g) and anhydrous sodium acetate (0.27 g) in acetic acid (15 ml) over a 45-min period. Water (75 ml) was added and the crystalline precipitate was filtered off. The filtrate was extracted with ether thoroughly. Analysis by TLC of the precipitate and the solvent-free extracts indicated a ca. 1:1 ratio of **7**:**8**. Only a trace of **6** was detected. See Table I. (3) Bromination of ketone **4** in carbon tetrachloride as in part 1 led to a similar set of products but in ca. one-half the yield. (4) Attempted reaction of ketone **4** with NBS (equimolar, 1-hr reflux) gave an 80% recovery of **4** with no apparent bromination. (5) Attempted reaction as in **4** with NBS and a trace of benzoyl peroxide at 25° for 8 hr likewise was unsuccessful (94% recovery of **4**).

Chlorination Studies. (1) Ketone **4** (1.0 g, 5.8 mmol) in dry carbon tetrachloride (29 ml) was treated dropwise with sulfuryl chloride (5.2 ml, 6.4 mmol) in carbon tetrachloride (8 ml) at ambient temperature. After 2 hr the solution was poured into ice water. The organic layer was neutralized with sodium bicarbonate solution, separated, dried, and evaporated. The residue (1.42 g) was analyzed by TLC. By comparison of relative R_f values with the bromo analogs, the product consisted principally of the axial chloro ketone **7**-Cl and the axial,axial′ dichloro ketone **8**-Cl, with a trace of the equatorial chloro ketone **6**-Cl. The dichloro ketone was the only pure product isolated: mp 153–155° from cyclohexane–hexane; δ ($CDCl_3$, partial spectrum) 4.15 (dd, H-2, 4).

Anal. Calcd for $C_{12}H_{10}OCl_2$: C, 59.78; H, 4.18. Found: C, 60.11; H, 4.31.

Impure **7**-Cl, mp 54–64° from hexane, was also isolated, δ ($CDCl_3$, partial spectrum) 4.02 (m, H-2). (2) Reaction of ketone **4** (0.5 g), benzoyl peroxide (40 mg), and *N*-chlorosuccinimide (0.4 g) in carbon tetrachloride under reflux for 8 hr gave crude **7**-Cl in quantitative yield (0.6 g). Only trace amounts of the other chloro ketones were evident by TLC analysis.

Favorskii Reaction of Bromo Ketone 6. A. In Methanol. A solution of sodium methoxide in methanol (2 *M*, 20 ml) was stirred with bromo ketone **6** (0.25 g, 1.0 mmol) at 25° for 4 hr. The solution was chilled to 0° and neutralized with glacial acetic acid. Ether (80 ml) was added and the precipitate of sodium acetate was separated. The ether was evaporated from the filtrate and the residual yellow oil (0.18 g) was analyzed by GLC on a silicone gum rubber column (10% SE-52 on Chromosorb W) at 180°. The chromatograms were calibrated with known samples. The yield of combined esters was 82%; the percentage composition was **9**:**10**, 88.3:16.7. Under these conditions endo ester **10** eluted before its exo isomer **9** (relative retention times 0.95:1).

Methyl benzonorbornene-*exo*-2-carboxylate (9) was identical with an authentic sample[11] as was the corresponding acid, mp 112–113° (lit.[11] mp 112–113°), obtained from it by saponification.

Methyl benzonorbornene-*endo*-2-carboxylate (10) was obtained as a colorless oil: ν ($CHCl_3$) 1728 cm^{-1} (C=O); δ ($DCDl_3$) 7.11 (m, ArH), 3.65 (m, H-1), 3.49 (s, $COOCH_3$), 3.37 (m, H-4), 3.17 (doublet of triplets, H-2, $J_{2,exo\text{-}3}$ = 10, $J_{1,2}$ = $J_{2,endo\text{-}3}$ = 4 Hz), 2.10 (eight-line multiplet, exo H-3), 1.9–1.5 (m, endo H-3, 7-CH_2).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.89; H, 6.67.

Ester **10** was identical with a sample prepared in a totally independent fashion.[12b] Saponification of **10** with 1 *N* aqueous methanolic sodium hydroxide (25°, 20 hr) afforded benzonorbornene-*endo*-2-carboxylic acid: mp 131–132° from hexane; ν ($CHCl_3$) 3540, 3300–2500 (broad), 1750 (sh), 1710 cm^{-1} (COOH); δ ($CDCl_3$) 9.03 (broad, COOH), 7.12 (m, ArH), 3.67 (m, H-1), 3.40 (m, H-4), 3.20 (doublet of triplets, H-2, J's as in ester **10**), 2.10 (eight-line multiplet, exo H-3), 1.9–1.45 (m, endo H-3, 7-CH_2).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.52; H, 6.41.

Use of dilute sodium methoxide (0.1 *M*) in the above reaction for 52 hr was less satisfactory. The reaction led to ester **9** in only 44% yield and a number of uncharacterized by-products were observed. No endo ester **10** was detected although small amounts could have been overlooked in the complex GLC and NMR traces. Early stages of the reaction were followed by TLC. Partial isomerization of bromo ketone **6** to the axial isomer **7** was pronounced in the initial stages. Seemingly, the two were "equilibrated" in ca. 3 hr. Thereafter **7** afforded **9** while **6** slowly disappeared, at least partially, through isomerization to **7**.

B. In 1,2-Dimethoxyethane (Glyme). A suspension of sodium methoxide in glyme was prepared from sodium metal (0.12 g, 5 mg-atoms) and methanol (0.55 g) in hot solvent (7 ml). At 25°, bromo ketone **6** (0.25 g, 1.0 mmol) in glyme (1 ml) was added and the mixture was stirred for 1 hr. The reaction material was chilled to 0° and processed as described above. The yield of esters was 94.2% and the percentage composition was **9**:**10**, 58.5:41.5.

Favorskii Reaction of Bromo Ketone 7. These reactions were performed in exactly the same manner as described for **6**. The results are given in Table III.

Epimerization Studies. A. In Methanol. Ester **9** (1 mmol) was substituted for bromo ketone **6** in the procedure given above for the Favorskii reaction of the latter in methanol. The procedure used was identical and the recovered ester was analyzed by GLC as

stated there. Recovery was essentially quantitative. The percentage composition determined by GLC was **9:10**, 90.2:9.8. The composition determined by NMR analysis was **9:10**, 87:13.

B. In Glyme. Ester **9** (1 mmol) was substituted for bromo ketone **6** in the procedure given above for the Favorskii reaction of the latter in glyme. The procedure used was identical and the recovered ester (~100%) was analyzed: by GLC, **9:10**, 58.1:41.9; by NMR, *9:10*, 60:40.

Acknowledgment. The authors thank Dr. R. S. Egan and Ms. R. Stanaszek of Abbott Laboratories for their assistance in the NMR aspects of this work.

Registry No.—**2**, 54143-19-0; **4**, 13351-26-3; **6**, 54143-20-3; **6** DNP, 54143-21-4; **7**, 54164-79-3; **7** DNP, 54164-80-6; **8**, 54143-22-5; **8** Cl, 54143-23-6; **9**, 54143-24-7; **10**, 54164-81-7; **10** free acid, 54274-40-7; 2,4-DNP derivative of (a)-2-ethoxybenzc[6,7]bicyclo[3.2.1]oct-6-en-3-one, 54143-25-8; phenyltrimethylammonium tribromide, 4207-56-1.

References and Notes

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(29) Complete spectra may be found in the M.S. Thesis of R.R.R., 1973.
(30) Cf. (chloroallyl)indene **1**, λ_{max} (hexane) 243 nm (ϵ 13,110).

Addition of Diphenyldiazomethane to 7-*tert*-Butoxynorbornadiene. Formation of *exo*- and *endo*-3,3-Diphenyltricyclo[3.2.1.$0^{2,4}$]octene Derivatives[1,2]

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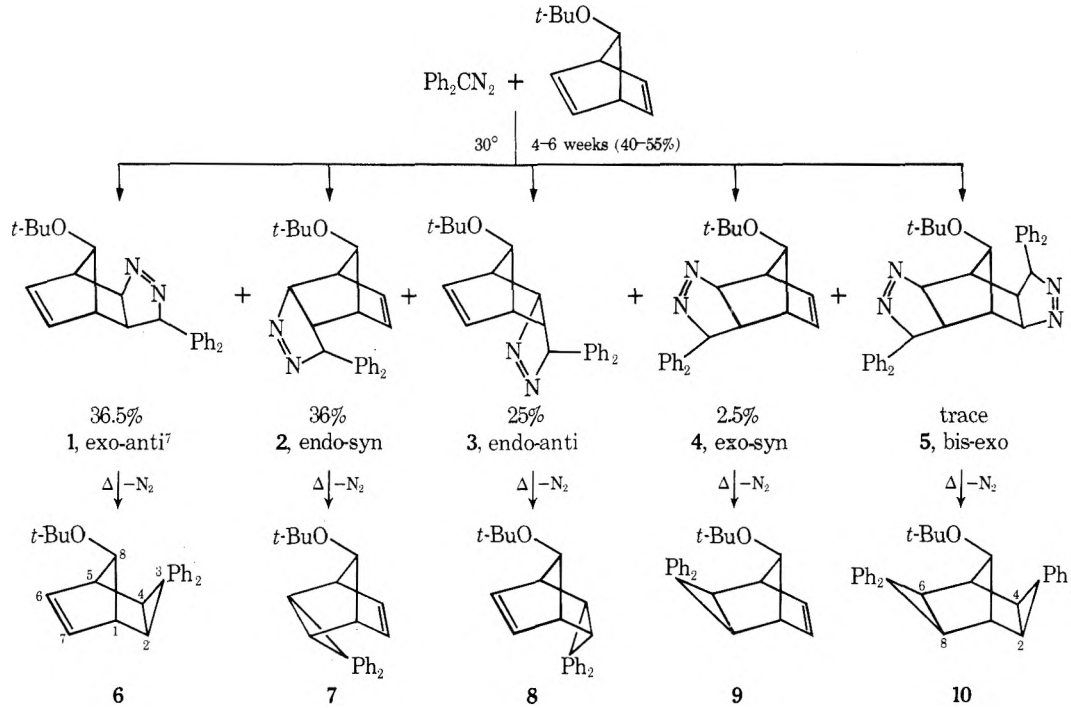
Room temperature addition of the title two reactants (diene in excess) led to all of the monoadducts possible (40–55%) in roughly comparable amounts except for the exo-syn adduct, which was formed in very low yield. Minor amounts of bis adducts were observed. Some factors involved in this nonselective 1,3-dipolar cycloaddition are discussed. Pyrolysis of the adducts led to the corresponding tricyclic ethers in high yield. These ethers serve as convenient entries into the *exo*- and *endo*-3,3-diphenyltricyclo[3.2.1.$0^{2,4}$]octane systems. As examples of some transformations possible with these ethers, the exo-anti ether was converted via acetolysis and hydrolysis to its alcohol with complete retention of configuration. Similarly, the endo-syn ether was converted to its alcohol and eventually to the interesting parent hydrocarbon, *endo*-3,3-diphenyltricyclo[3.2.1.$0^{2,4}$]octene. The endo-anti and exo-syn ethers did not behave analogously. The former underwent an apparently deep-seated change upon acetolysis, whereas the latter smoothly rearranged to a bicyclo[3.2.1]octene derivative. The pathways of these reactions are discussed briefly, along with the presentation of confirmatory physical data for the structures assigned.

Work on another aspect of this general area[3] necessitated the synthesis of alcohol 6-OH (vide infra). The first step in its preparation was the 1,3-dipolar cycloaddition of diphenyldiazomethane to 7-*tert*-butoxynorbornadiene. This addition resulted in a variety of adducts, all of which have potential utility in the study of 3,3-diphenyltricy-

clo[3.2.1.$0^{2,4}$]octanes. We describe here the characterization of these adducts and some of the transformations that they undergo.

Results

Slow (4–6 weeks) addition of diphenyldiazomethane to excess 7-*tert*-butoxynorbornadiene (no other solvent) at room temperature afforded all of the possible monoadducts **1**–**4** as well as small amounts of bis adducts, of which **5** was characterized. The adducts were largely separable by column chromatography. Although these adducts had spectra consonant with the assigned structure,[4,5] the orientation of the addition in each case was better assigned by inspection of the tricyclic ether formed in high yield from each by pyrolysis at 165–175°.[6] The reactions are shown in eq 1.

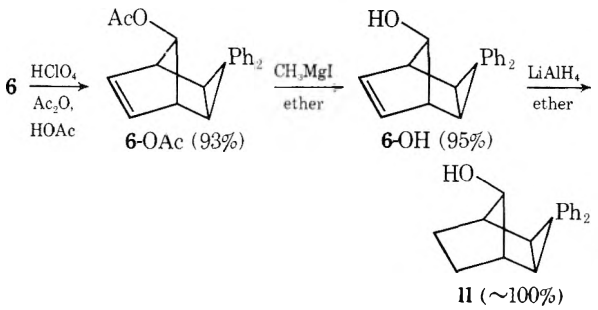


(1)

The cyclopropyl and vinyl protons in each of the ethers are unique. The exo/endo orientation of the fused cyclopropane ring can be determined by the multiplicity of the H-2,4 proton resonance and its chemical shift.[3] In **6** and **9** the H-2,4 pair is a singlet ($W_{1/2}$ = 2 Hz) whereas in **7** and **8** this pair is a multiplet. In the former cases, the H-2,4 pair is endo and does not couple with the bridgehead pair H-1,5 owing to unfavorable geometry. Some weak coupling of the long-range "W" type between H-2,4 and H-8 may broaden the singlet slightly in **9**, however. Such coupling is manifested in **10**, where the H-2,4 singlet is narrower ($W_{1/2}$ = 2 Hz) than the H-6,8 singlet ($W_{1/2}$ = 2.5 Hz). Conversely, in **7** and **8**, there is coupling due to a more favorable geometry between the now exo H-2,4 and H-1,5 pairs, resulting in distorted multiplets (three lines for **7** and four lines for **8**). As would be anticipated, the endo H-2,4 pair in **6** and **9** was upfield (δ 1.75 and 1.83, respectively) from the exo H-2,4 pair in **7** and **8** (δ 2.38 and 2.02, respectively).

The vinyl protons H-6,7 present a dramatic difference in these ethers. In **6** and **9** the vinyl resonance is at δ 6.48 and 6.51, respectively. In **7** and **8**, however, the underlying phenyl group attached to the endo cyclopropane moiety exerts a shielding effect on these vinyl protons, causing an upfield shift to δ 5.13 in **7** and δ 5.14 in **8**. Whereas this resonance was a sharp norbornene-type "triplet"[9] in **7** and **9**, additional broadening into a poorly resolved multiplet was evident in the vinyl resonance of **6** and **8**. These different resonances clearly are the result of the different orientation of the 8-*tert*-butoxy group, allowing some long-range coupling in these last two ethers.

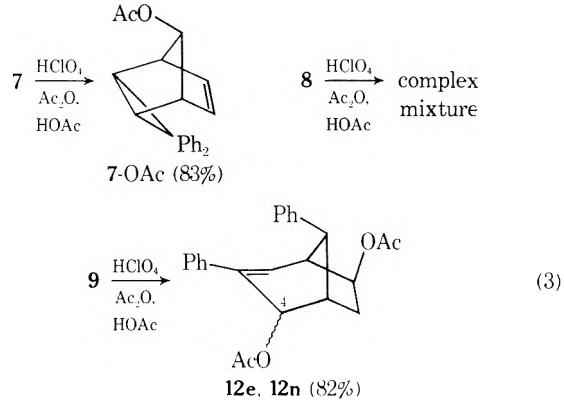
The syn/anti orientation of the *tert*-butoxy group in the endo adducts was decided by spin-decoupling results. As expected, irradiation of H-8 in **7** had no effect on the vinyl proton resonance. Irradiation of H-8 in **8**, however, cleanly sharpened the initial vinyl multiplet into a triplet. Also, irradiation of the vinyl protons in **8** changed the H-8 resonance from a complex multiplet into a triplet, $J_{1(5),8}$ = 2 Hz. So the *tert*-butoxy group is syn in **7** and anti in **8**. In the exo adducts, the *tert*-butoxy group in **6** was shown to be anti by conversion to the saturated alcohol **11** as in eq 2.[10] Alcohol **11** had been prepared earlier[3] and completely characterized. The sequence in eq 2 involved no gross structural change because in their NMR spectra both **6**-OAc and **6**-OH retained the H-2,4 singlet and complex vinyl proton multiplet characteristic of the **6** system. By elimination, the other exo adduct **9** obviously then has a syn *tert*-butoxy group.



(2)

As seen in eq 2, ether **6** smoothly afforded **6**-OAc upon acetolysis in the presence of perchloric acid. Likewise, ether **7** produced **7**-OAc. This ester showed the proper endo-type NMR spectrum. The cyclopropyl pair H-2,4 was a triplet centered at δ 2.32, as was the vinyl pair H-6,7 at δ 5.17. The syn acetoxy group orientation was assumed from the contrary behavior observed with **8** and from the generally observed retention of configuration in such reactions. Ether **8**, in this regard, gave a variety of uncharacterized products (at least seven by TLC analysis) in this reaction and the matter has not been pursued as yet.[11] Clearly, however, the endo-anti acetate expected (**8**-OAc) is unstable

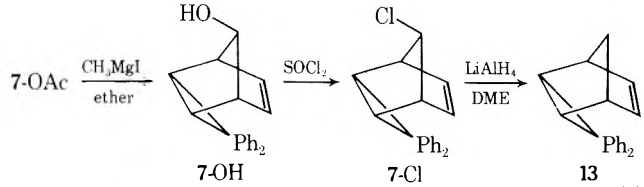
under these reaction conditions and generates other products, or *some* intermediate is formed which does so (with 8-OAc perhaps among the products). Ether **9** underwent a structural rearrangement under these acetolytic conditions to form a mixture of acetates **12.** These and the other reactions mentioned are illustrated in eq 3. Each ester in the



(3)

pair **12** had only one vinyl proton (δ 6.46 in **12e,** 6.28 in **12n**) and an unperturbed styrene chromophore [λ_{max} (EtOH) 248 nm (log ϵ 4.06) for **12e,** 249 nm (log ϵ 4.00) for **12n**]. Two CHOAc resonances were obvious in each ester but assignment was difficult. One, a broad singlet centered at δ 5.35, was assigned to H-4 in **12e** because of the geometry present in its case. Using this as the structural reference, one could then assign the remaining resonances: δ 5.31, H-4 in **12n;** 5.47, H-7 in **12e;** and 5.50, H-7 in **12n.**

One of the goals in the present study was the preparation of *endo*-3,3-diphenyltricyclo[3.2.1.$0^{2,4}$]octene itself (**13**). A comparison of its chemistry relative to that already known for its exo analog[13] should be interesting. Conversion of **7**-OAc to **7**-OH was straightforward. Because its tosylate proved to be elusive, reductive solvolysis of the *p*-nitrobenzoate ester of **7**-OH in diglyme with sodium borohydride[14] was attempted. No **13** was observed, however, and the reaction led rather to the parent alcohol and an uncharacterized oil. Alcohol **7**-OH did, nonetheless, easily form **7**-Cl upon treatment with thionyl chloride. This chloride was a reactive compound. It gave the corresponding methyl ether simply upon dissolution in warm methanol. Reduction of **7**-Cl to **13** succeeded with lithium aluminum hydride in dimethoxymethane under reflux[15] (eq 4). Reduction of **7**-Cl



(4)

with tri-*n*-butyltin hydride did not yield **13.** The crude product contained no norbornene double bond in the NMR spectrum. Hydrocarbon **13** was a crystalline solid, mp 74–75°. Its uv spectrum was similar to that of the exo isomer.[13] Their NMR spectra differed, and the shielding influence of the endo diphenylcyclopropyl ring upon the vinyl protons in **13** was pronounced. In **13** these protons appeared at δ 5.18, whereas in the exo isomer they appeared at δ 6.57.

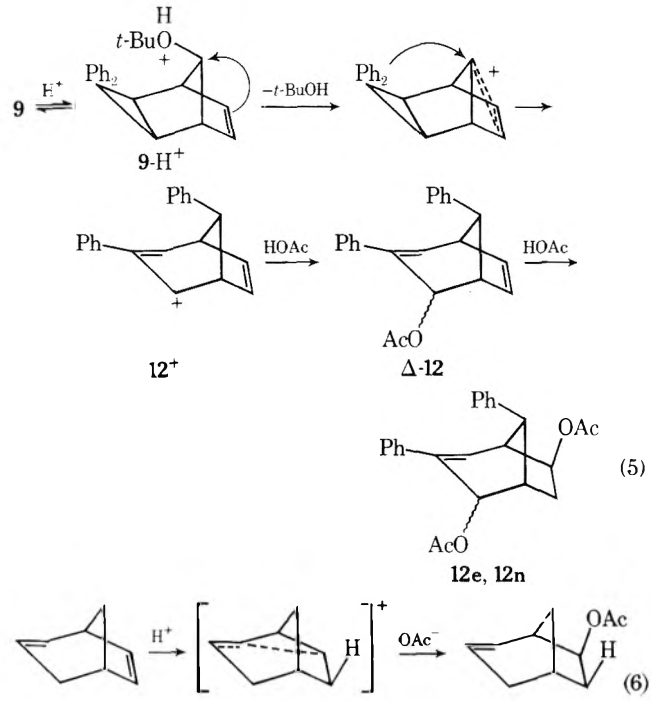
Discussion

1,3-Dipolar cycloadditions to norbornenes follow the Alder and Stein[16] "exo rule", the basis of which is still somewhat controversial. Abundant examples illustrate this rule and the matter need not be developed further here. Such additions to norbornadienes are less specific, however. Phenyl azide adds to norbornadiene preferentially exo (exo/endo = 11)[17] and diphenyldiazomethane adds exclusively exo to this diene,[13] as does diazofluorene.[18] The bis adduct from the former is also exo-exo (as would be expected once one addition had occurred because the second would then follow the "exo rule"). However, steric factors can effect the success of such reactions and cases are known where *no* addition occurs rather than endo addition.[19] Of all such additions, however, the most pertinent to the present study is the addition of phenyl azide to 7-*tert*-butoxynorbornadiene reported by Klumpp and coworkers.[20] Triazolines related to pyrazolines **1, 2,** and **4** were produced in percentage compositions of 30, 55, and 15%, respectively. No triazoline related to **3** was apparently formed. The 30% of exo-anti adduct presumably reflected the "exo rule" coupled with a favorable steric approach. On the other hand, Klumpp attributed the 15% exo-syn adduct to a "special coordination effect" between the *tert*-butoxy group and phenyl azide which compensated somewhat for the crowded transition state involved in this case. The major product, an endo-syn adduct, was postulated to result from a sterically favorable endo addition to the syn double bond. This double bond was theorized to be the more reactive because of electronic factors involving again the *tert*-butoxy group. Such results with phenyl azide are very much like those here reported for diphenyldiazomethane addition. Because the diazo compound is a more bulky dipolar reagent, however, the transition state for its addition probably involves more steric hindrance.[21] So exo-syn addition (i.e., to form **4**) is diminished. Presumably the formation of endo-anti adduct **3** also illustrates this steric influence and accounts for the mildly increased overall endo addition with the diazo compound (61%) compared with phenyl azide (55%). Our studies do not contribute to any claim of coordination effects or of enhanced reactivity of the syn norbornadiene double bond nor do they explain the absence of a triazoline product related to **3** in Klumpp's work. Clearly, steric and electronic factors are in delicate balance in these reactions and subtle shifts in these factors cause the minor differences in the two additions. However, obviously, the "exo rule" is not adhered to in these 1,3-dipolar cycloadditions.[23]

The conversions of **6** and **7** to the acetates (eq 2 and 3) exemplify the known retention of configuration that attends such ether cleavages.[3] The rest of the sequence in eq 2 mirrors that previously reported[3] for the saturated analog. The complex acetolysis of **8** is not yet understood.[11] The reaction of ether **9** may be rationalized as shown in eq 5.

Three points of interest might be mentioned concerning this sequence. First, the loss of *tert*-butyl alcohol from **9**-H^+ is believed to result from the anti double bond participation, a well-known effect. Such a loss may also be involved in the previously mentioned conversion of **7** to **7**-OAc, but *not* in the conversion of **6** to **6**-OAc. Had the latter conversion involved the creation of cationic charge at C-8, then a phenyl migration would have followed to rearrange the tricyclic system.[24] From the present and past work, it is concluded that an anti double bond or cyclopropyl group will participate in the acetolysis of such 8-*tert*-butyl ethers to cause C-8 charge creation, but a proximate 3-phenyl group will not.

The second point of interest is the complete specificity of addition of acetic acid to Δ-12. Addition of acetic acid to bicyclo[3.2.1]octadiene occurs as shown in eq 6, presumably via the delocalized cation shown.[25] This is a clear precedent for the stereospecific addition in eq 5 to form **12.** As the



(5)

(6)

last point of interest, the nonstereospecific capture of ion 12^+ by acetic acid also was observed with the 6,7-dihydro analog, and indicates that the charge in 12^+ is not delocalized over the dienic system, presumably because such delocalization would lead to antiaromatic character in the ion.

The additions of acetic acid are believed to occur in the order shown in eq 5. The possibility that addition of acetic acid to **9** preceded the acetolysis seems remote for two reasons: only unchanged **9** was isolable from purposely incomplete reactions, and the high reactivity of **9** necessitates the presence of the anti bond.

With an entry available now to these various tricyclic systems, future papers will report on efforts to explore these systems further.

Experimental Section[26]

Reaction of Diphenyldiazomethane and 7-*tert*-Butoxynorbornadiene. The diazo compound[27] was added to freshly distilled diene[23] in aliquots such that the molar ratio of diene to diazo compound was never less than 100:1. It was convenient to add 0.5 portions of the latter with stirring to ca. 100 g of the former at 25–30°. Further additions were made as the purple color of the solution faded to pale yellow. After 4–6 weeks monoadduct began to precipitate. The solution was steam distilled to recover excess diene, which was recycled. The residue was dissolved in a minimal volume of benzene and dried by azeotropic distillation. It was then chromatographed on alumina (Matheson Coleman and Bell "chromatographic grade", 80–325 mesh, used as received). A practical weight ratio of alumina to residue was 100:1. Elution with 10% ether–hexane removed a trace of diene reactant. Use of 50% ether–hexane gave adducts[29] **1** and **2**, the initial fractions being richer in **2**. Continued elution next afforded pure **1**, mp 143–144° dec.[4] Fractional crystallization of the mixed adducts above from methanol eventually gave pure **2**, mp 142.5–143.5° dec.[4] The slower eluting adduct **3** was finally obtained by longer elution with 50% ether–hexane. Recrystallization from methanol gave **3**, mp 162.5–163.5° dec.[4] Although sharp-melting, **3** was not obtained pure enough for acceptable C, H analysis. Adduct **4** was difficult to obtain also. After five reactions to obtain all of the above, the mother liquors from all recrystallizations were combined and rechromatographed. Adduct **4** was observed spectrally in those fractions rich in **1** and **2**. A pure sample of **4** was, however, not obtained.[4] Bis adduct **5** was eventually obtained by elution with 50% ether–chloroform. Recrystallization from methanol gave pure **5**, mp 186–186.5° dec.[4,5] Other bis adducts were probably present as well, but no serious effort was made to isolate them.

Owing to considerable tar formation an accurate yield of **1–4** was not determined. Based on diazo reactant, *isolated* yields ranged from 40 to 55%. The composition of the adduct mixture was determined by NMR integration of the *tert*-butoxy singlets. The NMR sample was a steam-distilled residue that had been freed from tars by rapid passage through a short alumina column.

Pyrolysis of Pyrazolines. The individual adducts **1–5** were heated in an oil bath at 165–175° (230° for **5**) until nitrogen evolution ceased. The residue was taken up in a small volume of chloroform and passed through a short alumina column with 10% ether–hexane. Evaporation of the solvent gave the colorless, crystalline ethers. The ethers were recrystallized from methanol.[4] The yields were 84–96%. The melting points of the ethers follow: **6**, 167–168°; **7**, 124.5–125.5°; **8**, 114.5–115.5°; **9**, 173.5–174.5°; **10**, 263–264° dec. Once the pyrazoline adducts had been characterized, it was found to be more economical to pyrolyze the mixture of adducts **1**, **2**, and **4** previously mentioned as the initial eluate with 50% ether–hexane through alumina. The ethers were then separated by chromatography on 200 wt % of Florisil (MCB, 100 mesh and finer). Elution with hexane readily gave ether **9**, while elution with 5% ether–hexane gave first **7** and then **6**, all of which were obtained in analytical purity.[4]

Acetolysis of the Ethers. The cleavage of ethers **6** and **7** was performed as reported[3] for the saturated analog of **6**, except that, after reaction, the acidic solution was neutralized with solid sodium carbonate and the acetate product extracted with methylene chloride. Removal of solvent from the dried extracts gave the crude acetates. Esters **6**-OAc and **7**-OAc were formed in 93 and 83% yield, respectively.[4] Upon recrystallization from methanol followed by hexane or pentane they both formed colorless needles: **6**-OAc, mp 141–142°; **7**-OAc, mp 96.5–97.5°. Ether **8** gave an off-white solid product in this cleavage. By TLC (30% ethyl acetate–hexane) analysis, seven distinct fractions were noted, but none was isolated or characterized except to the extent that the NMR spectrum showed no evidence of the parent tricyclic system. Other cleavage methods using various concentrations of sulfuric acid and another using triphenylphosphine dibromide in acetonitrile failed. Ether **8** was stable, however, to acetic acid–acetic anhydride mixtures (25°, 10 hr). Cleavage of ether **9** (300 mg) gave a mixture of esters **12** (280 mg) in the ratio of two parts **12n** to three parts **12e**. Separation was accomplished by chromatography on Florisil (80 g/g of acetates). Acetate **12n** eluted first with 4% ethyl acetate–hexane and it was recrystallized from methanol, mp 129.5–130.5°.[4] Acetate **12e** was obtained as a glass which could not be recrystallized satisfactorily, mp 45–55°.[4]

Formation of 3,3-Diphenyltricyclo[3.2.1.$0^{2,4}$]oct-6-enols, 6-OH and 7-OH. Acetates **6**-OAc and **7**-OAc were treated with excess methymagnesium iodide as described earlier[3] for the saturated analog of **6**-OAc. The exo-anti alcohol **6**-OH (95% yield) was recrystallized from hexane, mp 126.5–127°.[4] The endo-syn alcohol **7**-OH (97% yield) had mp 140–141° from hexane.[4]

Reduction of 6-OH to 11.[10] Alcohol **6**-OH (100 mg) in dry ether (15 ml) was added to a slurry of lithium aluminum hydride (100 mg) in dry ether (15 ml). The mixture was stirred at 25° for 6 hr and hydrolyzed by cautious addition of water followed by sulfuric acid (10%). The ether layer was separated, washed with sodium carbonate (10%) and water, and then evaporated to afford alcohol **11** (100 mg, 100% yield, mp 153–155° from hexane). The product was identical by mixture melting point and spectra with authentic material.[3]

Reduction of 7-OH to 13. Attempted conversion of **7**-OH to its tosylate in pyridine was unsuccessful (84 hr, 5–10°). However, work-up over crushed ice–10% hydrochloric acid returned only 10% of the original material. The *p*-nitrobenzoate derivative (mp 168–169° from chloroform–methanol) was prepared in pyridine with *p*-nitrobenzoyl chloride. Reaction of this ester with sodium borohydride in aqueous diglyme[12] (90°, 4 hr) gave back **7**-OH (63% recovery) and an uncharacterized oil that had no spectral characteristics of the parent tricyclic system.

Treatment of **7**-OH (300 mg) with purified thionyl chloride (100 mg) at 25° led to the evolution of gases which were removed in a nitrogen stream. Evaporation of the slight excess of thionyl chloride led to an off-white solid, 310 mg, mp 111–115°, which was judged by NMR analysis to be ca. 90% pure **7**-Cl.[4] Attempted recrystallization of the chloride from all solvents tried was unrewarding except for methanol. However, the recrystallized product from methanol was clearly the methyl ether **7**-OMe [mp 74–75°, δ 3.18 (s, OCH_3), other resonances indicative of 7 system[4]].

Chloride **7**-Cl (unrecrystallized, 500 mg) in dry 1,2-dimethoxyethane (DME, 10 ml) was added dropwise to a slurry of lithium aluminum hydride (200 mg) in DME (50 ml) at 25°.[15] The solution was heated to reflux, whereupon it turned deep blue. After a 14-hr

heating period (TLC analysis indicated a 12-hr minimum time for reaction), the excess hydride was decomposed by the careful addition of water at 0–5°. The inorganic salts were dissolved by addition of 5% sulfuric acid. The homogeneous, aqueous DME solution was evaporated and the residue was taken up in ether. The ether solution was washed with 5% sulfuric acid, water, 10% sodium carbonate, and water, and then dried over sodium sulfate. Removal of the ether left an oil which was passed through alumina (50 g) with hexane. The hexane was evaporated to yield **13** (360 mg, 83%, mp 74–75° from methanol).[4]

Reaction of 7-Cl in benzene with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile initiator under relux (nitrogen atmosphere) for 48 hr gave a tarry product that possessed no vinyl protons in the NMR spectrum.

Registry No.—**1**, 54120-24-0; **2**, 54163-78-9; **3**, 54163-79-0; **4**, 54163-80-3; **5**, 54120-31-9; **6**, 54120-25-1; 6-OH, 54120-26-2; 6-OAc, 54120-27-3; **7**, 54163-81-4; 7-OH, 54163-82-5; 7-OAc, 54163-83-6; 7-OMe, 54120-28-4; 7-Cl, 54120-29-5; 7-O-*p*-NB, 54120-30-8; **8**, 54163-84-7; **9**, 54163-85-8; **10**, 54120-32-0; **11**, 29266-06-6; **12n**, 54120-33-1; **12e**, 54163-86-9; **13**, 54163-87-0; diphenyldiazomethane, 883-40-9; 7-*tert*-butoxynorbornadiene, 877-06-5.

Supplementary Material Available. Melting points, combustion analytical data (asterisked compounds), and significant ir and complete NMR data for **1***, **2***, **3***, **4**, **5***, **6***, **7***, **8***, **9***, **10**, 6-OAc*, 7-OAc*, 6-OH*, 7-OH*, 7-*p*-NB, 7-Cl, 7-OMe, **13*** (uv also), **12e*** (uv also), and **12n** (uv also) 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 $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1036.

References and Notes

(1) Studies on 3,3-Diaryltricyclo[3.2.1.0^{2,4}]octanes. IV. Part III: J. W. Wilt and J. R. Flanyak, *J. Org. Chem.*, **39**, 716 (1974).
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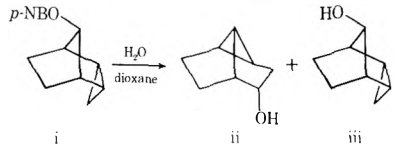
(3) J. W. Wilt, T. P. Malloy, P. K. Mookerjee, and D. R. Sullivan, *J. Org. Chem.*, **39**, 1327 (1974).
(4) See paragraph at end of paper regarding supplementary material.
(5) Bis adduct **5** was assigned its sturcture because the bridgehead protons possessed the same chemical shift. The alternative structure resulting from identical exo additions of the diphenyldiazomethane should have given a bis adduct possessing two different chemical shifts for the bridgehead protons.
(6) Suprafacial, concerted elimination of nitrogen from these pyrazolines should require photochemical conditions. Because these eliminations did succeed thermally, the concerted loss of nitrogen under these conditions may be more difficult (anc therefore require high temperatures) or, more likely, the loss may be stepwise.
(7) It is customary[8] in such compounds to name the orientation of the added moiety first and the orientation of the bridge substituent with respect to the added moiety second. Some confusion is inevitable, but it must be stressed that syn and anti refer to the orientation of the substituent with respect to the pyrazolino (or later, cyclopropyl) ring and not the norbornene double bond.
(8) J. Haywood-Farmer, *Chem. Rev.*, **74**, 315 (1974).
(9) The norbornene vinyl triplet is deceptively simple. The vinyl and bridgehead protons actually comprise an AA′XX′ system.
(10) The reduction of a norbornene double bond syn to an oxygen function (–OH, –OR) by lithium aluminum hydride is well documented. Cf. B. Franzus and E. J. Snyder, *J. Am. Chem. Soc.*, **87**, 3423 (1965), and P. R. Story, *J. Org. Chem.*, **26**, 287 (1961). The reduction of an anti norbornene double bond in such compounds does not occur with this reagent.
(11) Because ester i solvolyzed principally (84.3%) to alcohol ii with only 0.1% skeletally retained product iii,[12] it is likely that such gross rearrangement occurred with **8** as well.



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(20) W. Klumpp, A. Veefkind, W. deGraaf, and F. Bickelhaupt, *Justus Liebigs Ann. Chem.*, **706**, 47 (1967).
(21) Such steric hindrance may be the reason why diphenyldiazomethane additions have less favorable $\Delta S^{\ddagger}$ parameters compared to phenyl azide additions.[22]
(22) R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (9161); R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.*, **100**, 2494 (1967).
(23) After submission of this manuscript, a paper by M. Franck-Neumann and M. Sedrati, *Angew. Chem., Int. Ed. Engl.*, **3**, 606 (1974), was noticed by us and subsequently impressed upon us by a referee. These workers observed only endo-anti addition of diazomethane and diazoethane to 7-halonorbornadienes and considerable endo-anti additon of diazoethane to 7-norbornadienol. The aforementioned referee asked that we comment on these results in the light of the results we report in the present paper. First of all, Franck-Neumann and Sedrati report only exo and "probably" syn addition of diazoethane to 7-*tert*-butoxynorbornadiene, the dipolarophile germane to our work. So the frontier orbital considerations that they adduce to explain the endo-anti additions to the 7-halo compound and the 7-alcohol clearly are not applicable to the 7-*tert*-butoxy substance. Moreover, Franck-Neumann and Sedrati comment neither on their own result with the 7-*tert*-butoxy case nor on Klumpp's,[18] a situation that makes a comment from us gratuitous and premature. We prefer to await the result of a study of diphenyldiazomethane additions to the 7-halonorbornadienes before making such a comment.
(24) This argument has been used in the acetolysis of the saturated analog of **6** as well.[3]
(25) N. LeBel and R. Maxwell, *J. Am. Chem. Soc.*, **91**, 2307 (1969).
(26) Melting points were taken on a calibrated Fisher-Johns block. Infrared spectra (ir) were determined on a Beckman IR-5A instrument as 1–3% mixtures in potassium bromide disks. Ultraviolet spectra (uv) were measured on a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained on a Varian A-60A instrument using tetramethylsilane as an internal standard. Integration of signals was within 10% of the theoretical value. The usual splitting abbreviations are used. Chemical shifts are for deuteriochloroform solutions. Homonuclear decoupling experiments were performed with a Varian V-6058A spin decoupler. Complete ir, uv, and NMR spectra are available in the dissertation of D.R.S.
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(28) P. Story, *J. Org. Chem.*, **26**, 287 (1961).
(29) The (at times complicated) names of these compounds, along with other details, are given in the supplementary tables.[4]

The Effect of Phenyl Substitution at the Double Bond of Δ^3-Cyclopentenylethyl *p*-Nitrobenzenesulfonate upon the Rate of Acetolysis to Norbornyl Products[1]

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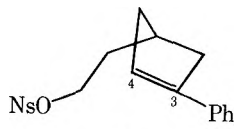
The relative rates of acetolysis of 2-cyclopentylethyl, 2-(Δ^3-cyclopentenyl)ethyl, 2-(3-phenyl-Δ^3-cyclopentenyl)ethyl, and 2-(3,4-diphenyl-Δ^3-cyclopentenyl)ethyl *p*-nitrobenzenesulfonates at ~60° are 0.011, 1.0, 1.70, and 0.87, respectively. The latter two substrates give, within experimental precision, only 2-phenylnorbornene and 1,2-diphenylnorbornene, respectively, as products under the conditions of acetolysis, 60.4° in acetic acid containing sodium acetate and a trace of acetic anhydride. A transition state resembling a classical 2-phenylnorbornyl cation therefore appears to be excluded, and it is concluded, based on analogies, that π-route transition states generally resemble π complexes.

We have synthesized and studied the acetolysis rates and products of 2-(3-phenyl-Δ^3-cyclopentenyl)ethyl and 2-(3,4-diphenyl-Δ^3-cyclopentenyl)ethyl *p*-nitrobenzenesulfonates (nosylates, ONs), **1** and **2**, for comparison with similar substances studied by others. It was anticipated by analogy with the unsubstituted and mono- and dimethyl-substituted species[2-4] that closure to the norbornyl skeleton by the π route would occur upon acetolysis and that the 2-phenyl-2-norbornyl and 1,2-diphenyl-2-norbornyl cations would be intermediates, respectively. Since these anticipated cations are known to be classical through NMR studies in acidic solutions,[5-8] it would be expected that the acetolysis transition states would closely resemble a classical 2-norbornyl cation–nosylate anion pair.[9]



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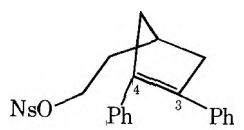

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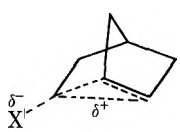
However, information on the methyl-substituted analogs of **1** and **2** indicates that the π-route transition state is nearly symmetrically bridged and not close to a classical 2-norbornyl cation–nosylate anion pair, in that a methyl group at carbon 3 increases the rate of acetolysis 7-fold, while methyl groups at both carbons 3 and 4 increase the rate 38.3-fold.[10] If the transition states for acetolysis of the unsubstituted, 3-methyl, and 3,4-dimethyl derivatives are symmetrically bridged, then the rate enhancement for the monomethyl derivative should be approximately $(38.3)^{1/2} = 6.2$, quite close to the observed 7-fold effect. In contrast, the rate enhancement for monomethyl should be approximately $38.3/2 = 19.2$ if all three transition states are classical. Also, both the relatively small rate effect of methyl substitution at the double bond and the pattern of multiplicative rather than additive behavior in the rate enhancement of methyl relative to dimethyl substitution indicate a symmetrically bridged transition state equilibrium nuclear geometry (ENG), **3**, rather than a classical, nonsymmetrically bonded ENG, **4**, by comparison with other reactions of olefins generally throught to proceed via bridged (peracetic acid oxidation) or classical (acid-catalyzed hydration) transition states.[10]



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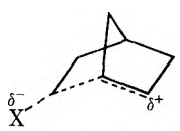

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Subsequently, it was shown that methanolysis of optically active 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate[11] and chloride[12] leads to optically active product of partially retained configuration. The amount of retention was found to be independent of both counterion and temperature, a result seemingly consistent solely with totally unassisted ionization to a nonbridged intermediate, which only subsequently, with understandably little selectivity regarding counterion or temperature, partially racemizes.[12] It has also been shown that the 2-methyl-2-norbornyl cation[13] and the 1,2-dimethylnorbornyl cation[14,15] in highly acidic solvents exist essentially entirely in the classical (tertiary cation) form, although a "partially delocalized" ENG has been suggested from NMR and photoelectron spectroscopic evidence.[16,17] A symmetrically bridged structure has been suggested for the 2-norbornyl cation itself.[6,17]

The evidence in the methyl system thus suggests that the π-route transition state is bridged, but that the σ-route transition state is not bridged, and the intermediate cations are classical in the case of both mono- and dimethyl substitution. Great controversy still exists over whether the σ-route transition state is bridged,[18,19] and even over the nature of the 2-norbornyl cation.[17,18] It is generally agreed that the σ-route transition state for solvolysis of 2-phenyl-2-norbornyl derivatives is classical,[7,18] whereas there is not agreement about the classical vs. bridged character in the transition state for solvolysis of 1-phenyl-2-norbornyl derivatives.[18,20,21]

In view of the results with methyl-substituted compounds, it seems probable that systems which can solvolyze through a classical transition state by the σ route nevertheless go through a bridged transition state when carried through the π route. Since it is also probable that σ-route transition states may not be bridged even if there is some degree of bridging in the more electron-demanding carbonium ions,[7] it is of interest to determine whether the acetolysis of **1** and **2** is best described by transition state **3** or **4**.

Results

The substrates were prepared as described in the Experimental Section.

For product determination, the acetolyses were carried out at the same temperature, 60.4°, used for the rate studies. The *p*-nitrobenzenesulfonates **1** and **2** were solvolyzed in anhydrous acetic acid in the presence of excess sodium acetate to neutralize the strong acid released from the reactions. The product isolated from acetolysis of **1** was 95% 2-phenyl-2-norbornene and that from **2** was 95% 1,2-diphenyl-2-norbornene, as shown by comparison with authentic samples prepared by known routes.

Table I
Rate Constants for Acetolysis of RCH_2CH_2ONs

R	Temp, °C	$10^4 k$, sec^{-1}	Relative rate
Cyclopentyl	60	0.0116[a]	0.011
Δ^3-Cyclopentenyl	60	1.10[a]	1.0
	61.83	1.31[b]	
3-Phenyl-Δ^3-cyclopentenyl	60.4	1.865 ± 0.015[c]	1.70
3,4-Diphenyl-Δ^3-cyclopentenyl	60.4	0.955 ± 0.014[c]	0.87

[a] Reference 2. [b] Reference 3. [c] Error limits are the standard deviations of mean values.

For rate studies, solutions of ~1–2 × 10^{-4} *M* for compound **1** and ~5–10 × 10^{-5} *M* for compound **2** in anhydrous acetic acid buffered with 0.03 *M* sodium acetate were heated at 60.4°, the rates being followed spectrophotometrically. The rate constants are given in Table I. These rate constants, since they are much larger than that for the saturated analog (R = cyclopentyl), clearly demonstrate participation of the double bond in the rate-determining step of solvolysis, leading essentially exclusively to the observed ring-closure products. Ring closure is therefore the process by which the double bond accelerates acetolysis.

Discussion

Three kinds of rate comparisons can be made for the phenyl- and diphenyl-substituted compounds **1** and **2**: the rate effect of phenyl substitution at the double bond relative to the rate effect of the double bond alone, all in comparison with the saturated compound; the nature of the cumulative effects of one and two phenyl groups on the double bond; and the effects of phenyl substitution in this acetolysis reaction relative to the effects of phenyl substitution in other, known reactions of carbon–carbon π bonds which are analogous.

Noting the rate effects in Table I, which are ~100-fold for all three Δ^3-cyclopentenyl substrates relative to cyclopentyl, it can be seen that significant double-bond participation is not accompanied by any significant additional effect of one or two phenyl groups attached in conjugation with the double bond. These observations strongly suggest that the participation of the double bond does not involve appreciable development of classical carbonium ion character at either carbon atom in the transition state, nor does it involve appreciable steric interactions in the case of phenyl substitution. Fortuitous near equality of inductive and delocalization effects may well be involved, but the near cancellation required by the small rate effects can only be expected if little development of classical carbonium ion character has ocurred at the double-bond carbon atoms in the transition state.

The rate effects of phenyl substitution do not match either the additive behavior expected for a nonsymmetric transition state ENG **4**, or the multiplicative behavior expected for symmetric **3**.[10,22,23] There clearly are steric interactions of the phenyl groups in analogous compounds such as *cis*-α,α'-dimethylstilbene and *trans*-α,β-dimethylstyrene (*cis*-methyl groups).[24] Had phenyl substitution produced the large rate enhancements expected for mechanisms involving appreciable classical carbonium ion character at the doubly bonded carbon atoms, steric interactions would probably have had only a minor influence on the cumulative effects of one and two phenyl groups. However, in view of the observed very small effect of phenyl substitution, it is hardly surprising that steric effects, different in the monophenyl and diphenyl substrates and transition states, preclude a priori use of the cumulative effect to decide between transition state types **3** and **4**. Considerable effort was directed toward making mono- and dianisyl derivatives, but these compounds were not forthcoming.

Typical electrophilic reactions of olefins include acid-catalyzed hydration, halogen addition, and peroxy acid epoxidation.[25] Trends with methyl-substituted ethylenes have been discussed previously in connection with the methyl-substituted 2-(Δ^3-cyclopentenyl)ethyl nosylates.[10] There is not a large volume of data on phenyl-substituted systems, but enough examples are available to characterize the trend of phenyl substitution. Substitution of one phenyl group onto a carbon–carbon double bond enhances the rate of electrophilic attack, in amounts varying from very large to relatively small, depending on the nature of the electrophilic reagent. However, substitution of a second phenyl group at the other end of the double bond tends to decrease the rate relative to the monophenyl compound.

In acid-catalyzed hydration, phenyl substitution typically increases the rate by a few thousandfold.[25] This reaction is clearly "classical", as even methyl substitution increases the rate by on the order of a thousandfold or more (depending on reaction conditions), but a second methyl group at the other end of the double bond decreases that rate enhancement somewhat.[26]

Bromination and chlorination of olefins show the same kinds of trends, with monophenyl substitution giving faster rates by on the order of a few hundred to over 1000, but with diphenyl substitution giving rates only a few times (up to 20) faster than the unsubstituted olefin.[25,27-31] A mechanism involving a bridged, though possibly unsymmetrically bridged, transition state for bromination has been suggested, and it was concluded that this type of transition state leads to a bromonium ion in the case of alkyl-substituted olefins, but it leads to an open α-bromocarbonium ion in the case of phenyl-substituted olefins.[31] The latter case was noted[31] as something of a problem with respect to Hammond's postulate,[9] and thus the bromination data parallel the present data on **1** and **2**, presenting the following problem. Why should a reaction leading to a classical carbonium ion structure proceed through a rate-determining transition state ENG which seems not to resemble the classical carbonium ion so much as it resembles a bridged, nonclassical structure?

Peracid epoxidation of olefins is a mildly electrophilic reaction,[32] which is thought generally to proceed through a cyclic rate-determining transition state and not to a carbonium ion, or even an oxonium ion.[25] Data on phenyl-substituted ethylenes,[33] making reasonable allowances for temperature differences, indicates that substitution of a single phenyl group onto an olefin increases the rate of peracetic acid oxidation by factors of ~15–60, while a second phenyl group at the other end of the double bond decreases this enhancement by factors of ~2–8. The epoxidation rates maintain the same pattern seen in halogenation and in the π-route solvolyses, while bridging the gap in rate enhancements produced by phenyl substitution, which are only somewhat larger in the case of epoxidation than in solvolysis.

These experimental analogies show that one cannot distinguish between classical and bridged transition states directly on the basis of the cumulative effects of mono- and diphenyl substitution of the double bond, since both classical (hydration) and bridged (halogenation, epoxidation) mechanisms are slowed by substitution of a second phenyl group at the other end of the double bond. While steric effects are no doubt the cause of this difficulty, it is never-

theless possible to compare the *orders of magnitude* expected for additive (classical mechanism) and multiplicative (bridged mechanism) effects. If one phenyl group increases the rate by 10^3, then two phenyl groups should give 2×10^3 (classical) or 10^6 (bridged); other sets of corresponding numbers are 10^2, 2×10^2, 10^4; and 10, 20, 100. With very large rate enhancements, as in olefin hydration, the discrepancy between experiment and prediction for the bridged mechanism is enormous. With lower rate enhancements, the classical prediction still is closer to experiment, but the discrepancy between the bridged prediction and experiment is not so large, and may readily be interpreted as a steric effect. Unsymmetrically bridged transition states would reduce the discrepancy still further (approaching in the limit the classical mechanism).

Based on the above three kinds of rate comparisons, we conclude that the small rate effects of phenyl substitution on the double bond of the Δ^3-cyclopentenylethyl system relative to the large (100-fold) effect of the double bond itself rule out a transition-state structure closely resembling a classical norbornyl cation. The transition state in the phenyl-substituted case (1 and 2) appears to be bridged, but with little electron deficiency in the participating π system. Expectations of relatively small substituent effects, particularly for phenyl groups, in bridged cationic structures appear to reinforce the idea that these π-route transition states are not like classical carbonium ions and are probably bridged.[20,34]

Substantial π-bond assistance is evident in these reactions, since the Δ^3-cyclopentenylethyl compounds undergo acetolysis 100 times faster than the corresponding saturated-ring compound which uses solvent assistance. The major feature of these π-route solvolyses thus appears to be an almost "vertical" interaction of the π bond, distorting the π-electron distribution so little that substitution of the π-bonded carbon atoms produces little additional effect. The transition state may thus be thought of as similar to a π complex,[35-36] although it may, of course, be unsymmetrically bridged in cases such as 1 and 2. This interpretation is further supported by evidence that π-route transition states do not resemble classical cations in solvolytic cyclizations involving unsymmetrical participation by double and triple bonds.[37]

There appears to be substantial carbon–oxygen bond breaking at the transition state, since the rate ratio for leaving groups ONs/OTs is 12.4 (Δ^3, 62°) or 11.1 (saturated, 101°).[10] The near equality of these ratios and the effective ρ values of a little more than unity indicate that the sulfonate anions are rather completely formed at the transition state (as expected for the solvent-assisted reaction of the primary, saturated system). Molecules may generally be expected to avoid primary carbonium ions as intermediates, but this does not preclude transition states resembling ion-paired primary carbonium ions. In the π-route transition state, this reasoning suggests that the structure is like a loose π complex of a primary carbonium ion with relatively little charge deficiency in the π system itself.

Since the unsubstituted and methyl-substituted Δ^3-cyclopentenylethyl substrates appear to go through transition states which are symmetrically bridged, it is of interest to ask whether a symmetrically bridged intermediate is required. Such a single, symmetrically bridged rate-determining transition state is required by the symmetry of the reaction coordinate motion to lead initially to a symmetric ENG.[38-40] However, there are still two possibilities, for this symmetric ENG may be either an intermediate or a transition state—a nonclassical ion or the symmetrically bridged transition state for the rapid Wagner–Meerwein (W–M) rearrangement of two classical ions. A sketch of the latter

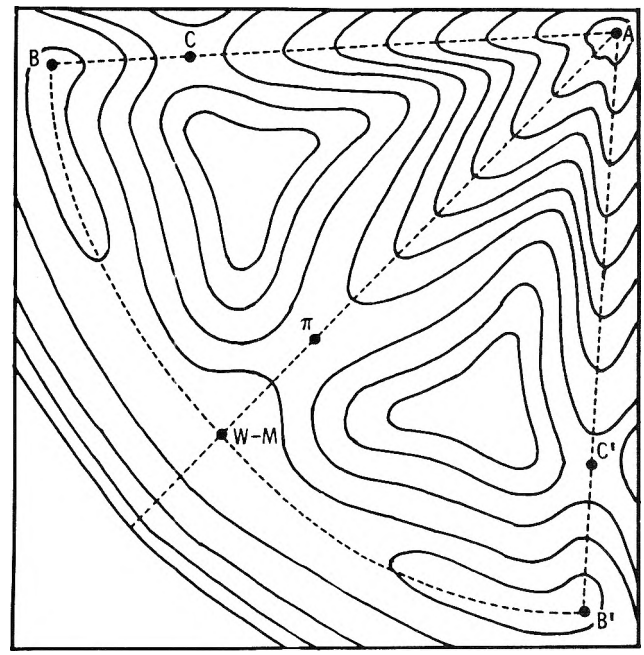

Figure 1. Sketch of possible potential energy surface for 1,2-dimethylnorbornyl cation system. Starting from 2-(3,4-dimethyl-Δ^3-cyclopentenyl)ethyl nosylate, A, the lowest energy route involves passage through transition state, π to a symmetrical ENG, **W–M**, which is itself the transition state for Wagner-Meerwein rearrangement of the classical 1,2-dimethylnorbornyl cations B $\rightleftarrows$ B′. The two coordinates plotted are the C_2–C_6 and the C_6–C_1 distances (norbornyl numbering). It is assumed that other nuclear coordinates have been relaxed to the most stable nuclear geometry for the given values of the C_2–C_6 and C_6–C_1 distances. The bond from carbon (C_6) to nosylate in A is assumed to be broken as the carbonium ions are formed, and ENG's B, B′, and **W–M** are assumed not to have the (already formed) nosylate anion associated with them. C and C′ are unsymmetrical, higher energy transition states for direct formation of the classical carbonium ions. The energy contours might represent ~3 kcal mol^{-1} increments.

situation is shown in Figure 1. The essential feature can be described, with some looseness of meaning as this: What *was* the symmetric reaction coordinate of the π-route transition state becomes a true vibration of the W–M transition state, while the antisymmetric stretching vibration of the partially formed carbon–carbon bonds of the π-route transition state becomes the reaction coordinate of the W–M transition state. Thus, both transition states are well-defined ENG's.

A surface involving a nonclassical ion in equilibrium with classical ions would be similar to Figure 1, except that the region around **W–M** would be a basin rather than a saddle point. By suitable changes, π could be made higher in energy than C and C′, or B and B′ could be made higher in energy than **W–M**, or made nonexistent as ENG's. Unsymmetrically bridged π-transition states could result by changing the routes through π or C and C′, or by having them merge.

In a case such as the reactions of 1 and 2, it is possible that two π-like transition states exist in *place* of the single transition state π in Figure 1, passing by curved valleys from A near π to B and again from A near π to B′. However, it is difficult to fit such routes onto the same surface and still provide barriers between them and the B $\rightleftarrows$ B′ route. Figure 1 nicely suffices to explain the possibility that the methyl-substituted Δ^3-cyclopentenylethyl systems actually may proceed through a symmetrical transition state, while still forming classical, not bridged, ions as the first intermediate (but not the first ENG).

This idea of two consecutive transition states has suggested itself before in studies of imidazole catalysis.[41] It may also apply to some cases of bromination.[31]

The surface also suggests an explanation of why the transition state appears not to resemble the classical carbonium ion, as predicted by Hammond's postulate.[9] The transition state should resemble the consecutively formed ENG closer to it in energy, but this ENG need not be an intermediate; it may be a transition state. In the present case, the transition state π and the classical carbonium ion intermediates B and B′ are not consecutive ENG's, and π resembles W–M more closely than it resembles B or B′.

While it is impossible here to review the literature on the norbornyl system,[1b] we would like to revive the interpretation of rapidly equilibrating classical $\rightleftarrows$ nonclassical $\rightleftarrows$ classical ions, which was previously considered unnecessary, as it would still require that the classical ion exhibit high exo/endo selectivity.[42] Classical ions have been implicated in reactions of *endo*-2-norbornyl derivatives.[43-45] Ion-pairing effects can explain differences between exo and endo systems.[44-50] Although NMR studies indicate that the 2-norbornyl cation itself is bridged,[6,17] a carbon-14-labeling experiment, the π-route formolysis of 2-(Δ^3-cyclopentenyl)-2-^{14}C-ethyl nosylate,[51] gives a product ^{14}C distribution, which is incompatible with exclusive formation of a symmetrically bridged ion,[52] and evidence, that in solvolytic reactions *exo*-norbornyl derivatives are unusually fast and that high exo/endo selectivity characterizes bridged structures,[19] has been forcefully held to be inconclusive.[18,53,54]

We would suggest that perhaps exo is unusually fast as a result of carbon–carbon hyperconjugation[36,55,56] in a transition state resembling the classical carbonium ion. The results of the Foote–Schleyer correlation[57,58] may be more readily explained in this way: since steric/torsional effects may be expected to favor exo over endo,[59-62] the near-normal rate for endo may be the result of compensating steric/torsional and hyperconjugative effects. Hyperconjugative effects should be present in the endo transition state as well as the exo, if it resembles a carbonium ion–counterion pair. The fast rate for exo would then result from reinforcement of steric/torsional and hyperconjugative effects, and the exo/endo rate and product ratios would be primarily determined by steric/torsional differences,[18] since the hyperconjugative accelerations would be present for both endo and exo and thus cancel. The ^{14}C-labeling results noted above[51,52] are consistent with the classical $\rightleftarrows$ nonclassical $\rightleftarrows$ classical scheme (even though they are not consistent with a scheme involving only nonclassical ions), if the nonclassical ion does not undergo 6,2 hydride shift appreciably in comparison with the classical ion, for then the 6,2 equilibration process need not give equal amounts of the two acetates which can result from 6,2 hydride shifts.[63] Perhaps this scheme is not the answer, but there is evidence *suggesting*, if not requiring, both classical and nonclassical ions in different phenomena in the 2-norbornyl system, and so it seems not unreasonable to suggest that this scheme be re-examined. The extremely rapid W–M rearrangements of such skeletons are well explained by the presence of a relatively low-energy, bridged intermediate for the interconversion of the classical carbonium ion structures in cases where the classical ENG is more stable than the nonclassical.

Experimental Section

Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points, determined with a Thomas-Hoover capillary melting point apparatus, are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. NMR spectra were run on a Varian Model A-60A spectrometer. Samples were run as dilute solutions in the solvent indicated using tetramethylsilane (TMS) as an internal reference. An Aerograph Model A-700 was used for GLC. Dry pyridine was distilled from BaO and stored over KOH pellets. Petroleum ether had bp 70–90°.

3-Phenyl-Δ^3-cyclopentenecarboxylic Acid. Methylphenylvinylcarbinol, prepared by reaction of vinylmagnesium bromide and acetophenone,[64] was dehydrated by heating with aniline hydrobromide[64] (Eastman) to give 2-phenyl-1,3-butadiene, bp 55–64° (13 mm) [lit.[64] bp 57–63° (13 mm)]. This butadiene was heated with ethyl diazoacetate[65] (Aldrich) at 95 ± 2° for 18 hr to give 1-(1-phenylvinyl)-2-carboethoxycyclopropane, yield 29%, bp 95–104° (0.7 mm). 1-(1-Phenylvinyl)-2-carboethoxycyclopropane was pyrolyzed[10,66] at 500° to give two rearranged products, ethyl 3-phenyl-Δ^3-cyclopentenecarboxylate, and the free acid which was separated by alkaline extraction. The ester was saponified with 10% aqueous KOH solution and acidified, and the combined carboxylic acid was recrystallized from cyclohexane: yield 51%; needles; mp 93–94°; ir (Nujol mull) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.67–3.55 (m, 5 H), 6.03 (br, 1 H, vinyl), 7.29 (m, 5 H, aromatic), 12.05 (s, 1 H, COOH).

2-(3-Phenyl-Δ^3-cyclopentenyl)acetic Acid. Reduction of 3-phenyl-Δ^3-cyclopentenecarboxylic acid with $LiAlH_4$[67] gave (3-phenyl-Δ^3-cyclopentenyl)methanol, yield 81%, mp 49–50° (from benzene–pentane). This alcohol was converted to the tosylate with tosyl chloride,[68] yield 84%, mp 78–80°. The tosylate was then heated with KCN in ethylene glycol[69] at 100° for 2.5 hr. The crude nitrile without further purification was refluxed with 20% aqueous KOH solution for 20 hr. The product was isolated by acidification of the aqueous solution to give crude acid: yield 68% based on the tosylate; mp 105–107°; ir (Nujol mull) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.0–3.3 (m, 7 H), 6.02 (br, 1 H, vinyl), 7.24 (m, 5 H, aromatic), 11.42 (s, 1 H, COOH).

2-(3-Phenyl-Δ^3-cyclopentenyl)ethyl *p*-Nitrobenzenesulfonate (1). Reduction of the above acid with $LiAlH_4$[67] gave 2-(3-phenyl-Δ^3-cyclopentenyl)ethanol, yield 93%, mp 50–51° (from petroleum ether). This alcohol was converted to the nosylate with *p*-nitrobenzenesulfonyl chloride:[70] yield 56%; mp 102–103° (from benzene–pentane); ir (Nujol mull) no trace of OH, 1530, 1350 (nitro group), 1368, 1190 cm^{-1} (sulfonate); NMR ($CDCl_3$) δ 1.66–3.04 (m, 7 H), 4.21 (t, 2 H, J = 6.4 Hz), 6.03 (br, 1 H, vinyl), 7.26 (br, 5 H, aromatic), AA′BB′ pattern centered at 8.17 (4 H).

Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.12; H, 5.13; N, 3.75; S, 8.57. Found: C, 61.14; H, 5.10; N, 3.64; S, 8.43.

3,4-Diphenyl-Δ^3-cyclopentenone. 4-Hydroxy-3,4-diphenyl-Δ^2-cyclopentenone, prepared by the reaction of benzil and acetone,[71] was converted to 4-chloro-3,4-diphenyl-Δ^2-cyclopentenone with acetyl chloride,[72] yield 65%, mp 117–118° (lit.[72] mp 116–117°). This chloride was reduced to the ketone with Zn and CH_3CO_2H in ether:[73] yield 95%; light yellow needles (from acetone); mp 143–144° (lit.[73] mp 147°); ir (Nujol mull) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.42 (s, 4 H, methylene), 7.16 (s, 10 H, aromatic).

3,4-Diphenyl-Δ^3-cyclopentenylacetic Acid. Reduction of 3,4-diphenyl-Δ^3-cyclopentenone with $LiAlH_4$[74] in ether gave, after recrystallization from cyclohexane, 3,4-diphenyl-Δ^3-cyclopentenol, yield 93%, colorless crystals, mp 103–104° (lit.[75] mp 102–104°). This alcohol was converted to the tosylate with tosyl chloride,[68] yield 95%, mp 103–104°. The tosylate was condensed with sodium diethylmalonate[76] in ethanol solution to give a brown oil, which upon hydrolysis with 10% aqueous KOH for 20 hr produced, after acidification with 10% sulfuric acid, a pale yellow, crystalline solid. Decarboxylation of the crude diacid in refluxing pyridine[76] gave, after recrystallization from 95% ethanol, colorless needles: yield 39% based on tosylate; mp 160–161°; ir (Nujol mull) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.42–3.42 (m, 7 H), 7.1 (s, 10 H, aromatic), 11.45 (s, 1 H, COOH).

2-(3,4-Diphenyl-Δ^3-cyclopentenyl)ethyl *p*-Nitrobenzenesulfonate (2). Reduction of 3,4-diphenyl-Δ^3-cyclopentenylacetic acid with $LiAlH_4$[67] in ether gave, after recrystallization from benzene–petroleum ether, 2-(3,4-diphenyl-Δ^3-cyclopentenyl)ethanol, yield 84%, colorless fibrous crystals, mp 71–72°. This alcohol was converted to the nosylate with *p*-nitrobenzenesulfonyl chloride[70] (Eastman): yield 52%; pale yellow crystals; mp 99–100° (blue melt); ir (Nujol mull), no trace of OH, 1545, 1355 (nitro group), 1372, 1183 cm^{-1} (sulfonate); NMR ($CDCl_3$) δ 1.93 (br quin, 2 H, $J \simeq J' \simeq 6$ Hz), 2.25–3.12 (m, 5 H), 4.22 (t, 2 H, J = 6 Hz), 7.06 (s, 10 H, aromatic), AA′BB′ pattern centered at 8.16 (4 H).

Anal. Calcd for $C_{25}H_{23}NO_5S$: C, 66.81; H, 5.16; N, 3.12; S, 7.12. Found: C, 66.74; H, 5.43; N, 3.14; S, 7.09.

2-Phenyl-2-norbornene and 1,2-diphenyl-2-norbornene were prepared from the corresponding 2-norbornanols by pub-

Table II
Comparison of Molar Absorptivity of Spent Reaction Mixture (10 Half-Lives) with Total Molar Absorptivity of Authentic Samples of Acetolysis Products[a]

λ, nm	$10^{-3}\epsilon_{Ph_1}$ or $10^{-3}\epsilon_{Ph_2}$	$10^{-3}\epsilon_{nos}$	$10^{-3}\epsilon_{tot}$	$10^{-3}\epsilon_{inf}$
		Compound **1**		
281	3.62 ± 0.12	5.2 ± 0.2	8.8 ± 0.2	9.1 ± 0.4
283	2.80 ± 0.08	4.6 ± 0.2	7.4 ± 0.2	7.5 ± 0.2
285	2.10 ± 0.06	4.1 ± 0.2	6.2 ± 0.2	6.3 ± 0.2
288	1.49 ± 0.04	3.4 ± 0.2	4.9 ± 0.2	5.0 ± 0.2
		Compound **2**		
283	1.57 ± 0.04	4.6 ± 0.2	6.2 ± 0.2	6.5 ± 0.4
285	1.42 ± 0.03	4.1 ± 0.2	5.5 ± 0.2	5.6 ± 0.3
288	0.78 ± 0.02	3.4 ± 0.2	4.2 ± 0.2	4.6 ± 0.2
293	0.34 ± 0.01	2.5 ± 0.1	2.8 ± 0.1	3.2 ± 0.2

[a] Error limits are standard deviations of mean values. The compound for measurement of ϵ_{Ph1} had to be freshly purified.

lished procedures,[77-79] for use as authentic samples of the acetolysis products of **1** and **2**, respectively.

Kinetics. Anhydrous acetic acid was prepared by allowing glacial acetic acid to reflux with 5% added acetic anhydride and a trace of sodium acetate for at least 24 hr, followed by fractional distillation in a dry atmosphere. A solution containing 0.03 *M* sodium acetate was prepared by careful addition of anhydrous acetic acid to a solution of anhydrous sodium carbonate in acetic anhydride, such that ~0.5% acetic anhydride remained after the water of neutralization was removed.

Solutions for kinetics were prepared by weighing 4–6 mg of **1** or 2–4 mg of **2** into a 100-ml volumetric flask, diluting to the mark with anhydrous acetic acid containing 0.03 *M* sodium acetate, and transferring ~5-ml aliquots to Pyrex ampoules which were chilled and sealed. The ampoules were allowed to equilibrate in a constant temperature bath at 60.40 ± 0.04° for at least 20 min before the first kinetic point was taken; the infinity point was taken after 10 half-lives. Ampules were quenched in Dry Ice–acetone. Before ultraviolet measurements, the ampoules were allowed to warm to room temperature, the contents were transferred to a quartz cell, and the absorbance was read at 281 nm for **1** and 293 nm for **2** with a Cary Model 16 spectrophotometer. Rate constants were calculated by fitting the absorbance data to the first-order rate equation by means of a nonlinear least-squares computer program.

Acetolysis Products. A solution of 155 mg (4.2 mmol) of **1** and 50.4 mg (6.2 mmol) of anhydrous sodium acetate in 50 ml of anhydrous acetic acid was heated in a sealed glass tube at 60.4° for 15.5 hr (~15 half-lives). The solution was cooled, poured into 100 ml of ice–water, and exhaustively extracted with purified ether. The combined ether extracts were successively washed with water, 5% aqueous Na_2CO_3, water, and saturated NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of the ether left 67.1 mg (95%) of a viscous light yellow oil with a very strong camphorlike odor (like that of authentic 2-phenyl-2-norbornene). This crude oil had the same NMR pattern as the authentic sample, except for a small amount of impurity, probably ether solvent. Integration of the vinyl and other protons demonstrated that little acetate product could be present. The infrared spectrum of the crude oil was essentially identical with that of the authentic sample. GLC on a 6.2 m × 0.94 cm column, packed with 20% SE-30 on 60–80 mesh Chromosorb W at 180°, helium flow rate 85 ml/min, showed only one peak, retention time 22.3 min, identical with that of the authentic sample.

A solution of 248 mg (5.5 mmol) of **2** and 69.3 mg (8.4 mmol) of anhydrous sodium acetate in 50 ml of anhydrous acetic acid was heated in a sealed glass tube at 60.4° for 23 hr (~11 half-lives), and the product was worked up as described above for **1**. Evaporation of the ether left 130 mg (95%) of a crude yellow solid which had the same NMR pattern as the authentic sample of 1,2-diphenyl-2-norbornene, except for impurity, probably ether. Integration of the vinyl and other protons demonstrated again that little acetate product could be present. The infrared spectrum of the crude solid was essentially identical with that of the authentic sample. The crude product was recrystallized once from pentane, giving colorless needles, mp 103–104°, undepressed by admixture with authentic sample (mp 103–104°).

Ultraviolet Absorbance Studies. Absorbance measurements were made on reaction mixtures after 10 half-lives, at four different wavelengths. The molar absorptivities, ϵ_{inf}, were compared with the sum of molar absorptivities, ϵ_{tot}, of authentic product 2-phenyl-2-norbornene, ϵ_{Ph_1}, or 1,2-diphenyl-2-norbornene, ϵ_{Ph_2}, respectively, and authentic nosylate ion, ϵ_{nos}, as shown in Table II. The agreement is considered to be adequate to demonstrate that the reactions proceed to give the products previously isolated, and that the ultraviolet method of following the kinetics provides a real measure of the progress of the reactions.[80]

Acknowledgments. Support by the National Science Foundation and the Department of Chemistry and the Computer Center, University of Pennsylvania, is gratefully acknowledged.

Registry No.—**1**, 49698-52-4; **2**, 49698-53-5; 3-phenyl-Δ^3-cyclopentenecarboxylic acid, 54143-11-2; methylphenylvinylcarbinol, 6051-52-1; aniline hydrobromide, 542-11-0; 2-phenyl-1,3-butadiene, 2288-18-8; ethyl diazoacetate, 623-73-4; 1-(1-phenylvinyl)-2-carboethoxycyclopropane, 54143-12-3; 2-(3-phenyl-Δ^3-cyclopentenyl)acetic acid, 54143-13-4; (3-phenyl-Δ^3-cyclopentenyl)methanol, 54143-14-5; (3-phenyl-Δ^3-cyclopentenyl)methyl tosylate, 54143-15-6; 2-(3-phenyl-Δ^3-cyclopentenyl)ethanol, 54143-16-7; *p*-nitrobenzenesulfonyl chloride, 98-74-8; 3,4-diphenyl-Δ^3-cyclopentenone, 7402-06-4; 4-hydroxy-3,4-diphenyl-Δ^2-cyclopentenone, 5587-78-0; 3,4-diphenyl-Δ^3-cyclopentenylacetic acid, 54143-17-8; 3,4-diphenyl-Δ^3-cyclopentenol, 4997-50-6; 3,4-diphenyl-Δ^3-cyclopentenyl tosylate, 35115-43-6; 2-(3,4-diphenyl-Δ^3-cyclopentenyl)ethanol, 54143-18-9.

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(80) Professor Paul D. Bartlett has kindly informed us of work by himself, Maurice J. Nugent, Raymond Owyang, and Saul Cherkovsky on a variety of substituted Δ^3-cyclopentenylethyl nosylates and related compounds. Their data on 1 and 2 agree with ours. They have also succeeded in making the mono- and dianisyl analogs, which solvolyze only ~3 and 5 times faster than 1 and 2, respectively.

Acetolysis of 3,3-Disubstituted Cyclobutyl Tosylates[1]

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The syntheses and acetolyses of 3,3-diphenyl- and 3,3-dimethylcyclobutyl tosylates have been carried out. The diphenyl compound was prepared from the corresponding cyclobutanone which, in turn, was obtained in the reaction of diphenylketene with diazomethane. The dimethyl compound was prepared by a multistage synthesis. The compounds were solvolyzed in acetic acid containing excess sodium acetate. The activation parameters for the acetolyses were for the diphenyl compound $\Delta H^{\ddagger} = 27.6$ kcal/mol, $\Delta S^{\ddagger} = -9.6$ eu, and for the dimethyl $\Delta H^{\ddagger} = 26.1$ kcal/mol, $\Delta S^{\ddagger} = -5.8$ eu. The products of the reactions as well as the kinetic evidence suggest ionization concerted with rearrangement, which finally result in ring opening. The mechanistic details are discussed.

The solvolysis of the cyclobutyl system has been one of the most thoroughly studied reactions in physical organic chemistry. The solvolysis of 3-substituted cyclobutyl derivatives, however, has received little attention until relatively recently. Part of the reason for this has been the relative difficulty of making such compounds.

Hasek, Clark, and Chaudet[2] reported that the acid-catalyzed ring opening of *trans*-2,2,4,4-tetramethyl-1,3-cyclobutanediol was very much faster than that of the cis isomer. To explain this curious result they suggested that there was participation of the trans hydroxyl to give the bicyclic oxonium ion 1.

That this hypothesis was untenable was shown by the work of Wilcox and his coworkers[3] and Dolby and Wilkins.[4] The latter workers, using both *cis*- and *trans*-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylates, found that, indeed, the trans/cis ratio was about 100 but that the faster rate of the trans compound was not due to the across-the-ring participation. They concluded that the ionization of the tosylate was concerted with the breaking of the 2,3 carbon–carbon bond. They further assumed that the ring opening was disrotatory and hence the cis 3-hydroxyl would interact strongly with the methyl substituent on carbon 2, as shown in 2. Thus the rate of the cis isomer was slow and the rate of the trans was "normal". Indeed, introduction of the fifth methyl group in place of the hydrogen at C-3 reduced the trans/cis ratio to only about 4.

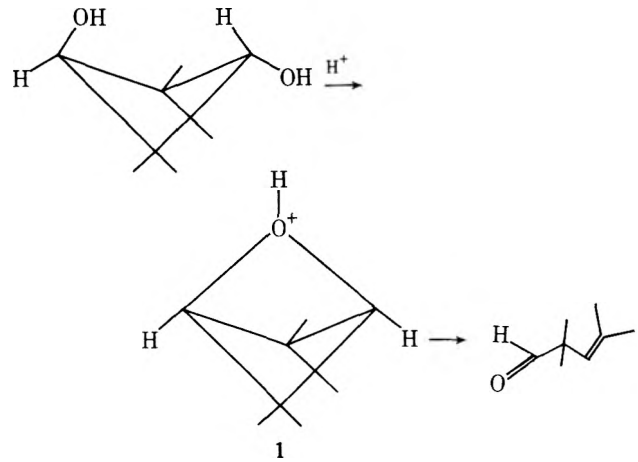

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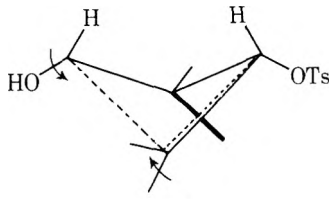
Table I
First-Order Constants and Activation Parameters for Acetolysis of Cyclobutyl Tosylates

Tosylate	Temp, °C	k, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, eu[a]	Rel rate
3,3-Dimethylcyclobutyl	86.6	5.81×10^{-5}, 5.82×10^{-5}	26.1	−5.8	1/30
	95.0	1.33×10^{-4}, 1.34×10^{-4}			
	103.0	2.99×10^{-4}, 2.94×10^{-4}			
3,3-Diphenylcyclobutyl	127.0	5.86×10^{-5}, 5.70×10^{-5}	27.6	−9.6	1/1000
	136.2	1.02×10^{-4}, 1.06×10^{-4}			
	142.2	2.13×10^{-4}, 2.33×10^{-4}			
Cyclobutyl[b]	50.0	3.58×10^{-5}	23.8	−5	1
	74.8	5.42×10^{-4}			

[a] The $\Delta S^{\ddagger}$ data are probably not better than ±4 eu. [b] Unpublished data: J. Longanbach, Yale University. Personal communication from Professor Wiberg.



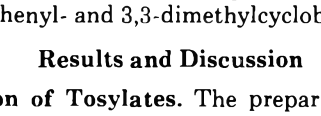
2

Other data, however, indicated that introduction of any aryl or alkyl substituents into the 3 position of a cyclobutyl tosylate caused a decrease in the rate of solvolysis, relative to the unsubstituted case.[5-7] The cis isomer was generally slower than the trans. Wiberg, Hess, and Ashe[8] suggested that the available data indicated that the 3-substituted cyclobutyl tosylates rearranged stereospecifically initially to the cyclopropylcarbinyl ion, which then opened to the allylcarbinyl ion.

In this paper we describe the preparation and the acetolysis of 3,3-diphenyl- and 3,3-dimethylcyclobutyl tosylates.

Results and Discussion

Preparation of Tosylates. The preparation of 3,3-diphenylcyclobutyl tosylate was carried out according to the following sequence. This preparation was based on the formation of 3,3-dimethylcyclobutanone from dimethylketene and diazomethane.[9] The important difference in the present reaction was that the solution of the ketene was poured into the solution of the diazomethane. In this way the diazomethane was always in excess and moderate yields of the cyclobutanone could be obtained. If the reverse addition was used the reaction took a different course. Very little cyclobutanone was formed; the principal isolated product (20–30%) was the keto ester 4. This product was formed



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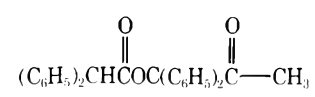
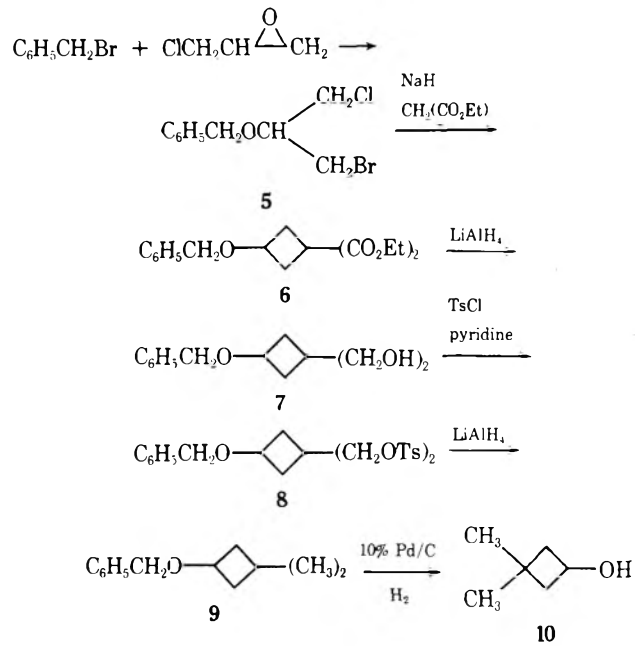


4

from the addition of diphenylacetic acid to the intermediate cyclopropanone. It was not formed immediately, but crystallized out of the reaction mixture after a few hours of standing.

Although 3,3-dimethylcyclobutanone could be prepared by the reaction of dimethylketene with diazomethane,[9] the fact that it is formed together with the 2,2 isomer led us to consider an alternative route, since the two isomers are relatively difficult to separate on a larger scale. The procedure used is outlined below.



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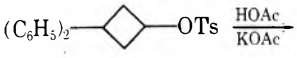
The advantage of this procedure was that in spite of the large number of steps involved, high-purity 3,3-dimethylcyclobutanol could be prepared without the use of the very pyrophoric dimethylketene and large quantities of equally unpleasant diazomethane. All the steps, except the cyclization step, proceeded in relatively high yields and could be carried out on any scale desired. The detailed procedure is given in the Experimental Section.

Kinetics and Product Studies. The rates of acetolysis were determined using the ampoule technique.[10] Solutions of the cyclobutyl tosylates in glacial acetic acid containing 1% of acetic anhydride and an excess of potassium acetate were sealed in a dozen ampoules and placed in a temperature-regulated oil bath. The temperatures were held constant to better than 0.1°. At periodic intervals the ampoules were withdrawn, the reaction was quenched by cooling, and the contents of the tube were titrated with perchloric acid. Because of discoloration of the solutions past 50% reaction the end points were determined using a pH meter. The rates were linear for better than 85% reaction. The rates and activation parameters are summarized in Table I. The rate constants were calculated using the LSKIN-1 program adapted for the IBM 360/65 computer.[11]

All the products of both solvolyses resulted from ring-opening reactions. In the diphenyl case the only characteri-

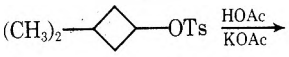
zable product was 1,1-diphenylbutadiene (**11**). This was formed in 56.5% isolated yield (70% crude yield). The compound was isolated by column chromatography. Its spectral (ir, NMR) characteristics were identical with those of an authentic sample.[12] The rest of the reaction mixture resulted from polymerization and/or oligomerization of the butadiene. A similar mixture was obtained from the authentic butadiene when it was heated in glacial acetic acid under solvolysis conditions.

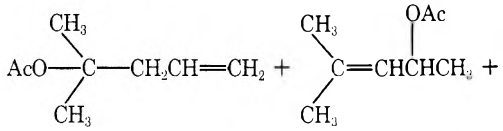
The products of the dimethyl compound were slightly more complex. The principal product (74 ± 5% of the crude reaction mixture) was 4-acetoxy-4-methyl-1-pentene (**12**), formed by the reaction of the dimethylallylcarbinyl ion with acetate. There also was obtained a 15 ± 5% yield of 2-methyl-4-acetoxy-2-pentene (**13**). This product was also formed when authentic 4-methyl-1,3-pentadiene (Aldrich Chemical Corp.) was heated in glacial acetic acid under solvolysis conditions. Thus it apparently arises from the pentadiene, which is thus probably one of the original products of the solvolysis. No pentadiene was observed in the final products. The rest of the material could also be accounted for as having arisen from the pentadiene. These results are summarized in the following reactions. The acetolysis of



$(C_6H_5)_2C{=}CHCH{=}CH_2$ + polymer

11 (70%)



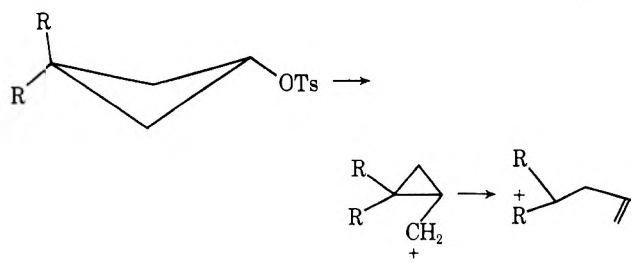


12 (74 ± 5%) **13** (15 ± 5%)

unidentified minor products

3,3-dimethylcyclobutyl brosylate has been reported.[13] The main product of the reaction was **12** (62% yield).

The data presented in this report are in line with those reported by others[8] on the solvolysis of 3-substituted cyclobutyl tosylates. The important findings in the present work are that both the 3,3-diphenyl- and the 3,3-dimethylcyclobutyl tosylates solvolyzed more slowly than the unsubstituted cyclobutyl tosylate and that no cyclic products were formed during the reaction.[14] The slowness of the reaction seems to militate against the concerted ring opening to the allylcarbinyl ion accompanying ionization. In both cases the substituents in the 3 position would have stabilized the developing positive charge. On the other hand, the lack of any cyclobutyl products suggests that the initial formation of the cyclobutyl ion does not occur either. Wiberg et al.[8] suggest that all 3-substituted cyclobutyl derivatives (except 3-ethoxycyclobutyl tosylate) ionize initially to the cyclopropylcarbinyl ions, which then undergo a rapid ring opening to the corresponding allylcarbinyl ions. Our data are in line with this hypothesis. It must be said, however, that none of the data at hand (ours and other) prove the mechanism above. In fact, if the rate of cyclopropylcarbinyl ion opening is exceedingly fast, then its existence as an intermediate may be questioned. In that limiting case the solvolysis would be via a concerted ionization and disrotatory[15] ring opening. The rate of such a reaction, which would be governed by strict orbital symmetry control considerations, would depend on the steric interactions in the attainment of the transition state leading to the allylcarbinyl ion. This type of a mechanism was proposed by Dolby and Wilkins[4] to explain their data on the solvolysis of the highly substituted cyclobutyl tosylates.



Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were measured with a Perkin-Elmer Model 237 spectrophotometer. The NMR spectra were measured with Varian A-60, A-60D, and HA-100 spectrometers. The calculations were carried out on the University of Nebraska IBM 360/65 computer. Analyses were performed by A. Bernhardt, Elbach über Engelskirchen, West Germany.

3,3-Diphenylcyclobutanone. Diphenylketene.[16] A solution of 50 g (0.23 mol) of diphenylacetic acid in 150 ml of dry benzene was placed into a 500-ml three-necked flask equipped with a reflux condenser and an addition funnel and protected by a drying tube. The solution was heated at reflux and 132 g (1.1 mol) of thionyl chloride was added dropwise during 30 min. The heating was continued for 7 hr. At the end of that time the benzene and the excess thionyl chloride were removed by distillation to leave a pale yellow oil. To remove the last traces of thionyl chloride, 10 ml of benzene was added and the solution was again distilled. The residue was dissolved in 100 ml of hot, anhydrous hexane. The solution was treated with charcoal, filtered, and chilled at 0°. The product crystallized out as white plates. The crystals were recrystallized twice from dry hexane and dried in vacuo at room temperature. The yield of diphenylacetyl chloride was 36 g (73%), mp 52–53° (lit.[16] mp 51–53°).

A solution of 9.7 g (0.042 mol) of diphenylacetyl chloride in 100 ml of dry ether and 75 ml of dry hexane was placed in a 500-ml three-necked flask equipped with a magnetic stirrer, a gas inlet tube, an addition funnel, and a drying tube. The solution was chilled in an ice bath and was flushed thoroughly with dry nitrogen. To this solution 4.4 g (0.044 mol) of dry triethylamine was added dropwise with stirring over a period of 30 min. Triethylamine hydrochloride began precipitating immediately and the supernatant solution became bright yellow. After the addition was complete the flask was stoppered tightly and was kept at 0° for 4 hr. The hydrochloride was filtered using a sintered glass filter which could be attached directly to the reaction vessel via a standard taper. The filtration was accomplished by simply inverting the reaction flask so that the contents flowed into the filter. The filtrate flowed into another flask attached to the fiter via a second standard taper. Suction was applied to the system through a side arm on the filter, below the sintered glass disk. In this way the ketene solution was not exposed to the atmosphere or to moisture. The yellow ketene solution was used in the next step without further isolation. Pure ketene in yields of about 60–70% could be obtained by rapid distillation of the solution.[16]

Diazomethane was prepared from Aldrich Chemical Co. Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) using the procedure for obtaining the ethanol-free product.[17] The diazomethane solution was dried over solid potassium hydroxide.

Diphenylcyclobutanone. To a solution of excess diazomethane in ether contained in a 1-l. erlenmeyer flask was added a solution of diphenylketene, prepared as described above. The addition was accomplished simply by slowly pouring one solution into the other, with intermittent swirling. The evolution of nitrogen started immediately. After standing for several hours the solution was greenish-blue in color. Evaporation of solvent in vacuo gave a dark oil which showed a prominent peak at 1780 cm^{-1} in its infrared spectrum.

The crude reaction mixture (8.4 g) was applied to a chromatography column made from 200 g of silicic acid and 50 g of Celite. The column was initially eluted with 1 l. of Skellysolve B, then with 1 l. of Skellysolve B containing 1% ether. The latter solvent eluted 0.6 g of 1,1-diphenylethylene from the column. The polarity of the solvent was increased gradually to 3.5% ether in Skellysolve B for 2 l. of eluting solvent. During this time various uncharacter-

ized oils were eluted. There was then a break in fractions and the desired product was eluted. The yield of 3,3-diphenylcyclobutanone was 1.5 g (22% of total products, 16% of theory): mp 84–85°; ir (CCl_4) 1793 cm^{-1}; NMR (CCl_4) δ 7.2 (s, 10 H), 3.67 (s, 4 H).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.36. Found: C, 86.31; H, 6.36.

3,3-Diphenylcyclobutyl Tosylate (3). A solution of 3.14 g (0.015 mol) of 3,3-diphenylcyclobutanone in 25 ml of dry ether was added dropwise to a stirred solution of 0.32 g (0.08 mol) of lithium aluminum hydride in 50 ml of dry ether. After the addition was complete the reaction mixture was stirred for an additional 6 hr. After this period the excess reducing agent was decomposed with 50 ml of water. The ether layer was separated and the water layer was washed three times with ether. The combined ether solutions were dried and the solvent was evaporated off. The crude 3,3-diphenylcyclobutanol was recrystallized from 200 ml of hexane. The yield was 2.78 g (84%): mp 104–105°; ir (CCl_4) 3610 cm^{-1}; NMR ($CDCl_3$) δ 7.19, 7.29 (10 H), 4.20 (1 H), 3.06, 2.48 (4 H), 2.88 (1 H).

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.88, H, 7.10.

The NMR spectrum of the cyclobutanol is of some interest because of the large cross-ring coupling. The spectrum was calculated using the LAOCN3 program.[18] Table II lists the calculated coupling constants and the chemical shifts.

The tosylate from the above cyclobutanol was prepared by the sodium hydride method. The yield from 3.74 g of the alcohol was 2.99 g (47%), after three recrystallizations: mp 117–118°; ir (CCl_4) 2900, 1290 s, 1450 w, 1500 s, 1185 s, 1200 s, 1045 s, 1110 s, 950, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.0–8.0 (14 H, aromatic), 4.68 (m, 1 H), 2.00 (m, 4 H), 2.35 s, 3 H).

Anal. Calcd for $C_{23}H_{22}O_3$: C, 73.00; H, 5.82; S, 8.47. Found: C, 72.98; H, 5.52; S, 8.35.

3,3-Dimethylcyclobutanol. 1-Chloro-2-benzyloxy-3-bromopropane (5). The procedure of Nenitzescu et al.[19] was followed. A mixture of benzyl bromide (254 g, 1.48 mol), epichlorohydrin (138 g, 1.48 mol), and 0.25 g of mercurous chloride was heated for 12 hr at 150–160°. The product was separated from the dark brown reaction mixture by distillation through a 12-in. Vigreux column: yield 211 g (54.3%); bp 142–145° (0.3 mm) [lit.[19] bp 146–150° (5 mm)]; NMR (CCl_4) δ 7.26 (s, 5 H), 4.58 (s, 2 H), 3.34–3.9 (m, 4 H).

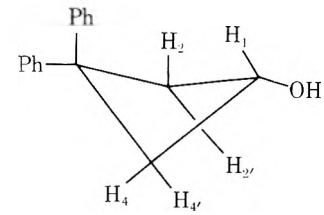
Diethyl 3-Benzyloxycyclobutane-1,1-dicarboxylate (6). The procedure of Beard and Burger[20] was followed. In a 3-l., three-necked flask equipped with a stirrer, an addition funnel, and a reflux condenser and which was swept with dry nitrogen was placed 19.8 g (0.8 mol) of sodium hydride in 500 ml of dry dioxane. To this stirred mixture 128 g (0.8 mol) of diethyl malonate was added dropwise over 20 min. After this addition was complete 211 g (0.8 mol) of **5** was added dropwise in 20 min. Upon completion of the reaction the solution became red but changed to yellow on standing. The mixture was heated at reflux for 44 hr. After cooling to room temperature 19.8 g of sodium hydride in a little dioxane was added to the mixture and heating at reflux was continued for an additional 120 hr. The solvent was partially removed under reduced pressure and the mixture was treated with 500 ml of water. The organic layer was extracted into ether. The ether extracts were dried and concentrated and the residue was distilled under reduced pressure. The distillate, which formed two immiscible layers, was collected at 174–176° (0.9 mm). The heavier layer was the desired product: yield 100.9 g (40.5%) [lit.[20] bp 157° (0.45 mm)]: NMR (CCl_4) δ 7.23 (s, 5 H), 4.13 (q, 4 H, J = 7 Hz), 4.34 (s, 2 H), 4.0–4.7 (m, 1 H), 2.2–3.0 (m, 4 H), 1.23 (t, 6 H, J = 7 Hz).

1,1-Di(hydroxymethylene)-3-benzyloxycyclobutane (7).[21] Diethyl 3-benzyloxycyclobutane-1,1-dicarboxylate (50 g, 0.16 mol) was reduced by 11.4 g of lithium aluminum hydride in 100 ml of ether in the usual manner. There was obtained 24 g (71%) of **9**: mp 66–68° (lit.[21] mp 71°); NMR ($CDCl_3$) δ 7.36 (s, 5 H), 4.41 (s, 2 H), 3.3–4.2 (m, 7 H), 1.4–2.4 (m 4 H).

1,1-Di(tosyloxymethylene)-3-benzyloxycyclobutane (8). To a solution of 48 g (0.22 mol) of **7** in 150 ml of dry pyridine was added 85 g (0.44 mol) of *p*-toluenesulfonyl chloride. The reaction mixture was kept at about 5° overnight. The mixture was poured into water and the product was extracted with ether. The ether extracts were washed thoroughly with 5% hydrochloric acid, 5% potassium carbonate, and finally with water. After drying and concentration of the ether solution the ditosylate crystallized, yield 84.2 g (74.3%), mp 85–86° (lit.[21] mp 86–87°).

1-Benzyloxy-3,3-dimethylcyclobutane (9). The ditosylate **8** (84.2 g, 0.16 mol) was added as a solid, in portions, to a stirred suspension of 12 g of lithium aluminum hydride in 1000 ml of dry ether. The reaction mixture was flushed with nitrogen and chilled in an ice bath. After the addition was complete the mixture was heated at reflux for 24 hr. After the decomposition of the excess hydride with water the mixture was extracted with ether. The ethereal extracts were dried and concentrated and the residue was distilled to give 20.5 g (71%) of the product: bp 127–132° (12–15 mm); NMR (CCl_4) δ 7.25 (s, 5 H), 4.21 (s, 2 H), 3.95 (q, 1 H), 1.4–D.4 (m, 4 H), 1.12 (s, 3 H), and 1.09 (s, 3 H).

Table II
NMR Parameters for 3,3-Diphenylcyclobutyl Alcohol



Coupling constants, Hz	Chemical shifts (60 MHz) Proton	Shift, Hz
$J_{2,4}$ = 5.20		
$J_{2,4'}$ = 0.0	1	251.5
$J_{2,2'}$ = $J_{4,4'}$ = 11.10	2	187.0
$J_{2,4'}$ = $J_{4,2'}$ = −0.60	4	187.0
$J_{1,4}$ = $J_{1,2}$ = 7.00	2′	151.2
$J_{1,4'}$ = $J_{1,2'}$ = 8.20	4′	151.2

3,3-Dimethylcyclobutanol (10). A solution of 10 g (0.052 mol) of benzyl ether **9** in 10 ml of ethanol was mixed with a suspension of 0.3 g of 10% palladium on charcoal in 20 ml of ethanol. The mixture was hydrogenated for 3 hr under 30 psi of hydrogen in a Parr shaker. The catalyst was filtered off and the solvent was evaporated. Distillation of the residue gave 3 g (57%) of 3,3-dimethylcyclobutanol: bp 112–114° (20 mm); NMR (CCl_4) 4.17 (q), 3.84 (s, 1 H), 1.44–2.35 (m, 4 H), 1.12 (s, 3 H), and 1.08 (s, 3 H).

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.68; H, 11.86.

3,3-Dimethylcyclobutyl Tosylate. This compound was prepared in the same manner as 3,3-diphenylcyclobutyl tosylate. Starting with 6 g of the cyclobutanol, there was obtained 4.1 g of the pure tosylate: mp 21–22°. The crude tosylate was purified by chromatography over a short (10 in.) column of Florisil, using pentane as the eluent. The product was recrystallized from pentane: NMR (CCl_4) δ 7.47 (d, 4 H), 4.74 (q, 1 H), 2.44 (s, 3 H), 1.60–2.38 (m, 4 H), 1.10 (s, 3 H), and 1.03 (s, 3 H).

Anal. Calcd for $C_{16}H_{18}O_3S$: C, 61.42; H, 7.09; S, 12.60. Found: C, 61.19; H, 7.10; S, 12.49.

Kinetic Procedures. The method used was essentially that of Winstein et al.[10] Solutions of the tosylates (ca. 0.02 *M*) in glacial acetic acid, containing 1% acetic anhydride and 0.045–0.056 *M* in dry potassium acetate, were sealed in Pyrex ampoules and placed in a constant-temperature oil bath. The bath temperature was held constant to better than 0.1° and was measured with a calibrated total immersion thermometer. The ampoules were withdrawn at periodic intervals and accurately measured aliquots were titrated with perchloric acid. The end points were determined with a pH meter; the use of visual indicators was precluded by discoloration of the samples after 50% reaction. The last ampoule was withdrawn after 10 half-lives. The rate constants were calculated using a nonlinear least-squares program, LSKIN-1.[11] The activation parameters were also calculated using a least-squares program. The rates were strictly first order over at least 85% reaction. The statistical analysis of the data (residual plot) showed that all the deviations were random.

Solvolysis Product Studies. In all cases the solvolyses were carried out under the same[22] conditions as the kinetic runs, i.e., the solutions were sealed in ampoules and placed in the constant-temperature bath for at least 10 half-lives.

3,3-Diphenylcyclobutyl Tosylate. A solution containing 1.50 g (0.04 mol) of the tosylate and 0.55 g of dry potassium acetate in 50 ml of glacial acetic acid containing 1% acetic anhydride was divided between and sealed in six ampoules. The tubes were heated in a constant-temperature bath at 136° for 20 hr. At the end of that period the solution was poured into 100 ml of ether, to which was then added 100 ml of water. The solution was neutralized by addition of solid potassium carbonate. The aqueous layer was extracted

with ether (four times) and the combined ethereal layers were dried and concentrated to give 0.86 g of crude product.

The crude reaction mixture was placed on a chromatography column made up from 32 g of silicic acid and 10 g of Celite. The column was eluted with petroleum ether. The main product of the reaction, 1,1-diphenyl-1,3-butadiene, was obtained in 56.5% yield. The examination of the NMR spectrum of the crude mixture revealed it to be about 70% butadiene. Addition of small amounts of ether to the eluent caused the elution of products which contained an acetate group (20% of the crude mixture). Further addition of ether to the eluent caused the appearance of several trace fractions which were not identified.

The butadiene was identified by its ir and NMR spectrum and comparison with an authentic sample.[12] Authentic 1,1-diphenyl-1,3-butadiene was heated in glacial acetic acid in the presence of potassium acetate under the same conditions as the solvolysis. After an identical work-up and chromatography, polymeric and oligomeric acetates were isolated, virtually identical with those obtained in the solvolysis reaction.

3,3-Dimethylcyclobutyl Tosylate. The product study solvolysis of this compound was carried out using similar conditions to the diphenyl tosylate. A solution of 0.98 g (0.038 mol) of the tosylate and 0.56 g (0.056 mol) of potassium acetate in 40 ml of glacial acetic acid was heated at 105° for 24 hr. The contents of the tubes were dissolved in 75 ml of ether contained in a 250-ml flask equipped with a stirrer and an addition funnel and connected to a Dry Ice trap. The solution was cooled, 50 ml of water was added, and the solution was carefully neutralized with cold, concentrated potassium hydroxide. The solution was then extracted with ether; the extracts were dried and concentrated by careful distillation. No volatile products were recovered from the Dry Ice trap. The solvolysis products were separated by GLC using a 4-ft glass column packed with 5% Apiezon N on Chromosorb W and operated at 50° with 47 ml/min He flow rate. The main component, 74 ± 5% of the crude reaction mixture, was 4-acetoxy-4-methyl-1-pentene (**12**). It was identified by its ir spectrum ($\nu_{C=O}$ 1735 cm^{-1}) and NMR spectrum (CCl_4) [δ 1.44 (s, 6 H), 1.94 (s, 3 H), 2.56 (d, 2 H), and 4.9–6.25 (m, 3 H)]. The NMR spectrum was essentially identical, except for the acetate methyl group, with the spectrum of 4-hydroxy-4-methyl-1-pentene, prepared by the addition of allylmagnesium bromide to acetone.

Another fraction, formed in 15 ± 5% yield, was identified as 2-methyl-4-acetoxy-2-pentene (**13**): ir (CCl_4) 1730, 1600 cm^{-1}; NMR (CCl_4) δ 1.28 (d, 3 H, J = 6.0 Hz), 1.66, 1.68 (two s, 6 H), 1.89 (s, 3 H), 4.0–5.7 (m, 1 H), 1.5–2.0 (m, 1 H, buried under Me resonances). The same product was formed when authentic 4-methyl-1,3-pentadiene (Aldrich Chemical Co.) was heated in acetic acid under the solvolysis conditions.

Two other minor (1–2%) volatile components, which were not identified, were isolated. These were also obtained when the pentadiene was heated in acetic acid.

Acknowledgments. Partial financial support from the University of Nebraska Research Council is gratefully acknowledged. Helpful discussions with Drs. C. L. Wilkins and Arno Kroniger were appreciated. R.W.C. was supported for part of the time by research assistantships derived from a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and a Development Grant from the NSF to the Department of Chemistry (NSF-GU2054).

Registry No.—**3,** 54166-14-2; **5,** 54307-67-4; **6,** 54166-15-3; **7,** 20061-24-9; **8,** 20440-61-3; **9,** 54166-16-4; **10,** 54166-17-5; **10** tosylate, 54166-18-6; **11,** 4165-81-5; **12,** 926-22-7; **13,** 54166-19-7; 3,3-diphenylcyclobutanone, 54166-20-0; diphenylketene, 525-06-4; diphenylacetic acid, 117-34-0; diphenylacetyl chloride, 1871-76-7; 3,3-diphenylcyclobutanol, 54166-21-1; *p*-toluenesulfonyl chloride, 98-59-9.

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Studies on Anticoccidial Agents. III. Selective Esterification and Acyl Transfer in α^4-Norpyridoxol

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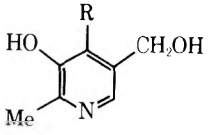
Acyl and aroyl substituents attached to the ring hydroxyl group of α^4-norpyridoxol have been found to transfer to the side-chain hydroxyl at the α^5 position. This intermolecular rearrangement takes place on heating 3-*O*-acyl-α^4-norpyridoxol in pyridine. The mechanism of this rearrangement has been studied and could be explained by a two-stage intermolecular transesterification via the 3,α^5 diester. Some α^5 aromatic esters have also been prepared by selective hydrolysis of 3-*O*-acetyl-α^5-*O*-aroyl-α^4-norpyridoxol.

4-Deoxypyridoxol (**1**) and α^4-norpyridoxol (**2**) have been shown to exhibit coccidiostatic effects and the latter compound was found to be the more desirable drug.[1,2] In the



1, R = Me
2, R = H

present study, the selective esterification of **2** has been examined in order to obtain derivatives for evaluation as potential anticoccidial agents. Perez-Medina et al.[3] prepared **5a** hydrochloride from **2** by refluxing in acetyl chloride. We have prepared a series of diesters **5** by treating **2** with excess acid chloride or anhydride in pyridine.

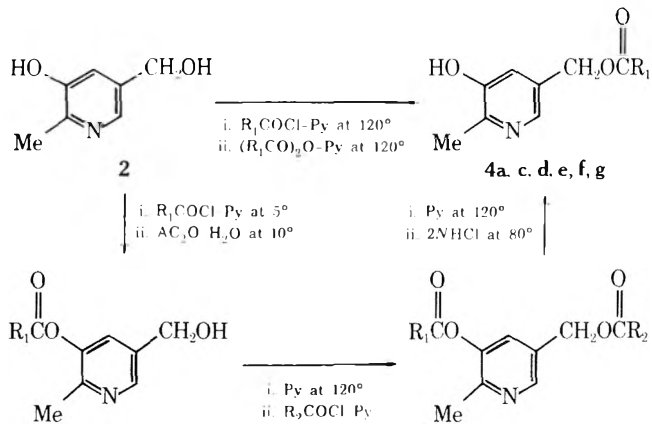
We obtained 3-*O*-monoesters **3** by treating **2** with 1 equiv of an acid chloride at 5°. 3-*O*-Acetoxy-5-hydroxymethyl-2-methylpyridine (**3a**) was prepared by treating **2** with acetic anhydride in water under vigorous stirring. These monoesters gave a negative ferric chloride test, indicating substitution of the phenolic hydroxyl group.

In an attempt to obtain 3-hexanoyloxy-5-hydroxymethyl-2-methylpyridine, we treated **2** with 1 mol of *n*-hexanoic anhydride in pyridine at about 120° for 10 hr. The resulting monohexanoate was not the same as the product obtained from **2** and *n*-hexanoyl chloride in pyridine under cooling and gave a positive ferric chloride test, indicating the presence of a phenolic hydroxyl group as could be expected from the rearranged product (**4**). The ir spectrum of the monoester **4e** on comparison with that of 3-*O*-monohexanoate **3e** confirmed the structural assignment. The carbonyl absorption band of the ring-substituted hexanoyl group appeared at 1770 cm^{-1} while that of the α^5-*O*-hexanoyl group appeared at 1730 cm^{-1}. The α^5-*O*-hexanoate **4e** was in fact obtained by heating a pyridine solution of the hydrochloride of 3-*O*-*n*-hexanoate **3e**.

Analogous rearrangements were shown to occur in other aliphatic, alicyclic, and aromatic esters, namely 3-*O*-acetyl, 3-*O*-valeryl, 3-*O*-pivaloyl, 3-*O*-cyclohexanecarbonyl, and 3-*O*-benzoyl esters of **2**. The sterically hindered pivaloyl moiety in the 3-*O*-pivaloate **3d** migrated more slowly than the unhindered hexanoyl function in 3-*O*-hexanoate **3e**. The transfer of 3-*O*-benzoate **3g** was effected only under the prolonged reaction conditions. The reason for this difficulty for rearrangement may be related to the greater stability of the aromatic esters as compared with the corresponding aliphatic esters.

Korytnyk et al.[4-6] observed the intramolecular acyl rearrangement via an ortho acid in the synthesis of α^4-O-acylpyridoxols. Now we observed the acyl transfer in the synthesis of α^5-*O*-acyl-α^4-norpyridoxols.

To clarify the mechanism of these acyl rearrangements, we examined the behavior of 3-*O*-pivaloate **3d** in pyridine at about 120°. Heating a pyridine solution of **3d** at 120° for 10 hr produced 3,α^5-*O*-pivaloate **5d**, α^5-*O*-pivaloate **4d**, and **2** together with some starting material (**3d**). The 3,α^5-*O*-pivaloate hydrochloride (**5d**) obtained was again heated in pyridine at 120° for 10 hr, which resulted in partial hydrolysis to α^5-*O*-pivaloate **4d** (12.8%). When the diester hydrochloride (**5d**) was heated in the presence of **2** under the same conditions, the transfer of the 3-*O*-pivaloyl group of **5d** to the 5-hydroxymethyl group of **2** was very effective (58.3%). On the other hand, heating the pyridine solution of the α^5-*O*-pivaloate **4d** in the absence as well as in the presence of 2 at 120° for 10 hr afforded only unchanged starting material. Thus the chemical evidences described above have shown that the 3-*O*-acyl transfer to the α^5-O position can be explained by a two-stage intermolecular transesterification via the 3,α^5-*O*-diester **5**.

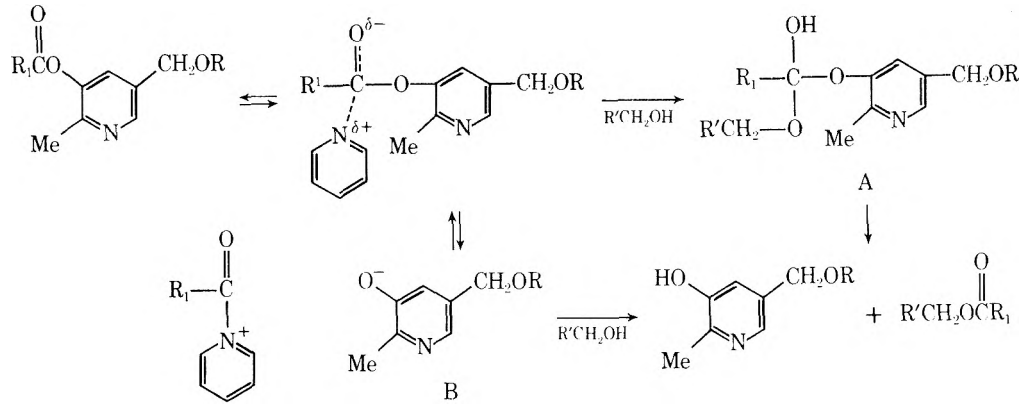


2 — **4a, c, d, e, f, g** — **3a, d, e, f, g, h** — **5a, b, d, f, g, h, i, j**

a, R_1 = Me
b, $R_1 = R_2$ = iso-C_3H_7
c, R_1 = *n*-C_7H_{15}
d, $R_1 = R_2$ = *t*-C_4H_9
e, R_1 = *n*-C_5H_{11}
f, R_1 = cyclohexyl
g, $R_1 = R_2$ = Ph
h, $R_1 = R_2$ = *p*-PhOMe
i, R_1 = Me; R_2 = Ph
j, R_1 = Me; R_2 = *p*-PhOMe

In the acyl shift from 3 to α^5, participation of pyridine molecule precedes an attack of the α^5-hydroxyl on the 3-*O*-ester carbonyl, since the transfer has not been observed in toluene but in pyridine as well as in toluene containing a trace of pyridine at 120° for 10 hr. So the acyl transfer may proceed by way of the ortho acid (A) or the pyridinium salt (B).

In addition α^5-O-monoaromatic esters (**4**) have been obtained by the interaction of 3-*O*-acetate **3a** with aroyl chlorides to produce the corresponding esters (**5**), followed by selective hydrolysis with 2 *N* HCl. The α^5-*O*-acetate **4a** was



also prepared from **2** via 5-bromomethyl-3-hydroxy-2-methylpyridine under conditions essentially identical with those applied to the synthesis of 5-acetoxymethyl-3-hydroxy-2,4-dimethylpyridine.[7] All the esters prepared were found to be active against *Eimeria acervulina*, and 3-*O*-monoacetate **3a** and α^5-O-monoacetate **4a** have almost the same activity as **2** HCl.

Experimental Section

Melting points are uncorrected. Ir spectra were determined using a Perkin-Elmer 221 and Jasco IRA-2 spectrometers. NMR spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Typical experimental procedures are described for the preparation of the ester derivatives.

3,α^5-*O*-Dibenzoyl-α^4-norpyridoxol. **2** HCl (0.9 g, 5.13 mmol) was dissolved in pyridine (5 ml) and cooled at 5° and benzoyl chloride (1.5 g, 10.66 mmol) was added. The solution was stirred at room temperature overnight, poured into water, and extracted with chloroform. The extract was dried and the solvent was removed, leaving a crystalline material which was recrystallized from ethyl acetate–*n*-hexane to give 1.6 g (90%) of the dibenzoate: mp 85–86°; ir (Nujol) 1738, 1722 cm^{-1}.

Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.63; H, 4.83; N, 4.23.

3,α^5-*O*-Dianisoyl-α^4-norpyridoxol (prepared by the above procedure) had mp 135–136° from ethyl acetate–*n*-hexane (92% yield): ir (Nujol) 1730, 1715 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO_6$: C, 67.80; H, 5.20; N, 3.44. Found: C, 67.75; H, 5.15; N, 3.43.

3,α^5-*O*-Diisobutyryl-α^4-norpyridoxol hydrochloride (prepared by the above procedure) had mp 134–136° from ethanol–ethyl acetate (95% yield): ir (Nujol) 1762, 1738 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}ClNO_4$: C, 57.10; H, 6.97; N, 4.43; Cl, 11.25. Found: C, 57.14; H, 6.94; N, 4.45; Cl, 11.27.

3-*O*-Acetyl-α^4-norpyridoxol Hydrochloride (3a). An aqueous solution (15 ml) of 2 HCl (3.5 g) was neutralized with $NaHCO_3$ and to this solution acetic anhydride (2.5 g) was added at 15° under vigorous stirring. After addition was completed, the solution was stirred for 20 min and then extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to a small volume and addition of ethanol containing 15% hydrogen chloride afforded **3a** (3.4 g, 86.8%): mp 134–135°; ir (Nujol) 3300, 1786 cm^{-1}; NMR (D_2O) 2.52 (s, 3, OCOMe), 2.72 (s, 3, C_2 Me), 4.91 (s, 2, C_5 CH_2OH), 8.42 (d, 1, J = 2.0 Hz, C_4 H), 8.61 ppm (d, 1, J = 2.0 Hz, C_6 H).

Anal. Calcd for $C_9H_{12}ClNO_3$: C, 49.61; H, 5.56; N, 6.48. Found: C, 49.82; H, 5.62; N, 6.58.

3-*O*-Cyclohexanecarbonyl-α^4-norpyridoxol Hydrochloride (3f). A solution of cyclohexanecarbonyl chloride (1.47 g, 10 mmol) in pyridine (10 ml) was added dropwise in 15 min at 5° into a solution of **2** HCl (1.76 g, 10 mmol) in pyridine (20 ml). The mixture was stirred at 10° for 16 hr, diluted with ice–water, and extracted with chloroform. The extract was washed with water and dried and the solvent was removed to leave an oil, which was again dissolved in ethyl acetate, and addition of ethanol containing 15% hydrogen chloride yielded 1.9 g (66.7%) of **3f**: mp 148–150°; ir (Nujol) 3250, 1770 cm^{-1}; NMR (CF_3COOH) 7.6–8.9 (m, 11), 7.18 (s, 3, C_2 Me), 4.84 (s, 2, CH_2OH), 1.54 (broad s, 1, C_4 H), 1.28 (broad s, 1, C_6 H).

Anal. Calcd for $C_{14}H_{20}ClNO_3$: C, 58.75; H, 7.05; N, 4.90; Cl, 12.40. Found: C, 59.00; H, 7.10; N, 4.96; Cl, 12.64.

The following four derivatives were prepared by the above procedure.

3-*O*-*n*-Hexanoyl-α^4-norpyridoxol hydrochloride (3e) had mp 127–129° on recrystallization from ethanol–ethyl acetate (59.1%); ir (Nujol) 3260, 1770 cm^{-1}; NMR (D_2O) 0.93 (t, 3, J = 6 Hz), 1.2–2.0 (m, 6), 2.67 (s, 3, C_2 Me), 2.83 (t, 3, J = 7.5 Hz), 4.90 (s, 2, C_5 CH_2OH), 8.38 (d, 1, J = 1.5 Hz, C_4 H), 8.63 ppm (d, 1, J = 1.5 Hz, C_6 H).

Anal. Calcd for $C_{13}H_{20}ClNO_3$: C, 57.00; H, 7.31; N, 5.12; Cl, 12.97. Found: C, 57.28; H, 7.40; N, 5.32; Cl, 12.99.

3-*O*-Pivaloyl-α^4-norpyridoxol hydrochloride (3d) had mp 162–163° as recrystallized from ethanol–ethyl acetate (64.0%); ir (Nujol) 3240, 1765 cm^{-1}; NMR (D_2O) 1.38 (s, 9, CMe_3), 2.68 (s, 3, C_2 Me), 4.88 (s, 2, C_5 CH_2OH), 8.38 (d, 1, J = 1.5 Hz, C_4 H), 8.63 ppm (d, 1, J = 1.5 Hz, C_6 H).

Anal. Calcd for $C_{12}H_{18}ClNO_3$: C, 55.50; H, 6.98; N, 5.38; Cl, 13.65. Found: C, 55.65; H, 7.08; N, 5.48; Cl, 13.57

3-O-Benzoyl-α^4-norpyridoxol (3g) had mp 81–82° on recrystallization from ethyl acetate–*n*-hexane (86.5%); ir (Nujol) 3180, 1740 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.38; N, 5.76. Found: C, 69.08; H, 5.36; N, 5.60.

3-*O*-*p*-Anisoyl-α^4-norpyridoxol (3h) had mp 103–104° on recrystallization from ethyl acetate–*n*-hexane (81%); ir (Nujol) 3200, 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.77; H, 5.50; N, 5.01.

α^5-*O*-Valeryl-α^4-norpyridoxol (4c). A mixture of **2** HCl (0.88 g, 5 mmol) and *n*-valeryl chloride (0.66 g, 5.57 mmol) in pyridine (5 ml) was stirred at 120° for 20 hr, diluted with water, and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4) and the solvent was removed to leave an oily product, which gradually solidified. Recrystallization from ethyl acetate–*n*-hexane gave **4c** (0.73 g, 65%): mp 114–115°; ir (Nujol) 2600, 2500, 1730 cm^{-1}; NMR ($CDCl_3$) 0.88 (t, 3, J = 6.0 Hz), 1.1–1.8 (m, 4), 2.35 (t, 2, J = 7.5 Hz), 2.59 (s, 3, C_2 Me), 5.09 (s, 2, C_5 CH_2), 7.26 (d, 1, J = 1.5 Hz, C_4 H), 8.03 ppm (d, 1, J = 1.5 Hz, C_6 H).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.64; H, 7.68; N, 6.35.

α^5-*O*-Hexanoyl-α^4-norpyridoxol (4e). To a solution of **2** HCl (0.88 g, 5 mmol) in pyridine (10 ml), *n*-hexanoic anhydride (1.07 g, 5 mmol) was added dropwise. The mixture was stirred at 120° for 10 hr and worked up as described above to give a crystalline residue, which was recrystallized from ethyl acetate–*n*-hexane to afford **4e** (0.73 g, 61.3%): mp 111–112°; ir (Nujol) 2630, 2500, 1730 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.79; H, 7.92; N, 5.82.

Rearrangement of 3-*O*-Pivaloyl-α^4-norpyridoxol (3d). A. A solution of 3-*O*-pivaloate **3d** (1.6 g) in pyridine (6 ml) was stirred at 120° for 10 hr. After removal of pyridine, the residue was diluted with water, neutralized with aqueous $NaHCO_3$, and extracted with ethyl acetate. The resulting oil after evaporation of the solvent was chromatographed on dry silica gel, eluting with benzene–ethyl acetate (1:1).

The major product (0.48 g) was the starting material. The second product (0.38 g, oil) was identified as 3,α^5-*O*-dipivaloyl-α^4-norpyridoxol (**5d**), which was converted into a hydrochloride: mp 142–143°; ir (Nujol) 1765, 1730 cm^{-1}; NMR (D_2O) 1.17 (s, 9), 1.37 (s, 9), 2.68 (s, 3, C_2 Me), 5.34 (s, 2, C_5 CH_2), 8.38 (d, 1, J = 2 Hz, C_4 H), 8.63 ppm (d, 1, J = 2 Hz, C_6 H).

Anal. Calcd for $C_{17}H_{26}ClNO_4$: C, 59.30; H, 7.62; N, 4.07; Cl,

10.62. Found: C, 59.15; H, 7.60; N, 4.11; Cl, 10.54.

The third product (0.17 g) was α^5-*O*-pivaloyl-α^4-norpyridoxol (**4d**), which was recrystallized from ethyl acetate–*n*-hexane: mp 170°; ir (Nujol) 2650, 1715 cm^{-1}; NMR ($CDCl_3$) 1.14 (s, 9), 2.56 (s, 3, C_2 Me), 5.05 (s, 2, C_5 CH_2), 7.21 (d, 1, J = 2 Hz, C_4 H), 7.98 ppm (d, 1, J = 2 Hz, C_6 H).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.80; H, 7.80; N, 6.46.

The aqueous layer after extraction with ethyl acetate was concentrated and again extracted with a large quantity of hot ethyl acetate. The extract was dried and concentrated and addition of anhydrous ethanol–HCl gave 2 HCl (0.047 g).

B. A solution of **3d** (1.0 g) in dry toluene (15 ml) containing pyridine (0.3 ml) was heated at 120° for 10 hr and worked up as described above to give **3d** (0.89 g) and **5d** (0.015 g).

Conversion of 3,α^5-*O*-Dipivaloate (5d) to α^5-*O*-Pivaloate (4d) in Pyridine. A. A solution of 3,α^5-*O*-dipivaloate hydrochloride (**5d**, 0.300 g) in pyridine (1.5 ml) was stirred at 120° for 10 hr, diluted with water, and extracted with chloroform. The extract was washed with water and dried and the solvent was removed to leave a semisolid. Chromatography on silica gel with benzene–ethyl acetate (1:1) gave the starting material (**5d**, 0.234 g) and α^5-*O*-pivaloate (**4d**, 0.025 g).

B. A solution of 3,α^5-*O*-dipivaloate hydrochloride (**5d**, 0.69 g, 2 mmol) and **2** (0.280 g, 2 mmol) in pyridine (3 ml) was stirred at 120° for 10 hr and woked up as described above. The starting material (0.34 g) and α^5-*O*-pivaloate **4d** (0.26 g), mp 169–170°, were obtained.

Heating of α^5-*O*-Pivaloate (4d) with α^4-Norpyridoxol in Pyridine. A solution of **4d** (0.250 g) and **2** HCl (0.192 g) in pyridine (5 ml) was heated at 120° for 10 hr and the solvent was removed, diluted with water, neutralized with aqueous $NaHCO_3$, and extracted with ethyl acetate. The extract, after being dried over Na_2SO_4, was concentrated and addition of *n*-hexane gave **4d** (0.23 g). The aqueous layer was again extracted with a large quantity of hot ethyl acetate. The extract was concentrated and addition of anhydrous ethanol–HCl gave **2** HCl (0.187 g).

Rearrangement of 3-*O*-Cyclohexanecarbonyl-α^4-norpyridoxol (3f). A solution of **3f** (0.47 g) in pyridine (1.5 ml) was heated at 120° for 10 hr and worked up as described above. The crystalline residue obtained was chromatographed on a dry silica gel column. Elution with benzene–ethyl acetate (1:1) gave 3,α^5-*O*-dicyclohexanecarboxylate **5f** (0.12 g) and α^5-*O*-cyclohexanecarboxylate **4f** (0.22 g).

5f was an oil, which was converted to a hydrochloride: mp 150–151°; ir (Nujol) 1765, 1735 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}ClNO_4$: C, 63.73; H, 7.68; N, 3.54; Cl, 8.95. Found: C, 63.91; H, 7.67; N, 3.75; Cl, 8.99.

4f melted at 175–177°; ir (Nujol) 2650, 1720 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.51; H, 7.77; N, 5.78.

When the reaction was continued for 22 hr, the only product was α^5-*O*-cyclohexanecarboxylate **4f**.

α^5-*O*-Acetyl-α^4-norpyridoxol (4a). A. 3-*O*-Acetate hydrochloride (**3a**, 0.2 g) was converted to α^5-*O*-acetate **4a** (0.1 g) in pyridine (1 ml) under heating at 120° for 10 hr: mp 170–172°; ir (Nujol) 2634, 2500, 1757 cm^{-1}; NMR (DMF-d_7) 2.08 (s, 3, OAc), 2.40 (s, 3, C_2 Me), 5.08 (s, 2, CH_2OAc), 7.21 (d, 1, J = 2.0 Hz, C_4 H), 8.00 (d, 1, J = 2.0 Hz, C_6 H).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.73; H, 6.03; N, 7.78.

B. 2 HCl (2.0 g) was dissolved in 47% hydrobromic acid and the solution was refluxed for 30 min, cooled, and made alkaline with aqueous $NaHCO_3$ to give 5-bromomethyl-3-hydroxy-2-methylpyridine (1.2 g), mp 282–285° dec.

Anal. Calcd for C_7H_8BrNO: C, 41.60; H, 3.99; N, 6.93; Br, 39.58. Found: C, 41.70; H, 4.05; N, 6.89; Br, 39.70.

A mixture of the bromomethyl compound (1.2 g), AgOAc (3.5 g), and KOAc (22 g) in AcOH (80 ml) was stirred at 130° for 1.5 hr. After evaporation of the solvent, the residue was extracted with ethyl acetate. The extract was washed with water, dried, and concentrated into a small volume to afford **4a** (0.2 g), mp 170–172°.

3-*O*-Acetyl-α^5-*O*-benzoyl-α^4-norpyridoxol (5i). To a solution of 3-*O*-acetate **3a** (1.1 g) in pyridine (10 ml), benzoyl chloride (0.8 g) was added dropwise at 5°. The mixture was diluted with ice–water and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and concentrated to dryness to give an oil. Crystallization from ethyl acetate–*n*-hexane afforded **5i** (1.37 g): mp 57°; ir (Nujol) 1760, 1720 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.36; H, 5.17; N, 4.82.

3-*O*-Acetyl-α^5-*O*-anisoyl-α^4-norpyridoxol (5j) was prepared by a similar procedure: mp 65–66°; ir (Nujol) 1765, 1705 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.65; H, 5.38; N, 4.29.

α^5-*O*-Benzoyl-α^4-norpyridoxol (4g). A. A solution of **5i** (0.5 g) in 2 *N* HCl (25 ml) was stirred at 80° for 1 hr, cooled, and neutralized with aqueous $NaHCO_3$. A colorless product (0.2 g) separated. Recrystallization from ethanol gave **4g**: mp 221–223°; ir (Nujol) 2500, 1720 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.18; H, 5.30; N, 5.65.

B. 3-*O*-Benzoate hydrochloride (**3g**, 0.5 g) was heated in pyridine at 120° (5 ml) for 60 hr and chromatographed on silica gel to give α^5-*O*-benzoate **4g** (0.085 g) together with 3,α^5-*O*-dibenzoate **5g** (0.070 g) and the starting material **3g** (0.210 g).

α^5-*O*-Anisoyl-α^4-norpyridoxol hydrochloride (4h) was prepared from **5j** by the above procedure and isolated as a hydrochloride: mp 224–225° dec; ir (Nujol) 2500, 1715 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}ClNO_4$: C, 58.16; H, 5.20; N, 4.51; Cl, 11.44; Found: C, 58.09; H, 5.10; N, 4.40; Cl, 11.56.

Acknowledgments We wish to express our gratitude to Dr. G. Sunagawa, Director of these laboratories, and to Dr. K. Murayama, Assistant Director, for their encouragement and discussion. We are also indebted to Mr. T. Sakamoto and Mrs. F. Saito for their technical assistance.

Registry No.—2 HCl, 3816-44-2; **3a**, 54193-37-2; **3a** HCl, 53054-35-6; **3d**, 54193-38-3; **3d** HCl, 54193-39-4; **3e** HCl, 53123-11-8; **3f**, 54293-21-9; **3f** HCl, 54193-40-7; **3g**, 53054-39-0; **3g** HCl, 54193-41-8; **3h**, 53054-40-3; **4a**, 53054-46-9; **4c**, 53054-48-1; **4d**, 54193-42-9; **4e**, 54193-43-0; **4f**, 54193-44-1; **4g**, 53054-52-7; **4h** HCl, 53054-69-6; **5b** HCl, 53054-23-2; **5d**, 54193-45-2; **5d** HCl, 54193-46-3; **5f**, 53054-59-4; **5f** HCl, 54193-47-4; **5g**, 53054-72-1; **5h**, 54193-48-5; **5i**, 53054-56-1; **5j**, 53054-57-2; benzoyl chloride, 98-88-4; anisoyl chloride, 100-07-2; isobutyryl chloride, 79-30-1; acetic anhydride, 108-24-7; cyclohexanecarbonyl chloride, 2719-27-9; hexanoyl chloride, 142-61-0; pivaloyl chloride, 3282-30-2; *n*-valeryl chloride, 638-29-9; *n*-hexanoic anhydride, 2051-49-2; 5-bromomethyl-3-hydroxy-2-methylpyridine, 54193-49-6.

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Neighboring-Group Participation in Carbohydrate Chemistry. V.[1] Direct Evidence for the Participation of the β-Trans-Axial Benzoyloxy Group in the Nucleophilic Displacement of Methylsulfonate of Methyl 4,6-Di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside and Methyl 2,6-Di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside[2]

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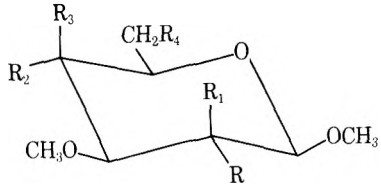
Refluxing of an *N,N*-dimethylformamide solution of methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**) (120 hr) or methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside (**11**) (10 hr) with potassium benzoate gave methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside (**4**) and methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (**6**) as the only isolable products, the **6**:**4** ratio being the same in both cases (~3:1). The greater reactivity of **11** vs. **7**, as well as the predominant formation of **6** vs. **4** was rationalized in terms of the electron-withdrawing effect of the anomeric carbon atom.

It is known that the reactivity of the sulfonyloxy group of a hexopyranoside toward direct nucleophilic displacement strongly depends upon its position in the carbohydrate molecule,[4] and upon the energy of the SN2 transition state,[3-5] i.e., upon the torsional strain, steric nonbonded and electrostatic interactions between the approaching nucleophile or leaving sulfonate, and other substituents of the pyranoside ring.

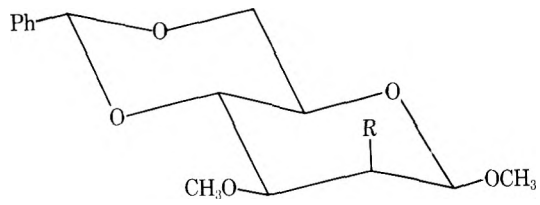
Except for the 6-sulfonate of galactopyranoside derivatives, direct nucleophilic displacement of the sulfonyloxy group attached to the primary (C-6) carbon atom is considerably faster than direct nucleophilic displacement of sulfonates attached to a secondary carbon atom of the pyranoid ring, permitting thus the selective displacement of the former.[4,7]

In the absence of a β-trans-axial substituent, the C-4 sulfonyloxy group of a β-D-hexopyranoside is much more reactive toward the direct nucleophilic displacement than the C-2 sulfonate. Thus, whereas the direct nucleophilic displacement with benzoate of an equatorially oriented C-4 sulfonyloxy group in refluxing *N,N*-dimethylformamide is complete in 16 hr (D-galacto isomer reacts ca. five times faster than the D-gluco isomer[6]), the direct nucleophilic displacement of an equatorially oriented C-2 sulfonyloxy group requires ca. 120 hr for completion.[3]

In connection with some other work we have attempted the nucleophilic displacement of methylsulfonyloxy groups of methyl 3-*O*-methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (**2**) with potassium benzoate in refluxing *N,N*-dimethylformamide. By monitoring the reaction with thin layer chromatography (using 7:1 benzene–ethyl acetate) the following observations have been made. After 15 min the starting material **2** was completely consumed and the reaction mixture consisted of methyl 6-*O*-benzoyl-3-*O*-methyl-2,4-di-*O*-methylsulfonyl-β-D-glucopyranoside (**3**, 68%) (identified by its ir and NMR spectra and by microanalysis) and, in trace amount, of methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**) (identified by chromatographic comparison with the authentic material). After 6 hr the reaction mixture contained significantly increased amounts of **7**, whereas the amount of **3** was proportionately decreased. Furthermore, the formation of two additional, less polar products **4** and **6** has been observed. After 16 hr the galactopyranoside dibenzoate **7** was the predominant product of the reaction (72%), and the amounts of the two less polar products **4** and **6** were markedly increased, whereas the glucopyranoside



1, R = R_2 = R_4 = OH; R_1 = R_3 = H
2, R = R_2 = R_4 = CH_3SO_3; R_1 = R_3 = H
3, R = R_2 = CH_3SO_3; R_1 = R_3 = H; R_4 = C_6H_5COO
4, R = R_3 = R_4 = C_6H_5COO; R_1 = R_2 = H
5, R = R_3 = R_4 = OH; R_1 = R_2 = H
6, R = R_3 = H; R_1 = R_2 = R_4 = C_6H_5COO
7, R = CH_3SO_3; R_1 = R_2 = H; R_3 = R_4 = C_6H_5COO
8, R = R_3 = H; R_1 = C_6H_5COO; R_2 = R_4 = OH
10, R = R_3 = H; R_1 = C_6H_5COO; R_2 = R_4 = CH_3SO_3
11, R = R_3 = H; R_1 = R_4 = C_6H_5COO; R_2 = CH_3SO_3
12, R = CH_3SO_3; R_1 = R_2 = H; R_3 = R_4 = OH
13, R = CH_3SO_3; R_1 = R_2 = H; R_3 = R_4 = CH_3O
15, R = R_4 = CH_3O; R_1 = R_2 = H; R_3 = CH_3SO_3



9, R = C_6H_5COO
16, R = CH_3SO_3

monobenzoate **3** was not present in the reaction mixture anymore.

When an *N,N*-dimethylformamide solution of methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**) was heated at reflux with potassium benzoate for 120 hr, the galactodibenzoate **7** was completely consumed and products **4** and **6** were obtained in a good yield (18 and 54%, respectively).

The NMR spectra of **4** and **6** indicated that each product contains three benzoyl and two methoxy groups, thus excluding the elimination as the possible pathway for their formation. The possibility that either **4** or **6** has been formed by direct displacement of the equatorially oriented C-2 methylsulfonyloxy group with benzoate was ruled out on the basis of previous findings that direct displacement of an equatorially oriented sulfonyloxy group of a pyrano-

side is strongly impeded in the presence of a trans-axial substituent at the β carbon atom[5,9-11] and it was unambiguously excluded on the basis of the following chemical evidence. Refluxing of an *N,N*-dimethylformamide solution of methyl 3,4,6-tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**13**) with potassium benzoate for 120 hr gave as the only isolable product the starting material. The unreactivity of **13** under the described experimental conditions also suggested that neither **4** nor **6** could be the product of ring contraction of **7**, as it has been previously observed in cases where direct substitution of an equatorially oriented sulfonyloxy group was not possible owing to the presence of a β-trans-axial substituent [e.g., methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methylsulfonyl-α-D- (or L-) mannopyranosides[12,13]].

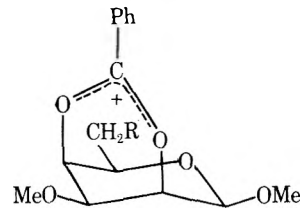
It has been therefore concluded that products **4** and **6** have been formed by intramolecular displacement of the C-2 methylsulfonyloxy group of **7** with the axially oriented C-4 benzoyl group, resulting in the formation of the six-membered benzoyloxonium intermediate **14** and followed by a nucleophilic attack with benzoate at either the C-2 or the C-4 carbon atom. Consequently, methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside should be formed in the former, and methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside in the latter case. That these were indeed the structures of **4** and **6** was proven by benzoylation of methyl 3-*O*-methyl-β-D-galactopyranoside (**5**)[14] and methyl 2-*O*-benzoyl-3-*O* methyl-β-D-mannopyranoside (**8**) with benzoyl chloride in pyridine. The product obtained by benzoylation of **5** (an amorphous solid) was identical (ir and NMR spectra) with **4**, whereas the product obtained by benzoylation of **8** (an amorphous solid) was identical (ir and NMR spectra) with **6**.

Since the same cyclic six-membered benzoyloxonium intermediate **14** could be expected to be formed by nucleophilic displacement of the equatorially oriented C-4 methylsulfonyl group in the presence of the C-2 trans-axial acyloxy group, the reaction of methyl 2-*O*-benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (**10**) with potassium benzoate in refluxing *N,N*-dimethylformamide was investigated. The reaction was monitored by thin layer chromatography using 7:1 benzene–ethyl acetate as eluent.

After 10 min the reaction mixture did not contain starting material **10** anymore, and in addition to trace amount of two less polar products, chromatographically identical with **4** and **6**, methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside (**11**, 87%) (identified by ir and NMR spectra, and by microanalysis) was the predominant product of the reaction. After refluxing an *N,N*-dimethylformamide solution of **10** with potassium benzoate for 10 hr, the only products isolated from the reaction mixture were **4** (20%) and **6** (65%). The **6:4** ratio (3.2:1) was practically the same as has been found by using **2** under the same experimental conditions (3:1).

Although the participation by a β-trans-acyloxy group with formation of a cyclic six-membered acyloxonium intermediate was already postulated in the acid-catalyzed conversion of methyl 6-*O*-acetyl-3,4-anhydro-2-*O*-benzyl-α-D-altropyranoside[15] into methyl 6-*O*-acetyl-2-*O*-benzyl-α-D-idopyranoside and in the isomerization of 3,4,6-tri-*O*-acetyl-α-D-glucopyranose-1,2-*O*-acetoxonium hexachloroantimonate into 1,2,3,4-tetra-*O*-acetyl-α-D-idopyranose,[16] the formation of galactotribenzoate **4** and mannotribenzoate **6** is, to the best of our knowledge, the first example for the participation of a β-trans-acyloxy group with the formation of a cyclic six-membered acyloxonium intermediate in the nucleophilic displacement of a sulfonyloxy group attached to a pyranoside ring.[17]

The finding that the mannotribenzoate **6** was the predominant product in nucleophilic displacement with benzoate of the C-2 methylsulfonate of **7** as well as the C-4 methylsulfonate of **11** (the manno:galacto ratio was 3.1:1 in the former and 3.2:1 in the latter case) indicated that the C-4 carbon of the cyclic six-membered benzoyloxonium intermediate **14** is considerably more susceptible to the nu-



14, R = C_6H_5COO

cleophilic attack than the C-2 carbon atom. This is in a good agreement with our observation[6] that the direct nucleophilic displacement of the C-4 methylsulfonate of methyl 2,3,6-tri-*O*-methyl-4-*O*-methylsulfonyl-β-D-galactopyranoside (**15**) is ca. 2.7 times faster than direct nucleophilic displacement of the C-2 methylsulfonyloxy group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-mannopyranoside (**16**). The observed difference in reactivities of the C-2 and the C-4 carbon atoms of the cyclic six-membered benzoyloxonium intermediate **14** toward the nucleophilic attack, as well as the observed large difference in reactivity of the C-2 carbon atom of **7** and the C-4 carbon atom of **11** (120 vs. 10 hr), is compatible with the postulated rationalization[18] that the electropositive character of the α carbon to the reacting carbon atom should decrease the rate of the nucleophilic displacement if the amount of positive charge on the reacting carbon atom in the transition state is greater than in the ground state. Furthermore, the observation that both the intramolecular displacement of the C-2 methylsulfonate of **7** with the participation of the β-trans-axial benzoyloxy group and the direct displacement with benzoate of the C-2 methylsulfonate of **16** require ca. 120 hr for completion, in spite of the fact that in the former case the attacking nucleophile is the uncharged C-4 benzoyloxy group whereas in the latter case the attacking nucleophile is negatively charged benzoate anion, suggests that the dipolar interactions between the axially approaching nucleophile and the C_1–O_1 and C_1–O_5 dipoles, proposed recently[3] as the possible explanation for the observed low reactivity of the C-2 methylsulfonate of **16** toward the direct displacement, seem to be, under the given experimental conditions (refluxing *N,N*-dimethylformamide), relatively unimportant.

Experimental Section

General. The silica gel used for column chromatography was E. Merck (Darmstadt, Germany) silica gel, particle size <0.08 mm and M. Woelm (Eschwege, Germany) silica gel, particle size <0.063 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267. The proton NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm).

Methyl 3-*O*-methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2). To a pyridine solution (100 ml) of **1** (1.300 g, 6.24 mmol), methanesulfonyl chloride (7.00 ml, 41.27 mmol) was added dropwise and the reaction mixture was kept at room temperature for 6 hr. The excess of methanesulfonyl chloride was destroyed with methanol and the solvents were evaporated in vacuo. The residue (3.800 g) was chromatographed on silica gel (170 g). Elution with 5:1 benzene–ethyl acetate gave impure **2** (2.800 g), which was rechromatographed on silica gel (140 g). Elu-

tion with 5:1 benzene–ether afforded pure **2** (2.260 g, 88%) as an amorphous solid: $[\alpha]^{27}D$ −25° (c 0.57, $CHCl_3$); ir ($CHCl_3$) 1362 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 4.8–4.1 (m, 5, H-1, H-2, H-4, H-6, and H-6′), 4.0–3.4 (m, 2, H-3 and H-5), 3.72 and 3.57 (two s, 6, C-1 and C-3 methoxy groups), 3.17, 3.12, and 3.07 (three s, 9, methyl from C-2, C-4, and C-6 methylsulfonyl groups).

Anal. Calcd for $C_{11}H_{22}O_{12}S_3$: C, 29.86; H, 5.01; S, 21.74. Found: C, 30.06; H, 5.04; S, 22.01.

Reaction of Methyl 3-*O*-Methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (15 min). An *N,N*-dimethylformamide solution (5 ml) containing **2** (117 mg, 0.26 mmol) and potassium benzoate (212 mg, 1.32 mmol) was heated at reflux for 15 min. After the reaction mixture was cooled to room temperature, it was diluted with chloroform, the precipitate was filtered off, and the filtrate was evaporated in vacuo. The crude product (134 mg) was chromatographed on silica gel (15 g). Elution with 3:1 benzene–ethyl acetate gave pure **3** (84 mg, 68%): $[\alpha]^{27}D$ −27° (c 1.17, $CHCl_3$); ir ($CHCl_3$) 1720 and 1270 (C=O and C–O stretch, benzoate), 1360, and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5, phenyl), 5.0–4.4 (m, 2, H-1 and H-2), 4.47 (t, $J_{3,4} \approx J_{4,5} = 8.0$ Hz, 1, H-4), 4.47 (d, $J_{5,6} = 6.4$ Hz, 2, H-6 and H-6′), 4.0–3.4 (m, 2, H-3 and H-5), 3.67 and 3.50 (two s, 6, C-1 and C-3 methoxy groups), 3.11 and 3.10 (two s, 6, methyl from C-2 and C-4 methylsulfonyl groups).

Anal. Calcd for $C_{17}H_{24}O_{11}S_2$: C, 43.58; H, 5.16; S, 13.69. Found: C, 43.79; H, 5.12; S, 13.45.

Reaction of Methyl 3-*O*-Methyl-2,4,6-tri-*O*-methylsulfonyl-β-D-glucopyranoside (2) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (16 hr). An *N,N*-dimethylformamide solution (20 ml) containing **2** (260 mg, 0.63 mmol) and potassium benzoate (470 mg, 2.93 mmol) was heated at reflux for 16 hr. The solvent was then evaporated in vacuo, water was added to the residue, and the suspension obtained was extracted with chloroform. After the combined chloroform extract was dried over anhydrous $MgSO_4$, the chloroform was removed in vacuo and the residue (485 mg) was chromatographed on silica gel (50 g). Elution with 7:1 benzene–ethyl acetate gave three fractions. The first fraction (26 mg, 8.5%) was methyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranoside (**4**), whose structure was deduced from comparison (ir and NMR spectra) with an authentic sample synthesized by benzoylation of methyl 3-*O*-methyl-β-D-galactopyranoside (**5**) (vide infra). The second fraction (79 mg, 25.8%) was pure methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (**6**), whose structure was proved by comparison (ir and NMR spectra) with an authentic sample synthesized by benzoylation of methyl 3-*O*-methyl-β-D-mannopyranoside (**8**) with benzoyl chloride in pyridine (vide infra). The third fraction (134 mg, 46.1%) was pure crystalline methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (**7**). An analytical sample of **7** was obtained by recrystallization from acetone–isopropyl ether: mp 152–152.5°; $[\alpha]^{27}D$ −24° (c 1.3, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 (C=O and C–O stretch, benzoate), 1362, and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5, phenyl), 5.87 (two d, $J_{3,4} < 1.6$ and $J_{4,5} = 3.4$ Hz, 1, H-4), 4.9–3.6 (m, 6, H-1, H-2, H-3, H-5, H-6, and H-6′), 3.59 and 3.46 (two s, 6, C-1 and C-3 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

Anal. Calcd for $C_{23}H_{26}O_{10}S$: C, 55.87; H, 5.30; S, 6.48. Found: C, 56.07; H, 5.30; S, 6.21.

Reaction of Methyl 4,6-Di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (7) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (120 hr). An *N,N*-dimethylformamide solution (40 ml) of **7** (260 mg, 0.53 mmol) was heated with potassium benzoate (421 mg, 2.63 mmol) at reflux for 120 hr. The solvent was removed in vacuo and the residue (245 mg) was chromatographed on silica gel (12 g). Elution with 5:1 benzene–ethyl acetate gave two fractions. The first fraction (51 mg, 17.6%) was pure **4**, whereas the second fraction (156 mg, 54.0%) was pure **6**, the **6**:**4** ratio being thus 3.1:1.

Methyl 2,4,6-Tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside (4). A pyridine solution (1 ml) containing **5** (48 mg, 0.23 mmol) and benzoyl chloride (0.4 ml, 2.36 mmol) was kept at room temperature for 1 hr; the reaction mixture was then poured into saturated aqueous $NaHCO_3$ solution and extracted with chloroform. The combined chloroform extract was dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue (390 mg) was chromatographed on silica gel (15 g). Elution with 7:1 benzene–ethyl acetate gave pure **4** (106 mg, 88%) as an amorphous solid: $[\alpha]^{27}D$ +34° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 cm^{-1} (C=O and C–O stretch, benzoate); NMR ($CDCl_3$) δ 8.2–7.2 (m, 15, three phenyl groups), 5.93 (two d, $J_{3,4} = 3.4$ and $J_{4,5} < 1$ Hz, 1, H-4), 5.53 (two d, $J_{1,2} = 1.8$ and $J_{2,3} = 9.8$ Hz, 1, H-2), 4.72 (d, $J_{1,2} = 1.8$ Hz, 1, H-1), 4.8–3.9 (m, 3, H-5, H-6, and H-6′), 3.70 (two d, $J_{2,3} = 9.8$ and $J_{3,4} = 3.4$ Hz, 1, H-3), 3.52 and 3.37 (two s, 6, C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{29}H_{28}O_9$: C, 66.91; H, 5.42. Found: C, 67.16; H, 5.61.

Methyl 2,4,6-Tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (6). To a pyridine solution (4 ml) of **8** (49 mg, 0.16 mmol), benzoyl chloride (0.08 ml, 0.47 mmol) was added and the reaction mixture was kept at room temperature for 3 hr. The pyridine was then removed in vacuo and the residue was chromatographed on silica gel (15 g). Elution with 7:1 benzene–ethyl acetate gave pure **6** (74 mg, 90%) as an amorphous solid: $[\alpha]^{27}D$ −95° (c 2.19, $CHCl_3$); ir ($CHCl_3$) 1720 and 1265 cm^{-1} (C=O and C–O stretch, benzoate); NMR ($CDCl_3$) δ 8.2–7.2 (m, 15, three phenyl groups), 5.90 (broad d, $J_{1,2} < 1$ and $J_{2,3} = 3.4$ Hz, 1, H-2), 5.77 (t, $J_{3,4} \approx J_{4,5} = 9.4$ Hz, 1, H-4), 4.9–4.3 (m, 3, H-1, H-6, and H-6′), 4.2–3.8 (m, 1, H-5), 3.74 (two d, $J_{2,3} = 3.4$ and $J_{3,4} = 9.4$ Hz, 1, H-3), 3.52 and 3.39 (two s, 6, C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{29}H_{28}O_9$: C, 66.91; H, 5.42. Found: C, 67.08; H, 5.55.

Methyl 2-*O*-Benzoyl-3-*O*-methyl-β-D-mannopyranoside (8). A 50% aqueous acetic acid solution (5 ml) of **9** (188 mg, 0.47 mmol) was heated at 100° for 30 min. The solvent was removed in vacuo and the residue (160 mg) was chromatographed on silica gel (20 g). Elution with 6:1 benzene–methanol afforded pure **8** (137 mg, 93%) as an amorphous solid: $[\alpha]^{27}D$ −94° (c, 1.23, CH_3OH); ir ($CHCl_3$) 3420 (broad peak, OH), 1715, and 1270 cm^{-1} (C=O and C–O stretch, benzoate); NMR ($CDCl_3$) δ 8.1–7.2 (m, 5, phenyl), 5.68 (broad d, $J_{1,2} < 1$ and $J_{2,3} = 3.0$ Hz, 1, H-2), 4.48 (broad s, $J_{1,2} < 1$ Hz, 1, H-1), 4.1–3.7 (m, 3, H-4, H-6, and H-6′), 3.5–3.10 (m, 2, H-3 and H-5), 3.41 and 3.35 (two s, 6, C-1 and C-3 methoxy groups), 2.99 and 2.94 (two broad d, 2, C-4 and C-6 hydroxyl groups).

Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.46. Found: C, 57.58; H, 6.54.

Methyl 2-*O*-Benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (10). To a pyridine solution (5 ml) of **8** (137 mg, 0.44 mmol), methanesulfonyl chloride (0.27 ml, 1.62 mmol) was added and the reaction mixture was kept at room temperature for 2 hr. The pyridine was then removed in vacuo and the residue was chromatographed on silica gel (20 g). Elution with 9:1 benzene–methanol afforded slightly impure **10** (212 mg), which was rechromatographed on silica gel (20 g). Elution with 95:5 benzene–2-propanol gave pure crystalline **10** (192 mg, 93%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 165–166° dec; $[\alpha]^{27}D$ −65° (c 1.11, $CHCl_3$); ir ($CHCl_3$) 1720 and 1262 (C=O and C–O stretch, benzoate), 1362 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.3 (m, 5, phenyl), 5.87 (broad d, $J_{1,2} \leq 1$ and $J_{2,3} = 3.4$ Hz, 1, H-2), 4.80 (t, $J_{3,4} \approx J_{4,5} = 10.0$ Hz, 1, H-4), 4.7–4.4 (m, 3, H-1, H-6, and H-6′), 4.0–3.7 (m, 1, H-5), 3.64 (q, $J_{2,3} = 3.4$ and $J_{3,4} = 10.0$ Hz, 1, H-3), 3.52 and 3.47 (two s, 6, C-1 and C-3 methoxy groups), 3.10 (s, 6, methyl from C-4 and C-6 methylsulfonyl groups).

Anal. Calcd for $C_{17}H_{24}O_{11}S_2$: C, 43.58; H, 5.16; S, 13.69. Found: C, 43.61; H, 5.26; S, 13.43.

Reaction of Methyl 2-*O*-Benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (10) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (10 min). An *N,N*-dimethylformamide solution (20 ml) containing **10** (176 mg, 0.38 mmol) and potassium benzoate (399 mg, 2.49 mmol) was heated at reflux for 10 min. The solvent was removed in vacuo and the residue was chromatographed on silica gel (30 g). Elution with 4:1 benzene–ethyl acetate afforded pure methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside (**11**) as white needles (161 mg, 87%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 177.5–178°; $[\alpha]^{27}D$ −95° (c 0.77, $CHCl_3$); ir ($CHCl_3$) 1720 and 1270 (C=O and C–O stretch, benzoate), 1362, and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 8.2–7.1 (m, 10, two phenyl groups), 5.85 (q, $J_{1,2} = 2.2$ and $J_{2,3} = 3.0$ Hz, 1, H-2), 5.03 (t, $J_{3,4} \approx J_{4,5} = 9.0$ Hz, 1, H-4), 4.82 (d, $J_{1,2} = 2.2$ Hz, 1, H-1), 4.7–4.3 (m, 2, H-6 and H-6′), 4.2–3.5 (m, 2, H-3 and H-5), 3.45 (s, 6, C-1 and C-3 methoxy groups), 3.08 (s, 3, methyl from C-4 methylsulfonyl group).

Anal. Calcd for $C_{23}H_{26}O_{10}S$: C, 55.87; H, 5.30; S, 6.49. Found: C, 56.03: H, 5.38; S, 6.33.

Reaction of Methyl 2-*O*-Benzoyl-3-*O*-methyl-4,6-di-*O*-methylsulfonyl-β-D-mannopyranoside (10) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (10 hr). An *N,N*-dimethylformamide solution (10 ml) containing **10** (105 mg, 0.22 mmol) and potassium benzoate (250 mg, 1.56 mmol) was heated at reflux for 10 hr. The precipitate was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (30 g). Elution with 7:1 benzene–ethyl acetate gave two fractions. The first fraction (23 mg, 20%) was pure **4**, whereas the second fraction (75 mg, 65%) was pure **6**, the **6**:**4** ratio being 3.2:1.

Methyl 3-*O*-Methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (12). To a methanolic solution (10 ml) of **7** (220 mg, 0.44 mmol), metallic sodium (55 mg, 2.30 mmol) was added and the reaction mixture was heated at 60° for 30 min. The solution was neutralized with acetic acid and the solvents were evaporated in vacuo. The residue was chromatographed on Al_2O_3 (12 g). Elution with benzene (20 ml), ethyl acetate (20 ml), and 1:1 ethyl acetate–methanol (40 ml) gave pure **12** (125 mg, 98%): mp 164–165°; $[\alpha]^{27}D$ +3° (*c* 1.12, CH_3OH); ir ($CHCl_3$) 3500 cm^{-1} (broad peak, OH); NMR ($CDCl_3$) δ 3.37 and 3.28 (two s, 6, C-1 and C-3 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

Anal. Calcd for $C_9H_{18}O_8S$: C, 37.76; H, 6.34; S, 11.20. Found: C, 37.82; H, 6.27; S, 10.98.

Methyl 3,4,6-Tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (13). To a benzene solution (20 ml) of **12** (117 mg, 0.41 mmol), Ag_2CO_3 (300 mg, 1.1 mmol) and methyl iodide (1 ml, 15.96 mmol) were added and the reaction mixture was heated at reflux for 6 hr. [after 2 hr additional amounts of silver carbonate (300 mg) and methyl iodide (1 ml) were added]. The precipitate was filtered off and the filtrate was evaporated in vacuo. The crystalline residue (132 mg) was chromatographed on silica gel (10 g). Elution with 95:5 benzene–2-propanol gave pure crystalline **13** (119 mg, 92%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 138°; $[\alpha]^{27}D$ −22° (*c* 0.50, $CHCl_3$); ir ($CHCl_3$) 1360 and 1175 cm^{-1} (asymmetric and symmetric SO_2 stretch); NMR ($CDCl_3$) δ 4.69 (two d, $J_{1,2}$ = 7.8 and $J_{2,3}$ = 9.8 Hz, 1, H-2), 4.31 (d, $J_{1,2}$ = 7.8 Hz, 1, H-1), 3.77 (two d, $J_{3,4} \leq 1$ and $J_{4,5}$ = 3.0 Hz, 1, H-4), 3.56, 3.51 and 3.40 (three s, 12, C-1, C-3, C-4, and C-6 methoxy groups), 3.07 (s, 3, methyl from C-2 methylsulfonyl group).

Anal. Calcd for $C_{11}H_{22}O_8S$: C, 42.03; H, 7.06; S, 10.20. Found: C, 42.36; H, 7.06; S, 9.96.

Reaction of Methyl 3,4,6-Tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside (13) with Potassium Benzoate in Refluxing *N,N*-Dimethylformamide (120 hr). An *N,N*-dimethylformamide solution (15 ml) containing **13** (81 mg, 0.26 mmol) and potassium benzoate (206 mg, 1.29 mmol) was heated at reflux for 120 hr. The solvent was evaporated in vacuo and the residue (168 mg) was chromatographed on silica gel (15 g). Elution with 95:5 benzene–2-propanol gave the pure crystalline starting material (44 mg, 54%) as the only isolable product.

Registry No.—**1**, 14982-01-5; **2**, 54307-86-7; **3**, 54307-87-8; **4**, 34939-95-2; **5**, 34698-07-2; **6**, 54307-88-9; **7**, 54307-89-0; **8**, 54307-90-3; **9**, 52260-50-1; **10**, 54307-91-4; **11**, 54307-92-5; **12**, 51385-26-3; **13**, 54307-93-6; methanesulfonyl chloride, 124-63-0; potassium benzoate, 582-25-2; benzoyl chloride, 98-88-4.

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Structural Relationships and Interconversions of Isomeric Astilbins[1a]

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Several isomers of astilbin [2(*R*):3(*R*)-3,3′,4′,5,7-pentahydroxyflavanone-3-α-L-rhamnoside] (**1**) are assigned absolute configurations on the basis of NMR and chiroptical properties. Neoastilbin (**2**), isoastilbin (**3**), and neoisoastilbin (**4**) are assigned 2(*S*):3(*S*), 2(*R*):3(*S*), and 2(*S*):3(*R*) configurations respectively. Similar configurational assignments are made in the engeletin series. Studies of the isomerization of **1** have shown that heating **1** with D_2O–pyridine at 75° results in chalcone formation, while isomerization of **1** in ethanolic NaOAc at room temperature yields selective epimerization at C-2 and C-3.

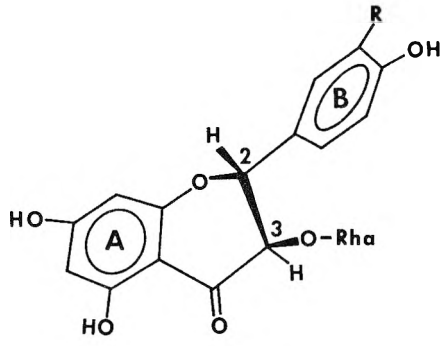
Astilbin (**1**) and engeletin (**5**) from wood bark are members of a rare group of natural products,[2] 3-*O*-glycosyl derivatives of 3-hydroxyflavanones. In 1960, Tominaga described isomeric compounds of **1**[3] and **5**[4] and suggested the existence of cis,trans isomers[5,6] involving C-2 and C-3 of the heterocyclic ring. The preparation of cis-3-substituted flavanones is difficult since acid epimerization readily gives a mixture of cis and trans isomers. cis-3-Hydroxyflavanones are unknown, although *cis*-3-methoxy,[7] *cis*-3-bromo,[8] and *cis*-3-methylflavanones[9] have been prepared[7a,8,9] or isolated.[7b] The structures of the isomeric astilbins and engeletins are established herein and their mecha-

Table I
NMR Spectra[a] of Isomeric Astilbins and Engeletins

Compd	$J_{2,3}$, Hz	H-2	H-3	H-1''[b]	$C_{5''}$-Me[c]
Astilbin (1)	9.5	5.23	4.58	4.15	1.08
Neoastilbin (2)	10.5	5.10	4.64	4.98	0.84
Isoastilbin (3)	2.5	5.50	4.23	4.79	0.86
Neoisoastilbin (4)	2.0	5.43	4.12	4.19	1.01
Engeletin (5)	10.0	5.29	4.66	4.07	1.05
Neoengeletin (6)	10.5	5.17	4.73	5.01	0.81
Isoengeletin (7)	2.5	5.57	4.21	4.79	0.84
Neoisoengeletin (8)	2.0	5.43	4.11	4.19	1.00

[a] Spectra were obtained in DMSO-d_6 at 60°. Chemical shifts are in parts per million from Me_4Si. [b] Anomeric proton of rhamnose. [c] Methyl group on C-5'' of rhamnose.

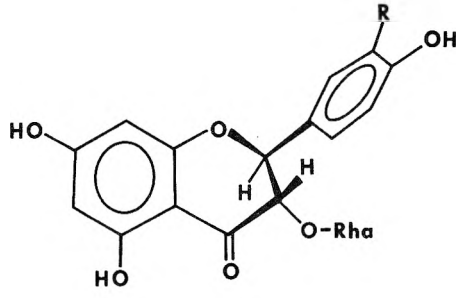
nism of formation under different conditions is discussed. The cis isomers of 1 and 5 represent the first chiral cis-3-substituted flavanones reported.[10]



1 R=OH

5 R=H

Structure of Isomeric Astilbins and Engeletins. Tominaga isolated a trans isomer, neoastilbin (2), and a cis



2 R=OH

6 R=H

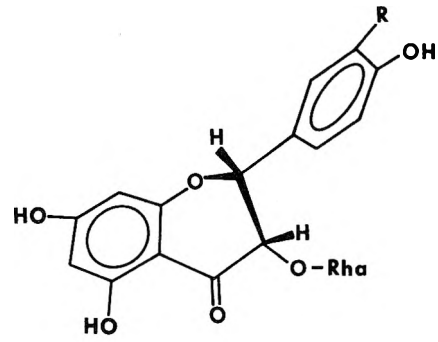
isomer, isoastilbin (3), upon heating 1 in aqueous pyridine. Another cis isomer, neoisoastilbin (4), was isolated upon treating 1 with ethanolic sodium acetate. The cis,trans assignments of 2, 3, and 4 were based[5] upon dehydrogenation of the four isomers to quercitrin and by acidic hydrolysis of the isomers to L-rhamnose and either (+)- or (−)-*trans*-dihydroquercetin in addition to red-shifted uv spectra shown by two of the isomers.

Examination of the NMR spectra (Table I) showed that 1 and 2 possess trans configurations, since they show coupling constants $J_{2,3}$ of 9.5 and 10.5 Hz, respectively; cis configurations are assigned to 3 and 4 which show coupling constants $J_{2,3}$ of 2.5 and 2.0 Hz, respectively.

Table II
CD Spectra[a] of Isomeric Astilbins and Engeletins

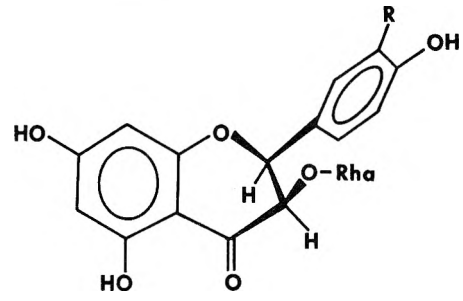
Compd	n → π*	π → π*
Astilbin (1)	$[\theta]_{329}$ +14,000	$[\theta]_{294}$ −31,800
Neoastilbin (2)	$[\theta]_{331}$ −13,400	$[\theta]_{295}$ +31,200
Isoastilbin[b] (3)	$[\theta]_{343}$ +15,200	$[\theta]_{296}$ −37,700
Neoisoastilbin (4)	$[\theta]_{342}$ −18,900	$[\theta]_{296}$ +49,000
Engeletin (5)	$[\theta]_{327}$ +15,500	$[\theta]_{292}$ −42,300
Neoengeletin (6)	$[\theta]_{328}$ −12,600	$[\theta]_{292}$ +31,200
Isoengeletin (7)	$[\theta]_{343}$ +17,500	$[\theta]_{299}$ −36,300
Neoisoengeletin (8)	$[\theta]_{341}$ −16,100	$[\theta]_{296}$ +45,400

[a] All measurements were obtained in methanol. [b] Contaminated with 25–30% astilbin.



3 R=OH

7 R=H



4 R=OH

8 R=H

Compound 1, of known 2(*R*):3(*R*) configuration,[2,11] shows a positive Cotton effect near 330 nm and 2, obviously of 2(*S*):3(*S*) configuration, has a negative n → π* CD band (Table II). Since CD measurements of 3-hydroxyflavanones and their glycosides are known[12,13] to reflect the ring chirality of the sofa conformation of the heterocyclic ring, the chiroptical data of trans isomers 1 and 2 may serve as standards. The positive CD of 3 and negative CD of 4 establish the ring chiralities of these two cis isomers as shown. The question remaining concerns which of the two bulky groups in the cis compounds is axial and which equatorial.[14] Inspection of molecular models show severe steric crowding if the 2-aryl group is axially oriented. Furthermore, the 3-rhamnosyl group is able to adopt a more sterically favorable quasi-axial position owing to the neighboring sp^2 carbonyl group. In addition, CD spectra favor axial orientation for the 3-rhamnosyl group in 3 and 4 since the Cotton effects are red shifted by 12–13 nm in comparison to 1 and 2. α-Axial substitution by an electronegative group often red shifts the uv maximum and corresponding CD band of car-

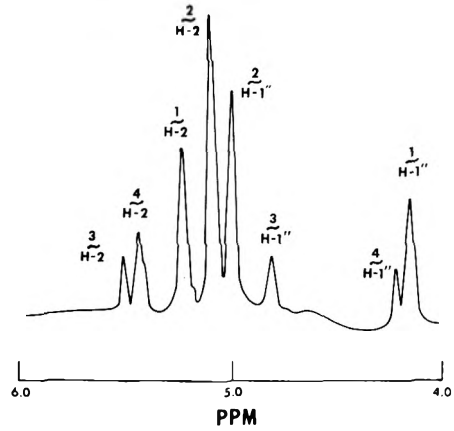
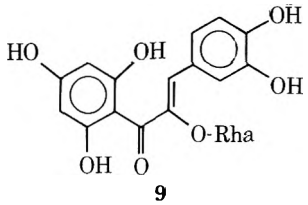


Figure 1. Partial NMR spectrum (100 MHz) of isomers resulting from treatment of 1 with D_2O–pyridine at 75°. The spectra in this and subsequent figures were obtained in DMSO-d_6 at 60°.

bonyl n → π^* transitions.[15] Therefore, **3** and **4** can be assigned 2(*R*):3(*S*) and 2(S):3(*R*) configurations,[16] respectively. Similarly **5**, neoengeletin (**6**), isoengeletin (**7**), and neoisoengeletin[17] (**8**) are 2(*R*):3(*R*), 2(S):3(S), 2(R):3(S),[18] and 2(S):3(R),[18] respectively.

Since trans isomers **1** and **2** and cis isomers **3** and **4** are diastereomers and not enantiomers, they should possess slightly different preferred conformations in solution. Subtle differences are observed in the CD curves, since neither **1** and **2** nor **3** and **4** possess exact mirror image curves. More impressive evidence is seen by NMR, where the anomeric proton is deshielded 0.6–0.8 ppm in **2** and **3** relative to **1** and **4**. Also, the *C*-methyl protons in **2** and **3** are shielded ~0.2 ppm relative to the same resonances in **1** and **4**. These NMR shifts reflect interactions between the rhamnose and B ring. Apparently, *cis*-**3** and *trans*-**2** have similar preferred solution conformations in which the rhamnose has the $C_{5''}$-methyl located above the center of the B ring in the shielding cone and the H-1″ near the circumference of the B ring in a deshielding region. On the other hand, this conformation(s) is not as prominent in *cis*-**4** and *trans*-**1**.

Interconversion of Isomeric Astilbins.[19] The isomerization of compounds **1**, **2**, **3**, and **4** was studied via NMR spectroscopy of a mixture of the four isomers. Heating astilbin at 75° in D_2O–pyridine for several hours produced all four isomers and incorporated deuterium at C-3 in each one. Under protonating conditions the C-2 protons appear as doublets, since they are coupled to the C-3 protons located at higher field, but in D_2O–pyridine the C-2 resonances collapsed to singlets (Figure 1). Only eight singlets remained in the spectrum of the deuterated products between 4.0 and 5.7 ppm, the four at lower field due to C-2 resonances and the four upfield due to anomeric protons of **1**, **2**, **3**, and **4**. These results implicate a chalcone (**9**) as an intermediate,[20] since all four isomers could arise from such an intermediate. The proton at C-3 would be expelled upon formation of **9**, being replaced upon recyclization by deuterium. Isomerization of astilbin in aqueous pyridine at 75° probably produces an equilibrium mixture of isomers, since **9** should allow product distribution as a function of thermodynamic stability. Trans isomers **1** and **2** comprised 68% of the reaction product and cis isomers **3** and **4** 32%, a ratio very similar to the equilibrium ratio of trans to cis isomers found[21] for a substituted 3-methoxyflavanone. Molecular models indicate that either a methoxy or rhamnosyl group can be accommodated equally well in a quasi-axial 3 position of a 3-hydroxyflavanone. The fact that **2** predominated over **1** in the trans series and that **3** occurred in greater amounts than **4** in the cis pair is consistent with the observation of interactions between the rhamnose and B ring in **2** and **3** (vide supra). These interactions could stabilize **2** and **3** and result in their preferential formation under equilibrium conditions such as the aqueous pyridine isomerization at 75°.



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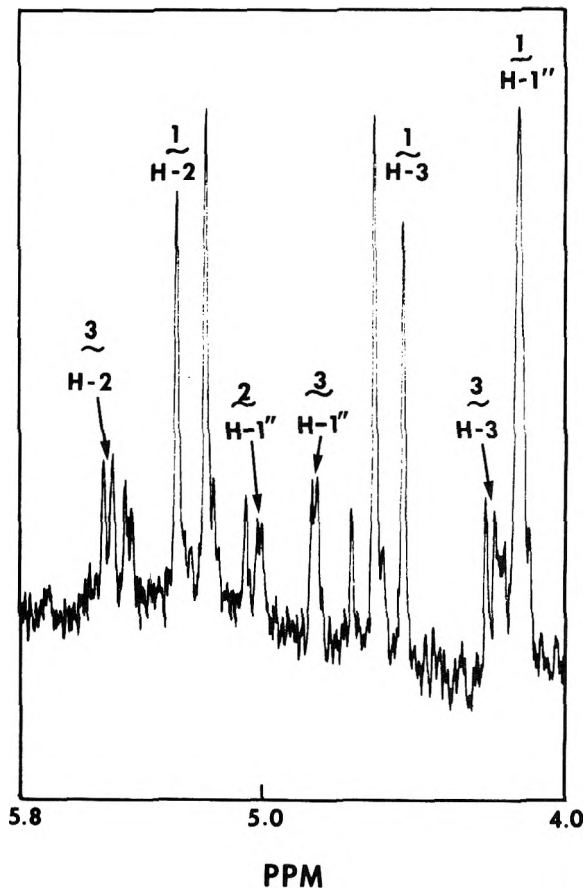
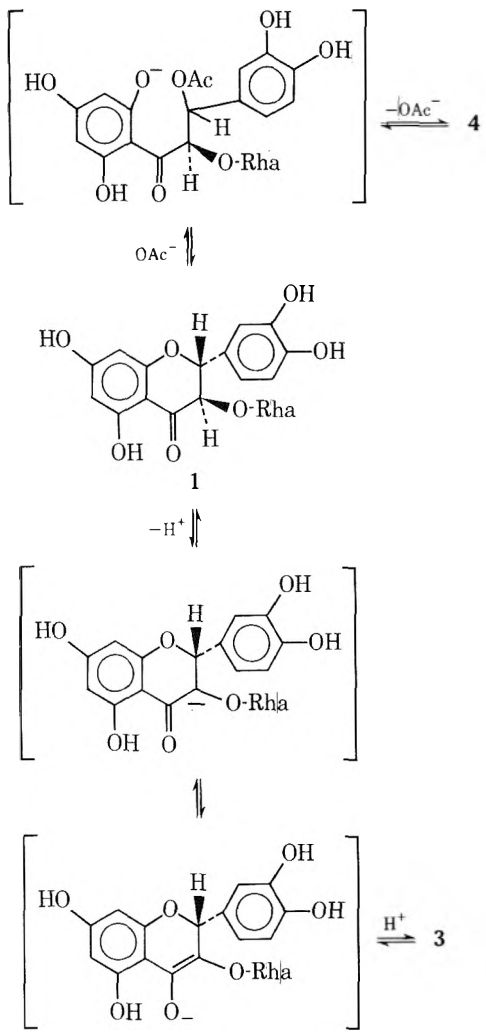


Figure 2. Partial NMR spectrum (100 MHz) of isomers resulting from treatment of 1 with aqueous ethanolic NaOAc at room temperature.

On the other hand, treatment of **1** with ethanolic sodium acetate at room temperature leads to different results. Examination of the NMR spectrum (Figure 2) of the reaction products under protonating conditions in ethanolic sodium acetate shows the presence of all four isomers, although **2** consists of only 7–13% of the reaction product. Since this trans isomer is the most stable of the four isomers (vide supra), its presence in such small amounts rules out the chalcone intermediate. The major reaction products are cis isomers **3** and **4**, each in 15–20% yield. The reaction product contains 55% astilbin, most of which is unreacted starting material. One notable change was observed in the NMR spectrum (Figure 3) of the reaction products obtained in D_2O-ethanol-*O*-d_1-NaOAc. The C-3 proton of **3** has been largely replaced by deuterium, thus causing the collapse of the C-2 proton resonance to a singlet. These results suggest that the cis isomers are formed by selective epimerization of **1**. A possible pathway is outlined in Scheme I. The C-2 epimer, **4**, could be formed by ring opening without chal-

Scheme I



cone formation and then ring closure giving both 1 and 4. This reaction could readily occur in the presence of acetate, since C-2 should possess considerable carbonium ion character. The C-3 epimer, 3, could result from proton removal at C-3 with formation of a carbanion or enolate anion followed by proton return to yield 3 or 1. The small amount of 2 formed could result from either mechanism operating on cis isomers 3 and 4. Apparently the isomerization of 1 in ethanolic sodium acetate at room temperature proceeds under kinetic control. Isomerization of 1 in D_2O–pyridine at room temperature gave results similar to the ambient studies in ethanolic sodium acetate. After standing for 24 hr only cis isomers 3 and 4 had been produced while longer reaction times eventually led to predominant formation of 2.

Finally, isomerization of 1 in refluxing D_2O solution gave an isomeric mixture in which all isomers possessed deuterium at C-3. However, the isomeric ratio was quite different from the aqueous pyridine isomerization at 75°, since some of the astilbin was obviously unreacted. Probably the chalcone intermediate is primarily responsible for the isomerization resulting from refluxing 1 in water for 48 hr.

Experimental Section[22]

Materials. The data in Tables I and II were obtained on isomeric astilbin and engeletin samples provided by Tominaga (cf. ref 3–6). Astilbin used for isomerization studies (Figures 1–3) was obtained by ethanol extraction of *Quintinnia serrata* bark.[23] Ethanol-O-d_1 was prepared according to Streitwieser et al.[24] and was 99.3% deuterated by NMR measurements. THF was distilled twice, first from CaH_2, then from $NaAlH_2(OCH_2CH_2OCH_3)_2$, and estimated to contain 0.2% water by ir measurements. Sodium acetate was fused in a low-humidity room and found to contain 0.15% HDO by NMR measurement against a known amount of D_2O in dioxane. The labile protons in astilbin samples used for isomerization studies were exchanged by treatment with D_2O.

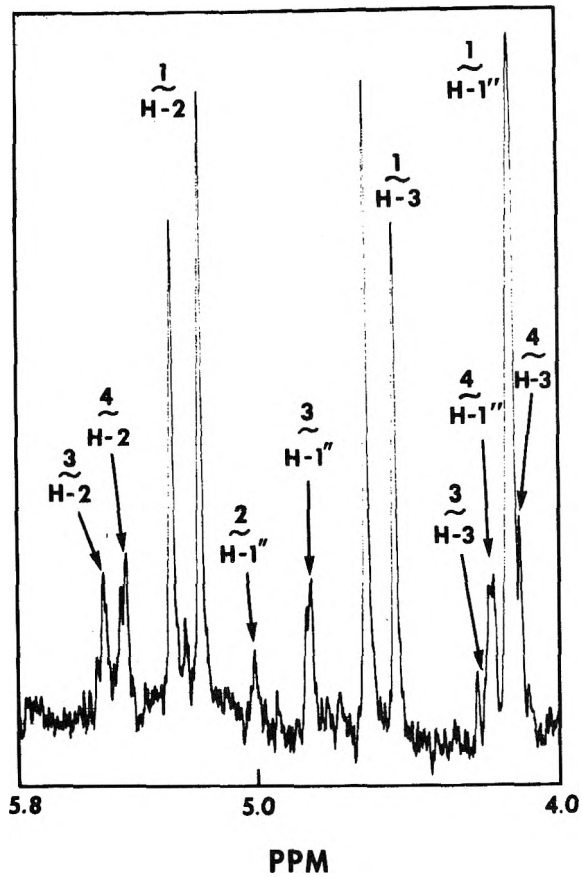


Figure 3. Partial NMR spectrum (100 MHz) of isomers resulting from treatment of 1 with D_2O–ethanol-O-d_1–NaOAc at room temperature.

Isomerization Studies. A. Pyridine–D_2O. Astilbin (0.20 g) was dissolved in dry pyridine (4 ml) and D_2O (36 ml) and heated for 3.5 hr at 75° under nitrogen. The apparent pH of the reaction mixture was 7.3. After solvent removal in vacuo at 0.05 Torr (room temperature) and drying over P_2O_5 at 100° (0.2 Torr), 0.18 g of isomeric product was obtained containing 24% 1, 46% 2, 16%, 3, and 14% 4 (see Figure 1).

A similar run under protonating conditions gave a mixture containing 22% 1, 46% 2, 19% 3, and 13% 4.

B. Ethanolic Sodium Acetate. Astilbin (0.20 g) and NaOAc (0.50 g) were dissolved in ethanol-O-d_1 (50 ml) and D_2O (20 ml). After standing in a drybox for 48 hr with occasional shaking, the reaction mixture was taken to dryness in vacuo (0.05 Torr) at room temperature. Three portions (10 ml) of carefully dried THF were used to extract the isomeric astilbins from the NaOAc. After solvent removal and drying, 0.12 g of product was obtained consisting of 49% 1, 7% 2, 24% 3, and 20% 4.

A similar run under protonating conditions gave 47% 1, 13% 2, 23% 3, and 17% 4.

C. D_2O. Astilbin (0.15 g) was dissolved in D_2O (99.8%) and refluxed for 48 hr under nitrogen. The apparent pH of the reaction mixture was 4.1. After work-up as in A, a reaction product (0.12 g) consisting of 40% 1, 26% 2, 14% 3, and 20% 4 was obtained. The A-ring protons were completely exchanged under these conditions.[25]

A similar run under protonating conditions gave 51% 1, 17% 2, 10% 3, and 22% 4.

Registry No.—1, 29838-67-3; 2, 54081-47-9; 3, 54081-48-0; 4, 54141-72-9; 5, 572-31-6; 6, 54081-49-1; 7, 30987-58-7; 8, 54081-50-4.

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(1) (a) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971; see Abstracts, CELL-65. (b) Agricultural Research Service, U.S. Department of

Agriculture.
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(16) These configurations are opposite to those originally proposed in ref 5.
(17) The existence of stable rhamnosides of *cis*-3-hydroxyflavanones suggests that mild hydrolytic conditions, such as enzymatic, might yield the presently unknown *cis*-3-hydroxyflavanones. However, our cursory attempts to hydrolyze neoisoengeletin with fungal hemicellulase were unsuccessful.
(18) These configurations are opposite to those originally proposed in ref 6.
(19) We have studied the isomerization of **1** in aqueous pyridine at 75° and in ethanolic sodium acetate at room temperature for the reason that the original preparation[3] of **2**, **3**, and **4** was conducted under similar conditions.
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(21) J. W. Clark-Lewis and V. Nair, *Tetrahedron Lett.*, 5467 (1966).
(22) NMR spectra were measured on a Varian HA-100 spectrometer with tetramethylsilane (Me_4Si) as the internal standard. CD spectra were obtained with the aid of a Cary 6003 dichrometer.
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A Simple Method for Determining the Configurations of Tertiary Alcoholic Centers in Branched-Chain Carbohydrate Derivatives by Use of Europium(III)-Induced Shifts in the ^1H Nuclear Magnetic Resonance Spectrum[1-3]

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The addition of graduated amounts of a solution of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III) [Eu(fod)$_3$] to solutions of the sugar derivatives methyl 3,4-*O*-isopropylidene-2-*C*-(2-methyl-1,3-dithian-2-yl)-β-D-ribopyranoside (**1**), methyl 2-*C*-(1,3-dithian-2-yl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (**2**), 4,6-dideoxy-1,2-*O*-isopropylidene-3-*C*-(2-methyl-1,3-dithian-2-yl)-α-D-*ribo*-hexopyranose (**3**), 4,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (**4**), methyl 6-deoxy-2,3-*O*-isopropylidene-4-*C*-(2-methyl-1,3-dithian-2-yl)-α-L-talopyranoside (**5**), methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**6**), 3-*C*-(1,3-dithian-2-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**7**), and 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**8**) produces displacements of the resonance frequencies of protons in approximate proportion to the amount of Eu(fod)$_3$ added. Comparison of the magnitudes of this proportionality (shift gradient) for each identifiable proton resonance of a tertiary alcoholic derivative (**1**, **3**, **5**, or **7**) with that of the corresponding proton resonance of an alcohol of known stereochemistry (**2**, **4**, **6**, or **8**, respectively) is used to relate the configuration of the tertiary alcoholic center at the chain-branched position to that of the reference compound; uniform correspondence of the entire set of shift gradients is taken as evidence that the same relative configuration prevails in both the chain-branched tertiary alcohol and the reference molecule, whereas any gross deviation from parallelism in magnitude of corresponding shift-gradient terms in the two sets of values indicates that the tertiary alcoholic center is epimeric to the corresponding center in the reference alcohol. Statistical analysis of these shift-gradient data further supports the configurational assignments.

Configurational assignment of secondary alcoholic centers in carbohydrate molecules is often accomplished, after appropriate derivatization, by analysis of spin-coupling interactions observed in the NMR signal of the secondary CH proton.[4] Analogous molecules having tertiary alcoholic centers, which are accessible by the addition of carbon nucleophiles to a free carbonyl group in glycosulose derivatives,[5] have no proton at the newly formed asymmetric center and thus cannot be examined by the direct ^1H NMR technique. The stereochemistry at C-2 of methyl 2-*C*-formyl-β-L-arabinopyranoside was identifiable[5] because the formyl group forms an internal hemiacetal with the 4-hydroxyl group. Continued efforts in the same laboratory revealed that the change in electrophoretic mobility caused by complexation with benzeneboronic acid is configurationally determined and that the intramolecularly hydrogen-bonded O–H stretching frequency in the infrared spectrum is dependent upon the axial or equatorial disposition of the hydroxyl group involved; both of these observations can be applied to configurational elucidation[6] of a somewhat broader, but still limited range of examples.

Synthetic programs in our two laboratories have applied nucleophilic addition to free carbonyl groups in protected sugar derivatives as a general means of extending[7-9] or branching[9-12] the carbon chain of sugar molecules. The utility of these addends as potential intermediates in synthetic schemes has occasioned a renewal in our laboratories of the quest for convenient, general methods of assigning the relative configuration of the tertiary alcoholic center of molecules such as those formed in the quaternization reaction of glycosulose precursors.

^{13}C NMR spectroscopy has been employed successfully

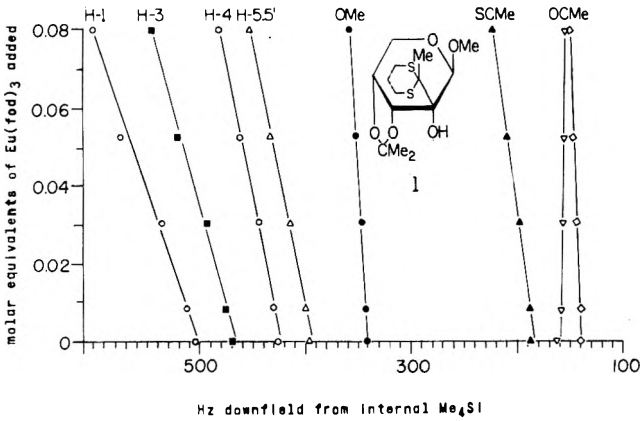

Figure 1. Chemical-shift values measured for solutions of methyl 3,4-*O*-isopropylidene-2-*C*-(2-methyl-1,3-dithian-2-yl)-β-D-ribopyranoside (1) in the presence of different concentrations of $Eu(fod)_3$.

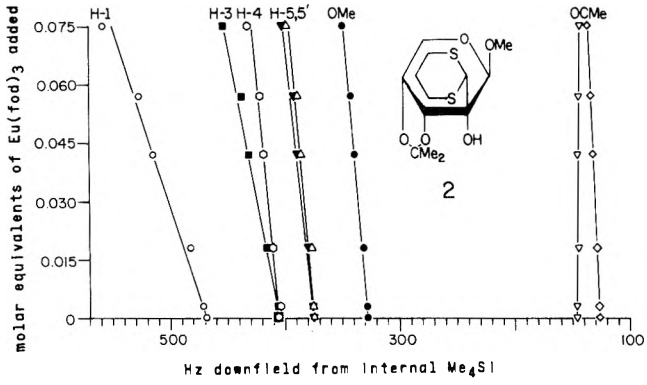

Figure 2. Chemical-shift values measured for solutions of methyl 2-*C*-(1,3-dithian-2-yl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (2) in the presence of different concentrations of $Eu(fod)_3$.

in configurational elucidation of synthetic, tertiary alcoholic derivatives of carbohydrates;[13] this promises to be a general method, but it requires a number of reference compounds for comparison of chemical shifts, a fairly sizable sample, and a rather specialized item of spectroscopic equipment. Another method that has provided reliable identification of a few branched-chain tertiary alcoholic derivatives in which all the other substituent heteroatoms are derivatized[2,8] is lanthanide-shifted ^1H NMR spectroscopy.[14] The latter technique offers the advantages that it requires rather less sample and that it may be performed with relatively commonplace equipment; however, the simple relationship derived[15] to describe shifts caused by a pseudocontact (dipolar) mechanism, which was assumed[16] to apply to lanthanide ion–monofunctional ligand interactions, can apply to more extensively functionalized molecules only when the separation of substituents is sufficient to preclude[17] bidentate[18] coordination. Furthermore, direct, elementary interpretations of shifts produced by paramagnetic cations have subsequently been assailed as unsound,[19] and recent reports attest that neither the basic theory[20] of this effect nor the mechanism[21] by which it acts for europium(III) complexes is simple.

Evidence suggests, however, that induced shifts measured at low relative concentrations of the lanthanide ion are linearly related to this concentration,[22,23] and that the conformation of a tertiary alcoholic product of nucleophilic addition to a glycopyranosidulose derivative is not altered significantly from that of the identically derivatized secondary alcoholic analog having the same relative configuration.[2,8] Assuming these two conditions, it is possible to evade the complications inherent in a direct interpretation of the lanthanide-induced shift by comparing the induced shifts resulting from an arbitrary amount of added lanthanide (the shift gradients) for protons occupying analogous locations in the unknown tertiary alcoholic derivative and in a second molecule that is presumed to possess the same relative stereochemistry; if the configurations are the same, the interactions with the paramagnetic center will be similar, and the set of shift gradients measured for the sample will be linearly related to those measured for the reference, whereas if the configurations are different, different interactions will prevail in the two examples and comparison of the two sets of shift gradients will reveal that they are not linearly related. As common factors contribute to produce the induced shifts in complexes of configurationally and conformationally related molecules with $Eu(fod)_3$, an interpretation may be based confidently upon the simple, direct observation either of two sets of shift gradients that are systematically related, in pairs, by a common factor, or of two sets of shift-gradient values that are not related in any systematic manner.

This relationship may be stated algebraically as follows (eq 1), in which $\Delta\delta_{U(i)}$ and $\Delta\delta_{R(i)}$ are, respectively, the shift

$$\Delta\delta_{U(i)} = k\,\Delta\delta_{R(i)} \qquad (1)$$

gradient of the ith proton in a (configurationally) unknown molecule (U) and that of the corresponding proton in a reference molecule (R, of known configuration), and k is a proportionality constant that relates all such pairs of shift gradients measured for the two molecules. The method thus consists of a visual estimate of the uniformity of k; if k is close to unity and deviates little from this value it is reasonable to conclude that the conformations are in direct correspondence, whereas if k exhibits major variations from a uniform value near unity, the conformations differ, reflecting a configurational difference.

Experimental Section

The 100-MHz NMR spectra of compounds **2–6** were recorded at ~30° on solutions of ~50 mg of sample dissolved in 0.3 ml of carbon tetrachloride, and spectra of compounds **1**, **7**, and **8** were recorded under similar conditions in chloroform-*d*, by using a Varian HA-100 spectrometer in the frequency-sweep mode. Five percent Me_4Si was present in each solution as an internal reference and lock signal. Graduated amounts of a saturated solution of tris(6,6,7,7,8,8,8 - heptafluoro - 2,2 - dimethyl - 3,5 - heptanedionato)europium[24](III) [$Eu(fod)_3$, Aldrich] in carbon tetrachloride were added dropwise (with vigorous mixing) between spectral acquisitions on each sample until sufficient information had been accumulated; no extraordinary precautions were taken to exclude water or air. Integration of the *tert*-butyl proton resonance of $Eu(fod)_3$ was used to verify the relative concentration of shift reagent added to the sample. Data for compound **2**, which are reported in ref 2, were acquired under the same conditions.

Discussion

Figures 1–8 illustrate the dependence of chemical shifts of identifiable proton magnetic resonance signals upon the concentration of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III)[24] added to solutions of methyl 3,4-*O*-isopropylidene-2-*C*-(2-methyl-1,3-dithian-2-yl)-β-D-ribopyranoside (**1**), methyl 2-*C*-(1,3-dithian-2-yl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (**2**), 4,6-dideoxy-1,2-*O*-isopropylidene-3-*C*-(2-methyl-1,3-dithian-2-yl)-α-D-*ribo*-hexopyranose (**3**), 4,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (**4**), methyl 6-deoxy-2,3-*O*-isopropylidene-4-*C*-(2-methyl-1,3-dithian-2-yl)-α-L-talopyranoside (**5**), methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**6**), 3-*C*-(1,3-dithian-2-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**7**), and 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**8**), respec-

Table I
Shift Gradients Measured[a] for Compounds 1–8 Complexed with Eu(fod)$_3$

Signal	1[b]	2[c]	3[c]	4[c]	5[c]	6[c]	7[b]	8[b]
H-1	12	12	6	20	12	2.7	7	1.2
H-1′							2.8	1.3
H-2			13	34	10	4		
H-3	9	6.5		48	11	10		17.2
H-4	6.5	3.6		16		11	11	17
H-4′				35				
H-5	6.5	4.0	7.5	15	10	5.5		6.8
H-5′		3.5						
H-6			2	12	2.4	1.6		4.5
H-6′								4.2
OH			15	170	17	24	45	25
OMe	2	2.7			2.6	1.5		
SCH		15.5					24	
SCMe	5		4		6			
OCMe	1.5	0.4	2.5	6.5	2.6	2.4	4	4.2
	−0.6	−1.3	0.5	4	0.2	2.3	2.5	3.8
							1	1.2
							−4.3	0.5

[a] In parts per million per molar equivalent of Eu(fod)$_3$ added. [b] In chloroform-*d*. [c] In carbon tetrachloride.

tively. The slopes describing the best (visual) straight-line fits for these data are recorded in Table I as shift gradients ($\Delta\delta$), expressed in parts per million per molar equivalent of Eu(fod)$_3$ added.

Methyl 3,4-*O*-Isopropylidene-2-*C*-(2-methyl-1,3-dithian-2-yl)-β-D-ribopyranoside (1). The chemical-shift alterations induced by addition of Eu(fod)$_3$ to solutions of methyl 3,4-*O*-isopropylidene-2-*C*-(2-methyl-1,3-dithian-2-yl)-β-D-ribo- (or arabino-) pyranoside (1), for which it is desired to determine the configuration generated at C-2 by addition[11] of the 2-methyl-1,3-dithian-2-yl anion to the carbonyl group of methyl 3,4-*O*-isopropylidene-β-D-*erythro*-pentopyranosid-2-ulose, and for the configurationally related, similarly derivatized analog, methyl 2-*C*-(1,3-dithian-2-yl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (2), for which the configuration has been determined[2,13] already, are displayed in Figures 1 and 2, respectively. Complete separation of signals is effected in the spectrum of 2 by Eu(fod)$_3$, so that a complete set of shift gradients is measurable. In the spectrum of 1, the resonances of the methylene protons (H-5 and H-5′) were not separable, and the data in Figure 1 for these signals, as well as the shift gradient recorded in Table I, represent a composite of these two signals; all other signals were separated. It was possible to identify each isolated signal for both 1 and 2 by inspection on the basis of initial chemical shift, intensity, multiplicity, and line spacings, and, accordingly, to determine the shift gradient associated with each signal. The close overall similarity of all shift gradients for 1 and 2 (Figures 1 and 2) indicates the same relative (ribo) stereochemistry for both compounds, so that the D-ribo configuration may be confidently assigned to 1.

The shift gradients of the isopropylidene methyl groups are quite small, so that slight changes in their value exert profound influence upon the ratio of two such values. For shift gradients of magnitude greater than 1 ppm per molar equivalent of Eu(fod)$_3$ added, however, the ratios of corresponding signals in 1 and 2 (the nominal constant k in eq 1) range from a maximum of 1.8 (H-4) to a minimum of 0.75 (OMe); this approximates fairly closely to a constant value of unity, and the discrepancies may be amplified by the fact that a different solvent (CCl_4 for 2, $CDCl_3$ for 1) was used for the two determinations. One isopropylidene methyl resonance of both 1 and 2 experiences an upfield shift under the influence of Eu(fod)$_3$; this constitutes confirmatory evidence for the configurational identity of 1 with 2 because both *C*-methyl resonances of an analogue having arabino stereochemistry undergo displacement[2] to lower field.

4,6-Dideoxy-1,2-*O*-isopropylidene-3-*C*-(2-methyl-1,3-dithian-2-yl)-α-D-*ribo*-hexopyranose (3). Addition of Eu(fod)$_3$ to solutions of 4,6-dideoxy-1,2-*O*-isopropylidene-3-*C*-(2-methyl-1,3-dithian-2-yl)-α-D-*ribo*- (or *xylo*-) hexopyranose (3), which, like 1, contains an asymmetric, tertiary alcoholic group of stereochemistry to be determined, and 4,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (4), which is the immediate precursor[12] of the glycosulose from which 3 is prepared, was slightly less successful in producing a completely separated NMR spectrum than in the preceding example. Nonetheless, seven of the proton resonances of 3 and all of the proton resonances of 4 were identified, and the slopes of the straight lines fitted to the induced-shift data plotted in Figures 3 and 4 for these two derivatives are recorded in Table I as shift gradients for the respective signals. Comparison of the slopes of corresponding lines in these two figures (particularly the OH resonances) reveals that, in contrast to the preceding example, the values of shift-gradient ratios (the nominal constant k in eq 1) for 3 and 4 range from 0.09 (for the OH signal) to 0.5 (for the C-6 methyl resonance). This discrepancy (a factor of 5.5) alone is sufficient to indicate that 3 and 4 are configurationally dissimilar; in addition, the observation that the average ratio (k_{av}) is considerably smaller than unity signals a major alteration in the characteristics of the two ligand–lanthanide complexes, affording further evidence for the interpretation of different relative stereochemistry in 3 and 4. As 3 was prepared from 4 by a two-step sequence of oxidation followed by nucleophilic addition that should affect only the underivatized hydroxyl group, net inversion is indicated, and 3 is assigned the D-ribo configuration.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-4-*C*-(2-methyl-1,3-dithian-2-yl)-α-L-talopyranoside (5). Chemical shifts measured for the proton resonances of a methyl 6-deoxy-2,3-*O*-isopropylidene-4-C-(2-methyl-1,3-dithian-2-yl)-α-L-hexopyranoside (5) having either the talo or the manno configuration are plotted in Figure 5 as a function of the relative concentration of Eu(fod)$_3$ added. Similar

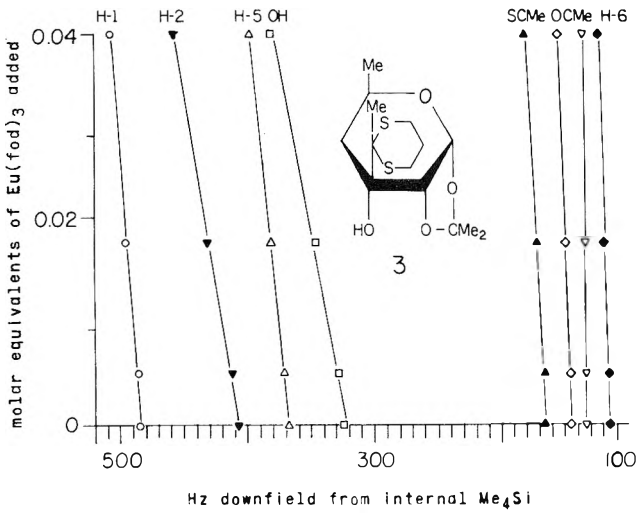

Figure 3. Chemical-shift values measured for solutions of 4,6-dideoxy-1,2-*O*-isopropylidene-3-*C*-(2-methyl-1,3-dithian-2-yl)-α-D-*ribo*-hexopyranose (**3**) in the presence of different concentrations of $Eu(fod)_3$.

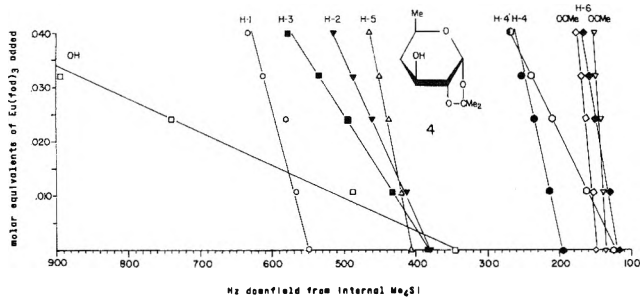

Figure 4. Chemical-shift values measured for solutions of 4,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranose (**4**) in the presence of different concentrations of $Eu(fod)_3$.

data are presented in Figure 6 for methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**6**), which is the precursor of **5** in a two-step scheme[12] of oxidation of the 4-hydroxyl group followed by addition of the 2-methyl-1,3-dithian-2-yl anion to the newly generated carbonyl group. Shift-gradient values, determined as the slopes of the respective straight lines drawn through the data points in these two plots, are recorded in Table I; every signal in both spectra was identified so that a complete set of data was obtained. Comparison of shift-gradient values for the various protons occupying similar positions in the two molecules reveals a range from 4.4 (for H-1) to 0.7 (for the OH proton), the discrepancy amounting to a factor of 6.3 (4.4/0.7). By consideration of the very small shift-gradient values of the isopropylidene methyl groups (which are potentially hypersensitive to slight errors of measurement), the discrepancy is raised to a factor of nearly 50, and direct consideration of the *C*-methyl resonances reveals that both *C*-methyl signals of **6** experience nearly equal displacements downfield by $Eu(fod)_3$, whereas one of the two *C*-methyl resonances of **5** is virtually unshifted. Each of these observations supports the same conclusion, namely, that the configurations of **5** and **6** are not identical and that, therefore, **5** had the L-talo configuration.

3-*C*-(1,3-Dithian-2-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-*ribo*-hexulopyranose (7). Relatively poor signal separation is produced by graduated additions of $Eu(fod)_3$ to a solution of 3-*C*-(1,3-dithian-2-yl)-1,2:4,5-di-*O*-isopropylidene-β-*ribo*- (or *arabino*-) hexulopyranose[12] (**7**) in chloroform-*d*, although it was possible to identify all of the 12 proton resonances except for H-4, H-5, and the two H-6

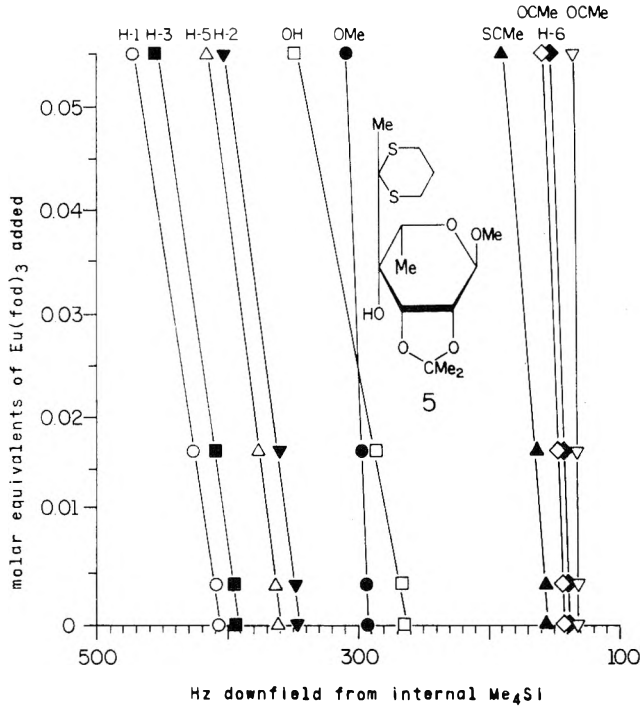

Figure 5. Chemical-shift values measured for solutions of methyl 6-deoxy-2,3-*O*-isopropylidene-4-*C*-(2-methyl-1,3-dithian-2-yl)-α-L-talopyranoside (**5**) in the presence of different concentrations of $Eu(fod)_3$.

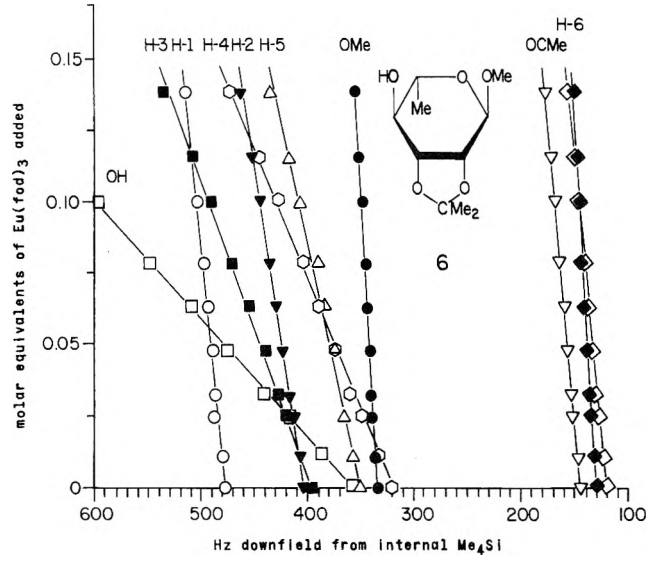

Figure 6. Chemical-shift values measured for solutions of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (**6**) in the presence of different concentrations of $Eu(fod)_3$.

protons; data for the eight identifiable signals (plus H-2′ of the 1,3-dithianyl group) are plotted in Figure 7 as a function of the number of molar equivalents of $Eu(fod)_3$ added. Figure 8 displays the chemical shifts obtained by similar examination of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**8**), which is the antecedent of **7** in the synthetic sequence[12] of oxidizing the 3-hydroxyl group to a ketonic function and adding the 1,3-dithian-2-yl anion to the carbonyl group to produce the tertiary alcoholic branched-chain alcohol **7**; this may be formed with net retention or inversion of configuration at C-3, depending upon the stereochemistry of the attack.

Shift-gradient values in Table I [the slopes of lines in Figures 7 and 8, expressed in parts per million per molar equivalent of $Eu(fod)_3$] exhibit a number of gross, qualitative disparities for corresponding signals in **7** and **8**. The

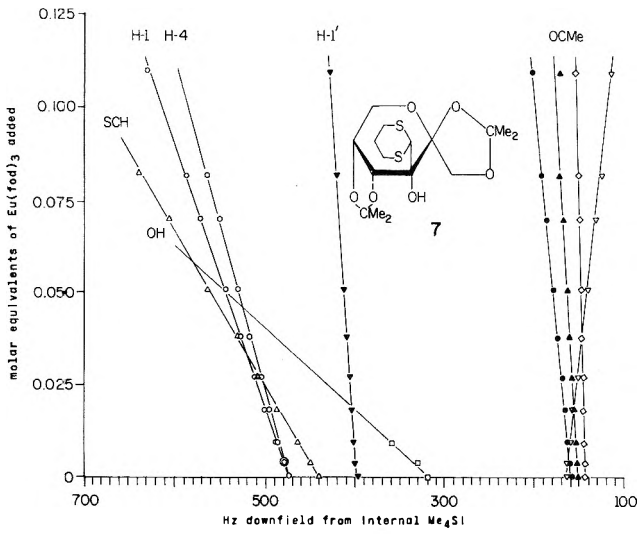

Figure 7. Chemical-shift values measured for solutions of 3-*C*-(1,3-dithian-2-yl)-1,2:4,5-di-*O*-isopropylidene-β-D-psicopyranose (**7**) in the presence of different concentrations of $Eu(fod)_3$.

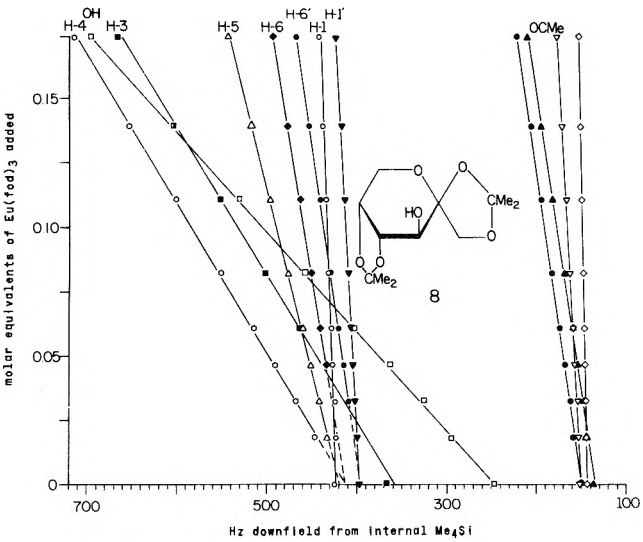

Figure 8. Chemical-shift values measured for solutions of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**8**) in the presence of different concentrations of $Eu(fod)_3$.

H-4 signal of **7** shifts only 0.65 as strongly as the H-4 signal of **8**, whereas the lower field H-1 signal of **1** is shifted six times as strongly as the corresponding signal in the spectrum of **8**, a discrepancy factor exceeding 9. Furthermore, both H-1 signals of **8** are displayed by a similar amount, whereas the H-1 resonance of **7** is shifted 2.5 times more strongly than the H-1′ signal, and the resonances of all four *C*-methyl groups of **8** are displaced to low field by $Eu(fod)_3$ whereas one *C*-methyl resonance of **7** experiences *a strong upfield shift*. It is, therefore, clear that the conversion of **8** into **7** is accomplished with effective inversion of configuration at C-3 and that **7** does indeed possess the ribo configuration.

No special attempt was made to exclude water from the solvents or from **1–8**, although conditions used in preparation of solutions were uniform, so that numerical values reported in Table I represent lower limit approximations to true induced shifts of the 1:1 complexes with $Eu(fod)_3$. Within a set of values for a given compound, however, the deviation from true values will take the form of a multiplicative factor common to all members of that set. Thus, systematic comparison of corresponding terms within two sets of shift gradients measured for configurationally related

Table II
Correlation Coefficients (*r* Values) and Best-Fit Slopes (k_{av}) Determined by Linear Regression Analysis[a] of Data in Table I and Ref 2

Related			Unrelated		
Pair	*r*	k_{av}	Pair	*r*	k_{av}
1–2	0.903	0.885	**3–4**	0.746	0.058
9–10[b]	0.96	1.16	**5–6**	0.778	0.505
9–11[b]	0.98	1.24	**7–8**	0.861	1.403
12–13[b]	0.89	1.14	**12–14**[b]	0.81	0.80
			15–16[b]	−0.05	−0.04

[a] Calculated with a Hewlett-Packard 9100B calculator by using the stock program. [b] These compounds are methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-(1,3-dithian-2-yl)-α-D-*ribo*-hexopyranoside (**9**) and its 3-*C*-(1-butyl) analog (**10**), methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**11**), methyl 2-*C*-(1,3-dithian-2-yl)-3,4-*O*-isopropylidene-β-D-ribopyranoside (**12**), methyl 2-*C*-deuterio-3,4-*O*-isopropylidene-β-L-ribopyranoside (**13**), methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside (**14**), 3-*C*-(1,3-dithian-2-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**15**), and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**); see ref 2.

molecules should compensate both for the vicissitudes of direct interpretation of induced shift magnitudes and for minor, systematic interferences arising in the course of experimentation.

Linear Regression Analysis of the Data. As eq 1 is of the form $y = mx + b$, linear regression analysis would be expected to provide a statistical measure whereby this approach might be evaluated. Table II presents the results of such an analysis of the data of Table I, and incorporates also the data for five pairs of compounds discussed in ref 2.

The range of the correlation factors is rather low, but it must be borne in mind (a) that the sample population is relatively small and that the probable errors of measurement are admittedly[2] rather substantial, and (b) that the character of the molecules examined deviates from randomness sufficiently that a correlation coefficient (*r*) as high as 0.75 was calculated even for the data of **4** and **5**, which would otherwise be almost completely uncorrelated. An *r* value of 1.0 would be required for identical coordination behavior by a pair of compounds. Of the four sample pairs from the present study in Table II, only **1–2** displays both a large *r* value (>0.9) and a k_{av} value (derived from regression analysis of data fit to eq 1), close to unity (1 ± 0.2); this corroborates the conclusion that **1** and **2** are configurationally related. The configurationally different pairs **3–4** and **5–6** exhibit significantly smaller *r* values, on the order of 0.75 (a value which was also found for the configurationally *and* structurally unrelated pair **4–5**). The value 0.86 of *r* for the pair **7–8** is relatively large, but the value of k_{av} (1.4) is far enough from unity to warrant the conclusion that the configurations are different. Similar analysis of data in ref 2 reveals *r* (k_{av}) values of −0.05 (−0.04) and 0.81 (0.80) for the two examples having dissimilar configurations, as compared with 0.96 (1.16), 0.98 (1.24), and 0.89 (1.14) for the three pairs that are configurationally related.

The foregoing examples demonstrate clearly (a) that *relative* (but not necessarily *absolute*) shift gradients for corresponding protons within a conformationally homogeneous series of derivatives having similar substitution are closely similar, and (b) that this property affords a reliable method of determining directly the configuration of nonprotonated carbon atoms (as in synthetic, branched-chain sugars) simply by comparing shift gradients found for the configurationally unknown molecule with those of a related compound (frequently a precursor in the synthesis) whose

configuration is known. Supporting evidence may be derived from a linear regression treatment of the shift-gradient data.

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Registry No.—**1**, 39707-76-1; **2**, 35784-92-0; **3**, 54797-99-8; **4**, 54307-95-8; **5**, 53438-14-5; **6**, 14133-63-2; **7**, 54307-96-9; **8**, 25018-67-1; Eu(fod)$_3$, 17631-68-4.

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Syntheses of 2-Substituted 1,N^6-Ethenoadenosines[1]

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The syntheses of some 2-substituted (–SH, –SC_2H_5, –SO_3^-, –OH, –$NHNH_2$, –N_3, and –NH_2) 1,N^6-ethenoadenosines are described. The fluorescent properties of the derivatives were affected by the substituents. While substituents –SH, –SC_2H_5, –NH_2, –$NHNH_2$, and –N_3 quenched the fluorescence, substituents –OH and –SO_3^- enhanced the fluorescence.

1,N^6-Ethenoadenosine[1] (ϵ-adenosine, **1**) is a fluorescent analog of adenosine. The phosphate derivatives of ϵ-adenosine have been found to be useful substrates in numerous enzyme reactions.[2] However, the fluorescence emission maximum of these derivatives is 410 nm and they are not suitable for cytochemical investigation where either tissues or cells possess autofluorescence in this range. The synthesis of a new fluorescent adenosine analog, 2-aza-ϵ-adenosine (**3**), that could be useful for such purposes was therefore undertaken in our laboratory. The synthesis of this new compound and its properties have recently been reported.[3] In several instances, the phosphate derivatives of this new fluorescent adenosine analog have been found to be better substrates than the corresponding ϵ analogs.[4,5] Furthermore, compound **3** was found to be cytotoxic against a mammary tumor cell line.[6] Since the synthetic objectives in our laboratory are to provide, first, fluorescence nucleosides and nucleotides that could be useful probes for protein–oligonucleotide interaction,[7,8] second, fluorescent nucleoside substrates that can be used as histochemical or cytochemical substrates for localizing enzymes at cellular level,[9,10] and third, potential chemotherapeutic agents, the preparation of other 2-substituted ethenoadenosines is therefore of interest. The present paper reports the synthesis and some properties of these new nucleoside derivatives.

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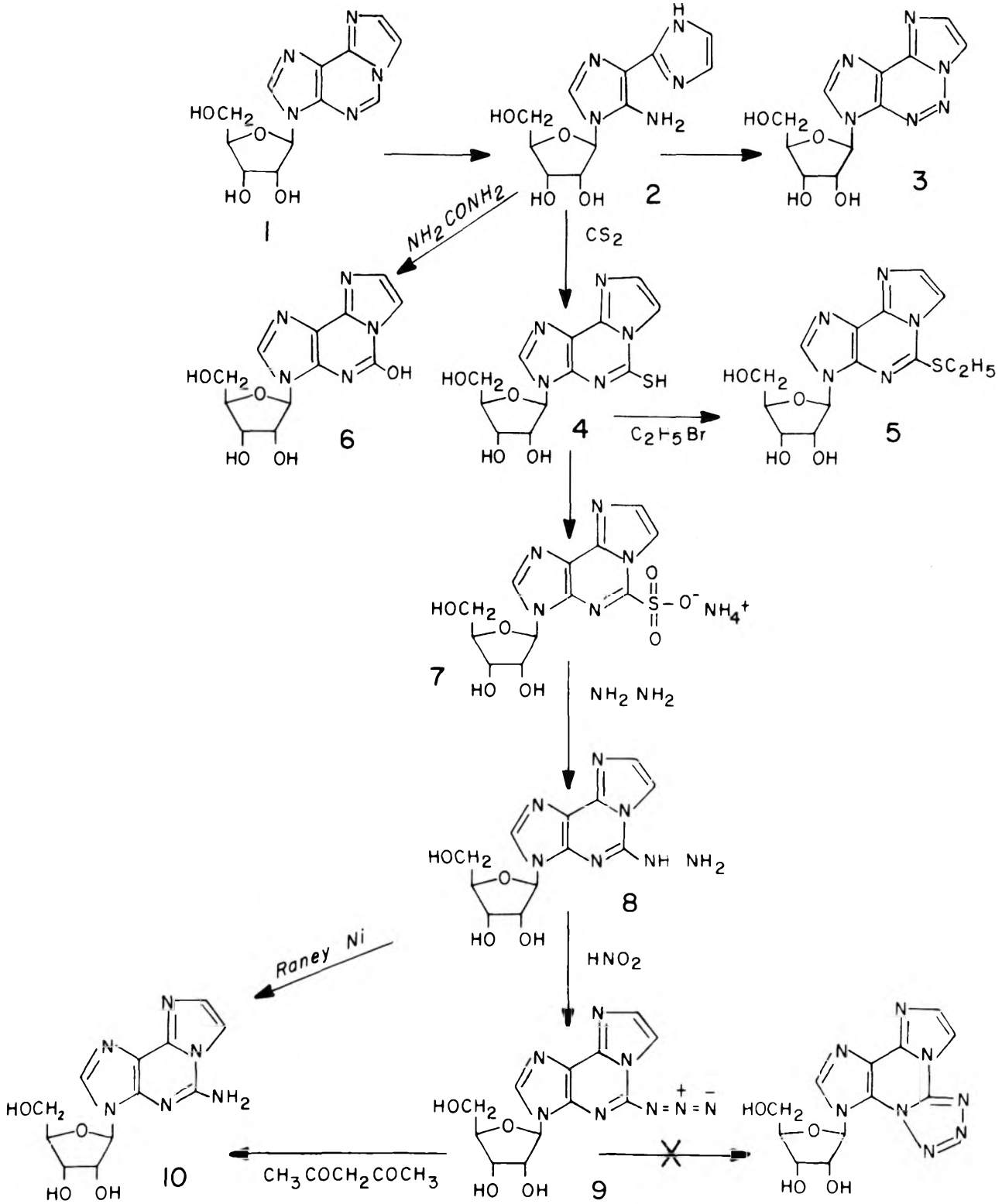
The preparation of **2** was described in our recent paper[6] (Scheme I). Conversion of **2** to 1,N^6-etheno-2-mercaptoadenosine (2-mercapto-ϵ-A, **4**) was accomplished by carbon disulfide in pyridine. The ultraviolet absorption spectrum of the nucleoside **4** showed a maximum (pH 7) at 317 nm, but when alkylated as in **5**, the uv spectrum (Table I) showed a hypsochromic shift of 35 nm to 282 nm (pH 7). Thus, it is likely that **4** exists predominantly in the thiono form in neutral solution, as in the case of 6-mercaptopurine riboside[11] and 2-mercaptoinosine.[12] When **2** was heated with urea at 150° under nitrogen, 1,N^6-etheno-2-hydroxyadenosine (2-hydroxy-ϵA, **6**) was isolated as the major product. This compound, however, does exist in the enol form, as its ir spectrum shows no carbonyl absorption. Compound **6** is also a good fluorescent compound with emission maximum at 430 nm and an excitation maximum at 315 nm (Table II). While the mercapto derivative **4** is nonfluorescent, the quantum yield of **6** was 0.68 at pH 5.5. The fluorescence of this compound is unique among all other fluorescent ϵ-adenosine derivatives. These compounds are usually quenched in acidic solution because of the protonation of the imidazole ring,[1b] but the fluorescence of **6** was quenched at alkaline pH as well as acidic pH (Figure 1). Two pK_a values of 2.40 and 6.75 were found from the titration curve. The low pK_a was due to the protonation of the imidazole ring and the higher pK_a corresponded to the ionization of the phenolic acidic proton, as shown in Scheme

Scheme I



II. Therefore, only the neutral form of **6** fluoresces, and this property should serve as a useful indicator in cytochemical experiments in biological systems.

Compound **5** was prepared by ethylation of **4**. Similar to other 2-alkylthiopurine ribosides, this compound was found to resist nucleophilic substitution reaction.[13] It did not undergo amination reaction and was stable in alkaline solution. In order to facilitate the nucleophilic substitution on the ethylthio group, the conversion of **5** into 2-ethylsulfonyl-ϵ-A was attempted with oxidizing agents, including hydrogen peroxide and *N*-chlorosuccinimide, without success. An alternate route to obtain other 2-substituted compounds from **4** was therefore investigated. It was found that compound **4** was rapidly oxidized with *N*-chlorosuccinimide to yield the ammonium salt of ϵ-adenosine-2-sulfonic acid (ϵ-A-2-sulfonate), **7**, in good yield. The structure of **7** was confirmed by its ir spectrum with an absorption band at 1210 cm^{-1} for the sulfonic acid group. Compound **7** was also found to have a fluorescence emission maximum at 460 nm when excited at 335 nm, and formed an insoluble salt when silver ion was added to a solution of less than 10^{-4} *M*. The fluorescence characteristic as well as the low

Table I
Some Analytical Data on 2-Substituted 1,N^6-Ethenoadenosine

Compd	Name	Mp, °C	R_f value TLC$_1$ S_1	R_f value TLC$_2$ S_2	Uv max, nm (ε) pH 1	pH 7	pH 13	Empirical formula	Calcd/Found C	H	N
4	2-Mercapto-ε-A	225–227 dec		0.55	312 (18,000)	317 (15,200)	318 (14,400)	$C_{12}H_{13}N_5O_4S \cdot H_2O$	42.22 42.29	4.42 4.26	
5	2-Ethylthio-ε-A	186–187	0.50		292 (17,100)	282 (8800)	292 (9350)	$C_{14}H_{17}N_5O_4S$	47.86 47.91	4.88 4.80	19.94 20.01
6	2-Hydroxy-ε-A	194 dec	0.15	0.65	294 (14,200)	292 (13,000)	281 (15,300)	$C_{12}H_{13}N_5O_5 \cdot H_2O$	44.31 43.80	4.54 4.53	21.53 21.86
7	ε-A-2-Sulfonate	223–225		0.70	280[a] (9030)	312[b] (4200)	264[c] (9240)	$C_{12}H_{12}N_5O_7S \cdot NH_4$	37.12 37.12	4.15 4.35	21.65 21.68
8	2-Hydrazino-ε-A	146–148	0.22	0.54	282 (11,100)	280 (11,100)	291 (11,700)	$C_{12}H_{15}N_7O_4 \cdot 1^1/_2H_2O$	41.37 41.19	5.20 5.14	28.14 27.83
9	2-Azido-ε-A	162–164 dec	0.67	0.75	278 (15,400)	283 (7160)	273 (8330)	$C_{12}H_{12}N_8O_4$	43.37 43.28	3.64 3.81	33.73 33.73
10	2-Amino-ε-A	169–171	0.45	0.70	278 (11,500)	283 (10,900)	276 (12,400)	$C_{12}H_{14}N_6O_4 \cdot {}^1/_2H_2O$	45.71 45.77	4.79 5.09	26.66 26.57

[a] Also 233 nm (ε 19,500). [b] Also 270 nm (ε 5250) and 235 (21,000). [c] Also 235 nm (ε 22,000).

Table II
Fluorescence Properties of 2-Substituted 1,N^6-Ethenoadenosines

Compd[a, b]	Excitation max, nm	Emission max, nm	Buffer (pH)	Quantum yield
1	300	415	Phosphate (7.0)	0.56[b]
3	358	495	Citrate (7.0)	0.16
6	315	430	Citrate (5.5)	0.68
7	335	460	Citrate (7.0)	0.69

[a] Compounds 2, 4, 5, 8, 9, and 10 are nonfluorescent. [b] See ref 2.

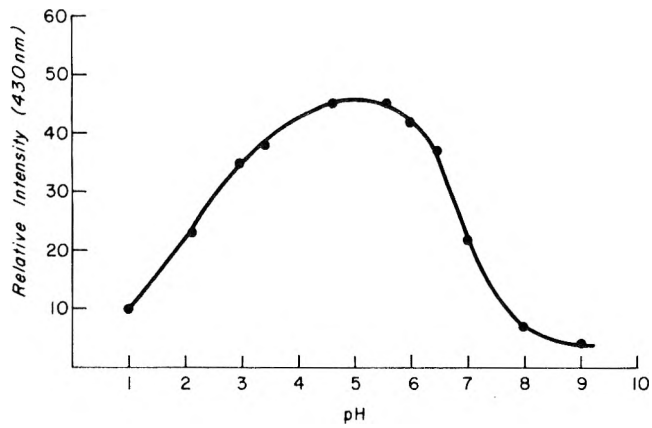


Figure 1. Variation in fluorescent intensity of **6** with pH. Potassium citrate (0.1 *M*) was used as buffer (excitation at 315 nm).

solubility of the silver salt should make **7** a useful probe for our electron cytochemical study. ε-A-2-sulfonate was stable under acidic conditions, but lost fluorescence irreversibly at alkaline pH. The sulfonic acid group was resistant to amination at 50° after treatment with ammonia for 2 days, but when treated with hydrazine, readily converted at room temperature to 1,N^6-etheno-2-hydrazinoadenosine (2-hydrazino-ε-A, **8**), in good yield. Compound **8** was nonfluorescent and stable at neutral and acidic pH, but could be oxidized easily in alkaline solution.

When 2-hydrazino-ε-A was treated with nitrous acid, the azide derivative **9** was obtained. Its structure was confirmed by the characteristic ir absorption of the azide group.[14,15] The NMR spectrum of **9** in DMSO revealed only one set of protons, which ruled out any possibility of the tetrazole form (Scheme II). Thus, it is obvious that while other 2-azido purines do rearrange to the tetrazole form, the 2-azido-ε-adenosine exists exclusively in the azido form. 2-Azido-ε-A is only slightly soluble in water and is sensitive to light. The use of this compound for photolabeling is currently under study in our laboratory. As expected, compound **9**, when treated with triphenylphosphine, yielded a yellow triphenylphosphine imine. When **9** was allowed to react with acetylacetone in an alcohol solution in the presence of triethylamine,[16] 1,N^6-etheno-2-aminoadenosine (2-amino-ε-A, **10**) was obtained in good yield. This novel method of preparing **10** is preferred over the alternate route via Raney nickel reduction of **8**. The structure of **10** was confirmed by both NMR and mass spectra.

It is well known that the substituents in the 2 position of purine nucleosides are less reactive than substituents in the

Scheme II

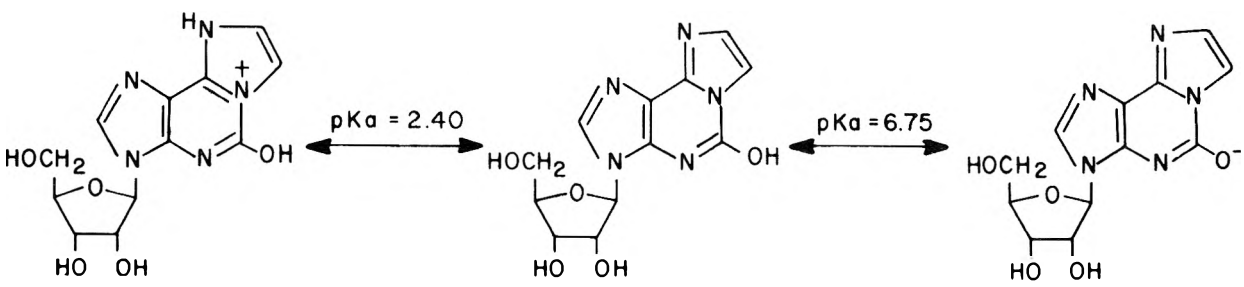
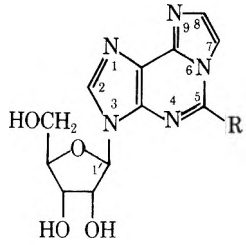


Table III
NMR Chemical Shifts and Coupling Constants of 2-Substituted 1,N^6-Ethenoadenosine[a]



Compd	R	δH_7 ($J_{H_7-H_8}$)	δH_8	δH_2	δH_5	$\delta H_{1'}$ ($J_{H_{1'}-H_{2'}}$)
1	H	8.61 (2.0)	8.20	9.01	9.80	6.18 (5.5)
3	C^5–R = N	8.85 (1.8)	8.01	9.13		6.36 (4.5)
4	SH	8.40 (2.0)	7.83	8.43		6.04 (5.0)
5[b]	SC_2H_5	7.83 (1.3)	7.66	8.50		6.10 (5.5)
6	OH	7.75 (2.0)	7.52	8.09		5.87 (5.0)
7	$-SO_3^-NH_4^+$	8.47 (1.5)	7.66	8.70		6.17 (5.5)
8	$-NHNH_2$	7.98 (1.5)	7.44	8.18		6.02 (5.5)
9	$-N_3$	7.71 (1.8)	7.55	8.50		6.00 (5.5)
10	$-NH_2$	7.99 (1.5)	7.53	8.18		5.96 (5.5)

[a] The spectra were measured in a 10% solution of DMSO-d_6 at 38°. [b] Also δ 1.33 (t, J = 7.5 Hz), 3.05 (q, J = 7.5 Hz).

6 position. The present study has shown that the substituent in the 5 position (equivalent to the 2 position of purine) of the 1,N^6-ethenoadenosine is even less reactive than substituents in the 2 position of purine nucleosides. The 2-mercapto, 2-ethylthio, and even ϵ-A-2-sulfonate were resistant to hydrolysis and amination. Only ϵ-A-2-sulfonate reacted with hydrazine successfully. Thus, the etheno ring influence on the 2 position bears no resemblance to the 9,10 position of the phenanthrene ring.

All NMR spectra of the ϵ-adenosine derivative show one singlet and two doublets in the aromatic region for the base protons. The assignment of these signals is listed in Table III. Interestingly, all fluorescent derivatives have a lower field absorption than the nonfluorescent derivatives. The biochemical properties, as well as the chemotherapeutic aspect of these compounds, will be reported later.

Experimental Section

Uv absorption spectra were measured on a Beckman Model DB-G recording spectrophotometer. Fluorescence spectra were determined with an Aminco-Bowman spectrofluorometer. NMR spectra were measured with a Varian NMR spectrometer, Model A-60. Chemical shifts are given in parts per million on a δ scale; coupling constants are expressed in Hz; Me_4Si was used as internal standard. Thin layer chromatography was carried out by the ascending method with Eastman Chromagram Sheets 6065 (cellulose with fluorescent indicators, TLC_1) and 6060 (silica gel with fluorescent indicators, TLC_2). Solvent systems are: S_1, ethanol–ammonium acetate, 1 M (7:3, v/v); S_2, methanol–chloroform (1:2, v/v). Elemental analysis (C, H, N) were performed by Micro-Analysis, Wilmington, Del. Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected.

1,N^6-Etheno-2-ethylthioadenosine (5). To a suspension of 2-mercapto-ϵ-A[6] (650 mg, 2 mmol) and anhydrous potassium carbonate (276 mg, 2 mmol) in DMF (7 ml) was added 150 μl of ethyl bromide (2.2 mmol). The mixture was heated at 55° (oil bath) for 1 hr. Judging by TLC_2 (S_2), all 2-mercapto-ϵ-A (R_f 0.10) had reacted to give a single spot with R_f 0.50. The solvent was removed by evaporation after removal of the inorganic insoluble material by filtration. The residue was crystallized with absolute ethanol to give pure **5** (580 mg, 83%).

1,N^6-Etheno-2-hydroxyadenosine (6). A mixture of **2**[6] (1 g, 3.5 mmol) and urea (2 g, 3.3 mmol) was heated in an oil bath (150–160°) under a slow stream of nitrogen for 8 hr. Judging by TLC_2 (S_2), most of **2** had reacted. The reaction mixture was cooled to room temperature and the residue was taken up by 20 ml of water and evaporated to dryness. The residue was washed with ethanol and acetone and finally recrystallized in 20 ml of ethanol to give 0.34 g (31%) of **6**. A small amount of unreacted urea in the product was removed by a silica gel column. The column was first washed with 20% methanol in chloroform to elute the urea and the product was recovered by 40% methanol in chloroform.

Ammonium 1,N^6-Ethenoadenosine-2-sulfonate (7). To a suspension of 2-mercapto-ϵ-A (1 g, 3.1 mmol) in 30 ml of water, N-chlorosuccinimide (1.25 g, 9.3 mmol) was added. The mixture was allowed to stand at 40° for 2 hr. After 1 hr, a clear solution was obtained. The reaction mixture was then neutralized carefully with concentrated ammonium hydroxide. The solid was then washed with 20 ml of absolute ethanol to remove the succinimide. The insoluble residue was again washed with 5 ml of cold water to remove the inorganic salt, and recrystallized in hot water after treatment with charcoal to give 0.6 g of **7** (53%) as a creamy white solid.

1,N^6-Etheno-2-hydrazinoadenosine (8). Compound **7** (1 g, 2.6 mmol) was added slowly to 10 ml of 98% hydrazine with stirring. After the completion of this addition, the brown solution was allowed to stand at room temperature for 15 min. Ice water (15 ml) was then added to this solution and the solution was concentrated with a rotary evaporator. The residue was washed with 5 ml of water to remove the inorganic salt and the product was then dissolved in 60 ml of hot 50% ethanol. Upon standing at 0° overnight, pure **8** crystallized and was filtered and dried to give 0.58 g (69%) as white crystals. It is stable in the solid state, but it can easily be oxidized in alkali or on TLC plates by air to give a blue-colored compound: mass spectrum m/e 174 (B + 1 − NH).

1,N^6-Etheno-2-azidoadenosine (9). To a solution of **8** (200 mg, 0.63 mmol) in 5 ml of acetic acid and 1 ml of water at 0°, sodium nitrite (50 mg, 0.65 mmol) in 1 ml of water was added dropwise. The mixture was allowed to stand at 0° for 15 min and then concentrated to remove the solvents. The last traces of acetic acid were removed by coevaporation with two 5-ml portions of water. The residue was crystallized with 20 ml of 50% ethanol after treatment with charcoal to give pure **9** as needle-like crystals (180 mg, 87%).

1,N^6-Etheno-2-aminoadenosine (10). A. Conversion from 8 with Raney Nickel. A suspension of **8** (640 mg, 2 mmol) in 20 ml of water was treated with 1 ml of Raney nickel (Alfa Inorganics, Inc.). The mixture was heated in a water bath (90–95°) for 3 hr. Judging by TLC_2 (S_2), all of the 2-hydrazine-ϵ-A had reacted. The catalyst was removed by filtration and washed well with hot water. The filtrate was evaporated to dryness and the residue was crystallized in 80% ethanol after being treated with charcoal. Compound **10**, 260 mg (42%), was recovered as a white solid: mass spectrum m/e 306 (parent ion), 174 (B + 1).

B. Conversion from 9 with Acetylacetone. Compound **9** (500 mg, 1.5 mmol) was mixed with 4 ml of acetylacetone, 3 ml of triethylamine, and 4 ml of ethanol. The solid dissolved slowly under stirring. The solution was allowed to stand at room temperature for 30 min. The product precipitated as a white solid. The solvent was re-

moved by rotary evaporator, and the residue was recrystallized with 50% ethanol to give 420 mg (91%) of product that has the same R_f values and uv spectra as **10**.

Registry No.—**1**, 39007-51-7; **2**, 50663-83-7; **3**, 50663-82-6; **4**, 54277-40-6; **5**, 54277-41-7; **6**, 54277-42-8; **7**, 54277-43-9; **8**, 54277-44-0; **9**, 54277-45-1; **10**, 54277-46-2; urea, 57-13-6; *N*-chlorosuccinimide, 128-09-6; hydrazine, 302-01-2; acetylacetone, 123-54-6.

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Reactions of Grignard Reagents with Nitrosamines[1a]

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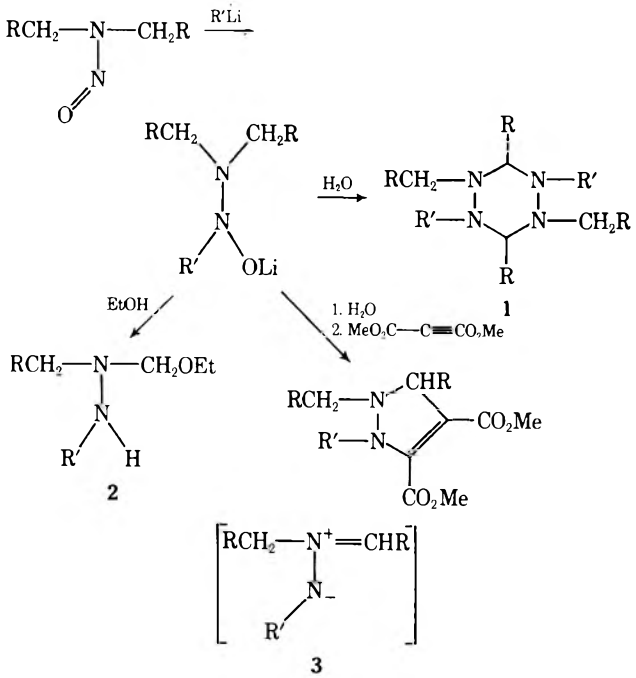
Reaction of aliphatic and alicyclic nitrosamines with excess phenyl-, cyclohexyl-, or *tert*-butylmagnesium halide gave trisubstituted hydrazines resulting from α-carbon and nitroso nitrogen alkylation. Benzylmagnesium chloride and *N*-nitrosodimethylamine gave hydrazones.

In previous reports[2,3] we described the reactions of some nitrosamines[4] with phenyl- and *tert*-butyllithium. This study (Scheme I) demonstrated that nucleophilic attack on the nitroso moiety gave *sym*-hexahydrotetrazines **1**, ethoxymethylhydrazines **2**, and other products, all presumably derived from a dipolar intermediate **3** generated after addition of either water or ethanol to the reaction mixture. The intermediate **3** was readily trapped with dimethyl acetylenedicarboxylate.

Scheme I
Reactions of Nitrosamines with Organolithium Reagents



We have extended our investigation to include reactions of Grignard reagents which serve to complement previous work and offer an expanded view of the reactions of nitrosamines with organometallics.

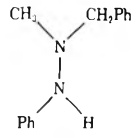
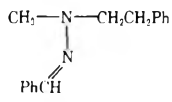
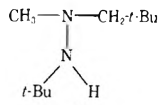
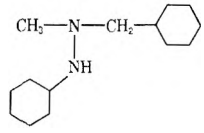
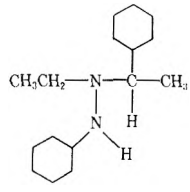
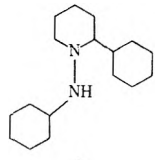
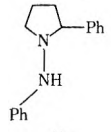
The earliest studies on the reaction of nitrosamines with Grignard reagents were reported over 60 years ago.[5,6] Wieland and Fressel[5] examined possible routes to the synthesis of hydroxyhydrazines, nitrogen homologs of hydroxylamines, by the condensation of nitrosamines with Grignard reagents. They found, however, that the reaction of ethylmagnesium iodide with diethylnitrosamine (DENA) gave the diethylhydrazone of acetaldehyde. Phenylmagnesium bromide and DENA gave 1,1-diethyl-2-phenylhydrazine and 1-ethyl-1-(α-phenylethyl)-2-phenylhydrazine. It was postulated that the latter product was formed via a diaziridine intermediate, which opened to add an additional mole of Grignard reagent to an α carbon.

Formation of Trisubstituted α-Carbon Substituted Hydrazines. In the present study dimethylnitrosamine (DMNA), diethylnitrosamine (DENA), *N*-nitrosopiperidine (PipNO), and *N*-nitrosopyrrolidine (PyrNO) were treated with cyclohexyl-, *tert*-butyl-, phenyl-, and benzylmagnesium halides. All reactions were run in ether solvent at 0° in an inert atmosphere with reaction times of 1–3 hr.

The addition of an excess of organomagnesium reagent to the nitrosamine gave, after work-up, a trisubstituted hydrazine which had incorporated 2 mol of Grignard reagent, one at a nitroso nitrogen and one at an α carbon of the aliphatic nitrosamine (Table I). Structure assignments were based on NMR and ir analyses. For example, the NMR spectrum of hydrazine **4** displayed singlets at 2.20 (3 H, *N*-methyl) and 3.55 ppm (2 H, *N*-benzyl), an exchangeable proton (NH) at 4.10 ppm, and aromatic multiplets between 6.5 and 7.3 ppm. The ir spectrum displayed an NH stretch at 3.07 μ.

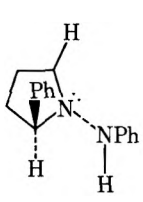
The NMR spectrum of 1-ethyl-1-(α-cyclohexylethyl)-2-cyclohexylhydrazine (**8**) from the reaction between DENA

Table I
α-Carbon Substituted Hydrazines and Hydrazones from the Reaction of Aliphatic Nitrosamines with Grignard Reagents

Nitrosamine	Grignard reagent	α-C alkylated hydrazine	Bp, °C (mm)	Mp of HCl salt, °C	Isolated yield, %
DMNA	PhMgBr	 4	135–136 (1.7)	177.5–180.5	30
DMNA	$PhCH_2MgCl$	 5		45–45.5 (free base)	Undetermined
DMNA	*t*-BuMgBr	 6	30–32 (1.6)		50
DMNA	$C_6H_{11}MgBr$	 7	113–115 (1.8)	199–201	48 (75–80 GC)
DENA	$C_6H_{11}MgBr$	 8	122–124 (0.35)	159–160	47
PipNA	$C_6H_{11}MgBr$	 9	124–127 (0.3)	216–217.5	52
PyrNA	PhMgBr	 10	129–132 (0.6)	67–68 (free base)	51

and cyclohexyl bromide showed a doublet at 0.79 ppm due to the β-methyl group. The integrity of the *N*-ethyl group was indicated by a three-proton triplet at 0.94 ppm (CH_2CH_3). An exchangeable one-proton singlet at 1.96 ppm (NH) and ir absorption at 3.1 μ demonstrated that the hydrazine was trisubstituted.

The NMR spectrum of hydrazine **10**, derived from PyrNO and phenylmagnesium bromide, exhibited some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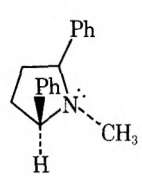
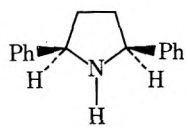
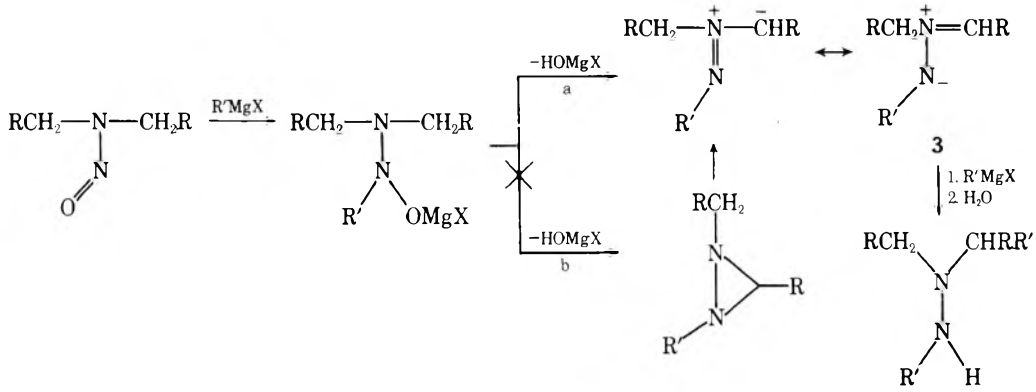

11


12

unusual chemical shifts for α protons. The α-methylene proton signals (CCl_4) were at 3.6 and 2.3 ppm, well separated from each other when compared to the signals from the methylene protons of pyrrolidine[11] and 2-phenylpyrrolidine, which appear at approximately the same position, 2.78–2.90 ppm. In addition, the benzylic methine proton signal was apparently shifted upfield, 3.6 ppm (cf. 2-phenylpyrrolidone and *cis*-2,5-diphenylpyrrolidine, 3.92 and 4.25 ppm, respectively in $CDCl_3$[11]) and overlapped with that of one of the α-methylene protons. An NMR spectrum of **10** in trifluoroacetic acid showed the α-methylene signals at approximately the same field, 3.9 ppm. The signal due to the benzylic methine proton was separate and shifted downfield to 4.9 ppm. This suggested that the lone pair(s) of electrons on nitrogen might be the source of this effect.

It has been demonstrated that electron lone pairs in six-membered rings are responsible for shielding adjacent protons.[7-10] The effect, however, has only recently been observed in five-membered rings, specifically, *N*-alkyl-α,α′-disubstituted pyrrolidines, by Breuer and Melumad.[11] They conclude that α protons of pyrrolidines are shielded when situated trans to an electron pair and cis to an *N*-methyl group. Therefore, *N*-methyl-*cis*-2,5-diphenylpyrrolidine (**11**), which should exist mainly in the transoid form, reflects this shielding effect in its benzylic chemical shift (3.34 ppm) when compared to *cis*-2,5-diphenylpyrrolidine (**12**) (4.25 ppm), which probably exists as a 1:1 mixture of invertomers.[11]

Scheme II
Reactions of Nitrosamines with Grignard Reagents



Although hydrazine **10** does not fall directly into the substitution pattern described by Breuer and Melumad, it becomes apparent, after examination of its NMR spectrum, that similar lone-pair effects predominate. Therefore, the preferred conformation of **10** can be assigned on the basis of nitrogen lone-pair shielding and as presented below. This result is not unexpected when nonbonded interactions are examined; however, this observation expands nitrogen lone-pair effects in establishing the stereochemistry of N-substituted pyrrolidines.

Mechanism Studies. The α-C substitution of Grignard reagents was observed for both cyclic and acyclic aliphatic nitrosamines. The structure of the products from the reaction between nitrosamines and Grignard reagents strongly suggests that an intermediate has been generated which permits nucleophilic attack on an activated α carbon.[12]

Two reaction paths are outlined in Scheme II which might account for observed products. Path b, which incorporates Wieland's diaziridine intermediate,[5] was the most easily accessible to experimental scrutiny.

Diaziridines have been proposed to undergo ring opening under thermal, acidic, and photochemical conditions to give dipolar species[13-17] which could react with nucleophiles such as Grignard reagents. 1-Cyclohexyl-2-ethyl-3-methyldiaziridine, a proposed intermediate[18] in the reaction of DENA with cyclohexylmagnesium bromide, was prepared from acetaldehydecyclohexylimine and *N*-chloroethylamine by the method of Schmitz and Schinkowski.[19] When this compound was treated with cyclohexylmagnesium bromide, 1-ethyl-1-(α-cyclohexylethyl)-2-cyclohexylhydrazine (**8**) was not detected by GC. Similarly 1-cyclohexyl-2-methyl-3-ethyldiaziridine[19] did not react with phenylmagnesium bromide under conditions in which Grignard reagents react with nitrosamines.

Reaction path a, which includes the direct formation of a dipolar species, is consistent with our observations using organolithium reagents.[2,3] However, with organomagnesium halides, elimination to give the azomethineimine proceeds readily during the reaction, whereas elimination after the addition of phenyl- or *tert*-butyllithium to the nitroso moiety requires protonation by water or ethanol. This difference apparently diminishes with some primary alkyllithium compounds, as in the reaction of DENA with methyllithium, where elimination during reaction can account for observed products.[20]

Azomethineimines such as **3** can undergo addition with appropriate dipolarphiles to form isolable adducts.[3,14,21-23] Attempts to trap such a species with norbornene[24] during the addition of phenylmagnesium bromide to DMNA were unsuccessful and no observable change in products was detected by NMR. It is interesting to note that the normally intense yellow color that appears during the addition of phenylmagnesium bromide to DMNA was absent when norbornene was present. Optimum yields (75–80%) of the α-C-alkylated trisubstituted hydrazine **7** were obtained after the addition of 2 mol of Grignard reagent (cf. Experimental Section).

Hydrazone Formation. The addition of benzylmagnesium chloride to DMNA gave, after work-up, benzaldehyde dimethylhydrazone in 33–37% yield. Three additional compounds, benzaldehyde 1-methyl-1-(β-phenylethyl)-hydrazone (**5**) and compounds tentatively identified as 1,1-dimethyl-2,2-dibenzylhydrazine and 1-methyl-1-(β-phenylethyl)-2-benzylhydrazine, were detected by gas chromatographic analysis.

The formation of hydrazones appears to be significant in the reaction of primary alkylmagnesium halides with nitrosamines.[5,20] Elimination to form a hydrazone is probably competitive with hydrogen abstraction from an α carbon. Cyclohexylmagnesium bromide, a secondary Grignard reagent, gave only a trace amount of cyclohexanone 1,1-dimethylhydrazone during reaction with DMNA.

Although phenylmagnesium bromide and aliphatic[25] nitrosamines form α-C phenylated products, substantial amounts of *N*-phenylhydrazines without substitution at an α carbon have been found.[5,20] Similarly, we have isolated 1,1-dimethyl-2-phenylhydrazine (20%) from the reaction of phenylmagnesium bromide and DMNA. This may have been formed via reduction of the adduct $Me_2NN(Ph)$-OMgBr by an additional 2 mol of the Grignard reagent.[26]

In addition to products which were discussed above, trace amounts of compounds which incorporated 3 mol of Grignard reagent were detected by mass spectroscopy and NMR.

Experimental Section

Infrared absorption spectra were determined using a Beckman IR5A spectrophotometer and ultraviolet absorption spectra were determined using a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. A Varian A-60 or Jeolco 100 nuclear magnetic resonance spectrometer was used to record the NMR spectra spectra. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D mass spectrometer.

Melting points were determined on a Mel-Temp or Fisher-Johns melting point apparatus. Both melting points and boiling points are uncorrected.

Gas chromatographic analyses were determined on an F & M Model 720 gas chromatograph. The column used was a 2-ft stainless steel column (0.5 in. o.d.) packed with 20% by weight DC-200 on Chromosorb W. The column was conditioned overnight at 220°. Analysis conditions were as follows: the helium flow rate was 60 ml/min and the temperature was programmed at 7.5°/min from 70 to 220° and then maintained isothermally. Microanalysis were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn.

Materials. The Grignard reagents[27] were standardized according to the method of Gilman.[28] The nitrosmines,[3] benzaldehyde

N,N-dimethylhydrazone,[29] 2-phenylpyrrolidine,[30] and 1-cyclohexyl-2-methyl-3-ethyldiaziridine[19] were prepared by previously described methods or purchased.

Reaction of Nitrosamines with Grignard Reagents. The reaction between DENA and cyclohexylmagnesium bromide is representative and will be described in detail. The product hydrazines were usually converted to the hydrochloride salt, which gave well-defined solids which were readily recrystallized.

1-Ethyl-1-(α-cyclohexylethyl)-2-cyclohexylhydrazine (8). A solution of DENA (8.16 g, 80 mmol) in 500 ml of anhydrous ether was cooled to 0° under an argon atmosphere. Cyclohexylmagnesium bromide (165 ml of a 1.95 *M* solution) was added slowly with stirring. The reaction mixture was stirred for 2 hr and then quenched with water. The ether layer was separated, dried, and evaporated in vacuo. The yellow liquid was distilled and the fraction boiling at 106–110° (0.25 mm) was collected (9.4 g, 47%). Redistillation at 0.35 mm gave pure 8: bp 122–124°; ir (neat) 3.10 (w), 6.9 (s), 7.3 (s), 11.25 (m), 11.82 (m), and 13.5 μ (m); NMR (100 MMz, CCl_4) δ 0.79 (d), 0.94 (t), 1.16 (br m), 1.64 (br m) (27 H), 1.96 (s, 1 H), and 2.1–2.7 (m, 4 H); mass spectrum (70 eV) *m/e* 252 (M^+, 10%), 169 (100%). The hydrochloride salt was recrystallized from 1-propanol: mp 159–160°; ir (Nujol) 3.74 (m), 6.30 (m), 7.25 (m), and 13.05 μ (w). Anal. Calcd for $C_{16}H_{33}N_2Cl$: C, 66.52; H, 11.51; N, 9.70. Found: C, 66.61; H, 11.37; N, 9.63.

1-Methyl-1-(cyclohexylmethyl)-2-cyclohexylhydrazine (7). A. Preparation. The reaction between DMNA (3.85 g, 52 mmol) and cyclohexylmagnesium bromide (208 mmol) gave 7 as a pale yellow oil. The product was distilled and the fraction which boiled at 113–115° (1.8 mm) was collected (5.7 g, 48%): ir (neat) 3.10 (w), 6.92 (s), 9.07 (m), 11.45 (m), and 12.7–13.1 μ (m); NMR (CCl_4) δ 0.8–2.2 (m, 24 H), 2.25 (s, 3 H), and 2.4–2.8 (br m, 1 H); mass spectrum (70 eV) *m/e* 224 (M^+, 18%), 141 (100%). The hydrochloride salt was recrystallized from ethyl acetate and sublimed (140°, 0.3 mm): mp 199–201°; ir (Nujol) 6.30 (m), 6.65 (m), 6.86 (s), 7.26 (s), and 12.13 μ (m). Anal. Calcd for $C_{14}H_{29}N_2Cl$: C, 64.46; H, 11.21; N, 10.74. Found: C, 64.57; H, 11.42; N, 10.61.

B. Stoichiometric Determination. DMNA (1.45 g, 19.6 mmol) and biphenyl (1.54 g, 10 mmol) were dissolved in 250 ml of anhydrous ether in a stirred flask fitted with a rubber septum and a 50-ml burette which contained 40 ml of cyclohexylmagnesium bromide (1.96 mequiv/ml). The system was maintained under an argon atmosphere and kept at 2–5° throughout the reaction.

The Grignard reagent was added slowly, and at each 5-ml interval an aliquot of approximately 1 ml was removed from the reaction mixture by syringe. The sample was quenched and 10–15 μl of the ether layer was analyzed by GC by comparing the ratio of dimethylnitrosamine and 1-methyl-1-(methylcyclohexyl)-2-cyclohexylhydrazine to the biphenyl standard. A ratio of 2:1 (cyclohexylmagnesium bromide:DMNA) was found to give the highest yield of 7 (75–80%).

1-Methyl-1-neopentyl-2-*tert*-butylhydrazine (6). The reaction between DMNA (2.5 g, 34 mmol) and *tert*-butylmagnesium bromide (130 mmol) gave 6 as a pale yellow oil. Distillation of 0.8 mm gave a fraction (2.9 g, 50%), bp 25–28°, which was redistilled: bp 30–32° (1.6 mm); ir (neat) 3.03 (w), 6.73 (s), 7.20 (m), 7.35 (s), and 11.46 μ (s); NMR (CCl_4) δ 0.95 (s, 9 H), 1.08 (s, 9 H) 1.90 (br s, 1 H), and 2.49 (s, 5 H); mass spectrum (70 eV) *m/e* 172 (M^+, 46%), 59 (100%). Anal. Calcd for $C_{10}H_{24}N_2$: C, 69.70; H, 14.04; N, 16.26. Found: C, 69.48; H, 13.88; N, 16.56.

***N*-Cyclohexylamino-2-cyclohexylpiperidine (9).** This compound was obtained from PipNA (3.42 g, 33 mmol) and cyclohexylmagnesium bromide (132 mmol): bp 124–127° (0.3 mm) (4.5 g, 52%); ir (neat) 3.1 (w), 6.89 (s), 7.27 (m), 8.98 (m), 11.25 (m), 11.55 (m), and 13.24 μ (m); NMR (CCl_4) δ 0.9–2.2 (br m) and 2.2–3.0 (br m) (31 H) and 3.4 (br m, 1 H); mass spectrum (70 eV) *m/e* 264 (M^+, 8%), 99 (100%). The hydrochloride salt was recrystallized from ethyl acetate–methanol: mp 216–217.5°; ir (Nujol) 3.12 (m), 6.41 (w), 6.88 (s), 7.24 (m), 11.42 (m), and 12.15 μ (m). Anal. Calcd for $C_{17}H_{32}N_2Cl$: C, 67.86; H, 11.05; N, 9.31. Found: C, 67.87; H, 10.89; N, 9.38.

***N*-Anilino-2-phenylpyrrolidine (10).** This compound was obtained from PyrNA (12.0 g, 120 mmol) and phenylmagnesium bromide (324 mmol), bp 129–132° (0.60 mm) (12 g, 51%). The viscous oil solidified and was recrystallized from heptane: mp 67–68°; ir (Nujol) 3.1 (w), 6.24 (s), 6.68 (s), 7.95 (m), 11.31 (m), 13.2–13.4 (s), 14.25 (s), and 14.45 μ (s); NMR (100 MHz, CCl_4) δ 1.88 (m) and 2.3 (m) (5 H), 3.6 (t overlapping m, 2 H), 3.84 (br s, 1 H), and 6.4–7.4 (m, 10 H); mass spectrum (70 eV) *m/e* 238 (M^+, 79%), 77 (100%). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.48; H, 7.67; N, 11.85.

Reaction of DMNA with Phenylmagnesium Bromide. DMNA (5.85 g, 79 mmol) and phenylmagnesium bromide (32 mmol) were reacted as described above. After quenching with water and drying over anhydrous potassium carbonate, the ether solution was cooled in a Dry Ice–acetone bath. Hydrogen chloride was passed into the solution until precipitation was complete. The ether was decanted and the oil was washed with ether and then an additional 100 ml of ether was added. A concentrated solution of sodium hydroxide was added dropwise to the stirred mixture cooled in ice until the water layer was strongly basic. The ether layer was separated, dried, and evaporated, and the residue was distilled. The fractions boiling at 71° (2.7 mm) and 149–151° (3.0 mm) were collected.

The higher boiling fraction was redistilled to give 1-methyl-1-benzyl-2-phenylhydrazine (**4**, 5.0 g, 30%): bp 135–136° (1.7 mm); ir (neat) 3.07 (w), 6.24 (s), 6.69 (s), 6.98 (m), 11.4 (m), 13.4 (s), and 14.45 μ (s); NMR (CCl_4) δ 2.20 (s, 3 H), 3.55 (s, 2 H), 4.10 (s, 1 H), and 6.5–7.3 (m, 10 H); mass spectrum (70 eV) *m/e* 212 (M^+, 52%), 121 (100%).

The hydrochloride salt was recrystallized from ethanol: mp 177.5–180.5°; ir (Nujol) 3.15 (m), 6.24 (m), 12.9 (m), 13.33 (m), and 14.43 μ (s). Anal. Calcd for $C_{14}H_{17}N_2Cl$: C, 67.60; H, 6.89; N, 11.26; Cl, 14.25. Found: C, 67.71; H, 6.82; N, 11.23; Cl, 14.34.

The lower boiling fraction (2.0 g, 19%) was identified as 1,1-dimethyl-2-phenylhydrazine: ir (neat) 3.08 (m), 6.24 (s), 13.30, and 14.45 μ (s); NMR (CCl_4) δ 2.34 (s, 6 H), 4.0 (br s, 1 H), and 6.7–7.3 (m, 5 H).

Benzaldehyde *N,N*-Dimethylhydrazone. Benzaldehyde *N,N*-dimethylhydrazone was produced in 33–37% yield (GC) from the reaction between DMNA and a fourfold excess of benzylmagnesium chloride. It was identical with a known sample.[29] Three additional products with longer retention times were detected by GC. These compounds were separated from benzaldehyde *N,N*-dimethylhydrazone by distillation. The fraction boiling at 130–133° (0.2 mm), which contained the three additional compounds, was chromatographed on silica gel (100–200 mesh) using the following solvent sequence: hexane, CCl_4, benzene, and $CHCl_3$.

Benzaldehyde 1-Methyl-1-(β-phenylethyl)hydrazone (5). The least polar of the three products was present in the chloroform fraction (vide supra) and solidified after evaporation of solvent, mp 43–44°. Recrystallization from water–1-propanol and sublimation (55°, 0.55 mm) gave 5 as a white solid: mp 45–45.5°; ir (neat) 6.27 (m), 6.41 (m), 9.55 (m), 13.30 (s), and 14.40 μ (s); NMR (100 MHz, CCl_4) δ 2.78 (s) overlapping 2.81 (t) (5 H), 3.42 (m, 2 H), and 7.0–7.5 (m, 11 H); mass spectrum (70 eV) *m/e* 238 (M^+, 87%), 147 (100%). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.32; H, 7.69; N, 11.88.

1-Cyclohexyl-2-ethyl-3-methyldiaziridine. According to the method of Schmitz and Schinkowski[19] for the synthesis of diaziridines, a solution of acetaldehydecyclohexylimine[31] (15 g, 0.12 mol) and cyclohexylamine (10 g, 0.12 mol) in 100 ml of ether was cooled in an ice bath with stirring. *N*-Chloroethylamine[19] (0.12 mol) in 130 ml of ether was added and the reaction mixture was stirred overnight at room temperature. The precipitate of cyclohexylamine hydrochloride was filtered with suction and the solution was concentrated and filtered until no precipitate formed. The solution was extracted with aqueous saturated sodium bicarbonate, dried, and concentrated to an oil. Fractional distillation gave unreacted imine and amine at 30–40° (10 mm). The pressure was then reduced to 0.3 mm and the fraction boiling at 75–78° was collected. Further purification via the hexacyanoferrate salt[16b] and GC gave 1-cyclohexyl-2-ethyl-3-methyldiaziridine as a colorless oil: ir (neat) 6.90 (m), 7.12 (m), 9.09 (m), 11.19 (m), and 12.91 μ (w); NMR (neat) δ 0.9–2.1 (m), 1.30 (d), and 2.1–2.7 (m); mass spectrum (70 eV) *m/e* 168 (M^+, 11%), 71 (100%). Anal. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.64. Found: C, 70.95, 71.01; H, 11.67, 11.80; N, 16.15, 16.32.

Addition of Cyclohexylmagnesium Bromide to 1-Cyclohexyl-2-ethyl-3-methyldiaziridine. A solution containing 50 ml of ether and 200 mg (1.2 mmol) of 1-cyclohexyl-2-ethyl-3-methyldiaziridine was cooled to 0° under a nitrogen atmosphere. Cyclohexylmagnesium bromide (6.0 mmol) in 15 ml of ether was added dropwise to this solution. After 15 min the solution was quenched with water, and the ether layer was separated, dried, and evaporated in vacuo. Gas chromatographic analysis of the liquid residue showed only starting material and no 1-ethyl-1-(α-cyclohexylethyl)-2-cyclohexylhydrazine when compared to a standard sample.

Addition of Phenylmagnesium Bromide to Cyclohexyl-2-methyl-3-ethyldiaziridine. A solution of 1.89 g (11.25 mmol) of 1-cyclohexyl-2-methyl-3-ethyldiaziridine in 75 ml of anhydrous

ether was cooled to 0–5° under a nitrogen atmosphere. To this solution was added 45 mmol of phenylmagnesium bromide in 50 ml of ether with stirring. After 1 hr the solution was quenched with water. The ether layer was separated and dried over anhydrous potassium carbonate and then evaporated in vacuo. The liquid residue was identical with starting material.

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Registry No.—**4**, 54193-54-3; **4** HCl, 54193-55-4; **5**, 54193-56-5; **6**, 54193-57-6; **7**, 54193-58-7; **7** HCl, 54193-59-8; **8**, 54193-60-1; **8** HCl, 54193-61-2; **9**, 54193-62-3; **9** HCl, 54193-63-4; **10**, 54193-64-5; DMNA, 62-75-9; DENA, 55-18-5; PipNA, 100-75-4; PyrNA, 930-55-2; PhBr, 108-86-1; $PhCH_2Cl$, 100-44-7; *t*-BuBr, 507-19-7; $C_6H_{11}Br$, 108-85-0; 1-cyclohexyl-2-ethyl-3-methyldiaziridine, 54193-65-6; acetaldehydecyclohexylimine, 1193-93-7; cyclohexylamine, 108-91-8; *N*-chloroethylamine, 24948-82-1.

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Reductive Cyclization of Aminobenzoic Acids

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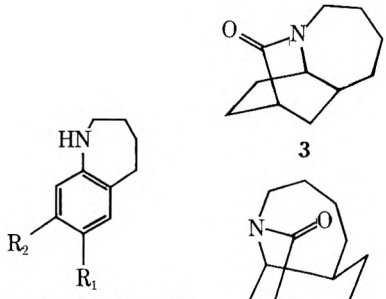
Hydrogenation of 3- and 4-aminobenzoic acids over a ruthenium catalyst at 150° under 1600 psig of hydrogen gave fair yields of the bicyclic lactams **8** and **6**, respectively. Cyclization also occurs on hydrogenation of 3-methyl-4-aminobenzoic acid, but on hydrogenation of the 3,4-diaminobenzoic acid one of the amine groups is lost. The 4-amine is lost twice as readily as is the 3-amine. With the 3-hydroxy-4-aminobenzoic acid complete hydrogenolysis of the amine group occurs.

It was previously found that on hydrogenation of the carboxybenzazepines **1**[1] and **2**[2] good yields were obtained of the cyclic lactams **3** and **4**, respectively. Since this reaction was of general synthetic interest, the hydrogenation of other aminobenzoic acids was also run to determine whether the simpler bicyclic lactams would be formed.



1, $R_1 = -CO_2H$; $R_2 = H$
2, $R_1 = H$; $R_2 = -CO_2H$

3

4

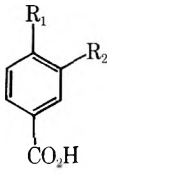
Hydrogenation of 4-aminobenzoic acid (**5**) occurred readily in methanol over a ruthenium on charcoal catalyst at 160° and 1600 psig to give a 40–50% yield of isoquinuclidone (**6**). 3-Aminobenzoic acid (**7**), on hydrogenation under these same conditions, afforded a 35–45% yield of the bicyclo[3.2.1]lactam, **8**, along with a small amount of another material.

The mass spectrum of **6** was analogous to that of 2-piperidone[3] with fragmentation occurring by the successive loss of the two C_2H_4 bridges giving a base peak at mass 69 ($M - C_4H_8$) and a strong peak at mass 97 ($M - C_2H_4$). Fragmentation of **8** followed the pattern observed in the mass spectrum of ε-caprolactam[4] with a base peak at mass 83 ($M - C_2H_4N$) and no other large peaks present. The minor component obtained on hydrogenation of **7** had a mass spectrum which was unlike that of **8** but similar to that of *N*-methylcaprolactam,[4] a base peak at mass 97 ($M - C_2H_4N$) and strong peaks at mass 110 ($M - CH_3N$) and 96 ($M - C_2H_5N$). On this basis, this material was tentatively identified as the *N*-methyllactam, **9**.

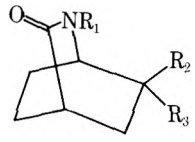
Hydrogenation of 3-methyl-4-aminobenzoic acid (**10**) gave four compounds in 8.5, 5, 65, and 10% yields, respectively, as determined by gas chromatographic analysis

(GC). GC–MS analysis of this reaction mixture showed that the first two components each had a molecular ion at mass 153, a base peak at mass 83 (69 + 14) and a strong peak at mass 111 (97 + 14). Thus, these materials were considered to be the *exo*- and *endo*-*N*-methyllactams, **11** and **12.** The second two compounds each had a molecular ion at mass 139, a base peak at mass 69 and a strong peak at mass 97 as expected for the fragmentation of the [2.2.2] bicyclic lactams **13** and **14.** Since there was only a small peak at mass 111 in the spectra of these compounds, the loss of the substituted bridge must occur more readily than the cleavage of the unsubstituted one. As it is known that hydrogenation of polysubstituted benzenes over ruthenium gives predominantly the all cis product,[5] the major component in this reaction mixture was assigned the exo configuration, **13.**

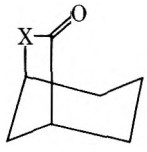
This obtaining of an exo:endo isomer mixture was contrary to a recent report[6] in which it was found that only the exo isomer was obtained from the reductive cyclization of substituted aminobenzoic esters. To clarify this discrepancy, **10** was hydrogenated under the conditions used in this latter study (RuO_2, ethanol, 125°, and 1900 psig).[6] The product from this reaction was shown by GC analysis to be composed of a single compound, presumably the exo isomer,[5] in an 80% yield. Further NMR and mass spectral analysis showed this material to be the *N*-ethyllactam, **15.** Thus, at the lower temperature endo isomer formation does not take place.



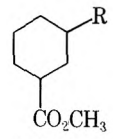
5, $R_1 = NH_2$; $R_2 = H$
7, $R_1 = H$; $R_2 = NH_2$
10, $R_1 = NH_2$; $R_2 = CH_3$
16, $R_1 = R_2 = NH_2$
18, $R_1 = NH_2$; $R_2 = OH$



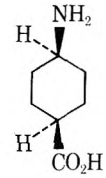
6, $R_1 = R_2 = R_3 = H$
11, $R_1 = R_2 = CH_3$; $R_3 = H$
12, $R_1 = R_3 = CH_3$; $R_2 = H$
13, $R_1 = R_3 = H$; $R_2 = CH_3$
14, $R_1 = R_2 = H$; $R_3 = CH_3$
15, $R_1 = C_2H_5$; $R_2 = CH_3$; $R_3 = H$



8, X = NH
9, $X = NCH_3$
19, X = O



17, R = H
20, R = OH



21

Attention was then shifted to the hydrogenation of 3,4-diaminobenzoic acid (**16**) to determine which of the two possible lactams would be formed preferentially. From this reaction an 80% yield of a clear viscous oil was obtained. This oil was shown by GC–MS analysis to be composed of 8% of **9,** 56% of **8,** and 32% of **6,** along with a small amount of methyl cyclohexanecarboxylate (**17**). The complete absence of amine substituents on the bicyclic lactams was unexpected since hydrogenolysis of aromatic amines does not normally occur over ruthenium catalysts.[7,8] About the only exception to this generalization is the reported cleavage of the dialkylamine group on hydrogenation of *p*-dialkylaminoanilines over ruthenium.[9]

There were present in **16** some factors which could have facilitated this amine hydrogenolysis. The para carboxy group was probably influential since twice as much of the 4-amine was lost than was the 3 substituent. This cannot be the only influence, though, since more 4-amine cleavage occurred with **16** than was observed on hydrogenation of **5** or **10.** The only difference between **16** and **5** or **10** is the presence in **16** of a substituent ortho to the amine group which is capable of hydrogen bonding with it. The importance of this factor was further illustrated in the hydrogenation of 4-amino-3-hydroxybenzoic acid (**18**).

On attempted reductive cyclization of **18**[10] a 92% yield of product was recovered. The infrared spectrum of this material showed no lactam carbonyl absorption but instead had a strong lactone and/or ester carbonyl band at 1725 cm^{-1}. The product was shown by GC–MS analysis to be composed primarily of two species in 15 and 65% yields, respectively. The mass spectrum of the minor component had the molecular ion peak at mass 126, a typical lactone peak[13] at M − CH_2CO_2H (mass 67) as well as a peak at M − C_3H_7 (mass 84) which is a characteristic caprolactam cleavage.[13] On the basis of this spectrum and comparison with an authentic sample[14] the minor component was assigned structure **19.** The major component in this reaction mixture was identified as methyl 3-hydroxycyclohexanecarboxylate (**20**) again by comparison with a known sample.[15] The hydrogenolysis of the amine rather than the hydroxy group on hydrogenation of **18** was contrary to previous reports concerned with the competitive cleavage of aromatic oxygen and nitrogen containing functional groups over ruthenium catalysts.[9,16] In the present instance, though, the loss of the amine is facilitated by the presence of the para carboxy group and by the ortho OH, with hydrogen bonding proably an important factor in the latter instance.

While this reaction is not of general synthetic utility, it was still of interest to determine whether the cyclization occurred by a thermal process after the ring was hydrogenated or if it took place as the substrate was being desorbed from the catalyst but before it could attain the stable boat conformation. Since the reaction conditions used for the reductive cyclization were milder than those commonly used for the thermal cyclization of aminocyclohexanecarboxylic acids,[17–19] it was felt that the latter explanation seemed more valid. To determine if this assumption were correct, samples of the known *cis*-4-aminocyclohexanecarboxylic acid (**21**) were heated under reductive cyclization conditions but in the absence of any metal catalyst. The sample which was heated at 120° was recovered unchanged while that heated at 150° was about 50% cyclized to **6.** Thus, at the lower temperature cyclization to the bicyclic lactam must occur in conjunction with ring hydrogenation while at the higher temperature no definitive conclusion can be reached. It would seem reasonable, though, that since at 120° cyclization must occur during substrate desorption, this process must also take place, at least to some extent, at 150° as well.

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. Microanalyses were run either with an F & M Model 185 automated CHN analyzer or by Micro Analysis, Inc., Wilmington, Del.

Infrared spectra were recorded on a Beckman IR-10 spectrophotometer in chloroform solutions. Nuclear magnetic resonance spectra were obtained on a Varian A-60A instrument using $DCCl_3$ as solvent and Me_4Si as the internal standard. Vapor phase chromatographic analyses were run using an F & M Model 720 chromatograph with either a 6 ft × 0.25 in. 20% Carbowax 20 on Chromosorb P or a 6 ft × 0.25 in. 25% SE-30 on Gas Chrom P column. Mass spectra were run on a Perkin-Elmer 270 gas chromatograph–mass spectrometer (GC–MS) coupled to a Varian 100 MS data system using a source temperature of 200°. The spectra were run at 70 eV. The gas chromatograph was a Perkin-Elmer 900 instrument with either a 16 ft × 0.125 in. 2% Carbowax 20M on Gas Chrom P or a 16 ft × 0.125 in. 2% GE-SF-96 on Chromosorb Q column. The

hydrogenations were run in an Autoclave Engineers 300-ml Magne-stir Autoclave.

General Hydrogenation Conditions. A solution of 10 g of the aminobenzoic acid in 150 ml of methanol was hydrogenated over 10 g of 5% ruthenium on charcoal under 1600 psig of hydrogen at 160° for 24 hr. After cooling, the catalyst was removed by filtration and washed thoroughly with more methanol. Evaporation of the solvent gave the crude product.

2-Azabicyclo[2.2.2]octan-3-one (6) was obtained from the hydrogenation of 4-aminobenzoic acid (**5**) in 40–50% yield after chromatography of the reaction mixture on a silica gel column (5% MeOH in $CHCl_3$) and purification by dissolution in water, extraction with ether, and evaporation of the water (in vacuo) to give **6**: mp 192–193° after recrystallization from hexane (lit.[17] mp 197–198°); ir 3420 and 3200 (NH) and 1667 cm^{-1} (C=O); NMR δ 7.8 (s, 1, NH), 3.65 (s, 1, NCH), 2.5 (s, 1, C(=O)CH), and 1.71 (s, 8, CH_2); MS *m/e* (rel intensity) 67 (48), 68 (47), 69 (100), 82 (22), 96 (30), 97 (54), and 125 (53) molecular ion.

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.16; H, 8.56; N, 10.92.

6-Azabicyclo[3.2.1]octan-7-one (**8**) was obtained in 35–45% yield from 3-aminobenzoic acid (**7**) on recrystallization of the crude reaction mixture from hexane: mp 191–192°; ir 1690 cm^{-1} (C=O); NMR δ 7.12 (s, 1, NH), 3.77 (s, 1, NCH), 2.36 (s, 1, C(=O)CH), and 1.68 (m, 8, CH_2); MS *m/e* (rel intensity) 67 (28), 82 (28), 83 (100), 96 (27), and 125 (30) molecular ion.

Anal: Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.45; H, 9.16; N, 10.97.

GC–MS analysis of the reaction mixture showed the presence of about 4% of another material tentatively identified as the *N*-methyllactam, **9**: MS *m/e* (rel intensity) 68 (23), 83 (11), 96 (69), 97 (100), 110 (96), and 139 (58) molecular ion.

The hydrogenation of 3-methyl-4-aminobenzoic acid (10) gave a mixture of products which by GC–MS were identified as **11** (9%) [MS *m/e* (rel intensity) 55 (21), 82 (54), 83 (100), 110 (20), 111 (34), and 153 (36) molecular ion], **12** (5%) [MS 55 (23), 82 (47), 83 (100), 110 (19), 111 (33), and 153 (39) molecular ion], **13** (65%) and **14** (10%) [MS 55 (21), 68 (51), 69 (100), 96 (22), 97 (49), and 139 (22) molecular ion]. A small sample of pure **13** was isolated as a thick oil by chromatography on silica gel (2% MeOH in $CHCl_3$): NMR δ 7.95 (s, 1, NH), 3.3 (d, 1, NCH), 2.4 (s, 1, C(=O)CH), 2.1–1.8 (m, 7), and 0.92 (d, 3, CCH_3); MS 55 (27), 68 (48), 69 (48), 69 (100), 96 (26), 97 (52), and 139 (35) molecular ion.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 9.95. Found: C, 69.19; H, 9.54; N, 9.95.

In addition a fraction composed of almost equal amounts of **13** and **14** was also obtained.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 9.95. Found: C, 69.38; H, 9.36; N, 10.04.

2-Ethyl-6-methyl-2-azabicyclo[2.2.2]octan-3-one (15). A solution of 1 g of **10** in 75 ml of ethanol was hydrogenated over 1 g of RuO_2 under 1900 psig of hydrogen at 125° for 24 hr.[6] The catalyst was removed and the solvent evaporated to give 1.2 g of the crude product which was shown by gas chromatographic or GC–MS analysis to be composed of about 80% of one component which was neither **11**, **12**, **13** nor **14**. On distillation a pure material was obtained which was identified as the *N*-ethyllactam, **15**: bp 74–76° (0.3 mmHg); NMR δ 3.0–4.0 (m, 2, $-CH_2CH_3$), 3.3 (s, 1, NCH), 2.51 (s, 1, C(=O)CH), 1.12 (t, 3, CH_2CH_3), and 0.93 (d, 3, CCH_3); MS *m/e* (rel intensity) 55 (24), 56 (20), 96 (37), 97 (100), 124 (22), 125 (30), and 167 (34) molecular ion.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.53; H, 10.64; N, 8.08.

The hydrogenation of 3,4-diaminobenzoic acid (16) using the general conditions described above gave a mixture of products which was shown by gas chromatographic analysis to be composed of 8% of **9**, 56% of **8**, and 32% of **6**. In addition a small amount of methyl cyclohexanecarboxylate, identified by comparison with an authentic sample, was also formed.

Hydrogenation of 3-Hydroxy-4-aminobenzoic Acid (18). Sublimed 3-hydroxy-4-nitrobenzoic acid[11] was hydrogenated under the general reaction conditions described above. An initial, rapid uptake of 3 equiv of hydrogen indicated that this material was converted into **18**[12] before the reactor began heating up to the temperature required for ring hydrogenation. Gas chromatographic analysis of the product showed the presence of two major components in 15 and 65% yields. GC–MS comparison with a sample of the known material[14] indicated that the smaller of these was the lactone, **19**: MS *m/e* (rel intensity) 54 (89), 55 (48), 67 (100), 70 (38), 82 (43), 83 (37), 84 (69), and 126 (2) molecular ion. The major component was identified as methyl 3-hydroxycyclohexanecarboxylate (**20**) by comparison with an authentic sample.[15] MS 53 (18), 54 (29), 55 (82), 56 (13), 57 (71), 59 (23), 67 (26), 69 (26), 70 (29), 71 (11), 74 (12), 78 (11), 79 (27), 80 (44), 81 (100), 82 (17), 83 (30), 84 (50), 87 (52), 88 (49), 97 (38), 98 (41), 99 (25), 109 (19), 116 (37), 126 (29), 127 (12), 129 (14), 140 (5), and 158 (4) molecular ion.

Methyl 3-Hydroxycyclohexanecarboxylate (20). A solution of 20 g of 3-hydroxybenzoic acid in 150 ml of methanol was hydrogenated over 5 g of 5% ruthenium on charcoal under 1700 psig of hydrogen at 140° for 18 hr. After cooling, the catalyst was removed by filtration and the solvent evaporated to give 19 g of crude product which on distillation gave 13 g of **20**: bp 95° (1.1 mmHg); $n^{25}D$ 1.4369 [lit.[15] bp 134–146° (19 mmHg); $n^{25}D$ 1.4667]; ir 3400 (OH) and 1725 cm^{-1} (C=O); NMR δ 4.0 (s, 1, HOC*H*) and 3.67 (s, 3, CO_2CH_3); MS *m/e* (rel intensity) 53 (20), 54 (45), 55 (82), 56 (12), 57 (58), 59 (25), 67 (44), 68 (14), 69 (24), 70 (33), 71 (10), 74 (10), 77 (15), 78 (16), 79 (35), 80 (46), 81 (100), 82 (23), 83 (31), 84 (46), 87 (51), 88 (34), 97 (34), 98 (49), 99 (18), 100 (13), 108 (16), 109 (11), 116 (17), 126 (20), 127 (11), 129 (10), and 140 (4).

6-Oxabicyclo[3.2.1]octan-7-one (19). A solution of 5 g of **20** in 50 ml of 10% sodium hydroxide was stirred at room temperature overnight. The resulting mixture was extracted with ether. The aqueous phase was acidified with concentrated HCl and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated to give about 4 g of a thick viscous oil which on heating in a short path distillation column to about 200° under vacuum (20 mm) resulted in the distillation of a waxy semisolid material identified as **19**:[14] ir 1725 cm^{-1} (C=O); nmr δ 4.83 (m, 1, OCH) and 2.63 (m, 1, O=CCH); MS *m/e* 54 (92), 55 (45), 67 (100), 70 (35), 82 (50), 83 (34), 84 (63), and 126 (2) molecular ion.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.40; H, 8.22.

Thermal Cyclization of *cis*-4-Carboxycyclohexylamine (21). A 1.09-g sample of **21**, prepared by the hydrogenation of *p*-aminobenzoic [mp 299–300° (lit.[19] mp 303°)] was heated in 75 ml of methanol at 120° under 1900 psig of hydrogen for 24 hr. On evaporation of the solvent, 1 g of residue was recovered which was shown to be only unreacted **21** by infrared spectral comparisons.

When this reaction was repeated at 150° 1 g of residue was again obtained. This was washed with chloroform and the insoluble material removed by filtration. This residue, which was the starting material, **21**, weighed 0.5 g. Evaporation of the chloroform gave 0.57 g of **6**, identified by infrared spectral comparison.

Registry No. —**5**, 150-13-0; **6**, 3306-69-2; **7**, 99-05-8; **8**, 6142-56-9; **9**, 24173-53-3; **10**, 2486-70-6; **11**, 53862-59-2; **12**, 53862-60-5; **13**, 53862-61-6; **14**, 53906-41-5; **15**, 53862-62-7; **16**, 619-05-6; **18**, 34021-72-2; **19**, 4350-83-8; **20**, 37722-82-0; **21**, 3685-23-2; 3-hydroxy-4-nitrobenzoic acid, 619-14-7; 3-hydroxybenzoic acid, 99-06-9.

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The Effect of Structural Rigidity on the Photoreduction of Imines[1]

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Upon irradiation in 2-propanol, $\Delta^{1,9}$-octahydroquinoline (**1**) gives *trans*-decahydroquinoline, 2-methyl-Δ^1-piperideine (**2**) gives 2-methylpiperidine, *N*-isopropylidenepropylamine (**7**) gives *N*-propyl-2-aminopropane, and 2-phenyl-Δ^1-pyrroline (**8**) gives 2,2′-diphenyl-2,2′-bipyrrolidine (**9**). Comparative photolyses of **2** and **7** and **8** and *N*-benzylidenecyclohexylamine (**10**) show that cyclic imines **2** and **8** do not show enhanced reactivity toward photochemical hydrogen abstraction reactions when compared with acyclic analogs. It is concluded that the low reactivity of the carbon–nitrogen double bond toward photochemical hydrogen abstraction reactions is not due only to rapid radiationless decay by twisting about the carbon–nitrogen bond.

Among the most common reactions of compounds containing the carbonyl chromophore, upon irradiation in solvents containing readily abstractable hydrogens, is photoreduction.[2] Although the photochemical reactions of compounds containing a carbon–nitrogen double bond have received less attention than those containing a carbon–oxygen double bond, reactions analogous to the photoreduction of the carbonyl group have been observed.[3-5] While a mechanism similar to that postulated for ketone photoreduction can be written for imines (Scheme I), the actual mechanism has been demonstrated[3,4] not to involve an excited state of the imine at all. Instead, a carbonyl compound (as added sensitizer, from hydrolysis of the imine, or as a photogenerated species), after being excited to its triplet state, abstracts a hydrogen atom to produce a ketyl radical (Scheme II). This radical then transfers a hydrogen atom to the imine to generate an α-aminoalkyl radical (eq 9). Products are then produced as shown in eq 4 and 5.

Scheme I

$$R_2C{=}NR \xrightarrow{h\nu} R_2C{=}NR^* \quad (1)$$

$$R_2C{=}NR^* + CH_3CH_2OH \longrightarrow R_2\dot{C}{-}NHR + CH_3\dot{C}HOH \quad (2)$$

$$R_2C{=}NR^* \longrightarrow R_2C{=}NR \quad (3)$$

$$2R_2\dot{C}{-}NHR \longrightarrow R_2C(NHR)-(NHR)CR_2 \quad (4)$$

$$2R_2\dot{C}{-}NHR \longrightarrow R_2CHNHR + R_2C{=}NR \quad (5)$$

Scheme II

$$R_2C{=}NR + H_2O \rightleftharpoons R_2CO + H_2NR \quad (6)$$

$$R_2CO \longrightarrow R_2CO^* \quad (7)$$

$$R_2CO^* + CH_3CH_2OH \longrightarrow R_2\dot{C}OH + CH_3\dot{C}HOH \quad (8)$$

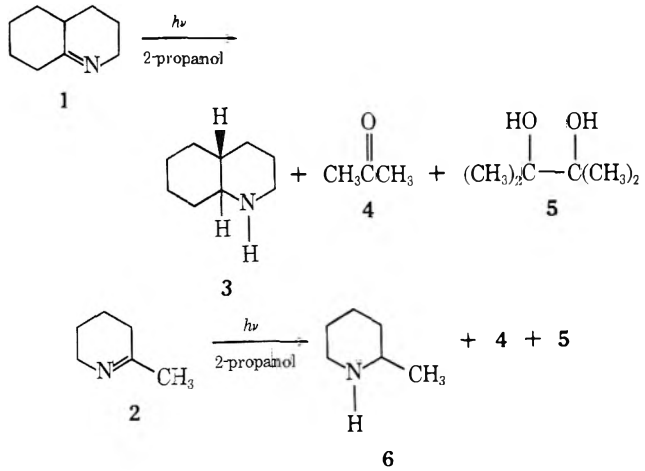
$$R_2\dot{C}OH + R_2C{=}NR \longrightarrow R_2CO + R_2\dot{C}NHR \quad (9)$$

There are several possible reasons for the low reactivity of excited imines toward hydrogen abstraction reactions. First, the rate of hydrogen abstractions by the excited imine (eq 2) may be slow, as postulated by Fischer.[3] Alternatively, it may be that the rate of radiationless decay of the excited imine (eq 3) is much faster than hydrogen abstraction (eq 2). Padwa and coworkers[4,6,7] have postulated the latter explanation and have further suggested that twisting about the carbon–nitrogen double bond is responsible for this rapid radiationless decay. The result of such twisting, syn–anti isomerization, is a known photochemical reaction of the carbon–nitrogen double bond,[8-11] lending support to this decay mechanism.

We report here our investigations of photochemical reductions of some cyclic imines in 2-propanol. The incorporation of the carbon–nitrogen double bond into a ring system should prevent twisting as a deactivation mechanism and might therefore allow observation of photoprocesses normally obscured by syn–anti isomerization.

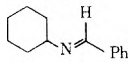
Results and Discussion

Our initial studies focused on $\Delta^{1,9}$-octahydroquinoline (**1**)[12] and 2-methyl-Δ^1-piperideine (**2**).[13] Upon irradiation in reagent 2-propanol, **1** produced *trans*-decahydroquinoline (**3**) in 98% yield, acetone (**4**), and 2,3-dimethyl-2,3-butanediol (**5**). No *cis*-decahydroquinoline was detected by



GC analysis of the photolysis solution. Under similar conditions, **2** produced 2-methylpiperidine (**6**) in 72% yield, along with **4** and **5**. In addition, small amounts of several unidentified products, with longer GC retention times, were observed. The production of acetone in the photolysis suggested that this compound might be acting as a chemical sensitizer[3,4] for the reaction. That this was indeed the case was confirmed by several experiments. The disappearance of **2** accelerated as the reaction proceeded. Thus in one experiment, ca. 16% of **2** had reacted after 30 min of irradiation and ca. 50% had reacted after 60 min. This is attributed to increasing chemical sensitization by acetone as its concentration increased throughout the course of the reaction. Addition of a large molar excess of acetone drastically accelerated the rate of reduction. Finally, we found the reagent 2-propanol contained ca. 0.002 *M* acetone impurity. By careful purification it was possible to decrease the acetone concentration to less than 10^{-4} *M*. Upon comparative irradiation in the purified and in reagent 2-propanol, **6** was produced more rapidly in the latter solvent (see Table I).

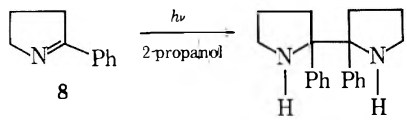
Table I
Amounts of Photolysis Products

Compd	Run[a]	Acetone concn, *M*	Photoproduct, mmol
2	A	$<10^{-4}$	0.033
2	A	0.002	0.038
 **7**	A	$<10^{-4}$	0.202
8	B	$<10^{-4}$	0.125
 **10**	B	$<10^{-4}$	0.122

[a] In each run, samples of imine in 2-propanol were irradiated in parallel and concentrations were adjusted to ensure equal light absorption at the beginning of the run.

It was felt that the best evidence for the effect of twisting on the decay processes of imines could be obtained from a comparison of the relative quantum yields of photoreduction of a cyclic imine and an acyclic model. *N*-Isopropylidenepropylamine[14] (**7**) was chosen as an acyclic model for **2**. Upon irradiation in 2-propanol, **7** produced *N*-propyl-2-aminopropane in 88% yield. When **2** and **7** were irradiated in parallel, **7** was found to react faster than **2** (Table I). However, **7** was observed to undergo substantial hydrolysis to acetone and 1-aminopropane owing to traces[15] of water in the photolysis solvent. Thus, chemical sensitization by acetone probably accounts for the enhanced rate of reaction of **7**.

To avoid the problem of chemical sensitization by traces of acetone, the photochemical behavior of 2-phenyl-Δ^1-pyrroline[17,18] (**8**) was investigated. Upon irradiation in 2-propanol, **8** produced 2,2′-diphenyl-2,2′-bipyrrolidine[19] (**9**) in 87% yield. The identity of **9** was established by comparison of its melting point and spectral properties with those of a sample prepared by the aluminum amalgam[20] reduction of **8**. Comparison with an acyclic model compound, *N*-benzylidenecyclohexylamine (**10**), previously studied by Padwa and coworkers,[4] does not show an enhanced reactivity toward photoreduction for **8**[21] (Table I).



8 **9**

These results indicate that imines with the carbon–nitrogen double bond in a five- or six-membered ring, like acyclic imines, are much less reactive toward photochemical hydrogen abstraction than are carbonyl compounds. Evidence[23] from alkene photochemistry indicates that confinement of a carbon–carbon double bond in a six-membered ring is sufficient to slow the rate of cis–trans isomerization enough to allow the di-π-methane rearrangement to occur via the triplet state. However, evidence[24] from the ionic addition of alchols to cyclic alkenes upon irradiation indicates that cyclohexenes are able to twist enough for this reaction to occur, while cyclopentenes are unable to attain a sufficient degree of twisting. Thus, while the evidence is somewhat inconclusive on the ability of **2** to undergo radiationless decay by twisting, **8** is unable to twist to a significant degree. Therefore, the low reactivity of **8** must be due to factors other than rapid radiationless decay by twisting. Other possible explanations for this low reactivity include a slow rate of hydrogen abstraction (eq 2), or other rapid decay processes.

Finally, it is interesting to note that the α-aminoalkyl radicals derived from **1**, **2**, and **7** undergo disproportionation (eq 5), while the radical derived from **8** couples instead (eq 4). This is in accord with results observed with carbon radicals, which have demonstrated that delocalization of the unpaired electron favors coupling over disproportionation.[25]

Experimental Section[26]

$\Delta^{1,9}$-Octahydroquinoline (**1**),[12] λ_{max} (2-propanol) 244 nm (ϵ 230), 2-methyl-Δ^1-piperideine (**2**),[13] λ_{max} (2-propanol) 237 nm (ϵ 180), *N*-isopropylidenepropylamine (**7**),[14] λ_{max} (2-propanol) 235 nm (ϵ 210), 2-phenyl-Δ^1-pyrroline (**8**),[17] λ_{max} (2-propanol) 242 nm (ϵ 15,600), benzaldehyde *N*-cyclohexylimine (**10**)[4], λ_{max} (2-propanol) 244 nm (ϵ 17,600), and *N*,*N*′-dicyclohexyl-1,2-diphenyl-1,2-diaminoethane[20] were prepared by literature procedures.

***N*-Propyl-2-aminopropane.** This secondary amine was prepared by a variation of the procedure of Norton et al.[14] A solution of 9.9 g (0.10 mol) of **7** and 0.18 g of platinum oxide in 50 ml of anhydrous methanol was hydrogenated in a Parr hydrogenator at an initial pressure of 38 psi. After 15 min no further pressure drop was evident. The reaction was stopped after 40 min and the catalyst removed by filtration. The solvent was removed by distillation through a 12-in. Vigreux column and the residue was distilled through a 4-in., helices-packed column to give 4.4 g (44%) of amine, bp 89–90° (ca. 630 mm).

2,2′-Diphenyl-2,2′-bipyrrolidine (9). The general procedure of Jaunin[20] was used. To a solution of 1.00 g (0.0069 mol) of **8** in 150 ml of ether was added 0.38 g (0.014 mol) of aluminum foil, 0.031 g of mercuric chloride,[27] and 1 ml of water. After stirring overnight, the solids were removed by filtration and the solvent was removed in vacuo. The residue was recrystallized from ethanol–water to give 0.42 g (41%) of **9**:[19] mp 130–131°; NMR (CCl_4) τ 3.07 (s, 10 H, aromatics), 6.8–8.8 (series of overlapping multiplets, 14 H); ir (CCl_4) 3400, 3300, 3070, 2980, 1445, 1320, 1095, 1065, 1030 cm^{-1}; λ_{max} (2-propanol) 252 nm (ϵ 480), 258 (490), 264 (380), and 269 (shoulder, 240). Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58. Found: C, 82.21; H, 8.13; N, 9.60.

Purification of 2-Propanol for Photolysis. Reagent 2-propanol was found by GC and uv analysis to contain ca. 2×10^{-3} *M* acetone. After reflux over sodium borohydride followed by distillation from calcium hydride with a 14-in., helices-packed column, less than 1×10^{-4} *M* acetone was detectable.

Preparative Photolysis of $\Delta^{1,9}$-Octahydroquinoline (1). A solution of 1.02 g (0.00745 mol) of **1** in 300 ml of 2-propanol was purged with nitrogen and irradiated through quartz with a Hanovia 450-W high-pressure mercury lamp for 4 hr. Analysis by GC (6 ft × 0.125 in., 10% UCW-982 silicone gum rubber on 60/80 Chromosorb W at 120°) showed the reaction to be completed at this point. Distillation yielded 1.01 g (98%) of photoproduct, bp 76–78° (6 mm). The photoproduct was identified as **3** by comparison of its ir and NMR spectrum and GC retention time with those of an authentic sample. None of the cis isomer was detectable by GC.

Preparative Photolysis of 2-Methyl-Δ^1-piperideine (2). A solution of 3.0 g (0.031 mol) of **2** in 525 ml of reagent 2-propanol was purged with nitrogen and irradiated through quartz with a Hanovia 450-W high-pressure mercury lamp. Ice-bath cooling was used to maintain the temperature of the solution at 10–20°. After 8 hr of irradiation, GC analysis (UCW column described above, temperature-programmed run, 76–100°), with aniline as internal standard, showed that 90% of **2** had reacted to produce 1.96 g (72%) of **6**, 1.9 g of **5**, and ca. 12% of four unidentified components. The solution was concentrated and **6** and **5** were identified by isolation by preparative GC (5 ft × 0.25 in., 3% silicone gum rubber SE-30 at 80°) and comparison of their NMR and ir spectra with those of authentic samples.

Preparative Photolysis of 2-Phenyl-Δ^1-pyrroline (8). A solution of 2.0 g (0.014 mol) of **8** in 95% ethanol was purged with nitrogen and irradiated through quartz with a Hanovia 450-W high-pressure mercury lamp for 90 hr. The solvent was removed at reduced pressure and the residue crystallized upon standing. Upon recrystallization from ethanol, a solid, mp 130–131°, was obtained and identified as **9** by comparison of its NMR and ir spectra and melting point with those of an independently synthesized sample.

General Procedure for Analytical Photolyses. In each run, 15 ml of ca. 0.03 *M* solutions of imine in 2-propanol (concentrations were adjusted so that the amount of light absorbed initially was approximately the same for each tube in comparative runs)

were placed in quartz photolysis tubes and purged with nitrogen. Tubes were then irradiated with a Hanovia 450-W high-pressure mercury lamp, using a "merry-go-round" apparatus to ensure equal amounts of light incident on each tube. Analysis was conducted by GC using aniline as internal standard for **2** and **7** (UCW column described above at 90°) and naphthalene as internal standard for **8** and **10** (UCW column described above, temperature-programmed run, 150–250°).

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Registry No.—**1**, 1074-06-2; **2**, 1462-92-6; **3**, 767-92-0; **5**, 76-09-5; **6**, 109-05-7; **7**, 22023-64-9; **8**, 700-91-4; **9**, 54276-78-7; **10**, 2211-66-7; *N*-propyl-2-aminopropane, 21968-17-2.

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(26) Boiling points and melting points are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian Model EM-360 spectrometer. Ultraviolet spectra were obtained on a Beckman Acta V spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer Model 710A spectrophotometer. Gas–liquid partition chromatograms were obtained on a Hewlett-Packard Model 5750 chromatograph. Elemental analyses were obtained from Spang Microanalytical Laboratory, Ann Arbor, Mich.
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Synthesis of 2-Substituted 8,9-Dehydroadamantanes[1]

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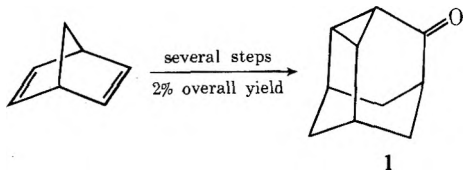
Acetone-sensitized photoisomerization of 2-protoadamantenone gives 8,9-dehydro-2-adamantanone (**1**). Several new 2-substituted 8,9-dehydroadamantanes have been prepared from **1**. A general route for the introduction of alkyl substituents at the C-8 bridgehead of **1** has been devised and is illustrated by the synthesis of 8-methyl-8,9-dehydro-2-adamantanone.

In view of the considerable interest in the properties and chemistry of adamantane derivatives,[2] it is striking that 8,9-dehydro-2-adamantanone (**1**), a structurally rigid conjugated cyclopropyl ketone which contains a plane of symmetry and is potentially of significant synthetic utility, has received only modest attention.[3–8] It would appear that this has been the case because it simply has not been convenient to employ **1** in synthesis. The only reported preparation of **1** involves a multistep reaction sequence which converts norbornadiene to **1** in an overall yield of 2%.[3] We



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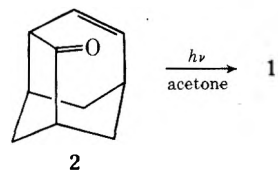
now wish to report (a) an alternative and improved procedure for the synthesis of **1**, (b) the preparation of several 2-substituted 8,9-dehydroadamantanes from **1**, and (c) a synthetic route for introducing alkyl substituents at C-8 of **1**.

Results and Discussion

It is well established that the triplet-sensitized photorearrangement of a β,γ-unsaturated ketone can lead to a formal [1,2] shift of the acyl group and the formation of an isomeric conjugated cyclopropyl ketone (the oxa-di-π-methane photorearrangement).[9] Thus, by analogy, **1** should be accessible by the photoisomerization of 2-protoadamantenone (**2**). The availability of **2**[10] led us to examine its photochemistry. Irradiation of a nitrogen-purged 0.5% solution of **2** [λ_{max}(EtOH) 296 nm (ε 230)] in acetone through a Pyrex filter with a Hanovia L 450-W lamp proceeds smoothly to give **1**.[11] Under these conditions **1** [λ_{max}(EtOH) 277 nm (ε 40)] undergoes slow photodecomposition, but this reaction does not effectively compete with the photo-



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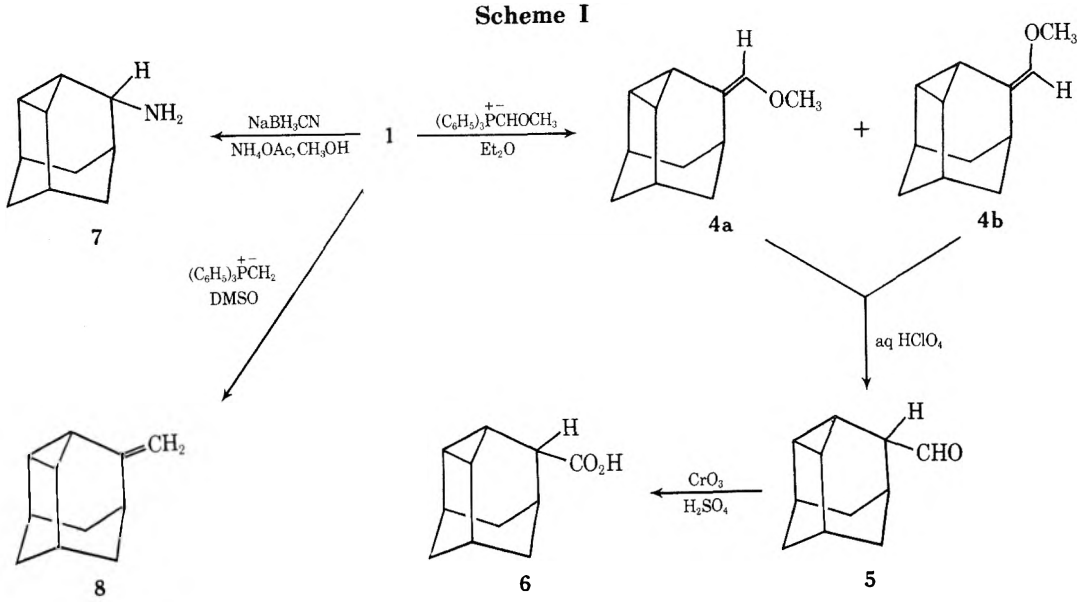
Scheme I



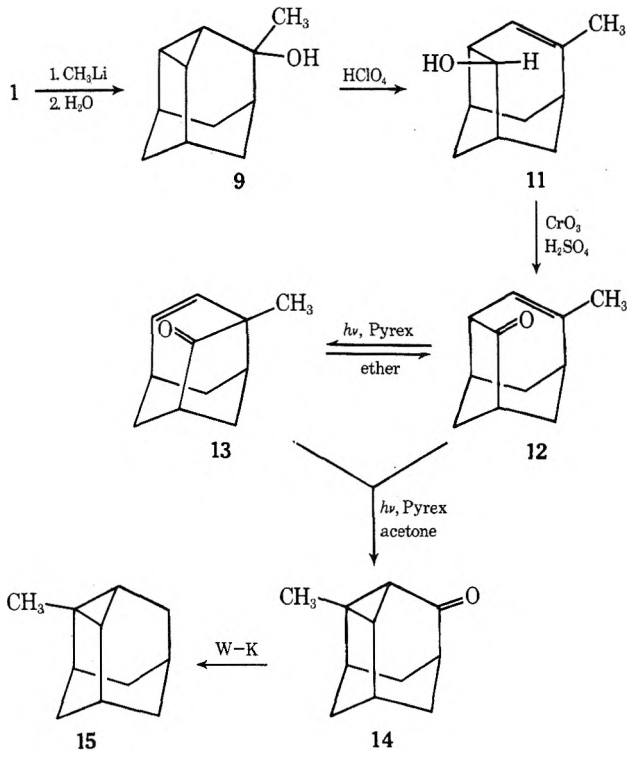
isomerization of **2** to **1**. Thus, irradiation of **2** to 80% conversion affords **1** in ca. 70% yield.

The only 2-substituted 8,9-dehydroadamantanes which have been reported are ketone **1**, 8,9-dehydro-2-adamantanol (**3**), and some derivatives prepared from **3**.[3,6] Routes to several new 2-substituted 8,9-dehydroadamantanes are summarized in Scheme I. Reaction of **1** with methoxymethylenetriphenylphosphorane[12] affords a 55:45 mixture of **4a**:**4b**. The isomer assignments follow from the relative ^{1}H NMR chemical shifts of the CH(OCH$_3$) protons. Reichardt et al. have prepared a series of 1-cycloalkyl-2-alkoxyethylenes and have found that the ^{1}H NMR chemical shifts of the CH(OCH$_3$) proton in the *Z* isomers consistently appear upfield relative to the corresponding proton in the *E* isomers.[13] Treatment of the mixture of enol ethers with aqueous perchloric acid gives 8,9-dehydro-2-adamantanecarboxaldehyde (**5**), which can be oxidized with Jones reagent to provide 8,9-dehydro-2-adamantanecarboxylic acid (**6**). By this sequence of reactions, **6** was prepared from **1** in an overall yield of 20%.[14] 2-Amino-8,9-dehydroadamantane (**7**) is readily obtained from **1** by the reductive amination procedure of Borch et al.[15] Treatment of **1** with sodium cyanohydridoborate and ammonium acetate in methanol affords amine **7** in ca. 40% yield. 2-Methylene-8,9-dehydroadamantane (**8**) can be prepared from **1** by Corey's modification[16] of the Wittig reaction.[17] The structures of **4**–**8** follow from their spectral and analytical properties (see Experimental Section) and their mode of formation.

It has previously been recognized that adamantanes, owing to their rigid skeletons and undistorted chair conformations, offer ideal models to investigate the influence of substituents on chemical shifts.[18] As is apparent from Table I, the CHX protons of 2-substituted 8,9-dehydroadamantanes consistently appear ca. 0.2–0.4 ppm downfield from the corresponding protons of 2-substituted adamantanes. As might be expected, this influence is diminished as the sensor group is moved farther from the cyclopropyl moiety. Thus, in 2-methyl-8,9-dehydro-2-adamantanol (**9**), which is readily prepared by treatment of **1** with methyllithium, the methyl protons appear at δ 1.41, whereas the chemical shift of the methyl protons in 2-methyl-2-adamantanol is δ 1.31.[18a]

Although 2,4-dehydroadamantane[19] and ketone **1** have been known for some time, no *bridgehead substituted* 2,4-dehydroadamantanes have been reported. In view of the successful photoisomerization of **2** to **1**, 8-substituted 8,9-dehydro-2-adamantanones should be accessible if substituents can be introduced at the 3 or 5 positions of **2**. A general route for preparing 5-alkyl-substituted 2-protoadamantenones is summarized in Scheme II. Recently, we have shown that treating alcohol **3** with dilute perchloric acid in refluxing 80% aqueous acetone affords 2-*exo*-protoadamantenol (**10**).[6] Similar treatment of methyl alcohol **9** gives 5-methyl-2-*exo*-protoadamantenol (**11**), which can be oxidized with Jones reagent to the corresponding ketone (**12**). Since the organic alkyllithium reagent that is employed in the initial step of this sequence can be varied considerably,

Scheme II



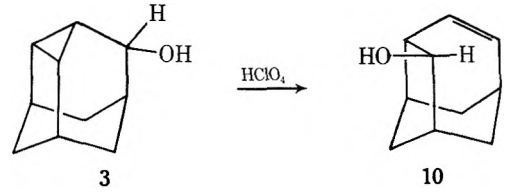
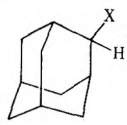
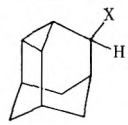


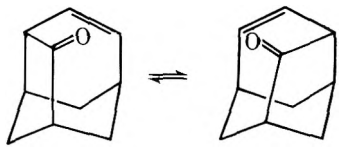
Table I
^{1}H NMR Chemical Shifts of CHX in 2-Substituted Adamantanes and 2-Substituted 8,9-Dehydroadamantanes[a]

X		
CHO	2.40[b]	2.64[c]
CO_2H	2.69[d]	2.87[c]
NH_2	2.98[e]	3.18[c]
OCH_3	3.30[f]	3.67[g]
OH	3.75[e]	4.15[i]
	3.80[h]	
Cl	4.30[j]	4.70[g]
	4.39[e]	

[a] Chemical shifts are given in δ units relative to TMS. [b] J. Scharp, H. Wynberg, and J. Strating, *Recl. Trav. Chim. Pays-Bas*, **89**, 18 (1970). [c] Present report. [d] G. Snatzke and D. Marquarding, *Chem. Ber.*, **100**, 1710 (1967). [e] Reference 18b. [f] A. C. Udding, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968). [g] Reference 6. [h] Reference 18a. [i] Reference 3. [j] W. Hoek, J. Strating, and H. Wynberg, *Recl. Trav. Chim. Pays-Bas*, 85, 1045 (1966).

this set of reactions offers a route for the preparation of a variety of 5-alkyl-substituted 2-protoadamantenones.

Several β,γ-unsaturated ketones are known to undergo a formal [1,3] shift of the acyl group to give isomeric β,γ-unsubstituted ketones on direct irradiation, whereas triplet-sensitized photolysis of these enones leads to a formal [1,2] shift of the acyl group and the formation of isomeric cyclopropyl ketones.[20] Such is the photochemical behavior of enone **12**. Irradiation of an ether solution of **12** through a Pyrex filter with a Hanovia L 450-W lamp produces an approximately 1:1 photoequilibrium mixture of **12** and 3-methyl-2-protoadamantenone (**13**).[21] Irradiation of **13** under identical conditions also affords a ca. 1:1 photostationary mixture of **12** and **13**. Of course, this aspect of the photochemistry of 2-protoadamantenones is not detected in **2**, as the analogous photoisomerization in **2** is degenerate.



Irradiation of an acetone solution of **12** through a Pyrex filter gives 8-methyl-8,9-dehydro-2-adamantanone (**14**) in ca. 65% yield. Enone **13** is also detected in the early stages of this photolysis, but **13** disappears on continued irradiation, and irradiation of the photostationary mixture of **12** and **13** under these conditions provides only **14**.[22] Treatment of **14** under the conditions of the normal Huang-Minlon modification of the Wolff–Kishner reduction[23] gives 2-methyl-2,4-dehydroadamantane (**15**).[24] Ketone **14** and hydrocarbon **15** thus provide the first reported examples of bridgehead substituted 2,4-dehydroadamantanes.

Experimental Section

All melting points were obtained in sealed capillary tubes using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers and proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers. Apparent splittings are given in all cases. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^{1}H NMR spectrum of the product(s) vs. the signal of a predetermined amount of added standard (generally trichloroethylene) and are regarded as being accurate to ca. ±10%. Mass spectra were obtained on a CEC 21-110B instrument at an ionization potential of 70 eV. Ultraviolet spectra were determined on a Cary 14 spectrophotometer. Elemental analyses were performed by Micro-Analysis Inc., Wilmington, Del.

8,9-Dehydro-2-adamantanone (1). A nitrogen-purged solution of 294 mg of 2-protoadamantenone[10] (**2**) in 35 ml of acetone was irradiated through a Pyrex filter with a Hanovia L 450-W high-pressure mercury lamp. Monitoring the photolysis by GLC (5 ft × 0.25 in. FFAP column, 175°) showed a gradual disappearance of **2** and the appearance of a photoproduct of longer retention time. After irradiation for 24 hr, no starting material remained and only the photoisomer was present. Irradiation for considerably longer periods of time produced a small decrease in the concentration of the initial photoproduct and the formation of a trace of a photoproduct with a shorter GLC retention time. This latter reaction was not investigated further. Evaporation of the solvent at reduced pressure gave a yellow oil which was chromatographed on silica gel with benzene as eluent to give 206 mg of **1** (70% yield). The physical and spectral properties of **1** are in complete agreement with those previously reported for this compound.[3]

(*E*)- and (*Z*)-2-Methoxymethylene-8,9-dehydroadamantane (4a and 4b). Sodium-dried ether (100 ml) and methoxymethyltriphenylphosphonium chloride (1.568 g, 4.58 mmol) were added under nitrogen to a thoroughly dried flask.[12] The mixture was cooled in an ice bath and an equimolar quantity of *n*-butyllithium (2.0 ml of 21.8 wt % in hexane) was added with stirring. The resulting red solution was stirred for 15 min. To this solution was added **1** (243 mg, 1.64 mmol) and the reaction mixture was stirred overnight. Finally, zinc chloride (1 g) was added with vigorous stirring, and the resulting precipitate was filtered and washed with ether. The filtrate and ether washings were combined and the solvent was evaporated at reduced pressure to give an oil. Chromatography of this oil on silica gel with pentane as eluent provided 113 mg (39% yield) of a ca. 55:45 mixture (by ^{1}H NMR) of **4a** and **4b**, respectively. Purification of **4** by GLC (5 ft × 0.25 in. FFAP column, 135°) afforded a clear oil: $\delta_{TMS}(CDCl_3)$ 1.4–3.1 (br m, 12 H), 3.53 and 3.56 (each s, 3 H together, OCH_3), and 5.80 and 6.00 [each s, 1 H together, C**H**(OCH_3) of **4b** and **4a**, respectively]; $\nu(CHCl_3)$ 3035, 3005, 2930, 2855, 1675, 1455, 1385, 1245, 1200, 1115, 1060, 1030, 985, and 860 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.00; H, 9.08.

8,9-Dehydro-2-adamantanecarboxaldehyde (5). To 10 ml of ether was added 52 mg (0.3 mmol) of **4** and 1 ml of 35% perchloric acid.[12] The resulting solution was stirred at reflux for 1 hr and then poured into water (20 ml). Additional ether (75 ml) was added, the aqueous layer was separated, and the ether layer was washed with water (2 × 10 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 45 mg of an oil which by ^{1}H NMR analysis contained a ca. 35% yield of **5**. Purification of **5** by GLC (5 ft × 0.25 in. FFAP column, 150°) provided a clear oil: $\delta_{TMS}(CDCl_3)$ 1.1–2.5 (br m, 12 H), 2.64 (br m, 1 H, CHCHO), and 9.89 (s, 1 H, CHO); $\nu(CHCl_3)$ 3030, 2930, 2855, 2800, 2700, 1720, 1675, 1455, 1440, 1330, 1205, 1185, 1120, 1065, 1005, 945, 910, and 880 cm^{-1}.

8,9-Dehydro-2-adamantanecarboxylic Acid (6). To a solution of **5** (90 mg, 0.6 mmol) in acetone (20 ml) was added 700 μl of a freshly prepared solution of Jones reagent (2.8 g of chromic anhydride, 4.5 ml of sulfuric acid, and 12 ml of water). The reaction mixture was stirred at 0–5° for 3 hr, then quenched with water (40 ml) and extracted with ether (5 × 30 ml). The combined ether extracts were in turn extracted with 1 *N* sodium hydroxide (5 × 30 ml). The basic extracts were acidified to pH 2, saturated with sodium chloride, and extracted with ether (5 × 50 ml). The combined ether extracts were washed with water (2 × 20 ml) and dried over anhydrous magnesium sulfate. Evaporation of the ether gave **6** in ca. 60% yield by ^{1}H NMR analysis. Purification of **6** by GLC (5 ft × 0.25 in. FFAP column, 210°) afforded a waxy solid: $\delta_{TMS}(CDCl_3)$ 0.9–2.7 (br m, 12 H), 2.87 (br m, 1 H, CHCOOH), and 8.95 (br s, 1 H, COOH); $\nu(CHCl_3)$ 3500–2500 (br), 2940, 2860, 1705, 1410, 1235, 1165, 1110, 1105, 1060, 1035, 1020, 1005, and 865 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.93; H, 7.89.

2-Amino-8,9-dehydroadamantane (7). A solution of **1** (194 mg, 1.31 mmol), ammonium acetate (7.7 g, 0.1 mol), and sodium cyanohydridoborate (165 mg, 2.62 mmol) in 30 ml of freshly distilled methanol was stirred for 48 hr at 25° with 3 Å molecular sieves.[15] The residue was filtered and washed with methanol. Concentrated

hydrochloric acid was added to the filtrate until pH <2, and the methanol was then evaporated at reduced pressure. The resulting residue was dissolved in water (20 ml) and extracted with ether (5 × 30 ml). The aqueous solution was then brought to pH >10 by the addition of solid potassium hydroxide, saturated with sodium chloride, and extracted with ether (5 × 30 ml). The combined ether extracts were washed with 5% aqueous sodium hydroxide (2 × 100 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided an oil which by ^{1}H NMR analysis contained **7** in ca. 40% yield. Sublimation (25° at 0.5 mm) gave **7** as a white solid at −78° which became a clear oil at 25°: $\delta_{TMS}(CDCl_3)$ 1.0–2.5 (br m, 14 H) and 3.18 [br s, 1 H, C**H**(NH_2)]; $\nu(CHCl_3)$ 3450–3100 (br), 3040, 2940, 2860, 1575, 1460, 1335, 1080, 1055, 1040, 1010, 885, and 855 cm^{-1}.

The 3,5-dinitrobenzamide derivative of **7** was prepared by adding 115 mg (0.5 mmol) of 3,5-dinitrobenzoyl chloride to a solution of **7** (30 mg, 0.2 mmol) in 2.5 ml of pyridine. The mixture was refluxed for 1 hr and then quenched with water (40 ml). The aqueous solution was extracted with ether (5 × 25 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was exhaustively evaporated at reduced pressure. Two recrystallizations of the residue from chloroform–heptane gave an off-white solid: mp 203–204°; $\delta_{TMS}(CDCl_3)$ 1.1–2.5 (br m, 12 H), 4.60 [br d of t, J = 7 and 2.5 Hz, 1 H, C**H**(NHBz)], 6.80 (br d, J = 7 Hz, 1 H, N**H**Bz), and 8.9–9.15 (br m, 3 H, aromatic protons).

Anal. calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.41; H, 5.16; N, 12.39.

2-Methylene-8,9-dehydroadamantane (8). The mineral oil was removed from a sodium hydride mineral oil dispersion (478 mg, 20 mmol as sodium hydride) by washing with several portions of *n*-pentane. Dimethyl sulfoxide (DMSO) (4 ml) was introduced, and the mixture was heated with stirring under nitrogen at 90° until hydrogen evolution ceased (ca. 45 min).[16] The solution was cooled and methyltriphenylphosphonium bromide (3.9 g, 10.9 mmol) in DMSO (20 ml) was added. After stirring for ca. 10 min, **1** (303 mg, 2.0 mmol) was added and the stirred solution was heated at 55–60° for 10 hr. The solution was cooled and poured into 150 ml of water, and the aqueous portion was extracted with pentane (4 × 100 ml). The combined pentane extracts were washed with water (2 × 50 ml) and saturated sodium chloride solution (2 × 50 ml), and dried over anhydrous magnesium sulfate. Evaporation of the pentane provided a yellow oil which contained **8** in ca. 25% yield by ^{1}H NMR analysis. Column chromatography of the crude product on silica gel with pentane as eluent, followed by purification by GLC (5 ft × 0.25 in. FFAP column, 115°), gave **8** as a clear oil: $\delta_{TMS}(CDCl_3)$ 1.4–2.6 (br m, 12 H) and 4.67 (apparent s, 2 H, olefinic protons); ν (CCl_4) 3070, 3030, 2935, 2860, 1650, 1460, 1440, 1330, 1070, 1030, 895, and 865 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.50; H, 9.49.

2-Methyl-8,9-dehydro-2-adamantanol (9). A solution of methyllithium (3.5 mmol) in ether was added at 0° to a solution of **1** (101 mg, 0.67 mmol) in 20 ml of anhydrous ether (freshly distilled from lithium aluminum hydride). Stirring was maintained for 1 hr at 0°, at which point 30 ml of water was carefully added. The reaction mixture was extracted with ether (3 × 30 ml) and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a clear oil which contained **9** in quantitative yield by ^{1}H NMR analysis. Purification of **9** by sublimation (50° at 1 mm) or crystallization from pentane afforded a white solid: mp 72–80°; $\delta_{TMS}(CDCl_3)$ 1.41 (s, 3 H, CH_3) and 1.1–2.4 (br m, 12 H); ν (CCl_4) 3610, 3440 (br), 3035, 3000, 2940, 2865, 1440, 1370, 1330, 1115, 1045, 1030, 980, 920 and 890 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.63; H, 9.57.

5-Methyl-2-*exo*-protoadamantenol (11). A solution of **9** (865 mg, 5.27 mmol) in 15 ml of 80% aqueous acetone which was 0.005 *M* in perchloric acid was stirred at ca. 70° for 16 hr. The solution was then saturated with sodium chloride and extracted with ether (4 × 50 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave an oil which by ^{1}H NMR analysis contained **11** in ca. 70% yield. GLC analysis (10 ft × 0.25 in. FFAP column, 190°) showed a single component to be present which was purified by GLC (identical conditions) to give **11** as a clear oil: $\delta_{TMS}(CDCl_3)$ 1.1–2.7 (br m, 13 H) which includes 1.68 (d, J = 1.5 Hz, 3 H, CH_3), 3.68 [br s, 1 H, C**H**(OH)], and 5.63 [br d, J = 5 Hz, 1 H, $(CH_3)C$=C**H**]; ν (CCl_4) 3630, 3350 (br), 3015, 2915, 1460, 1430, 1095, 1060, 1050, 1030, 1015, 1000, 970, 945, 920, 895, and 870 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.18; H, 9.92.

5-Methyl-2-protoadamantenone (12). To a stirred solution of **11** (582 mg, 3.55 mmol) in 15 ml of acetone at 0° was added 2.2 ml of a freshly prepared solution of Jones reagent. The reaction mixture was stirred at 0° for 1 hr and then at room temperature for 2 hr, at which point the mixture was diluted with 5 ml of water and stirred for an additional 0.5 hr. The solution was saturated with sodium chloride and neutralized with a saturated solution of sodium bicarbonate. The resulting solution was extracted with ether (4 × 50 ml), the combined ether extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated at reduced pressure. ^{1}H NMR analysis of the residue indicated that **12** was obtained in ca. 90% yield. GLC analysis (5 ft × 0.25 in. FFAP column, 165°) showed a single component to be present and purification of **12** by GLC (identical conditions) gave a clear oil: $\delta_{TMS}(CDCl_3)$ 1.1–3.0 (br m, 13 H) which includes 1.77 (d, J = 1.5 Hz, 3 H, CH_3), and 5.62 [br d, J = 7 Hz, 1 H, $(CH_3)C$=C**H**)]; ν (CCl_4) 3020, 2960, 2880, 1430, 1190, 1135, 1085, 1060, 1040, 895, and 860 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.56; H, 8.53.

3-Methyl-2-protoadamantenone (13). A solution of 158 mg of **12** in 25 ml of ether was irradiated through a Pyrex filter with a Hanovia L 450-W high-pressure mercury lamp. The reaction was monitored by GLC (5 ft × 0.25 in. FFAP column, 175°) at hourly increments for a total of 12 hr of irradiation. As the reaction proceeded, the starting material gradually decreased in concentration and concurrently a photoproduct appeared at a shorter retention time and increased in concentration until a photostationary state was reached after 10 hr of irradiation. Evaporation of the solvent at reduced pressure provided an oil, and ^{1}H NMR analysis of the residue showed that the reaction had proceeded with ca. 50% conversion of **12** to give **13** in nearly quantitative yield. Purification of **13** by GLC (above conditions) afforded a white solid: mp 117–119°; $\delta_{TMS}(CDCl_3)$ 1.27 (s, 3 H, CH_3), 1.4–2.7 (br m, 9 H), 5.57 [d, J = 8.8 Hz, 1 H, $(CH_3)CC$**H**=CH], and 6.42 [dd, J = 8.8 and 8.5 Hz, 1 H, $(CH_3)CCH$=C**H**]; ν (CCl_4) 3050, 2950, 2880, 1745, 1260, 1210, 1160, 1090, 1070, 1035, 970, and 875 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.38; H, 8.68.

The photoequilibrium of **12** and **13** was confirmed by irradiation (above conditions) of a solution of 10 mg of **13** in 1 ml of ether. Monitoring the reaction by GLC (above conditions) indicated that upon irradiation the concentration of **13** diminished and a photoproduct with a retention time identical with that of **12** appeared. The reaction reached a photostationary state after 4 hr irradiation, at which point the GLC trace of the photomixture was virtually identical with the GLC trace obtained after photoequilibrium was established beginning with pure **12**.

8-Methyl-8,9-dehydro-2-adamantanone (14). A solution of 141 mg of **12** in 30 ml of acetone was irradiated through a Pyrex filter with a Hanovia L 450-W high-pressure mercury lamp. Monitoring the photolysis by GLC (5 ft × 0.25 in. FFAP column, 175°) showed that after 3 hr irradiation the concentration of **12** had significantly decreased and a photoproduct with a longer retention time than **12** had appeared. A photoproduct with a shorter retention time than **12** was also detected and, following isolation by GLC, this compound proved to be **13**. After irradiation for 25 hr, GLC analysis indicated the presence of only the photoproduct of longest retention time. Evaporation of the solvent at reduced pressure followed by column chromatography of the residue on silica gel with benzene as eluent gave 93 mg (66% yield) of **14**. Final purification of **14** by GLC (above conditions) provided a clear oil: $\delta_{TMS}(CDCl_3)$ 1.33 (s, 3 H, CH_3) and 1.5–2.6 (br m, 11 H); ν (CCl_4) 3030, 2945, 2865, 1710, 1450, 1340, 1250, 1150, 1120, 1095, 1085, 1030, 985, 885, and 860 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.17; H, 8.70.

2-Methyl-2,4-dehydroadamantane (15). A solution of **14** (85 mg, 0.53 mmol), 400 mg of 95% hydrazine, and 500 mg of potassium hydroxide in 5 ml of diethylene glycol was stirred in an oil bath at 110°.[23] The temperature was raised over 0.5 hr to 180° and the reaction mixture was maintained at reflux (180°) for 3 hr. The reaction mixture was then cooled to room temperature and the contents of both the condenser and the pot were rinsed with cyclohexane (50 ml) and then water (30 ml). The combined aqueous

rinses were saturated with sodium chloride and extracted with cyclohexane (2 × 25 ml). The combined cyclohexane rinses and extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure. GLC analysis (10 ft × 0.25 in. FFAP column, 100°) of the residue indicated a single hydrocarbon product, which was purified by GLC (above conditions) to give **15** as a clear oil: $\delta_{TMS}(CDCl_3)$ 1.16 (s, 3 H, CH_3) and 0.8–2.3 (br m, 13 H); ν (CCl_4) 3020, 2990, 2875, 2850, 1455, 1340, 1160, 1140, 1105, 1055, 990, 965, and 945 cm^{-1}; MS *m/e* (rel intensity) 148 (100), 133 (60), 107 (36), 106 (71), 105 (50), 93 (52), 92 (52), 91 (73), and 79 (80).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.96; H, 10.99.

Acknowledgment. This work was supported by grants from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the University of Delaware Research Foundation, and the Delaware Institute of Medical Education and Research.

Registry No.—**1**, 10497-56-0; **2**, 28673-75-8; **4a**, 54003-44-0; **4b**, 54003-45-1; **5**, 54003-46-2; **6**, 54003-47-3; **7**, 54019-69-1; **7** 3,5-dinitrobenzamide derivative, 54003-48-4; **8**, 54003-49-5; **9**, 53075-01-7; **11**, 53075-02-8; **12**, 53075-00-6; **13**, 53075-04-0; **14**, 53075-03-9; **15**, 54003-50-8.

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(22) P. S. Engel and M. A. Schexnayder have previously reported [*J. Am. Chem. Soc.*, **94**, 9252 (1972)] an "unprecedented triplet 1,3-acyl shift" in the photochemistry of a β,γ-unsaturated ketone. It is not clear if a similar isomerization is occurring in the present study or if the formation of **13** from **12** with triplet sensitization simply results from some "leakage" to the excited singlet of **12** under the photolysis conditions employed.
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A Palladium-Catalyzed Conjugated Diene Synthesis from Vinylic Halides and Olefinic Compounds

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Conjugated dienes are obtained when vinylic bromides or iodides are treated with olefinic compounds in the presence of a trialkylamine and a catalytic amount of $Pd[P(C_6H_5)_3]_2(OAc)_2$ at 100–150°. In some instances, with the less substituted reactants, the initially formed dienes undergo subsequent Diels–Alder reactions. The new conjugated diene synthesis shows appreciable stereospecificity when (*Z*)- or (*E*)-vinylic halides are treated.

The palladium-catalyzed reaction of vinylic halides with olefinic compounds in the presence of a trialkylamine to form conjugated dienes has been noted previously,[1,2] but the scope of the reaction has not been investigated. We report herein an investigation of the reaction with a variety of vinylic halides and olefinic compounds.

Results and Discussion

Eight vinylic halides with different structural features were treated with various olefinic compounds to demonstrate several applications of the reaction. The results are summarized in Table I.

The reaction is believed to occur in three steps.[2] The "catalyst" is first reduced by the olefinic compound to a palladium(0) phosphine complex, which then reacts with the vinylic halide by oxidative addition. The vinylic palladium complex formed next adds to the olefin and the adduct eliminates an hydridopalladium group, forming the conjugated diene. The hydrido complex then loses hydrogen halide to the tertiary amine present, re-forming the palladium(0) phosphine complex, and the cycle is complete.

The reaction may be complicated by the conjugated diene product undergoing subsequent reactions such as double-bond isomerization or Diels–Alder reactions with starting material. The reaction of the 1-halo-1-hexenes with ethylene, for example, produces mainly the rearranged diene, 2,4-octadiene, rather than the expected 1,3-octa-

Table I
Olefin Vinylation Reactions

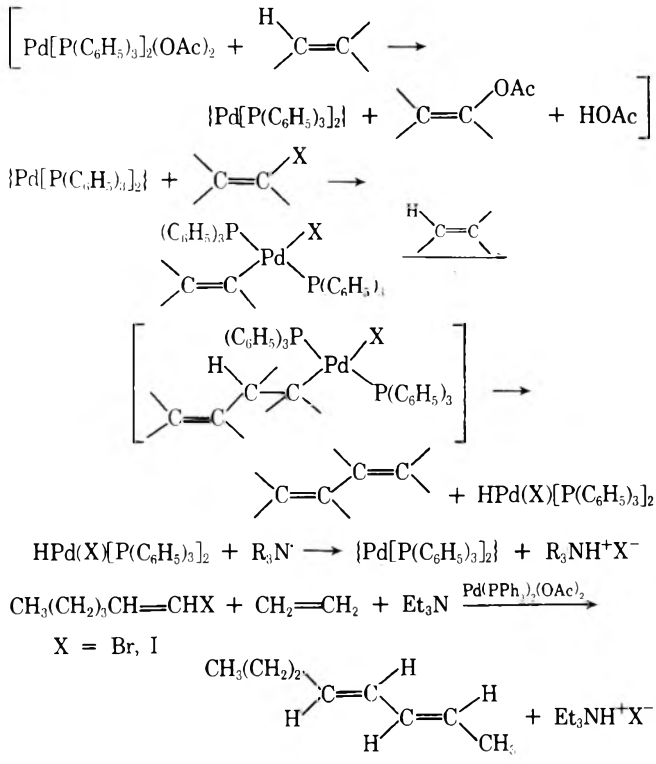
Vinylic halide (mmol) (registry no.)	Olefinic reactant (mmol) (registry no.)	Et_3N, mmol	Catalyst[a]	Reaction time, hr	Products (% yield) (registry no.)	Bp or mp (reported), °C	NMR spectrum, τ
Vinyl iodide (20) (593-66-8)	Methyl acrylate (50) (96-33-3)	25	A	32[b]	Dimethyl *cis*-cyclohexene-3,4-dicarboxylate (54354-48-2)	bp 100–110 (1.3 mm)	(CCl_4) s (broad) 4.37 (2 H), s 6.36 (6 H), m 6.45–8.30 (6 H)
					Dimethyl cyclohexene-2,3-dicarboxylate (52)[c,d] (41902-36-7)		(CCl_4) m 3.07 (1 H), s 6.34 (3 H), s 6.39 (3 H), m 6.64 (1 H), m 7.60–8.70 (6 H)
2-Bromopropene (40) (557-93-7)	Methyl acrylate (100)	50	A	36[b]	Dimethyl *cis*-1-methylcyclohexene-3,4-dicarboxylate (62.5) (54354-49-3)	bp 98–100° (1.3 mm)[e]	(CCl_4) m 4.66 (1 H), s 6.37 (6 H), m 6.48–8.15 (6 H), s (broad) 8.32 (3 H)
2-Bromopropene (20)	Styrene (25) (100-42-5)	25	B	96[b]	Dimethyl 1-methyl-3-phenylcyclohexene-4,5-dicarboxylate	Solid,[f] mp 111–112 bp 138–150 (0.15 mm)	(C_6D_6) s 2.88 (5 H), m (broad) 4.51–4.82 (1 H), m 5.85–7.22 (3 H), s 6.57 (3 H), s 6.77 (3 H), m (broad) 7.56–8.00 (2 H), s (broad) 8.42 (3 H)
	Dimethyl maleate (25) (624-48-6)				Two isomers: solid (24.2) (54354-50-6), liquid (28.0) (54382-88-6)	Liquid[g] bp 138–150 (0.15 mm)	(C_6D_6) s 2.83 (5 H), m (broad) 4.71 (1 H), m 5.55–7.22 (3 H), s 6.62 (3 H), s 6.77 (3 H), m 7.67–7.93 (2 H), s (broad) 8.50 (3 H)
1-Bromo-2-methyl-propene (20) (3017-69-4)	Methyl acrylate (25)	25	A	70[b]	Methyl 5-methyl-2,4-hexadienoate (75)[2]		
Methyl (*E*)-3-bromo-2-methylpropenoate (200) (40053-01-8)	Methyl acrylate (250)	250	A	6[b,h]	Dimethyl (*E,E*)-5-methyl-2,4-hexadienedioate (60)[i] (39995-94-3)	bp 89 (0.65 mm), mp 54.5–55.5 (55.5)[j]	(CCl_4) 2 d 2.42 (1 H), 2 q 2.83 (1 H), d 3.85 (1 H) ($J_{\beta\gamma}$ = 11, $J_{\gamma\delta}$ = 14, $J_{\beta\text{-}CH_3}$ = ~1 Hz), s 6.24 (6 H), d 7.95 (3 H)
(*E*)-1-Iodo-1-hexene (20) (16644-98-7)	Methyl acrylate (25)	25	A	38[b]	Methyl (*E,E*)-2,4-nonadienoate (45)[c,k] (54354-51-7)		(CCl_4) m 2.65, m 2.9 (1 H), m 3.70–3.95 (2 H), d 4.25 (J = 15) (1 H), s 6.30 (3 H), m 7.60–8.05 (2 H), m 8.35–8.84, m 8.95–9.35 (peak at 9.08) (7 H)
					Methyl (*E,Z*)-2,4-nonadienoate (8)[c,l] (39924-44-2)		(CCl_4) 2 d 2.43 (1 H), m 3.65–4.35 ($J_{\alpha\beta}$ = 15, $J_{\gamma\delta}$ = 11 Hz) (3 H), s 4.30 (3 H), m 7.45–7.90 (2 H), m 8.30–8.85, m 8.90–9.25 (7 H)

(*Z*)-1-Iodo-1-hexene (10) (16538-47-9)	Methyl acrylate (12.5)	12.5	A	15[b]	Dimethyl (*E*,*Z*)-2,4-nonadienoate (30)[c] Dimethyl (*E*,*E*)-2,4-nonadienoate (51)[c]		
(*Z*)-1-Iodo-1-hexene (10)	Methyl acrylate (12.5)	12.5	A	150[m]	Dimethyl (*E*,*Z*)-2,4-nonadienoate (44)[c] Dimethyl (*E*,*E*)-2,4-nonadienoate (39)[c]		
(*Z*)-1-Bromo-1-hexene (5) (13154-12-6)	Methyl acrylate (6.25)	6.25	B	21[b]	Dimethyl (*E*,*Z*)-2,4-nonadienoate (40)[c] Dimethyl (*E*,*E*)-2,4-nonadienoate (18)[c]		
(*Z*)-1-Bromo-1-hexene (5)	Methyl acrylate (6.25)	6.25	B + 6 mol % Ph_3P	19[b]	Dimethyl (*E*,*Z*)-2,4-nonadienoate (71)[c] Dimethyl (*E*,*E*)-2,4-nonadienoate (10)[c]		
(*Z*)-1-Bromo-1-hexene (5)	Methyl acrylate (12.5)	6.25	B + 6 mol % Ph_3P	21[b]	Dimethyl (*E*,*Z*)-2,4-nonadienoate (79)[c] Dimethyl (*E*,*E*)-2,4-nonadienoate (13)[c]		
(*Z*)-1-Bromo-1-hexene (5)	Methyl acrylate (6.25)	12.5	B + 6 mol % Ph_3P	19[b]	Dimethyl (*E*,*Z*)-2,4-nonadienoate (82)[c] Dimethyl (*E*,*E*)-2,4-nonadienoate (10)[c]		
1-Bromo-2-methylpropene (50)	Styrene (100)	62.5	C	300[b]	(*E*)-1-Phenyl-4-methyl-1,3-pentadiene (57.9)[n] (39491-73-1)	bp 78–80 (1.2 mm)	(neat) m 2.77, d 3.18 (6 H), d 4.07 (1 H), 2 m 4.05 (1 H) ($J_{\alpha\beta}$ = 16, $J_{\beta\gamma}$ = 11 Hz), s (broad) 8.33 (6 H)
Methyl (*E*)-3-Bromo-2-methylpropenoate (20)	Styrene (40)	25	B	21[b]	Methyl (*E*,*E*)-2-methyl-5-phenyl-2,4-pentadienoate (78) (20414-95-3)	mp 86.5–87 (86–87)[o]	(C_6D_6) m 2.33–2.95, 3.01, 3.21, 3.30, 3.54 (8 H), s 6.46 (3 H), s 8.03 (3 H)
(*E*)-2-Bromostyrene (30) (588-72-7)	Styrene (60)	37.5	B	135[b]	(*E*,*E*)-1,4-Diphenyl-1,3-butadiene (49) (538-81-8)	mp 150–151 (150–151)[p]	
1-Bromo-2-methylpropene (80)	(*E*)- and (*Z*)-Crotononitrile (100) (627-29-6, 1190-76-7)	100	B	340[b]	(*E*)- and (*Z*)-1-Cyano-2,4-dimethyl-1,3-pentadiene (26.5)[d,q] (54354-52-8, 54354-53-9)	bp 92–94 (23 mm)	*E* (CCl_4) s (broad) 4.28 (1 H), s (broad) 4.97 (1 H), s 7.89 (3 H), s 8.16 (6 H) *Z* (CCl_4) s (broad) 4.10 (1 H), s (broad) 4.95 (1 H), s 8.02 (3 H), s 8.10 (3 H), s 8.18 (3 H)
Methyl (*E*)-3-Bromo-2-methylpropenoate (40)	Methyl methacrylate (50)	50	B	48[b]	Dimethyl (*E*,*E*)-2,5-dimethyl-2,4-hexadienedioate (33.4)[r] (23119-30-4) Dimethyl (*E*,*Z*)-2,5-dimethyl-2,4-hexadienedioate (28.3)[t] (54354-54-0)	mp 101.5–102.5 (99–100)[s]	(CCl_4) s 2.55 (2 H), s 6.22 (6 H), s 8.03 (6 H) (CCl_4) d 2.19 (1 H), d 3.48 (1 H) (J = 12 Hz), s 6.28 (6 H), s (broad) 8.12 (6 H)

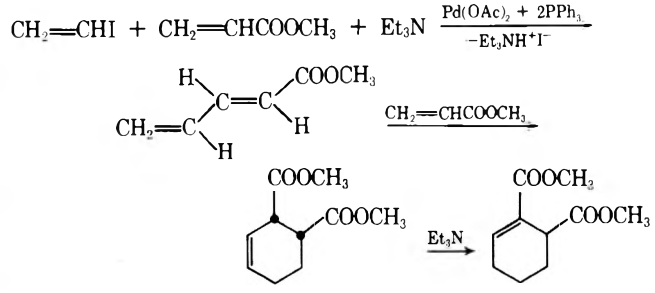
Table I
(Continued)

Vinylic halide (mmol) (registry no.)	Olefinic reactant (mmol) (registry no.)	Et_3N, mmol	Catalyst[a]	Reaction time, hr	Products (% yield) (registry no.)	Bp or mp (reported), °C	NMR spectrum, τ
(*Z*)-1-Iodo-1-hexene (5)	Ethylene (74-85-1)	6.25	B	139[u]	1,3-Octadiene (13.5)[c]		
					2,4-Octadiene (62.2)[c]		
(*Z*)-1-Bromo-1-hexene (10)	Ethylene	12.5	B	38[u]	1,3-Octadiene (36.1)[c]		
					2,4-Octadiene (56.9)[c]		
(*E*)-1-Iodo-1-hexene (10)	Ethylene	12.5	B	88[v]	1,3-Octadiene (5.9)[c]		
					2,4-Octadiene (67.8)[c]		

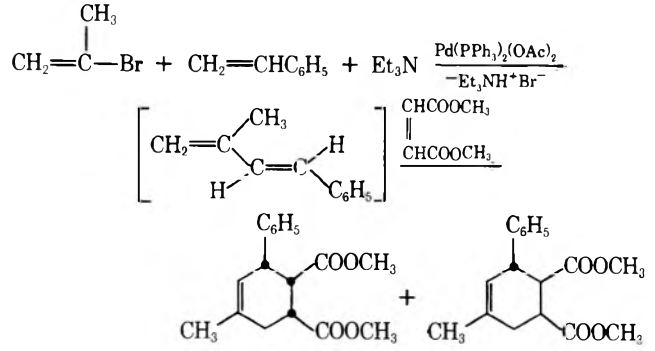
[a] A, 1 mol % $Pd(OAc)_2$, 2 mol % Ph_3P based on vinylic halide; B, 1 mol % $(Ph_3P)_2Pd(OAc)_2$; C, 1 mol % $(Ph_3P)_2Pd(OAc)_2$ then 0.5 mol % after 170 hr. [b] Reaction temperature 100°. [c] Yield determined by VPC. [d] Pure samples isolated by VPC. [e] Calcd: C, 62.25; H, 7.60. Found: C, 62.75; H, 7.78. [f] Calcd: C, 70.81; H, 6.99. Found: C, 70.90; H, 7.10. [g] Calcd: C, 70.81; H, 6.99. Found: C, 70.68; H, 7.01. [h] Reaction carried out in an open system under reflux. A similar reaction in a capped tube at 100° required 2 hr to reach completion and yield was approximately the same. [i] Calcd mol wt: 184.074. Found: 184.073. [j] M. Ohno, Y. Inoue, and T. Sugita, *Bull. Inst. Chem. Res., Kyoto Univ.*, **38**, 8 (1960); *Chem Abstr.*, **56**, 333*i* (1962). [k] Calcd mol wt: 168.115. Found: 168.115. [l] Calcd mol wt: 168.115. Found: 168.115. [m] Reaction temperature 70°. [n] Calcd mol wt: 158.110. Found: 158.107. [o] G. Pattendon and B. C. L. Weedon, *J. Chem. Soc. C*, 1997 (1968). [p] W. P. Weber, R. A. Felix, A. K. Willard, and K. E. Koenig, *Tetrahedron Lett.*, 4701 (1971). [q] Calcd mol wt (*E*): 121.089. Found: 121.088. Calcd mol wt (*Z*): 121.089. Found: 121.088. [r] Calcd mol wt: 198.089. Found: 198.087. [s] J. A. Elvidge, R. P. Linstead, and J. F. Smith, *J. Chem. Soc.*, 1026 (1953). [t] Calcd mol wt: 198.089. Found: 198.089. [u] Reaction temperature 130°. [v] Reaction temperature 155°.



diene. Both vinyl iodide and 2-bromopropene react with excess methyl acrylate to form only Diels–Alder adducts with none of the expected dienes being isolable even when only equivalent amounts of the ester were used. The vinyl iodide reaction was complicated further by the problem that the initially formed Diels–Alder product partially underwent a rearrangement of the double bond catalyzed by the triethylamine present. The related methyl derivative



formed from 2-bromopropene and methyl acrylate does not rearrange under the same conditions. The stereochemistry of the initial adduct formed in the vinyl iodide reaction was established by hydrogenating it to the known dimethyl *cis*-1,2-cyclohexanedicarboxylate. A similar result was observed in the reaction of 2-bromopropene with styrene, and a high molecular weight, apparently Diels–Alder, product was formed. This product was not identified; however, the intermediate conjugated diene could be captured with dimethyl maleate if it was added to the reaction mixture, since it is a better dienophile than either of the reactants,



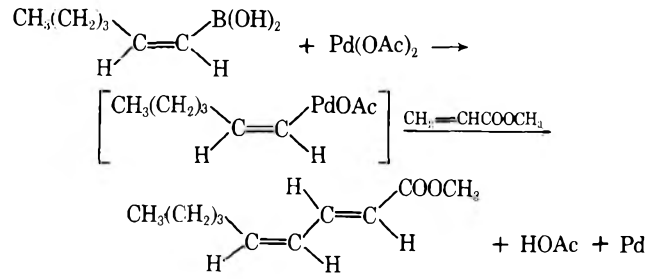
and it is relatively unreactive in the vinylation reaction. Two isomeric products were obtained in this example. These are likely formed by endo and exo Diels–Alder additions, since the other possible isomers involve isomerization at the carbons α to the ester groups. This isomerization would not be expected to occur because it did not in the closely related dimethyl cyclohexenedicarboxylates described above under the same conditions.

The yields of dienes obtained and the rates at which the dienes are formed depend on the structures of both the vinylic halides and the olefinic compounds. The reactivities of vinylic bromides and iodides are rather similar. In the reactions of the 1-halo-1-hexenes, the bromide is apparently somewhat more reactive with ethylene, while the iodide is a little more reactive with methyl acrylate. Substituents β to the halo group exert a significant effect; electron-supplying groups (alkyl) decrease reactivity, while electron-withdrawing groups (carbomethoxyl, aryl) increase it. The methyl substituent on the α carbon in 2-bromopropene has much less effect than the two β-methyls in 1-bromo-2-methyl-1-propene. Replacement of one of the two β-methyls in the last compound by a carbomethoxyl group led to about a tenfold increase in the reaction rate with methyl acrylate.

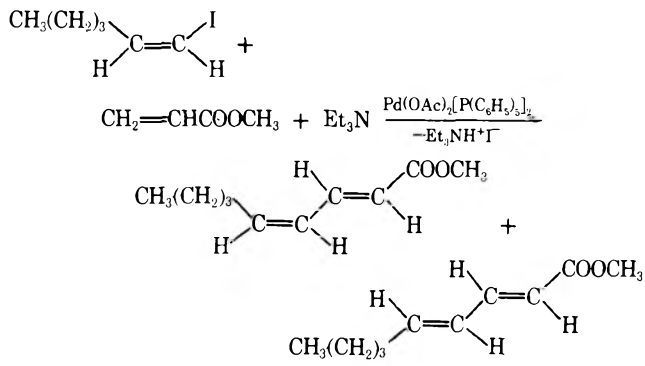
The reactivity of disubstituted olefinic compounds in the vinylic halide reaction is considerably lower than that of the related monosubstituted olefinic compounds, as has been noted previously.[3] Thus, methyl (*E*)-3-bromo-2-methylpropenoate reacts with methyl acrylate about eight times faster than it does with methyl methacrylate. Crotononitrile reacts very slowly with 1-bromo-2-methyl-1-propene, giving only a 26.5% yield of the expected two isomeric dienes after 340 hr at 100°, when all of the bromide had disappeared.

The relatively low reactivity of ethylene compared with methyl acrylate or styrene is unexpected in view of the reverse order of reactivity found at room temperature in the addition of "phenylpalladium chloride" to the same olefins.[3] The explanation may be that in the present reactions all or part of the rearrangement proceeds by way of a π-allylic palladium intermediate (formed by metal hydride elimination–readdition steps). The π-allylic complex then must be decomposed thermally to regenerate the catalyst while the decomposition would be much easier in the arylpalladium halide–olefin reactions. The less substituted π-allylic complex from the ethylene reaction would be expected to be more stable thermally than the more substituted products expected from methyl acrylate or styrene. Of course, the 2,4-diene is thermodynamically favored in the ethylene reaction, while the unrearranged 2,4-dienoic ester is favored in the acrylate reaction. In any case, the arylpalladium–olefin reactions were carried out competitively and stoichiometrically and are not strictly comparable to the approximate individual reaction rates estimated in the present examples.

(*Z*)-1-Iodo-1-hexene reacts about twice as fast as the (*E*)-iodo compound with methyl acrylate. We have looked at the stereochemistry of this reaction in some detail, since we expected that the results would be typical of those that would be obtained in many other related reactions. The two expected products were readily obtained in good yields by the reactions of the (*Z*)- and (*E*)-1-hexenylboronic acids with stoichiometric amounts of palladium acetate in the presence of methyl acrylate at 0°. The *Z* compound produced methyl (*E,Z*)-2,4-nonadienoate in 70% yield and the *E* boronic acid gave the *E,E* ester in 82% yield. The more practical synthesis from the vinylic halides, which is catalytic in palladium, is not so stereospecific.

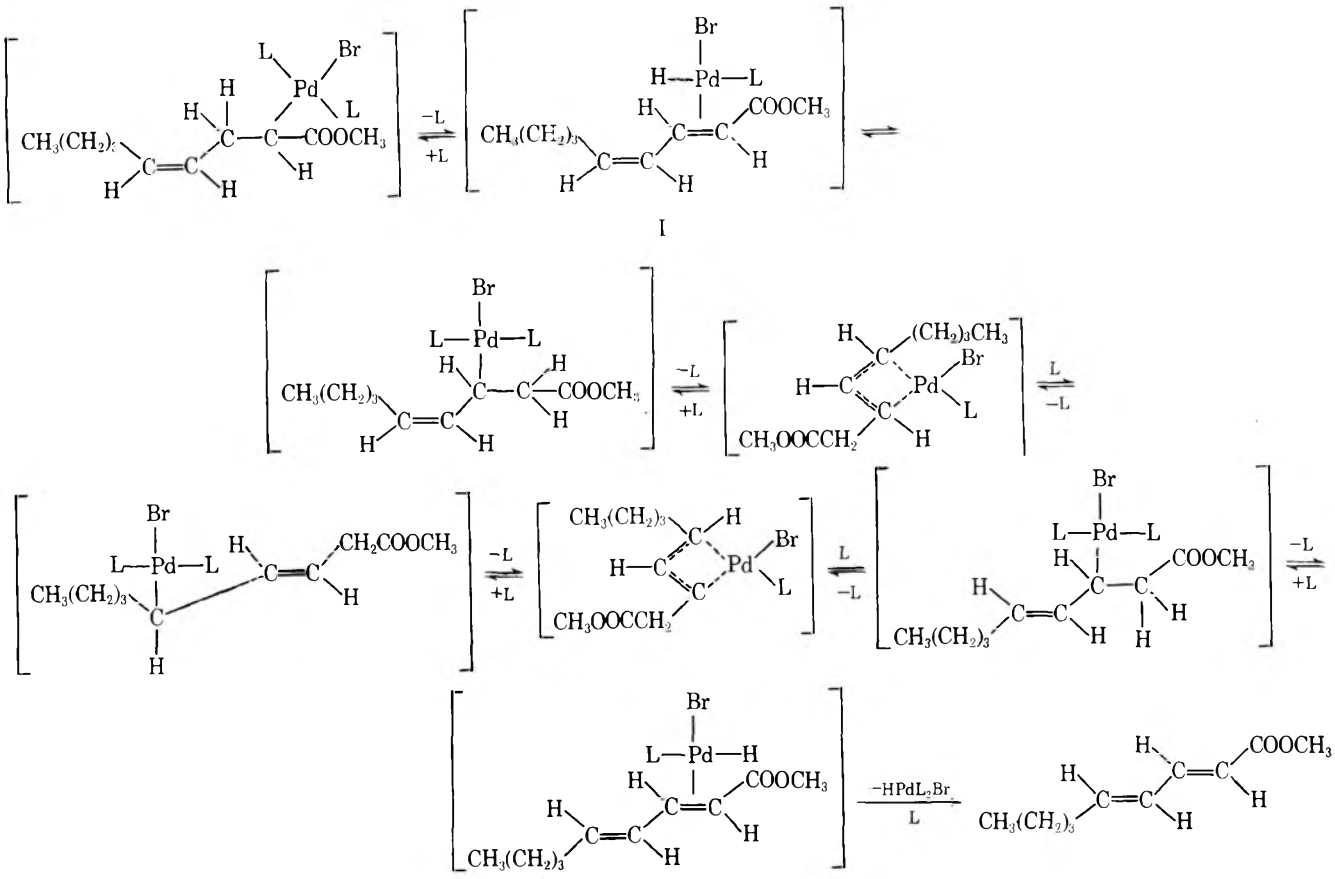


Under our usual reaction conditions, i.e., 100° with 1 mol % of $Pd(OAc)_2[P(C_6H_5)_3]_2$ or its equivalent, 1 mol % of $Pd(OAc)_2$ with 2 mol % of $P(C_6H_5)_3$ as catalyst, (*E*)-1-iodo-1-hexene and methyl acrylate produced methyl (*E,E*)-2,4-nonadienoate in 45% yield and the *E,Z* isomer in 8% yield in 38 hr, by which time the vinylic iodide had all reacted. The *Z* iodide under the same conditions reacted in about 15 hr, forming 51% of the *E,E* ester and 30% of the *E,Z* isomer. Lowering the reaction temperature to 70° in the last reaction improved the selectivity some; 39% *E,E* and 44% *E,Z* esters were now produced, but 150 hr was required for complete reaction. Very similar results were obtained from



the cis iodide without triphenylphosphine being present. The reaction proceeded only about half as fast, however, but the products were essentially identical.

The stereochemistry of the addition also depended upon the halide used and some other reaction conditions. The reaction of (*Z*)-1-bromo-1-hexene with methyl acrylate gave 40% *E,Z* and 18% *E,E* ester compared with 30 and 51%, respectively, with the *Z* iodo compound after all of the halide had reacted (31 hr for the bromide and 15 hr for the iodide). A very substantial improvement in the selectivity occurred when more than 2 mol % of triphenylphosphine per mole of vinylic halide was present per mole percent of palladium in the bromide reaction. With 8 mol % of the phosphine, after 15 hr at 100°, there was obtained 72% *E,Z* and only 10% *E,E* ester. Initially, almost pure *E,Z* isomer was formed. Longer reaction times lead to a slow formation of the *E,E* ester at the expense of the *E,Z* isomer. After 51 hr the yields were 27% *E,Z* and 56% *E,E*, for example. Increasing the methyl acrylate concentration relative to the bromide (from 1:1 to 2:1) had little effect upon the reaction, but increasing the triethylamine concentration from 1:1 to 2:1 relative to the bromide improved the reaction with the 8 mol % triphenylphosphine still further to give 83% *E,Z* and 11% *E,E* ester in 19 hr. Again, the relative amount of the *E,E* ester increased slowly with longer reaction times, but the initial more rapid diene isomerization was significantly decreased. Thus, it appears that there are at least three different mechanisms by which isomerization is occurring in this reaction. There are (1) the isomerization which is inhibited by excess triphenylphosphine, (2) an initial diene product isomerization which becomes less rapid with time and which is inhibited by diluting the reaction mixture with excess amine, and (3) a residual slow product



isomerization which continues after the first two isomerization reactions have stopped or are inhibited.

The excess triphenylphosphine may be stopping one kind of isomerization by displacing diene from palladium in complex I. This would prevent internal readdition of the hydridopalladium group in the opposite direction and the formation of a π-allylic intermediate which ultimately would eliminate again, possibly forming a different isomeric diene than was originally produced.

The initial diene product isomerization appears to be a second-order palladium hydride or a phosphinepalladium hydride catalyzed isomerization, since it stops when the reaction is over and is inhibited by dilution with the amine, a reagent which presumably (slowly) reconverts the hydrides into the palladium(0) catalysts.

The slow residual isomerization also appears to be palladium catalyzed, since the pure esters are stable at the reaction temperature. The esters also are stable at 100° in the presence of 5% Pd on carbon, $Pd[P(C_6H_5)_3]_4$, and $Pd(OAc)_2$. We have no idea what reaction is responsible for this slow isomerization, unless it is due to addition–elimination reactions of a small equilibrium amount of metal hydride formed from Pd(0) compounds and the amine salt formed.

Whatever the reasons are for the isomerization, quite high stereospecificity can be obtained under the proper conditions.

The experiments carried out indicate fairly broad utility for the vinylic halide–olefin reaction, although some limitations are also apparent. Aside from the problem that Diels–Alder reactions may occur with the less substituted dienes when the olefinic reactant is a good dienophile, there are limitations when too many substituents are present in the olefinic reactant. Apparently, the vinylic halides undergo some unknown decomposition reaction by themselves, and, if the olefinic compounds are not very reactive, the halides decompose without adding to the olefins. Poor yields also are to be expected with vinylic halides deactivated with electron-supplying substituents when they are treated with olefinic compounds of only moderate reactivity. Still, many useful combinations remain which should allow this reaction to be of considerable utility in the synthesis of various types of substituted conjugated dienes.

Experimental Section

(*E*)-1-Iodo-1-hexene. This compound was prepared by the method of Zweifel and Steele:[4] NMR ($CDCl_3$) τ 2 t, 3.47, 3.72 (1 H) (J = 7 Hz); d, 4.16 (J = 15 Hz) (1 H); m 7.80–8.31 (2 H); m 8.49–8.98 (4 H), m 8.98–9.35 (3 H).

1-Iodo-1-hexyne. 1-Hexyne (36 g, 0.44 mol) in 200 ml of ether was placed in a dry 1-l. three-necked flask equipped with a pressure-equalizing dropping funnel, a reflux condenser, and a mechanical stirrer. The system was flushed with argon and maintained under argon throughout the course of the reaction. Then 300 ml (0.5 mol) of 1.67 M methyllithium in ether (commercial) was added through the dropping funnel at such a rate as to cause gentle refluxing. After the addition, the mixture was stirred for 1 hr at room temperature. After cooling in an acetone–Dry Ice bath, 127 g (0.5 mol) of iodine was added. The bath was allowed to come gradually to room temperature (ca. 2 hr) and the reaction was continued overnight at room temperature. Water (200 ml) was added and the entire mixture was combined with 300 ml more water in a separatory funnel. The phases were separated and the aqueous phase was extracted with two 100-ml portions of ether. The ether phases were combined, washed with 300 ml of a saturated aqueous sodium thiosulfate solution, dried over magnesium sulfate, and filtered. The ether was removed under reduced pressure and the residue was distilled, yielding 77 g (84%) of 1-iodo-1-hexyne, bp 75° (20 mm).[5]

(*Z*)-1-Iodo-1-hexene. Our attempts to prepare this compound via dicyclohexylborane reduction of 1-iodo-2-hexyne[5] resulted in a product containing about 15% of the E isomer. Diimide reduction, on the other hand, was much more specific.

Dipotassium azodicarboxylate was prepared by adding 90 g (0.77 mol) of azodicarbonamide to a mechanically stirred 40% aqueous potassium hydroxide solution (270 ml), cooled by an external acetone–ice bath at a rate such that the temperature of the reaction mixture did not exceed 10° (~30 min). After the addition the mixture was stirred for an additional 45 min (below 10°) and then filtered and washed with 300 ml of cold methanol.

The solid potassium salt was placed in a 1-l. flask with 400 ml of methanol and 20 g (0.096 mol) of 1-iodo-1-hexyne was added. The mixture was stirred magnetically while a solution of 75 ml of acetic acid in 200 ml of methanol was added at such a rate as to cause gentle boiling. After the addition, the mixture was colorless. The reaction mixture was transferred to a separatory funnel containing 2 l. of water and extracted with three 250-ml portions of pentane. The pentane fractions were combined, washed with two 1-l. portions of water, dried over magnesium sulfate, and filtered. The pentane was removed under reduced pressure. VPC examination of the residue showed that all of the 1-iodo-1-hexyne had reacted, but that in addition to the desired (*Z*)-1-iodo-1-hexene, a significant amount of 1-iodohexane had also been formed. The residue was dissolved in 75 ml of *n*-butylamine and the solution was allowed to stand at room temperature. After 45 min, VPC analysis showed that all of the 1-iodohexane had reacted. The solution was diluted with 200 ml of pentane and washed with two 300-ml portions of water, 300 ml of cold 10% HCl (aqueous), and then with 300 ml more of water. The organic phase was dried over magnesium sulfate and filtered and the pentane was removed under reduced pressure, leaving 11.2 g (55.5%) of (*Z*)-1-iodo-1-hexene as a colorless liquid which was shown to be pure by VPC and NMR: NMR (neat) τ m, 3.72–4.17, s 3.89 (2 H), m 7.68–8.15 (2 H), m 8.33–8.78 (4 H), m 8.78–9.32 (3 H).

(*Z*)-1-Hexene-1-boronic Acid. A solution of 20 ml (44 mmol) of 2.2 *M* *n*-butyllithium (commercial) in hexane and 10 ml of anhydrous ether was placed in a dry, argon-filled, 250-ml, three-neck flask equipped with a pressure equalizer, a dropping funnel, and a magnetic stirring bar. The mixture was cooled in an acetone–Dry Ice bath and 6.3 g (30 mmol) of (*Z*)-1-iodo-1-hexene in 15 ml of ether was added over a 15-min period. The mixture was stirred for 3 hr at −78° and then 15 g (76 mmol) of tri-*n*-butyl borate was added over a 10-min period. The acetone–Dry Ice bath was allowed to come gradually to room temperature (ca. 3 hr) and the mixture was stirred at room temperature overnight (ca. 16 hr). The reaction mixture was diluted with 200 ml of water and extracted with three 50-ml portions of ether which were then combined and extracted with two 100-ml portions of 10% aqueous sodium hydroxide. The aqueous fractions were combined, washed with 50 ml of ether, made acidic with cold 5% HCl, and extracted with four 50-ml portions of ether. The ether phases were combined, dried over anhydrous magnesium sulfate, and filtered. The ether was removed under reduced pressure, leaving a clear, colorless oil which was presumed to be the boronic anhydride. The addition of 20 ml of water caused almost instantaneous formation of a white solid. The mixture was stirred for 30 min at room temperature and then at 5° for 30 min. The solid was filtered and allowed to air dry, giving 1.01 g (26%): mp 62–63°; NMR (acetone-d_6) τ s (broad), 3.16 (2 H); 2 t, 3.57, 3.79 (J = 7 Hz) (1 H), d, 4.63 (J = 13 Hz) (1 H); m, 7.30–7.75 (2 H); m, 8.38–8.80 (4 H); m, 8.80–9.26 (3 H).

(*E*)-1-Hexene-1-boronic Acid. This compound was prepared by the method of Brown and Gupta:[6] NMR (acetone-d_6) τ s (broad), 3.08 (2 H); 2 t, 3.29, 3.59 (J = 7 Hz) (1 H); 2 t, 4.48, 4.78 (J = 1 Hz) (1 H); m, 7.70–8.12 (2 H); m, 8.41–8.90 (4 H); m, 8.90–9.35 (3 H).

(*Z*)-1-Bromo-1-hexene. This material was prepared essentially by the method of Brown et al.[7] A solution of 25.6 g (0.2 mol) of *trans*-1-hexene-1-boronic acid in 200 ml of methylene chloride and 100 ml of ether was cooled to −20°, while 32 g (0.2 mol) of bromine was added keeping the reaction temperature below −20°. The reaction mixture was stirred for 1 hr at −20° and then 10.8 g (0.2 mol) of sodium methoxide in 200 ml of methanol was added while still maintaining the reaction temperature below −20°. After the addition, the mixture was stirred at −20° for 45 min and then warmed to room temperature, and shaken with 400 ml of water. The organic phase was separated and washed with saturated aqueous sodium thiosulfate and then dried over magnesium sulfate. Distillation yielded 16.5 g (50.7%) of (*Z*)-1-bromo-1-hexene: bp 47–48° (25 mm); NMR[8] (neat) τ m, 3.80–4.17, s 3.89 (2 H); m, 3.68–2.15 (2 H); m, 8.33–8.78 (4 H); m, 8.78–9.32 (3 H).

Methyl (*E*)-3-Bromo-2-methylpropenoate. This material was prepared by the method of Caubere:[9] NMR (neat) τ-q, 2.64 (J = 1.6 Hz) (1 H); s, 6.32 (3 H); d, 8.11 (J = 1.6 Hz) (3 H).

General Method for the Reaction of Vinylic Halides with Olefins. The indicated quantities (see Table I) of vinylic halide, olefin, amine, and catalyst were placed in a heavy-walled Pyrex reaction tube which was flushed with argon and capped with a self-sealing rubber-lined cap. The mixture was shaken well and heated at the indicated temperature.

In reactions where yields were determined by VPC analysis, an internal standard was added initially and the reactions were run until the yields of products no longer increased.

In cases where products were isolated, the reactions were run until VPC analysis showed that all of the starting halide had reacted. The tubes were then opened and the reaction mixtures were extracted several times with ether. The extracts were filtered, the ether was removed under reduced pressure, and the residue was either distilled (see Table I) or purified as described below.

1,4-Diphenyl-1,3-butadiene. The residue from the ether solution was first sublimed and then recrystallized from methanol.

(*E,E*)- and (*E,Z*)-Dimethyl 2,5-Dimethyl-2,4-hexadienoate. The residue from the ether solution was placed in the bottom of a sublimator. An aluminum foil dish was placed above the residue and under the cold finger. Cold water was run through the cold finger and the sublimator was heated on a steam bath overnight at 0.2 mm. A light yellow solid identified as the *E,E* isomer was deposited on the cold finger. This was recrystallized from hexane. The aluminum foil dish contained the *E,Z* isomer as a pale yellow oil.

Dimethyl 1-Methyl-3-phenylcyclohexene-4,5-dicarboxylate. 2-Bromopropene (2.42 g, 20 mmol), styrene (2.60 g, 25 mmol), dimethyl maleate (3.60 g, 25 mmol), triethylamine (2.52 g, 25 mmol), and diacetatobis(triphenylphosphine)palladium (0.149 g, 0.2 mmol) were placed in a heavy-walled Pyrex reaction tube. The tube was flushed with argon, capped, and then heated on a steam bath. After 96 hr, all of the 2-bromopropene had reacted (VPC). The mixture was cooled to room temperature and extracted several times with ether. The ether extracts were combined, treated with decolorizing carbon, and filtered. Ether was removed under reduced pressure, leaving a pale yellow oil. The residue was distilled at 0.15 mm; most of the material was distilled at 138–150° (0.15 mm). Addition of a small amount of ether to the distillate caused precipitation of a colorless solid which was filtered and air dried, mp 107–109.5°C, 1.39 g (24.2%). A NMR spectrum was consistent with that expected for the desired product. Recrystallization from ether gave material of mp 111–112°.

The ether-soluble portion was purified further by chromatography on silica gel. Elution with benzene and removal of the solvent yielded 1.61 g (28.0%) of a colorless liquid which was shown by NMR to be a second isomer of the above expected diester. An analytical sample of this material was obtained by preparative VPC (15 ft × 0.25 in., 20% SE-30, 325°, retention time 470 sec).

(*E,E*)-Dimethyl 2-Methyl-2,4-hexadienoate. Methyl (*E*)-3-bromo-2-methylpropenoate (35.8 g, 200 mmol), 21.4 g (250 mmol) of methyl acrylate, 25.2 g (250 mmol) of triethylamine, 0.448 g (2.0 mmol) of palladium acetate, and 1.04 g (4.0 mmol) of triphenylphosphine were placed in a 250-ml three-necked flask equipped with a mechanical stirrer and a reflux condenser. The flask was flushed with argon and maintained under an argon atmosphere throughout the course of the reaction. The reaction mixture was heated with stirring on a steam bath for 8 hr, after which time all of the starting bromide had reacted (VPC). The mixture was diluted with 300 ml of ether and filtered through a sintered glass funnel. The residue on the filter was washed well with about 500 ml more of ether. The ether, excess methyl acrylate, and triethylamine were removed under reduced pressure and the residue was distilled at 0.65 mm. A forerun boiling at less than 89° of 2.5 g was obtained, then the bulk of material distilled at 89°. This was then recrystallized from hexane, yielding 22 g (59.8%) of pure product.

Hydrogenation of Dimethyl Cyclohexenedicarboxylates. A mixture of 0.1 g of the distilled product from the reaction of vinyl iodide and methyl acrylate, 1 ml of tetrahydrofuran, and 0.075 g of PtO_2 was placed in a small bomb equipped with a magnetic stirring bar. The system was flushed several times with hydrogen, pressured to 700 psi with hydrogen, and heated with magnetic stirring in a steam bath for 16 hr. The bomb was cooled to room temperature and opened and the reaction mixture was filtered through cotton. A VPC examination showed that the two peaks for the starting cyclohexenes had disappeared and that a single new product had been formed. This was shown to be dimethyl *cis*-cyclohexane-1,2-dicarboxylate by VPC comparison with an authentic sample on three different columns (5 ft × 0.25 in., 20% SE-30, 175°, retention time ~230 sec; 10 ft × 0.25 in., 20% Carbowax 20M, 215°, retention time ~710 sec; 5 ft × 0.25 in., 20% DEGS, 185°, retention time ~160 sec). The authentic ester was obtained by reaction of diazomethane with the cis acid, mp 189–190° (reported mp 192°[10]).

Reaction of 1-Halo-1-hexenes with Ethylene. The olefinic halide (10 mmol), triethylamine (12.5 mmol), diacetatobis(triphenylphosphine)palladium (0.1 mmol), and *n*-nonane (2.5 mmol) were placed in a 60-ml Teflon-lined bomb with a magnetic stirring bar. The system was flushed several times with ethylene and then

pressured to 700 psi with ethylene and heated with magnetic stirring at the indicated temperatures. The extent of reaction was measured by VPC until no more of the starting olefinic halide remained. Yields were determined by using the *n*-nonane as the internal standard (10 ft × 0.25 in., 20% DC-550, 140°). Products were identified by comparison of their VPC retention times with those of authentic samples and by mass spectral and NMR analyses of samples isolated by VPC.

Reaction of (*E*)-1-Hexene-1-boronic Acid with Methyl Acrylate. (*E*)-1-Hexene-1-boronic acid (0.64 g, 5 mmol), 10 ml of methyl acrylate, and 2 ml of triethylamine were stirred magnetically at 0° in an ice bath and 1.12 g (5 mmol) of $Pd(OAc)_2$ was added. The bath was allowed to gradually come to room temperature and the reaction mixture was stirred overnight at room temperature.

The mixture was then centrifuged and the residue was washed several times with ether. The supernatant liquids were combined and put through an alumina column, eluting with 1 l. of ether. Removal of the ether, methyl acrylate, and triethylamine under reduced pressure left 0.697 g of a pale yellow oil which was identified by its NMR spectrum as essentially pure methyl (*E,E*)-2,4-nonadieneoate (82%).

Reaction of (Z)-1-Hexene-1-boronic Acid with Methyl Acrylate. (*Z*)-1-Hexene-1-boronic acid (0.256 g, 2 mmol), 5 ml of methyl acrylate, 1 ml of triethylamine, and 0.448 g (2 mmol) of $Pd(OAc)_2$ were allowed to react and the product was isolated as in the preceding experiment. There was obtained 0.282 g of product which, by NMR and VPC analysis, was found to be mainly (*E,Z*)-2,4-hexadienoate (no *E,E* ester was present). The residue was dissolved in ether with 0.154 g (1 mmol) of biphenyl and the yield of the *E,Z* ester was determined by VPC (5 ft × 0.25 in., 20% DEGS, 140°) to be 70%. A pure sample of the ester was isolated by VPC.

Acknowledgment. This research was supported by a grant from the National Science Foundation.

Registry No.—1-Iodo-1-hexyne, 1119-67-1; (*Z*)-1-hexene-1-boronic acid, 54354-55-1; tri-*n*-butyl borate, 688-74-4; (*E*)-1-hexene-1-boronic acid, 42599-18-8; $Pd[P(C_6H_5)_3]_2(OAc)_2$, 14588-08-0.

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Organosilicon Compounds. XX. Synthesis of Aromatic Diamines via Trimethylsilyl-Protecting Aniline Intermediates

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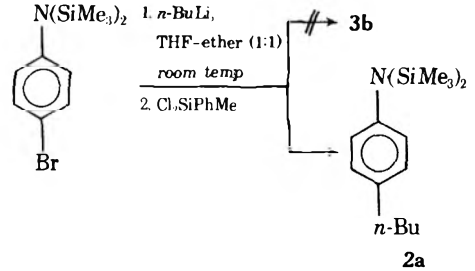
A synthetic approach using a trimethylsilyl protecting group was employed to produce silicon- and diketo-containing diamines. Thus, the halogen–metal interchange of *N,N*-bis(trimethylsilyl)bromoanilines with *n*-butyllithium in ether produced the corresponding lithium derivatives, which were treated with dichloro-substituted silanes or dinitriles to afford the *N,N*-bis(trimethylsilyl)silicon-containing dianilines or the corresponding lithioimines, respectively. Hydrolysis removed the trimethylsilyl-protecting groups and converted the lithioimines to the corresponding carbonyl compounds to afford the free diamines.

Two investigators[2,3] have reported the synthesis of substituted anilines by treating, e.g., *p*-bromo-*N,N*-bis(trimethylsilyl)aniline with *n*-butyllithium, followed by treating the resulting lithium derivative with chlorotrimethylsilane to afford *p*-trimethylsilyl-*N,N*-bis(trimethylsilyl)aniline. The trimethylsilyl moieties blocked the amine nitrogen atom to the effects of *n*-butyllithium, since this silicon–nitrogen bond was inert to *n*-butyllithium under the reaction conditions, yet allowed the more selective halogen–metal interchange to produce a highly reactive organolithium reagent. After the reaction with chlorotrimethylsilane, hydrolysis of the trimethylsilyl protecting groups afforded *p*-trimethylsilylaniline. This same technique was employed by Greber[4] to prepare several bis(*p*-aminophenyl)methylsiloxane oligomers. The need for aromatic diamines containing flexiblizing groups for the synthesis of thermally stable polyamides and polyimides led to the expansion of this protecting technique to prepare silicon- and diketo-containing diamine precursors.

Scheme I describes the preparation of both meta and para isomers of several silicon-containing diamines. *p*- or *m*-Bromo-*N,N*-bis(trimethylsilyl)aniline (**1** or **5**) was prepared by treating the corresponding bromoaniline (1 mol) with *n*-butyllithium (2.3 mol) in THF at room temperature, followed by chlorotrimethylsilane (2.3 mol). A maximum yield of reproducibly pure product was obtained when this excess of *n*-butyllithium–chlorotrimethylsilane was utilized. Without this excess an azeotrope, e.g., of **1** and *p*-bromo-*N*-trimethylsilylaniline, was invariably formed.

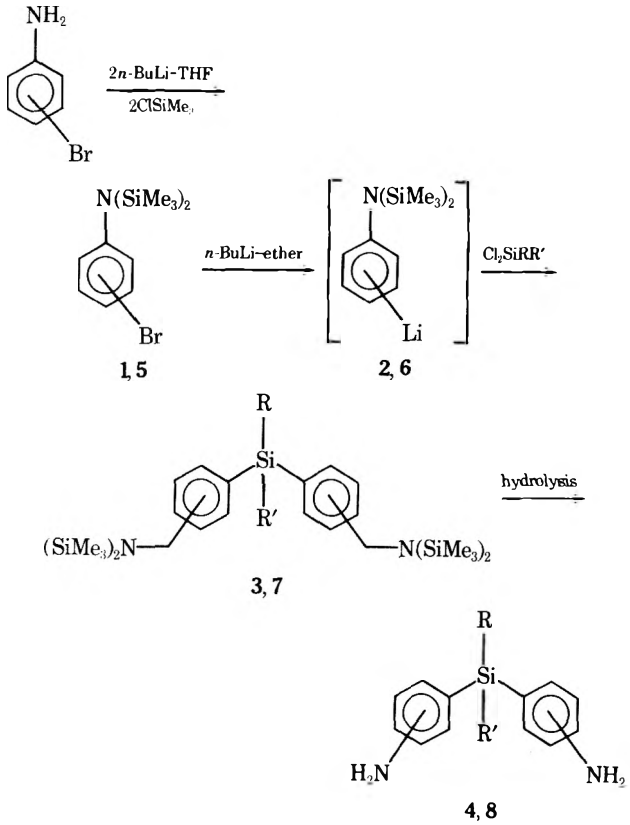
A halogen–metal interchange of the bromine atoms of **1** or **5** with *n*-butyllithium in ether at 0° was found to produce the lithium derivatives **2** or **6** most readily. These lithio species were treated in situ with the appropriately substituted dichlorosilanes to form the fully silylated diamines **3** or **7**. The attempted preparation of **2** (and subsequent conversion to **3b**) in THF–ether (1:1) at room temperature afforded 4-(*n*-butyl)-*N,N*-bis(trimethylsilyl)aniline (**2a**) in 42% yield.



2a

The fully trimethylsilylated diamines (**3** and **7**) were readily hydrolyzed to their silicon-containing free diamines (**4** and **8**) in wet acetone or with a saturated solution of an-

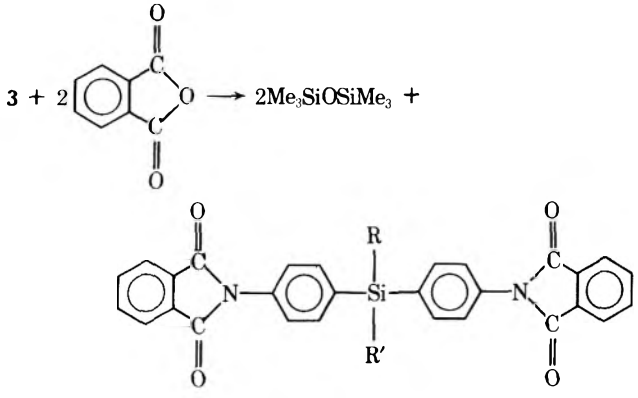
Scheme I



a, R = R′ = Me
b, R = Me; R′ = Ph
c, R = R′ = Ph
1-4 para isomeric sequence
5-8 meta isomeric sequence

hydrous HCl in ether, followed by neutralization. Pure **4a** was prepared by the hydrolysis of an analytical sample of **3a** in wet acetone, followed by drying with anhydrous $MgSO_4$ and molecular sieves and removal of all volatiles in vacuo at room temperature. This alternate procedure was required only for **4a** because of its decomposition during fractionation at reduced pressure to afford a small yield of impure **4a** and considerable resinous decomposition products. The attempted solvolysis of **3a** in refluxing ethanol or methanol afforded good yields of aniline. These findings substantiate an earlier report by Kipping and Cusa[5] of the instability of certain *p*-aminophenylsilanes.

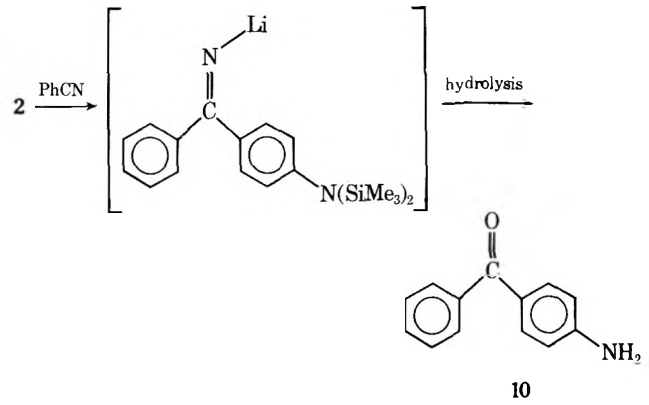
In addition, as previously reported,[6] the fully silylated diamines (**3**) were readily imidized directly to their di-



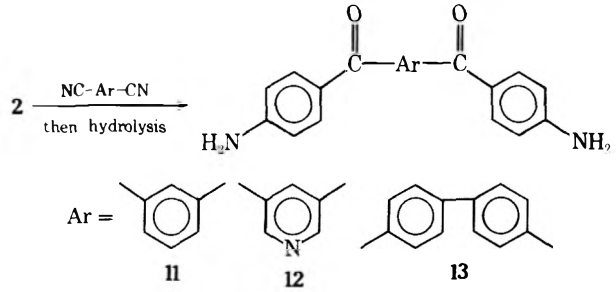
R = R′ = Me
R = Me; R′ = Ph
R = R′ = Ph

imides on treatment with 2 mol of phthalic anhydride and with loss of hexamethyldisiloxane.

Organolithium reagents are known to readily add to aromatic nitriles to form lithioimines, which can be hydrolyzed to ketones.[7] That trimethylsilyl-protected aniline organolithium reagents likewise react with nitriles was demonstrated in a model compound synthesis. *p*-Aminobenzophenone (**10**) was prepared by treating **2** with benzonitrile.

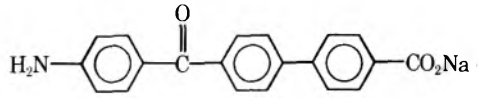


Likewise, the reaction of **2** with three aromatic dinitriles, 1,3-dicyanobenzene, 3,5-dicyanopyridine, and 4,4′-dicyanobiphenyl afforded their dilithioimines, which were hydrolyzed to the free diamines, 1,3-bis(4-aminobenzoyl)benzene (**11**), 3,5-bis(4-aminobenzoyl)pyridine (**12**), and 4,4′-bis(4-aminobenzoyl)biphenyl (**13**), respectively. Considerable by-



product formation accompanied the preparation of **12**. The reaction of **2** with 2,6-dicyanopyridine afforded a black, oily material which was not identified.

The only by-product from the preparation of **13** was 4-(4-aminobenzoyl)-4′-biphenylcarboxylic acid sodium salt.



When crude **13** was crystallized from acetone containing a few drops of dilute acid, the product displayed a carboxylic acid absorption in the ir.[8] Likewise, when precipitated from basic acetone solution, crude **13** displayed two NH_2 lines in the NMR. Repeated crystallization from pyridine–water (2:1) and acetone–water (1:1) afforded yellow crystals of pure **13**, which displayed only one NH_2 NMR absorption. The by-product would be expected to arise from incomplete addition of **2** to both nitrile moieties of 4,4′-dicyanobiphenyl, followed by acid hydrolysis of unreacted nitrile moiety to the carboxylic acid.

In summary, we have reported the reaction of two *N,N*-bis(trimethylsilyl)organolithium reagents with chlorosilanes and nitriles to produce, after hydrolysis and neutralization, new silicon- and keto-containing aromatic diamines. This technique in principle allows the synthesis of a number of isomers not obtainable by conventional electrophilic aromatic substitution reactions.

Table I[m]
Experimental Summary

Compd	Yield, %	Mp, °C	Bp, °C (mm)	n_D (°C)	NMR, δ	Ir, cm^{-1}	Formula
1[n]	61		155.5–158 (23)	1.5129 (28)	7.3 (2 H, d, aryl CH ortho to Br), 6.7 (2 H, d, aryl CH ortho to N), 0.0 (18 H, s, silyl CH_3)	1252, 840 (silyl CH_3)[f]	$C_{12}H_{22}BrSi_2$
2a	42		97 (0.34)	1.4830 (25)	6.75 and 7.0 (2 H each, d each, aryl CH), 2.55 (2 H, t, methylene α to ring), 0.75–1.9 (7 H, m, remaining aliphatic protons of *n*-butyl), 0.05 (18 H, s, silyl CH_3)	1250, 825 (silyl CH_3), 2940 (strong, complex alkyl CH)[f]	$C_{16}H_{31}NSi_2$
3a[o]	70		154.5–155 (0.02)	1.5120 (25)	7.25 (4 H, d, aryl CH ortho to Si), 6.8 (4 H, d, aryl CH ortho to N) 0.45 (6 H, s, silyl CH_3), 0.05 (36 H, s, silyl CH_3)	1250, 815 (silyl CH_3)[f]	$C_{26}H_{50}N_2Si_5$
3b	59	93–95	202–204.5 (0.03)	1.5369 (24)	7.1–7.65 (9 H, m, silyl Ph and aryl CH ortho to Si), 6.85 (4 H, d, aryl CH ortho to N), 0.75 (3 H, s, silyl CH_3), 0.05 (36 H, s, silyl CH_3)	1246, 830 (silyl CH_3), 1425, 1105, 695 (silyl Ph)[f]	$C_{31}H_{52}N_2Si_5$
3c	60		230–234 (0.005)		7.05–7.6 (14 H, m, silyl Ph and aryl CH ortho to Si), 6.85 (4 H, d, aryl CH ortho to N), 0.05(36 H, s, silyl CH_3)	1250, 830 (silyl CH_3), 1428, 1110, 700 (silyl Ph)[i]	$C_{36}H_{54}N_2Si_5$
4a	65		*b*		7.2 (4 H, d, aryl CH ortho to Si), 6.4 (4 H, d, aryl CH ortho to NH_2), 3.35 (4 H, s, NH_2), 0.4 (6 H, s, silyl CH_3)	3408 (doublet, NH_2), 1250, 820 (silyl CH_3)[f]	$C_{14}H_{18}N_2Si$
4b	81	97–98			6.85–7.6 (9 H, m, silyl Ph and aryl CH ortho to Si), 6.35 (4 H, d, aryl CH ortho to NH_2), 3.3 (4 H, s, NH_2), 0.6 (3 H, s, silyl CH_3)	3404 (doublet, NH_2), 1249, 820 (silyl CH_3), 1425, 1105, 690 (silyl Ph)[f]	$C_{19}H_{20}N_2Si$
4c	100[a]	205.5–207			6.9–8.0 (14 H, m, aryl CH) 6.7 (4 H, d, aryl CH ortho to NH_2), 5.3 (4 H, s, NH_2)[d]	3398 (doublet, NH_2), 1410, 1089, 688 (silyl Ph)[h]	$C_{24}H_{22}N_2Si$
5	58		149 (24)	1.5115 (24)	6.65–7.35 (4 H, m, aryl CH), 0.05 (18 H, s, silyl CH_3)[c]	1254, 841 (silyl CH_3)[f]	$C_{12}H_{22}BrNSi_2$
7a	67		140 (0.01)	1.5060 (24)	6.75–7.3 (8 H, m, aryl CH), 0.5 (6 H, s, silyl CH_3), 0.0 (36 H, s, silyl CH_3)	1250, 830 (silyl CH_3)[f]	$C_{26}H_{50}N_2Si_5$
7b	63		166 (0.005)	1.5301 (25)	6.75–7.7 (13 H, m, aryl CH), 0.75 (3 H, s, silyl CH_3), 0.05 (36 H, s, silyl CH_3 of N)	1250, 835 (silyl CH_3), 1430, 1100, 700 (silyl Ph)[f]	$C_{31}H_{52}N_2Si_5$
7c	79		191–193 (0.025)	1.5518 (25)	6.85–7.8 (18 H, m, aryl CH), 0.0 (36 H, s, silyl CH_3)	1250, 820 (silyl CH_3) 1430, 1108, 700 (silyl Ph)[f]	$C_{36}H_{54}N_2Si_5$
8a	81		156–156.5 (0.02)	1.6170 (25)	6.35–7.4 (8 H, m, aryl CH), 3.3 (4 H, s, NH_2), 0.4 (6 H, s, silyl CH_3)	3400 (doublet NH_2), 1248, 808 (silyl CH_3)[f]	$C_{14}H_{18}N_2Si$
8b	82	96–97	226–229 (0.075)		6.3–7.6 (13 H, m, aryl CH), 3.15 (4 H, s, NH_2), 0.7 (3 H, s, silyl CH_3)	3413 (doublet, NH_2), 1253, 780 (silyl CH_3), 1430, 1111, 700 (silyl Ph)[f]	$C_{19}H_{20}N_2Si$
8c	70	279–280.5			6.5–7.85 (18 H, m, aryl CH), 5.05 (4 H, s, NH_2)[d]	3408 (doublet, NH_2), 1415, 1098, 688 (silyl Ph)[h]	$C_{24}H_{22}N_2Si$

Table I
(Continued)

Compd	Yield, %	Mp, °C	Bp, °C (mm)	nD (°C)	NMR, δ	Ir, cm^{-1}	Formula
10	85[j]	106–107[k]			7.5 (5 H, s, aryl CH), 7.4 (2 H, d, aryl CH ortho to carbonyl), 6.7 (2 H, d aryl CH ortho to NH_2), 5.0 (2 H, broad s, NH_2)[e]	3350 (doublet, NH_2), 1628 (broad and strong carbonyl)[h]	$C_{13}H_{11}NO$
11	89[l]	216.5–217.5			7.4–8.0 (8 H, m, aryl CH ortho to carbonyl, aryl CH of center ring), 6.65 (4 H, d, aryl CH ortho to NH_2), 6.15 (4 H, s, NH_2)	3340 (doublet, NH_2), 1620 (broad and strong carbonyl)[h]	$C_{20}H_{16}N_2O_2$
12	18	292–294			8.95 (2 H, d, H_2 and H_6 Py), 8.1 (1 H, t, H_4 Py), 7.65 (4 H, d, aryl CH ortho to carbonyl), 6.7 (4 H, d, aryl CH ortho to NH_2), 6.3 (4 H, s, NH_2)[d]	3350 (doublet, NH_2), 1645 (strong carbonyl), 1600 (aryl C=C)[g]	$C_{19}H_{15}N_3O_2$
13	50	237–239			7.5–8.1 (12 H, m, biphenyl CH and aryl CH ortho to carbonyl), 6.7 (4 H, d, aryl CH ortho to NH_2), 6.2 (4 H, s, NH_2)[d]	3350 (doublet, NH_2), 1621 (broad carbonyl)[h]	$C_{26}H_{20}N_2O_2$

[a] Based on the hydrochloride salt, mp 134–135°. [b] See Experimental Section for **4a**. [c] Cyclohexane standard. [d] DMSO-d_6. [e] Acetone-d_6. [f] Neat. [g] Nujol. [h] KBr. [i] Hexane solution, 5%. [j] Based on the crude hydrochloride salt, mp 240–256°. [k] The NMR showed 2 mol of water per mole of **10**; the literature reports the melting point of **10** as 121–124°, undoubtedly the anhydrate. [l] Based on the crude hydrochloride salt. [m] Satisfactory analytical data for carbon and hydrogen (and nitrogen for 8b) were reported for all new compounds listed in Table I except 3c, which was a high-boiling oil. [n] Reference 3. [o] Reference 11.

Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were determined on a Varian A-60D spectrometer using tetramethylsilane as the internal standard in CCl_4, unless otherwise specified, at concentrations of approximately 30% by weight and are reported in parts per million. Analyses were performed by Chemalytics, Inc., Tempe, Ariz. All reactions employing *n*-butyllithium were carried out under anhydrous nitrogen in glassware previously dried for several hours at 110°. The free diamines were recrystallized under sparging nitrogen to prevent discoloration.

Table I provides an experimental summary of all compounds prepared. In addition, a detailed procedure of several typical reactions has been included.

4-Bromo-*N*,*N*-bis(trimethylsilyl)aniline (1). To a solution of *p*-bromoaniline (68.8 g, 0.40 mol) in 400 ml of freshly distilled THF[9] was added *n*-butyllithium (418 ml, 0.92 mol, a 15% excess) of 2.2 *M* in hexane dropwise at 0°. After a reaction period of 2–3 hr, during which the solution was allowed to warm to room temperature, chlorotrimethylsilane (117 ml, 0.92 mol, a 15% excess) was added dropwise, and the solution was stirred overnight. Filtration of the LiCl was conducted in a drybox under anhydrous nitrogen or, while exposed to the atmosphere, as rapidly as possible into freshly dried, lukewarm glassware.

Distillation afforded 77.3 g (61%) of **1**, bp 155.5–158° (23 mm), n^{28}D 1.5129. The literature[3] reports the preparation via ethylmagnesium bromide exchange in 43% yield, bp 106° (1.2mm), n^{25}D 1.5140.

Bis[*N*,*N*-bis(trimethylsilyl)-3-aminophenyl]diphenylsilane (7c). To a solution of **5** (86.6 g, 0.275 mol) in 500 ml of anhydrous ether[10] was added *n*-butyllithium (125 ml, 0.275 mol) of 2.2 *M* in hexane dropwise at 0°. After stirring for 2 hr at 0°, redistilled dichlorodiphenylsilane (34.6 g, 0.135 mol) was added dropwise, and the resulting mixture was stirred overnight and then refluxed for 1 hr. The LiCl was removed by filtration and the ether removed in vacuo. Distillation afforded 70.4 g (79%) of **7c**, bp 191–193° (0.025 mm), n^{25}D 1.5518.

Bis(3-aminophenyl)diphenylsilane (8c). A sample of **7c** in ether was hydrolyzed with sparging HCl gas for 2 min, and then neutralized with 5% aqueous NaOH solution under sparging nitrogen. After filtration, washing with water, and recrystallization from acetone under sparging nitrogen, a 70% yield of **8c**, mp 279–280.5°, was obtained.

Bis(4-aminophenyl)dimethylsilane (4a). A solution of **3a** (12.9 g, 0.024 mol) and water (3.5 g, 0.192 mol, a 100% excess) in 100 ml of acetone was stirred at room temperature overnight. The solution was then stirred for 24 hr with anhydrous $MgSO_4$ and for 12 hr with molecular sieves. Filtration and removal of the acetone in vacuo gave a pale tan oil which analyzed correctly and whose proposed structure corresponded to spectral data (see Table I).

This material could not be recrystallized; vacuum distillation afforded a small yield of broad-boiling **4a**, accompanied by considerable decomposition.

Earlier attempts to isolate **4a** following the ethanolysis of **3a** afforded an 89% yield of aniline; an attempted methanolysis of **3a** gave aniline also.[11]

1,3-Bis(4-aminobenzoyl)benzene (11). To a solution of **1** (30.0 g, 0.095 mol) in 600 ml of anhydrous ether was added *n*-butyllithium (40 ml, 0.095 mol) of 2.4 *M* in hexane at 0°. After the reaction mixture was allowed to stir for 2 hr at room temperature, the solution was again cooled to 0° and 1,3-dicyanobenzene (6.1 g, 0.048 mol) in 60 ml of anhydrous THF was added over a 10-min period. The resulting blood-red solution was allowed to stir for 4 hr at room temperature before it was hydrolyzed with excess aqueous 3 *N* HCl to yield 16.4 g (89%) of crude hydrochloride salt. A sample of this material was neutralized with 10% aqueous NaOH and recrystallized from ethanol–water (9:1) under sparging nitrogen to afford pure **11**, mp 216.5–217.5°.

Attempted Preparation of 2 in THF. Isolation of 4-(*n*-Butyl)-*N*,*N*-bis(trimethylsilyl)aniline (2a). To a solution of **1** (90.0 g, 0.285 mol) in 400 ml of anhydrous THF–ether (1:1) was added *n*-butyllithium (119 ml, 0.285 mol) of 2.39 *M* in hexane dropwise at 0°. The solution was allowed to stir at room temperature for 4 hr before dichloromethylphenylsilane (27.2 g, 0.143 mol) was added dropwise. After stirring overnight the LiCl was removed by filtration and the solvents were removed in vacuo. Fractionation afforded 35.4 g (42%) of **2a**, bp 97° (0.34 mm), n^{25}D 1.4830.

Acknowledgment. The authors express their thanks to NASA, Langley Research Center, for Grant No. 25-005-005-008.

Registry No.—1, 5089-33-8; **2a**, 54120-39-7; **3a**, 41992-38-5; **3b**, 42077-73-6; **3c**, 41992-39-6; **4a**, 54120-40-0; **4b**, 54120-41-1; **4c**, 3454-24-8; **5**, 54120-42-2; **7a**, 54120-43-3; **7b**, 54120-44-4; **7c**, 54120-45-5; **8a**, 54120-46-6; **8b**, 54181-91-8; **8c**, 54120-47-7; **10**, 1137-41-3; **11**, 54120-48-8; **12**, 54120-49-9; **13**, 54120-50-2; 1,3-dicyanobenzene, 626-17-5; 3,5-dicyanopyridine, 1195-58-0; 4,4′-dicyanobiphenyl, 1591-30-6; *p*-bromoaniline, 106-40-1; chlorotrimethylsilane, 75-77-4; dichlorodiphenylsilane, 80-10-4; dichloromethylphenylsilane, 149-74-6; dichlorodimethylsilane, 75-78-5.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of J. R. Pratt, University of Southern Mississippi, 1974.
(2) W. Broser and W. Harrer, *Angew. Chem.*, **77**, 1139 (1965); *Angew. Chem., Int. Ed. Engl.*, **4**, 1081 (1965).
(3) D. R. M. Walton, *J. Chem. Soc. C*, 1706 (1966).
(4) G. Greber, *J. Prakt. Chem.*, **313**, 461 (1971).
(5) F. S. Kipping and N. W. Cusa, *J. Chem. Soc.*, 1088 (1935).
(6) J. R. Pratt and S. F. Thames, *Synthesis*, **4**, 223 (1973).
(7) F. C. Schaefer, "Chemistry of the Cyano Groups", Z. Rappoport, Ed., Interscience, New York, N.Y., 1970, p 276.
(8) The crude material displayed a broad carboxylic dimer stretch at 2950 cm^{-1} and a strong acid carbonyl stretch at 1630 cm^{-1}. Both absorptions disappeared after recrystallization from acetone in the presence of dilute base.
(9) Redistilled from $LiAlH_4$ or CaH_2 under nitrogen and stored over molecular sieves.
(10) Stored over sodium ribbon.
(11) F. H. Pinkerton, Dissertation, University of Southern Mississippi, 1971, p 173.

Dipole Stabilized Carbanions. Reactions of Benzoate Esters with Lithium 2,2,6,6-Tetramethylpiperidide

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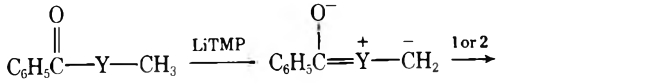
The reactions of benzyl benzoate (**3**), allyl benzoate (**5**), and vinyl benzoate (**12**) with lithium 2,2,6,6-tetramethylpiperidide at −78° in tetrahydrofuran give, respectively, benzoin benzoate (**4**), α-benzoyl allyl benzoate (**6**) and α-benzoyl-β-methyl vinyl benzoate (**7**), and α-benzoyl vinyl benzoate (**13**) via formation of a carbanion adjacent to oxygen followed by nucleophilic attack of the anion on the starting ester. However, methyl, ethyl, and the propyl and butyl benzoates, **15** and **17–22**, in the presence of the same base lose an ortho proton from the ring to provide, after benzoylation, the o-benzoylbenzoates **16** and **23–28** in a synthetically useful reaction. Related proton abstractions lead to substitution of benzophenone ortho to the carbonyl and to benzoylation of benzyl β,β-diphenylacrylate adjacent to the carbonyl group. It does not appear that the potential dipole stabilization of the ester function is sufficient, under these conditions and in the absence of additional stabilization, to direct proton abstraction to the carbon adjacent to oxygen.

The novel abstraction of a proton from the methyl groups of *N,N*-dimethylbenzamide and methyl thiobenzoate by lithium 2,2,6,6-tetramethylpiperidide (LiTMP) to generate the transient nitrogen- and sulfur-substituted dipole-stabilized carbanions **1** and **2** has been communicated.[1] Our interest in the possible generality of such species

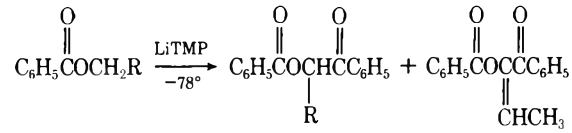


1, Y = NCH_3
2, Y = S

as well as their synthetic potential[2] prompted investigation of the reaction of benzoate esters with LiTMP. The present report establishes that formally dipole stabilized carbanions can be produced by abstraction of a proton from benzoate esters which have additional activation provided by unsaturation. In the absence of such activation, removal of an ortho proton occurs and the ultimate product is an *o*-benzoylbenzoate.

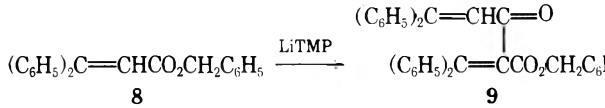
Results and Discussion

Benzyl Benzoate, Allyl Benzoate, and Vinyl Benzoate. The reaction of benzyl benzoate (**3**) with LiTMP[3] in tetrahydrofuran at −78° for 10 min provides benzoin benzoate (**4**) in 65% yield (77% conversion). A similar reaction of allyl benzoate (**5**) gives α-benzoyl allyl benzoate (**6**) and α-benzoyl-β-methyl vinyl benzoate (**7**) in a 4:1 ratio in 53% yield (75% conversion). The structural assignments for **6** and **7** are based on spectral and analytical properties. It appeared possible that **7** was produced by isomerization of **6**, since the conversion of **6** to **7** occurs on treatment of a mixture of these compounds with 10 mol % potassium *tert*-butoxide in *tert*-butyl alcohol. However, attempts to increase the yield of **6** and **7** or to alter their ratio by reaction with a twofold excess of LiTMP followed by quenching 20 min after mixing or by inverse addition of LiTMP to **5** produced no significant change in the yield or the ratio. The formation of **4** from **3** can also be observed in 50% yield at −78° if lithium diisopropylamide is the base.



3, R = C_6H_5 **4**, R = C_6H_5 **7**
5, R = CH=CH_2 **6**, R = CH=CH_2

The reactions of benzyl methyl phthalate, dibenzyl phthalate, benzyl acrylate, and benzyl β,β-diphenylacrylate (**8**) with LiTMP were investigated in an effort to achieve an intramolecular cyclization.[4] However, only in the case of **8** was a characterizable product obtained and it proved to be **9**, formed in 25% yield at both −78 and 25°. Clearly, **9** results from an intermolecular sequence which is probably initiated by removal of the vinyl proton from **8**.[5] The structure of **9** is based on its analytical and spectral properties, as well as its conversion to dibenzhydrylacetone after cata-



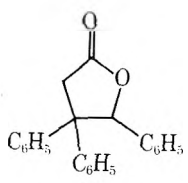
8 **9**

Table I
Formation of o-Benzoylbenzoates from Alkyl Benzoates and LiTMP at −78° in Tetrahydrofuran

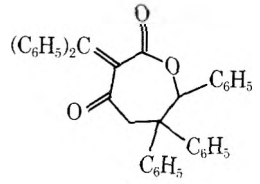
R	Reactant $C_6H_5CO_2R$	Product o-$C_6H_4(COC_6H_5)CO_2R$	Product,[a] %	Recovered reactant, %
Me	15	16	3.5[b]	72[b]
C_2H_5	17	23	44 (27)	27
C_2H_5	17	23	10[c]	79[b]
n-C_3H_7	18	24	46 (38)	27
i-C_3H_7	19	25	10 (6)	69
	19	25	18 (11)[c]	51[c]
n-C_4H_9	20	26	50 (38)	29
i-C_4H_9	21	27	52 (44)	30
t-C_4H_9	22	28	1.5[d]	86[d]

[a] Value in parentheses represents the yield of analytically pure material. [b] At −117°. [c] Reaction time is 90 min and an 8% yield of isopropyl 2,6-dibenzoylbenzoate is also obtained. [d] Reaction time is 30 min.

lytic hydrogenation and decarboxylation. The ^{13}C NMR and the latter conversion rule out the alternative structures *10 and 11. Substitution for a vinyl proton is also observed*

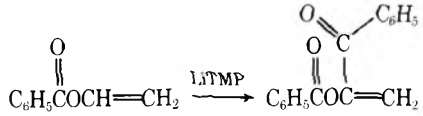


10



11

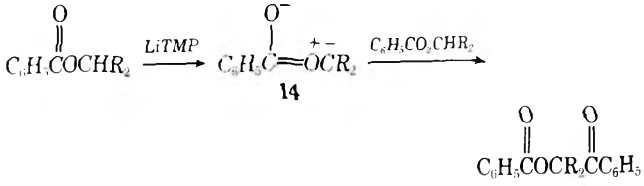
in the reaction of vinyl benzoate (**12**) with LiTMP to give in 3.5% yield α-benzoyl vinyl benzoate (**13**), which was characterized by spectral criteria.



12 13

The reactions of the esters **3, 5,** and **12** to give products of benzoylation α to oxygen may be rationalized by the intermediacy of the formally dipole stabilized carbanion **14** as shown in Scheme I.[6] The fact that activation by the in-

Scheme I

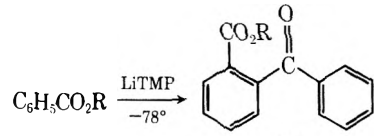


14

ductive, hybridization, and/or delocalization effects of unsaturation contributes to the acidity of the proton removed and that other alkyl benzoates do not form such anions (vide infra) suggests that dipole stabilization by the ester is not sufficient by itself to favor the formation of **14,** at least under the present conditions. The possibility that reaction proceeds via a homoenolate species[1,7] which undergoes ring *opening to an oxyanion which is subsequently benzoylated* is discounted only by analogy to the reaction of *N,N*-dimethylbenzamide, which has been shown not to involve a homoenolate,[8] although the need for unsaturative stabilization also implies a transition state for proton removal which has significant carbanionic character.

The potential use of dipole-stabilized carbanions as anionic synthetic equivalents[2] prompted a number of attempts to trap these species from **4** and **12** at −78 and −117° with electrophiles. All efforts were without success, suggesting that under the present conditions **14** is probably formed in low concentration and reacts rapidly with starting ester to give the observed products. It is also interesting to *note that 14 does not undergo the Wittig rearrangement*[9] under these conditions.

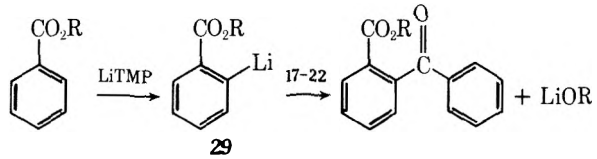
Alkyl Benzoates. Although reaction of methyl benzoate (**15**) at −78° gives uncharacterizable products, when the reaction is carried out at −117° a 3.5% yield of methyl 2-benzoylbenzoate can be detected along with 72% recovered reactant. The generality of this reaction is demonstrated by the fact that ethyl, propyl, and butyl benzoates, **17–22,** react with equimolar LiTMP at −78° in tetrahydrofuran for 10 min to produce the corresponding *o*-benzoylbenzoates, **23–28,** in yields of 1.5–52% and conversions of 10–74% (Table I). The yield of ethyl 2-benzoylbenzoate from **17** is reduced to less than 3% if lithium diisopropylamide is *used as the base.*



15 16
17–22 23–28

A mechanism for this reaction is given in Scheme II. There is considerable precedent for ortho lithiation[10] and the intermediate **29** is analogous to species produced by Parham and Sayed on lithiation of *o*-bromobenzoates.[11,12]

Scheme II



29

The convenience of the present procedure suggests that even though the yields may not have yet been optimized, it should be a synthetically useful alternative for the preparation of *o*-benzoylbenzoates which, in turn, can be useful *precursors to anthraquinones.*[11]

The possibility that ethyl benzoate reacts via initial proton removal from the carbon adjacent to oxygen, as for **3, 5,** and **12,** followed by rearrangement to **29**[13] is discounted by conversion of ethyl-d_5 benzoate to ethyl-d_5 2-benzoylbenzoate. If the possible rearrangement had occurred the product would contain an ethyl-d_4 group, and less than 2% ethyl-d_4 2-benzoylbenzoate was found.

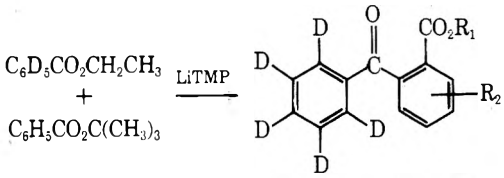
The fact that isopropyl and *tert*-butyl benzoates give the lowest yields of products (Table I) could be due either to unfavorable proton removal to form **29** or to a diminished

Table II
Deuterium Content of the Products from the Reaction of Equimolar Ethyl Benzoate and Ethyl Benzoate-d_5 with LiTMP at −78°

Product	m/e	Relative peak intensity[a]
23	254	1.00
33	259	1.12
34	258	0.11
35	263	0.09

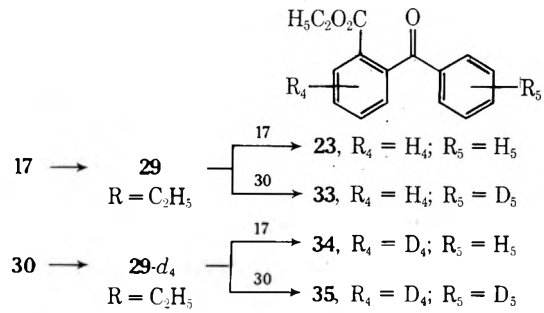
[a] From an average of four spectra at 10 eV ionizing voltage. The estimated error is 2%.

rate of nucleophilic addition of **29** to the ester. To distinguish between these possibilities, an equimolar mixture of ethyl benzoate-d_5 (**30**) and *tert*-butyl benzoate (**22**) was allowed to react with LiTMP at −78°. The products of the reaction were found to be *tert*-butyl 2-benzoyl-d_5-benzoate (**31**) in 25% yield and ethyl 2-benzoylbenzoate-d_9 (**32**) in 5% yield. It is estimated that less than 2% of other deuterated



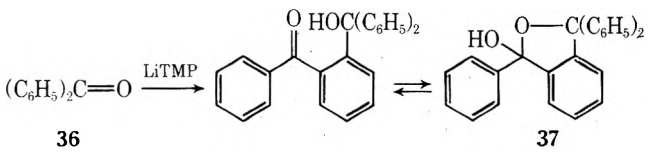
31, $R_1 = C(CH_3)_3$; $R_2 = H_4$
32, $R_1 = CH_2CH_3$; $R_2 = D_4$

isomers of *o*-benzoylbenzoates were formed and the recovered reactants (65%) showed that no detectable transesterification had occurred. Since **31** results from removal of the ortho proton of *tert*-butyl benzoate and products resulting from nucleophilic addition to *tert*-butyl benzoate by **29** (R = C_2H_5 or C_4H_9) are not observed, it appears that the low yields from *tert*-butyl benzoate are due primarily to inhibition of attack at the carbonyl carbon of the *tert*-butyl ester. The ratio of **31**:**32** also reflects a primary isotope effect toward removal of hydrogen. To assess this effect, equimolar amounts of ethyl benzoate (**17**) and ethyl benzoate-d_5 (**30**) were allowed to compete for a deficiency of LiTMP and the isotopic content of the product was determined by mass spectrometry. The analysis for d_0 (**23**), d_5 (**33**), d_4



(**34**), and d_9 (**35**) is summarized in Table II. The ratio of the products produced by proton abstraction from **17** to those produced by deuterium abstraction from **30**, **23** + **33**:**34** + **35**, is 10.6 ± 0.6 in support of the proposed mechanism with removal of the proton to give **29** effectively rate determining.[14]

It was also observed that benzophenone (**36**) reacts with LiTMP at −78° to give 42% 1,3,3-triphenyl-1-hydroxy-



36 **37**

phthalan (**37**). At 25° the yield is increased to 80%. Attempts to characterize the products from similar reactions of methoxymethyl benzoate, phenyl benzoate, and benzaldehyde were not successful.

Experimental Section

Melting points were taken on a Nalge hot stage and are uncorrected. Boiling points, taken from distillations, are also uncorrected. Infrared spectra calibrated with the 1601-cm^{-1} band of polystyrene were obtained with neat samples or in KBr pellets. Proton magnetic resonance spectra and ^{13}C Fourier transform nuclear magnetic resonance spectra were obtained in deuteriochloroform and peak positions are reported in δ (parts per million) from internal tetramethylsilane. Mass spectra were obtained on a Varian MAT CH5 spectrometer. Elemental analyses were performed by Mr. J. Nemeth and associates.

Materials. Commercially available solvents and starting materials were used as received. Tetrahydrofuran was distilled from sodium benzophenone ketyl in a nitrogen atmosphere and stored under nitrogen. Standardization of *n*-butyllithium (Ventron) was accomplished with *sec*-butyl alcohol in xylene with 1,10-phenanthroline indicator.[15] 2,2,6,6-Tetramethylpiperidine (Aldrich) was dried over molecular sieves before use.

Commercially available esters were purified by distillation or recrystallization. Those esters not available were synthesized from the corresponding acid chloride, alcohol, and pyridine in ether except for benzyl acylate, which was prepared by transesterification of methyl acrylate with benzyl alcohol and hydroquinone following the procedure of Rehberg and Fisher.[16] Vinyl benzoate (**12**) was prepared from vinyl acetate, benzoic acid, and mercury(II) sulfate according to the procedure of Aldelman.[17]

Methoxymethyl benzoate was prepared in 62% yield from sodium benzoates and excess chloromethyl methyl ether following a procedure similar to that of Clark, Cox, and Mack:[18] bp 94° (2 mm); ^1H NMR δ 3.50 (s, 3), 5.45 (s, 2), 7.60 (m, 3), and 8.07 (m, 2); ir (neat) 1740 (C=O), 1270, 1160, 1060, 1025, 925, and 710 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 45 (21.1), 61 (72.9), 105 (16.6), 106 (100), 166 (13.4).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.02. Found: C, 65.03; H, 6.20.

Benzyl β,β-diphenylacrylate (**8**) was prepared from the acid chloride[19] and benzyl alcohol with pyridine in ether and purified by chromatography on silica gel followed by recrystallization from hexane: mp 74–75°; ^1H NMR δ 5.00 (s, 2), 6.37 (s, 1), and 7.20 ppm (m, 15); ir 1730 (C=O), 1145, 978, 875, 751, and 692 cm^{-1}.

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.88; H, 5.70.

Benzyl methyl phthalate was prepared by the reaction of phthalic anhydride, benzyl chloride, triethylamine, and methanol following a published procedure.[20] Dibenzyl phthalate was prepared from phthaloyl chloride and benzyl alcohol and pyridine in ether. Both esters were purified by column chromatography.

General Procedure for the Reactions of Esters with Lithium 2,2,6,6-Tetramethylpiperidide (LiTMP). All reactions involving LiTMP were carried out in a dry nitrogen atmosphere. The following general procedure was followed in all cases unless noted. A weighed sample of the ester (3–4 mmol) was dissolved in 10–15 ml of THF and added dropwise to an equimolar amount of LiTMP in 10 ml of THF at −78° over 10 min. The LiTMP was generated by reaction of TMP and equimolar *n*-butyllithium at room temperature followed by cooling to −78°. The reaction was quenched at −78° immediately after addition was complete with 10% HCl and allowed to warm to room temperature. Extractive work up with ether with washes of 10% HCl, 5% HCl, and water (twice) and an ether backwash gave material for chromatography. Yields are calculated on the basis of 2 mol of ester required for 1 mol of product.

"Inverse" addition used with several esters refers to the addition of LiTMP solution to the ester at −78° with work-up identical to that described.

Chromatography was carried out on Brinkmann 0.05–0.2 mm silica gel. Starting esters were eluted with either hexane or 2% (v/v) ethyl acetate–hexane. Reaction products were eluted with 5–10% ethyl acetate–hexane unless otherwise noted. Reactions of selected esters with LiTMP are described in detail below.

Benzyl benzoate (3), 3.08 mmol, was allowed to react with 3.18 mmol of LiTMP. Chromatography gave 0.5 mmol (16%) of recovered **3**, identified by its NMR and ir spectrum, and 1.00 mmol (65%) of benzoin benzoate **4**, identified by its melting point, 124–

125° (lit.[21] mp 124–125°), ^{1}H NMR,[22] and ir spectrum,[22,23] which all were identical with those of authentic material prepared from benzoyl chloride and benzoin.[21]

Allyl Benzoate (5). Analysis by TLC of the reaction mixture from 3.94 mmol of **5** with LiTMP indicated two products with nearly identical R_f values, in addition to unreacted **5.** Chromatography gave 1.14 mmol (29%) of recovered **5,** and 1.04 mmol (53%) of a mixture of **6** (80% by ^{1}H NMR) and **7** (20%).

A sample of pure **6** could be obtained by careful chromatography in which pure **6** eluted just ahead of the mixture of **6** and **7.** Recrystallization from hexane afforded an analytical sample of **6:** mp 85–86°; ^{1}H NMR 5.30–5.75 (m, 2), 5.87–6.47 (m, 1), 6.53 (d, 1, J = 6 Hz), 7.18–7.67 (m, 6), and 7.90–8.17 ppm (m, 4); ir (KBr) 1726, 1696 (C=O), 1598, 1450, 1275, 1121, 947, 713, and 703 cm^{-1}, mass spectrum (10 eV) *m/e* (rel intensity) 105 (100), 106 (8.6), 144 (12.5).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.66; H, 5.35.

Isomerization of 6 to 7 Catalyzed by *tert*-Butoxide. A mixture of **6** and **7** (0.41 mmol) in dry *tert*-butyl alcohol was added to a solution of 0.042 mmol of potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction mixture turned deep red immediately, and after 20 min, TLC indicated only **7** in the reaction mixture. The reaction was quenched by the addition of 10% HCl and extractive work-up with ether provided a colorless oil which was chromatographed on 25% silica gel with 5% ethyl acetate–hexane to yield 0.30 mmol of **7** (73%). Recrystallization from hexane gave an analytical sample: mp 65–66°; ^{1}H NMR δ 1.71 (d, 3, J = 7 Hz), 6.28 (q, 1, J = 7 Hz), 7.18–7.61 (m, 6), 7.68–7.90 (m, 2), and 8.01–8.21 ppm (m, 2); ir (KBr) 1740, 1648 (C=O), 1252, 1262, 1170, 1100, 1063, and 710 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 51 (5.7), 77 (27.9), 105 (100), 266 (2.4).

Anal. Calcd for $C_{17}H_{14}O_3$, C, 76.68; H, 5.30. Found: C, 76.90; H, 5.32.

Benzyl β,β-diphenylacrylate (8), 2.74 mmol, was allowed to react with 2.70 mmol of LiTMP at −78°. Chromatography gave 1.45 mmol (53%) of recovered **8** and 0.35 mmol (26%) of **9.** Inverse addition, a reaction temperature of 25°, or use of excess LiTMP failed to significantly affect the yield of **9.** The amount of recovered **8,** however, varied from less than 2% with a twofold excess of LiTMP to 29% for reactions of equimolar ester and LiTMP at room temperature.

Purification was accomplished by recrystallization from hexane or methanol–water to give **9** as pale yellow crystals: mp 126–127.5°; ^{1}H NMR δ 4.92 (s, 2), 6.05 (s, 1), 6.43–6.67 (m, 4), and 6.83–7.48 ppm (m, 21); ^{13}C NMR δ 194.1 (C=O), 167.1 (O=CO), 154.8, 152.6 [$(C_6H_5)_2C$=], 141.7, 140.6, 138.9, 135.4, 133.4, 130.9, 138.8, 130.0, 129.5, 129.2, 192.5, 128.5, 128.2, 127.9 (>C=), 67.0 (-CH_2-); ir 1723, 1638 (C=O), and 703 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 105 (75.7), 429 (100), 430 (31.6), 520 (33.9), 521 (14.8).

Anal. Calcd for $C_{37}H_{28}O_3$: C, 85.38; H, 5.38. Found: C, 85.23; H, 5.39.

Hydrogenation and Decarboxylation of 9 to Dibenzhydrylacetone. Hydrogenation of **9** (0.11 mmol) was accomplished at atmospheric pressure over 10% Pd/C in 5 ml of ethyl acetate for 24 hr. The catalyst was removed by filtration and the solution was heated at reflux for 3 hr to effect decarboxylation. Evaporation of the ethyl acetate in vacuo left 0.106 mmol (97%) of a colorless oil with a ^{1}H NMR spectrum identical with that of dibenzhydrylacetone. Two recrystallizations from methanol gave white needles, mp 124–125°, identical in ir, ^{1}H NMR, mass spectrum, melting point, and mixture melting point with authentic dibenzhydrylacetone prepared from dibenzalacetone, benzene, and aluminum trichloride.[24]

Vinyl benzoate (12) was allowed to react with LiTMP both at −78 and 25° in either the normal or inverse modes of addition. Analysis by TLC indicated low yields of **13** in both cases. Combination of the crude mixtures from two runs at 25° gave, after chromatography, 35% recovered **12** and 3.5% of a yellow oil, the ^{1}H NMR of which indicated it to be mostly **13.** Rechromatography gave 1.4% **13** as a colorless oil which on recrystallization from hexane gave **13** as white needles: mp 91–93°; ^{1}H NMR δ 5.71 (d, 1, J = 2 Hz), 5.88 (d, 1, J = 2 Hz), 7.30–7.68 (m, 6), and 7.88–8.26 ppm (m, 4); ir (KBr) 1730, 1663 (C=O), 1450, 1270, 1186, 1169, 1088, 967, 922, 743, and 712 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 105 (100), 106 (8.4), 252 (1.14).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 75.62; H, 4.87.

Reaction of Methyl Benzoate and LiTMP at −117°. This reaction was carried out as described previously except that the solution of LiTMP was cooled to −117° in liquid nitrogen–ethanol slurry. The reaction produced only slight color changes in sharp contrast to the run at −78°. Quenching with methanol and work-up and chromatography as usual gave 72.5% recovered methyl benzoate and then 3.2% of crude methyl 2-benzoylbenzoate (**16**) identified by its NMR[25] and mass spectra.

Ethyl benzoate (17) was allowed to react with LiTMP. One major product was observed by TLC. Chromatography yielded recovered **17** (27%) and ethyl 2-benzoylbenzoate (**23,** 44%). The identity of **23** was established by its melting point, 58–59° (lit.[26] mp 56–58°), ^{1}H NMR[27] and ir[27] spectra, and elemental analysis.

***n*-Propyl benzoate (18)** was allowed to react with LiTMP at −78°. After chromatography 18 (26%) and *n*-propyl 2-benzoylbenzoate (**24,** 46%) were obtained. Final purification of **24** was accomplished by microvacuum distillation to yield 38% of **24** as a clear, viscous oil (lit.[28] bp 163.5° (0.3 mm): ^{1}H NMR δ 0.78 (t, distorted 3, J = 6 Hz), 1.38 (m, 2), 3.93 (t, 2, J = 6 Hz), and 7.16–8.11 ppm (m, 9); ir (neat) 1720, 1675 (C=O), 1596, 1280, 1128, 1082, 932, 770, 713, and 702 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 105 (16.4), 149 (57.1), 182 (31.7), 191 (26.1), 209 (77.4), 210 (28.4), 266 (33.9), 227 (39.5), 268 (100), 269 (19.9).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.12; H, 5.97. Found: C, 76.08; H, 6.15.

Isopropyl benzoate (19) gave a 9.6% yield of isopropyl 2-benzoylbenzoate (**25**) and 69% recovered **19** after being allowed to react with LiTMP for 10 min at −78°. Extension of the reaction time to 90 min gave 51% **19,** 17% **25,** and 8% of isopropyl 2,6-dibenzoylbenzoate. Purification of **25** was accomplished by two crystallization from 95% ethanol: mp 66–67° (lit.[29] mp 62°); ^{1}H NMR δ 1.01 (d, 6, J = 6 Hz), 4.95 (m, 1, J = 6 Hz), and 7.21–8.11 ppm (m, 9); ir (KBr) 1720, 1670 (C=O), 1290, 1132, 1110, 1090, 786, and 710 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 105 (18.1), 149 (100), 150 (19.2), 182 (26.6), 191 (46.7), 209 (67.0), 210 (98.2), 211 (28.6), 266 (30.2), 227 (27.8), 268 (72.5), 269 (21.05).

Purification of isopropyl 2,6-dibenzoylbenzoate was achieved by two recrystallization from 95% ethanol: mp 88–90°; ^{1}H NMR δ 0.78 and 1.00 (each a doublet, total integral 6, J = 6 Hz), 4.68 (m, 1), and 7.16–7.93 ppm (m, 13); ir (KBr) 1722, 1668 (C=O), 1274, 708, and 644 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 105 (29.1), 253 (53.2), 313 (51.2), 314 (100), 315 (27.6), 330 (29.2), 331 (43.2), 372 (17.7).

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.40; H, 5.54.

***n*-Butyl benzoate (20)** was allowed to react with LiTMP. Chromatography gave 29% recovered **20** and 50% *n*-butyl 2-benzoylbenzoate (**26**) as a pale yellow oil. Purification by a micro vacuum distillation gave pure **26** (38%) as a colorless, very viscous liquid [lit.[30] bp 241–244° (20 mm)]: ^{1}H NMR δ 0.80 (t, distorted, 3), 1.30 (m, 4), 3.99 (t, 2), and 7.16–8.08 ppm (m, 9); ir (neat) 1723, 1678 (C=O), 1285, 718, and 704 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.30; H, 6.27.

Isobutyl benzoate (21) was allowed to react with LiTMP. Chromatography gave 29% recovered **21** and 52% crude isobutyl 2-benzoylbenzoate (**27**). Purification by vacuum distillation gave 44% **27** as a clear, viscous liquid: ^{1}H NMR δ 0.79 (d, 6, J = 7 Hz), 1.71 (m, 1), 3.78 (d, 2, J = 6 Hz), and 7.16–8.13 ppm (m, 9); ir (neat) 1724, 1678 (C=O), 1598, 1678 (C=O), 1598, 1282, 1128, 1083, 933, 717, and 703 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.51; H, 6.52.

Reaction of *tert*-butyl benzoate (**22**) at −78° required 30 min for appearance of product (TLC). Chromatography gave 86.5% recovered **22** and 1.5% *tert*-butyl 2-benzoylbenzoate (**28**). Recrystallization from hexane gave white crystals: mp 67–68° (lit.[26] mp 68–69°); ^{1}H NMR δ 1.25 (s, 9) and 7.28–8.08 ppm (m, 9).

Ethyl-d_5 benzoate was prepared by reaction of benzoyl chloride, ethanol-d_6 (Stohler Isotope Chemicals), and pyridine (0.045 mol) in ether: bp 45° (0.8 mm); NMR δ 7.16–7.60 (m, 3) and 7.83–8.11 ppm (m, 2), less than 2% CH present; ir (neat) 2240 (m), 2160 (w), 2130 (w) (C–D), 1725 (C=O), 1458, 1233, 1305, 1201, 1182, 1130, 1103, 1065, 1031, and 713 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 105 (80.4), 123 (100), 154 (8.4), 155 (97.1)

Anal. Calcd for $C_9H_5D_5O_2$: C, 69.68; total H, 6.45. Found: C, 69.63; total H, 6.43.

Preparation of Ethyl Benzoate-d_5 (30). Benzoyl chloride-d_5, prepared via the sequence benzene-d_6, bromobenzene-d_5, benzoic acid-d_5, benzoyl chloride-d_5, was allowed to react with ethanol to give **30:** bp 52° (1.0 mm); ^{1}H NMR δ 1.36 (t, 3, J = 7 Hz) and 4.33 ppm (q, 2, J = 7 Hz), estimate less than 2% ArH; ir (neat) 2305

(w), 2280 (w) (C-D), 1726 (C=O), 1398, 1383, 1332, 1245, and 1085 cm^{-1}; mass spectrum (10 eV) *m/e* (rel intensity) 110 (24.8), 127 (78.3), 155 (100), 156 (9.8).

Anal. Calcd for $C_9H_5D_5O_2$: C, 69.68; total H, 6.45. Found: C, 69.54; total H, 6.65.

Reaction of Ethyl Benzoate-d_5 (30) and *tert*-Butyl Benzoate (22) with LiTMP. The reaction of **22** and **30** with LiTMP was carried out by addition of a THF solution of 2.07 mmol of **22** and 2.04 mmol of **30** to 4.10 mmol of LiTMP at −78°. After quenching and the usual work-up, the presence of both starting esters as well as both *tert*-butyl 2-benzoylbenzoate and ethyl 2-benzoylbenzoate were indicated as the major and minor products, respectively, by TLC. Chromatography on silica gel with 2% ethyl acetate eluted a mixture of **22** and **30** (65% by weight of the original esters) shown by ^1H NMR to be 45% **30** and 55% **22**. Continued elution gave 25% *tert*-butyl benzoyl-d_5-benzoate (**31**) and 5% ethyl 2-benzoylbenzoate-d_9 (**32**), which were purified as described previously.

Reaction between Ethyl Benzoate (17) and Ethyl Benzoate-d_5 (30) with LiTMP. A solution of 2.0 mmol of LiTMP in 15 ml of THF was added at −78° to a THF solution of 2.07 mmol of **17** and 2.18 mmol of **30** over a period of 10 min. The reaction was quenched wand worked up in the usual manner. The recovered ester mixture and ethyl 2-benzoylbenzoate products as a mixture of deuterated and undeuterated isomers were analyzed by mass spectrometry.

Reaction of Benzophenone with LiTMP. Reaction of equimolar quantities of benzophenone (**36**) and LiTMP at 25° for 10 min gave, after work-up and chromatography with 5% ethyl acetate, 6.5% recovered **36** and 80.5% **37**.[31] Crude **37** was washed with cold hexane, yielding white needles, mp 119–120° (lit.[31] mp 121°). The ^1H NMR, ir, NMR, mass spectrum, and analysis were consistent with the established structure.

Acknowledgment. We are grateful to the National Institutes of Health for support of this work and for funds used to purchase the mass spectrometers.

Registry No.—**3**, 120-51-4; **5**, 583-04-0; **6**, 54353-96-7; **7**, 54353-97-8; **8**, 54353-98-9; **9**, 54353-99-0; **12**, 769-78-8; **13**, 54354-00-6; **17**, 93-89-0; **18**, 2315-68-6; **19**, 939-48-0; **20**, 136-60-7; **21**, 120-50-3; **22**, 774-65-2; **24**, 604-62-6; **25**, 32017-66-6; **26**, 571-98-2; **27**, 54354-01-7; **28**, 54354-02-8; **30**, 54354-03-9; **36**, 119-61-9; LiTMP, 38227-87-1; methoxymethyl benzoate, 54354-04-0; sodium benzoate, 532-32-1; chloromethyl methyl ether, 107-30-2; β,β-diphenylacryloyl chloride, 4456-79-5; benzyl alcohol, 100-51-6; methyl benzoate, 93-58-3; isopropyl 2,6-dibenzoylbenzoate, 54354-05-1; ethyl-d_5 benzoate, 30684-04-9; benzoyl chloride, 98-88-4; ethanol-d_6, 1516-08-1; benzene-d_6, 1076-43-3.

References and Notes

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Block and Graft Copolymers by Selective Cationic Initiation. I. Selective Alkylation with Trialkylaluminums on the Chlorine of Chlorobrominated Alkanes

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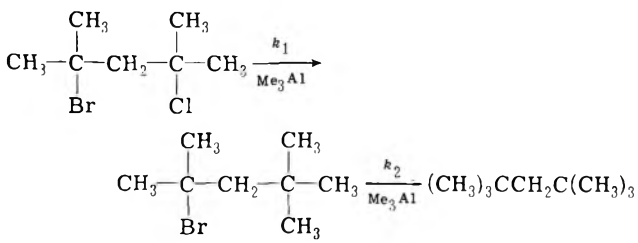
Selective alkylation with trialkylaluminum compounds on the chlorine of tertiary alkyl chloride and bromide mixtures, and chlorobrominated alkanes has been studied. Using trimethylaluminum and mixtures of *tert*-butyl chloride and bromide, methylation selectivity is limited owing to the early methylation of *tert*-butyl bromide by the dimethylaluminum chloride by-product formed in the fast methylation of *tert*-butyl chloride. Similar results have been obtained using mixtures of 2,6-dichloro-2,6-dimethylheptane and 2,6-dibromo-2,6-dimethylheptane. The reaction between 2-bromo-4-chloro-2,4-dimethylpentane and trimethylaluminum gave exclusively 2,2,4,4-tetramethylpentane. This observation was explained in terms of a rate-determining methylation on the chlorine followed by a rapid, strain relief induced methylation on the bromide. Satisfactory alkylation selectivity for subsequent block-copolymer synthesis was achieved with 2-bromo-6-chloro-2,6-dimethylheptane. While selective chlorine removal has been demonstrated with both trimethyl- and triethylaluminum, greatest selectivity was obtained with the latter, i.e., ~50% chlorine substitution before bromine loss.

In the course of our fundamental studies on cationic polymerization of olefins, it was found that the rate of reaction of *t*-BuX + Me_3Al → *t*-BuMe + Me_2AlX follows the sequence *t*-BuCl ≫ *t*-BuBr > *t*-BuI.[1,2] This unexpected observation has been exploited for the selective alkylation of tertiary chlorides with trialkylaluminums in the presence of tertiary alkyl bromides and subsequently in a synthetic method for the preparation of block copolymers.[3]

Results and Discussion

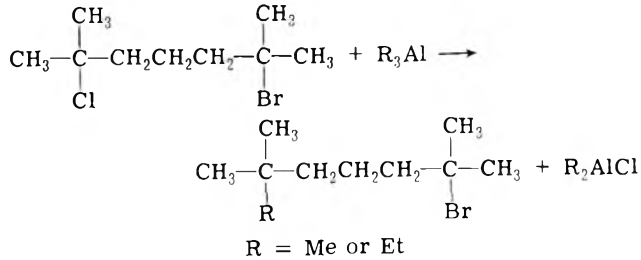
On the basis of the large differences in the rates of methylation of *t*-BuCl and *t*-BuBr with Me_3Al,[2] it was theorized that tertiary alkyl chlorides could be selectively methylated in the presence of tertiary alkyl bromides. Thus, we studied the rates of competitive methylation of mixtures of tertiary alkyl halides with Me_3Al in CH_3Cl by NMR spectroscopy. Results of experiments using mixtures of *t*-BuCl with *t*-BuBr, and 2,6-dichloro-2,6-dimethylheptane with 2,6-dibromo-2,6-dimethylheptane, are shown in Figure 1. Methylations proceeded quantitatively and faster with the tertiary chlorides than with tertiary bromides to yield the corresponding quaternary carbon compounds. That the tertiary alkyl bromides react faster in the presence of tertiary alkyl chlorides than in their absence[2] is due to the in situ formation of Me_2AlCl, a stronger Lewis acid and a more aggressive methylating agent than Me_3Al.

Subsequently, the alkylation by alkylaluminum compounds of chlorobrominated alkanes (containing tertiary chlorine and bromine in the same molecule) was studied. Interestingly, the reaction of 2-bromo-4-chloro-2,4-dimethylpentane with Me_3Al in CH_3Cl at −60° gave 2,2,4,4-tetramethylpentane and no monomethylated product was observed.



Evidently, the rate-determining step is most likely the substitution of the first halogen, presumably chlorine, while the subsequent (bromine) substitution must occur rapidly. At least two possibilities would account for this observation. The ionization of the chlorine is probably slowed down considerably because of the inductive electron-withdrawing effect of the bromine in β position. Furthermore, once formed, the transitory 2-bromo-2,4,4-trimethylpentane is expected to ionize rapidly owing to the energy gained in relieving internal strain.[4] In addition, the strong Lewis acid, Me_2AlCl, formed in the first methylation step would further accelerate the ionization of the tertiary bromine.

To overcome these unfavorable steric and inductive effects, we have synthesized 2-bromo-6-chloro-2,6-dimethylheptane and studied its rate of alkylation with Me_3Al and Et_3Al. Representative data are shown in Figure 2. In both experiments, chlorine is removed at a faster rate than bromine. Selectivity is greatest with Et_3Al, i.e., ~50% of chlorine substitution occurs before bromine loss. This observation can be explained in terms of relative Lewis acidities as follows.



R = Me or Et

The stronger Lewis acids, R_2AlCl, formed in the first methylation facilitate ionization of the bromine in the monoalkylated product. Increased selectivity obtained with Et_3Al is due to the relatively lower Lewis acidity of Et_2AlCl as compared to Me_2AlCl., i.e., Et_2AlCl is less active in mobilizing the tertiary bromine than Me_2AlCl. Also, the Lewis acidity difference between Et_3Al and Et_2AlCl is smaller than that between Me_3Al and Me_2AlCl.[5] This conclusion is supported by the fact that very little selectivity was observed when 2-bromo-6-chloro-2,6-dimethylheptane was treated with Me_2AlCl and Et_2AlCl, respectively, in CH_3Cl at −80°.

Since either ethylation or hydridation[5] can occur with Et_3Al and Et_2AlCl, three possible final products can arise from 2-bromo-6-chloro-2,6-dimethylheptane. Table I summarizes our results obtained by mass chromatography. Evidently ethylation predominates (~60%) with Et_3Al whereas hydridation prevails (~84%) with Et_2AlCl. Ethylation with

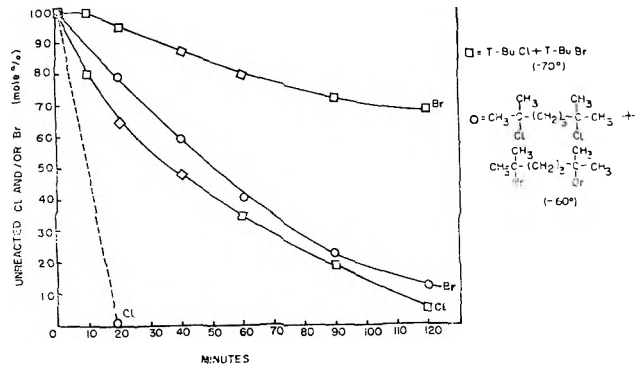


Figure 1. Relative reactivities of tertiary chloride and bromide mixtures with Me_3Al in CH_3Cl (concentrations: tertiary halides 0.1 *M*, Me_3Al 0.4 *M*).

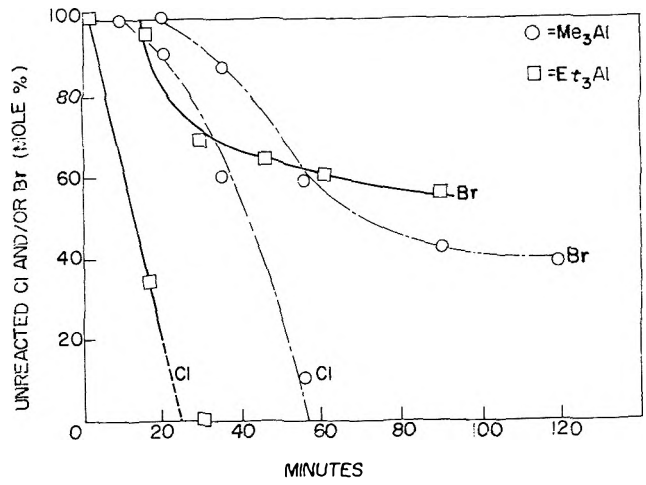
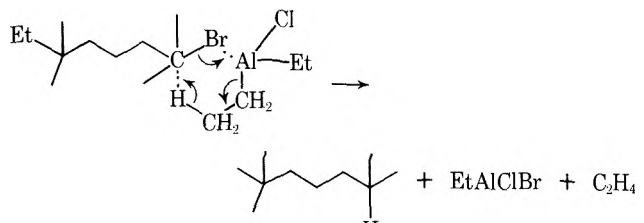


Figure 2. Reaction rate of 2-bromo-6-chloro-2,6-dimethylheptane with Me_3Al at −55° and with Et_3Al at −70° in CH_3Cl solvent.

Et_3Al has been shown to proceed by a conventional SN1 mechanism[2] while hydridation is proposed to proceed by a concerted mechanism.[5]



According to the results in Table I, Et_2AlCl is a much more effective hydridating agent than Et_3Al, the reason(s) for which is not understood.

Table I
Relative Amounts of Products Obtained from the Reaction of 2-Chloro-6-bromo-2,6-dimethylheptane with $AlEt_3$ and $AlEt_2Cl$[a]

	Obtained, %, with Et_3Al	Obtained, %, with Et_2AlCl
$CH_3CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_3$	6	84
$CH_3CH(CH_3)CH_2CH_2CH_2CEt(CH_3)CH_3$	34	14
$CH_3CEt(CH_3)CH_2CH_2CH_2CEt(CH_3)CH_3$	60	2

[a] Reaction conditions: $[AlEt_3]$ or $[AlEt_2Cl]$ = 0.4 *M*, [2-chloro-6-bromo-2,6-dimethylheptane] = 0.2 *M*, CH_3Cl solvent, −70°, time 5 min with $AlEt_2Cl$, 180 min with $AlEt_3$.

Since cationic polymerizations proceed rapidly even at low temperatures, bromine loss demonstrated in the later stages of these model reactions is not a serious problem in the synthesis of a polymer containing a tertiary bromine end group. We have demonstrated this[3] by adopting the selective conditions obtained with 2-bromo-6-chloro-2,6-dimethylheptane and Et_3Al to synthesize a block copolymer, *poly(styrene-b-isobutylene)*.

Experimental Section

Experiments were performed in a stainless steel enclosure under N_2 atmosphere (<50 ppm moisture). Alkylaluminums (Texas Alkyl Co.) were distilled prior to use. Methyl chloride (Linde) was purified by passing through a column packed with anhydrous molecular sieves, BaO, and Drierite. All tertiary halides were dried over CaH_2 before use. Methallyl chloride (Eastman Kodak Co.) and 6-methyl-5-hepten-2-one (Aldrich Chemical Co.) were used without further purification. NMR analysis was done on Varian A-60 and T-60 instruments. Molecular weights were obtained using a Chromalytics MC-2 mass chromatograph employing SF_6 and CO_2 carrier gases. Gas chromatographic analyses were carried out with an HP-5750 gas chromatograph with a flame ionization detector. Distillations were performed using a Nester-Faust adiabatic spinning band column. All melting and boiling points are uncorrected.

2-Bromo-4-chloro-2,4-dimethylpentane. 2,4-Dimethyl-4-hydroxy-1-pentene was obtained in 70% yield from the reaction of methallyl chloride (2.0 mol) and acetone (2.0 mol) with magnesium (2.3 mol) in ether using a procedure which minimizes Wurtz coupling.[6] This alcohol was purified by distillation, bp 59–61° (20 mm) [lit. bp 126° (760 mm)].[7] To 2,4-dimethyl-4-hydroxy-1-pentene (13.0 g) was added pyridine (9.5 ml) and CH_2Cl_2 (30 ml) followed by dropwise addition of thionyl chloride (9.0 ml) at 0°. After stirring at room temperature for 1 hr, the mixture was twice extracted with 75-ml portions of water. The organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed by vacuum. The residual organic material was distilled, resulting in a 35% yield of 4-chloro-2,4-dimethyl-1-pentene: bp 64° (100 mm); NMR (CCl_4) δ 1.60 (s, 6 H, CH_3), 1.65 (s, 3 H, CH_3), 1.78 (s, 2 H, CH_2), 5.05 (d, 2 H, $=CH_2$). HBr was bubbled directly into 4-chloro-2,4-dimethyl-1-pentene at −78° in a two-necked reaction vessel. The product solidified after 1 hr and melted at −30°. HBr addition was continued for an additional 1 hr, resulting in a 100% yield of 2-bromo-4-chloro-2,4-dimethylpentane, which was dried with anhydrous K_2CO_3: NMR (CCl_4) δ 1.82 [s, 6 H, $(CH_3)_2C$], 2.05 [s, 6 H, $(CH_3)_2C$], 2.65 (s, 2 H, CH_2). No further purification was necessary since NMR revealed no detectable impurities.

2-Bromo-6-chloro-2,6-dimethylheptane. Using a published procedure,[8] the reaction of 6-methyl-5-hepten-2-one (0.40 mol) with CH_3MgI (0.40 mol) in ether resulted in an 89% yield of 2,6-dimethyl-6-hydroxy-2-heptene: bp 85° (14 mm) [lit. bp 79° (13 mm)];[8] NMR (CCl_4) δ 1.10 [s, 6 H, $C(CH_3)_2$], 1.95 [m, 4 H, $(CH_2)_2$], 1.60 [d, 6 H, $=C(CH_3)_2$], 2.60 (m, 1 H, OH), 5.10 (t, 1 H, =CH–). Thionyl chloride (0.34 mol) was added dropwise at 0° to a stirred solution of 2,6-dimethyl-6-hydroxy-2-heptene (0.34 mol) in pyridine (0.34 mol) and CH_2Cl_2 (75 ml). The resultant mixture was stirred at room temperature for 1 hr followed by extraction with two portions of water (100 ml). The organic layer was dried over anhydrous $MgSO_4$ and filtered and the solvent was removed by vacuum. The organic residue was distilled, resulting in a 63% yield of 6-chloro-2,6-dimethyl-2-heptene: bp 68° (12 mm) [lit. bp 71–72° (15 mm)];[9] NMR (CCl_4) δ 1.58 [s, 6 H, $(CH_3)_2$], 1.63 [d, 6 H, $=C(CH_3)_2$], 2.00 [m, 4 H, $(CH_2)_2$], 5.00 (t, 1 H, =CH–). HBr was bubbled directly into 6-chloro-2,6-dimethyl-2-heptene (25 g) in CH_2Cl_2 (100 ml) at −78°. After 2 hr, the solution was warmed to room temperature, dried with anhydrous K_2CO_3, and filtered and the solvent was removed by vacuum. The product, 2-bromo-6-chloro-2,6-dimethylheptane, was recrystallized from ethanol: mp 33–34°; NMR (CCl_4) δ 1.58 (s, 6 H, CH_3) 1.90 (s, 6 H, CH_3), 1.90 (s, 6 H, CH_2); ir 2900, 1440, 1360, 1300, 1290, 1230, 1190, 1130, 840, and 730 cm^{-1}.

2,6-Dichloro-2,6-dimethylheptane. 2,6-dimethyl-6-hydroxy-2-heptene (5 g) was treated with 50 ml of concentrated HCl at 0°. The mixture was stirred at 0° for 15 min and extracted with 50 ml of CH_2Cl_2. The organic layer was dried with anhydrous K_2CO_3 and filtered and the solvent was removed by vacuum. After three treatments with concentrated HCl, a 100% conversion to 2,6-dichloro-2,6-dimethylheptane resulted which was recrystallized from etha-

nol: mp 40° (lit. mp 43°);[10] NMR (CCl_4) δ 1.60 (s, 12 H, CH_3), 1.78 (s, 6 H, CH_2).

2,6-Dibromo-2,6-dimethylheptane. 2,6-dimethyl-6-hydroxy-2-heptane (5 g) was cooled to −78° in CH_2Cl_2 (50 ml). HBr was bubbled into the solution for a total of 3.5 hr. The mixture was extracted with water (50 ml) and dried with K_2CO_3 and the solvent was removed. A 100% yield of 2,6-dibromo-2,6-dimethylheptane resulted which was recrystallized from ethanol: mp 34° (lit. mp 34°);[11] NMR (CCl_4) δ 1.90 (s, 12 H, CH_3), 1.90 (s, 6 H, CH_2).

Alkylation Experiments. A solution of the appropriate halide (0.2 *M*) in CH_3Cl was added to an equal volume of the trialkylaluminum (0.4 *M*) in CH_3Cl. Periodically, 5-ml samples were withdrawn and quenched with 1 ml of cold methanol. Saturated aqueous $KNaC_4H_4O_6$ was added to the samples and the organic layer was extracted into CCl_4 and dried with K_2CO_3. The samples were analyzed by GC, mass chromatography, and NMR,. The extent of alkylation was followed by NMR spectroscopy by determining the decrease in intensity of the methyl protons adjacent to the tertiary chlorine and tertiary bromine in the starting materials.

Final Hydrocarbon Products. 2,2,4,4-Tetramethylpentane resulting from the methylation of 2-bromo-4-chloro-2,4-dimethylpentane was identified by NMR and GC by comparison with an authentic sample (Chemical Samples Co.). 2,2,6,6-Tetramethylheptane[12] was identified by NMR and molecular weight: NMR (CCl_4) δ 0.93 (s, 18 H, CH_3), 1.15 (s, 6 H, CH_2). Calcd for $C_{11}H_{24}$: mol wt, 156.3. Found: mol wt, 155. Final products resulting from the reaction of Et_3Al and Et_2AlCl with 2-bromo-6-chloro-2,6-dimethylheptane (Table I) were analyzed by mass chromatography. Calcd for $C_{13}H_{28}$ (3,3,7,7-tetramethylnonane): mol wt, 184.4. Found: mol wt, 183. Calcd for $C_{11}H_{24}$ (2,6,6-trimethyloctane): mol wt, 156.3. Found: mol wt, 154. Calcd for C_9H_{20} (2,6-dimethylheptane[13]): mol wt, 128.29. Found: mol wt, 128. No other products were observed by gas chromatography.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this research.

Registry No.—$AlEt_3$, 97-93-8; $AlEt_2Cl$, 96-10-6; $AlMe_3$, 75-24-1; 2-bromo-4-chloro-2,4-dimethylpentane, 54191-86-5; 2,4-dimethyl-4-hydroxy-1-pentene, 19781-53-4; methallyl chloride, 563-47-3; acetone, 67-64-1; 4-chloro-2,4-dimethyl-1-pentene, 54166-29-9; 2,6-dimethyl-6-hydroxy-2-heptene, 6090-15-9; 6-chloro-2,6-dimethyl-2-heptene, 6076-48-8; 2,6-dichloro-2,6-dimethylheptane, 35951-36-1; 2,6-dibromo-2,6-dimethylheptane, 54166-30-2; 2,2,6,6-tetromethylheptane, 40117-45-1; 3,3,7,7-tetramethylnonane, 54166-31-3; 2,6,6-trimethyloctane, 54166-32-4; 2,6-dimethylheptane, 1072-05-5; 2-chloro-6-bromo-2,6-dimethylheptane, 54166-33-5.

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Diacylium Cations from Tetrahaloterephthalic Acids and Their Electrophilic Reactivity

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Diacylium bis bisulfate complexes are prepared from the reaction of sulfur trioxide with tetrabromoterephthalic acid, Br_4TA, and tetrachloroterephthalic acid, Cl_4TA. The spectra of the diacylium cations in the ultraviolet, visible, and infrared regions can be determined in SO_3–SO_2 and in SO_3–Freon 113 solvents. The diacylium complexes are excellent reagents for laboratory and industrial syntheses of diacid chlorides, diamides, and diesters of tetrahaloterephthalic acids; these products are obtained from the reactions of the complexes with chlorosulfonic acid, sulfamic acid, and alcohols, respectively. The diacylium complexes react with tetrahaloterephthalic acids to produce homopolymers and heteropolymers with an anhydride backbone. The perhalo polyanhydrides are stable at relatively high temperatures and are quite resistant to hydrolysis.

The extensive research of Olah and his coworkers[1] on stable oxocarbonium ions has demonstrated the possibility of generating diacylium cations from the acid fluorides of dicarboxylic acids. Thus, glutaryl fluoride and higher aliphatic diacid fluorides, as well as terephthaloyl fluoride, form 1:2 complexes with SbF_5 which have been formulated as diacylium bis(hexafluoroantimonate) salts, $SbF_6^-{}^+OC(CH_2)_xCO^+{}^-SbF_6$, on the basis of ir and NMR spectral data.

Diacylium cations have not, so far, been generated from dicarboxylic acids; however, monoacylium cations have been prepared from monocarboxylic acids by Deno and his coworkers.[2-4] These authors emphasized the potential value of such species in organic syntheses.

This paper describes the formation of diacylium cations from tetrahalogenated terephthalic acids, and from the corresponding terephthaloyl fluorides, $YCOC_6X_4COY$ (X = Br or Cl and Y = OH or F). The preparation of the diacylium cations from the reaction of SO_3 with tetrabromoterephthalic acid, Br_4TA, and with tetrachloroterephthalic acid, Cl_4TA, is economic and useful since the relatively stable dications serve as intermediates for the large-scale syntheses of acid chlorides, amides, nitriles, esters, and polyanhydrides derived from tetrahaloterephthalic acids. This type of dicarboxylic acid is notable for its lack of reactivity, as has been pointed out by several investigators.[5-7] The new perhalopolyanhydrides reported here are stable substances at relatively high temperature and are also quite resistant toward alkaline hydrolysis.

Results and Discussion

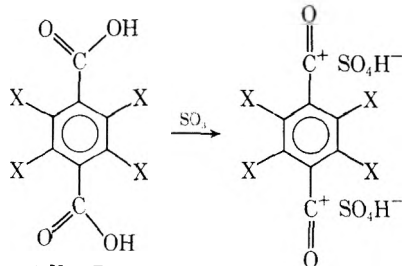
Spectrophotometric Detection of Diacylium Cations from the Reaction of Tetrahaloterephthalic Acids with Sulfur Trioxide. The Br_4TA (1) is soluble in a mixture of SO_3 and SO_2 in 85:15 wt % proportion. The resulting red solution has absorption maxima in the infrared, ultraviolet, and visible regions of the spectrum as shown in Table I. These data are consistent with the diacylium bis

Table I
Absorption Characteristics of Diacylium Complexes and Related Compounds

Compd	Solvent	Reagent	Ultraviolet and visible spectra: λ_{max}, mμ	Ultraviolet and visible spectra: Molar absorptivity	Infrared absorption frequencies, cm^{-1}
Tetrabromoterephthalic acid–sulfur trioxide complex	85% SO_3 / 15% SO_2	SO_3	541 432	1.4×10^3 6.2×10^{3b}	CO⁺ 2243[c]
Tetrabromoterephthalic acid–sulfur trioxide complex	SO_3–Freon 113	SO_3	445 (s) 326 (w)		
Tetrachloroterephthalic acid–sulfur trioxide complex	85% SO_3 / 15% SO_2	SO_3	503 413	7.6×10^3 7.0×10^{3b}	CO⁺ 2249[c]
Tetrachloroterephthalic acid–sulfur trioxide complex	SO_3–Freon 113	SO_3	433 (s) 300 (w)		
Tetrachloroterephthaloyl fluoride					C=O 1843[d]
Tetrachloroterephthaloyl fluoride–antimony pentafluoride complex	Fluorolube mull	SbF_5			CO⁺ 2243
Terephthaloyl fluoride[a]	Fluorolube mull				C=O 1812
Terephthaloyl fluoride–antimony pentafluoride complex[a]	Fluorolube mull	SbF_5			CO⁺ 2262

[a] Reference 1. [b] The apparent difference in molar absorptivities are due to deviations from Beer's law as they extrapolate to a common value at infinite dilution. [c] SO_3 solvent between thin Teflon sheets. [d] In KBr disk.

bisulfate structure **3**. Note, in particular, the $^+C{=}O$ absorption in the ir at 2243 cm^{-1}. Olah and Comisarow[1] assigned to the $^+C{=}O$ group the absorption band at 2262 cm^{-1} found in the ir spectrum of the complex obtained from the reaction of SbF_5 with the unsubstituted terephthaloyl fluoride.

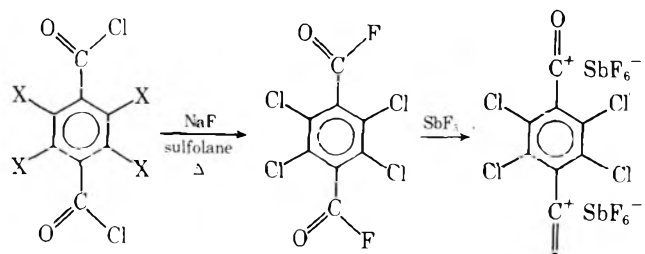


1. X = Br
2. X = Cl

3. X = Br
4. X = Cl

Tetrachloroterephthalic acid (**2**) responds in the same manner as Br_4TA in the SO_3–SO_2 solvent. The spectra of the orange-yellow solution of the diacylium cation **4** are summarized in Table I. The $^+C{=}O$ absorption is at 2249 cm^{-1}.

In order to obtain additional evidence on the structure of the species derived from the reaction of the tetrahalo diacids with SO_3, tetrachloroterephthaloyl fluoride (**7**) was treated with antimony pentafluoride in Freon 113[1] to form the hexafluoroantimonate salt, **8**. This salt can be isolated as an orange solid, mp 86–87°; the ir spectrum in a Fluorolube mull has a band at 2243 cm^{-1}.



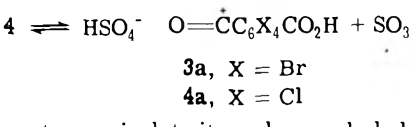
5. X = Br
6. X = Cl

7

8

The tetrabromoterephthaloyl fluoride could not be prepared from the reaction of the corresponding chloride, **5**, with NaF, owing to halogen scrambling under the conditions required for the substitution of chloride by fluoride.

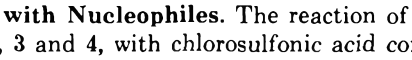
The addition of SO_3 to the Br_4TA (**1**) and the Cl_4TA (**2**) in the absence of SO_2 produces a suspension of the corresponding diacylium bis bisulfates, **3** and **4**. The ir spectra of the solid and the solution phases, examined within a thin Teflon envelope, show the bands of the diacylium cations. Dilution of the respective SO_3 phases with Freon 113 results in solutions with the uv spectra listed in Table I. There are significant differences between these uv spectra and the corresponding spectra of solutions of the diacylium cations, **3** and **4**, in the SO_3–SO_2 solvent. Two explanations seem possible for these differences. (a) The concentration of the salts, **3** and **4**, in the SO_3–Freon solvent is too low for observation of the weaker long-wavelength maxima (541 and 503 mμ, respectively). (b) In the solvent of lower polarity, the equilibrium which generates the diacylium bis bisulfates, **3** and **4**, from the monoacylium monosulfates, **3a** and **4a**, is shifted toward the monosulfates.



3a, X = Br
4a, X = Cl

From the spectroscopic data it can be concluded that the diacylium bis bisulfates, **3** and **4**, can be obtained either as a solution in SO_3–SO_2 solvent or as a solid. The solid salt, **3** or **4**, can be kept as a suspension in excess SO_3, or it can be freed from the SO_3 by extraction of the latter into Freon 113, or by vacuum distillation.

Reactions of the Tetrahaloterephthaloyl Diacylium Complexes with Nucleophiles. The reaction of the diacylium salts, **3** and **4**, with chlorosulfonic acid constitutes an excellent procedure for making the corresponding tetrahaloterephthaloyl chlorides, **5** and **6**.



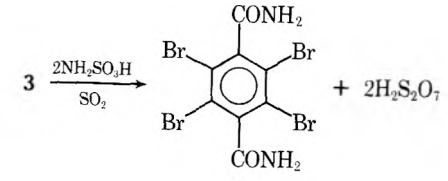
The tetrabromodiacylium bis bisulfate salt, **3**, can be treated with sulfamic acid in liquid SO_2 and this constitutes an excellent synthesis of tetrabromoterephthaldiamide (**9**).

Dialkyl esters of Br_4TA (**1**) and of Cl_4TA (**2**) are readily made from the diacylium salts, **3** and **4**, and the corresponding alcohols. As emphasized in the Experimental Sec-

Table II
Homopolymerization of Tetrabromoterephthalic Acid by Sulfur Trioxide without Preforming the Diacylium Complex

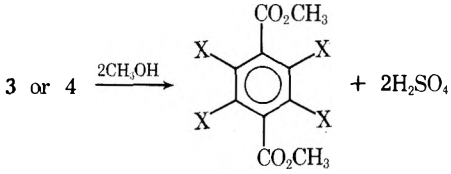
Br_4TA, g	SO_3, g	SO_2, g	SO_3/Br_4TA mole ratio	Polyanhydride yield, g (mol %)	Acid no., mg KOH/g	Average molecular weight	No. of Br_4TA units per polymer chain
15	2.5	139	1:1	9.9 (69)	10.8	10,400	22.4[a]
5.8	1.9	133	2:1	3.3 (59)	11.2	10,030	21.6
5.8	3.8	130	4:1	1.3 (23)	12.3	9,140	19.7

[a] Anal. Calcd for $C_8O_3Br_4$: Br, 68.9. Found: Br, 68.4.



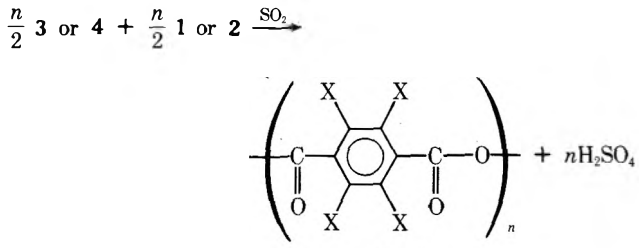
9

tion, the complete formation of the salts, **3** and **4**, from the acids, **1** and **2**, and SO_3 is aided by increasing the temperature or extending the reaction time.



10, X = Br
11, X = Cl

Homopolymerizations and Heteropolymerizations of Tetrahaloterephthalic Acids via Diacylium Complexes. The solid tetrabromodiacylium bis bisulfate salt, **3**, prepared by the Freon-extraction method, reacts with Br_4TA in SO_2 in the temperature range 120–130° to give a tetrabromoterephthalic acid polyanhydride, **12**. The structure of the polyanhydride **12** rests on infrared data, elemental analysis, and acid number derived by titration of acidic end groups with alkali. The tetrabromopolyanhydride **12** is obtained in 96.5 mol % yield, and the average polymer chain contains 21.4 monomer units.

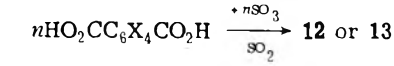


12, X = Br
13, X = Cl

The same type of polyanhydride, **12**, is formed, although only in 68.5 mol % yield, if the tetrabromodiacylium salt, **3**, is heated in SO_2, *in the absence of additional* Br_4TA (**1**). This suggests that the following equilibria are established in SO_2; in this manner, the nucleophilic Br_4TA becomes available to react with the electrophilic diacylium cation. The counterion in the polymer would then be pyrosulfate.

$$3 \rightleftharpoons 3a \rightleftharpoons 1$$
$$SO_4H^- + SO_3 \rightleftharpoons S_2O_7H^-$$

A tetrabromopolyanhydride, **12**, of about the same average molecular weight can also be made by the addition of stoichiometric amounts of SO_3 to Br_4TA (**1**) in SO_2, followed by heating to ca. 125°. This procedure generates the diacylium cation in situ. The results of such an experiment, with the mole ratio $SO_3/Br_4TA = 1$, are shown in Table II; note that the average polymer molecule contains 22.4 monomer units, although the yield has dropped to 69 mol %. Some polyanhydride is still produced at a mole ratio $SO_3/Br_4TA = 2$ and even at $SO_3/Br_4TA = 4$, although no polymer should have been produced if bisulfate, SO_4H^-, were the only possible counterion. In that case no nucleophilic carboxylic acid groups would have been present. Again the results suggest the formation of pyrosulfate anions, $S_2O_7H^-$, and anions of higher SO_3 content.



The solid tetrachlorodiacylium bis bisulfate salt, **4**, formed in the Freon-extraction method, reacts with Cl_4TA in SO_2 solvent at about 125° to give a tetrachloroterephthalic acid polyanhydride, **13**, of relatively low average molecular weight, 3300 (or 11.5 Cl_4TA units per polymer chain). On the other hand, Cl_4TA (1 mol) is polymerized by SO_3 (1 mol) in SO_2 solution at about the same temperature, but without isolation of the solid tetrachlorodiacylium complex, to give a tetrachloropolyanhydride of relatively high molecular weight, 8640 (or 30.1 Cl_4TA units per polymer chain).

Heteropolymeric anhydrides can be made from the reaction of solid tetrabromodiacylium bis bisulfate complex (**3**) with Cl_4TA, and by the reaction of solid tetrachlorodiacylium bis bisulfate complex (**4**) with Br_4TA, both in SO_2 medium. The polymer from 1 mol of tetrabromodiacylium complex and 2 mol of Cl_4TA has a 1:1.83 molar proportion of $C_8O_3Br_4$:$C_8O_3Cl_4$, with an average molecular weight of 3500, and an average of 3.5 tetrabromo- and 6.5 tetrachloroterephthalic acid units per polymer chain. The polymer represents a 47 mol % yield from Br_4TA and a 43 mol % yield from Cl_4 TA.

The polymer made from 1 mol of tetrachlorodiacylium complex and 1 mol of Br_4TA has a 1:1.37 molar proportion of $C_8O_3Cl_4$:$C_8O_3Br_4$, with an average molecular weight of 4677, and an average of 5.06 tetrachloro- and 6.93 tetrabromoterephthalic acid units per polymer chain. The polymer represents a 49 mol % yield from Cl_4TA and a 67 mol % yield from Br_4TA.

The perhalopolyanhydrides made available by the diacylium cation method are interesting materials. They are extremely resistant to hydrolysis, and prolonged digestion in boiling water causes no appreciable decomposition. Indeed, a sample of Br_4TA polyanhydride kept 15 days in contact with boiling aqueous potassium hydroxide (3 equiv of KOH per acid equivalent) shows no significant changes in the ir spectrum; no Br_4TA is obtained upon acidification of the alkaline extract.

In general, the yield of polyanhydride is lower from Cl_4TA than from Br_4TA. Moreover, the average chain length varies with the procedure used for Cl_4TA, but not

Table III
Partial Mass Spectra of $ClCOC_6X_4COCl$ Doubly Charged Ions

Ion composition[b]	Rel intensities,[a] X = H	X = Cl	X = Br
M ≡ Diacid chloride	0	0.2	Trace
M − Cl[c]	0	0.7	0.4
M − (Cl + CO)	0	1.2	0.4
M − 2Cl	8.8	23.5	29.8
M − (Cl + 2CO)	0	0.3	0.2
M − (2Cl + CO)	8.8	3.8	5.4
M − (2Cl + 2CO)	5.5	28.6	13.0

[a] Intensities are expressed on a scale defined by assigning a value of 100.0 to $[M - Cl]^+$, the most abundant ion species in each of the spectra. [b] The natural abundances of bromine and chlorine atoms result in multiplets of two or more peaks for each halogen-containing ion. The intensity profiles of such multiplets define the number and identities of the halogen atoms. The intensities of all the peaks in each such multiplet have been summed to arrive at the intensities shown in the table for the corresponding ion compositions. [c] The diacid chloride minus the indicated atom(s).

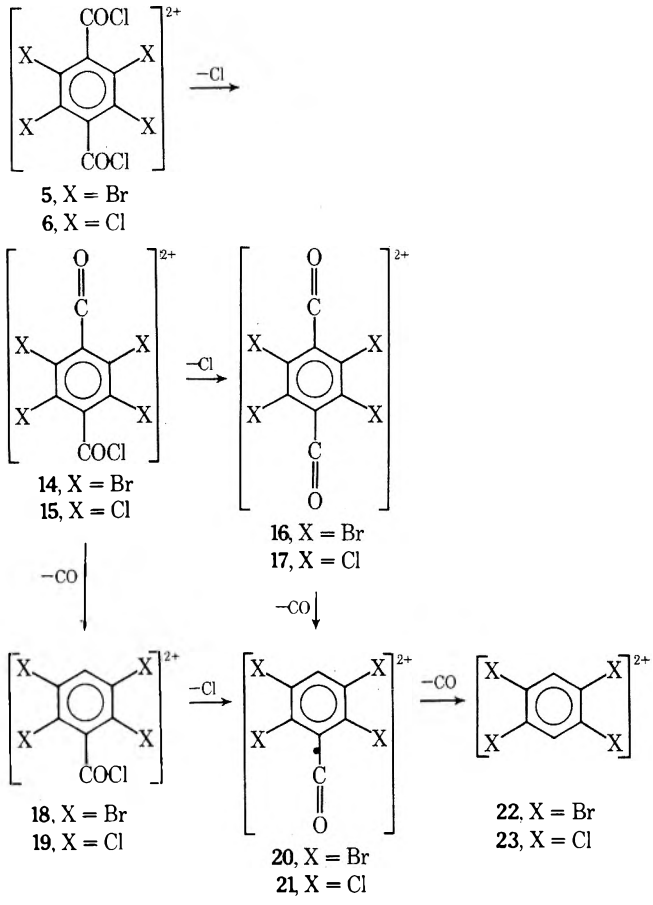
for Br_4TA. These differences may be related to the lower degree of stability of the chlorodiacylium vs. the bromodiacylium cations. The polymerization may occur by two different but related pathways when 1 mol of SO_3 is added to 1 mol of the tetrahalo acid. (1) The diacylium cation is formed, and this is followed by reaction with the free acid. (2) The monoacylium cation is formed and undergoes a head-to-tail polymerization. Regardless of the actual polymerization mechanism in the tetrahalo acid–SO_3–SO_2 procedure, there is no doubt that diacylium cations can be generated from the acids and SO_3, as shown by the spectral and the chemical evidence.

For comparison purposes the new tetrabromo diacid chloride, **5**, and the known tetrachloro diacid chloride,[6,7] **6**, were made also from the reaction of the corresponding acids, Br_4TA and Cl_4TA, with thionyl chloride. The mass spectra of these compounds and of terephthaloyl chloride are summarized in Table III. The data confirm the structures of the acid chlorides; moreover, the mass spectra indicate the relative probability with which the diacylium cation forms and survives intact in the vapor phase under electron impact. Note that for each of the three diacid chlorides a very intense peak for a doubly charged species corresponds to a process in which the two chlorine atoms have been removed from the diacid chloride. Furthermore, the doubly charged species is most abundant for the tetrabromo and least abundant for the unsubstituted diacid chloride, as would be expected from the relative stabilities of the diacylium cations.

For the tetrabromo and tetrachloro compounds, the important reactions involving the two acid chloride functional groups are shown in Scheme I. For tetrabromoterephthaloyl chloride (**5**) the loss of two chlorines forms **16** as the most abundant doubly charged species. The intensity of the species **22** from the subsequent loss of two carbonyl groups is less than half that of **16**. By contrast, tetrachloroterephthaloyl chloride (**6**) forms the doubly charged diacylium species, **17**, but this species is overshadowed by the greater relative intensity of **23**, the $C_6Cl_4^{2+}$ fragment.

These decompositions in the vapor phase seem to parallel the performance of the diacylium cations in homopolymerizations with the corresponding acids in liquid sulfur dioxide medium. Thus, the preformed diacylium bis bisulfate of Br_4TA reacted with Br_4TA to form the polyanhydride in 97 mol % yield. The corresponding homopolymerization of Cl_4TA formed the polyanhydride in only 43 mol %

Scheme I



yield. Furthermore, the average Br_4TA polymer chain contains almost twice the number of monomer units as does the the Cl_4TA anhydride polymer.

If we assume that the more efficient reactivity of the Br_4TA diacylium ion is realized because of its greater stability until reaction with Br_4TA can occur, then a parallel exists with the relative intensities of the mass spectra.

Experimental Section

Tetrabromoterephthalic Acid (Br_4TA). The tetrabromoterephthalic acid (**1**, Br_4TA) was made from terephthalic acid by bromination in fuming sulfuric acid with iodine catalyst under conditions more severe than for tetrabromophthalic anhydride[8] or for 2,5-dibromoterephthalic acid.[9] Terephthalic acid (322 g) was dissolved in 3666 g of fuming sulfuric acid (20% SO_3, 80% H_2SO_4) by heating to 69° with stirring in a three-neck, 3-l. round-bottom flask equipped with a stirrer, thermometer, and condenser protected from atmospheric moisture by concentrated sulfuric acid in a gas bubbler. The flask was protected from light by an aluminum foil shield. Iodine (12.5 g) was added to the flask as the solution cooled to room temperature. Bromine (702 g) was added and the flask was heated to reflux (60°). After 76 hr the pot temperature had risen to 125° and the heat was turned off. The cooled suspension was filtered on a fritted glass Buchner funnel. The filter cake was washed with 200 ml of concentrated sulfuric acid. The acid wet cake digested on the steam bath in 2 l. of water for 30 min. After cooling, the insoluble acid was filtered, washed on the filter successively with 700 ml of 10% hydrochloric acid and 400 ml of distilled water, and dried. The dry cake weighed 768.3 g. Its neutral equivalent was 245 and it contained 65.7% bromine. A sample was esterified with diazomethane and analyzed by gas chromatography. It contained 96.8 area % Br_4TA, 2.0% hexabromobenzene, 0.30% Br_3TA, and 0.68% Br_2TA.

Part of this crude product (384 g) was dissolved in 2 kg of 5% sodium hydroxide solution and was filtered to remove insoluble hexabromobenzene. The filtrate was added to 320 g of 44% sulfuric acid at 65–75° to recover the organic acids. After filtration and washing with 600 ml of water, the cake was recrystallized from methanol. The purified tetrabromoterephthalic acid weighed 273 g. Anal. Calcd for $C_8H_2Br_4O_4$: Br, 66.35; neut equiv, 240.9. Found:

Br. 66.5; neut equiv, 241.0. The ir (KBr disk) showed 1734 (s), 1659 (s), 1546 (w), 1445 (w), 1400 (s), 1337 (s), 1310 (s), 1257 (s), 1235 (s), 1180 (w), 1090 (m), and 776 cm^{-1} (m). A sample of the acid was converted to dimethyl tetrabromoterephthalate with diazomethae. The ester had a melting point of 229°; the ir (KBr disk) showed 1734 (s), 1439 (m), 1386 (m), 1332 (m), 1304 (w), 1238 (s), 1184 (w), 1081 (m), 944 (m), and 829 cm^{-1} (w).

Tetrachloroterephthalic Acid (Cl_4TA). Tetrachloroterephthalic acid was made following a published procedure[10] except that the chlorination was carried out at atmospheric pressure. The filter cake was digested in water to remove occluded sulfuric acid. Finally the crude Cl_4TA was recrystallized from methanol. Anal. Calcd for $C_8H_2O_4Cl_4$: Cl, 46.67; neut equiv. 151.97. Found: Cl, 46.75, neut equiv, 152.0.

Tetrabromoterephthaloyl Chloride from Tetrabromoterephthalic Acid and Thionyl Chloride. A mixture of Br_4 TA (1.0 g) and thionyl chloride (56 g) was kept for 1 hr at reflux temperature. The solution was evaporated almost to dryness without overheating the residue, which was then treated with water (25 ml), stirred, and filtered to yield the crude acid chloride. The latter was purified by trituration with methanol (40 ml) at 25° and drying at 60° under vacuum. Tetrabromoterephthaloyl chloride (1.0 g) had mp 196.0–196.5°, and ir bands (KBr disk) at 1850 (w), 1770 (s), 1318 (s), 1115 (s), and 870 cm^{-1} (s). Further characterization by mass spectrometry appears in Table III.

Tetrachloroterephthaloyl Chloride from Tetrachloroterephthalic Acid and Thionyl Chloride. A similar procedure gave tetrachloroterephthaloyl chloride: mp 145.5–146.0°; ir bands (KBr disk) at 1775 (s), 1355 (s), 1165 (s), 902 (s), and 890 cm^{-1} (s). The literature reports mp 144–145[7] and 147.5–148°,[11] and a comparable ir spectrum.

Preparation of Tetrachloroterephthaloyl Fluoride. The procedure of Tullock and Coffman[12] was satisfactory for the preparation of tetrachloroterephthaloyl fluoride. The reactants were heated for 1.5 hr at 215–226°. The product codistilled with the tetramethylene sulfone under vacuum (115° pot temperature, 1 mmHg), from which it was separated by dilution with water. This compound, after recrystallizing from a benzene–*n*-heptane solution, melted at 138.8–140.3° (lit.[13] mp 138.°). The ir spectrum (KBr) showed a strong carbonyl absorption at 1843 cm^{-1}.

Reaction of Tetrachloroterephthaloyl Fluoride with Antimony Pentafluoride. This reaction was carried out in 1,1,2-trifluorotrichloroethane (Freon 113) solution at 25° for 15 min, otherwise following the procedure of Olah and Comisarow[1] for the generation of the diacylium bis(hexafluoroantimonate) from terephthaloyl fluoride. The diacylium bis(hexafluoroantimonate) that precipitated from the solvent on adding a Freon solution of tetrachloroterephthaloyl fluoride to the Freon-diluted SbF_5 was reddish orange and had the ir spectrum shown in Table I.

Spectrophotometric Detection of the Diacylium Complexes Generated from the Reaction of Tetrahaloterephthalic Acids with Sulfur Trioxide. A. Spectra in 85:15 wt % SO_3:SO_2. Samples of the acids were weighed into volumetric flasks and made up to volume with a mixture of 85 wt % sulfur trioxide and 15 wt % sulfur dioxide. The solution from the tetrabromo acid was red, and the solution from the tetrachloro acid was yellow. The spectra were determined in the visible region, in quartz cells, in a Cary 16 spectrophotometer. The data are given in Table I.

B. Spectra in SO_3–Freon 113. Samples of the acids (0.3 g), Br_4TA and Cl_4TA, respectively, were triturated for 1 min with liquid sulfur trioxide (2.5 ml) in a dry nitrogen atmosphere. The corresponding suspension was diluted with Freon 113, and the clear supernatant solution was further diluted with appropriate volumes of Freon 113 for the determination of the spectra in the uv and visible regions, in quartz cells, in a Cary 14 spectrophotometer. See Table I.

Precautionary Note. Sulfur trioxide reacts vigorously with carbon tetrachloride to give phosgene and pyrosulfuryl chloride:[14] $2SO_3 + CCl_4 \rightarrow COCl_2 + ClSO_2OSO_2Cl$. Therefore, most of the SO_3 must be removed before CCl_4 is added as solvent in the following reactions. Furthermore, excessive amounts of pyrosulfuryl chloride render $ClSO_3H$ and CCl_4 miscible, and thus prevent the extraction of tetrachloroterephthaloyl chloride by CCl_4 from a mixture of the chloride and $ClSO_3H$.

Generation of Diacylium Complex from Tetrabromoterephthalic Acid and SO_3 and Reactions of the Complex with Nucleophiles. A. Reaction with Chlorosulfonic Acid. Tetrabromoterephthalic acid (1.0 g) was dissolved in sulfur trioxide (33 ml), with stirring, in a round-bottomed flask. The deep red solution became yellow as a dense layer separated from the main SO_3 solution. The mixture of two layers was distilled, first at 370 mm, and finally at 300 mm, at a bath temperature of 46°. To the residue from the distillation (6.7 g) was added chlorosulfonic acid (15 ml), and the mixture was kept at ambient temperature overnight. The contents of the flask were transferred to a separatory funnel by means of CCl_4 (30 ml), and the lower $ClSO_3H$ layer was separated and extracted further with two 20-ml portions of CCl_4. The combined CCl_4 extracts were evaporated at atmospheric pressure. The residue (5.7 g) was transferred to a sublimator (Kontes No. 5880), modified to carry the vapors to a cold receiver through an all-glass line. With the bath at 132°, the pressure at 10 mm, and steam passing through the condenser, the $ClSO_3H$ (4.6 g) that had been dissolved in the product was transferred to the cold receiver. With the bath at 280°, the pressure at 10 mm, and cold water passing through the condenser, tetrabromoterephthaloyl chloride (0.4 g) sublimed to the cold surface. The chloride melted at 199.5–200.5°; gas chromatography showed 99.9 area % purity.

A mass spectrum (low voltage) of the chloride was made by direct probe introduction, subjecting the sample to microdistillation in the instrument. Only one large peak was seen by the beam current signal, exhibiting maximum abundance in the vapor phase with the source and probe both at about 250°. The six spectra measured under this peak were identical except for intensity, and confirm the structure as $C_8Br_4Cl_2O_2$. The doubly charged ion $O{=}C^+C_6Br_4{}^+C{=}O$ was observed.

B. Reaction with Sulfamic Acid. A 3.5-g sample (7.26 mmol) of tetrabromoterephthalic acid was treated, under dry nitrogen, with 25 ml of sulfur trioxide in an open 300-ml Hastelloy C autoclave. After 8 min of stirring, 100 ml of Freon 113 was added to dissolve excess SO_3. The suspension was stirred and the clear liquid was decanted from the sticky solids in the vessel. Two 50-ml portions of Freon 113 were used to remove the remaining SO_3. Sulfamic acid (2.8 g, 29 mmol) was added to the autoclave, which was then closed and pressure tested with N_2; after venting, 130 g of sulfur dioxide was introduced from a tared cylinder. The temperature was raised to 108° (45 min, stirring at 2000–2400 rpm) and was held at 108–116° for an additional 100 min (pressure 450–485 psig) with stirring. The reactor was kept overnight at 23° (pressure 65 psig), and then was cooled in a Dry Ice–2-propanol bath and opened. After SO_2 evaporation, the residue was digested at 90° in 550 ml of water, cooled in an ice bath, filtered, and dried (50°, under vacuum) to yield 3.0 g of crystalline residue. This was refluxed in methanol to extract Br_4TA and leave insoluble 1.5 g of tetrabromoterephthaldiamide (mp ca. 342° dec). The ir spectrum (KBr disk) had bands at 1675 (s), 1595 (w), 1330 (m), 1305 (w), 1230 (m), 1120 (w), and 1080 cm^{-1} (w); the ir spectrum in Nujol mull showed the bands at 3442 and 3250 cm^{-1} for the NH_2 group. Microdistillation in the mass spectrometer showed one big peak due to tetrabromoterephthalodinitrile resulting from the dehydration of the diamide. Additional very weak peaks occurred at the diamide and the amide–nitrile masses.

C. Reaction with Methanol. Tetrabromoterephthalic acid (4.0 g) was suspended in 396 g of SO_3 and brought to a boil with stirring over a 1-hr period. A golden lower liquid layer developed. After cooling to 25° the upper sulfur trioxide phase was decanted, leaving 17.5 g of "underlayer". This layer was washed four times by suspending in 50-ml portions of Freon 113 and decanting to remove dissolved sulfur trioxide. The washed underlayer, which weighed 7.6 g, was added to 425 ml of absolute methanol with stirring. About 300 ml of methanol was distilled and the residual solution was cooled to 25°. A crystalline solid product was recovered by filtration. The filter cake was washed with 10 ml of methanol and dried to give dimethyl tetrabromoterephthalate (1.8 g, mp 207–210°); ir confirmed the identity of the diester. A gas chromatogram showed only one peak at the correct retention time.

In another experiment, 3.3 g of Br_4TA was similarly boiled in 50 ml of SO_3 and then cooled to room temperature. The upper SO_3 layer was decanted, and the golden underlayer was heated under vacuum for 30 min to a bath temperature of 56° to remove SO_3. To the residue (6.5 g), 35 ml of absolute methanol was added through a reflux condenser (vigorous reaction). After refluxing for 30 min, the suspension of white solids was cooled to room temperature, poured into 100 ml of water, digested on the steam bath, cooled, and filtered. The 2.5 g of dry solids was partitioned between chloroform and 5% sodium bicarbonate solution. On evaporation of the chloroform, 1.13 g of dimethyl tetrabromoterephthalate was recovered (mp 224.5°). The correct ir spectrum was obtained.

Generation of Diacylium Complex from Tetrachloroterephthalic Acid and SO_3, and Reaction of the Complex with Nucleophiles. A. Reaction with Chlorosulfonic Acid. Tetra-

chloroterephthalic acid (3.0 g) was dissolved in sulfur trioxide (150 ml), and the mixture was stirred for 1 hr at 25° in a closed flask. The initial orange solution turned pale yellow after the separation of a heavy layer (15 min). The excess SO_3 was distilled at 44–46° and atmospheric pressure (70° bath), and the residue was treated with chlorosulfonic acid (25 ml) and stirred for 90 min at ambient temperature. The mixture was extracted with five 50-ml portions of CCl_4, the combined extracts were evaporated, and the residue was sublimed as in the case of the bromo analog (bath temperature 190–204°, pressure 1 mm, time 50 min). Tetrachloroterephthaloyl chloride (2.0 g, mp 144.5–146.5°) was identified by comparison with a sample made from the acid and thionyl chloride.

In an identical experiment, except that the excess SO_3 was removed by dilution with Freon 113, decantation, and subsequent extraction of the solids with additional Freon, 2.1 g of tetrachloroterephthaloyl chloride was obtained.

B. Reaction with Methanol. Tetrachloroterephthalic acid (0.9 g) was added to 86 g of SO_3 in a covered erlenmeyer flask. The bright yellow suspension was heated and after 15 min became cloudy yellow with green solids out of solution. After 1 hr (about 20 min at boiling) the suspension was allowed to cool to room temperature. The yellow SO_3 upper layer was decanted from the greenish yellow solids, which were then cautiously added to methanol and allowed to stir. A crystalline product that precipitated from solution was filtered off, shaken with water, and dried to give dimethyl tetrachloroterephthalate (0.3 g), mp 152–154.5° (lit.[7] mp 154–155°). The ir spectrum (KBr) was identical with that of the dimethyl ester made by the reaction of Cl_4TA with diazomethane.

Homopolymerizations via the Tetrabromoterephthaloyl Diacylium Complex. A. With Preformed Diacylium Complex. Tetrabromoterephthalic acid (2.5 g) and SO_3 (25 ml) were allowed to react for 1 min under N_2 in a 300-ml Hastelloy C autoclave. The excess SO_3 was removed by extraction with one 100-ml and three 50-ml portions of Freon 113. The residual diacylium complex was mixed with additional Br_4TA (3.0 g) in the autoclave, which was then closed and pressurized with SO_2 (136 g). The mixture was kept for 25 min at 120–129°, with stirring (1600 rpm). The autoclave was cooled in a Dry Ice–2-propanol bath and opened. The liquid phase was decanted from a solid residue, which was washed with three 20-ml portions of Freon 113, and dried in a vacuum at 50°. This residue was refluxed with boiling methanol (95 ml), cooled, filtered, and dried to give 5.1 g (96.5 mol % yield) of tetrabromoterephthalic acid polyanhydride (mp >400°). The ir spectrum (KBr disk) had strong bands at 1820, 1780, 1130, and 980 cm^{-1}. A sample of the polyanhydride was titrated in a methanol suspension, giving an acid number of 11.3 mg KOH/g. On the assumption that only free acid end groups are titrated, this corresponds to a molecular weight of 9950. A thermogravimetric analysis in air showed a 5 wt % loss at 355°, an additional 5 wt % loss at 376°, and a further 2 wt % loss at 400°.

In an analogous reaction, Br_4TA (2.7 g) was allowed to react with SO_3 (25 ml); however, no additional Br_4TA was added to the diacylium complex prior to heating in liquid SO_2. The polyanhydride was obtained in 68.5 mol % yield (1.8 g); its acid number was 10.9.

B. Without Isolation of Diacylium Complex. In a series of reactions, Br_4TA and a predetermined amount of SO_3 were added to a Hastelloy C autoclave, the SO_2 solvent was introduced, and the mixture was heated for 70 min at 120–123° (570–620 psig) with stirring (2200 rpm). The autoclave was then cooled and opened, and the liquid phase was decanted and allowed to evaporate. The residue and the solid product from the autoclave were suspended in water (45 ml/g Br_4TA charged), digested at 90°, cooled, and filtered; the solid was washed with two 35-ml portions of water and dried. The polyanhydride was refluxed with boiling methanol (16 ml/g of crude product) to remove any unreacted Br_4TA, dried, and analyzed. The results are shown in Table II.

Homopolymerizations via the Tetrachloroterephthaloyl Diacylium Complex. A. With Preformed Diacylium Complex. Tetrachloroterephthalic acid and SO_3 were allowed to react for 15 min as described for the bromo analog, except that the mixture of diacylium complex, additional Cl_4TA, and SO_2 was brought to 105° (at 430 psig) during 37 min, and was kept for 15 min at 105–108° and 30 min at 115–125° (516–615 psig). The tetrachloroterephthalic acid polyanhydride was isolated as in the case of the bromo analog. From 2.5 g of Cl_4TA, 25 ml of SO_3, an additional 3.0 g charge of Cl_4TA, and 126 g of SO_2, 2.22 g of purified polyanhydride was obtained. The acid number was 34 mg KOH/g. The ir spectrum (KBr disk) had bands at 1820 (s), 1763 (w), 1170 (s), and 1000 cm^{-1} (s).

B. Without Isolation of Diacylium Cation. The Cl_4TA (9.45 g), SO_3 (2.5 g), and SO_2 (136 g) were allowed to react in the autoclave as described for the bromo analog. The autoclave was brought to 120° (576 psig) during 1 hr and was kept for 90 min at 123–129° (614–675 psig).

The chlorinated polyanhydride was isolated as in the case of the bromo analog. The yield of purified polyanhydride was 2.7 g; its acid number was 13 mg KOH/g. Anal. Calcd for $C_8O_3Cl_4$: Cl, 49.6. Found: Cl, 49.1.

Heteropolymerizations. A. Tetrabromoterephthaloyl Diacylium Complex with Tetrachloroterephthalic Acid. The bromodiacyl complex was made from Br_4TA (3.5 g) and SO_3 (25 ml) in 5 min, in an autoclave, as described above. After the excess SO_3 had been removed with Freon 113, the Cl_4TA (4.4 g) and the SO_2 (139 g) were added to the autoclave, which was heated for 70 min at 124–127° (622–648 psig). The tetrabromotetrachloroterephthalic acid polyanhydride (3.4 g) was isolated after purifying as in the case of homopolymers. The mixed polyanhydride had ir bands at 1820 (s), doublet 1785 and 1763 (both w), 1170 (s), 1145 (s), and 990 cm^{-1} (s). Elemental analysis gave 31.9% Br and 26.0% Cl, which corresponds to 46.3 wt % $C_8O_3Br_4$ and 52.4 wt % $C_8O_3Cl_4$. The acid number was 32 mg KOH/g.

B. Tetrachloroterephthaloyl Diacylium Complex with Tetrabromoterephthalic Acid. The chloro diacyl complex was made from Cl_4TA (2.20 g) and SO_3 (25 ml) in 5 min. The Br_4TA (3.49 g) and SO_2 (137 g) were introduced after the excess SO_3 had been removed by Freon 113 as described above. The autoclave was brought to 123° in 1 hr and was kept at 123–126° for 1.5 hr. The tetrachlorotetrabromoterephthalic acid polyanhydride (3.4 g) was isolated as described above. The ir spectrum had bands at 1820 (s), 1785 (s), 1763 (shoulder), 1173 (w), 1138 (s), and 990 cm^{-1} (s). Elemental analysis gave 14.7% Cl and 45.5% Br, which corresponds to 29.6 wt % $C_8O_3Cl_4$ and 66.0 wt % $C_8O_3Br_4$. The acid number was 24 mg KOH/g.

Attempted Alkaline Hydrolysis of the Polyanhydride of Tetrabromoterephthalic Acid. A 43.8-mg sample of the polyanhydride of Br_4TA was stirred at reflux in 100 ml of water containing 36.8 mg of potassium hydroxide for 15 days. The anhydride sample did not go into solution during this time. The cooled solution was filtered through a millipore filter, the filtrate was evaporated, and about 0.04 g of residue was recovered. An ir spectrum showed only H_2O and SiO_2. The filter cake had an ir spectrum essentially identical with that of the polyanhydride charged.

Acknowledgment. We thank Seymour Meyerson[15] for the mass spectra and for helpful discussions in their interpretations, A. G. Nerheim[15] for his innovative work in obtaining infrared and ultraviolet spectra, and Harry Claes for his invaluable laboratory assistance.

Registry No.—**1**, 5411-7-1; **2**, 2136-79-0; **3**, 54120-53-5; **4**, 54120-55-7; **5**, 54120-56-8; **6**, 719-32-4; **7**, 652-35-7; **8**, 54120-57-9; **9**, 54120-58-0; **10**, 54120-51-3; **11**, 1861-32-1; **12**, 54181-85-0; **13**, 54120-59-1; terephthalic acid, 100-21-0; antimony pentafluoride, 7783-70-2; sulfur trioxide, 7446-11-9; chlorosulfonic acid, 7790-94-5; sulfamic acid, 5329-14-6; tetrabromoterephthalodinitrile, 54181-84-9; methanol, 67-56-1; tetrabromotetrachloroterephthalic acid polyanhydride, 54120-60-4.

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Onium Ions. XIV.[1] Evidence for the Formation of Benzochlorophenium Ions[2]

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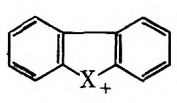
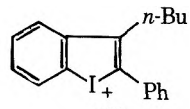
Benzochlorophenium ions were previously unknown. We have now studied, in the case of the 2-chlorobenzochlorophenium and 2-chloro-3-methylbenzochlorophenium ions, their possible preparation through the thermal dediazonation of o-(β,β-dichloroethenyl)phenyl- and o-(α-methyl-β,β-dichloroethenyl)phenyldiazonium hexafluorophosphate. Whereas the desired benzochlorophenium ions could not be isolated, formation of o-(β-chloroethenyl)chlorobenzene in the case of the former, as well as of 1-chloro-1-fluoro-2-(o-chlorophenyl)propen-1-ol and 1-chloro-1-(o-chlorophenyl)-2-fluoropropene-1 in the case of the latter, clearly indicates the intermediacy of the related benzochlorophenium ions.

Cyclic dibenzohalophenium ions (**1**), particularly dibenziodophenium ions, were previously prepared and studied.[2] Besides dibenzohalophenium ions (**1**), 2-phenyl-3-butyl-

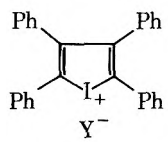


1

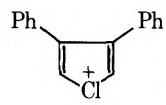
X = I, Br, Cl



2

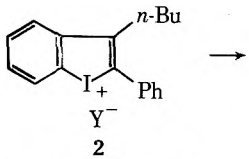


3a



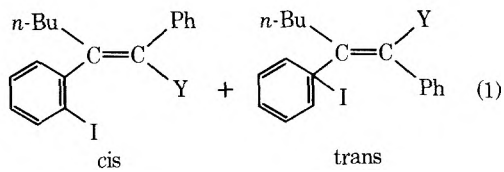
3b

benziodophenium (**2**) and tetraphenyliodophenium ions (**3a**) were among others synthesized by Beringer et al.[3] They reported that the iodophenium ion **2** underwent attack by nucleophiles, such as chloride, iodide, and methoxide ions, exclusively at the 2 position to give a mixture of trans and cis isomers (eq 1).



2

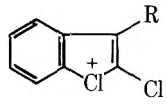
X = Cl^-, I^-, CH_3O^-



(1)

cis trans

The intermediacy of the 2,5-diphenylchlorophenium ion **3b** was recently also shown in the silver ion assisted solvolysis of halobutadienes.[4] The cyclic halophenium ions bear possible aromatic character, and their chemical reactivity is also of substantial interest.



PF_6^-

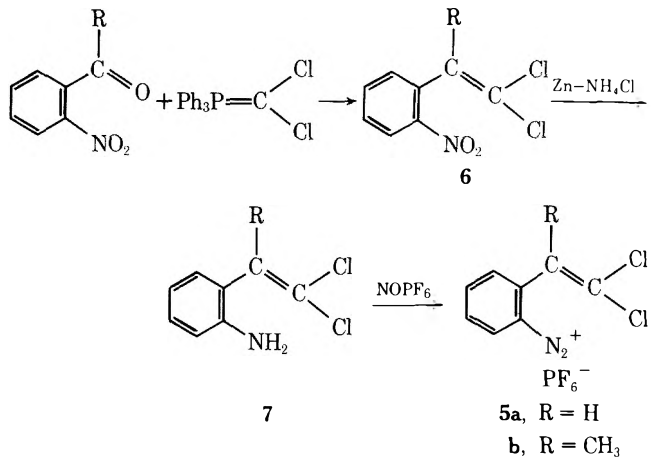
4a, R = H

b, R = CH_3

Results and Discussion

In an attempt to prepare and study the previously unknown class of benzochlorophenium ions, o-(β,β-dichloroethenyl)phenyl- (**5a**) and o-(α-methyl-β,β-dichloroethenyl)phenyl- (**5b**) diazonium fluorophosphate were used as precursors for synthesizing benzochlorophenium ions **4a** and **4b**, respectively. They were synthesized as shown in Scheme I.

Scheme I



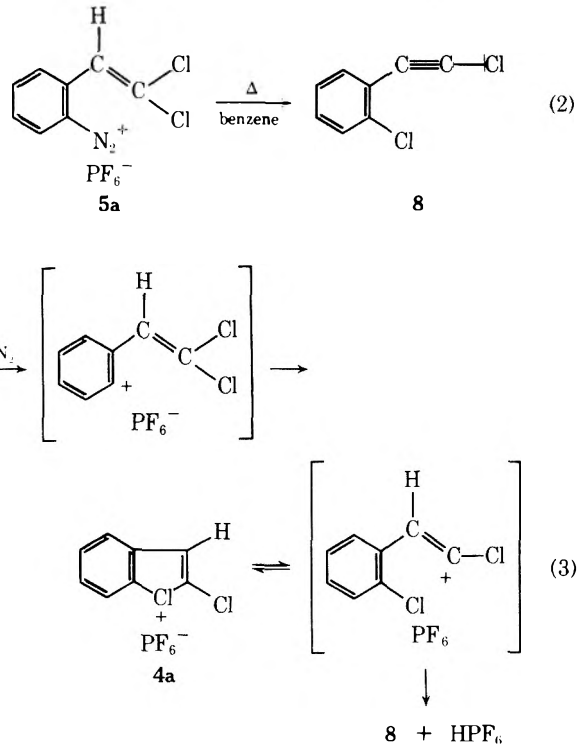
6

7

5a, R = H

b, R = CH_3

Dichloro olefins (**6**) were prepared from the corresponding carbonyl compounds with triphenylphosphonium dichloromethylide [R = H, 36.7%, mp 49–50°; R = CH_3, 56.0%, bp 110° (0.4 mm)], and were reduced with zinc powder and ammonium chloride in acetone–water to give the aniline derivatives **7** [R = H, 95.8%, bp 85–90° (0.03 mm); R = CH_3, 50%, bp 90° (1.3 mm)], which are, however, of only limited stability at room temperature. The aniline derivatives **7** were, therefore, immediately dissolved in acetonitrile, and were diazotized by using nitrosonium fluorophosphate in carbon tetrachloride to give the corresponding diazonium compounds **5** (R = H, 44.8%, mp 117–120° dec; R = CH_3, 28.4%, mp 99–100° dec).[5] Subsequently, we attempted the preparation of the 2-chlorobenzochlorophenium ion **4a** by the thermal decomposition of o-(β,β-dichloroethenyl)phenyldiazonium fluorophosphate (**5a**) in refluxing benzene for 1.5 hr. The desired benzochlorophenium ion (**4a**) could not be isolated, but o-(β-chloroethinyl)chlorobenzene (**8**)[6] was obtained in 99.0% yield (eq 2). The formation of **8** clearly shows the intermediacy of **4a**, which via ring opening and deprotonation gives **8** (eq 3). A concerted elimination process is considered less probable. **4a** is not sufficiently stable to be isolated under the reac-



(2)

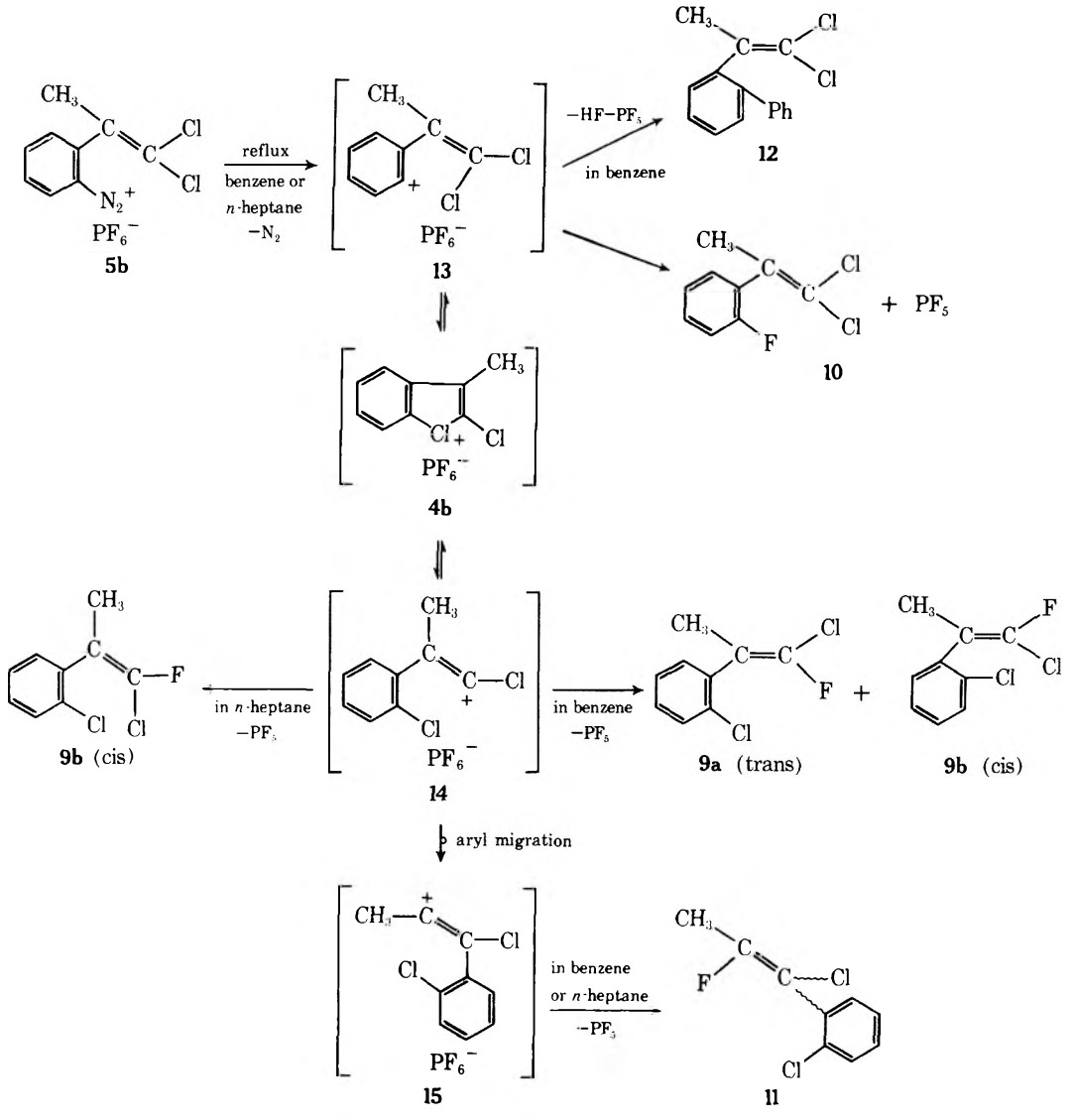
(3)

tion conditions. If the acidic proton at C_3 is absent in the benzochlorophenium ion, a different behavior is observed. The thermal decompositon of *o*-(*o*-methyl-β,β-dichloroethenyl)phenyldiazonium fluorophosphate (**5b**) in refluxing benzene (for 0.5 hr) gave a mixture[7] of 1-chloro-1-fluoro-2-(*o*-chlorophenyl)propene-1 (**9a** and **9b**) and 1,1-dichloro-2-(*o*-fluorophenyl)propene-1 (**10**, 25.6%), 1-chloro-1-(*o*-chlorophenyl)-2-fluoropropene-1 (**11**,[8] 24.5%), and 1,1-dichloro-2-(2-biphenyl)propene-1 (**12**, 46.5%)[9] (Scheme II). In refluxing *n*-heptane, the decomposition of **5b** gives a mixture of **9** and **10** (45.6%)[10] and **11** (34.2%).

In the reaction of **5b** in benzene, two isomers (**9a** and **9b**) of 1,1-chlorofluoro-2-(*o*-chlorophenyl)propene-1 were obtained. However, carrying out the reaction in refluxing *n*-heptane, only one isomer (**9b**) was obtained, and **12** was not found.

The formation of **9** and **11** shows the presence of 2-chloro-3-methylbenzochlorophenium ion (**4b**) as the intermediate, since only ring opening of **4b** can introduce chlorine into the ortho position of the phenyl ring. This result is quite different from that of the reaction of **4a**. **10** and **12** arise from the incipient phenyl cation **13**, which was generated not only by the loss of nitrogen of **5b**, but also from **4b** (equilibrium between **13** and **4b**). If the phenyl cation **13** is generated from **5b** it reacts with solvent benzene or fluoride ion to give the fluorinated product expected in the

Scheme II



Schiemann reaction. The phenyl cation formed from **5a** would also be expected to react in a similar fashion. However, the corresponding products **10** and **12** were not obtained in the reaction of **5**. This means that the chlorophenium ion (**4b**) is relatively stable compared to the chlorophenium ion (**4a**), and has two ways to cleave, giving the phenyl cation **13** or vinyl cation **14**. The vinyl cation **14** then reacts with fluoride anion to give **9a** (trans) and **9b** (cis). As the nucleophilicity of the hexafluorophosphate anion is low, the phenyl group of **14** can migrate to give the iomeric vinyl cation **15**, which reacts with fluoride anion to give **11** (giving only one isomer). When *n*-heptane was used as the solvent the yields of these products (**9, 10, 11**) increase and only one isomer of **9b** was obtained.

The differing behavior of **4b**, giving in benzene *trans*- and *cis*-1-chloro-1-fluoro-2-(*o*-chlorophenyl)propene-1 (in a ratio of 1:3), whereas in *n*-heptane only the trans isomer is formed, can probably be explained by the effect of the solvent. In benzene (a better solvating agent than *n*-heptane) the vinyl cation intermediate is more stabilized through solvation than in *n*-heptane, and two isomers are formed. However, in *n*-heptane the vinyl cation is less stabilized (compared to benzene), and some participation between the chlorine atom and the open vinyl cation formed subsequently from the benzochlorophenium ion, is taking place. Therefore, only the trans isomer could be formed. As aryl migration occurs, a free (or near-free) vinyl cation should be formed, which is then quenched by fluoride ion. Of course, it should be kept in mind that since the reaction in benzene gives us the major product **12** (in 46.5% yield) formation of which liberates an equimolecular amount of $HF-PF_5$, geometric isomerism in **9** via protonation–rotation–deprotonation also is possible.

The behavior of studied benzochlorophenium ions is quite different from the previously studied benzoiodophenium ions (**2**). This is not only due to the differing behavior of the benzochlorophenium ion, but also to the low nucleophilicity of the hexafluorophosphate anion used in their preparation via the corresponding arenediazonium ions, which allows a longer lifetime of the cationic center.

Experimental Section

Melting points are uncorrected.

Column chromatography was carried out using Sargent-Welch grade 60–200 mesh silica gel; TLC was done on Merck precoated PLC plates (silica gel F-254, layer thickness 2 mm). The NMR spectra were recorded on a Varian A-56/60 spectrometer using Me_4Si and trichlorofluoromethane as external standards for proton and fluorine NMR spectra. The infrared spectra were determined on a Beckman IR-10 spectrometer.

***o*-(α-Methyl-β,β-dichloroethenyl)nitrobenzene.** Potassium *tert*-butoxide was freshly prepared for use. Potassium (4.0 g, 0.1 g-atom) was added to 100 ml of dry *tert*-butyl alcohol (freshly distilled over sodium) and stirred for 5 hr. After the potassium completely reacted with *tert*-butyl alcohol, excess alcohol was distilled off. In order to eliminate *tert*-butyl alcohol completely, *n*-heptane (300 ml) was added to the still viscous residue, and distilled as the azeotrope. Triphenylphosphine (26.2 g, 0.1 mol in ca. 300 ml of heptane) was added to the mixture at under 5°, and then chloroform (11.9 g, 0.1 mol) in 100 ml of *n*-heptane again below 5° to give a yellow-colored solution which subsequently, on a vacuum evaporator, was concentrated to about 200 ml. o-Nitroacetophenone (16.5 g, 0.1 mol) in 100 ml of benzene was added below 10° and stirred for 1 hr in the ice bath and subsequently at room temperature overnight. The resulting brown-colored suspension was filtered off to give a red-colored solution. The solvent was evaporated to give a viscous liquid, which was separated by column chromatography (on silica gel with benzene as solvent) to give *o*-(α-methyl-β,β-dichloroethenyl)nitrobenzene (13.0 g, yield 56.0%): bp 110° (0.4 mmHg); NMR ($CDCl_3$) δ 2.70 (s, 3 H, $-CH_3$), 7.67–8.67 (m, 4 H, aromatic H).

Anal. Calcd for $C_9H_7Cl_2NO_2$: C, 46.58; H, 3.04; N, 6.04. Found: C, 46.19; H, 3.20; N, 6.29.

***o*-(α-Methyl-β,β-dichloroethenyl)aniline.** *o*-(α-Methy-β,β-dichloroethenyl)nitrobenzene (2.32 g, 0.01 mol) was mixed with 20 ml of acetone, 4 ml of water, and 1.0 g of ammonium chloride to give a homogeneous solution. Zinc powder (2.0 g) was added to the mixed solution below 55°, an additional 1.0 g of zinc powder was added, and the solution was refluxed for 30 min. After the reaction, the reaction mixture was filtered off to give a solution, which was evaporated off to give a yellow liquid. The resulting yellow liquid was extracted with ether, which was dried over anhydrous magnesium sulfate. The product was distilled to give *o*-(α-methyl-β,β-dichloroethenyl)aniline (1.00 g, yield 50.0%): bp 90° (1.3 mmHg); NMR ($CDCl_3$) δ 2.67 (s, 3 H, $-CH_3$), 4.67 (s, 2 H, $-NH_2$), 7.07–7.80 (m, 4 H, aromatic H).

Anal. Calcd for $C_9H_9Cl_2N$: C, 53.49; H, 4.49; N, 6.93. Found: C, 53.20; H, 4.67; N, 6.71.

***o*-(α-Methyl-β,β-dichloroethenyl)phenyldiazonium Hexafluorophosphate.** *o*-(α-Methyl-β,β-dichloroethenyl)aniline (0.530 g, 2.6 mmol) dissolved in 10 ml of acetonitrile was gradually added to the mixture of nitrosonium fluorophosphate (0.600 g, 3.4 mmol) and 15 ml of carbon tetrachloride below 0°, giving a brown-colored solution. After the reaction 2 ml of water was added to the reaction mixture, and the solvent was evaporated off to give a solid, which was washed with ether to give *o*-(α-methyl-β,β-dichlorethenyl)-phenyldiazonium fluorophosphate (0.270 g, yield 28.4%): mp 99–100° dec; NMR (DMSO-d_6) δ 2.70 (s, 3 H, $-CH_3$), 8.33–9.33 (m, 4 H, aromatic H).

Anal. Calcd for $C_9H_7Cl_2F_6N_2P$: C, 30.11; H, 1.97; N, 7.80. Found: C, 30.11; H, 1.90; N, 7.73.

Reaction of *o*-(α-Methyl-β,β-dichloroethenyl)phenyldiazonium Fluorophosphate. *o*-(α-Methyl-β,β-dichloroethenyl)-phenyldiazonium fluorophosphate (0.500 g, 1.39 mmol) was refluxed in 10 ml of benzene for 0.5 hr to give a brown-colored oil. It was separated by TLC to give a mixture of 1-chloro-1-fluoro-2-(o-chlorophenyl)propene-1 (trans and cis isomers) and 1,1-dichloro-2-(o-fluorophenyl)propene-1 (73 mg, yield 25.6%), 1-chloro-1-(*o*-chlorophenyl)-2-fluoropropene-1 (70 mg, 24.5%), and 1,1-dichloro-2-(2-biphenyl)propene-1 (170 mg, 46.5%). The mixture of **9a, 9b,** and **10** could not be isolated. Their physical, spectral, and analytical data are as follows: bp 80° (1.0 mmHg); **9a** (trans), δ 2.71 (d, J = 4.5 Hz), ϕ_F 100.9 (q, J = 4.5 Hz); **9b** (cis), δ 2.45 (d, J = 3.75 Hz), ϕ_F 82.3 (q, J = 3.75 Hz); **10,** δ 2.64, ϕ_F 113.9 (m). The aromatic protons appear at δ 7.54–7.94. The ratio of the mixture was as follows: **9a:9b:10,** 1:3:2.

Anal. Calcd for $C_9H_7Cl_2F$: C, 52.72; H, 3.64; F, 9.27. Found: C, 52.66; H, 3.33; F, 10.28.

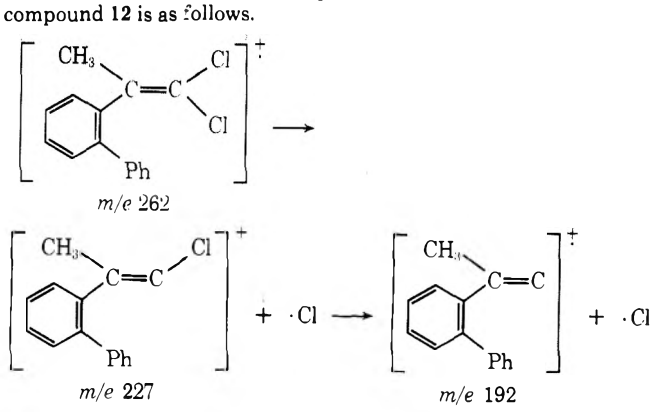
Compound 11: bp 90° (2.0 mmHg); NMR ($CDCl_3$) δ 2.40 (d, J = 17.0 Hz, 3 H, $-CH_3$), 7.90 (s, 4 H); ϕ_F 92.1 (q, J = 17.0 Hz).

Anal. Calcd for $C_9H_7Cl_2F$: C, 52.72; H, 3.44; Cl, 34.58. Found: C, 52.80; H, 3.63; Cl, 34.29.

Compound 12: mp 78–79° (*n*-hexane); NMR ($CDCl_3$) δ 2.40 (s, 3 H, $-CH_3$), 7.94 (s, 9 H, aromatic proton); mass spectrum (obtained on a Japan Electron Optics JMS-D100 spectrometermeter at the Tokyo Institute of Technology) *m/e* (rel intensity) 266 (3, M^+ + 4), 264 (20, M^+ + 2), 262 (32, M^+), 229 (7), 227 (25), 212 (14), 193 (18), 192 (100), 191 (64), 190 (16), 189 (39), 176 (16), 165 (34), 164 (14), 152 (11), 151 (18), 150 (14), 149 (34), 139 (9), 133 (18), 125 (14), 116 (9), 115 (55), 91 (23), 89 (20), 87 (18), 77 (23), 75 (25), 63 (34), 51 (45), 50 (25); uv spectrum λ_{max} (EtOH) 240 nm (obtained on a Hitachi EPS-3T spectrometer).

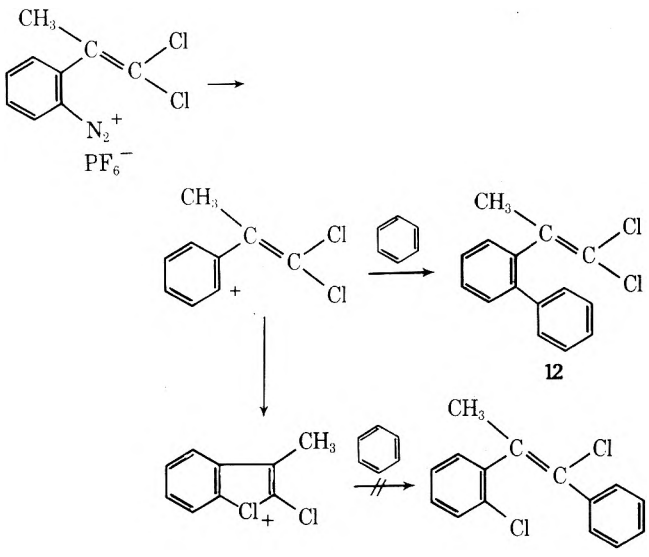
Anal. Calcd for $C_{15}H_{12}Cl_2$: C, 68.64; H, 4.60; Cl, 26.94. Found: C, 68.26; H, 4.49; Cl, 26.79.

The ratio of M^+ + 4:M^+ + 2:M^+ = 1:6:9 shows the presence of the two chlorine atoms in compound **12.** The fragmentation of compound **12** is as follows.



The loss of two chlorines from compound **12** is very typical to the geminal dichloride compound. The λ_{max} of compound **12** is very similar to that of styrene ($\pi \rightarrow \pi^*$ 244 nm). In the case of stilbene the λ_{max} appear at 280 (cis isomer) and 295.5 nm (trans isomer).

Therefore, the structure is not that of a stilbene, but of a styrene derivative. That is, the phenyl cation formed from the diazonium salt reacts with benzene to give the styrene derivative (compound



12). The reaction of cyclic chloronium ion with benzene should not occur.

Reaction of 5b in *n*-Heptane. *o*-(α-Methyl-β,β-dichloroethenyl)phenyldiazonium fluorophosphate (0.77 g, 2.14 mmol) was refluxed in 30 ml of *n*-heptane for 0.5 hr to give a pale yellow solution, which was separated in a similar manner to that described above to give a mixture of **9b** and **10** (200 g, yield 45.6%) and **11** (150 mg, yield 34.2%). The ratio of **9b** and **10** is 2:3.

***o*-(β,β-Dichloroethenyl)nitrobenzene.** Triphenylphosphine (26.2 g, 0.1 mol) was added to the potassium *tert*-butoxide made by the same way as described above; chloroform (11.9 g, 0.1 mol) in 100 ml of *n*-heptane was added to the mixed solution below 5°, and *o*-nitrobenzaldehyde (15.1 g, 0.1 mol) in 100 ml of benzene was added to the resulting brown-colored suspension below 10° and it was treated in the same way to give *o*-(β,β-dichloroethenyl)nitrobenzene (8.0 g, yield 36.7%): mp 49–50°; NMR (CCl_4) δ 7.25 (s, 1 H, olefinic H), 7.63 (m, 3 H, aromatic H), 8.10 (m, 1 H, aromatic H).

Anal. Calcd for $C_8H_5Cl_2NO_2$: C, 44.07; H, 2.31; N, 6.42; Cl, 32.25. Found: C, 44.18; H, 2.35; N, 6.36; Cl, 32.70.

***o*-(β,β-Dichloroethenyl)aniline.** *o*-(β,β-Dichloroethenyl)nitrobenzene (2.20 g, 0.01 mol) was mixed with 20 ml of acetone, 4 ml of water, and 1.0 g of ammonium chloride to give a homogeneous solution. Zinc powder (2.0 g) was added to the mixed solution below 55°, an additional 1.0 g of zinc powder was added, and the solution was refluxed for 30 min. After the reaction, the reaction mixture was treated in the same way as the case of *o*-(α-methyl-β,β-dichloroethenyl)aniline to give *o*-(β,β-dichloroethenyl)aniline (1.800 g, yield 95.8%): bp 85–90° (0.03 mmHg); NMR (CCl_4) δ 4.02 (s, 2 H, amine H), 7.16 (s, 1 H, olefinic H), 7.00–7.83 (m, 4 H, aromatic H).

Anal. Calcd for $C_8H_7Cl_2N$: C, 51.09; H, 3.75; N, 7.45; Cl, 37.43. Found: C, 50.91; H, 3.80; N, 7.55; Cl, 37.91.

***o*-(β,β-Dichloroethenyl)phenyldiazonium Hexafluorophosphate.** *o*-(β,β-Dichloroethenyl)aniline (1.46 g, 7.8 mmol) dissolved in 10 ml of acetonitrile was gradually added to the mixture of nitrosonium fluorophosphate (1.40 g, 8.0 mmol) and 15 ml of carbon tetrachloride below 0°, giving a brown-colored solution. After the reaction 2 ml of water was added to the reaction mixture and the solvent was evaporated off to give a solid, which was washed with ether to give *o*-(β,β-dichloroethenyl)phenyldiazonium fluorophosphate (1.200 g, yield 44.8%): mp 117–120° dec; NMR (acetone-d_6) δ 7.60 (s, 1 H, olefinic H), 8.30 (m, 2 H, aromatic H), 8.70 (m, 2 H, aromatic H).

Anal. Calcd for $C_8H_5Cl_2F_6N_2P$: C, 27.85; H, 1.46; N, 8.12; Cl, 20.29. Found: C, 28.09; H, 1.50; N, 8.15; Cl, 20.41.

Reaction of *o*-(β,β-Dichloroethenyl)phenyldiazonium Fluorophosphate. *o*-(2,2-Dichloroethenyl)phenyldiazonium fluorophosphate (0.100 g, 0.29 mmol) was refluxed in 10 ml of benzene for 0.5 hr, giving a brown-colord solution, which was distilled to give *o*-(β-chloroethinyl)chlorobenzene (0.049 g, yield 99.0%): bp 38° (0.13 mmHg); NMR (CCl_4) δ 7.40–7.90 (m, aromatic H); ir (NaCl) 2220 cm^{-1} (–C≡C–).

Anal. Calcd for $C_8H_4Cl_2$: C, 56.18; H, 2.35; Cl, 41.17. Found: C, 55.97; H, 3.19; Cl, 40.98.

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

Registry No.—**5a,** 54143-10-1; **5b,** 54142-99-3; **6a,** 51991-50-5; **6b,** 54143-00-9; **7a,** 54143-01-0; **7b,** 54143-02-1; **8,** 54143-03-2; **9a,** 54143-04-3; **9b,** 54143-05-4; **10,** 54143-06-5; **11,** 54143-07-6; **12,** 54143-08-7; *o*-nitroacetophenone, 577-59-3; triphenylphosphonium dichloromethylide, 6779-08-4; nitrosonium fluorophosphate, 16921-91-8; o-nitrobenzaldehyde, 552-89-6.

References and Notes

(1) (a) Part XIII: G. A. Olah and J. L. Grant, *J. Am. Chem. Soc.*, in press. (b) The naming dibenzoiodolium, -bromolium, and -chlorolium ions was used in the past. As the heteroaromatic ring system is analogous to thiophene, naming according to "halophenium Ions" seems proper. (c) Postdoctoral Research Associate, 1973–1974, from the Tokyo Institute of Technology, Tokyo, Japan.

(2) F. M. Beringer and L. L. Chang, *J. Org. Chem.*, **36,** 4055 (1971), and references cited therein.

(3) F. M. Beringer, P. Ganis, G. Avitabile, and H. Jaffe, *J. Org. Chem.*, **37,** 879 (1972).

(4) I. L. Reich and H. J. Reich, *J. Am. Chem. Soc.*, **96,** 2654 (1974).

(5) **Compound 5a:** ir (KBr) 2280 (–N≡N^+) and 865–830 cm^{-1} (PF_6^-); NMR (acetone-d_6) 7.60 (s, 1 H), 8.30 (m, 2 H), and 8.70 ppm (m, 2 H). Anal. Calcd for $C_8H_5Cl_2F_6N_2P$: C, 27.85; H, 1.46; N, 8.12. Found: C, 28.09; H, 1.50; N, 8.15. **Compound 5b:** ir (KBr) 2280 (–N≡N^+) and 800–900 cm^{-1} (PF_6^-); NMR (DMSO-d_6) 2.70 (s, 3 H), and 9.33–8.33 ppm (m, 4 H). Anal. Calcd for $C_9H_7Cl_2F_6N_2P$: C, 30.11; H, 1.97; N, 7.80. Found: C, 30.11; H, 1.90; N, 7.80. All other new compounds were fully characterized by their spectral and analytical properties.

(6) **Compound 8:** bp 38° (0.13 mm); ir 2220 cm^{-1} (C≡C); NMR ($CDCl_3$) δ 7.40–7.90 ppm (m). Anal. Calcd for $C_8H_4Cl_2$: C, 56.18; H, 2.35. Found: C, 55.97; H, 3.19.

(7) The mixture of **9a, 9b,** and **10** could not be separated by preparative TLC (silica gel), bp 80° (1.0 mm). By the coupling constants of fluorine, isomer **9a** is probably the trans form and isomer **9b** is the cis isomer: J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1968, p 912. The NMR spectra of the methyl proton and fluorine are as follows: **9a** (trans), δ 2.71 (d, J = 4.5 Hz), ϕ_F 100.9 ppm (q, J = 4.5 Hz); **9b** (cis), δ 2.45 (d, J = 3.75 Hz), ϕ_F 82.3 ppm (q, J = 3.75 Hz), **10,** δ 2.64 (s), ϕ_F 113.9 ppm (m). Their aromatic protons appear at δ 7.54–7.94 ppm. The ratio of the mixture is as follows: **9a:9b:10,** 1:3:2. Anal. Calcd for $C_9H_7Cl_2F$: C, 52.72; H, 3.64; Cl, 34.58; F, 9.27. Found: C, 52.66; H, 3.33; Cl, 34.28; F, 9.57.

(8) **Compound 11:** bp 90° (2.0 mm); NMR ($CDCl_3$) δ 2.40 (d, J = 17.0 Hz, 3 H), 7.90 ppm (s, 4 H), ϕ_F 92.1 ppm (q, J = 17.0 Hz). Anal. Calcd for $C_9H_7Cl_2F$: C, 52.72; H, 3.44; Cl, 34.58; F, 9.27. Found: C, 53.05; H, 3.63; Cl, 33.89; F, 9.12.

(9) **Compound 12:** mp 78–79° (*n*-hexane); NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.94 ppm (s, 9 H). Anal. Calcd for $C_{15}H_{12}Cl_2$: C, 68.46; H, 4.60; Cl, 26.94. Found: C, 68.26; H, 4.49; Cl, 26.79.

(10) The ratio of the mixture is as follows: **9b:10,** 2:3.

Secondary Orbital Interactions Determining Regioselectivity in the Lewis Acid Catalyzed Diels–Alder Reaction. II

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Frontier orbital theory and the theoretical model of the Lewis acid complexed dienophile have been used to predict the effect of Lewis acid catalysis on the regioselectivity of the Diels–Alder reaction between unsymmetrically substituted dienes and dienophiles. This theoretical approach is applied to the three general types of uncatalyzed Diels–Alder reactions and general cases for predicting the effect of catalysis on the regioselectivity of the normal electron demand reaction are given. The effect of polysubstitution on the frontier orbital coefficients of butadiene is also determined. Dipole–dipole interactions were not useful in predicting the changes in regioselectivity.

The use of frontier orbital theory to predict the reactivity and the regioselectivity of concerted cycloaddition reactions has been extremely successful.[1-6] General rules for predicting the regioselectivity of the uncatalyzed concerted $[2\pi + 2\pi]$ and $[4\pi + 2\pi]$ cycloaddition reactions from the frontier orbital interactions have been proposed.[1c,2d,4,5b] Also, the role of Lewis acid catalysis in the Diels–Alder reaction has been determined.[2c,5a] The important changes in the frontier orbital properties of the dienophile acrolein upon complexation with a Lewis acid was a substantial lowering of the frontier orbital energies, an increase in the magnitude of the LUMO coefficient of the carbonyl carbon, and an increase in the difference in the magnitudes of the LUMO coefficients of the alkene moiety. From these changes, a catalyzed transition state completely dominated by the HOMO diene–LUMO dienophile interaction and having greatly increased secondary orbital interactions was predicted. Houk and Strozier[2c] also proposed that Lewis acid catalysis will increase the regioselectivity from the uncatalyzed reaction for dienes with terminal coefficients of different magnitudes, while dienes with terminal coefficients of nearly equal magnitude will have no change or a decrease in regioselectivity.

In our investigation of the origin of the regioselectivity in the Lewis acid catalyzed Diels–Alder reaction between unsymmetrically substituted dienes and dienophiles, we have observed some discrepancies with experimental results in Houk and Strozier's explanation. However, these discrepancies are eliminated if secondary orbital interactions are considered. This is in agreement with our earlier investigations[1a] concerning the importance of secondary orbital interactions in determining the regioselectivity in the uncatalyzed Diels–Alder reaction. Consequently, in this paper, the theoretical model of the Lewis acid complexed dienophile and the frontier orbital approach (including secondary orbital interactions) is used to explain the origin of the change in the regioselectivity of the uncatalyzed Diels–Alder reaction with catalysis.

Results and Discussion

The frontier orbital approach to regioselectivity used in this paper is based on the second-order perturbation expression for the energy change which accompanies the orbital interaction of two molecules involved in a cycloaddition process. In this expression γ_{rs} is the atomic orbital transition state resonance integral for atomic orbitals r and s in the molecular orbitals, R and S. The c_r's and c_s's are the atomic orbital coefficients of the atomic orbitals in the molecular orbitals R and S, respectively, which have a bonding interaction in the transition state. The closed-shell repulsion is neglected in our approach because the overlap as represented by eq 1 has been shown to be the dominant interaction by many investigators.[1-6] The first-order charge interactions are also neglected because even when two polar molecules react as in the dimerization of acrolein, the regioselectivity is determined by the overlap and the first-order charge interactions favor the unobserved regioisomer.[1c] However, the effect of electrostatic forces will be considered later through the dipole–dipole interactions. A more detailed discussion of the theory is presented in a review by Herndon.[6]

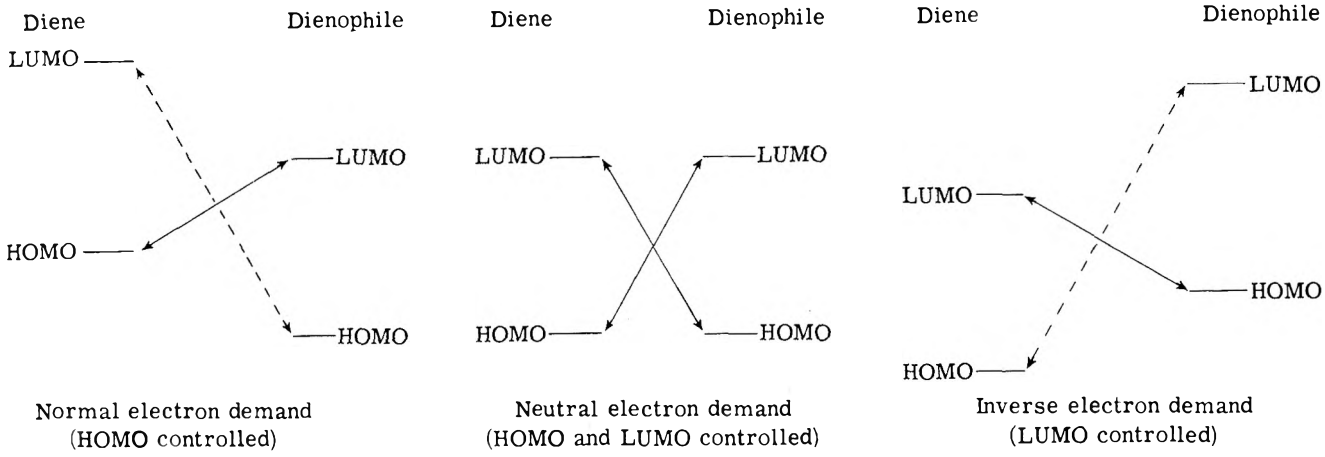
$$\Delta E = 2\left(\sum_{R}^{\text{occ}} \sum_{S}^{\text{unocc}} - \sum_{R}^{\text{unocc}} \sum_{S}^{\text{occ}} \right) \frac{\left(\sum_{rs} c_r c_s \gamma_{rs} \right)^2}{E_R - E_S} \qquad (1)$$

From eq 1, Sustmann[3] has classified the Diels–Alder reaction into three general types depending on the HOMO–LUMO arrangement of the diene and dienophile. The three types are the normal electron demand, the inverse electron demand, and the neutral electron demand (Chart I). The normal electron demand reaction is dominated by the HOMO diene–LUMO dienophile interaction, while the inverse electron demand reaction is dominated by the HOMO dienophile–LUMO diene interaction. In the neutral electron demand reaction, neither frontier orbital interaction is dominant and both significantly affect the regioselectivity and reactivity of the reaction. We will now apply the theoretical approach to the prediction of the effect of Lewis acid catalysis on the regioselectivity of the three types of Diels–Alder reactions.

Normal Electron Demand. The effect of Lewis acid catalysis on the regioselectivity of the normal electron demand Diels–Alder reaction can be simplified into the following two frontier orbital interactions: (1) interaction of the terminal HOMO coefficients of the diene with the LUMO coefficients of the alkene moiety of the dienophile; (2) interaction of the HOMO secondary orbital coefficients of the diene with the LUMO secondary orbital coefficient of the dienophile. By considering which regioisomer the two interactions favor and the relative importance of the two interactions, predictions concerning the change in the regioselectivity of the uncatalyzed Diels–Alder reaction with Lewis acid catalysis can be made. This approach is illustrated in the following experimental cases.

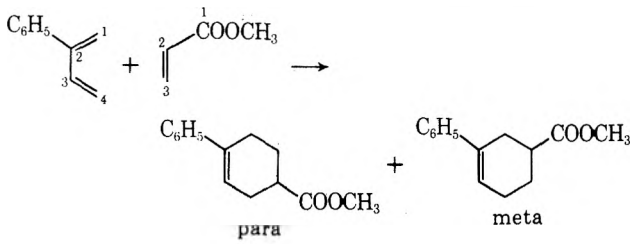
The reaction of 2-phenyl-1,3-butadiene with methyl acrylate is an example in which there is a large difference in the magnitudes of the terminal HOMO coefficients of the

Chart I
HOMO–LUMO Orbital Arrangements of the Three Types of Diels–Alder Reactions



Normal electron demand (HOMO controlled) | Neutral electron demand (HOMO and LUMO controlled) | Inverse electron demand (LUMO controlled)

diene. These coefficients favor the para regioisomer (Table I).[7] Since catalysis increases the difference in the magnitudes of the LUMO coefficients of the alkene moiety of the dienophile, these terminal interactions in the catalyzed reaction will favor the para regioisomer even more than in the uncatalyzed reaction. However, the secondary orbital

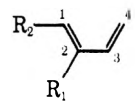


interactions between the HOMO of the diene and the LUMO of the dienophile favor the ortho regioisomer; that is, the endo transition state is more stable when the LUMO coefficient at C-1 of the dienophile is near the larger HOMO coefficient at C-2 of the diene (larger than the diene HOMO coefficient at C-3). Since secondary orbital interactions are increased with catalysis, they favor an increase in the amount of the ortho regioisomer formed. Thus, the two frontier orbital interactions predict opposite effects on the regioselectivity by catalysis. Experimentally, increased preference for the para regioisomer is observed (Table II); thus, the terminal interactions will dominate over the secondary orbital interactions in such cases. Also, the dienes, 2-methyl- and 2-chloro-1,3-butadiene, have similar HOMO coefficients to the 2-phenyl case and yield the predicted increase in regioselectivity with catalysis.[11]

The diene, 2-cyano-1,3-butadiene, has INDO and CNDO/2 HOMO coefficients similar to the 2-chloro and 2-methyl cases, but the regioselectivity in its catalyzed reaction with methyl acrylate is decreased from the uncatalyzed reaction. However, the semiempirical molecular orbital methods disagree on the relative HOMO coefficients of 2-cyano-1,3-butadiene (Table I); consequently, the regioselectivity cannot be reliably predicted from such coefficients. Also, for reactions between electron-deficient dienes and dienophiles, the HOMO dienophile–LUMO diene interaction could have a significant role in determining the regioselectivity.[4]

The 2-cyano-1,3-butadiene case points out a difficulty in the approach itself, which is that the relative magnitudes of

Table I
Eigenvectors of the HOMO of Monosubstituted 1,3-Butadienes



Registry no.	R_1	R_2	Molecular orbital method	Eigenvectors[a] C-1	C-2	C-3	C-4
78-79-5	CH_3	H	INDO	0.614	0.420	0.348	0.506
	CH_3	H	CNDO/2	0.621	0.417	0.340	0.498
2288-18-8	C_6H_5	H	INDO	0.572	0.341	0.214	0.335
	C_6H_5	H	CNDO/2	0.568	0.341	0.195	0.328
5167-62-4	CN	H	INDO	0.595	0.405	0.342	0.490
	CN	H	CNDO/2	0.600	0.405	0.335	0.485
	CN	H	Iterative extended Hückel	0.542	0.318	0.370	0.509
3036-66-6	H	OCH_3	CNDO/2	0.445	0.492	0.289	0.498
126-99-8	Cl	H	CNDO/2	0.546	0.346	0.266	0.397
	Cl	H	Iterative extended Hückel	0.601	0.334	0.224	0.394
381-81-7	CF_3	H	INDO	0.549	0.404	0.434	0.574
504-60-9	H	CH_3	INDO	0.531	0.456	0.350	0.534
	H	CH_3	CNDO/2	0.524	0.462	0.342	0.531
627-22-5	H	Cl	CNDO/2	0.423	0.400	0.266	0.423

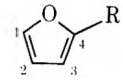
[a] These are the absolute values of the P_z coefficients. The other atomic orbital coefficients are zero for HOMO.

Table II
Regioisomer Ratios of the Diels–Alder Reaction between Unsymmetrically Substituted Dienes and Dienophiles

Diene	Dienophile	Uncatalyzed para:meta	Catalyzed para:meta	Ref
2-Phenyl-1,3-butadiene	Methyl acrylate	80:20	97:3	*a*
2-Chloro-1,3-butadiene	Methyl acrylate	87:13	98:2	*a*
2-Trifluoromethyl-1,3-butadiene	Methyl acrylate	55:45	51:49	*a*
2-Cyano-1,3-butadiene	Methyl acrylate	84:16	72:27	*a*
2-Methyl-1,3-butadiene	Methyl acrylate	69.5:30.5	95:5	*a*
2-Methyl-1,3-butadiene	Acrolein	59:41	96:4	*b*
1,2-Diphenyl-1,3-butadiene	β-Nitrostryene	75:25[e]	0:100[e]	*c*
1-Phenyl-2-methyl-1,3-butadiene	β-Nitrostryene	100:0[e]	0:100[e]	*c*
		Ortho:meta	Ortho:meta	
1-Methyl-1,3-butadiene	Methyl acrylate	90:10	98:2	*a*
2-Methylfuran	Ethyl propiolate		Ortho regioisomer formed >98%	*d*
2-Phenylfuran	Ethyl propiolate		Ortho regioisomer was only cyclo-addition product observed	*d*

[a] T. Inukai and T. Kojima, *J. Org. Chem.*, 36, 924 (1971). [b] K. L. Williamson and Y. L. Hsu, *J. Am. Chem. Soc.*, 92, 7385 (1970). [c] P. C. Jain, Y. N. Mukerjee, and N. Anad, ibid., 96, 2996 (1974). [d] A. W. McCulloch and A. G. McInnes, *Can. J. Chem.*, 49, 3152 (1971). [e] Nitro group is meta or para to 2 substituent of the diene.

Table III
INDO Frontier Orbital Coefficients of 1-Substituted Furans



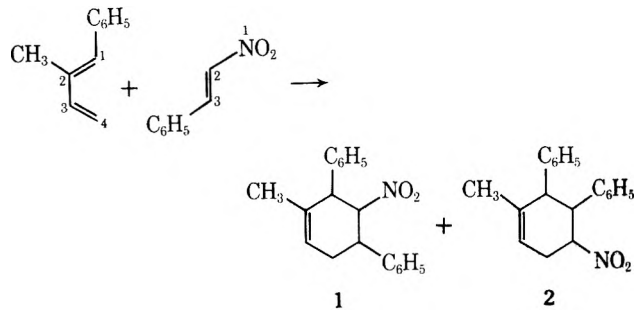
		P_z coefficients of HOMO[a]				P_z coefficients of LUMO[a]			
Registry no.	Substituent	C-1	C-2	C-3	C-4	C-1	C-2	C-3	C-4
534-22-5	CH_3	0.546	0.352	0.441	0.540	0.500	0.290	0.392	0.539
17113-33-6	C_6H_5	0.468	0.276	0.418	0.449	0.324	0.103	0.375	0.326

[a] These are absolute values. The other atomic orbital coefficients are zero for HOMO and LUMO.

the HOMO and LUMO eigenvectors of certain molecules depend on the type of calculation employed. In this work, we have used mainly the eigenvectors from INDO and CNDO/2 calculations because of their strong theoretical base[8,12] and earlier successful correlation with experimental results.[1a] Furthermore, other investigators[2a,4] have found that various semiempirical molecular orbital methods agree on the relative magnitudes of the frontier orbital coefficients of monosubstituted 1,3-butadienes for substituents other than electron withdrawing. Our molecular orbital methods do agree on the relative HOMO coefficients of 2-chloro-1,3-butadiene.

A different case is the reaction of 1-methyl-1,3-butadiene with methyl acrylate, where the terminal HOMO coefficients of the diene are of nearly the same magnitude, thereby favoring neither regioisomer. In such cases the regioselectivity is determined by the secondary orbital interactions and regioselectivity will always increase with catalysis. This increase was observed in this reaction (Table II). Another example of this case is the catalyzed reaction of 1-phenyl- and 1-methylfuran with ethyl propiolate. The terminal HOMO coefficients have nearly the same magnitudes (Table III) and the regioisomer favored by the secondary orbital interactions makes up >98% of the cycloaddition product.

A more dramatic example of the importance of secondary orbital interactions in determining the regioselectivity is the reaction between 1-phenyl-2-methyl-1,3-butadiene and β-nitrostyrene.[13] In this case the terminal HOMO coefficients of the diene have a significantly different magnitude and favor regioisomer 2 (Table IV). Secondary orbital interactions between the LUMO nitrogen coefficient of the

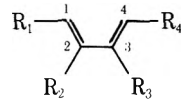


1 2

dienophile and the HOMO coefficients of the C-2 and C-3 positions of the diene favor regioisomer **1**. Since secondary orbital interactions are weak in the uncatalyzed reaction, the terminal interactions dominate and only regioisomer **2** is observed experimentally. However, in the catalyzed reaction, only regioisomer 1 is observed owing to the greatly enhanced secondary orbital interactions. More evidence for this conclusion is that the uncatalyzed reaction gave almost equal proportions of the endo and exo adducts (nitro group) while the catalyzed reactions gave exclusively the endo adduct. Similar experimental results were obtained for the analogous reaction of 1,2-diphenyl-1,3-butadiene with β-nitrostyrene (Table II).

These experimental cases have been discussed to demonstrate this approach. There are several other theoretical combinations of the two frontier interactions which may or

Table IV
CNDO/2 HOMO and LUMO Eigenvectors of Disubstituted 1,3-Butadienes

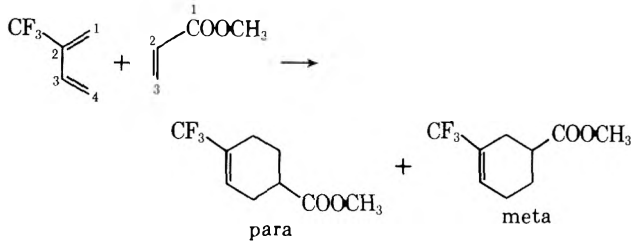


					Eigenvectors of HOMO[a]				Eigenvectors of LUMO[a]			
Registry no.	R_1	R_2	R_3	R_4	C-1	C-2	C-3	C-4	C-1	C-2	C-3	C-4
51034-43-6	Cl	H	H	CH_3	0.438	0.360	0.343	0.426	0.485	0.463	0.341	0.519
51034-44-7	H	Cl	H	CH_3	0.547	0.323	0.369	0.430	0.585	0.405	0.345	0.493
37710-49-9	H	H	Cl	CH_3	0.408	0.245	0.404	0.507	0.455	0.307	0.423	0.602
1608-27-1	C_6H_5	H	H	CH_3	0.419	0.407	0.294	0.417	0.407	0.432	0.255	0.419
21919-51-7	C_6H_5	H	CH_3	H	0.397	0.422	0.249	0.464	0.414	0.437	0.247	0.405
37580-42-0	C_6H_5	CH_3	H	H	0.433	0.433	0.208	0.388	0.415	0.443	0.247	0.411
22858-22-6	C_6H_5	H	H	Cl	0.380	0.390	0.269	0.395	0.436	0.392	0.335	0.411
54166-27-7	C_6H_5	H	Cl	H	0.380	0.422	0.228	0.438	0.420	0.408	0.281	0.470
54166-28-8	C_6H_5	Cl	H	H	0.414	0.408	0.193	0.365	0.461	0.427	0.210	0.373

[a] These are the absolute values of the P_z coefficients. The other atomic orbital coefficients are zero for the HOMO and the LUMO.

may not be observed experimentally, but the basis for rationalizing the changes in regioselectivity with catalysis is now available. The general cases are given in Table V. Finally, the effect of secondary orbital interactions on the regioselectivity will increase as the difference in the LUMO coefficient magnitudes of the diene moiety of the dienophile decreases.

Neutral Electron Demand. In the neutral electron demand reaction both frontier orbital interactions affect the regioselectivity. Upon catalysis, the HOMO diene–LUMO dienophile interaction becomes dominant; thus, the removal of the HOMO dienophile–LUMO diene interaction's effect on regioselectivity will also be important. The reaction of 2-trifluoromethyl-1,3-butadiene with methyl acrylate is an example of this removal affecting the regioselectivity. In the uncatalyzed case the HOMO dienophile–LUMO diene interaction favors the para regioisomer[14] and the HOMO diene–LUMO dienophile interaction favors the meta regioisomer. Experimental results indicate that the para regioisomer dominates slightly (Table II). Since this dominance originated from the HOMO dienophile–LUMO diene interaction, a decrease in the amount of para regioisomer is expected with catalysis. The decrease is observed experimentally with a near 50:50 ratio in the catalyzed case. This ratio is expected from examination of the terminal coefficients and secondary orbital coefficients of HOMO of the diene.



Inverse Electron Demand. The approach to predicting the effect of Lewis acid catalysis on the regioselectivity of the inverse electron demand reaction is the same as for the neutral electron demand reaction. Presently there are no experimental data available to test this approach for such reactions.[15]

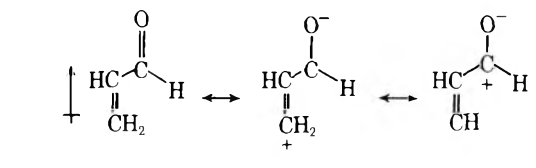
Frontier Orbital Eigenvectors of Polysubstituted Dienes. We have carried out CNDO/2 calculations on a series of disubstituted 1,3-butadienes (Table IV). The results are in accord with qualitative reasoning from summation of the individual substituent effects in the monosubstituted cases with the 1 substituent suppressing the effect of the 2 substituent somewhat. This slight dominance of the effect of the 1 substituent is expected, since the terminal coefficients of HOMO and LUMO of 1,3-butadiene are greater than the secondary orbital positions. The study also indicates that the difference in coefficient magnitudes at the secondary HOMO C-2 and C-3 positions will be a maximum for the 1,2-disubstituted case and a minimum for the 1,4-disubstituted case for a given set of substituents. Thus, for disubstituted dienes with similar terminal orbital coefficients, secondary orbital interactions will be most important in the 1,2-disubstituted case and least important in the 1,4-disubstituted case.

Dipole–Dipole Interactions. At a large distance of separation, electrostatic forces between polar reactant molecules can have a significant role in determining the orientation in the transition state. Consequently, the rationalization of preferred orientations through dipole–dipole interactions was investigated. The energy change due to dipole–dipole interactions is expressed by eq 2, where ΔE is in ki-

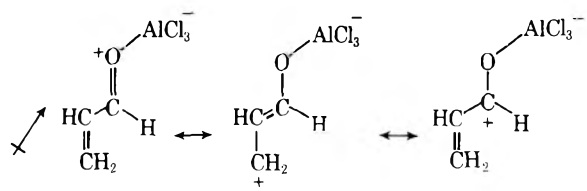
$$\Delta E = \pm \frac{14.4 \mu_A \mu_B}{r^3} \qquad (2)$$

localories/mole, μ is the dipole moment in Debye units, and r is the distance of separation in angstroms.[16] The orientation in which the dipoles line up in an antiparallel is favored. The directions of the dipole moments of the dienes and dienophiles were determined from vector analysis[17]

Chart II
Valence Bond Resonance Structures of Acrolein and Lewis Acid Complexed Acrolein



Acrolein



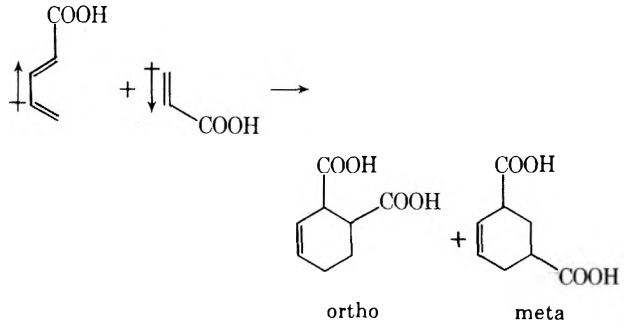
Lewis acid complexed acrolein

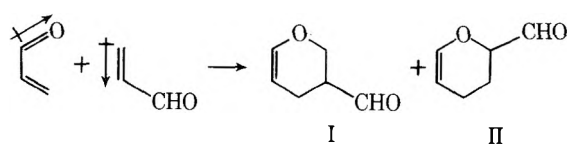
Table V
Effect of Lewis Acid Catalysis on the Regioselectivity of the Normal Electron Demand Diels–Alder Reaction

Case	Change in regioselectivity with catalysis
Terminal interactions and secondary orbital interactions favor the same regioisomer	Increased regioselectivity
Terminal interactions favor neither regioisomer and secondary orbital coefficients of the diene are significantly different	Increased regioselectivity
Secondary orbital coefficients favor neither regioisomer and the terminal coefficients of the diene are significantly different	Increased regioselectivity
Terminal interactions and secondary orbital interactions favor neither regioisomer	No change
Terminal interactions and secondary orbital interactions favor different regioisomers	1. When the difference in the magnitudes of the diene terminal coefficients is large, the terminal interactions will dominate and the regioselectivity will increase. 2. When the difference in the magnitudes of the diene terminal coefficients is small, the secondary orbital interactions will dominate and the amount of the minor regioisomer formed will increase.

and the semiempirical calculations. Lewis acid catalysis will increase the magnitude of the dipole moment, but will not change its direction (Chart II).

If dipole–dipole interactions are determining the regioselectivity of the Diels–Alder reactions in Table II, the following generalization should be observed. The Lewis acid catalyzed reaction will prefer the same regioisomer as the uncatalyzed reaction, only more so. However, this generalization is not even observed for the reactions with the polar dienes, 2-cyano-, and 2-trifluoromethyl-1,3-butadienes. More evidence against the importance of dipole–dipole interactions is obtained from the polar reaction of 1-carboxy-1,3-butadiene and acrylic acid. The dipole–dipole interaction favors the meta regioisomer while the ortho regioisomer is preferred 8.8:1. Another polar reaction in which the dipole–dipole interaction favor the unpreferred regioisomer





I II

(I) is the dimerization of acrolein. In both of these polar reactions overlap predicts the preferred regioisomer.[1]

Conclusion

The success of this frontier orbital approach allows the prediction of the effect of Lewis acid catalysis on the regioselectivity of the uncatalyzed Diels–Alder reaction between unsymmetrically substituted dienes and dienophiles. Also, this approach indicates that secondary orbital interactions have a significant and sometimes dominant effect in determining the regioselectivity of the catalyzed Diels–Alder reaction. The individual substituents effects on the frontier orbital coefficients are additive and the coefficients of the monosubstituted dienes can be used to qualitatively determine the relative coefficient magnitudes in polysubstituted dienes. Finally, the consideration of electrostatic interactions does not improve the theory.

Acknowledgment. The authors thank the Virginia Commonwealth University Computer Center for a grant of computer time.

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(4) N. D. Epiotis, *J. Am. Chem. Soc.*, **95**, 5624 (1973), and references cited therein.
(5) (a) N. T. Anh and J. Seyden-Penne, *Tetrahedron*, **29**, 3259 (1973); (b) O. Eisenstein, J.-M. Lefour, and N. T. Anh, *Chem. Commun.*, 969 (1971).
(6) W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972).
(7) The HOMO and LUMO coefficients of the dienes and dienophiles used in this investigation of regioselectivity were determined by the INDO,[8] CNDO/2,[8] and iterative extended Hückel[9] molecular orbital methods. A complete description of the geometries of diene and dienophiles used in the calculations is given in the first paper in this series.[1a] The experimental geometry of furan[10] with standard bond angles and bond lengths[8] for its substituents was used for the 1-substituted furans. The interpretations from the calculated eigenvectors and eigenvalues were independent of small changes in bond distances, bond angles, and rotational conformations.
(8) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970. Available from Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind. 47401, Program No. 141.
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(10) "Interatomic Distances", *Chem. Soc., Spec. Publ.*, **No. 11** (1958); *Suppl.*, **No. 18** (1965).
(11) Another source of the increase in regioselectivity in these cases is the decrease in the energy separation between the HOMO of the diene and the LUMO of the dienophile. As this energy separation decreases, the reaction becomes more sensitive to the substituent effect.
(12) The INDO and CNDO/2 wavefunctions are not above criticism: F. A. Van-Catledge, *J. Phys. Chem.*, **78**, 763 (1974).
(13) The CNDO/2 calculations predict that the LUMO coefficient (0.319) at

the C-2 position will be smaller than the LUMO coefficient (0.474) at the C-3 position for β-nitrostyrene.
(14) The LUMO coefficients (INDO) for 2-trifluoromethyl-1,3-butadiene are as follows: C-1, 0.626; C-2, 0.453; C-3, 0.338; C-4, 0.501.
(15) The classification of the specific uncatalyzed Diels–Alder reactions into the three general types was determined from the CNDO/2 and INDO orbital energies.
(16) R. A. Firestone, J. Org. Chem., 37, 2181 (1972).
(17) R. T. Morrison and R. N. Boyd, "Organic Chemistry", 3rd ed, Allyn and Bacon, Boston, Mass., 1973, p 22.

α-Methyleneoxetane. Study of a Retro-Diels–Alder Reaction

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Received September 3, 1974

As a precursor to α-methyleneoxetane (11), the anthracene adduct 7 was prepared in a four-step sequence from the ketone 2. Pyrolysis of 7 gave α-methyleneoxetane and anthracene, as well as the rearranged ether 8 and the olefin 15. The structure of the rearranged ether 8, also formed from 7 on some chromatography adsorbents or with acid, was determined with the aid of carbon-13 NMR spectroscopy and further confirmed by hydrogenation to the alcohol 9. α-Methyleneoxetane (11) was characterized by spectroscopy and by its reaction with phenyllithium.

α-Methyleneoxetane (11) has interested us for some time because of the possibility that nucleophilic displacement on the oxetane ring[1,2] could be used to generate a specific enolate of an unsymmetrical ketone; α-methyleneoxetane might thus serve as a potential 3-ketobutyl group in the Robinson annelation reaction.[3,4] Substituted compounds having the α-methyleneoxetane ring have been prepared by several methods[2,5–7] and have been proposed as reaction intermediates.[8] In 1971, we reported a preliminary account of the first synthesis of α-methyleneoxetane (11),[9,10] which we obtained in low yield from a retro-Diels–Alder reaction[9–14] by pyrolysis of the anthracene adduct 7. More recently, Haslouin and Rouessac have obtained 11 in higher yield by pyrolysis of the cyclopentadiene adduct.[11]

Since the pyrolysis of 7 gave α-methyleneoxetane in low yields only, we have investigated the composition of the nonvolatile residue from the pyrolysis experiments. In the course of this investigation we have also encountered an acid-catalyzed rearrangement of 7. We report here a full account of the pyrolysis and rearrangement of 7.

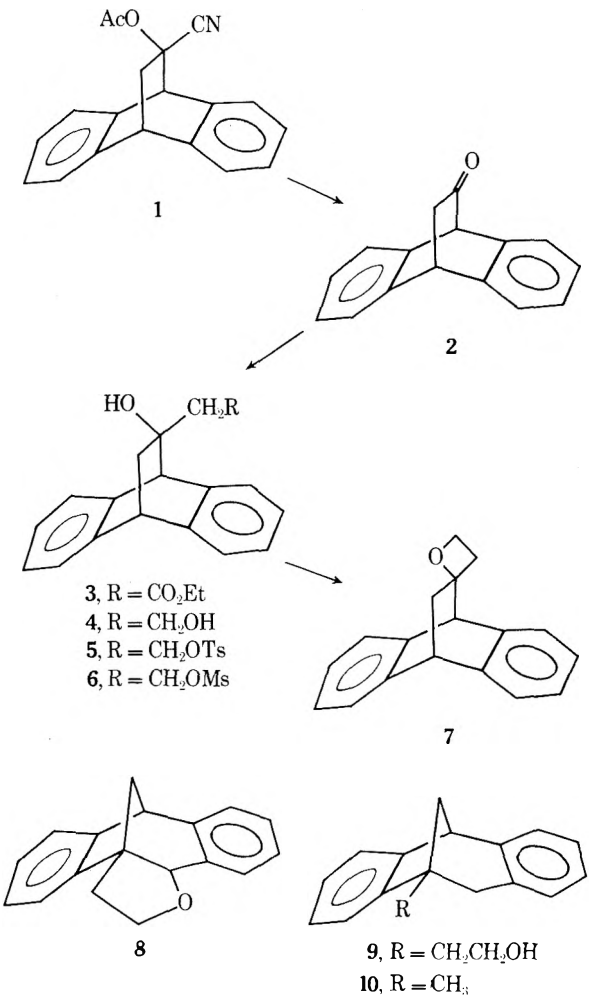
The anthracene adduct 7 was prepared as shown in Scheme I. Both the tosylate 5 and the mesylate 6 served as precursors to 7. The purity of 7 from both routes was indistinguishable (ir, NMR, TLC, melting point); we obtained higher yields from the mesylate.

The anthracene adduct 7 was always purified by chromatography on Florisil followed by recrystallization from ether. On one occasion, chromatography yielded none of 7 but instead an isomeric compound. The rearrangement of 7 to the isomer was found to take place on only certain batches of Florisil. The same rearrangement also occurred on acidic alumina, but not on silica gel or neutral or basic alumina. In addition, treatment with *p*-toluenesulfonic acid or sulfuric acid at room temperature caused the rearrangement of 7 to its isomer.

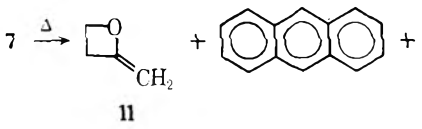
The isomer was assigned structure 8 on the basis of its analytical and spectral data, in particular the carbon-13 NMR data. The structure was further confirmed by catalytic hydrogenation to the alcohol 9. The chemical shifts and coupling constants in the proton NMR of 9 are very analogous to those reported for the related compound 10 prepared by Cristol.[15,16]

Pyrolyses of the anthracene adduct 7 were carried out on a small scale (50–500 mg) by heating at 330–350° in a slow stream of nitrogen for 5–25 min while collecting the volatile products in a receiver cooled in Dry Ice–acetone. The distillate, a colorless liquid, was identified as α-methyleneoxetane (11) by its ir, NMR, and mass spectra and its reaction with phenyllithium, which produced, after work-up, 4-phenyl-2-butanone (12),[17,18] 2-phenyl-3-buten-2-ol (13),[19,20] and 2,4-diphenyl-2-butanol (14).[18,21] In some pyrolyses, methyl vinyl ketone was formed as an impurity. On three occasions, the yield of α-methyleneoxetane was determined to be about 10%.[22]

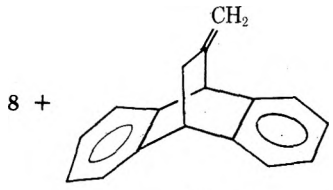
Scheme I



The NMR spectra of the nonvolatile residue from the pyrolyses suggested that several compounds were present. In addition to anthracene, the expected product from the retro-Diels–Alder reaction, and recovered 7, column chromatography produced samples of the rearranged isomer 8 and a compound assigned the olefin structure 15.[15,23] The



11



15

structure of the olefin was confirmed by independent synthesis using a Wittig reaction on the ketone 2. In one pyrolysis experiment (giving 10% of 11 and 2% of methyl vinyl ketone) the yields of the nonvolatile products were estimated to be 15% of anthracene, 21% of the olefin 15, 24% of recovered anthracene adduct 7, and 34% of the rearranged isomer 8.

The rearrangement of 7 to 8, which occurs as a major pathway with these pyrolysis conditions and as the sole pathway with acid treatment, is similar to carbonium ion rearrangements of several dibenzobicyclo[2.2.2]octadiene derivatives studied by Cristol.[24] The C–O bond of 7 is evidently easily broken; the geometry is suitable for neighboring group participation. It is interesting to note that this type of rearrangement is not reported for the cyclopentadiene adduct of 11, where the oxygen atom is endo and neighboring group participation for C–O cleavage is not favorable.[11]

In the pyrolysis of 7, fragmentation of the oxetane ring to give 15 evidently competes strongly with the retro-Diels–Alder reaction. Although thermal fragmentations of oxetanes are known,[25] normally one might not expect a [2 + 2] cycloreversion to compete with a [2 + 4] cycloreversion; oxetanes were stable to retro-Diels–Alder conditions in other systems.[10,11] This again suggests that the C–O bond of 7 is easily broken. Fragmentation of the oxetane in the other sense (giving ketone 2 and ethylene) was not observed.[26]

Experimental Section

Commercially available compounds were used without further purification unless otherwise noted. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride. Benzene was freshly distilled; the last half of the distillate was used. Pyridine was distilled from barium oxide. *tert*-Butyl alcohol was distilled from calcium hydride. Methanesulfonyl chloride was distilled (bp 63–64°, 20 mm) before use. *p*-Toluenesulfonyl chloride was decolorized with activated charcoal and was recrystallized (mp 68–68.5°) from hexane. Solutions of *n*-butyllithium and phenyllithium were obtained from Alfa Inorganics.

Unless otherwise specified, reactions were carried out in a nitrogen atmosphere using base-washed glassware. The use of the term "concentrated" refers to evaporation of solvent under reduced pressure (water aspirator) using a rotary evaporator.

Vapor phase chromatographic (VPC) analyses were performed on a Varian Aerograph Model 90-P instrument using helium as the carrier gas at a flow rate of 100 ml/min unless otherwise noted.[27] Silica gel G was used for thin layer chromatography (TLC). Florisil (60–100 mesh) used for column chromatography was obtained from Fisher Scientific Co.

Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and by Robertson Laboratory, Florham Park, N.J.

Infrared (ir) spectra were obtained using a Perkin-Elmer Model 137 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60 spectrometer unless otherwise noted, using tetramethylsilane as the internal reference. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-7 instrument.

9,10-Dihydro-11-acetoxy-9,10-ethanoanthracene-11-carbonitrile (1). A mixture of 16 g (0.09 mol) of anthracene and 5 g (0.045 mol) of α-acetoxyacrylonitrile[28] in 50 ml of *p*-xylene was heated at 140–150° for 32 hr[29] and allowed to cool to room temperature overnight. The reaction mixture was concentrated to remove the xylene, and the residue was stirred with methanol and filtered to partially remove excess anthracene. The filtrate was concentrated and the residue was chromatographed on 67 g of Florisil. Elution with hexane–CH_2Cl_2 mixtures produced 1 as an oil, homogeneous by tlc (R_f 0.3, benzene).[30] The product was partially crystallized with difficulty (CH_2Cl_2–hexane), producing 6.71 g of white crystals (mp 97.5–99°) and 3.86 g of oil (total 81% yield). The following spectra were obtained from the crystalline material: ir ($CHCl_3$) 5.71 μ; NMR ($CDCl_3$) δ 1.88 (s) partially overlapping with 2.06 (doublet of doublets, J = 14, 2.5 Hz) (total 4.3 H), 2.69 (doublet of doublets, 1.0 H, J = 14, 2.5 Hz), 4.35 (t, 1.0 H, J = 2.5 Hz), 5.08 (s, 1.0 H), 7.25 (m, 8.2 H); mass spectrum *m/e* 289 (M^+), 178 (base peak).

9,10-Dihydro-9,10-ethanoanthracen-11-one (2). To a solution of 9.57 g of the Diels–Alder adduct 1 (3.86 g of above oil and 5.71 g of above crystals) in 91.5 ml of THF and 16 ml of methanol was added 46 ml of 14% aqueous KOH.[31] The reaction mixture was stirred at 40° for 4 hr, then part of the solvent was removed under vacuum, and the resulting mixture was partitioned between ether and water. The aqueous layer was extracted twice with ether and the combined ether layers were washed with water, dried ($MgSO_4$), and concentrated, leaving a white, crystalline residue. Recrystallization from ether–hexane yielded white crystals: 4.23 g, mp 152.5–153°, and 2.42 g, mp 152–152.5° (total 91% yield) (lit.[32] mp 152.5–153°); ir ($CHCl_3$) 5.79 μ; NMR ($CDCl_3$) δ 2.30 (d, 1.9 H, J = 3 Hz), 4.52 (t, 1.0 H, J = 3 Hz), 4.80 (s, 1.0 H), 7.27 (m, 8.0 H).

9,10-Dihydro-11-hydroxy-9,10-ethanoanthracene-11-acetic Acid Ethyl Ester (3). A mixture of 13 g of activated zinc,[33] 100 ml of benzene, and 100 ml of anhydrous ether was heated to reflux. A solution of 5.65 g (0.0256 mol) of ketone 2 and 3.5 ml (0.032 mol) of ethyl bromoacetate in 50 ml of benzene was added dropwise.[33] The reaction started (became cloudy) with the addition of a crystal of iodine after about one-half of the ketone–ester solution had been added; the remainder was added over a 15-min period. Three additional 13-g portions of zinc along with a trace of iodine were added after 0.5, 1, and 2 hr; 1 ml (0.009 mol) of ethyl bromoacetate accompanied the last addition. Heating was then continued for 35 min. Acetic acid was added to the reaction mixture to dissolve the solids and the resulting solution was poured into water and extracted twice with ether. The combined ether extracts were washed (10% NH_4OH followed by brine), dried ($MgSO_4$), concentrated, and placed under oil pump vacuum for several hours. The crystalline residue was chromatographed on 50 g of Florisil. Elution with benzene–CH_2Cl_2 mixtures yielded 7.26 g (92%) of white crystals: mp 119–120°; ir[34] ($CHCl_3$) 2.8, 5.83 μ; NMR[34] ($CDCl_3$) δ 1.20 (t, 3 H, J = 7 Hz), 1.83 (d, 2 H, J = 3 Hz), 2.28 (s, 2 H), 3.32 (broad s, 1 H), 3.94–4.38 [several peaks which appear to be composed of 4.13 (q, J = 7 Hz) overlapping with 4.20 (crude t) and 4.31 (s) (total 4 H)], 7.18 (m, 8 H).

Three recrystallizations from ether gave white crystals: mp 121.5–122°; mass spectrum *m/e* 308 (M^+, small), 290 [$(M - H_2O)^+$], 263, 178 (base peak). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.89; H, 6.74.

9,10-Dihydro-11-hydroxy-9,10-ethanoanthracene-11-ethanol (4). To 3 g (0.08 mol) of lithium aluminum hydride in 75 ml of THF, a solution of 7.43 g (0.024 mol) of hydroxy ester 3 in 30 ml of THF was added dropwise. (Reaction mixture was protected from the atmosphere with a drying tube.) The mixture was heated at reflux for 3 hr, and then cooled in ice. About 20 ml of brine was added dropwise and the mixture was stirred at room temperature until the salts became white. The mixture was filtered (salts washed with ether), and the filtrate was dried ($MgSO_4$) and concentrated, leaving an oil which crystallized. Recrystallization from ether yielded 4.16 g (65%) of white crystals, mp 87–89.5°.

Three recrystallizations from ether gave white crystals, mp 92.5–93.5°. The spectral and analytical data indicated that 1,4-butanediol was present: ir ($CHCl_3$) 2.95 μ; NMR[35] ($CDCl_3$) δ 1.4–

2.1 (m, 6.05 H, CCH_2C of 4 and of butanediol), 2.7 (s, 1.08 H, OH), 3.2–4.0 (m, 6.05 H, $-CH_2O-$ of 4 and of butanediol and 2 OH), 4.3 (broad s, 1.95 H, benzylic H of 4), 7.0–7.5 (m, 8.0 H, aromatic H of 4). When the contents of the NMR tube were shaken with several drops of D_2O, the peaks in the general region of δ 1.4–1.6 and 3.2–3.6 were reduced in size (and the singlet at δ 2.7 disappeared and was replaced by a small singlet at lower field). The NMR spectrum of the material having mp 87–89.5° indicated that less 1,4-butanediol was present. The mass spectrum showed *m/e* 248 [$(M - H_2O)^+$], 230 [$(M - 2H_2O)^+$], 178 (base peak). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Calcd for $C_{40}H_{46}O_6$ (2:1 diol 4:1,4-butanediol): C, 77.14; H, 7.45. Found: C, 77.23; H, 7.58.

A ^{13}C NMR[36] ($CDCl_3$) was taken of a sample (mp 91.5–93.5°) from a similar experiment: δ 29.84 (C-2 of 1,4-butanediol), 41.98 (C-1′), 44.59 (C-10 or C-12), 44.89 (C-12 or C-10), 56.33 (C-9), 59.61 (C-2′), 62.57 (C-1 of 1,4-butanediol), 78.11 (weak, C-11).

Monotosylate (5) of 9,10-Dihydro-11-hydroxy-9,10-ethanoanthracene-11-ethanol. To an ice-cooled solution of 297.9 mg (1.1 mmol) of the diol 4 (mp 87–89.5°) in 3 ml of pyridine was added a solution of 500 mg (2.6 mmol) of *p*-toluenesulfonyl chloride in 3 ml of pyridine. (Reaction vessel was protected from the atmosphere with a drying tube.) The solution was stirred at ice temperature for 0.5 hr and was placed in a refrigerator overnight. The resulting mixture was poured into ice water and extracted with ether; the ether extract was washed twice with cold 1*N* HCl, followed by saturated $NaHCO_3$. The ether layer was dried (Na_2SO_4–K_2CO_3–$MgSO_4$) and concentrated; the residue was chromatographed on 5 g of Florisil. Elution with benzene followed by 2% CH_2Cl_2 in benzene produced 252.7 mg of oil, TLC R_f 0.23 (CH_2Cl_2). The major peaks of the NMR spectrum[34] (CCl_4) were a singlet at δ 2.38 and multiplets centered approximately about δ 1.5, 4.1, and 7.1 with a doublet at δ 7.7 (J = 8 Hz) (part of tosylate aromatic protons).

Monomesylate (6) of 9,10-Dihydro-11-hydroxy-9,10-ethanoanthracene-11-ethanol. Most of the benzene was distilled from a solution of 0.5 g (1.9 mmol) of the diol 4 (mp 85–90°) in 10 ml of benzene, to remove traces of water. Pyridine (3 ml) was added, the solution was cooled in ice, and 0.22 ml (2.9 mmol) of methanesulfonyl chloride was added dropwise. (Reaction vessel was protected from the atmosphere with a drying tube.) The solution was stirred at ice temperature for 30 min and placed in a refrigerator for 16 hr. The resulting mixture was poured into ice water and was extracted with ether. The ether extract was washed with two portions of cold 1*N* HCl followed by two portions of brine. (The second brine wash was neutral to pH paper.) The organic layer was dried (Na_2SO_4–$MgSO_4$) and concentrated, and the residue was placed under oil pump vacuum, leaving 0.65 g of a viscous, colorless oil, ir ($CHCl_3$ mull) 2.8, 7.4, 8.5 μ. The major peaks of the NMR ($CDCl_3$) spectrum were a sharp singlet (δ 2.86, 2.9 H) and multiplets centered approximately about δ 1.7 (5.3 H), 4.3 (3.8 H), and 7.2 (8.0 H). The TLC (1% CH_3OH in $CHCl_3$) showed one spot (R_f 0.22). The R_f value of 4 under the same conditions was 0.08.

9,10-Dihydrospiro[9,10-ethanoanthracene-11,2′-oxetane] (7). A mixture of 5 g of potassium in 80 ml of *tert*-butyl alcohol was heated at reflux until all the potassium dissolved. A solution of the entire crude mesylate 6 (0.65 g) from the above experiment in 4 ml of benzene was added dropwise at 50–60° and the reaction mixture was stirred for 2 hr at 60–70°. After cooling to room temperature, the reaction mixture was poured into saturated $NaHCO_3$ and extracted twice with ether. The combined ether extracts were dried (Na_2SO_4–$MgSO_4$), concentrated, and placed under oil pump vacuum. The oily residue was chromatographed on 10 g of Florisil. Elution with hexane–benzene mixtures produced material which was recrystallized from ether, yielding 0.34 g (73% from 4) of white crystals: mp 129–130°; ir[34] ($CHCl_3$) 10.4 μ (strong, broad); NMR[34] ($CDCl_3$) δ 2.13 (d, J = 2.5 Hz) overlapping with 2.1–2.9 (m) (total 4.0 H), 4.1–4.8 (*m*, 3.9 H), 6.9–7.6 (*m*, 8.1 H); ^{13}C NMR ($CDCl_3$)[34,36] δ 34.63 (t, C-1′), 44.59 (d, C-10 or C-9), 46.40 (t, C-12), 56.50 (d, C-9 or C-10), 64.26 (t, C-2′), 87.74 (weak, s, C-11).

A portion of the product prepared from 5 in a similar experiment was recrystallized three times from ether, giving white crystals: mp 130–130.5°; mass spectrum *m/e* 248 (M^+), 178 (base peak). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.03; H, 6.59.

2,3,8,12b-Tetrahydro-3a,8-methano-3a*H*-dibenzo[3,4:6,7]cyclohepta[1,2-*b*]furan (8). In an experiment similar to that described above, a mixture of 1.0 g (3.8 mmol) of the diol 4 (mp 91.5–93.5°) (dried as above by distilling benzene from a solution), 5 ml of pyridine, and 0.45 ml (0.68 g, 5.9 mmol) of methanesulfonyl chloride was stirred at 0° for 2 hr and placed in a refrigerator for 18 hr. The resulting mixture was poured into ice water; a white precipitate formed immediately. The mixture was filtered and the precipitate was dried under oil pump vacuum, leaving 0.302 g of white, crystalline material, mp 113–114°. The crystalline material had ir and NMR spectra identical with those of an authentic sample of 1,4-di(methanesulfonyloxy)butane, mp 115–115.5° (lit.[37] mp 116°), prepared from 1,4-butanediol and methanesulfonyl chloride by a procedure similar to that of Haggis and Owen.[37]

The filtrate was extracted with two 30-ml portions of ether. The combined ether extracts were washed with two portions of 1*N* HCl followed by two portions of brine, and were dried ($MgSO_4$) and concentrated, yielding 0.864 g of the oily monomesylate **6**. A solution of 0.85 g of this oil in 4 ml of benzene was added to a refluxing solution of potassium *tert*-butoxide in *tert*-butyl alcohol [prepared from 1.5 g (38 mmol) of potassium in 40 ml of *tert*-butyl alcohol]. The reaction mixture was heated at 70° for 2 hr, cooled to room temperature, poured into saturated $NaHCO_3$, and extracted three times with ether. The combined ether extracts were dried (Na_2SO_4–$MgSO_4$) and concentrated to give 0.73 g of residue which was chromatographed on 70 g of Florisil. Elution with CH_2Cl_2 gave 0.645 g of colorless oil which was crystallized with ether and recrystallized from ether, yielding 450 mg (49% from 4) of white crystals of **8**: mp 91–91.5°; ir ($CHCl_3$) 3.32, 3.35, 3.46, 6.72, 6.80, 6.85, 9.78, 9.82, 10.15 μ; NMR ($CDCl_3$) δ 1.88–3.12 (m) overlapping with 2.30 (d, J = 2.5 Hz) (total 4.1 H), 3.92–4.48 (m, 3.9 H), 7.04–7.50 (*m*, 8 H); ^{13}C NMR[36] ($CDCl_3$) δ 32.52 (t, C-1′), 45.11 (t, C-8), 46.69 (d, C-1), 54.09 (weak, s, C-5), 67.29 (t, C-2′), 81.83 (d, C-4); mass spectrum *m/e* 248 (M^+), 247, 246, 202, 178, 105.

A portion of the product was further recrystallized from ether, yielding white crystals, mp 93–93.5°. Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.84; H, 6.52.

Rearrangement of 7 to 8 on Chromatography Adsorbents.[38] In a typical experiment, a solution of 10 mg of **7** was adsorbed on 3 g of Florisil and allowed to stand for 24 hr. Elution with CH_2Cl_2 gave 10 mg of an oil having NMR spectrum ($CDCl_3$) identical with that of **8**.

This rearrangement was found to occur on only certain batches of Florisil and also on acidic alumina. Compound **7** was recovered unchanged after standing on basic alumina, neutral alumina, or silica gel.

Rearrangement of 7 to 8 with Acid. To a solution of 50 mg of the anthracene adduct **7** in 0.3 ml of $CDCl_3$ in an NMR tube (having the NMR spectrum reported above for **7**) was added 3 mg of *p*-toluenesulfonic acid. After standing for 1 hr at room temperature, the NMR spectrum was taken and was identical with that of the rearranged product **8** (above).

To a solution of 50 mg of **7** in 5 ml of $CHCl_3$ was added 10 ml of 6*M* H_2SO_4. After standing at room temperature for 16 hr in a covered flask, the reaction mixture was extracted with ether, and the ether extract was dried ($MgSO_4$) and concentrated, yielding 44 mg of pale, yellow oil. The NMR spectrum ($CDCl_3$) was identical with that of the rearranged product **8**.

Dibenzobicyclo[3.2.1]octadiene-5-ethanol (9). To a solution of 125 mg of the rearranged product **8** in 40 ml of absolute ethanol was added 34 mg of 10% Pd/C and 1 drop of 60% perchloric acid. The mixture was stirred under a hydrogen atmosphere for 92 hr at room temperature and atmospheric pressure. Filtration and concentration yielded 125 mg of colorless oil. A portion (115 mg) of the oil was purified by column chromatography on 20 g of Florisil. Elution with CH_2Cl_2 gave 105 mg of oil which was crystallized with ether and recrystallized from ether, yielding 98 mg of white crystals: mp 61.5–63°; ir ($CHCl_3$) 2.70, 2.82, 3.30, 3.36, 9.30, 9.98 μ; NMR[39] ($CDCl_3$) δ 1.53 (s, disappears with addition of D_2O), 1.95 (d, J = 10 Hz), 2.15 (t, J = 7 Hz), 2.33 (m, appearing as a doublet, J = 10 Hz, split into doublets, J = 4.5 Hz, split further into doublets, $J \approx$ 1.4 Hz), 2.52 (doublet of doublets, J = 16.5, 1.4 Hz), 3.04 (d, J = 16.5 Hz), 3.72 (t, J = 7 Hz) overlapping with 3.79 (d, J = 4 Hz), 6.6–7.0 (m). The relative areas upon integration are as follows: δ 1.53 (1.4 H), 1.8–2.7 (5 H), 2.9–3.2 (1 H), 3.6–3.9 (3 H), 6.6–7.0 (8.3 H). A ^{13}C NMR[36] ($CDCl_3$) was taken: δ 39.56 (C-1′ or C-4), 40.32 (C-4 or C-1′), 44.79 (C-8), 46.09 (weak, C-5), 46.71 (C-1), 59.56 (C-2′).

The product was recrystallized again from ether, yielding white crystals, mp 65–66.5°. The mass spectrum showed *m/e* 250 (M^+), 232, 231, 219, 206. Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.00; H, 7.56.

Pyrolysis of the Anthracene Adduct 7.[40] A 193.6-mg sample of the anthracene adduct **7** was placed in one arm of an all-glass apparatus consisting of two connecting U tubes. A slow stream of nitrogen was initiated; the receiving arm was cooled in a Dry Ice–acetone bath, then the arm containing **7** was immersed for 5 min in

a Wood's metal bath held at 340–350°. White crystals deposited on the tube immediately above the Wood's metal bath, and a small amount of a colorless liquid collected in the receiver. A 2-μl sample of cyclohexane (internal NMR integration standard) was added to the distillate, which was then transferred to a NMR tube with tetrachloroethylene: NMR[41] (C_2Cl_4) δ 1.43 (cyclohexane), 2.17 (methyl vinyl ketone), 3.16 (m, 2 H, appearing as triplet, J = 6.5 Hz, split into triplets, $J \approx 2$ Hz, allylic H of **11**), 3.63 (m, 1 H, appearing as doublet, J = 3.5 Hz, split into overlapping triplets, J = 1.8 Hz, vinyl H of **11** trans to O), 4.03 (m, 1 H, appearing as doublet, J = 3.5 Hz, split into overlapping triplets, J = 2.4 Hz, vinyl H of **11** cis to O), 4.50 (t, 2 H, J = 6.5 Hz, $-CH_2O-$ of **11**), 5.6–6.5 (methyl vinyl ketone). The yield of α-methyleneoxetane (**11**) (by NMR integration) was 10%, and that of methyl vinyl ketone was 2%. VPC analysis (SF-96, 49°)[27a] showed (in addition to solvent) peaks at 5.7 (major), 5.4 (shoulder) and 9.1 min (cyclohexane).[42]

The nonvolatile residue from the above pyrolysis was chromatographed[43] on 21 g of Florisil. Elution with hexane–benzene mixtures gave (1) 52.8 mg of white crystals and (2) 4.5 mg of white crystals. Further elution with benzene gave (3) 99.5 mg of oil, and elution with CH_2Cl_2 gave (4) 19.8 mg of oil. The integrated nmr spectrum ($CDCl_3$) of fraction 1 indicated that it consisted of a 5:6 molar ratio of anthracene:olefin **15** (see below). The ir and NMR spectra of fraction 2 indicated that it was pure olefin **15**. The NMR spectrum of fraction 3 indicated that it consisted of a mixture of recovered anthracene adduct **7** and the rearranged product **8**[44] (see below) in approximately a 1:2 ratio. The NMR spectrum of fraction 4 indicated that it consisted primarily of **7** with unknown impurities (estimated purity >75%). From these data, the yields of compounds in the nonvolatile residue were estimated at anthracene (15%), olefin **15** (21%), rearranged product **8** (34%), and recovered anthracene adduct **7** (24%).

The pentane-soluble portion of fraction 1 was rechromatographed on Florisil, yielding 12.8 mg of white crystals homogeneous by TLC (R_f 0.13, hexane) which were combined with fraction 2. Recrystallization twice from pentane (−22°) produced white crystals of **15**: mp 104.5–105° (lit.[23a] mp 103.5–104°); mass spectrum m/e 218 (M^+), 178 (base peak).

In a separate pyrolysis experiment (330–340°), the distillate was transferred to an ir cell and to an NMR tube with CCl_4: ir (CCl_4) 5.92, 8.44, 10.45 μ. The NMR was similar to that reported for **11** in C_2Cl_4; the corresponding chemical shifts were at δ 3.18, 3.60, 3.96, and 4.53. The NMR indicated that very little if any methyl vinyl ketone was present.

In a separate pyrolysis experiment (330–340°), the distillate was taken up in ether and analyzed by GC–MS:[45] m/e 70 (M^+), 55, 42, 39.

9,10-Dihydro-11-methylene-9,10-ethanoanthracene (15). A 320-mg sample of methyltriphenylphosphonium bromide was added in small portions to a solution of 0.34 ml of n-butyllithium (2.67 M in hexane) in 4 ml of anhydrous ether.[46] The reaction mixture was stirred at room temperature for 2.5 hr; then an additional 0.1 ml of n-butyllithium (2.67 M in hexane) was added (because much solid remained) and the stirring was continued for an additional 1.5 hr. A solution of 189.6 mg of ketone **2** in 8 ml of ether was added and the mixture was stirred for 0.5 hr at room temperature and overnight at reflux. After cooling to room temperature, the reaction mixture was filtered (precipitate washed with ether), and the filtrate was shaken with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed on 17 g of Florisil. Elution with hexane produced 94 mg (50%) of white crystals having essentially identical ir and NMR spectra to those of the olefin **15** obtained from the pyrolysis of **7** (above). The spectra were equivalent to the reported spectra of this compound.[23] One recrystallization from pentane (−22°) produced 50 mg of white crystals, mp 103.5–104.5° (lit.[23a] mp 103.5–104°).

Treatment of α-Methyleneoxetane with Phenyllithium. A 200-mg sample of the anthracene adduct **7** was pyrolyzed at 330–340° in the apparatus described above. The distillate was transferred in 1 ml of THF to a nitrogen-filled flask and was cooled in ice. Phenyllithium (0.8 ml, 2.2 M in 70:30 benzene-ether) was added dropwise and the reaction mixture was heated at 30–40° for 1 hr and at 80° for 4 hr. The mixture was cooled in ice; saturated NH_4Cl was added; the resulting mixture was extracted twice with ether. The combined ether extracts were dried (Na_2SO_4–$MgSO_4$) and concentrated. VPC analysis (SF-96, 125°)[27c] of the residue showed three major peaks at 2.9, 4.0, and 8.1 min in an area ratio of 1:1.7:4. The three components were separated by preparative VPC. The first component had ir and NMR spectra and VPC retention time essentially identical with those of a sample of 2-phenyl-3-buten-2-ol (**13**)[19] which was prepared from methyl vinyl ketone and phenyllithium, essentially the procedure of Buchta.[19a] The second component had ir and NMR spectra and VPC retention time essentially identical with those of a sample of 4-phenyl-2-butanone (**12**)[17,18] prepared by catalytic hydrogenation[17] (PtO_2, ethyl acetate) of benzalacetone.[47] The third component was identified as biphenyl by ir, NMR, and VPC.[48] At a higher temperature, VPC analysis (SF-96, 172°)[27c] of the crude product showed (in addition to early retention time peaks) peaks at 1.7 (corresponding in retention time to biphenyl) and 9.2 min in an area ratio of 2:1. From a separate experiment, the component representing the latter peak was purified by preparative VPC,[49] and had ir and NMR spectra and VPC retention time essentially identical with those of a sample of 2,4-diphenyl-2-butanol (**14**).[18,21] This sample was prepared from 4-phenyl-2-butanone (**12**) by the procedure of Stoermer[18] except that phenyllithium was used in place of phenylmagnesium bromide. The ir and NMR spectra of this sample were equivalent to the reported spectra.[21]

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Registry No.—**1**, 33988-20-4; **2**, 6372-63-0; **3**, 33190-01-1; **4**, 33084-39-8; 2:1 4-butanediol, 54119-94-7; **5**, 54119-95-8; **6**, 33988-19-1; **7**, 32869-16-2; **8**, 54119-96-9; **9**, 54119-97-0; **11**, 32869-14-0; **15**, 19978-14-4; anthracene, 120-12-7; α-acetoxyacrylonitrile, 3061-65-2; 1,4-di(methanesulfonyloxy)butane, 55-98-1.

References and Notes

(1) Ring-opening reactions of simple oxetanes with organometallic reagents are well known: (a) S. Searles, *J. Am. Chem. Soc.*, **73**, 124 (1951); (b) D. Wittenberg, D. Aoki, and H. Gilman, *ibid.*, **80**, 5933 (1958); (c) T. Cuvigny and H. Normant, *C. R. Acad. Sci., Ser. C*, **254**, 316 (1963); (d) S. H. Schroeter, *J. Org. Chem.*, **34**, 1188 (1969); (e) J.-C. Lahournère and J. Valade, *J. Organomet. Chem.*, **33**, C4 (1971).

(2) The ring-opening reactions of two substituted α-methyleneoxetanes with sodium methoxide have been reported: A. Feigenbaum and J. P. Pete, *Tetrahedron Lett.*, 2767 (1972).

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(4) The normally used methyl vinyl ketone gives an isomeric enolate which must undergo proton transfers before cyclization to a six-membered ring is possible.

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(8) (a) E. Wenkert et al., *J. Am. Chem. Soc.*, **92**, 1617 (1970); (b) N. J. Turro et al., *Tetrahedron Lett.*, 2535 (1971); (c) J. P. Pete and J. L. Wolfhugel, *ibid.*, 4637 (1973).

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(10) The isomeric 3-methyleneoxetane has been known for some time: D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956).

(11) J. Haslouin and F. Rouessac, *C. R. Acad. Sci., Ser. C*, **276**, 1691 (1973).

(12) For a review of the retro-Diels–Alder reaction, see H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968).

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(15) S. J. Cristol and G. O. Mayo, *J. Org. Chem.*, **34**, 2363 (1969).

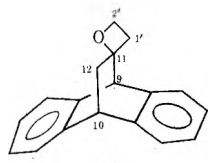
(16) For NMR spectra of compounds related to **10**, see S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **30**, 1956 (1965).

(17) Beilstein, "Handbuch der Organischen Chemie", Second Supplement, Vol. 7, Friedrich Richter, Springer-Verlag, West Berlin, 1948, p 243.

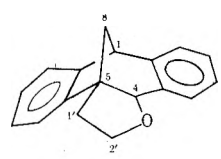
(18) R. Stoermer and H. Kootz, *Ber.*, **61B**, 2330 (1928).

(19) (a) E. Buchta and G. Satzinger, *Chem. Ber.*, **92**, 449 (1959); (b) C. S. Marvel and R. G. Woolford, *J. Org. Chem.*, **23**, 1658 (1968).

(20) Compound 13 may have been formed from a methyl vinyl ketone impurity.
(21) (a) R. Huisgen, R. Grashey, H. Seidl, and H. Hauck, *Chem. Ber.*, **101**, 2559 (1968); (b) S. S. Hall, *J. Org. Chem.*, **38**, 1738 (1973).
(22) Four batches of **7** were prepared and pyrolyzed under the above conditions. The pyrolysis of three batches was successful. Two batches were used to determine the yield of α-methyleneoxetane, which was found to be 10, 9, and 10%.
(23) (a) V. J. Shiner, Jr., and J. S. Humphrey, Jr., *J. Am. Chem. Soc.*, **85**, 2416 (1963); (b) H. K. Hall, Jr., J. B. Dence, and D. R. Wilson, *Macromolecules*, **2**, 475 (1969).
(24) (a) S. J. Cristol and R. K. Bly, *J. Am. Chem. Soc.*, **82**, 6155 (1960); (b) S. J. Cristol, J. R. Mohrig, and G. T. Tiedeman, *J. Org. Chem.*, **37**, 3239 (1972), and references cited therein.
(25) For examples of the thermal fragmentation of oxetanes, see (a) G. Jones, II, S. B. Schwartz, and M. T. Marton, *Chem. Commun.*, 374 (1973); (b) G. Jones, II, and J. C. Staires, *Tetrahedron Lett.*, 2099 (1974); (c) G. Jones, II, and H. H. Kleinman, *ibid.*, 2103 (1974).
(26) The close correspondence of the yields of anthracene with those of α-methyleneoxetane and methyl vinyl ketone suggest that the olefin **15** is not further cracking to anthracene and allene to a significant extent.
(27) The following columns were used for VPC analysis: (a) 10% SF-96 on Chromosorb W, 20 ft × 0.25 in. aluminum column, (b) 10% SE-30 on Chromosorb W, 10 ft × 0.25 in. aluminum column, (c) 15% SF-96 on Chromosorb W, 5 ft × 0.25 in. stainless steel column.
(28) R. M. Nowak, *J. Org. Chem.*, **28**, 1182 (1963). For the first use of α-acetoxyacrylonitrile as a ketene equivalent in the Diels–Alder reaction, see P. D. Bartlett and B. E. Tate, *J. Am. Chem. Soc.*, **78**, 2473 (1956).
(29) The time was incorrectly reported as 8 hr in the preliminary communication.[9]
(30) In a separate but similar experiment, the NMR spectrum of the chromatographed product before crystallization was essentially identical with the NMR of the crystalline material.
(31) The procedure is that of M. A. Qasseem, N. A. J. Rogers, and A. A. Othman, *Tetrahedron*, **24**, 4535 (1968).
(32) S. Wawzonek and J. V. Hallum, *J. Org. Chem.*, **18**, 288 (1953).
(33) The procedure is adapted from W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).
(34) This spectrum was taken of material of comparable purity from a separate but similar experiment.
(35) In a separate experiment, the crude diol **4** was chromatographed on Florisil. Elution with benzene followed by methylene chloride produced crystalline material having NMR ($CDCl_3$) δ 1.2–2.1 (m, 4.2 H), 2.1–3.5 (2 broad humps, 2.0 H), 3.5–4.0 (crude t, 2.0 H), 4.3 (broad s, 1.9 H), 7.0–7.5 (m, 9.7 H).
(36) Carbon-13 NMR spectra were determined on a Varian CFT-20 instrument; chemical shifts of the nonaromatic carbon atoms are reported in parts per million relative to tetramethylsilane (δ 0) as an internal reference, followed by the multiplicity observed with off-noise decoupling, and assignments. For consistency, compounds **4** and **7** are both numbered as shown below for compound **7**, and compounds **8** and **9** are both numbered as shown below for compound **8**.



7



8

(37) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 389 (1953).
(38) Florisil (60–100 mesh) and alumina (80–200 mesh, Brockman activity 1) were obtained from Fisher Scientific Co. Silica gel (60–200 mesh) was obtained from J. T. Baker Chemical Co.
(39) The NMR spectrum was taken on a Jeol MH-100 instrument.
(40) A number of pyrolyses were also carried out by dropping crystals of **7** (100–200 mg) directly through a 2.2 × 35 cm Vycor tube packed with short lengths of 5-mm Vycor tubing, at temperatures from 400 to 800° and 0.18–1-mm pressures. Anthracene, recovered **7**, **8**, **15**, allene, and formaldehyde were among the products detected in these pyrolyses, but little or no α-methyleneoxetane was formed.
(41) NMR spectra were obtained on Varian T-60 and HA-100 spectrometers. For the NMR spectra of compounds related to **11**, see ref 5c and L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, pp 184–190, 278–279.
(42) In a similar experiment [NMR (C_2Cl_4) showed less methyl vinyl ketone] VPC analysis (SE-30, 36°)[27b] showed (in addition to solvent) the major peak at 4.4 min with a shoulder at 4.0 min and a peak at 7.1 min (cyclohexane). Cyclobutanone under these conditions had a retention time of 6.05 min. See also ref **45**.
(43) An NMR spectrum was taken before chromatography to ascertain that the products isolated were not formed during the chromatography.
(44) From separate pyrolyses, careful chromatography of the nonvolatile residue produced samples of the rearranged product **8** as an oil, having essentially identical ir and NMR spectra with those of the crystalline sample of **8** prepared earlier. Pure crystalline samples of anthracene and **7** were similarly isolated.
(45) The mass spectrum of **11** was obtained on a Hitachi Perkin-Elmer Model RMU-7 instrument in conjunction with a Perkin-Elmer Model 881 gas chromatograph using a 10% SE-30 column (10 ft × 0.25 in.) at 68°, helium flow about 78 ml/min. VPC analysis showed peaks at 4.7 (corresponding in retention time to the ether solvent) and 9.1 min. The mass spectrum was taken of the material represented by the 9.1-min peak. THF under these conditions had a retention time of 9.7 min.
(46) The procedure is essentially that of G. Wittig and U. Schoellkopf, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 751.
(47) N. L. Drake and P. Allen, Jr., "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 77.
(48) Biphenyl was shown to be present in the phenyllithium solution.
(49) The product mixture from a similar reaction of phenyllithium with the distillate from the pyrolysis of **7** in benzene solvent was used. The composition of this mixture was similar by VPC to that of the reaction in THF.

Carbon-13 Spectra of Methoxyflavones

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Assignments of NMR chemical shifts for carbon of flavone, chromone, and seven methoxyflavones are reported. Qualitatively, the upfield shift induced by the methoxyl substituent is similar to that indicated by the shielding relationships given in major texts. However, the effect of methoxyl appears to be larger in compounds where important resonance forms can be written indicative of a high degree of double-bond character. The use of ^{13}C–H splittings of the various carbons to elucidate the position of substitution is covered. Splittings due to a proton meta to a given carbon are quite large (~8 Hz) and are very useful, but splittings due to ortho and para protons are irregular and of little use.

One great advantage of ^{13}C NMR spectroscopy has been in the characterization of aromatic and pseudoaromatic compounds, whose proton spectra are not well differentiated. This work is concerned with the application of ^{13}C spectroscopy to structure elucidation in a common class of naturally occurring compounds, namely, the flavones.

Proton NMR spectra of flavanoids have been studied in many laboratories since the first extensive correlation of aromatic proton signals in 1962.[1] Other studies described the use of deuterated dimethyl sulfoxide as a solvent for polyhydroxyflavones,[2] and trimethylsilylation as solubilization techniques for NMR analysis of flavanoids.[3] Several aspects of flavone NMR spectra have continued to be of interest, including an extensive study of the effect of acidic media.[4a] Solvent-induced shifts are a valuable technique for study of polysubstituted flavones.[4b] Detailed reviews of flavone NMR spectra are available.[5] Apparently no systematic ^{13}C NMR studies of the flavanoids have appeared, however.[6] The ^{13}C correlations reported herein complement these other techniques and should provide future in-

Table I
^{13}C Chemical Shifts of Isomeric Methoxyflavones[c]

Registry no.	Compd	Subst	CH_3O	2′	3′	4′	5′	6′	3	5	6	7	8	4a	8a	CO	Other
525-82-6	1	Flavone		126.0	128.8	131.3	128.8	126.0	107.3	125.4[a]	124.9[a]	133.5	117.9	123.7	156.0	178.0	131.5 163.0
491-38-3	1a	Chromone[e]							112.7	125.5[a]	124.9[a]	133.4	117.9	124.6	156.2	177.1	*f*
19725-47-4	2	2′-CH_3O	55.6	157.8	111.6	132.2	120.5	129.1	112.5	125.4[a]	124.6[a]	133.3	117.8		156.2	178.7	120.7 160.6
53906-83-5	3	3′-CH_3O	55.3	111.5	159.7	116.9[b]	129.8	118.5[b]	107.5	125.4[a]	124.9[a]	133.2	117.9[b]	123.7	155.9	178.0	132.8 162.8
4143-74-2	4	4′-CH_3O	55.3	127.7	114.2	162.1	114.2	127.7	105.9	125.3[a]	124.7[a]	133.0	117.7	123.7	155.8	177.9	*d* 163.0
42079-78-7	5	5-CH_3O	56.3	125.6	128.6	131.0	128.6	125.6	108.7	159.4	109.8	133.4	106.2	~114	157.9	177.8	131.9 160.6
26964-24-9	6	6-CH_3O		126.1	128.9	131.3	128.9	126.1	106.7	104.8		123.6	119.4				
22395-22-8	7	7-CH_3O	55.9	125.8	128.7	131.1	128.7	125.8	107.2	126.7	114.1	163.7	100.2	117.6	157.7	177.4	131.6 162.6
26964-26-1	8	8-CH_3O	56.2	126.1	128.7	131.2	128.7	126.1	107.1	114.2	124.6	116.1	148.8	~124	~146	178.0	131.6 162.6

[a] Tentative assignment only. These pairs may be interchanged. [b] Tentative assignment only. [c] In deuteriochloroform solution, at 25.2 MHz vs. tetramethylsilane [taken as 76.9 ppm from deuteriochloroform (center)]. [d] Nothing at ~132 ppm. [e] Chromone lacks ring B. [f] C_2 occurs at 155.0 ppm.

vestigators with a battery of powerful techniques that can be applied to structure elucidation.

The ^{13}C chemical shift assignments relative to TMS for flavone, chromone, and seven methoxy derivatives are given in Table I. Some of these data are reproduced with the compound in question in Scheme I. The 3-methoxy isomer was not available for this study; however, substitution in the 3 position is easily determined by proton NMR since the conspicuous peak for H-3 is missing.[5] In these ^{13}C spectra, certain carbons have very similar chemical shifts, e.g., C-5 and C-6 in compounds **1**–**4**. Specific assignments cannot be made for these carbons. Compound **3** also has several carbons that absorb on or near 118 ppm. Specific assignments await deuteration studies.

In most other cases, specific assignments were possible using the known effect of a methoxyl group upon the resonances of ortho and para carbon atoms, as shown by Lauterbur[7] and also Spiesecke and Schneider,[8] and now tabulated in major texts.[9,10] In simple benzene derivatives, carbons ortho to methoxyl are shielded by ~15 ppm and para carbons are shielded by ~9 ppm. Meta carbons are only slightly affected. Thus, a sequential change of the position of methoxyl group around rings B and A will result in a sequential shielding of carbons which are in an ortho position to methoxyl (Table I).

Of equal use in assigning resonances to specific carbons were splittings observed in high-resolution coupled spectra. The off-resonance technique was of little use. As shown by Weigert and Roberts,[11] protons meta to a given ^{13}C split the signal for that carbon by ~7 Hz. For example, the coupled spectrum of **5** (5-methoxyflavone) shows a double triplet for the resonance assigned to C-4′ (Figure 1). The widely spaced doublet (^1J = 161 Hz) is due to the proton directly attached to C-4′. The triplet into which each of the arms of the doublet is split (^3J ~ 7 Hz) indicates that C-4′ is meta to two hydrogens. In another example, for compound **5**, the resonance for C-7 appears as a 'simple' doublet (^1J = 164 Hz), indicating no meta hydrogens; this resonance can be assigned only to C-7 or C-3 (since this resonance disappears altogether in **7**, it must be due to C-7). In compounds **5**–**8**, C-2′ (C-6′) and C-3′ (C-5′) appear as multiplets due to the non-first-order nature of the couplings (essentially X of a AA′XX′ system is observed).

The splitting patterns for carbons 5–8 are also informative. These carbons are split either into doublets (^1J ~ 165 Hz) or double doublets depending on whether or not the position meta to the carbon in question is substituted by methoxyl.

As Scheme I shows, C-7 is strongly affected by the influence of the carbonyl (C-7 is 5 ppm more deshielded than benzene, and 2 ppm more deshielded than the para carbon

Scheme I

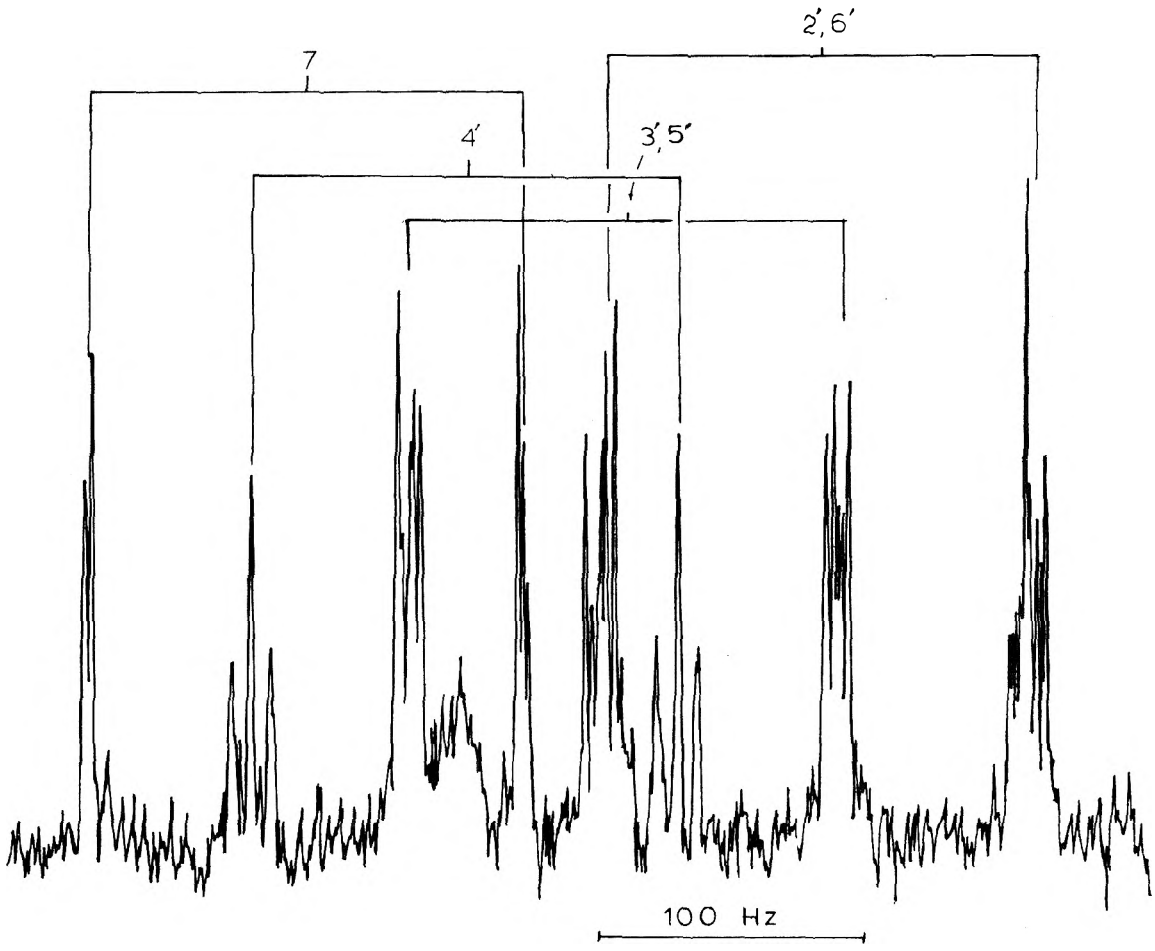


Figure 1. Portion of the coupled ^{13}C spectrum of **5**, showing the doublet of triplets pattern for C(4').

of acetophenone). However, C-5 is 3 ppm more shielded than benzene or the ortho carbon of acetophenone, perhaps owing to a steric effect between H-5 and CO. Resonance with carbonyl renders C-5 and C-7 electron deficient, which should cause deshielding of these carbons. On the other hand, C-6 and C-8 are much more shielded than benzene owing to resonance with O-1, which increases electron density at these carbons. The chemical shifts of C-6 and C-8 are less extreme than those of para and ortho carbons of anisole, but the shifts are rather similar to those found in diphenyl ether (Scheme I). Similar to diphenyl ether, the nonbonded electrons at oxygen are delocalized into more than one ring; in flavone these electrons are required to support a degree of aromaticity in ring C, and the nonbonded electrons are relatively unavailable for delocalization into ring A.

The weak peaks due to carbons not directly bonded to hydrogen were somewhat difficult to observe under high-resolution coupled conditions, and in other cases they were buried under larger absorptions. However, if these peaks can be located, and observed with sufficient resolution, they can afford a great deal of structural information, especially concerning substitution in ring A. In ring A, the data from the intense peaks for C-5–C-8 often do not permit a decision between two possible structures. For example, under coupled conditions, C-8a appeared to be a triplet (each member of the triplet also had considerable fine splitting) except for compounds **5** and **7**. In **7**, the splitting was indistinct, but it clearly was not a triplet. In **5**, the pattern for C-8a was a clear double doublet ($^3J \sim 6$, $^2J \sim 1$ Hz), since one position meta to C-8a was blocked by the substituent. Carbon 8a occurs in a region of the spectrum (~156 ppm) in which it will not be buried by larger peaks, but it occurs close by the resonance of C-2 (~162 ppm), which has a similar appearance in some cases. The triplet for C-2 in **2** (Figure 2), however, has a narrower spacing (~3 Hz). Evidently C-2 is coupled to protons in ring B.

Carbon 4a can also yield information about the substitution pattern in ring A, but it is frequently obscured by larger peaks. For example, in compounds **5** and **7**, C-4a is shifted upfield from its usual position at 123 ppm by 10 and 6 ppm, respectively. This shift is again the effect of the methoxyl substituent. In **4**, C-4a was a clear double triplet. The ^3J values of ~7 Hz observed in the triplet showed C-4a to be meta to two hydrogens. On the other hand, in **8**, C-4a appeared as a double doublet ($^3J \sim 7$, $^2J \sim 1$), since one meta position is filled.

Generally speaking, the small splittings of a given carbon by ortho or para hydrogens (^2J and ^4J, both ~1 Hz) were in evidence in some cases and not in others. These small splittings were of no use owing to their irregular incidence.

The methoxyl absorption (56 ppm) was relatively invariant, and offers no structural information. In a more highly substituted flavone, however, steric shifts should be in evidence for these carbons. The carbon substituted by methoxyl is highly deshielded, like C-8a. Under coupled conditions, the peak due to the methoxylated carbon was broad and ill defined (Figure 2). This also occurred in certain model compounds such as anisic acid. The broadness is believed to be due to a three-bond coupling to the methoxyl hydrogens in addition to couplings to several ring hydrogens. Thus, this carbon is easily identified among other low-intensity (but sharper) absorptions.

The chemical shift for carbonyl (~178 ppm) is quite constant in **1**–**8** (cf., however, **9** and **10**). This chemical shift occurs far upfield from the carbonyl resonances in model ke-

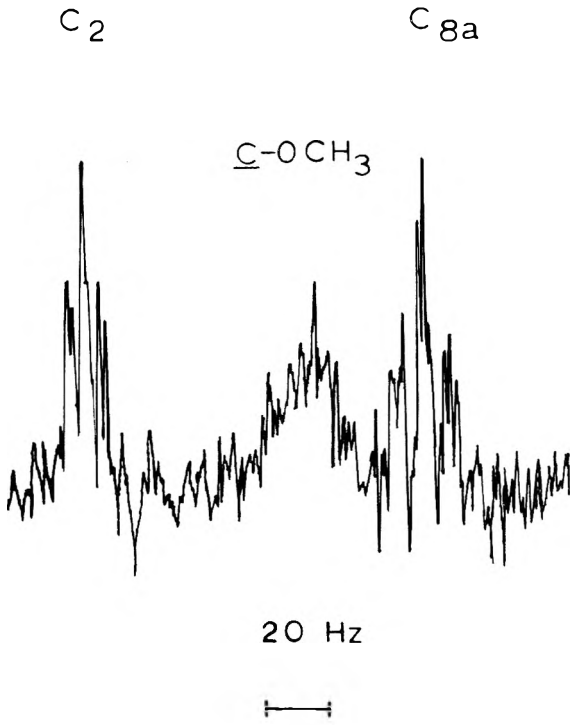


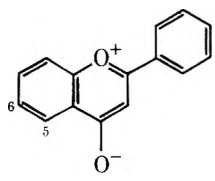
Figure 2. Portion of the coupled ^{13}C spectrum for **2**, showing the similarity of the splitting patterns for C(2) and C(8a).

tones such as acetophenone (196 ppm). This shift (18 ppm) is slightly larger than that in other α,β-unsaturated ketones (~12 ppm), which may reflect the fact that this carbonyl is part of a vinylogous ester function.[12]

The upfield shifts induced by ortho methoxyl groups are rather irregular in moving from compound to compound. A C-2′ methoxyl group shifts C-3′ ~17 ppm upfield, and C-1′ ~12 ppm upfield. A C-3′ methoxyl group shifts C-4′ 14 ppm and C-2′ 14 ppm. A C-4′ methoxyl group shifts C-3′ 15 ppm. Thus, for ring B, the upfield shifts are similar to those found for simple benzene derivatives ± 3 ppm.

However, the methoxyl substitution in ring A results in a rather larger spread of shifts. Thus a C-5 methoxyl shifts C-6 15 ppm, but C-4a is shifted only 10 ppm. A C-6 methoxyl shifts C-7 only 10 ppm, but C-5 is shifted 20 ppm. A C-7 methoxyl shifts C-8 18 ppm, but C-6 is shifted only 11 ppm. Finally, a C-8 methoxyl shifts C-8a only 10 ppm, but C-7 is shifted 17 ppm. Thus, the shifts determined for simple benzene derivatives (15 ppm for methoxyl) should be applied for substituents in ring A with caution.

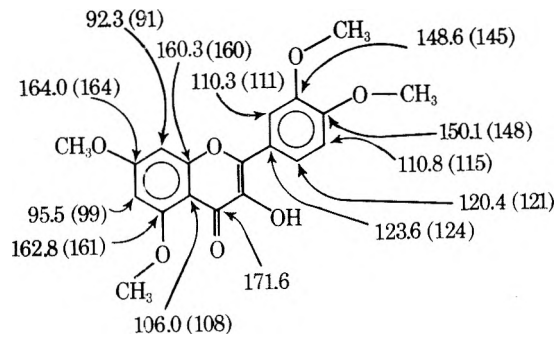
Structure a represents a presumably quite stable resonance form of flavone, as both ring A and ring C have a sta-



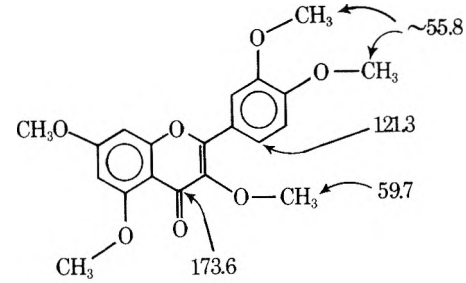
a

ble benzenoid arrangement of double and single bonds. It is noteworthy that methoxyl substitution in ring A at a given carbon will cause a large shift of the ortho carbon if the two carbons are joined by bonds of predominantly double-bond character, e.g., C-5 and C-6. On the other hand, if two carbons are joined by a bond of predominantly single-bond character, methoxyl substitution seems to result in a small shift (e.g., C-6 and C-7). However, the tentative idea that bond localization affects the degree of shielding awaits verification in other systems. However, similar effects occur in certain substituted thiophenes.[13]

Scheme II



9



10

The usefulness of the data listed in Table I depends upon whether it can be applied to other, more highly substituted flavones. As a test, the spectra of a polymethoxylflavone, **9**, and its close relative, **10**, were run. For a carbon at position **x**, a methoxyl at position y will have a certain effect and a substituent at position z will have a different effect. The sum of these effects, as derived from the data in Table I, is given in Scheme II beside the observed chemical shift. Thus, for C-5, the basic chemical shift (from compound **5**) is 159.4. The effect of a C-7 methoxyl group on C-5 is +1.4 ppm. The net chemical shift expected is ~161 ppm, very close to the observed value. The agreement for most carbons is quite acceptable, but C-3′, C-5′, and C-6 show substantial deviations between the calculated and observed chemical shifts. It seems likely that steric effects in other highly substituted natural flavanoids would also cause deviations.

The C-3 hydroxyl group of **9** has become methylated in **10**. Minor changes in chemical shift were noted except for carbonyl. The C-3 methoxyl group, however, does have an anomalous chemical shift (59.7 vs. ~55.8 ppm for the other methoxyl groups).

Experimental Section

The methoxyflavones were available from other studies: **1**, mp 96–97°; **2**, mp 102–103°; **3**, mp 130–131°; **4**, mp 156–157°; **5**, mp 133–135°; **7**, mp 110–111°; and **8**, mp 200–201°. The NMR spectra were run on a Varian XL-100 instrument at 25.2 MHz. In a typical run (for **5**), a 5000-Hz spectral width was used, collecting 4K of transients, using a decoupler setting of 7 W (high power) and a 1.5K bandwidth. An acquisition time of 0.4 sec, a pulse delay of 0.1 sec, and a 30-μsec pulse were used.

The high-resolution undecoupled spectra were run either by not using the decoupler at all or using the "gated" mode of decoupler operation.[14] For **5**, the decoupler was not used. A 2500-Hz spectral width was used, with a 1.3-sec acquisition time and a 1.0-sec pulse delay, and a 30-μsec pulse width. A total of 13.5K of transients were collected. For **4**, the "gated" mode of operation was used, and a 2.5K spectral width, 0.8-sec acquisition time, and a 2.0-sec pulse delay. A total of 4.5K of transients were collected. For **6**, owing to its low concentration, the "long term averaging" routine possible with the Varian equipment was used. A spectral width of 5K was used (gated mode), using 0.8-sec acquisition time and a 2.0-sec

pulse delay. Thirty blocks of 500 transients were collected. The methoxyl quartet appeared in this run, although it was missing in the normal run even though 4096 data points were utilized.

The spectra were all run in deuteriochloroform solution at the following concentrations (percent w/v): **1**, 9.5; **2**, ca. 6; **3**, 5.5; **4**, ca. 8; 5, 7.3; **6**, 1.8; **7**, 10.8; and **8**, 9.2. In no case did either the ^1H or the ^{13}C spectra indicate impurities. The chemical shifts were taken from the computer-generated print-out; the actual standard used was the center line of $CDCl_3$ but the data are reported vs. TMS, which was taken as 76.9 ppm from $CDCl_3$

Acknowledgment. Partial funds for purchase of the XL-100 were provided by NSF Grant GP-10293, which is gratefully acknowledged.

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Oxidative Decarbonylation of 2,4,6-Tri-*tert*-butylresorcinol via a Probable *m*-Quinone Intermediate

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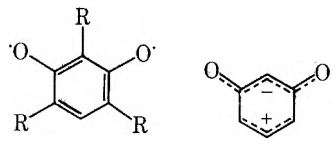
Oxidation of mixtures of 2,4,6-tri-*tert*-butylresorcinol (**4**) and its diketo tautomer (**5**) with alkaline ferricyanide at room temperature gives 2,3,5-tri-*tert*-butylcyclopentadienone (**8**) and carbon monoxide as major products. Control experiments show that these products are derived almost exclusively from **4** rather than **5**. The oxidation is suggested to involve conversion of **4** into a singlet *m*-quinone (**1b**), which cyclizes into a cyclopropanone derivative (**3b**) capable of undergoing rapid decarbonylation. This mechanism is shown to be consistent with theoretical expectations and experimental data for related systems.

In connection with other studies in this laboratory on the chemistry of phenolic antioxidants, we became interested several years ago in the properties of *m*-quinone (**1a**), the hypothetical species which would result from homolytic abstraction of the hydroxyl hydrogens of resorcinol. Our interest in **1a** was intensified, to some extent, by the results of a simple Hückel molecular orbital (HMO) calculation,[2] which predicted that **1a** would contain five nondegenerate bonding orbitals with delocalization energies of 2.314, 1.802, 1.287, 0.590, and 0.445β. Since *m*-quinone has eight π electrons, its ground-state electronic configuration was thus required to be a singlet;[3] consideration of this result, together with the bond orders and electron densities calculated for *m*-quinone by our procedure, suggested that the substance could be represented, at least to a first approximation, by the dipolar structure **2**. This species might be expected to collapse to the fully covalent structure **3a**,



1a, R = H
b, R = *t*-Bu

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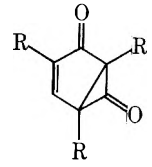
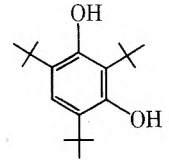


3a, R = H
b, R = *t*-Bu

which should reveal its presence by undergoing characteristic cyclopropanone reactions[4] such as nucleophilic addition or decarbonylation.

However, in view of the approximations involved in the simple HMO method, it was realized that these conclusions could not be accepted without reservation; and, in particular, it seemed that the prediction of a singlet ground state for **1a** was likely to be in error. Since the two highest bonding orbitals had been found to differ in energy by only 0.145β, it was clear that they might actually prefer to exist as a degenerate pair, owing to electron repulsions that had been neglected in the simple HMO treatment.[5] Nevertheless, thermal population of a low-lying singlet state of **1a** remained as a reasonable possibility, and we therefore decided to attempt the preparation of a suitable derivative of *m*-quinone in order to examine its chemical properties.[6] Oxidative dehydrogenation of 2,4,6-tri-*tert*-butylresorcinol (**4**) seemed especially attractive in this regard, since the *tert*-butyl groups would be expected to perturb the π system of **1b** to only a minor extent, while preventing undesirable reactions of an anticipated monophenoxy radical intermediate.[7] However, attempts to prepare **4** by direct alkylation gave 4,6-di-*tert*-butylresorcinol instead,[8] and after a brief exploration of other potential routes to **4**, its synthesis was temporarily abandoned.



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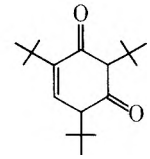

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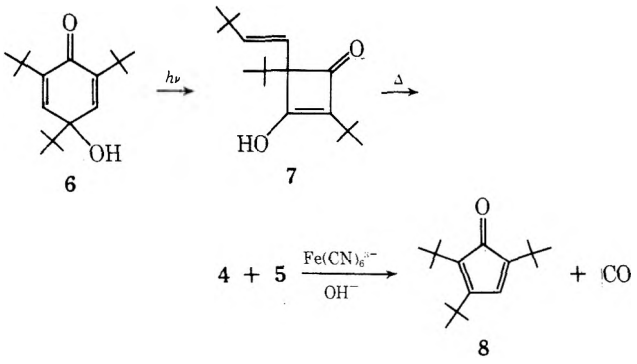
At a later date, our interest was revived by the reported isolation of diketone **5** as a minor product from the irradiation of cyclohexadienone **6**.[9] Realizing that oxidation of **5** under conditions conducive to tautomerization might give results equivalent to those anticipated for **4**, we attempted to synthesize **5** by repeating its published preparation. Our observations were quite unexpected, and some of them have already been reported.[10] In our hands, irradiation of **6** gave a considerable amount of the novel cyclobutenone, **7**[10a] which could be smoothly converted into mixtures of **4** and **5** by brief periods of heating[10b] (Scheme I). With both **4** and **5** available, it was now possible to pursue our original objective, and the results of this investigation are described in the present paper.

Results and Discussions

Use of alkaline ferricyanide as an oxidant seemed particularly attractive for our purposes, since this reagent was known to give excellent yields of phenoxy radicals from many hindered phenols.[11] Moreover, basic conditions were expected to cause tautomerization of **5** and also prevent a potential acid-catalyzed loss of *tert*-butyl from the sterically crowded 2 position.[9] In actuality, oxidation of mixtures of **4** and **5** with alkaline ferricyanide occurred rapidly at room temperature to give good yields (based on **4**) of 2,3,5-tri-*tert*-butylcyclopentadienone (**8**) and carbon monoxide, in approximately equal amounts (Scheme I). Unlike most

Scheme I

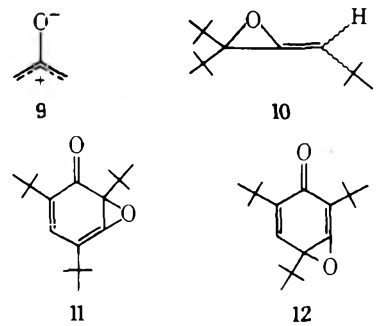


alkyl-substituted cyclopentadienones,[12] compound **8** is stable toward dimerization for periods of several days; its structure was established by spectral methods and by conversion to dimethyl 3,4,6-tri-*tert*-butylphthalate upon treatment with dimethyl acetylenedicarboxylate.[13] That carbon monoxide and **8** were derived almost exclusively from **4** rather than **5** was shown by the recovery of considerable amounts of **5** from the oxidates, and by the failure of **5** to give appreciable amounts of carbon monoxide and **8** (or, indeed, any identifiable products) when attempts were made to oxidize it alone under comparable conditions.

Although conversion of **5** into **4** had been previously shown to be difficult,[9,10b] it was thought that our failure to accomplish a clean oxidation of **5** might have been due to its lack of solubility in the aqueous oxidizing medium. We therefore attempted to oxidize mixtures of **4** and **5** in a homogeneous system using pyridine as the solvent and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as oxidizing agent. However, dealkylation occurred despite the presence of the nitrogen base, giving 4,6-di-*tert*-butylresorcinol as the major product; little, if any, oxidation occurred under these conditions.

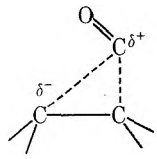
In the interim following our early attempts to prepare **4**, Güsten et al.[14] had reported the formation of arylated cyclopentadienones and carbon monoxide from reactions of tetraphenylresorcinol, 2,4,6-triphenylresorcinol, and 2,4-diphenyl-1,3-naphthalenediol with various one-electron oxidants.[15] The oxidative decarbonylation of resorcinols thus appears to have some generality; and, indeed, our demonstration of its occurrence with a substrate containing only alkyl substituents suggests that it may, in fact, be characteristic of the *m*-quinone π system, per se. However, bulky groups have been present in all examples reported to date; thus the role of steric factors needs clarification.

The sequence **4** → **1b** (singlet) → **3b** → **8** + CO constitutes an attractive rationale for our results and is analogous to the scheme proposed by Güsten et al.[14b] for oxidative decarbonylation of arylresorcinols. In hopes of trapping an intermediate cyclopropanone (or zwitterion), we carried out a ferricyanide oxidation of **4** and **5** using furan[16] as the organic solvent. Entrapment was not observed, but this result was hardly surprising in view of the rapidity of the decarbonylation process. In any event, the suggested path seems to be consistent with theoretical principles and experimental observations on related systems. Thus, the disrotatory cyclization of **1b** to form **3b** is in keeping with the stereochemical consequences of orbital theory,[5,17] if **1b** can be regarded as a derivative of the cyclopropanone isomer, "oxyallyl" (**9**, cf. **2**). Theory also predicts a strong thermodynamic driving force for cyclopropanone formation in the case of **9** itself,[17,18] and this prediction is consistent with



the results of experimental structural studies.[19] However, cyclopropanone **3b** is inordinately strained; thus it may represent an atypical situation. Cyclopropanones bearing cis *tert*-butyls have not been previously described in the literature; and, indeed, the failure of attempts to prepare tri-*tert*-butylcyclopropanone[20] from the *E* and *Z* forms of **10** suggests that *cis*-*tert*-butylcyclopropanones may be less stable than their allene oxide isomers in certain cases. Nevertheless, the thermodynamic stability of **3b** is not necessarily less than that of **11** and **12**, since these allene oxides would be destabilized, themselves, by the presence of a bridgehead olefinic linkage.[21] Furthermore, **3b** is not required to be present in high concentration if its decarbonylation is sufficiently fast. Prediction of the effects of steric factors on decarbonylation rate is difficult in this case, as no good model systems are available for comparison.[22] However, there are good reasons for believing that the rate may be greatly influenced by electronic factors, as well. In this connection, we note that the concerted decarbonylation of cyclopropanone is a disrotatory cheletropic reaction which is required by orbital symmetry rules to proceed by a nonlinear path.[23] Extended Hückel calculations[23b] indicate that the transition state for decarbonylation can be approximated by a structure, **13** (the complete charge distribution[23b] is not shown), which will be strongly stabilized by groups that can delocalize the negative charge on carbon. Decarbonylation of **3b** (and related compounds)[14] should thus be much faster than that of cyclopropanones which lack effective delocalizing substituents, and this conclusion could also apply to a nonconcerted decarbonylation process

involving complete heterolysis of one C–C bond[23b,24] (cf. **13**) as the initial step. The facile decarbonylation reported



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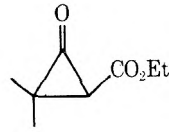

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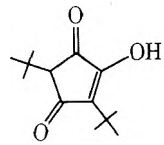
for another negatively substituted cyclopropanone,[24] **14**, offers experimental support for this hypothesis,[25] and the recent literature contains several other examples of reactions which appear to involve thermal decarbonylation of cyclopropanones bearing α-carbonyl substituents.[26]

Finally, we wish to comment on the possible relevance of our results to oxidations of other resorcinol-type compounds. Resorcinol itself gives carbon monoxide upon autoxidation in aqueous alkali,[27] but the yield is miniscule and *is lower, in fact, than the yields of carbon monoxide* obtained from the other isomeric dihydroxybenzenes in an identical experimental situation.[27] Thus there is no need to invoke the "*m*-quinone mechanism" for resorcinol oxidation under these conditions. Alkaline autoxidation of 4,6-di-*tert*-butylpyrogallol gives a product, **15**,[28] which can be



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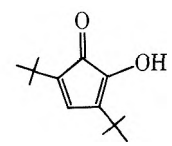

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envisaged to arise from further oxidation of an hydroxycyclopentadienone intermediate (**16**, or its diketo tautomer). However, other routes to **15** are clearly available; thus its formation provides no real evidence for oxidation via a *m*-quinone. The same comment applies, and with equal force, to the reported formation of carbon monoxide in oxidations of pyrogallol itself.[27,29]

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. NMR spectra were obtained with Varian Model HA-100 or A-60 instruments using dilute solutions containing Me_4Si as internal standard. Infrared measurements were made with a Perkin-Elmer spectrometer, Model 21; mass spectra were recorded with an AEI MS-9 instrument using c = 12 amu as the reference standard for exact measurements of *m/e*. Organic solutions were dried over Drierite; evaporations were carried out on rotary evaporators at room temperature under *ca.* 10 mm of pressure, unless noted otherwise. Petroleum ether had a nominal boiling point of 30–60°; all chemicals were of the highest purity available commercially. Purities were verified by spectral measurements and the determination of appropriate physical constants.

2,4,6-Tri-*tert*-butylresorcinol (4) and 2,4,6-Tri-*tert*-butyl-4-cyclohexene-1,3-dione (5). The preparation of 90:10 mixtures of **4**:**5** by thermolysis of **7** in tetrachlorothiophene was described in an earlier paper.[10b] Unfortunately, the physical constants of tetrachlorothiophene made it an inconvenient solvent for preparative work, and efforts to convert **5** into **4** gave results that were unsatisfactory.[9,10b] We therefore attempted to develop a more practical synthesis of **4** by thermolyzing neat **7** under various conditions. A series of aliquots taken from a large sample of **7** all gave 30:70 mixtures of **4**:**5** (analysis by NMR in C_6D_6 solution) upon heating at various constant temperatures ranging from 120 to 180°. These results were rather disappointing, but we were encouraged to find that recrystallization of the large sample of **7** from aqueous methanol gave a material that yielded a higher ratio of **4**:**5** (60:40) after thermolysis at 160°. Nevertheless, the thermolysis results showed no further improvement after an additional recrystallization of **7**, and other batches of **7** gave **4**:**5** ratios ranging from ca. 25:75 to 50:50 under various thermolysis conditions. These experiments were discontinued when it was found that **4** could be oxidized readily in the presence of **5** (see below). However, after the present work was completed, good methods were developed for preparing either **4** or **5** from the corresponding monoketo tautomer.[30]

Oxidations of Mixtures of 4 and 5 with Alkaline Ferricyanide. In a typical experiment, 2.00 g (7.18 mmol) of **7** was converted into a **4**:**5** mixture (*ca.* 40:60) by heating in a round-bottom flask for 265 sec at 160°. The mixture was dissolved in benzene (20 ml), and a magnetic stirring bar was introduced; then the flask was attached to a short condenser connected to a demountable gas trap and a gas buret containing mercury. After careful degassing by the freeze–thaw method, the apparatus was filled with nitrogen and allowed to warm to room temperature, while a separate solution of potassium ferricyanide (10.0 g, 30.4 mmol) and potassium hydroxide (1.4 g, 25 mmol) in water (50 ml) was being degassed by nitrogen ebullition. The ferricyanide solution was introduced into the reaction vessel through a rubber septum by means of a hypodermic syringe, and the reaction was then allowed to proceed for 1.0 hr at 26–28° with rapid stirring. Gas evolution was essentially complete after 0.45 hr; ca. 85% of the gas evolved during the initial 0.2 hr of reaction. VPC analysis using a standard procedure developed by the Analytical Division of these laboratories showed that the gas was essentially pure carbon monoxide (2.14 mmol, 75% yield based on **4**). The liquid layers were separated, and the aqueous phase was back-extracted several times with ether. The combined organic layers were washed repeatedly with water until a neutral aqueous moiety was obtained, then dried and evaporated to give 1.64 g of material which was dissolved in a minimum amount of petroleum ether and subjected to column chromatography on Alcoa F-20 alumina (94 g) using petroleum ether as eluent. Continued elution caused separation of an orange band which crystallized into slender orange needles of cyclopentadienone **8**: 0.47 g (66% yield based on **4**); mp 52.5–53.5° (lit.[13,31] mp 55–55.5°); ir (CCl_4) 1710 cm^{-1} (strong, C=O), no OH [lit. ir (CCl_4)[31] 1690 cm^{-1}, ir (KBr)[13] 1715 cm^{-1}]; NMR (100 MHz, CCl_4) singlets at δ1.11 (9, *t*-Bu), 1.28 (9, *t*-Bu), 1.30 (9, *t*-Bu), and 6.56 ppm (1, vinyl H) (cf. NMR in ref 31).

A similar experiment was performed using furan in place of benzene. The yield of carbon monoxide was not reduced, and NMR analysis of the crude product mixture showed that **8** was a major constituent. The high resolution mass spectrum of the mixture gave no evidence for the presence of an adduct derived from **3b** (or **1b**) and furan.

In another experiment, 7.42 g (26.7 mmol) of **7** was pyrolyzed for 300 sec at 160°. The pyrolysate was dissolved in benzene (75 ml) and oxidized in the usual manner (room temperature, 1.0 hr) with potassium ferricyanide (40.0 g, 122 mmol) and potassium hydroxide (5.0 g, 89 mmol) in water (200 ml). Work-up in the usual way gave 6.73 g of crude product which afforded 2.51 g (34% yield based on **7**) of crude **5** as pale yellow granules, mp 95–112° (mostly at 103–112°), upon crystallization from methanol at 0°. Pure **5** melted at 117–119° (lit.[9] mp 114–115.5°) after recrystallization from petroleum ether; its NMR spectrum (60 MHz) was identical with the spectrum previously described.[9] The material remaining in the mother liquor gave 1.40 g (21% yield based on **7**) of **8**, mp 52.5–53.5°, after column chromatography in the manner described above.

Attempted Oxidation of Mixtures of 4 and 5 with 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Compound **7** (180 mg, 0.647 mmol) was converted into a mixture of **4** and **5** by thermolysis in the usual way. A solution of this mixture and DDQ (147 mg, 0.647 mmol) in pyridine (5.0 ml) was kept under nitrogen for 1.5 hr at 25–26°, then for 18.4 hr at 100°. After cooling, the mixture was poured into water (100 ml) and extracted with four 50-ml portions of ether. The combined ether layers were extracted with two 50-ml portions of 5% hydrochloric acid, then washed repeatedly with 30-ml quantities of aqueous sodium bicarbonate until a neutral aqueous layer was obtained. Evaporation of the dried ether solution gave 0.20 g of material whose NMR spectrum provided no evidence for the presence of **4**, **5**, or **8**. Peaks attributable to 4,6-di-*tert*-butylresorcinol comprised 75% of the total area, and the presence of this substance was confirmed by rerunning the spectrum after adding an authentic specimen: NMR (60 MHz, $CDCl_3$) singlets at δ1.39(18, *t*-Bu's), 4.72 (broad, 2, OH's), 6.06 (1, 2-H), and 7.13 ppm (1, 5-H).

Efforts were also made to oxidize mixtures of **4** and **5** with DDQ in methanol under several sets of conditions. These experiments gave product mixtures that were shown by NMR analysis to be extremely complex; isolations were not attempted.

Dimethyl 3,4,6-Tri-*tert*-butylphthalate from 8. A solution of **8** (100 mg, 0.403 mmol) in dimethyl acetylenedicarboxylate (1.00 ml, 1.56 g, 11.0 mmol) was stirred under nitrogen for 0.2 hr at

199–201°, then evaporated with gentle warming at ca. 1 mm pressure in order to remove most of the excess of starting ester. Examination of the residue by NMR suggested that essentially all of **8** had been converted into the anticipated phthalate product: no extraneous peaks appeared in the *tert*-butyl or aromatic regions of the spectrum. Crystallization of the residue from absolute ethanol gave an oil which solidified into a mixture of amorphous material and colorless plates after 2 days of standing at room temperature. The plates were separated manually and identified as dimethyl 3,4,6-tri-*tert*-butylphthalate by the following observations: mp 118–119° (lit.[13] mp 122–123°); ir (CS_2) 1736 cm^{-1} (strong, ester C=O); NMR (100 MHz, CCl_4) singlets at δ 1.33 (9, *t*-Bu), 1.43 (9, *t*-Bu), 1.51 (9, *t*-Bu), 3.67 (6, MeO's), and 7.52 ppm (1, 5-H); mass spectrum (70 eV) *m/e* 362.2446 (parent ion; calcd for $C_{22}H_{34}O_4$, 362.2457).

Oxidation of 5 with Alkaline Ferricyanide. A solution of **5** (150 mg, 0.539 mmol) in benzene (5.0 ml) was combined with a solution of potassium ferricyanide (3.00 g, 9.11 mmol) and potassium hydroxide (0.50 g, 8.9 mmol) in water (15 ml) after rigorous degassing and blanketing with nitrogen in the manner described above for other ferricyanide oxidations. The mixture was stirred at room temperature for 16.2 hr and then at 70° for an additional 23.8 hr. No gas evolution could be detected volumetrically within the limits of experimental error, although VPC analysis of the vapor phase showed that ca. 0.025 mmol (yield ca. 5%) of CO had, in fact, been produced. The organic layer was separated, diluted with additional benzene to a volume of approximately 100 ml, and worked up according to the procedure employed for similar oxidation experiments (see above). Analysis of the total crude product (0.12 g) by ir and 100-MHz NMR showed that it was a complex mixture containing no **5** and little, if any, of **8**.

Acknowledgments. The authors are indebted to Mr. H. J. Tarski for excellent technical assistance, to Drs. F. H. Field and H. G. Schutze for administrative support, and to several members of the Analytical Division of these laboratories for instrumental analyses. We also wish to thank Drs. R. Pettit and L. C. Snyder for their constructive comments on this work.

Registry No.—**4**, 24851-96-5; **5**, 20784-81-0; **7**, 54036-86-1; **8**, 36319-95-6; DDQ, 84-58-2; dimethyl 3,4,6-tri-*tert*-butylphthalate, 54036-87-2.

References and Notes

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Homoallylic Participation in the Acid-Catalyzed Rearrangement of an α,β-Epoxy Ketone

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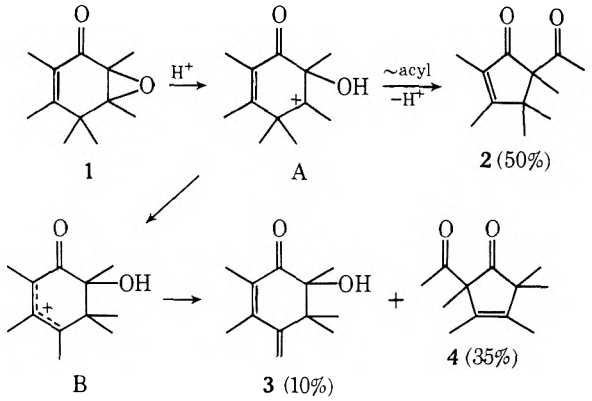
The α,β-epoxy ketones **6c** and **6t** (*cis*- and *trans*-2,3-epoxy-2,3,4,5,6-pentamethyl-4-vinyl-5-cyclohexenones) rearrange in acid exclusively by vinyl migration, in preference to the acyl and methyl migration observed previously in analogous compounds with a methyl group in place of the 4-vinyl substituent. When the vinyl group and epoxide ring were trans (**6t**) rearrangement was much faster than with the cis isomer (**6c**), owing to homoallylic participation during the epoxide ring opening. However the rearrangement products in both instances were identical, i.e., a 1:4 mixture of *cis*- and *trans*-2-acetyl-5-vinyl-2,3,4,5-tetramethyl-3-cyclopentenones (**7c** and **7t**).

In a recent study[1] it was shown that acyl and methyl migration compete approximately equally in the acid-catalyzed rearrangement of the α,β-epoxy ketone **1**. Thus on treatment with trifluoroacetic acid, **1** rearranged (Scheme I) to nearly equal mixtures of **2** and (**3** + **4**).[1] Protonation

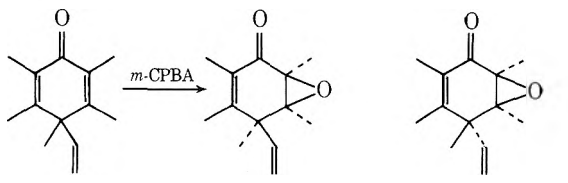
Scheme I



and ring opening of **1** occur in such a manner as to place the positive charge remote from the carbonyl group, giving ion A. Acyl migration and proton loss affords the major product **2**. Methyl migration competes effectively, giving the allylic ion B, which may either lose a proton to give **3** or rearrange by a more complex process, eventually to give **4**.[2]

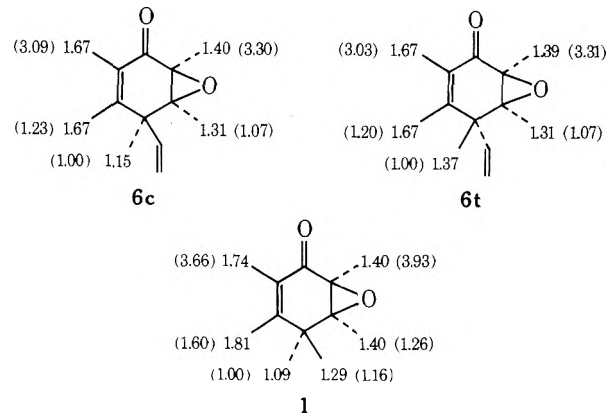
We now wish to report that replacement of one of the *gem*-dimethyl groups in **1** by a vinyl group markedly alters the outcome of the rearrangement, and that the reaction rate depends upon whether the vinyl group and epoxide ring are cis or trans to one another.

Preparation of 6c and 6t. Treatment of the vinyl cyclohexadienone **5**[3] with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride gave a mixture of two monoepoxides, **6c** and **6t**, in which the vinyl group and epoxide ring are cis



or trans to one another, respectively.[4] Although it was not possible to separate the two isomers, it was clear from the nmr spectrum of the mixture that epoxidation had occurred exclusively at the α,β double bond. The area ratio of vinyl protons (multiplet, δ 4.8–6.1) to aliphatic protons (δ 1.1–1.7) was 1:5. With the aid of europium shift reagent and a 100-Mhz spectrometer, and as a consequence of isolating one of the isomers in pure form (**6c**, vide infra), it was possible to completely assign the NMR spectrum of each isomer. The ratio of **6c** to **6t**, as determined by integration of the europium-shifted NMR spectrum, was approximately 3:2.

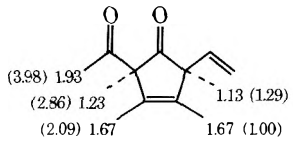
When a methylene chloride solution of the mixture of **6c** and **6t** was treated with trifluoroacetic acid for 1 hr at room temperature, *only one of the two isomers reacted.* The unreacted isomer was separated from the rearrangement products by preparative VPC, and we assign it structure **6c**. The chemical shifts and europium shift slopes[5] of the five methyl groups are shown on the structure. The most striking difference in the NMR spectra of **6c** and **6t** is the chemical shift of the methyl at C-4; these signals are 0.22 ppm apart in the two isomers. This result is consistent with the NMR spectrum of **1**,[6] shown for comparison. The methyl assignments at C-4 in **1** were based on the assumptions that (a) the methyl cis to the electronegative epoxide oxygen should appear at lowest field, and (b) the methyl cis to the epoxide oxygen, a possible coordination site for europium shift reagent should have a slightly larger europium-shift slope than the methyl trans to the epoxide ring (the main coordination site for europium is clearly, however, the carbonyl oxygen). On these grounds one can assign structure **6c** to the epoxy ketone which is recovered from mild treatment of **6c** + **6t** with trifluoroacetic acid, since its C-4 methyl appears at higher field (thus trans to the epoxide ring) than the C-4 methyl in its isomer. As will be seen, this assignment is consistent with mechanistic rationalizations of the acid-catalyzed rearrangement of **6**.



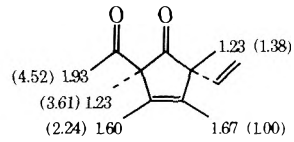
Structures of the Rearrangement Products. In addition to recovered **6c**, two rearrangement products were isolated from the mild treatment of **6c** + **6t** with trifluoroacetic acid. They were separated by preparative VPC and are assigned structures **7c** and **7t** (ratio 1:4), in which the methyls at C-2 and C-5 of the cyclopentenone ring are cis or trans, respectively. Each isomer showed two strong car-

bonyl bands in the infrared (~1700, 1740 cm^{-1}) for the acetyl and cyclopentenone carbonyl groups; the uv spectra also showed that neither carbonyl group was conjugated with a carbon–carbon double bond. The NMR spectrum of each isomer showed an acetyl methyl, two allylic methyls, two aliphatic methyls, and three vinyl protons. The mass spectra of **7c** and **7t** were nearly identical; striking features were a very weak parent peak (*m/e* 206), a base peak at *m/e* 164 corresponding to the loss of ketene, and three additional intense peaks for the further loss of 15, 28, and 43 amu. All of the spectra resemble closely the published spectra of **4**.[1]

The distinction between **7c** and **7t** is based on different chemical shifts and europium slopes of the C-5 methyl (adjacent to the vinyl substituent). This signal appears at lower field and is affected more by shift reagent when the methyl is cis to the acetyl group at C-2 (i.e., in **7t**). Also



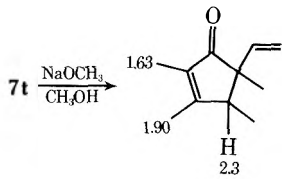
7c



7t

noteworthy are the lower overall europium shift slopes in **7c** compared with **7t**, presumably because the large vinyl group cis to the acetyl group in **7c** diminishes the interaction with the shift reagent.

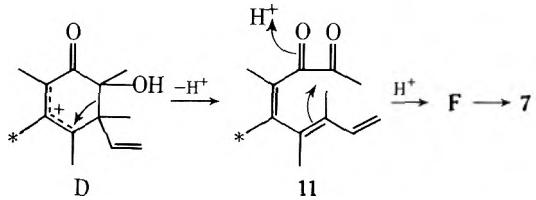
Chemical evidence for the structure of **7** was obtained by base cleavage. The major isomer (**7t**) was treated with sodium methoxide in methanol at room temperature (12 hr) to give a mixture of two stereoisomers of a cyclopentenone assigned structure **8**. The ir ($\nu_{C=O}$ 1700 cm^{-1}) and uv spectra



8

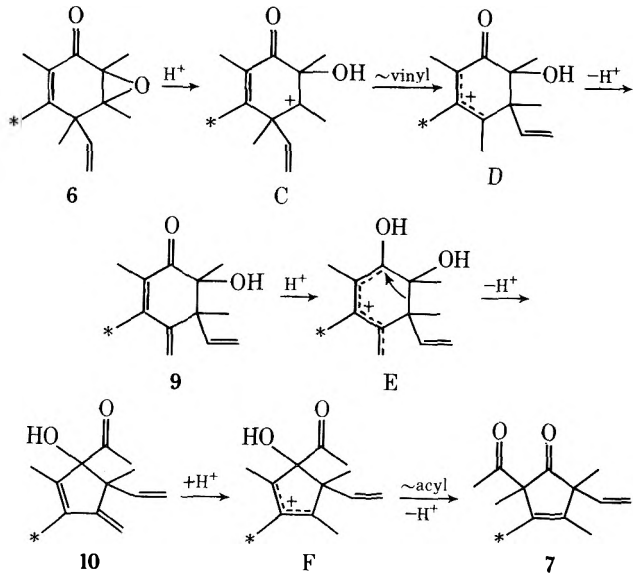
[λ_{max} (MeOH) 237 nm (ϵ 8800)] support the presence of a cyclopentenone moiety, and the NMR spectrum showed two homoallylically coupled methyls (δ 1.63, 1.90, J = 1 Hz), three vinyl protons (δ 4.6–5.8), two aliphatic methyls (δ ~1.0), and the methine proton (m, δ 2.3). The structure of **8** was further supported by the observation that treatment with $NaOCH_3$–CH_3OD gave **8**-d_4, in which the NMR signals at δ 1.90 and 2.3 were absent, that at δ 1.63 sharpened to a singlet, and the aliphatic methyl signals simplified to sharp singlets.

Rearrangement Mechanism. A plausible mechanism for the formation of **7** from **6** is shown in Scheme II (the question of stereochemistry is deferred for later discussion; vide infra). Protonation of the epoxide oxygen and ring opening gives ion C (analogous to A from **1**, Scheme I). Vinyl migration would give the allylic cation D (analogous to B from A, Scheme I). Proton loss could give **9** (analogous to **3**, Scheme I), which, however, was not observed. Reprotonation, ring contraction (to give **10**), and a 1,2-acetyl migration account for the product. Alternatively D could suffer ring opening to **11**, which, on protonation and ring closure, could lead directly to F, then **7**. These schemes are



D 11

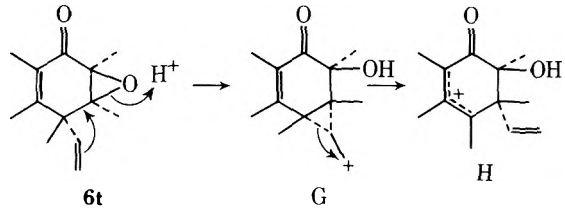
Scheme II



analogous to the mechanisms established for the formation of **4** from **1**.[1]

A labeling experiment was performed to test the general accuracy of Scheme II. Treatment of **6** (a mixture of cis and trans isomers) with DMSO-d_6 and potassium *tert*-butoxide gave **6***, whose NMR spectrum was identical with that of **6** except that the area of the peak at δ 1.67 was reduced in area by 50% (label at C-5). Treatment of **6*** with TFA at room temperature for 1 hr gave **6c*** (signal at δ 1.67 reduced in area by 50%, and a somewhat sharper singlet than for **6c**) and **7t*** whose NMR spectrum lacked the signal at δ 1.60 and had a sharpened singlet at δ 1.67.[7] These results clearly establish that a vinyl migration occurred during the rearrangement of **6** to **7** (the vinyl and labeled methyl in **6*** are on adjacent carbons, whereas in **7*** they are separated by an additional carbon) as outlined in Scheme II.

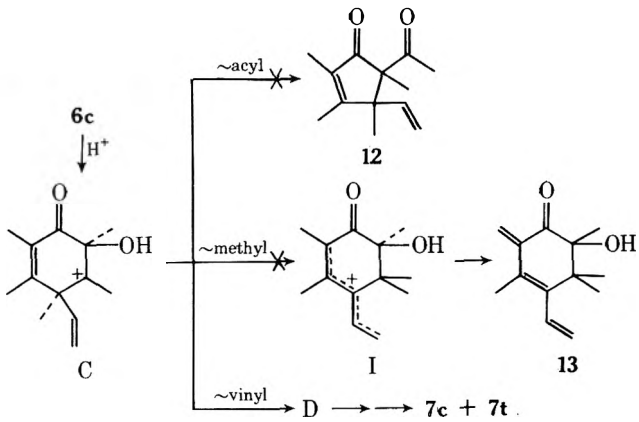
The observation that **6t** is rapidly converted by TFA into **7** under conditions where **6c** is recovered unchanged strongly suggested that Scheme II is oversimplified, and that homoallylic participation occurs in the ring opening of epoxide **6t**. That is, the initially formed ion from **6t** is not the tertiary carbonium ion C but a cyclopropylcarbinyl cation, one contributor of which is shown as structure G. Vinyl



6t G H

migration should give H (corresponds to D in Scheme II) in which the vinyl and hydroxyl groups are trans. Unfortunately, further steps in the mechanistic scheme allow for stereochemical ambiguity and the product is a mixture of **7t** and **7c**.

In isomer **6c**, where the vinyl and epoxide groups are cis, homoallylic participation in the ionization step is not possible. Consequently, **6c** is recovered unchanged under these reaction conditions. It seemed important to determine whether **6c** would also rearrange in acid under more forcing conditions. We found that **6c** was inert to TFA at room temperature, even after 12 hr. However, when the temperature was raised to 60°, **6c** did rearrange slowly, reaction being 85% complete in 7.5 hr. The products were **7c** and **7t**, identical with those obtained from **6t**. We conclude that



both **6c** and **6t** rearrange exclusively by vinyl migration. They do so, however, by different mechanisms, **6t** rearranging with homoallylic participation (via G, H, etc.) and **6c** rearranging without participation (via C, D, etc.). Even when the reaction occurs *without* participation, however, acyl or methyl migration are unable to compete with vinyl migration. Thus products such as **12** (which could be formed via acyl migration) or **13** (which could be formed by proton loss from the highly delocalized intermediate cation I) were not observed. One can conclude that vinyl migration is preferred over acyl or methyl migration even when homoallylic participation in the ionization step is not possible.

Experimental Section[8]

Epoxidation of 2,3,4,5,6-Pentamethyl-4-vinyl-2,5-cyclohexadienone (5). To a solution containing 100 mg (0.53 mmol) of **5**[3] in 5 ml of methylene chloride was added, at 0°, a solution of *m*-chloroperbenzoic acid (93.5 mg, 0.54 mmol) in 3 ml of methylene chloride. The reaction, which was followed by NMR, was complete in about 2 hr, during which time *m*-chlorobenzoic acid precipitated from solution. The solvent was removed by rotary evaporation, petroleum ether (bp 30–60°) was added, and the *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed with aqueous sodium bicarbonate, then with saturated sodium chloride, and dried (Na_2SO_4). The solvent was rotary evaporated, and the residue was chromatographed on Florisil (80–100 mesh) using ethyl acetate–hexane (1:4) as eluent. The first fraction was a mixture of the monoepoxides **6c** and **6t** (43 mg, 88% based on unrecovered dienone). The second fraction was unreacted **5** (55 mg, 55%). The mixture of **6c** and **6t** had the following properties: ir (neat) 1660 (s), 1625 (w), 1385 (m), 1350 (w), 1030 (w), 885 (w), 685 cm^{-1} (w); uv λ_{max} (MeOH) 253 nm (ϵ 12,700), 212 (6800); NMR (CCl_4) δ 1.15 (s) and 1.31–1.40 (overlapping singlets), combined area 9 H, 1.67 (m, 6 H), 4.9–6.1 (m, 3 H). Europium shift reagent,[5] Eu(fod)$_3$, resolved the spectrum and at 100 MHz separate peaks due to the five methyl groups in each stereoisomer were discernible. The area ratio for peaks assigned to **6c** and **6t** was 3:2. The mass spectrum (70 eV) of the epoxide mixture was *m/e* (rel intensity) 206 (11), 191 (30), 190 (39), 175 (53), 174 (39), 165 (16), 164 (100), 163 (56), 159 (36), 149 (83), 147 (57), 136 (52), 135 (85), 121 (67), 120 (32), 119 (78), 108 (25), 107 (36), 105 (55), 93 (65), 91 (78), 79 (65), 77 (55), 65 (37).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.73; H, 8.82.

In an effort to decrease the amount of unreacted **5** in the above epoxidation, the ratio of peracid to dienone was increased to 3:1. To a solution containing 100 mg (0.53 mmol) of **5** in 5 ml of methylene chloride was added, at 0°, a solution of 280 mg (1.62 mmol) of *m*-chloroperbenzoic acid in 10 ml of methylene chloride. The mixture was stirred at room temperature overnight, then worked up as described above. Chromatography of the crude product over Florisil (80–100 mesh) with ethyl acetate–hexane (1:4) as eluent gave as the first fraction the diepoxides[4] i_c and i_t (58 mg, 50%) and as the second fraction the monoepoxides **6c** and **6t** (43 mg, 40%). There was no unreacted **5**. The diepoxide mixture (2,3:5,6-diepoxy-2,3,4,5,6-pentamethyl-4-vinylcyclohexanone) had the following properties: ir (KBr) 1690 (s), 1380 (m), 1100 (m), 950 (m), 870 (w), 680 cm^{-1} (w), uv λ_{max} (MeOH) 210 nm (ϵ 2900); NMR (CCl_4) δ 1.07 (s), 1.20 (overlapping singlets), 1.33 (s), 1.50 (s), area from δ 1.07–1.50, 15 H, 4.8–6.4 (m, 3 H); Eu(fod)$_3$ shift reagent showed that there were two sets of methyl singlets, each with area ratios 1:2:2; for the NMR assignments and europium shift slopes, see the structures in ref 4; the two isomers were present in a 3:2 ratio; mass spectrum (70 eV) *m/e* (rel intensity) 222 (<1), 179 (18), 165 (13), 151 (49), 137 (70), 125 (23), 124 (24), 109 (100), 93 (34), 91 (30), 81 (34), 79 (37), 77 (31), 67 (35), 55 (29), 53 (54).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.28; H, 8.21.

Repetition of the epoxidation exactly as above but with 374 mg (2.2 mmol) of *m*-chloroperbenzoic acid and 100 mg (0.53 mmol) of **5** in a total of 20 ml of methylene chloride gave 99 mg (85%) of the diepoxide mixture i_c and i_t and, as the second fraction from Florisil chromatography, 10 mg (8%) of triepoxide ii: ir (CCl_4) 1695 (s), 1450 (w), 1375 (m), 1080 cm^{-1} (w); uv λ_{max} (MeOH) 215 nm (ϵ 6000); NMR (CCl_4) δ 0.83 (s), 1.35–1.6 (overlapping singlets; total area from δ 0.8–1.7, 15 H), 2.60–3.32 (m, 3 H), no vinyl protons; mass spectrum (70 eV) *m/e* (rel intensity) 238 (1), 195 (13), 167 (77), 164 (33(= [63 (28), 153 (50), 150 (30), 149 (100), 147 (33), 137 (73), 135 (65), 133 (42), 125 (86), 123 (86), 121 (36), 119 (44), 109 (70), 107 (94), 105 (55), 97 (28), 95 (26), 93 (52), 91 (97), 84 (20), 81 (45), 79 (80), 77 (64), 67 (60), 65 (39), 55 (63), 53 (75).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.63; H, 7.59.

Acid-Catalyzed Rearrangement of *cis*- and *trans*-2,3-Epoxy-2,3,4,5,6-pentamethyl-4-vinyl-5-cyclohexenone (6c and 6t). A solution of **6c** and **6t** (200 mg, 0.97 mmol) in 1 ml of trifluoroacetic acid was stirred at room temperature for 1 hr, then poured into a slurry of aqueous sodium bicarbonate solution and methylene chloride. The organic layer was separated, washed successively with aqueous sodium bicarbonate and saturated aqueous sodium chloride, and dried (Na_2SO_4). Evaporation of the solvent left 186 mg of a light yellow oil which, when subjected to analytical VPC (5 ft × 0.125 in. column, 3% SE-30 on Raroporl 30, 100–120 mesh, 125°), showed two peaks corresponding to **7c + 7t** (retention time 5.5 min, 42%) and unreacted **6c** (retention time 9.5 min, 51%). Preparative VPC (5 ft × 0.25 in. column, 10% SE-30 on Chromosorb W, 80–100 mesh, 125°) gave pure ***cis*-2,3-epoxy-2,3,4,5,6-pentamethyl-4-vinyl-5-cyclohexenone (6c):** ir (CCl_4) 1660 (s), 1630 (w), 1390 (m), 1250 (m), 935 (w), 880 cm^{-1} (s); uv λ_{max} (MeOH) 250 nm (ϵ 10,000), 215 (4830); NMR (CCl_4), see structure; all methyl peaks were sharp singlets except that at δ 1.67, which was slightly broadened; the three vinyl protons appeared as a multiplet, δ 4.8–6.0; mass spectrum (70 eV) *m/e* (rel intensity) 206 (12), 191 (22), 164 (50), 163 (40), 149 (62), 147 (20), 137 (10), 136 (50), 135 (100), 121 (57), 120 (35), 119 (65), 107 (25), 105 (49), 93 (45), 91 (55), 77 (48), 65 (22). By comparing the NMR spectrum of the mixture of **6c** and **6t** with that of pure **6c** and by plotting the chemical shifts vs. europium shift reagent concentration and extrapolating back to zero shift reagent it was possible to assign the NMR spectrum of **6t** (see structure).

VPC [5 ft × 0.125 in. column, 5% TCEP (tetracyanoethylated pentaerythritol) on Chromosorb W, 80–100 mesh, 125°, FID] resolved the chromatograph of **7c** and **7t** into two peaks, **7t** (80%, retention time 75 min) and **7c** (20%, retention time 90 min). Preparative VPC (5 ft × 0.25 in. column, 15% TCEP on Chromosorb W, 80–100 mesh, 125°) gave each pure isomer. ***trans*-2-Acetyl-5-vinyl-2,3,4,5-tetramethyl-3-cyclopentenone (7t):** ir (CCl_4) 1740 (s), 1710 (s), 1250 (s), 935 (w), 875 cm^{-1} (s); uv λ_{max} (MeOH) 219 nm (ϵ 2650), 285 (720); NMR (CCl_4), see structure; the peaks at δ 1.60 and 1.67 were mutually coupled quartets, J = 1.5 Hz, other methyl peaks were sharp singlets, and the vinyl protons appeared at δ 4.6–5.8 (m, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 206 (<1), 164 (100), 149 (63), 136 (54), 135 (29), 121 (73), 119 (28), 105 (30), 91 (26), 77 (19), 66 (27), 65 (23), 44 (36).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.56; H, 9.03.

***cis*-2-Acetyl-5-vinyl-2,3,4,5-tetramethyl-3-cyclopentenone (7c):** ir (CCl_4) 1740 (m), 1700 (s), 1250 (s), 875 cm^{-1} (s); uv λ_{max} (MeOH) 218 nm (ϵ 1150), 283 (30); NMR (CCl_4), see structure; all peaks were sharp singlets except for the vinyl protons at δ 4.7–5.4 (m, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 206 (<1), 164 (100), 149 (69), 136 (52), 135 (24), 121 (76), 119 (26), 105 (30), 91 (28), 77 (23), 66 (77), 65 (56).

Cleavage of 7t with Base. A solution of **7t** (26 mg) and sodium methoxide (20 mg) in 3 ml of methanol was stirred at room temperature for 12 hr, then poured into ice–water and extracted with ether. The combined ether layers were washed with saturated sodium chloride and dried (Na_2SO_4). Evaporation of the solvent and analysis of the residue by VPC (5 ft × 0.125 in. column, 3% SE-30

on Raroporl 30, 100–120 mesh, 120°) showed that all the **7t** was converted to a single product, assigned the structure **2,3,4,5-tetramethyl-5-vinyl-2-cyclopentenone (8)**. Pure 8 was collected by preparative VPC (5 ft × 0.25 in. column, 10% SE-30 on Chromosorb W, 80–100 mesh, 120°): ir (CCl_4) 1700 (s), 1650 (w), 1250 (m), 885 cm^{-1} (s); uv λ_{max} (MeOH) 237 nm (ε 8820); NMR (CCl_4) δ 1.0–1.2 (m, 6 H), 1.63 (q, 3 H, J = 1 Hz), 1.90 (q, 3 H, J = 1 Hz), 2.3 (m, 1 H), 4.6–5.8 (m, 3 H); mass spectrum (70 eV) m/e (rel intensity) 164 (85), 149 (100), 135 (49), 121 (60), 119 (20), 105 (38), 93 (30), 91 (29), 79 (25), 77 (23), 67 (25), 65 (15), 53 (26).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.47; H, 9.92.

Treatment of 8 (10 mg) with excess sodium methoxide in CH_3OD for 5 hr at room temperature followed by work-up analogous to that used in the preparation of 8 from **7t** gave 8-d_4, whose NMR spectrum consisted of two sharp singlets at δ 1.00 and 1.13 (3 H), a sharp singlet at 1.63 (3 H), and a vinyl proton multiplet at 4.6–5.8 (3 H).

5-Trideuteriomethyl-2,3-epoxy-2,3,4,6-tetramethyl-4-vinyl-5-cyclohexenone (6*). To a solution containing 145 mg (0.7 mmol) of a mixture of **6c** and **6t** (as obtained from epoxidation of **5**) in 5 ml of dimethyl sulfoxide-d_6 was added, with stirring and under N_2, 95 mg (0.85 mmol) of potassium *tert*-butoxide. The mixture was stirred at room temperature for 4.5 hr, then quenched with ice–water and extracted with ether. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to give a nearly quantitative yield of **6***. The NMR spectrum was identical with that of the starting material, except that the peak at δ 1.67 was decreased in area by 50%.

Acid-Catalyzed Rearrangement of 6*. The procedure and work-up were as described for the treatment of **6c** and **6t** with trifluoroacetic acid. The recovered unreacted **6c*** had an NMR spectrum identical with that of pure **6c** except that the signal at δ 1.67 had sharpened and was reduced in area to only 3 H. The major rearrangement product 7t* had an NMR spectrum identical with that of pure **7t** except that the signal at δ 1.60 was absent, and that at δ 1.67 had sharpened to a singlet. The amount of **7c*** collected was insufficient for an NMR spectrum.

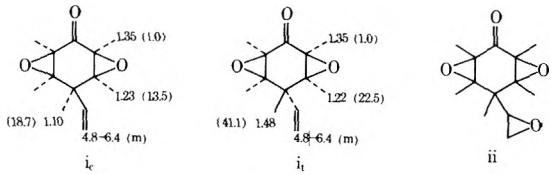
Acid-Catalyzed Rearrangement of 6c. A solution of pure **6c** (22 mg, recovered from the treatment of a mixture of **6c** and **6t** with trifluoroacetic acid at room temperature for 1 hr) in 0.5 ml of trifluoroacetic acid was allowed to stand at room temperature for 12 hr. There was no change in the NMR spectrum. The solution was then heated at 60° and the NMR spectrum gradually changed. After 7.5 hr the reaction was essentially complete and the solution was poured into a slurry of aqueous sodium bicarbonate and methylene chloride and worked up (vide supra). VPC (5 ft × 0.25 in. column, 10% SE-30 on Chromosorb W, 80–100 mesh, 135°) gave 15% recovered **6c** and 85% of a mixture (4:1) of **7t** and **7c** whose spectra (ir, NMR) were identical with those described above.

Acknowledgment. We are indebted to the National Institutes of Health for a grant (GM-15997) in support of this research.

Registry No.—i_c, 54277-18-8; i_t, 54353-09-2; ii, 54325-80-3; **5**, 54277-19-9; **6c**, 54325-81-4; **6t**, 54353-10-5; **7c**, 54277-20-2; **7t**, 54277-21-3; **8c**, 54277-22-4; **8t**, 54277-23-5.

References and Notes

(1) H. Hart, I. Huang, and P. Lavrik, *J. Org. Chem.*, **39**, 999 (1974).
(2) For the mechanistic details of the latter process, including deuterium labeling experiments, see ref 1.
(3) H. Hart and M. Nitta, *Tetrahedron Lett.*, 2113 (1974).
(4) When excess *m*-chloroperbenzoic acid was used, di- and triepoxides of **5** were formed. The diepoxides were a mixture of i_c and i_t in which the two epoxide rings are cis to one another and either cis or trans to the vinyl group. There was no detectable amount of the isomer with the two epoxide rings trans to one another. The stereochemistry of the triepoxide ii is not known, though it seems probable that the two epoxide oxygens on the cyclohexanone ring are cis. Spectral properties of i and ii are given in the Experimental Section.



i_c i_t ii

(5) Chemical shifts are in δ units, with relative downfield shifts in the presence of Eu(fod)$_3$ given in parentheses; see D. R. Kelsey, *J. Am. Chem. Soc.*, **94**, 1764 (1972).
(6) H. Hart, M. Verma, and I. Wang, *J. Org. Chem.*, **38**, 3418 (1973).
(7) Insufficient **7c*** was isolated for spectral examination.
(8) NMR spectra were obtained on either a Varian Associates T-60 or HA-100 spectrometer; ir spectra were measured on a Unicam SP-200 spectrophotometer and were calibrated against a polystyrene film, uv spectra on a Unicam SP-800 spectrophotometer, and mass spectra at 70 eV on a Hitachi Perkin-Elmer RMU-6 spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., or Clark Microanalytical Laboratories, Urbana, Ill. Analytical gas chromatography (VPC) was done on a Varian Aerograph Model 1400 (flame ionization detector), and preparative VPC was done with a Varian Aerograph Autoprep Model 700 instrument (thermal conductivity detector).

Generalized Syntheses of γ Diketones. I. Addition of Dimetalloacetylides to Aldehydes. II. Dialkylation of Bisdithianes[1a]

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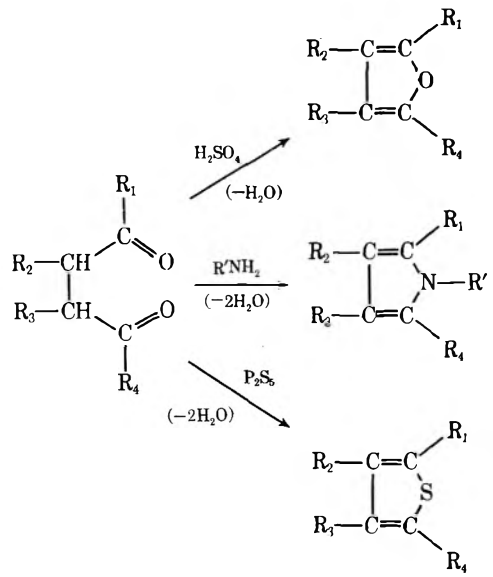
γ diketones are synthetically very useful but not generally accessible. Extensive preliminary studies revealed that the addition of dimetalloacetylides to aldehydes followed by catalytic reduction of the carbon–carbon triple bond and then oxidation of the saturated glycol to the diketone was one of the more promising approaches. The development of this method into a general, preparative procedure yielding a variety of 1,4 diketones in 20–60% overall yields is reported. The generality of application of the Corey–Seebach bisthio carbanions to the preparation of γ diketones via both single-step and stepwise dialkylations has also been examined. For the less reactive primary alkyl derivatives, the single-step approach and, for all other primary alkyl halides, the stepwise approach seem to offer the best general route to the target compounds. Thus this procedure is complementary to the dimetalloacetylide route which is superior when R is secondary or tertiary alkyl, and in which the bisthio carbanion approach generally fails. Many of the compounds made have not been reported heretofore.

γ diketones (1,4-dicarbonyl compounds) have great utility in organic synthesis, e.g., they readily undergo enolic dehydration and Knorr–Paal condensations to form furans, pyrroles, and thiophenes. Work carried out in this laboratory[2] has expanded the application of the Knorr–Paal pyrrole synthesis to produce a number of highly sterically

crowded heterocycles. However, the application of these syntheses is severely limited by the availability of appropriately substituted γ diketones.



Aromatic diketones, in which R_1 and R_4 are phenyl or substituted phenyl radicals, are fairly readily available by Friedel–Crafts acylation with the corresponding dicarboxylic acid chlorides.[3] However, the only commercially available γ diketone is the simplest possible aliphatic one, 2,5-hexanedione or acetonylacetone. The synthetic utility of the acetoacetic ester process by which this compound is made breaks down when applied to higher homologs. Cyclopentenones become the principal products instead of γ diketones.[4] Various methods have been reported in the literature for making a number of γ diketones, but these methods are usually quite cumbersome, often very limited in scope, and generally give only low yields of the desired products.[4] Therefore the work herein described was undertaken with the purpose of developing more general synthetic procedures for making γ diketones.

Initial efforts were directed toward ketone-forming reactions with dibasic acids, including succinic, fumaric, maleic, and acetylenedicarboxylic acids and their various derivatives.

(1) Addition of organometallic reagents to diesters at low temperature gave only very low yields of diketones in the presence of much unreacted starting material. The use of ferric chloride catalysis gave only slight increases in yield.

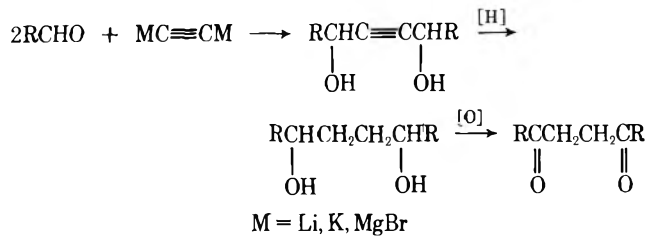
(2) Reaction of organolithium reagents with dicarboxylic acids resulted only in neutralization of the acids. Further reaction may have been prevented owing to insolubility of the intermediate salt.[5]

(3) Addition of organometallic reagents to dinitriles resulted only in formation of tars. No ketonic products could be isolated.

(4) Addition of organometallic reagents to dicarboxylic acid chlorides uder ferric chloride catalysis produces low yields of diketone accompanied by large amounts of lacetone by-product.[6] Isolation of the small amount of the desired product was impractical.

I. Addition of Dimetalloacetylides to Aldehydes. A potential, indirect route to γ diketones would be the condensation of acetylene with 2 mol of an aldehyde to give an acetylenic glycol. The glycol might then be hydrogenated to the saturated diol with subsequent oxidation producing the diketone. Only two reports were found in the literature in which this scheme had been tried. The preparation of 2,7-dimethyl-3,6-octanedione via acetylenebismagnesium bromide was reported in 1948 by Deemer, Lutwak, and Strong.[7] The overall yield of diketone was low since the acetylenic glycol was obtained in only 27% yield (purified) and after reduction and oxidation (yields not stated) the product was isolated only as the dioxime derivative. Using a similar procedure, Jones and coworkers[8] have reported a 48% yield of 4,7-decanedione starting with *n*-butyraldehyde. The only other reference to this synthetic scheme is the statement by Hunsdiecker[4] that γ diketones may be made this way but *"nur mit schlechter Ausbeute"*. No specific details were given.

We now report the development of the acetylenic glycol process on a preparative scale and the extension of it to prepare a variety of γ diketones as shown.



After our work was completed there has appeared recently[9] a paper reporting a 1,4-diketone synthesis of comparable generality and in approximately equivalent overall yields from organolithium reagents and *N,N,N'N'*-tetramethyldiamides at −78°. This procedure has the advantage of being a one-step rather than a three-step procedure, but also the disadvantage of requiring less accessible reagents. Furthermore, it is not necessary in the three-step procedure to purify the intermediates.

Preparation of Acetylenic Glycols. The preparation of acetylenic glycols from aldehydes and ketones has been discussed in several reviews.[10] Besides the bisbromomagnesium derivative of acetylene, glycols have been made from sodium, lithium, and potassium acetylides. The acetylenebismagnesium bromide reagent was the one used most extensively in our work.

This reagent was prepared by rapidly bubbling purified acetylene through ethereal ethylmagnesium bromide. It separates as a dark, oily, ether-insoluble phase by disproportionation of the initially formed monometallic derivative. The literature[11] suggests a 24–72-hr reaction period, but in our hands a 6–12-hr period gave equivalent results. Furthermore, the reagent could be formed as a gray, insoluble powder in benzene in 3–6 hr.

Dilithium acetylide was prepared by bubbling acetylene through either a solution of butyllithium or a solution of lithium metal in liquid ammonia. In the latter case the acetylide was isolated as a white powder. The dilithium compound is also commercially available from Alfa Chemicals, but only the in situ prepared ether suspension of the acetylide gave a successful reaction with aldehydes in our experience. The use of the isolated samples of the acetylide appeared to result in mostly aldol condensation products. Dipotassium acetylide was prepared by passing acetylene through a fine suspension of potassium hydroxide in diglyme or acetone dimethyl ketal.

The acetylenic glycols prepared according to the general scheme are shown in Table I. In most of the preparations of acetylenic glycols, the major by-products were those resulting from self-condensation of the aldehyde and from monoaddition of the acetylene derivative. The aldol condensation products were especially prominent with the low molecular weight, straight-chain aldehydes. Formation of these by-products may be inhibitable by using even slower rates of addition of the aldehydes, or by using solvents such

Table I
1,4 Diketones via Dimetalloacetylides

$$2RC{=}O + MC{\equiv}CM^{a-d} \longrightarrow RCHOHC{\equiv}CCHOHR \longrightarrow RCHOHCH_2CH_2CHOHR \longrightarrow RC(=O)CH_2CH_2C(=O)R$$

R	Acetylenic glycol[e] % yield,[f] physical properties	Hydrogenated glycol[e] % yield,[f] physical properties	Ketone[e] % yield,[f] physical properties
Et	32,[a,d] 72 (crude);[b] bp 90–95° (0.05 Torr) [lit.[h] bp 90–95° (1 Torr)]	44; bp 80–82° (0.7 Torr) [lit.[h] bp 101–102° (3 Torr)]	80 (18);[g] bp 45–50° (0.25 Torr) [lit.[j] bp 98° (14 Torr)]
n-Pr	46;[a] bp 77–95° (0.05 Torr) [lit.[n] bp 113–114° (1 Torr)]	96 (crude)	44 (19);[g] mp 22–25° bp 62–64° (0.3 Torr), N^{20}_0 1.4230 [lit.[o] bp 53.5° (0.1 Torr), N^{20}_0 1.4230]
i-Pr	68,[a] 22;[b] two white solid stereomers, mp 65–68°, 104–105° (lit.[k] mp 61–63°, 104–105°)	97 (crude)	95 (62);[g] bp 100–102° (9 Torr) [lit.[l] bp 100–102° (10–11 Torr)]
t-Bu	31,[a] 22;[c] two white solid stereomers; mp 110.5–111°; 129–131°	85; mp 160–165° (isomer mixture)	96 (24);[g] mp 16–19° (lit.[m] mp 16.5–18°)
n-Hexyl	50,[a] 38;[d] white, solid mixture of stereomers, mp 47–49° (lit.[p] mp 47–49°)	99, mp 74–89° (isomer mixture) (lit.[p] mp 85–86° and 105–106°)	92; mp 67–68°
Ph	35;[a] white solid mixture of stereomers, mp 132–135° (lit.[q] mp 129–130°)	100; mp 89–99° (isomer mixture) (lit.[r] mp 90° and 113°)	70 (24);[g] mp 142–143° (lit.[s] mp 143–144°)
Cyclohexyl	32,[a] 31;[d] white, solid mixture of stereomers, mp 102–106°; after separation by recrystallization, mp 100.5–102.5, 126.2–127.2°	96; two stereomers, mp 149.2–149.8° and 186–186.5°	95 (29);[g] bp 17–171° (1 Torr)

[a] BrMgC≡CMgBr (ether). [b] LiC≡CLi. [c] KC≡CK. [d] BrMgC≡CMgBr (benzene). [e] Spectral and analytical data for new compounds are provided in the Experimental Section. [f] Percentage yield in the individual step if the intermediate was isolated. [g] Overall yield without purifying intermediates based on the amount of magnesium originally employed in formation of the ethylmagnesium bromide used in making the acetylide. [h] W. J. Doran and E. M. Van Heyningen, U.S. Patent 2,561,688 (1951). [j] E. E. Blaise, *C. R. Acad. Sci.*, **158**, 504 (1914). [k] Cf. ref 7. [l] A. Spassoff, *Bull. Soc. Chim. Fr.*, **4**, 1658 (1937). [m] W. A. Brown and G. T. Wright, *Can. J. Chem.*, **35**, 236 (1957). [n] C. S. Marvel and W. W. Williams, *J. Am. Chem. Soc.*, **61**, 2714 (1939). [o] D. Chakravarti, N. K. Rorp, A. Chakravarti, and V. Sarkar, *J. Indian Chem. Soc.*, **44**, 463 (1967). [p] Y. Zal'kind and V. J. Tzereshkv, *J. Gen. Chem. USSR*, **5**, 1768 (1925); *Chem. Abstr.*, **30**, 3408 (1936). [q] Cf. ref 8. [r] R. E. Lutz and J. S. Gillespie, Jr., *J. Am. Chem. Soc.*, **72**, 344, 2002 (1950). [s] J. B. Conant and R. E. Lutz, *J. Am. Chem. Soc.*, **45**, 1303 (1923).

as chloroform or dichloromethane in which the acetylene-bismagnesium bromide is reported to be soluble. The acetylenic carbinol by-products are probably formed from some of the mono compound, acetylenemagnesium bromide, which did not disproportionate. It should be noted here that care must be exercised in the handling of any acetylenic carbinols since at least two of them, 1-hexyn-3-ol and 4-ethyl-1-octyn-3-ol, are known to be toxic when inhaled or absorbed through the skin.[12]

Hydrogenation of Acetylenic Glycols. The triple bonds of the acetylenic glycols were conveniently hydrogenated in the presence of common catalysts such as platinum, palladium, or nickel.

Reduction in ethanol at 60 psi generally took place rapidly and cleanly, giving the desired product after filtration and evaporation of solvent. In the case of the sterically hindered glycol, 2,2,7,7-tetramethyl-4-octyne-3,6-diol, the hydrogenation reaction was somewhat slower and required 2 hr for the theoretical uptake of hydrogen. Also some side reactions were evidenced with some of the lower molecular weight compounds, principally owing to hydrogenolysis. Efforts to reduce this side reaction by hydrogenating the acetylene glycol diacetate gave only marginal improvements.

Oxidation of γ Dialcohols. A wide variety of oxidizing agents are known that are capable of converting secondary alcohols to ketones, but not all are applicable to a bifunctional system or a system containing easily oxidizable carbon atoms bearing tertiary hydrogens. Deemer, Lutwak, and Strong[7] used a two-phase system consisting of benzene and an aqueous solution of sodium dichromate, sulfuric acid, and acetic acid for the oxidation of 2,7-dimethyl-3,6-octanediol. We investigated this oxidation procedure, but regularly obtained major amounts of a ketonic by-product of undetermined structure (C=O absorption at 1775 cm^{-1}), e.g., reaction of 2,7-dimethyl-3,6-octanediol gave a mixture with diketone to by-product ketone ratio of 1.6:1. The Jones procedure[8] likewise proved to be unsatisfactory, yielding a 2.7:1 ratio of the two products from the same diol.

Ultimately the Sarett procedure[13] as modified by Cornforth[14] and further by Collins[15] proved to be the cleanest even for alcohols containing no tertiary hydrogen, and so it was employed in all cases. The diketones thus obtained are listed in Table I. The low yield of 3,6-octanedione is ascribed to losses due to volatility whereas that of 4,7-decanedione reflects a 50% loss due to hydrogenolysis to 4-decanone in the reduction step.

Table II
1,4-Diketones via Bis(*m*-dithianes)

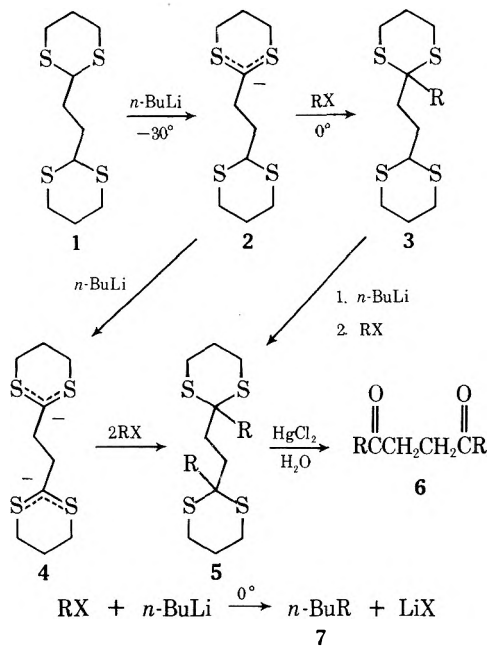
	R	Dithane (5) Yield (1 → 5), %	Dithane (5) Mp, °C	Diketone (6), overall yield (1 → 6) %, physical properties
Single-step dialkylation (1 → 5) and subsequent hydrolysis	Et	54	130–131[c]	46[d]
	i-Pr	*a*	*a*	50[b,d]
	n-Bu	54	79.5–81[c]	49 (78[b]), mp 48–49°[c]
Stepwise dialkylation (1 → 5) and subsequent hydrolysis	*n*-Pr	79	121.5–123.5[c]	68[d]
	i-Pr	43	109–110[c]	40[d]
	$PhCH_2$	57	133.5–135[c]	52 mp 63–64° (lit.[e] mp 64–65°)
	i-Bu	62	84–85.5[c]	49[f]
	i-$BuCH_2$	*a*	*a*	77[b,c] mp 32–34°[c]

[a] Solid, purified compound not isolated. [b] Unpurified intermediate hydrolyzed directly. [c] Spectral and analytical data for new compounds are provided in the Experimental Section. [d] Physical properties same as those of material reported in Table I. [e] D. Ivanov and N. Marekov, *Annu. Fac. Sci. Nat. Univ., Skopje, Math. Phys. Chim.*, **47**, 41 (1952); *Chem. Abstr.*, **48**, 10591 (1954); *Chem. Zentr.*, 9087 (1955). [f] Characterized by GC, ir, and NMR. Previously reported by O. Dann, E. Pietschmann, and W. Dimmling, *Arch. Pharm. (Weinheim)*, **292**, 508 (1959).

II. Dialkylation of Bisdithianes. In 1965 Corey and Seebach[16] reported a method for thioacetalization of aldehydes with 1,3-propanedithiol. Alkylation of the substituted *m*-dithianes thus obtained followed by hydrolysis led to ketones. That this approach likewise offers promise as a route to diketones was established by the synthesis of 1,4-cycloheptanedione.[17]

We report herein our study on the generality and utility of this approach to the synthesis of symmetrical acyclic γ-diketones via dialkylation of 2,2′-ethylenebis(*m*-dithiane) (**1**), a substance we had already been investigating ourselves in a related connection[18] prior to the appearance of the Corey papers.

Dialkylation might be carried out by successive monoalkylations, each requiring ionization of the intermediate bis(*m*-dithiane) followed by treatment with the alkylating agent (route **1** → **2** → **3** → **5**), or, in an operationally simpler alternative, by adding 2 equiv of the ionizing base (*n*-butyllithium) all at once followed by 2 equiv of alkylating agent (route **1** → (**4**) → **5**). The success of the latter approach would depend, of course, either on the possibility of generating the dianion (**4**) directly, or, more likely, the ability of the excess alkylating agent to survive attack by the second equivalent of ionizing base to form **7** while the first alkylation step on the monoanion (**2**) was in progress. The second alkylation step (**3** → **5**) could then proceed in the same manner as the first.



The progress of the reaction was conveniently followed by NMR spectrometry. The NMR absorption of the two methine protons in 2,2′-ethylenebis(*m*-dithiane) occurs as a multiplet at δ 4.05 whereas methylene protons adjacent to sulfur atoms resonate at δ 2.8 ppm. Thus monoalkylation is accompanied by a decrease in the ratio of methine to the above-mentioned methylene protons from 1:4 to 1:8, and complete dialkylation results in the disappearance of the methine proton resonances altogether.

The deprotonation (metalation) was initially carried out using 2 equiv of *n*-butyllithium at −30°; then 2 equiv of alkyl halide was added at −5° followed by a 3-day period at 0° for completion of the reaction. Under these conditions the results in Table I were obtained from the first three alkyl halides tried. It is evident that single-step dialkylation was successfully accomplished in these instances in preparatively acceptable yields.

However, when the more reactive alkylating agent benzyl bromide was employed under the same conditions, only the monalkylated crystalline intermediate bis(*m*-dithiane) (**3**) could be obtained; none of the dialkylated product (**5**) was found. A significant amount of the side-product, 1-phenylpentane (**7**), was also isolated.

The extent of ionization of **1** under the reaction conditions was then determined by quenching a solution of the anion in deuterium oxide. The NMR spectrum of the recovered product revealed that just one-half of the methine protons had been replaced, indicating that only the monoanion, **2**, had formed in significant amounts. Doubling the amount of *n* butyllithium (4:1 base-substrate ratio) resulted in a 75% deuteration upon quenching, suggesting that the dianion **4** is formed to some extent in the presence of excess *n*-butyllithium.

Therefore, successful single-step dialkylation in the three cases reported in Table II must have occurred, because ionization of the second methine proton and subsequent coupling with the alkyl halide were faster than direct nucleophilic displacement on the halide by *n*-butyllithium, but the converse is true with benzyl bromide.

Accordingly, stepwise dialkylation was employed in the remainder of the reactions studied. Analysis of the initially formed anion demonstrated that **2** was quantitatively formed in the presence of only 1 mol of base.

Stepwise alkylations with isopropyl iodide and benzyl

bromide were carried out for comparison with the single-step approach. In addition three additional stepwise dialkylations were done. The results are recorded in Table II.

All attempts at alkylation with tertiary and secondary halides, including *tert*-butyl chloride, *tert*-butyl bromide, 2-bromobutane, 2-iodooctane, and cyclopentyl iodide, failed with the single exception of isopropyl iodide, presumably owing to precedence of direct β-elimination of HX from the halides.

In summary, the synthesis of γ diketones of the type $RCOCH_2CH_2COR$ via dialkylation of 2,2′-ethylenbis(*m*-dithiane) appears to be preparatively successful for primary alkyl halides and isopropyl halide. Furthermore, overall yields for the same product are superior to those obtained via the dimetalloacetylide procedure while at the same time being more convenient and less time consuming. The bis(*m*-dithiane) approach should also be readily amenable to the synthesis of unsymmetrical diketones via stepwise alkylation.

Finally, it should be noted that the two methods nicely complement each other since the dimetalloacetylide process succeeds when R = aryl, secondary alkyl, and tertiary alkyl whereas the bis(*m*-dithiane) approach does not.

All the dialkylated bis(*m*-dithianes) reported here, four of the intermediate glycols, and four of the γ diketones (5,8-dodecanedione,[19] 2,11-dimethyl-5,8-dodecanedione, 7,10-hexadecanedione, and 1,4-dicyclohexyl-1,4-butanedione) are new compounds. Spectral (ir and NMR) and analytical data were obtained consistent with the assigned structures for all compounds reported.

Experimental Section

Starting Materials. Tetrahydrofuran (THF) was refluxed overnight over excess-powdered $LiAlH_4$ and then distilled off the $LiAlH_4$ just prior to use.[20]

***n*-Butyllithium** (commercial, Foote or Alfa) in hexane solution was used as received.

Alkyl bromides and iodides were prepared from the corresponding alcohols using HBr and H_2SO_4, constant-boiling HI, or phosphorus and iodine. The Corey and Anderson o-phenylene phosphate method[21] proved to be more cumbersome and gave lower yields. The halides were dried over $CaCl_2$ and distilled prior to use.

2,2′-Ethylenebis(*m*-dithiane) (1) was prepared basically as described in the literature[17] in 80–90% yields. Carbon tetrachloride was found to be much superior as the recrystallizing solvent to the chloroform–methanol solvent reported, giving a higher purity product, mp 135–136° (lit.[17] 132–135°).

Preparation of Acetylides. Preparation of Acetylenebismagnesium Bromide. In a typical run a solution of ethylmagnesium bromide in ether was prepared from 24 g (1.0 g-atom) of magnesium turnings and 109 g of ethyl bromide. The solution was stirred rapidly under nitrogen at room temperature while a stream of purified acetylene[22] was then introduced into the liquid via a long dropper tube. After 6–12 hr of treatment with acetylene (depending upon the rate of addition), the acetylenebismagnesium bromide separated out as a dark, viscous, ether-insoluble oil. Anhydrous ether had to be added periodically to maintain the volume unless a Dry Ice condenser was employed. The addition of acetylene was continued until hydrolysis of an aliquot of the supernatant liquid formed only a negligible amount of base as determined by titration.[23]

In the case in which benzene solvent was used, the ethyl Grignard reagent was prepared in the usual manner, and the bulk of the ether was distilled off. An equal volume of dry benzene was then added, and the acetylene treatment was carried out as described above. The use of benzene cut the reaction time to approximately 3–5 hr. The acetylenebismagnesium bromide separated as a gray, powdery suspension rather than as an oil.

Preparation of Dilithium Acetylide. Purified acetylene was bubbled rapidly for 2 hr through a stirred mixture of 100 ml of 1.6 *M* commercial hexane solution of *n*-butyllithium (Alfa) and 150 ml of anhydrous ether, additional ether being added to compensate evaporation losses. During this time the solution turned a milky white. The mixture was stirred for several more hours to complete reaction and to allow for disproportionation of any monolithium acetylide.

Preparation of Dipotassium Acetylide. A *p*-dioxane suspension was prepared from KOH and acetylene.[24]

Preparation of Acetylenic Glycols. The following example is illustrative. Pivalaldehyde (0.2 mol) in 10 ml of anhydrous ether was added dropwise to an excess of the acetylenebismagnesium bromide prepared as described above and the yellow suspension was allowed to stand for 36 hr at room temperature. Hydrolysis was accomplished by cooling and stirring with 30 ml of saturated aqueous NH_4Cl. The ether layer was decanted, the gray precipitate was washed further, and the combined ether portions were evaporated to leave 11.2 g of moist solid. Titration with petroleum ether left 4.8 g of the acetylenic glycol (2,2,7,7-tetramethyloct-4-yne-3,6-diol). Several more crops were obtained by concentrating the mother liquor and chromatography on alumina to give a total yield of 6.15 g (31%) of mixed stereomers: mp 111–118°; ir (KBr) 3240 (s, broad, H-bonded OH), 1120, 1080, 1010 (all s), and 1385, 1360 cm^{-1} (m, *t*-Bu); NMR ($CDCl_3$) δ 4.05 (m, 1, CHOH), 2.63 (m, 1, OH), and 1.00 ppm [s, 9, $C(CH_3)_3$].

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.52; H, 11.46.

1,4-Dicyclohexyl-2-butyne-1,4-diol was a mixture of stereomers: mp 102–106°; ir (KBr) 3250 (s, broad, H-bonded OH), 1140 (m), 1070 cm^{-1} (s); NMR ($CDCl_3$) δ 4.19 (m, 1, CH), 3.10 (m, 1, OH), and 1.45 ppm (m, 11, cyclohexyl).

Anal. Calcd for $C_{16}H_{26}O_2$ (higher melting stereomer, mp 126.2–127.2°): C, 76.75; H, 10.47. Found: C, 77.01; H, 10.46.

Hydrogenation of Acetylenic Glycols. The general procedure followed is illustrated by the following example. Two grams (0.01 mol) of 2,2,7,7-tetramethyloct-4-yne-3,6-diol (stereomeric mixture) dissolved in 50 ml of 95% EtOH was shaken under 4 atm of H_2 until the theoretical uptake was complete (2 hr). (Analysis of an aliquot after 45 min showed the presence of olefinic hydrogen atoms in the NMR spectrum). Crystallization from the filtered solvent yielded 1.7 g (84%) of **2,2,7,7-tetramethyloctane-3,6-diol:** mp 160–165°; ir (KBr) 3340 (s, broad, H-bonded OH), 1075 (s, secondary OH), and 1390, 1355 cm^{-1} (m, *t*-Bu).

Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 71.44; H, 12.79.

1,4-Dicyclohexyl-1,4-butanediol: ir (KBr) 3330 (s, broad, H-bonded OH), 1080 (m), 1060, 1040, 985 cm^{-1} (all s).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.78; H, 11.62.

Oxidation of the Saturated Diols. The following is illustrative of the oxidation reactions. For each 0.1 mol of diol to be oxidized a solution was prepared by adding 62 g of CrO_3 dissolved in 62 ml of H_2O to 620 ml of reagent-grade pyridine at 0°. To this solution the alcohol in enough additional pyridine to dissolve it was added with swirling, and the mixture was allowed to stand at room temperature for 1–5 days. The reaction mixture was then poured into a threefold volume of water and extracted several times with ether. After concentrating the extract by evaporation, it was washed with dilute aqueous HCl until no further reaction, then dried and evaporated. In a specific instance 4.0 g (0.016 mol) of 1,4-dicyclohexyl-1,4-butanediol in 60 ml of pyridine was oxidized in 3.5 days to produce 3.7 g (95%) of **1,4-dicyclohexyl-1,4-butanedione:** bp 170–171° (1 Torr); ir (film) 1700 cm^{-1} (ketonic C=O, no evidence of lactone); NMR (CCl_4) δ 2.7 (s, 4, $CH_2C{=}O$), 2.4 (m, 2, CH), and 1.5 ppm (m, 20, cyclohexyl CH_2).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 77.03; H, 10.50

7,10-Hexadecanedione: mp 68.2–69°; musty, slightly sweet odor; ir (KBr) 1690 cm^{-1} (s, C=O); NMR (CCl_4) δ 2.55 (s, 2, $-COCH_2CH_2CO-$), 2.4 (t, 2, $-COCH_2CH_2CH_2CH-$), 1.3 (m, 8, CH_2-), 0.9 ppm (t, 3, CH_3).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.65; H, 11.95.

Single-Step Dialkylation (1 → 5). General Procedure. In a typical reaction 6.1 g (0.023 mol) of 2,2′-ethylenebis(*m*-dithiane) dissolved in 150 ml of THF was placed under dry nitrogen atmosphere in a stirred reaction flask and cooled to −30° with a Dry Ice–isopropyl alcohol bath. Then 2 molar equiv (35 ml, a sight excess) of 1.6 *M* *n*-butyllithium in hexane was added dropwise from a syringe over a 10-min period. Stirring was continued for 3 hr at −20 to −30°, during which time a deep orange solution formed.

The temperature was then allowed to rise to −5° and 0.055 mol of the halide dissolved in 50 ml of THF was added dropwise at that temperature, during which time the solution color changed to light

yellow. After allowing the reaction mixture to stand at 0° in a refrigerator for 3 days, it was quenched with several milliliters of water, concentrated to ca. 50 ml, diluted with 150 ml of water, and extracted three times with ether, pentane, or CH_2Cl_2. The combined extract was washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and evaporated. The product, usually obtained as an off-white solid or slowly crystallizing oil, was further purified by trituration with ether or recyrstallization from acetone or CCl_4.

2,2′-Ethylenebis(2-ethyl-*m*-dithiane): NMR (CCl_4) δ 2.80 (m, 4, SCH_2), 1.90 (m, 6, $SCCH_2$), and 1.01 ppm (t, 3, CH_3).

Anal. Calcd for $C_{14}H_{26}S_4$: C, 52.12; H, 8.12. Found: C, 52.02; H, 8.19.

2,2′-Ethylenebis(2-*n*-butyl-*m*-dithiane): NMR ($CDCl_3$) δ 2.80 (m, 4, SCH_2O, 1.67 (m, 10), and 0.93 ppm (t, 3, CH_3).

Anal. Calcd for $C_{18}H_{34}S_4$: C, 57.09; H, 9.05. Found: C, 57.21; H, 9.28.

Stepwise Dialkylation (1 → 2 → 3 → 5). General Procedure. A solution of the monanion, 2-lithio-2,2′-ethylenebis(*m*-dithiane), was prepared following the same procedure given above except that only 1 molar equiv of *n*-butyllithium was used. After a 3-hr period at −20 to −30° the mixture was allowed to warm to −5°, and a solution of 1 molar equiv of alkyl halide in THF was added. The solution was stirred for 1 hr at 0°, then cooled again to −30° and the sequence repeated with another molar equivalent of base and halide. After storing the mixture for 3 days at 0°, it was worked up as in the procedure above.

2,2′-Ethylenebis(2-*n*-propyl-*m*-dithiane): analytical sample mp 123.9–124.4°; NMR ($CDCl_3$) δ 2.87 (m, 4, SCH_2), 2.12 (s, 2 $SCCH_2CH_2CS$), 1.73 (m, 6), and 0.95 ppm (t, 3, CH_3).

Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.80; H, 8.62. Found: C, 54.84; H, 8.62.

2,2′-Ethylenebis(2-isopropyl-*m*-dithiane): NMR ($CDCl_3$) δ 2.8 (m, 4, SCH_2), 2.25 (s, 2, $SCCH_2CH_2CS$), 2.0 (m, 3, SCCH, secondary and primary), and 1.15 ppm [d, 6, $-CH(CH_3)_2$].

Anal. Calcd for $C_{16}H_{30}S_4$: C, 54.80; H, 8.62. Found: C, 54.67; H, 8.61.

2,2′-Ethylenebis(2-isobutyl-*m*-dithiane): mp 86.8–87.9° (analytical sample); NMR ($CDCl_3$) δ 2.83 (m, 4, SCH_2), 2.18 (s, 2, $SCCH_2CH_2CS$), 1.90 (m, 5), and 1.04 ppm [d, 6, $CH(CH_3)_2$].

Anal. Calcd for $C_{18}H_{34}S_4$: C, 57.09; H, 9.05. Found: C, 57.00; H, 9.15.

2,2′-Ethylenebis(2-benzyl-*m*-dithiane): mp 137.2–137.8° (analytical sample); NMR ($CDCl_3$) δ 7.26 (s, 5, C_6H_5), 3.10 (s, 2, $PhCH_2$), 2.83 (m, 4, SCH_2), 2.18 (s, 2, $SCCH_2CH_2CS$), and 1.92 ppm (m, 2, $SCCH_2$).

Anal. Calcd for $C_{24}H_{30}S_4$: C, 64.52; H, 6.77. Found: C, 64.79; H, 6.85.

Hydrolysis of 2,2′-Ethylenebis(2-alkyl-*m*-dithianes) (5). General Procedure. Following essentially the procedure of Seeach, Jones, and Corey[17] a mixture of 1.16 g of $HgCl_2$, 0.36 g of HgO, 1.5 ml of H_2O, and 25 ml of MeOH for each millimole of substrate was refluxed for 4–5 hr while vigorously stirring with a Vibro Mixer (Chemie-Apparatebau, Zurich). After cooling, filtering, and concentrating the organic phase, it was diluted with water, extracted with CH_2Cl_2, dried, and evaporated to yield the desired diketone, which could be used as such in Knorr–Paal type procedures or further purified by crystallization.

5,8-Dodecanedione: ir (KBr) 1695 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 2.57 (s, 2, $O{=}CCH_2CH_2C{=}O$), 2.40 (t, 2, $COCH_2CH_2C$), 1.43 (m, 4, CH_2), and 0.9 ppm (t, 3, CH_3).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.93; H, 11.42.

2,11-Dimethyl-5,8-dodecanedione: bp 92° (0.3 Torr); ir 1705 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 2.67 (s, 2, $COCH_2CH_2CO$), 2.43 (t, 2, $COCH_2$), 1.50 (m, 3, $-CH_2CH<$), and 0.9 ppm [d, 6, $CH(CH_3)_2$].

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.13; H, 11.31.

Registry No.—**1**, 14947-53-6; **5** (R = Et), 54276-92-5; **5** (R = *n*-Bu), 54276-93-6; **5** (R = *n*-Pr), 54276-94-7; **5** (R = *i*-Pr), 54276-95-8; **5** (R = *i*-Bu), 54276-96-9; **5** (R = $PhCH_2$), 54276-97-0; **5** (R = *i*-$BuCH_2$), 54325-79-0; **6** (R = *n*-Bu), 15982-65-7; **6** (R = *i*-$BuCH_2$), 54276-98-1; **6** (R = Et), 2955-65-9; **6** (R = *i*-Pr), 51513-41-8; **6** (R = *n*-Pr), 22633-21-2; **6** (R = $PhCH_2$), 54276-99-2; **6** (R = *i*-Bu), 54277-00-8; **6** (R = *t*-Bu), 27610-88-4; **6** (R = hexyl), 54277-01-9; **6** (R = Ph), 495-71-6; **6** (R = cyclohexyl), 18986-63-5; propionaldehyde, 123-38-6; butyraldehyde, 123-72-8; isobutyraldehyde, 78-84-2; pivalaldehyde, 630-19-3; heptanal, 111-71-7; benzaldehyde, 100-52-7; cyclohexanecarboxaldehyde, 2043-61-0; 4-octyne-3,6-diol, 24434-07-9; 5-decyne-4,7-diol, 1070-40-2; *meso*-2,7-dimethyl-4-octyne-3,6-diol, 54277-02-0; *dl*-2,7-dimethyl-4-octyne-3,6-diol, 54277-03-1; *meso*-2,2,7,7-tetramethyl-4-octyne-3,6-diol, 54277-04-2; *dl*-2,2,7,7-tetrimethyl-4-octyne-3,6-diol, 54277-05-3; *meso*-8-hexadecyne-7,10-diol, 54277-06-4; *dl*-8-hexadecyne-7,10-diol, 54277-07-5; *meso*-1,4-diphenyl-2-butyne-1,4-diol, 54277-08-6; *dl*-diphenyl-2-butyne-1,4-diol, 54277-09-7; *meso*-1,4-dicyclohexyl-2-butyne-1,4-diol, 54277-10-0; *dl*-1,4-dicyclohexyl-2-butyne-1,4-diol, 54277-11-1; 3,6-octanediol, 24434-09-1; 4,7-decanediol, 4469-89-0; 2,7-dimethyl-3,6-octanediol, 31206-61-8; *meso*-2,2,7,7-tetramethyloctane-3,6-diol, 54277-12-2; *dl*-2,2,7,7-tetramethyloctane-3,6-diol, 54277-13-3; *meso*-7,10-hexadecanediol, 54277-14-4; *dl*-7,10-hexadecanediol, 54277-15-5; *meso*-1,4-diphenylbutane-1,4-diol, 13401-42-8; *dl*-1,4-diphenylbutane-1,4-diol, 13401-43-9; *meso*-1,4-dicyclohexyl-1,4-butanediol, 54277-16-6; *dl*-1,4-dicyclohexyl-1,4-butanediol, 54277-17-7; acetylenebismagnesium bromide, 4301-15-9; ethyl bromide, 74-96-4; acetylene, 74-86-2; dilithium acetylide, 1070-75-3; dipotassium acetylide, 22754-96-7.

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Photochemistry of Di-π-silanes

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The excited-state chemistry of di-π-silane systems, in which two vinyl or π moieties are attached to a quaternary silicon atom, has been studied in an exploratory and mechanistic fashion. The compounds investigated are *trans*-β-styryltriphenylsilane (**3t**), *trans,trans*-bis(β-styryl)dimethylsilane (**1tt**), and *trans,trans*-bis(β-styryl)diphenylsilane (**2tt**). Our results from studies of the direct and triplet-sensitized irradiations of these compounds have demonstrated that (1) these di-π-silanes, having structures closely analogous to hydrocarbon systems which undergo the di-π-methane rearrangement, fail to isomerize to corresponding π-substituted silacyclopropanes, (2) cis–trans isomerization about π bonds are the energy dissipating and exclusive reaction modes observed upon excitation of **1–3**, and (3) the preferred mechanism for cis–trans isomerization for the bis(β-styryl)silane **1tt** does not appear to involve interaction between the two "nonconjugated" π chromophores.

Organic photochemistry remains one of the more potent areas of synthetic innovation in organic chemistry. Photochemical methods in many cases offer convenient routes for the preparation of highly strained compounds, which normally do not survive common ground-state reaction conditions. Our interests in this area are focused on the development of methods for the preparation of small-ring heterocyclic systems.

The specific aim of the present study was to design simple and efficient synthetic sequences for the preparation of silacyclopropanes.[1] The plan was to utilize the general di-π-methane rearrangement,[2] which transforms 1,4-dienes into corresponding vinylcyclopropanes, as the key ring-building step. Thus, the photochemistry of di-π-silanes, in which the central quaternary carbon atom of di-π-methanes is replaced by silicon, might offer a simple entry into the viylsilacyclopropanes (eq 1). Our interest in investigat-

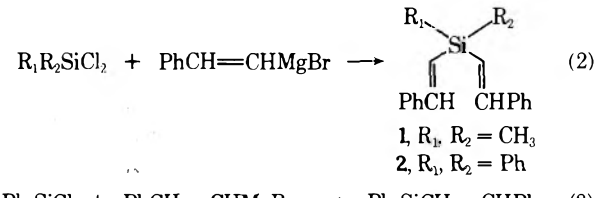
(1)

ing the excited state chemistry of di-π-silanes was further stimulated by the lack of literature examples of di-π-methane type reactions of systems containing heteroatoms other than oxygen in the reactive chromophores.[3]

The recent reports of Connolly[4] and Koch[5] on the excited-state chemistry of compounds closely related to the ones to be described prompts us to relate the results of the photochemical study of several di-π-silanes. We have observed (1) a reluctance of di-π-silanes, having structures closely analogous to reactive hydrocarbon systems which undergo the general di-π-methane rearrangement, to isomerize to π-substituted silacyclopropanes upon either direct or sensitized irradiation; (2) that cis–trans isomerization about the π bonds is an efficient energy-dissipating process upon both direct and triplet-sensitized excitation; and (3) that the preferred mechanism for cis–trans isomerization for bis(β-styryl)silanes does not appear to involve interaction between the two "nonconjugated" π chromophores.[6]

Results

Syntheses. The di-π-silanes used in these studies are prepared by reaction of dichloro- and monochlorosilanes with β-styryl Grignard reagents (eq 2 and 3). Compounds



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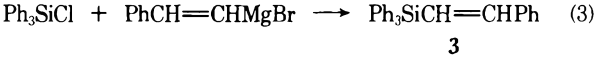


(3)

3

prepared in this way are bis(β-styryl)dimethylsilane (**1**), bis(β-styryl)diphenylsilane (**2**), and β-styryltriphenylsilane (**3**).

The proton NMR and ultraviolet spectral data for these compounds, recorded in Table I, serve as strong confirmation of both the expected structures and π-bond stereochemistries in **1–3**. Isomerically pure samples of the trans,trans isomer of **2** and the trans isomer of **3** were obtained by fractional recrystallization. The three stereoisomers of the dimethyldistyrylsilane **1** (**1tt, 1ct,** and **1cc**) were separated and removed from significant quantities of the coupling by-product, 1,4-diphenylbutadiene, by spinning band distillation. Proton magnetic resonance spectra were definitive in establishing the stereochemistry about the π bonds in each of the synthesized compounds. The cis and trans coupling constants were easily identified as 15.0 Hz and 19.0 Hz, respectively. In addition, the ultraviolet spectra of silanes **1–3** were all similar and nearly superimposable on that of the models, *cis*- and *trans*-(β-styryl)trimethylsilane. These observations support the fact that no strong interaction exists between the "nonconjugated" π chromophores in the ground or initially populated singlet excited states of these systems.

Preparative Photochemistry. Exploratory photochemical studies of the di-π-silanes were undertaken. These initial investigations were not specifically designed to detect the potentially labile π-substituted silacyclopropanes (eq 1).[1,8] The conditions utilized, however, would have allowed detection of secondary products whose structure would have suggested the type of excited-state process occurring.

Direct irradiation of the di-π-silanes, **1tt** and **3,** at room temperature in either methanol or cyclohexane led only to recovered starting materials together with products of cis–trans isomerization about the π bonds. Similar results were obtained when the reactions were triplet sensitized with various ketone sensitizers.

Mechanistic Photochemistry. In an attempt to more closely investigate the reasons for the lack of π-substituted silacyclopropane forming photoprocesses upon irradiation of these di-π-silane systems, a more thorough study of the excited-state behavior of the dimethyldistyrylsilane, **1tt,** was undertaken. One factor which could contribute to the low rearrangement and high isomerization efficiencies upon direct irradiation is an enhanced intersystem-crossing efficiency from the initially populated di-π-silane singlet excited state. In analogy with carbon systems, this pathway would effectively block rearrangement by producing a "free-rotor" di-π-silane triplet capable of energy dissipation by π-bond isomerization.[10] Quenching experiments were carried out to explore this possibility. No reduction in the conversion of **1tt** to its isomers, **1ct** and **1cc,** was ob-

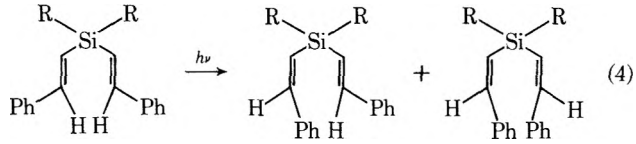
Table I
NMR and Uv Data for the Di-π-silanes 1–3

Compd	Proton NMR: Chemical shifts[a] H_a	H_b	$SiCH_3$	J_{ab}, Hz	Uv[b] λmax (log ε)
$Me_2Si(CH_a{=}CH_bPh)_2$					
trans, trans (1tt)	6.50 (d)	6.95 (d)	0.32 (s)	19.0	265 (4.64)
					294 (3.83)
cis,	5.89 (d)	7.44 (d)	0.16 (s)	15.0	260 (4.43)
trans (1ct)	6.40 (d)	6.86 (d)		19.0	286 (3.84)
					294 (3.55)
cis, cis (1cc)	5.86 (d)	7.32 (d)	0.01 (s)	15.0	255 (4.36)
					295 (3.29)
$Ph_2Si(CH_a{=}CH_bPh)_2$					
trans, trans (2tt)	6.86 (d)	7.08 (d)		19.0	263 (6.69)
					294 (5.99)
$PhSi(CH_a{=}CH_bPh)$					
trans (3t)	7.18 (d)	7.21 (d)		18.5	252 (6.37)
					262 (6.44)
					294 (5.67)

[a] Chemical shifts measured in parts per million (ppm) downfield from tetramethylsilane (internal). Letters in parentheses represent multiplicities: d, doublet; s, singlet. [b] Uv spectra were run in cyclohexane solvent.

served when direct irradiations were performed in the presence of 2,3-dimethyl-1,3-butadiene. These results suggest, but do not conclusively prove, that the singlet and not the triplet of the di-π-silane is the excited state responsible for cis–trans isomerization.

In order to evaluate how substitution on the silicon might affect the preferred photochemical pathways followed by these systems, the diphenylsilane, **2**, was irradiated under direct and triplet-sensitized conditions (eq 4).



(4)

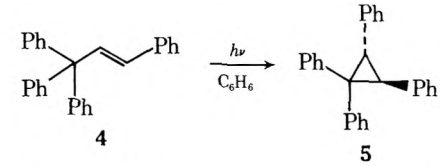
1tt, R = CH_3 **1ct** **1cc**
2tt, R = Ph **2ct** **2cc**

Surprisingly, no products of rearrangement were detected. As with **1tt**, cis–trans isomerization was the only observed reaction, resulting in a mixture of the three stereoisomers of **2**.

These observations raise the interesting question of the mechanism for cis–trans isomerization in the distyrylsilanes **1** and **2**. The absence of di-π-methane-like reactivity could very well be a result of the inability of these systems to undergo C-2–C-4 carbon–carbon bonding in the singlet or triplet manifold (eq 4). The ability of these systems to undergo C-2–C-4 carbon–carbon bond formation might be reflected in whether or not cis–trans isomerization proceed via a common bridged intermediate as has been proposed for related carbon systems.[11,12] With this in mind, varying conversion direct and sensitized irradiations were conducted on rigorously purified **1tt** (99.6% isomeric purity) using Pyrex filtered light for the direct runs and uranium glass filtered light for the benzophenone runs. The results of these experiments are summarized in Tables II and III and plotted in Figures 1 and 2 in terms of the relative percentage of **1tt**, **1ct**, and **1cc** vs. irradiation time.

Discussion

The di-π-silanes that have been prepared and studied contain structural features which make them closely related to hydrocarbon analogs which undergo efficient di-π-methane photorearrangements. For example, Griffin[13] has shown that the carbon counterpart of β-styryltriphenylsilane (**3**), 1,3,3,3-tetraphenylpropene (**4**), affords the tetraphenylcyclopropane **5** upon direct irradiation (eq 5). Similarly, a host of hydrocarbons related to the distyrylsilanes **1** and **2**, e.g., the tetraphenyldiene **6**,[10] react efficiently to yield vinylcyclopropane products from their corresponding singlet excited states (eq 6). Thus, these examples serve



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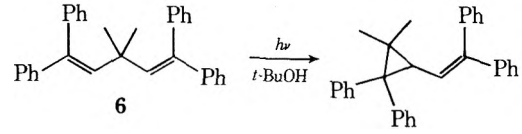
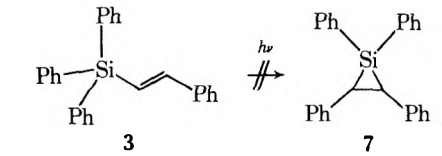
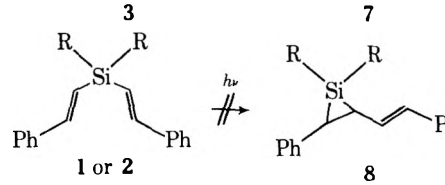


(6)

as strong precedents for the postulated photochemical reactions of di-π-silanes leading to π-substituted silacyclopropanes and, therefore, for postulated reaction sequences yielding convenient entries into the silacylopropane series. The complete inertness to photorearrangement of the styrylsilanes **1–3**, however, indicates that the silicon heteroatom in these systems introduces factors which cause the pathway to π-substituted silacyclopropanes, such as **7** and **8**, to be less efficient than in the carbon analogs (eq 7 and 8).



(7)



(8)

Several factors can be considered in assessing how the silicon heteroatom blocks di-π-methane-like reactivity in

Table II
The *cis,trans*- to *cis,cis*-Bis(β-styryl)dimethylsilane Isomer Compositions from Direct Irradiations of the Trans,Trans Isomer, 1tt, at Low Conversions (<50%) and at the Photostationary State

% conversion[a]	% cis,trans isomer[b] (1ct)	% cis,cis isomer[b] (1cc)	Cis,cis to cis,trans isomer ratio[b] (1cc/1ct)
2.0	2.0	0.0	0.00
9.7	9.7	0.0	0.00
14.2	13.9	0.3	0.02
17.6	20.6	0.6	0.03
28.0	28.0	0.8	0.03
35.9	34.0	2.0	0.06
43.0	39.6	3.4	0.09
Photostationary state	43.5	46.1	1.06

[a] Calculated as 100% minus the percent 1tt measured. [b] See Experimental Section for method of analysis.

Table III
The *cis,trans*- to *cis,cis*-Bis(β-styryl)dimethylsilane Isomer Compositions from Benzophenone-Sensitized Irradiations of the Trans,Trans Isomer, 1tt, at Low Conversions (<50%) and at the Photostationary State

% conversion[a]	% cis,trans isomer[b] (1ct)	% cis,cis isomer[b] (1cc)	Cis,cis to cis,trans isomer ratio[b] (1cc/1ct)
4.0	4.1	0.0	0.00
14.2	13.4	0.8	0.06
18.3	17.2	1.0	0.06
21.0	19.1	1.9	0.10
26.9	25.0	2.0	0.08
35.0	31.5	3.5	0.11
37.9	33.2	4.7	0.14
47.0	41.2	5.8	0.14
Photostationary state	50.2	33.8	0.67

[a] Calculated as 100% minus the percent 1tt measured. [b] See Experimental Section for method of analysis.

these systems. Silicon can either enhance the efficiency of alternate excited state deactivation modes or decrease the efficiency of di-π-methane reaction by destabilizing intermediates along the reaction coordinate.

One possible consequence of replacement of carbon by silicon in these systems might be a silicon-induced, enhanced intersystem crossing efficiency from the initially populated singlet excited states of **1**–**3**. This would be expected to have a dramatic effect on the efficiency of potential di-π-silane reactions, since it has been well documented that acyclic 1,4-diene triplet excited states utilize cis–trans isomerization as a major energy-dissipating, reaction mode.[2,10] Unfortunately, evidence accumulated to determine whether the silicon atom in these systems serves to enhance the intersytem crossing rate is minimal. High concentrations of the known triplet quencher, 2,3-dimethyl-1,3-butadiene ($E_T \simeq 58$ kcal/mol) appear to have absolutely no effect upon the efficiency of cis–trans isomerization of **1tt** (note Experimental Section). However, this observation might be explained by either a singlet isomerization mechanism or by the fact that the triplet state of **1tt** is shortlived. Another observation which concerns this point is the

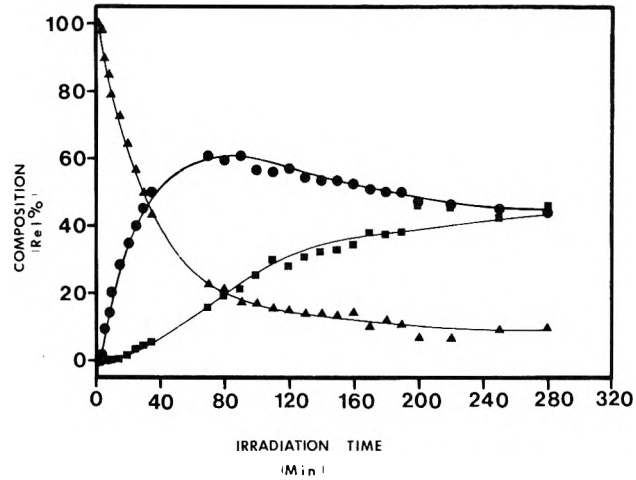


Figure 1. Direct irradiations of the *trans,trans*-distyrylsilane **1tt**. Plots of isomer composition (**1tt**, ▲; **1ct**, ●; **1cc**, ■) as relative percentages vs. irradiation time in cyclohexane.

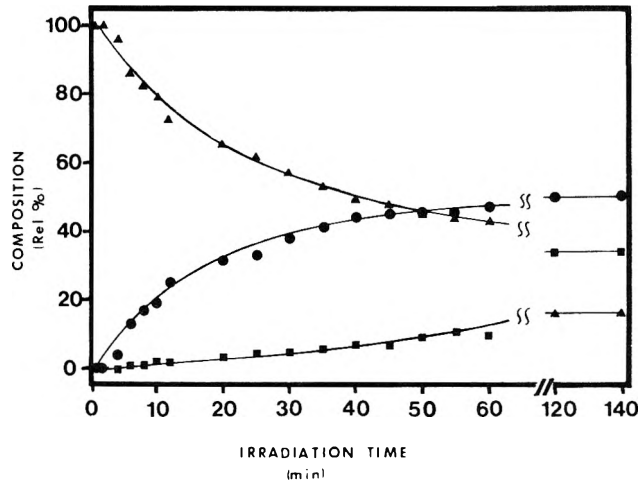
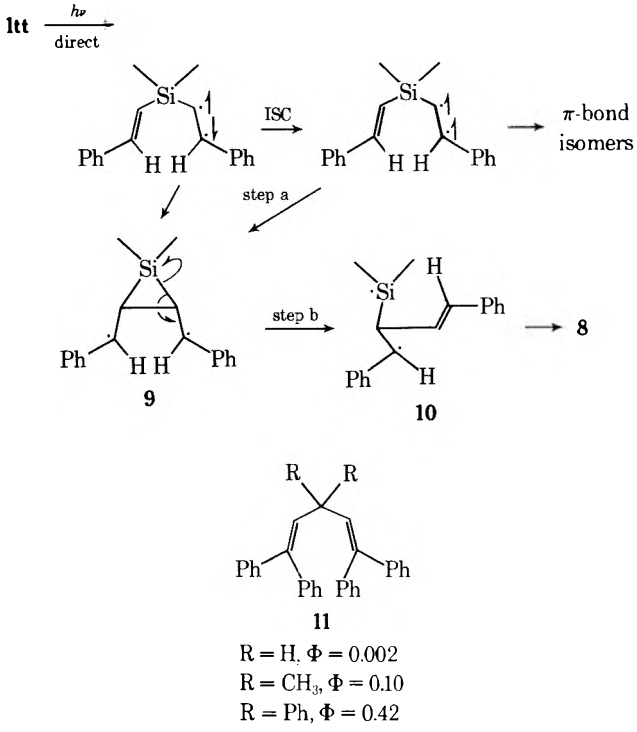


Figure 2. Benzophenone-sensitized irradiations of the *trans,trans*-distyrylsilane **1tt**. Plots of isomer composition (**1tt**, ▲; **1ct**, ●; **1cc**, ■) as relative percentages vs. irradiation time in cyclohexane.

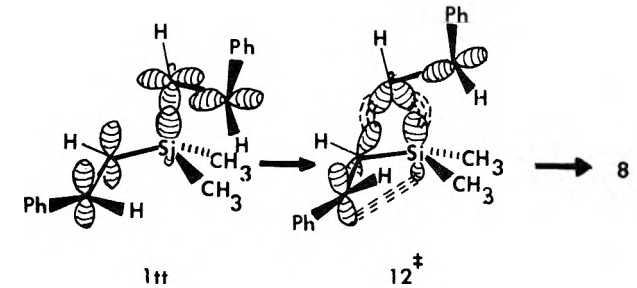
nondetectable fluorescence of the distyrylsilane **1tt** under conditions in which a reasonable model, β-methylstyrene, displays strong fluorescence. This decreased efficiency of singlet emission might very well be a reflection of a silicon enhancement of k_{ISC}. Our results, however, offer no firm conclusions on this point.

Another possibility for the absence of di-π-silane reactivity in the systems studied may be related to the effect silicon has on the ease with which silacyclopropyldicarbinyl diradicals, like **9** in Scheme I, undergo bond rupture to produce 2-vinylsilatrimethylene diradicals, e.g., **10**.[14] Zimmerman and coworkers[15] have demonstrated the effect of central carbon atom substitution on the efficiency of the di-π-methane process. In the absence of radical stabilizing groups on the central carbon atom, the di-π-methane reaction efficiency drops to zero. Demonstrative of this effect is the comparison of the quantum yields for rearrangement of the series of 1,4-dienes **11**. Interestingly, the di-π-silane rearrangement is inefficient for styrylsilanes **2** and **3** in spite of phenyl substituents on silicon, which might have the potential of increasing the stability of diradicals like **10**. In addition, estimates of silicon–carbon vs. carbon–carbon bond dissociation energies in silacyclopropanes vs. cyclopropanes yield the conclusion that step b in the hypothetical di-π-silane reaction pathway (see Scheme I) should be *more* facile for silicon.[16]

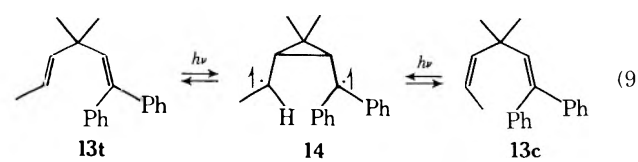
Scheme I



Probably the most important effect of silicon on the excited state reactivity of di-π-silane systems may be a result of its ability to *decrease* the direct (through space) interaction between the nonconjugated diene (or π) chromophores in the excited states of 1–3. It seems reasonable to postulate that formation of silacyclopropyldicarbinyl diradicals like **9** in the excited states of distyrylsilanes would suffer from the same prohibitive features of high ring strain as do ground-state silacyclopropanes.[1,16] This ring strain effect due to silicon at early stages in a nonconcerted pathway (step a in Scheme I) or in the transition state $12^{\ddagger}$ of a concerted reaction, could be controlling in causing di-π-silane rearrangements to be of high energy.

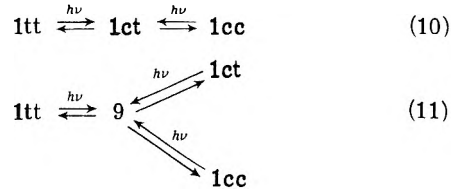


A possible experimental test for whether or not the silicon atom prevents interaction between the excited styryl moieties of **1tt** is suggested by the results of Zimmerman and Pratt in which cis–trans ismerization about the higher triplet energy propenyl π bond in the hexadiene **13** was rationalized in terms of a mechanism involving the intermediacy of the bridged cyclopropyldicarbinyl diradical **14** (eq 9).[11] Thus, the mechanism for π-bond isomerization of



(9)

1tt compared to the analogous carbon system should indicate whether the central silicon atom blocks C-2–C-4 carbon–carbon bridging. Specifically, in order to distinguish between a consecutive (eq 10) or a simultaneous (eq 11) mechanism for cis–trans isomerization of **1tt,** measure-



(10)

(11)

ments of the **1ct** to **1cc** isomer ratios after low-conversion irradiations of **1tt** were made. Note that in the consecutive mechanism no direct pathway exists for the interconversion of **1tt** to **1cc.** However, in the simultaneous mechanism a direct route is available through the intermediate **9.** The results summarized in Table II and Figure 1 demonstrate that the **1cc** to **1tt** isomer ratios at low conversions from direct irradiation of **1tt** remain nearly zero up to 27.9% conversion. After this point the ratio rises to its photostationary state value of 1.06. These observations are consistent with a mechanism for cis–trans isomerization of **1tt** which involves the formation of **1cc** in a second photochemical step from the excited state of the initially formed **1ct** (eq 10). Only after significant quantities of **1ct** are produced and, thus, significant quantities of light are absorbed by **1ct** does the cis–cis isomer appear. Therefore, the consecutive mechanisms seems more probable.

In order to completely rule out the possibility that these results are due to a simultaneous mechanism in which the bridged intermediate **9** decays much more rapidly to **1ct** than **1cc,**[17] the photostationary state compositions of both **1cc** and **1ct** were analyzed. In a simultaneous mechanism, two factors will determine the photostationary ratio of **1cc** to **1ct,** the relative rate constants for collapse of **9** to **1cc** and **1ct** (k_{cc} and k_{ct}) and the relative intensities of light absorbed by **1cc** and **1ct** (I_{cc} and I_{ct}), according to eq 12. The

$$\frac{[\mathbf{1cc}]_{\text{pss, direct}}}{[\mathbf{1ct}]_{\text{pss, direct}}} = \frac{I_{ct}}{I_{cc}} \cdot \frac{k_{cc}}{k_{ct}} \qquad (12)$$

intensity ratio, calculated approximately from relative integrated extinction coefficients of the two isomers,[18] was 1.12 and the photostationary state ratio was 1.06. Therefore, if the simultaneous mechanism were operating, the initial, low-conversion **1cc** to **1ct** ratios, determined by k_{cc}/k_{ct}, should have been about 0.94, a value clearly not observed. These observations support the consecutive mechanism for π-bond isomerization in the distyrylsilane systems and rule out the intermediacy of silacyclopropyldicarbinyl diradical **9.**

Results from benzophenone-sensitized isomerizations can be similarly interpreted.[19] In this case, the predicted intital **1cc** to **1ct** ratio for a simultaneous mechanism can be obtained from eq 13, which relates the photostationary

$$\frac{[\mathbf{1cc}]_{\text{pss, sensit}}}{[\mathbf{1ct}]_{\text{pss, sensit}}} = \frac{k_{et,ct}}{k_{et,cc}} \times \frac{k_{cc}}{k_{ct}} \qquad (13)$$

state isomer ratio to ratios of the rate constants for collapse of a bridged intermediate and the rates of energy transfer (k_{et}) from benzophenone triplets to the cis,cis and cis,trans isomers. We have assumed the latter ratio to be unity based upon measurements of photostationary state isomer ratios from sensitized photolysis using various triplet energy sensitizers (see Experimental Section).[20] According to this estimate, k_{cc}/k_{ct} should be on the order of 0.67. The experimentally observed **1cc** to **1ct** ratios at low conversions in the benzophenone-sensitized runs vary from 0.00 to 0.19 in conversions from 4.0 to 54.0%.

These observations can be interpreted in terms of mech-

anism(s) for π-bond isomerization which do not pass through an intermediate resulting from C-2–C-4 carbon–carbon bridging. It seems likely that the different photochemical reactivity of di-π-silanes and their carbon analogs is due to the ability of silicon to destabilize the first bridged diradical intermediate along the reaction coordinate or the transition state, $12^{\ddagger}$, for a one-step process.

However, it may well be that photochemistry can offer an entry into the silacyclopropane ring system if we take into account the limitations which are apparent from the results presented in this paper. Studies aimed at obtaining more information for silicon containing π systems in which cis–trans isomerization is precluded are continuing.

Experimental Section

General. All NMR spectra were obtained on a Varian Associates Model HA-100 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane (internal). Ultraviolet spectra were obtained on a Beckman Acta III spectrophotometer in 1-cm matched quartz cells. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Gas chromatographic analyses were run using a Varian 940 GC with a flame ionization detector. All melting points are recorded uncorrected.

Bis(β-styryl)dimethylsilane (1). β-Bromostyrene (102.0 g, 0.56 mol; ca. 90% trans and 10% cis) was added over a 2-hr period to a suspension of magnesium turnings (15.0 g, 0.63 g-atom) in a solution of dimethyldichlorosilane (35.0 g, 0.27 mol) dissolved in 400 ml of tetrahydrofuran. After initiation, the temperature of the reaction was maintained between 0 and 15°. After the addition was complete, the reaction mixture was stirred for 2 hr at room temperature and poured into aqueous sodium bicarbonate. The ether layer was separated, dried over calcium chloride, and concentrated in vacuo, giving 88.0 g of crude material which was distilled. The fraction between 192 and 210° (8 mm) was found to contain a mixture of the three stereoisomers and a small amount of the coupling product, 1,4-diphenylbutadiene (37.7 g, 52.7% yield). This fraction was distilled carefully using a spinning band column to give fractions containing a mixture of cis,cis and cis,trans isomers along with 1,4-dipheylbutadiene, and pure trans,trans-bis(β-styryl)dimethylsilane [15.2 g, bp 124–125.5° (0.2 mm)]. Gas chromatographic analysis of this material indicated the absence of stereoisomeric impurities.

Anal. Calcd for $C_{18}H_{20}Si$: C, 81.75; H, 7.62. Found: C, 81.63; H, 7.85.

Bis(β-styryl)diphenylsilane (2). This compound was prepared by essentially the same procedure as described for **1** from β-styrylmagnesium bromide and diphenyldichlorosilane. The crude product was chromatographed on a silica gel column (Davison grade 920, 100–200 mesh) using hexane as eluent. The crystalline material obtained was recrystallized from hexane to yield a white, crystalline product (45.8% yield, mp 67–69°). The spectral data, recorded in Table I, indicate that the structure is *trans,trans*-bis(β-styryl)diphenylsilane (**2**).

Anal. Calcd for $C_{28}H_{24}Si$: mol wt, 388.165. Found (by high-resolution mass spectrum): mol wt, 388.164.

β-Styryltriphenylsilane (3). This material was prepared from triphenylchlorosilane and β-styrylmagnesium bromide by essentially the same method as described for **1**. The crude product was recrystallized from 9:1 ethanol–acetone to yield pure *trans*-β-styryltriphenylsilane (24.8% yield), mp 148.5–150.0° (lit.[7] mp 148–148.5°).

Preparative Photochemical Runs. Direct Irradiations of Bis(β-styryl)dimethylsilane (1). Preparative irradiations of pure *trans,trans*-bis(β-styryl)dimethylsilane (**1tt**) were carried out on degassed, nitrogen-purged solutions of cyclohexane or methanol (500 mg per 500 ml) in an apparatus consisting of a quartz, water-cooled, immersion well containing a Hanovia 450-W medium-pressure lamp and Corex glass filter. Irradiations for ca. 2 hr were sufficient to reach a photostationary state mixture of **1tt, 1ct** and **1cc**, the presence of which was detected by gas chromatographic analysis (7 ft × 0.125 in. column, 3% SE-30 on Anachrom ABS, 60/70, at 165°). The order of elution and the relative percentages of the three stereoisomers are as follows: **1cc,** 46.1%; **1ct,** 43.5%; and **1tt,** 10.4%. The spectral data for **1cc** and **1ct,** collected by preparative gas chromatography, are recorded in Table I.

Anal. (**1cc**). Calcd for $C_{18}H_{20}Si$: C, 81.75; H, 7.62; Si, 10.63. Found: C, 81.65; H, 7.86; Si, 10.45.

Table IV
Irradiations of 1tt in the Presence of 2,3-Dimethyl-1,3-butadiene

Irradiation time, min	Concn of 2,3-dimethyl-1,3-butadiene, *M*	% conversion	% 1ct	% 1cc
15	0.00	22.0	19.3	2.7
15	0.50	22.3	19.8	2.5
15	1.00	20.7	18.6	2.1
25	0.00	30.4	26.0	4.4
25	0.50	33.2	28.7	4.5
25	1.00	29.1	25.0	4.1
90	0.05	85.2	56.7	28.5
90	0.10	86.0	55.8	30.2
90	0.20	86.5	55.3	31.2

Table V
Triplet-Sensitized Irradiations of 1tt Using Various Triplet Energy Sensitizers

Triplet sensitizer	E_T, kcal/mol	Photostationary state compositions: % 1tt	% 1ct	% 1cc
Benzil	54	33.6	11.2	55.2
1-Acetonaphthone	59	19.9	28.3	51.8
Benzophenone	69	16.0	33.8	50.2
Acetone	76	18.7	30.4	50.9

Anal. (**1ct**). Calcd for $C_{18}H_{20}Si$: C, 81.75; H, 7.62; Si, 10.63. Found: C, 81.86; H, 7.47; Si, 10.88.

Sensitized Irradiations of 1tt. Sensitized irradiations were conducted using the apparatus previously described containing cyclohexane solutions (500 ml) of 1.00 g of **1tt** and 2.0 g of benzophenone, and using a uranium glass filter ($T > 320$ nm). The photostationary state mixture of the three stereoisomers, reached after 3.0 hr of irradiation, was found to be 88.8% **1cc,** 50.2% **1ct,** and 16.0% **1tt.**

Varying Conversion Runs. Direct Irradiation of 1tt. Irradiation of 128.1 mg (1.94×10^{-3} mol) of *trans,trans*-bis(β-styryl)dimethylsilane in 250 ml of degassed and nitrogen-purged spectrograde cyclohexane was conducted in the preparative apparatus previously described using a Pyrex glss filter ($T > 290$ nm). One-half milliliter aliquots were removed at varying time intervals during the irradiations through a septum-capped inlet port. Samples were stored in the dark until they were analyzed by gas chromatography using a 5 ft × 0.125 in., 1.5% OV-101 on 100/200 Varaport column at 150°. The peak areas were determined by the triangulation method and were then used to calculate the relative percentages of the three stereoisomers, **1cc, 1ct,** and **1tt.** The results of these measurements are tabulated in part in Table II and plotted in full in Figure 1.

Sensitized Irradiations of 1tt. Irradiation of a solution of 36.8 mg (5.56×10^{-4} mol) of **1tt** and 12.8 mg (2.8×10^{-4} mol) of benzophenone in 250 ml of degassed and nitrogen-purged Spectrograde cyclohexane was conducted in the preparative apparatus previously described, using a uranium glass filter. These conditions ensured that greater than 99% of the light was absorbed by benzophenone. Relative percentages of **1cc, 1ct,** and **1tt,** obtained by gas chromatographic analyses, of aliquots removed at varying time intervals during irradiation are tabulated in part in Table III and plotted in full in Figure 2.

Irradiations of 1tt in the Presence of 2,3-Dimethyl-1,3-butadiene. Irradiations were carried out in a "merry-go-round" apparatus with a Corex glass filter on degassed spectrograde cyclohexane solutions, 5.4×10^{-3} *M* in **1tt** and containing varying concentrations of 2,3-dimethyl-1,3-butadiene, in quartz glass test tubes. Three tubes, containing the three different quencher concentrations, were removed at varying time intervals during the irradiations. Analyses of these solutions were conducted to determine the percent conversion of **1tt** and the relative percentages of

the three stereoisomers. The results of this experiment are recorded in Table IV.

Photostationary State Compositions from Irradiations of 1tt with Various Triplet Sensitizers. Spectrograde cyclohexane solutions of *trans,trans*-bis(β-styryl)dimethylsilane (1.0×10^{-2} M) and the various triplet sensitizers (acetone, benzophenone, 1-acetonaphthone, and benzil), each 2.0×10^{-2} *M*, were placed individually in Pyrex test tubes and irradiated with Pyrex-filtered light until the photostationary states were obtained. Analyses of these solutions by gas chromatography yielded photostationary state isomer compositions tabulated in Table V.

Acknowledgment. Support of these studies by the Robert A. Welch Foundation is gratefully acknowledged. P.S.M. would like to thank the Environmental Quality Program at Texas A&M University for funds to purchase gas chromatographic equipment used in these studies.

Registry No.—**1tt**, 54366-27-7; **1ct**, 54366-28-8; **1cc**, 54366-29-9; **2**, 54366-30-2; **3**, 33105-34-9; *cis*-β-bromostyrene, 588-73-8; *trans*-β-bromostyrene, 588-72-7; dimethyldichlorosilane, 75-78-5; triphenylchlorosilane, 76-86-8.

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(2) S. S. Hixson, P. S. Mariano, and H. E. Zimmerman, *Chem. Rev.*, **73**, 531 (1973).
(3) (a) The oxadi-π-methane rearrangement of β,γ-unsaturated ketones and aldehydes to cyclopropyl ketones and aldehydes was first discussed mechanistically by Swenton[3b] and related to the carbon analog by Givens;[3c] (b) J. S. Swenton, *J. Chem. Educ.*, **46**, 217 (1969); (c) R. S. Givens and W. F. Oettle, *Chem. Commun.*, 1164 (1969).
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(6) The initial results of this study, reported at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 26–31, 1973, Abstracts, No. ORGN-153, were found to be in error owing to impurities present in the starting materials which presumably changed the product ratios.
(7) R. A. Benkeser and R. A. Hickner, *J. Am. Chem. Soc.*, **80**, 5298 (1958).
(8) It is very likely that the potential vinylsilacyclopropanes expected in these reactions will not survive the reaction conditions but will either rearrange to silacyclopentenes[9a,9b] or react with the alcoholic solvent to yield methyl allylsilyl ethers.[5,9a]
(9) (a) Y. Nakadaira, S. Kanouchi, and H. Sakurai, *J. Am. Chem. Soc.*, **96**, 5621 (1974); (b) Y.-N. Tang, G. P. Gennaro, and Y. Y. Su, ibid., **94**, 4355 (1972).
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(13) G. W. Griffin et al., *Tetrahedron Lett.*, 2951 (1965).
(14) The evidence accumulated to date indicates that the di-π-methane reaction in the singlet excited manifold is most probably a concerted process.[15a,b] However, the effect of central[15c] and terminal[15d] carbon atom substitution indicates that stabilization of diradicaloids along the reaction coordinate is influential in determining the efficiency of the process.
(15) (a) P. S. Mariano and J. K. . Ko, *J. Am. Chem. Soc.*, **95**, 8670 (1973); (b) H. E. Zimmerman et al., ibid., **96**, 1459 (1974); (c) H. E. Zimmerman et al., ibid., **95**, 2155, 2157 (1973); (d) H. E. Zimmerman and A. A. Baum, ibid., **93**, 3646 (1971).
(16) P. S. Skell and E. J. Goldstein, *J. Am. Chem. Soc.*, **86**, 1442 (1964).
(17) The lower limit of our detectability of **1tt** is ca. 0.1% and thus **1cc/1ct** ratios of less than 0.01 could not be measured.
(18) The relative integrated extinction coefficients of **1cc** and **1ct** were calculated from considerations of the relative absorption spectra of the two isomers along with the wavelength dependencies of the lamp output and Pyrex glass filter transmittance.
(19) The possibility does exist that the triplet excited state of **1tt** is responsible for π-bond isomerization in both the direct and sensitized irradiations. The quenching studies using 2,3-dimethyl-1,3-butadiene can be interpreted in terms of a direct irradiation singlet process or a fast unquenchable triplet process.
(20) The triplet energies of the three stereoisomers of **1** should all fall in the range of 62 kcal/mol, like that of styrene. Thus, triplet energy transfer from benzophenone (69 kcal/mol) to all three should be highly exothermic and should occur at the diffusion-controlled rates.[21] The constancy of the photostationary state isomer compositions when changing from acetone (76 kcal/mol) sensitization to benzophenone to 1-acetonaphthone (59 kcal/mol) sensitization indicates the correctness of the assumption that $k_{et,cc} \approx k_{et,ct}$ in the benzophenone-sensitized irradiation.[22]
(21) K. Sandros and H. Backstrom, *Acta Chem. Scand.*, **12**, 3 (1958).
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Photochemical Ring-Opening Reactions of Substituted Chromenes and Isochromenes[1]

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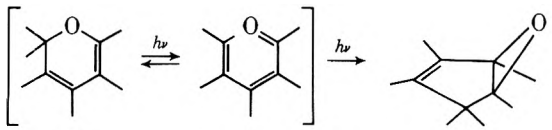
Irradiation of a number of substituted chromenes in methanol give products derived from an *o*-quinoneallide intermediate. The fate of the *o*-quinoneallide depends on the experimental conditions. The primary mode of reaction corresponds to 1,4 and 1,6 addition of methanol across the C–C double bonds of the *o*-quinoneallide intermediate. In nonreactive solvents, the *o*-quinoneallide undergoes a 1,7-sigmatropic hydrogen shift. Irradiation of several substituted isochromenes, on the other hand, give indene epoxides which produce ring-opened hydroxy ethers on further irradiation. The mechanism involves opening of the isochromene ring to give an *o*-quinoidal intermediate which undergoes a subsequent intramolecular [4 + 2] cycloaddition reaction. A similar path occurs with 4-phenylisothiochromene, except that in this case the initially formed indene episulfide loses sulfur on further irradiation to give a substituted indene.

Light-induced transformations of cyclic dienes have been the subject of recent intensive study.[2,3] Derivatives of 1,3-cyclohexadiene, for example, have been transformed into a vast array of photoproducts via ring-opening processes,[4–12] valence-bond tautomerization reactions,[13–15] bond-switching mechanisms,[16–22] and dimerization pathways.[23,24] Despite the fact that photochemical isomerizations of cyclic dienes have been well documented, investigation of suitable heterocyclic analogs in light-induced reactions has been somewhat limited.[25] With a desire to discover new photochemical pathways of appropriate heterocyclic dienes, we have examined the photochemical behavior of several substituted chromenes and isochromenes.[26] A number of investigators had previously observed that a ring–chain tautomerization could be established between substituted cis dienones **1** and 2*H*-pyrans **2**.[27–29] Transformations of this type are known to be responsible for the photochromism encountered on irradiation of 2*H*-chromenes[30,31] and *o*-vinylphenones.[32] Extended irradiation of the photoequilibrated dienone–pyran mixture might be expected to afford an oxabicyclo[3.1.0]hex-2-ene (**3**) as the ultimate photoproduct. This transformation would be



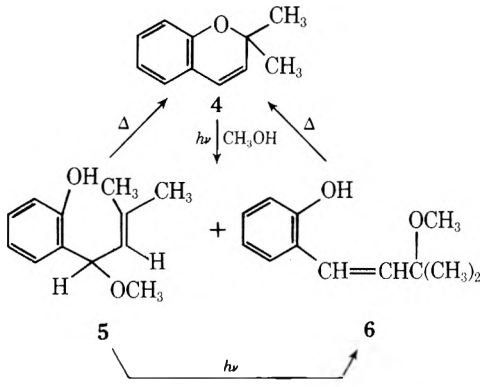
2 1 3

closely analogous to the photo-Diels–Alder reaction encountered with 1,3,5-hexatrienes.[33] Although rearrangements of this type have been reported for nitrogen analogs of cyclohexadienes,[34] no structurally related oxycyclic diene has been shown to undergo a photoreaction of this type.

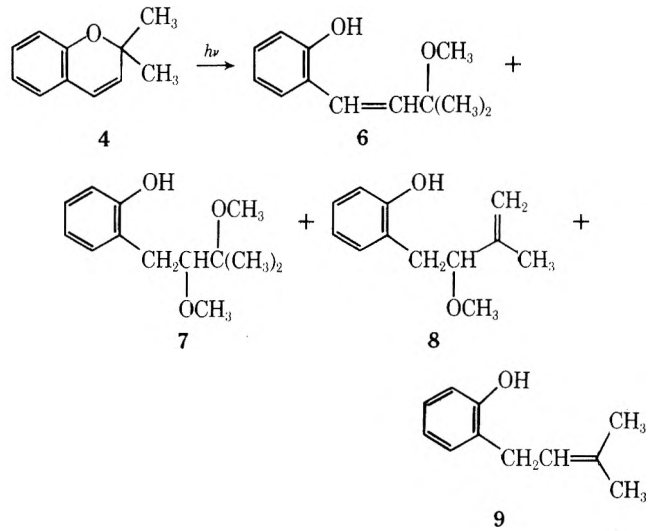
The present paper describes the photochemical ring opening reaction of a number of substituted chromenes and isochromenes to give *o*-quinoidal intermediates. The fate of the *o*-quinoidal intermediate was found to depend on the nature of the substituent groups as well as the photolysis conditions. The primary mode of reaction of the intermediate generated from the 2*H*-chromene system involves 1,4 or 1,6 addition of alcohol across the reactive double bonds. In the isochromene system, however, the initially generated o-quinoidal intermediate undergoes a subsequent intramolecular [4 + 2] cycloaddition reaction to give an oxabenzobicyclo[3.1.0]hexene as the final photoproduct.

Results and Discussion

Irradiation of 2,2-dimethylchromene (**4**) in methanol through Pyrex using a 550-W Hanovia lamp gave two major products whose relative yields varied as a function of exposure duration. When a 0.018 *M* solution of **4** was irradiated for 5 hr, approximately 50% of starting material was consumed and the two products, isolated by preparative thick layer chromatography, were shown to be methanol adducts **5** and **6**. The identification of the photoproducts was based

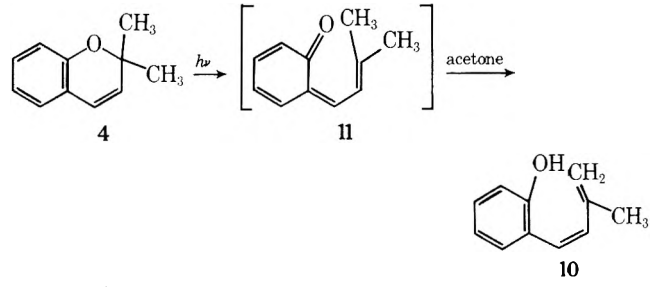


on their characteristic spectral data (see Experimental Section). Both adducts were found to revert to starting material on standing in the dark. This thermal reversion is analogous to some recent reactions reported by Schmid and coworkers,[35] who found that the thermolysis of a number of (o-hydroxyaryl)-2-propen-1-ols produced 2*H*-chromenes by 1,4 elimination of water followed by thermal cyclization of the initially generated *o*-quinone methide intermediates. Further irradiation of the above solution for an additional 6 hr gave a mixture containing mainly **6** along with trace amounts of **5**. This observation suggests that at least part of **6** is formed from a secondary photoisomerization of **5**. When the irradiation of 2,2-dimethylchromene (**4**) was carried out in methanol using a Corex filter for 3 hr, a mixture of four products was obtained. In addition to adduct **6**, 2,3-dimethoxy-2-methyl-4-(*o*-hydroxyphenyl)butane (**7**, 19%), 2-methyl-3-methoxy-4-(*o*-hydroxyphenyl)but-1-ene (**8**, 8%), and 2-methyl-4-(*o*-hydroxyphenyl)but-2-ene (**9**, 17%) were isolated from the crude photolysate. These products were identified by their characteristic spectral properties (see Experimental Section). Photoadduct **7** was shown



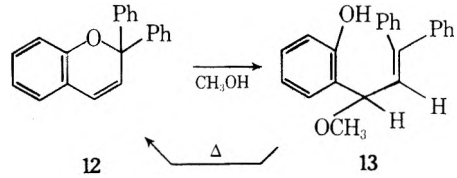
to be a secondary product resulting from further irradiation of the ether **6**. Interestingly, this compound corresponds to the anti-Markovnikov addition of methanol across the C–C double bond of **6**. Hixson had previously reported on the anti-Markovnikov photochemical addition of methanol to acyclic aryl olefins.[36] His observations provide reasonable chemical analogy for the above addition. Methoxy ether **8** was shown to be a secondary product derived from an acid-catalyzed elimination of methanol from **7**.

In contrast to the complex behavior encountered with the direct irradiation of **4**, the acetone-sensitized photolysis gave 2-methyl-4-(*o*-hydroxyphenyl)-1,3-butadiene (**10**) as the exclusive photoproduct: NMR δ 1.86 (s, 3 H), 4.86 (m, 2 H), 5.30 (s, 1 H), and 6.4–7.2 (m, 6 H). Irradiation of **4** in benzene both with and without benzophenone sensitization likewise produced **10**.



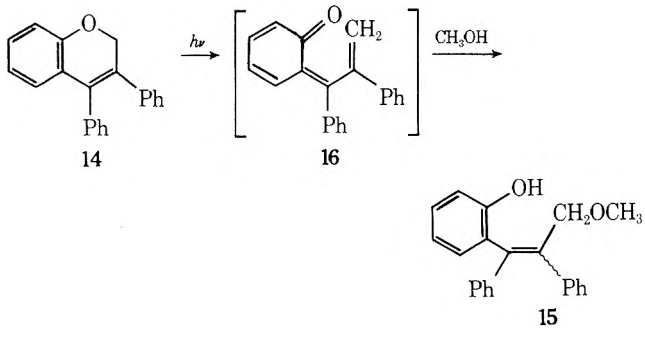
The observed results are best rationalized in terms of a photochemical ring opening of **4** to give an o-quinoneallide intermediate (**11**).[30] The fate of **11** depends on the experimental conditions. The primary mode of reaction (i.e., formation of **5** and **6**) corresponds to 1,4 and 1,6 addition of methanol across the C–C double bonds of **11**. Allyl phenol **9** is apparently formed by 1,4 photoreduction of **11** (Corex filter). Similar photoreductions of o-quinoneallide intermediates have been observed by Becker and Kolc[30] and provides reasonable chemical analogy. In nonreactive solvents such as acetone (or benzene), the primary reaction path corresponds to a 1,7-sigmatropic hydrogen shift.

We have also examined the photobehavior of the related 2,2-diphenylchromene system **12**. Unlike the complex photochemistry observed with **4**, in which a plethora of products is obtained, the photochemistry of **12** was relatively simple. Irradiation of **12** in methanol gave a single photoad-



duct **13** which was unstable at room temperature and slowly reverted to starting material when left in the dark. The identity of **13** was established from its characteristic spectral properties (see Experimental Section). Irradiation of **12** in benzene (Pyrex) produced a deep red color which slowly disappeared upon sitting in the dark at room temperature. NMR analysis of the photolysate after removal of the solvent indicated that only starting chromene **12** was present. Attempts to trap the red-colored species with methanol in the dark failed. We can only suggest that thermal reversion of the labile *o*-quinoneallide intermediate is more rapid than 1,4 addition of methanol.

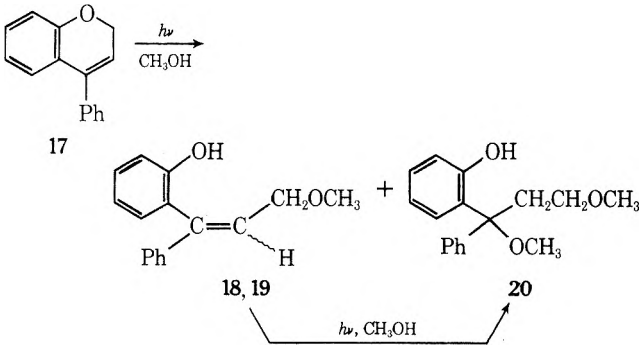
The photochemistry of the related 3,4-diphenylchromene (**14**) was also examined. Irradiation of **14** in methanol with Corex-filtered light gave a single photoadduct. Based on its spectral data, this compound has been identified as the 1,6-methanol adduct **15.** Here again, simple addition of



14 16 15

methanol to the intermediate *o*-quinoneallide **16** best rationalizes the observed result.

The photochemical ring opening reaction of 4-phenylchromene (**17**) was also studied. Irradiation of **17** in methanol with Corex-filtered light gave a mixture of three photoproducts. On the basis of their spectral properties (see Experimental Section) these compounds were identified as *cis*- and *trans*-1-phenyl-1-(*o*-hydroxyphenyl)-3-methoxy-1-propene (**18** and **19**) and 1-phenyl-1-(o-hydroxyphenyl)-1,3-dimethoxypropane (**20**). Photoadduct **20** was shown to be a secondary photoproduct derived from further irradiation of **18** or **19.** The products isolated in this case can also

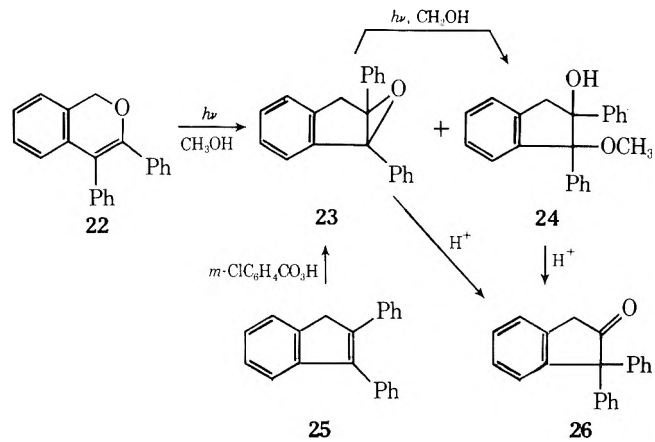


17 18, 19 20

be accommodated in terms of 1,6 addition of methanol to the initially formed *o*-quinoneallide intermediate.

All of the aforementioned reactions of the 2*H*-chromene system conform to the same pattern. Electronic excitation results in a photochemical ring opening to give an *o*-quinoneallide intermediate. Our results, as well as those of other investigators,[30,37-40] indicate that the initially produced *o*-quinoneallide intermediates are rapidly attacked by alcoholic solvents. The distinction between 1,4- and 1,6-methanol addition may well represent a measure of the steric hindrance to attack at the 4 or 6 position of the *o*-quinoneallide intermediate. In no case was evidence found to suggest the involvement of an oxabicyclo[3.1.0]hexene intermediate. This set of affairs differs markedly with the results we have obtained with the corresponding isochromene system. Electronic excitation of this ring system was found to result in a smooth rearrangement giving indene epoxides as the major photoproducts.

Irradiation of 3,4-diphenylisochromene (**22**) in methanol through Pyrex using a 450-W Hanovia lamp gave two major products whose relative yields varied with the time of irradiation. When a 0.003 *M* solution of **22** was irradiated for 8 hr, ca. 50% of starting material was consumed and the two products, isolated by preparative thick layer chromatography, were shown to be 2,3-epoxy-2,3-diphenylindan (**23**), mp 89–90° (80%) and 2-hydroxy-3-methoxy-2,3-diphenylindan (**24,** 20%). The products were identified by their

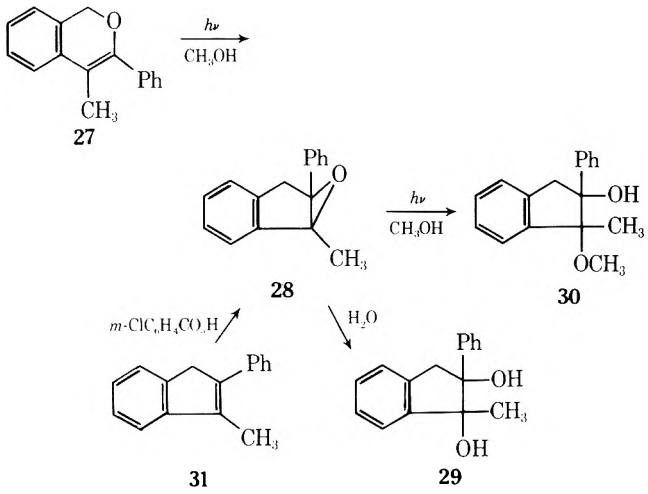


22 23 24 25 26

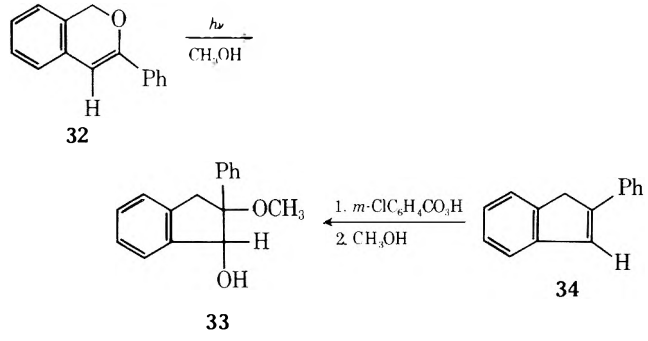
spectral data [NMR (**23**) τ 5.44 (broad s, 2 H) and 2.2–3.2 (m, 14 H); (**24**) τ 5.82 (s, 3 H), 5.35 (s, 2 H), 5.50 (s, 1 H, exchanged with D_2O), and 2.40–3.30 (m, 14 H)] and by comparison with authentic samples which were independently prepared by the peracid epoxidation of 2,3-diphenylindene (**25**). Treatment of **23** and/or **24** with a grain of *p*-toluenesulfonic acid in chloroform resulted in their quantitative rearrangement to 1,1-diphenyl-2-indanone (**26**). Irradiation of the solution for an additional 8 hr gave a mixture containing mainly **24** with traces of **23,** suggesting that **24** is formed in a secondary photoreaction of **23.** This was independently verified by irradiating a pure sample of **23** in methanol and obtaining a quantitative yield of the ring-opened product **24.** Although it is conceivable that the formation of **24** from **23** is an ionic reaction promoted by an acidic by-product formed adventitiously, this appears not to be the case. Photochemical oxidation of methanol to formic acid which then promotes an acid-catalyzed reaction has been reported in the literature[41] and merits consideration. This possibility, however, was eliminated by the finding that epoxide **23** is quantitatively converted into 1,1-diphenyl-2-indanone (**26**) on treatment with acidic methanol. The absence of **26** in the direct irradiation of **22** eliminates this ionic path. Also, the presence of sodium carbonate in the reaction mixture did not inhibit the formation of **24** from **23.** We conclude, therefore, that the ring-opening reaction of **23** is a photochemical process and not an acid-catalyzed reaction. There have been several cases reported in the literature where oxiranes have been noted to undergo photoaddition with protic solvents.[42-45] Tokumara and coworkers, for example, have reported that phenyloxirane undergoes photoaddition when 2-propanol, a substrate which is not readily oxidized to "acidic matter", is used as the solvent.[42] It would appear therefore, that epoxyindan **23** is another example of an epoxide which undergoes a bona fide photochemical ring-opening reaction.

A similar set of reactions was observed with 3-phenyl-4-methylisochromene (**27**). Irradiation of **27** in methanol

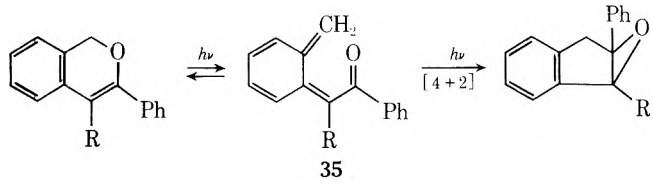
through Pyrex with a 450-W Hanovia lamp gave 2,3-epoxy-2-phenyl-3-methylindan (**28**) [NMR (CCl_4) δ 1.50 (s, 3 H), 3.40 (s, 2 H), and 6.9–7.7 (m, 9 H)] as the major photoproduct. Purification of epoxide **28** was not possible owing to the extreme ease with which it was converted into *trans*-2,3-dihydroxy-2-phenyl-3-methylindan (**29**). Further irradiation of **28** in methanol gave the ring-opened hydroxyalcohol **30** in high yield. All of these compounds were identified by comparison with authentic samples which were independently prepared by the epoxidation of 2-phenyl-3-methylindene (**31**).



The photochemical rearrangement of 3-phenylisochromene (**32**) was also examined. Irradiation of **32** in methanol for 20 hr with Pyrex-filtered light gave a single photoproduct, mp 103–105°. On the basis of its spectral data, this compound has been identified as *trans*-2-methoxy-3-hydroxy-2-phenylindan (**33**). This assignment was verified by comparison with an authentic sample prepared by treating the epoxide obtained from the peracid oxidation of 2-phenylindene (**34**) with methanol. In this case, the initially formed epoxide was converted to the ring-opened product **33** during the course of the irradiation.



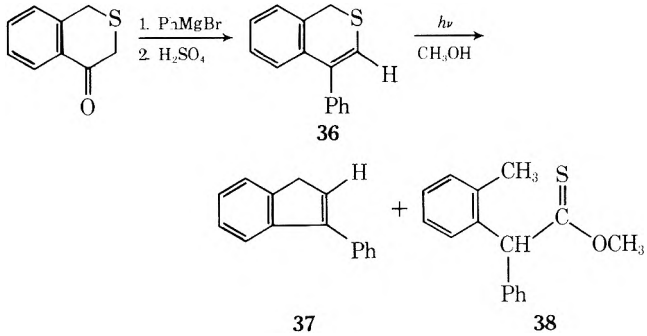
The formation of the indene epoxides is best explained by a photochemical ring opening of the isochromene ring to give an *o*-quinonoidal intermediate **35**, which can either revert to starting material or undergo a subsequent intramolecular [4 + 2] photocycloaddition reaction. The above reactions appear to proceed from the singlet state, since the photolyses could not be sensitized or quenched with standard triplet quenchers. The low quantum efficiences observed (i.e., $\Phi_{22} = 0.02$, $\Phi_{27} = 0.002$, $\Phi_{32} = 0.004$) are fully compatible with a two-photon process, in which the initially produced *o*-quinonoidal intermediate **35** partitions itself between starting material and product. It should be pointed out, however, that the low quantum efficiencies do not in any way require a two-photon process.



As was pointed out earlier, irradiation of the 2*H*-chromene ring produces an *o*-quinoneallide intermediate which does not undergo an intramolecular [4 + 2] cycloaddition, but rather is attacked by methanol to give a phenolic ether. Irradiation of the closely related isochromene system, on the other hand, results in the formation of an indene epoxide. The two systems behave similarly during the first phase of the photolysis. Both systems undergo an initial photochemical ring-opening reaction to produce an *o*-quinoidal intermediate. The difference in behavior of the two systems may be related to the difference in reactivity of the *o*-quinoidal intermediates. Michael addition of methanol to the labile *o*-quinoneallide obtained from the 2*H*-chromene system would be expected to occur quite readily. This facile conjugate addition destroys the necessary chromophore for the subsequent [4 + 2] photocycloaddition reaction. Attack by methanol on the *o*-quinoidal intermediate obtained from the isochromene system is not as rapid, and consequently this species is long enough lived to absorb another photon of light and undergo an intramolecular photocycloaddition reaction. An alternate explanation which could also rationalize the difference in the photochemical behavior of the two systems is based on conformational control of reactivity. The [4 + 2] photochemical cycloaddition in the hexatriene system has been shown to be derived from the s-trans,s-cis conformation.[3] It is perfectly possible to rationalize the difference between chromene and isochromene as being due to conformational preferences in the open, ketonic form.

Another point which is worthy of mention is a report by Griffin and coworkers on the photoisomerization of indene oxide into isochromene.[46] Although this transformation formally corresponds to the reverse reaction of that described above, the rearrangement has been proposed to proceed by a different path involving initial fission of the C–C bond of the oxirane ring followed by a hydrogen shift.[47] It should be kept in mind that the isochromene indene oxide photoreactions do not have the same two species in equilibrium and consequently microscopic reversibility would not be expected to apply.[48]

Although the photochemistry of 1,2-dihydronaphthalene[49,50] and its hetero analogs[34,51–54] has received some attention, relatively little is known about the photochemical behavior of heterocyclic systems isoelectronic with the isochromene ring. We therefore turned our attention to the related isothiochromene system in order to make a comparison with the photochemistry of the above isochromenes. In the present instance, the photochemical behavior of 4-phenylisothiochromene (**36**) was examined. This compound

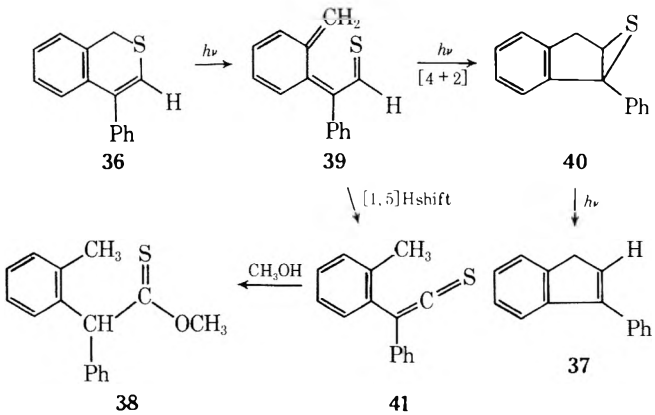


was synthesized from isothiochroman-4-one by phenyl Grignard addition followed by dehydration. The structure of

36 was elucidated on the basis of the physical and chemical data: NMR ($CDCl_3$) δ 3.86 (s, 2 H), 6.50 (s, 1 H), and 6.9–7.4 (m, 9 H); uv 325 and 243 nm (ϵ 2800 and 7900).

Irradiation of **36** in dilute methanol solution using a 450-W Hanovia mercury arc with a Pyrex filter gave a mixture of two compounds. Preparative thick layer chromatography of the crude photolysate permitted the purification and isolation of the two components. The products were identified as 3-phenylindene (**37**) and methyl phenyl (o-tolyl)thionoacetate (**38**). In addition, a significant quantity of elemental sulfur was isolated from the thick layer plate. The major component, **37** (51%), was identified by comparison with an authentic sample.[55] The minor product (6%) was assigned structure **38** on the basis of its spectral data: ir (CCl_4) 8.14 and 8.40 μ (S=$COCH_3$);[56] NMR ($CDCl_3$) δ 2.22 (s, 3 H), 4.03 (s, 3 H), 5.64 (s, 1 H), and 6.9–7.4 (m, 9 H); MS *m/e* 256, 224, 181 (base), 169, 165, and 161.

The products formed by photolysis of **36** with Pyrex-filtered light are consistent with a photochemical ring opening of **36** to give an *o*-quinoidal intermediate (**39**). This transient species undergoes a subsequent [4 + 2] intramolecular photocycloaddition to give episulfide **40** which loses sulfur on further irradiation. The photochemical extrusion of sulfur from episulfides is a well-known photoreaction[57] and provides reasonable analogy for the final step. The formation of **38** from **36** probably proceeds via a [1,5] hydrogen transfer from **39** to give **41**, which is subsequently attacked by methanol.



The major photoreaction obtained with 4-phenylisothiochromene is quite similar to that encountered with the closely related isochromene system. These reactions may be visualized as being analogous to the photochemical transformation of 1,2-dihydronaphthalenes into benzobicyclo[3.1.0]hexenes.[49,50]

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a Jeol MH-100 spectrometer.

2,2-Dimethylchromene (4) was prepared in 66% yield by the method of Shriner and Sharp[58] as a clear oil: bp 64° (1.5 mm) [lit.[58] bp 79–80° (2.5 mm)]; NMR (CCl_4) δ 1.35 (s, 6 H), 5.38 (d, 1 H, J = 10 Hz), 6.13 (d, 1 H, J = 10 Hz), and 6.5–7.0 (m, 4 H); ir (neat) 3.33, 6.07, 6.20, 6.71, 6.85, 7.26, 7.83, 7.90, 8.20, 8.90, 9.68, 10.37, 12.90, 13.45, and 14.05 μ; uv (methanol) 308, 273, and 264 nm (ϵ 2650, 3100, and 3920).

2,2-Diphenylchromene (12) was prepared in 67% yield by the method of Cottam et al.[59] as a white solid: mp 92–93° (lit.[58] mp 93–94°); NMR (CCl_4) δ 6.11 (d, 1 H, J = 10.5 Hz), 6.66 (d, 1 H, J = 10.5 Hz), 6.80–7.7 (m, 14 H); ir (KBr) 3.23, 6.04, 6.17, 6.68 μ; uv (acetonitrile) 307, 275, 265, 260, 255, and 248 nm (ϵ 3000, 4790, 6150, 5960, 5410, and 4980); MS *m/e* 284 (M^+), 207 (base), 178, 91, and 77.

3,4-Diphenylchromene (14) was prepared by adding 4-phenyl-3-chromanone (0.86 g)[60] in 30 ml of ether to a Grignard reagent prepared from 0.624 g of bromobenzene and 0.1 g of magnesium turnings in 20 ml of ether. The mixture was heated at reflux for 3 hr and then decomposed with 20% aqueous ammonium chloride. The solution was extracted with ether and the ethereal extracts were dried over magnesium sulfate. Removal of the solvent left 1.09 g of a yellow oil which was immediately taken up in 20 ml of pyridine. Phosphorus oxychloride (3.0 ml) was added to the above solution, which was then allowed to reflux for 3 hr. The solution was cooled and the excess phosphorus oxychloride was decomposed by the addition of water. The mixture was extracted with ether, and the ether layer was washed with 10% aqueous hydrochloric acid, dried, and concentrated under reduced pressure to leave behind an oily residue. Chromatography of the oil on an alumina column with benzene as the eluent gave 3,4-diphenylchromene (**14**) as a crystalline solid: mp 133–134° (lit.[60] mp 134°); NMR (CCl_4) δ 5.12 (s, 2 H) and 6.8–7.5 (m, 14 H).

4-Phenylchromene (17) was prepared by adding an excess of lithium aluminum hydride to a solution containing 450 mg of 4-phenyl-3-chromanone[60] in 25 ml of anhydrous ether. The resulting gray suspension was stirred at room temperature for 6 hr. The excess lithium aluminum hydride was destroyed by the addition of 2 ml of water and the inorganic salts were removed by filtration. The ether layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue obtained was immediately dehydrated according to the procedure of Dauben and Boswell.[61] The above alcohol was dissolved in 15 ml of pyridine and the solution was cooled to 0°. To this cooled solution was added 5 ml of phosphorous oxychloride. The solution was allowed to warm to room temperature and was stirred for an additional 2 hr. At the end of this time, water was carefully added to the red solution. The solution was extracted with ether and the combined ether layers were washed with 10% aqueous hydrochloric acid, followed by water, and then dried over magnesium sulfate. Removal of the solvent left 360 mg of 4-phenylchromene as a clear oil: NMR (CCl_4) δ 4.68 (d, 2 H, J = 4.0 Hz), 5.58 (t, 1 H, J = 4.0 Hz), and 6.58–7.24 (m, 9 H).[35]

3,4-Diphenylisochromene (22). A 2.5-g sample of 3-phenylisochromanone was added at 0° to a Grignard solution prepared by treating 500 mg of magnesium turnings with 2.5 g of bromobenzene in 15 ml of anhydrous ether. The mixture was stirred at room temperature for 1 hr and was then heated at reflux for an additional 2 hr. After cooling, the mixture was poured onto 5 ml of concentrated sulfuric acid suspended on crushed ice. The mixture was then extracted with ether and the ethereal extracts were washed with water, followed by a sodium bicarbonate solution (10%), then dried over magnesium sulfate and concentrated under reduced pressure to an amber oil. The oil was dissolved in 10 ml of glacial acetic acid which contained 10 drops of water. To this mixture was added 1 ml of concentrated sulfuric acid. The dark brown mixture was kept at 75° for 10 min and was then poured onto ice and extracted with ether. The ethereal extracts were washed several times with water, followed by a saturated sodium chloride solution. The solution was dried over magnesium sulfate and concentrated under reduced pressure to give 3.2 g of a dark oil. The oil was chromatographed on 300 g of silica gel using 5% ether in cyclohexane as the eluent. Removal of the solvent left 1.48 g (45%) of 3,4-diphenylisochromene: mp 92–94°; ir (KBr) 6.22, 6.75, 8.07, 9.20, 10.65, 13.12, 14.22, and 14.46 μ; uv (methanol) 316 nm (ϵ 12,250) and 232 (12,900); NMR ($CDCl_3$) τ 4.78 (s, 2 H) and 2.2–3.4 (m, 14 H).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.50; H, 5.90.

3-Phenyl-4-methylisochromene (27). A solution containing 500 mg of 3-phenylisochromanone in 10 ml of anhydrous ether was added to a Grignard solution prepared by treating 270 mg of magnesium turnings with 1.6 g of methyl iodide in 40 ml of anhydrous ether. The mixture was allowed to stir at room temperature for 8 hr and the excess Grignard reagent was decomposed with 10% sulfuric acid. The mixture was extracted with ether and the organic layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow oil which proved to be a mixture of isomeric alcohols: NMR ($CDCl_3$) δ 1.15 (s), 1.37 (s), 2.41, (s, OH), 4.50 (s), 4.90 (s), and 6.8–7.8 (m, 9 H); ir (neat) 2.90, 3.34, 6.68, 6.90, 7.30, 8.20 μ. The mixture of alcohols was subsequently dehydrated by stirring the mixture with 30 ml of 10% sulfuric acid in acetic acid for 2 min. Addition of water to the above solution followed by extraction with ether gave 250 mg

(50%) of 3-phenyl-4-methylisochromene, mp 84–85°, upon removal of the solvent. The structure of this material was assigned on the basis of its analytical and physical properties: ir (KBr) 6.15, 6.25, 6.75, 6.91, 7.30, 8.09, 8.28, 9.05, and 9.30 μ; NMR ($CDCl_3$) δ 2.13 (s, 3 H), 5.12 (s, 2 H), and 7.0–7.7 (m, 9 H); MS *m/e* 222 (M^+), 207, 193, 179 (base), 115, 105, 91, and 77; uv (methanol) 310 and 232 nm (ε 14,900 and 15,700).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.39; H, 6.44.

3-Phenylisochromene (32). To a solution containing 400 mg of 3-phenylisochromanone in 20 ml of methanol was added 100 mg of sodium borohydride. After stirring at room temperature for 90 min, the methanol was removed under reduced pressure. Ether was then added to the residue and the organic phase was washed with water, then dried over magnesium sulfate and concentrated under reduced pressure to give 360 mg of a white solid (89%): mp 95–110°; NMR ($CDCl_3$) δ 2.0 (s, OH), 4.3–5.0 (m, 4 H), and 6.9–7.6 (m, 9 H); ir (KBr) 2.90, 6.72, 6.90, 7.32, 9.14, 9.42 μ. The impure alcohol was dehyrated without further purification using 450 mg of Burgess reagent[62] in refluxing benzene for 30 min. The mixture was diluted with ether, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a crude solid which was recrystallized from 95% ethanol to give 280 mg (75%) of 3-phenylisochromene (**32**) as a white solid: mp 122–124°; NMR ($CDCl_3$) δ 5.17 (s, 2 H), 6.41 (s, 1 H), 6.8–7.8 (m, 9 H); ir (KBr) 6.18, 6.74, 6.90, 7.21, 7.84, 8.31, and 9.42 μ; uv (methanol) 323 and 235 nm (ε 14,700 and 14,600); MS *m/e* 208 (M^+), 181, 179 (base), 165, 152, 105, and 77.

Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.28; H, 5.82.

Irradiation of 2,2-Dimethylchromene. A solution containing 442 mg of 2,2-dimethylchromene in 160 ml of methanol was irradiated under an argon atmosphere with a 450-W Hanovia lamp equipped with a Pyrex filter for 3 hr. Removal of the solvent under reduced pressure left a crude oil which was subjected to thick layer chromatography. In addition to recovered starting material (43%), two new compounds were obtained as clear oils. The major component (15%) was assigned as 4-methoxy-4-(2-hydroxyphenyl)-2-methylbut-2-ene (**5**): NMR (CCl_4) δ 1.64 (s, 6 H), 3.20 (s, 3 H), 4.87 (d, 1 H, J = 9.0 Hz), 5.24 (d, 1 H, J = 9.0 Hz), and 6.4–7.0 (m, 5 H). The minor component (7%) was assigned as 3-methoxy-3-methyl-1-(2-hydroxyphenyl)but-1-ene (**6**): NMR (CCl_4) δ 1.20 (s, 6 H), 3.10 (s, 3 H), 5.64 (d, 1 H, J = 13.0 Hz), 6.28 (d, 1 H, J = 13.0 Hz), 6.54–7.16 (m, 4 H), and 7.30 (s, 1 H); ir (CCl_4) 3.05, 3.38, 6.35, 6.73, 6.90, 7.28, 7.32, 7.80, 8.18, 8.70, 9.28, 9.48, 10.62, 11.20, 11.85, and 14.02 μ; MS *m/e* 178, 160, 145 (base), 115, 91, and 77. Continued irradiation of the reaction mixture gave **6** as the major photoproduct with only traces of **5**, suggesting that at least part of **6** is formed from the secondary photoisomerization of **5**. Both methanol adducts slowly reverted to starting material **4** when left in the dark. In contrast to the complex behavior obtained from the direct irradiation of 2,2-dimethylchromene, the xanthone-sensitized photolysis cleanly gave the terminal ether **6** in high yield. Irradiation of a solution containing 397 mg of 2,2-dimethylchromene and 202 mg of xanthone in 160 ml of methanol with a 450-W Hanovia lamp equipped with a Pyrex filter for 3 hr gave 360 mg of terminal ether **6** on removal of the solvent. A small amount (35 mg) of unreacted chromene was also present.

Irradiation of 2,2-dimethylchromene in neat acetone gave 3-methyl-1-(2-hydroxyphenyl)buta-1,3-diene (**10**) as the only photoproduct. A solution containing 410 mg of 2,2-dimethylchromene in 200 ml of acetone was irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter for 2 hr. Removal of the solvent left a yellow oil which was chromatographed on a thick layer plate using methylene chloride as the eluent. In addition to unreacted starting material (206 mg) the only other product obtained was 80 mg of a clear oil whose structure is assigned as 3-methyl-1-(2-hydroxyphenyl)buta-1,3-diene (20%): NMR (CCl_4) δ 1.88 (s, 3 H), 4.90 (m, 2 H), 5.30 (broad s, 1 H), 6.44–7.30 (m, 6 H); MS *m/e* 161, 145 (base), 127, 115, 91, and 77.

Irradiation of 200 mg of **4** in 150 ml of methanol for 3 hr using a 450-W Hanovia lamp equipped with a Corex filter followed by removal of the solvent under reduced pressure gave a pale yellow residue. This material was subjected to thick layer chromatography and four products were obtained. The component present in the smallest quantity (4%) was identified as photoadduct **6** by comparison of its spectral properties with those of 3-methoxy-3-methyl-1-(2-hydroxyphenyl)but-1-ene (**6**). The major component isolated from the thick layer plate was identified as 2,3-dimethoxy-2-methyl-4-(*o*-hydroxyphenyl)butane (**7**, 19%): NMR ($CDCl_3$) δ 1.08 (s, 3 H), 1.21 (s, 3 H), 1.6–2.2 (m, 2 H), 3.11 (s, 3 H), 3.25 (s, 3 H), 4.40 (dd, 1 H, J = 7.3 and 3.3 Hz), 6.5–7.2 (m, 4 H), and 7.37 (s, 1 H). The next major fraction collected from the thick layer plate was identified as 2-methyl-4-(*o*-hydroxyphenyl)but-2-ene (**9**, 17%) on the basis of its NMR spectrum ($CDCl_3$): δ 1.69 (s, 6 H), 3.17 (d, 2 H, J = 8.0 Hz), 4.53 (s, 1 H), 5.12 (t, 1 H, J = 8.0 Hz), and 6.4–6.9 (m, 4 H). The remaining material isolated from the plate was identified as 2-methyl-3-methoxy-4-(*o*-hydroxyphenyl)but-1-ene (**8**, 8%): NMR ($CDCl_3$) δ 1.66 (s, 3 H), 2.30 (dd, 1 H, J = 15 and 8.0 Hz), 2.60 (dd, 1 H, J = 15 and 8.0 Hz), 3.33 (s, 3 H), 4.26 (t, 1 H, J = 8.0 Hz), 4.64 (d, 2 H), 6.5–7.2 (m, 4 H), and 7.20 (s, 1 H).

Irradiation of 2,2-Diphenylchromene in Methanol. A solution containing 228 mg of 2,2-diphenylchromene in 170 ml of methanol was irradiated under an argon atmosphere using a 450-W Hanovia lamp equipped with a Pyrex filter for 2 hr. Removal of the solvent left a yellow oil which was purified by thick layer chromatography. The major band contained 207 mg of a clear oil whose structure was assigned as 3-methoxy-3-(2-hydroxyphenyl)-1,1-diphenylpropene (**13**) on the basis of its characteristic spectra: ir (CCl_4) 2.97, 3.30, 6.32, 6.74, 6.94, 7.33, 8.10, 9.05, 9.40, 10.51, 10.69, 11.01, and 14.40 μ; NMR (CCl_4) δ 3.20 (s, 3 H), 4.72 (d, 1 H, J = 8.0 Hz), 6.12 (d, 1 H, J = 8.0 Hz), 6.4–7.4 (m, 14 H), and 7.64 (broad s, 1 H); MS *m/e* 316, 298, 296, 284, 207 (base), 178, 121, 119, 117, 83, and 77. When **13** (20 mg) was heated in methanol in the dark, the only product isolated was 2,2-diphenylchromene (**12**).

Irradiation of 3,4-Diphenylchromene in Methanol. A solution containing 50 mg of 3,4-diphenylchromene in 160 ml of methanol was irradiated under an argon atmoephere using a 450-W Hanovia lamp equipped with a Corex filter for 190 min. The solvent was removed under reduced pressure and the resulting oil was purified by thick layer chromatography. The major band contained 42 mg of a clear oil whose structure was assigned as 3-methoxy-1-(2-hydroxyphenyl)-1,2-diphenylpropene (**15**) on the basis of its characteristic spectra: ir (CCl_4) 3.25, 3.43, 6.25, 6.68, 8.36, 8.97, 9.08, 10.39, and 14.23 μ; NMR (CCl_4) δ 3.28 (s, 3 H), 4.67 (s, 2 H), 7.0–7.9 (m, 14 H), 8.90 (m, 1 H).

Irradiation of 4-Phenylchromene in Methanol. A solution containing 130 mg of 4-phenylchromene in 12 ml of methanol was irradiated in a quartz tube which had been purged with argon. Irradiation of the sample for 4 hr using a 450-W Hanovia lamp equipped with a Corex filter gave 185 mg of a crude residue. The thick oil obtained was subjected to thick layer chromatography using a cyclohexane–ether mixture as the eluent. The first band obtained (R_f 0.67) contained 64 mg of a clear oil whose structure was assigned as 1,3-dimethoxy-1-(2-hydroxyphenyl)-1-phenylpropane (**20**): ir (CCl_4) 3.0, 3.29, 3.40, 3.45, 6.19, 6.31, 6.73, 6.82, 6.91, 7.20, 7.71, 8.08, 8.50, 8.66, 8.96, 9.45, 10.29, 10.96 μ; NMR (CCl_4) δ 2.48 (t, 2 H, J = 7.0 Hz), 3.2 (m, 2 H), 3.14 (s, 3 H), 3.20 (s, 3 H), 6.58–7.12 (m, 9 H), and 7.92 (s, 1 H); MS *m/e* 240, 238, 209, 208, 207 (base), 181, 179, 178, 165, 152, and 131. The second band isolated from the thick layer plate (R_f 0.57) contained 43 mg of a clear oil whose spectral properties indicated it to be a 1:1 mixture of *cis*- and *trans*-3-methoxy-1-(2-hydroxyphenyl)-1-phenylpropene: NMR (CCl_4) δ 3.24 (s, 3 H), 3.76 (d, J = 7.0 Hz), 3.97 (d, J = 6.5 Hz), 5.29 (broad s, OH), 5.70 (s, OH), 5.94 (t, J = 6.5 Hz), 6.32 (t, J = 7.0 Hz), 6.6–7.4 (m, 9 H); MS *m/e* 240, 238, 224, 209, 208, 207 (base), 181, 178, 165, 152, 131, and 115. When the mixture of *cis*- and *trans*-3-methoxy-1-(2-hydroxyphenyl)-1-phenylpropene (**18** and **19**) was photolyzed in methanol for 3 hr, dimethoxypropane **20** was formed in quantitative yield.

Irradiation of 3,4-Diphenylisochromene in Methanol. A solution containing 80 mg of 3,4-diphenylisochromene in 120 ml of methanol under a nitrogen atmosphere was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter for 13 hr. Removal of the solvent left a crude residue which was separated into two major components by thick layer chromatography. The faster moving band contained 47 mg (59%) of a white solid, mp 89–90°, whose structure was assigned as 2,3-epoxy-2,3-diphenylindan (**23**) on the basis of its physical properties and by comparison with an authentic sample: ir (CCl_4) 6.92, 7.95, and 11.05 μ; NMR ($CDCl_3$) τ 5.44 (broad s, 2 H) and 3.2–2.20 (m, 14 H). An authentic sample of **23** was prepared by the peracid oxidation of 2,3-diphenylindene. A mixture containing 400 mg of 2,3-diphenylindene[63] (**25**) and 400 mg of *m*-chloroperbenzoic acid in 20 ml of methylene chloride was kept at −8° for 14 hr. At the end of this time a saturated sodium bicarbonate solution was added and the mixture was then extracted with ether. The extracts were dried over magnesium sulfate and concentrated under reduced pressure to give a crystalline solid. This material was purified by thick layer chromatography to give 205 mg (48%) of a white solid, mp 89–90°, whose physical proper-

ties were identical in every detail with those of the sample of 2,3-epoxy-2,3-diphenylindan isolated from the photolysis of 3,4-diphenylisochromene.

The slower moving component (25 mg, 27%) isolated from the thick layer plate was a clear oil whose structure was assigned as *trans*-2-hydroxy-3-methoxy-2,3-diphenylindan (**24**) on the basis of its physical and chemical properties: ir (CCl_4) 2.85, 6.91, 7.38, 7.95, 9.35, 9.80, 11.0, and 14.40 μ; uv (methanol) 287, 274, and 260 nm (ϵ 790, 650, and 725); NMR ($CDCl_3$) τ 5.82 (s, 3 H), 5.35 (s, 2 H), 5.50 (s, 1 H, exchanged with D_2O), and 3.3–2.40 (m, 14 H). Treatment of a 14-mg sample of *trans*-2-hydroxy-3-methoxy-2,3-diphenylindan in 0.5 ml of chloroform-*d* with a grain of *p*-toluenesulfonic acid for 9 hr resulted in the quantitative formation of 1,1-diphenylindanone (**26**): mp 120–121° (lit.[64] mp 120–121°); ir (CCl_4) 5.75, 6.22, 6.75, 6.98, 8.00, 8.44, 9.70, and 14.50 μ; uv (methanol) 305, 281, 273, and 268 nm (ϵ 675, 1420, 1440, and 1220); NMR (*CDCl*$_3$) τ 5.32 (s, 2 H) and 3.0–2.0 (m, 14 H).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.42; H, 5.66.

A similar reaction occurred when 2,3-epoxy-2,3-diphenylindan was treated with *p*-toluenesulfonic acid; however, when a 42-mg sample of 2,3-epoxy-2,3-diphenylindan was stirred with 4.0 g of silica gel in 20 ml of 5% ether–cyclohexane, the only product obtained was *trans*-2,3-dihydroxy-2,3-diphenylindan: ir (CCl_4) 2.80, 2.90, 6.22, 6.93, 9.50, 11.0, and 14.20 μ; uv (methanol) 305, 281, 273, and 268 nm (ϵ 6.75, 1420, 1440, and 1220); NMR ($CDCl_3$) τ 5.06–5.96 (AB quartet, 2 H, J = 17 Hz), 4.80 (s, 1 H, exchanged with D_2O), 4.30 (s, 1 H, exchanged with D_2O), and 2.40–3.40 (m, 14 H). Treatment of this diol with *p*-toluenesulfonic acid in chloroform-*d* gave a quantitative yield of 1,1-diphenyl-2-indanone (**26**).

2,3-Epoxy-2,3-diphenylindan (**23**, 15 mg) was quantitatively converted into *trans*-2-hydroxy-3-methoxy-2,3-diphenylindan by carrying out the irradiation in 6 ml of methanol for 15 hr. The conversion of epoxide **23** to **24** still proceeded when the irradiation was carried out in the presence of sodium bicarbonate.

Irradiation of 3-Phenyl-4-methylisochromene in Methanol. A solution containing 200 mg of 3-phenyl-4-methylisochromene (**27**) in 150 ml of methanol was irradiated under a nitrogen atmosphere with a 450-W Hanovia lamp equipped with a Pyrex filter for 23 hr. Removal of the solvent left a pale oil which was shown to contain 2,3-epoxy-2-phenyl-3-methylindan (**28**) as the major component by NMR analysis: NMR (CCl_4) δ 1.50 (s, 3 H), 3.40 (s, 2 H), and 6.9–7.7 (m, 9 H). Purification of the epoxide was not possible owing to the extreme ease with which it was converted into *trans*-2,3-hydroxy-2-phenyl-3-methylindan (**29**, 170 mg, 78%), mp 128–129°. The structure of epoxide **28** was verified by comparison with an authentic sample. A 200-mg sample of 2-phenyl-3-methylindene (**31**)[65] was dissolved in 5 ml of methylene chloride and cooled at 0°. To this solution was added 200 mg of *m*-chloroperbenzoic acid and the resulting solution was stirred at 0° for 25 min. The *m*-chlorobenzoic acid that had formed was filtered and the solvent was removed under reduced pressure to leave behind a pale oil whose NMR spectrum was identical with that obtained from the irradiation of 3-phenyl-4-methylisochromene (**27**). If the epoxidation reaction mixture was worked up by washing the methylene chloride layer with a dilute sodium bicarbonate solution the only product formed was *trans*-2,3-phenyl-3-methylindan: mp 128–129°; ir (KBr) 3.05, 6.25, 6.35, 6.70, 6.92, 7.35, 9.52 μ; NMR ($CDCl_3$) δ 3.12 (d, 1 H, J = 16.0 Hz), 3.65 (d, 1 H, J = 16.0 Hz), 3.94 (broad s, 2 H, exchanged with D_2O), and 7.2–7.64 (m, 9 H); *MS m/e 222, 204, 195, 179 (base), 165, 115, and 77.*

Irradiation of 100 mg of 3-phenyl-4-methylisochromene (**27**) in 150 ml of methanol with a 550-W Hanovia lamp for 32 hr did not give any significant quantities of epoxyindan **28** (<5%). Instead, the major product isolated from the thick layer plate was identified as *trans*-2-hydroxy-3-methoxy-2-phenyl-3-methylindan (**30**): NMR ($CDCl_3$) δ 1.06 (s, 3 H), 3.12 (s, 3 H), 3.38 (s, 2 H), 3.82 (broad s, 1 H, exchanged with D_2O), and 6.9–7.8 (m, 9 H).

Irradiation of 3-Phenylisochromene in Methanol. A solution containing 50 mg of 3-phenylisochromene (**32**) in 150 ml of methanol was irradiated under a nitrogen atmosphere with a 550-W Hanovia lamp equipped with a Pyrex filter for 20 hr. Removal of the solvent under reduced pressure left a yellow oil which was recrystallized from 95% ethanol to give 45 mg (87%) of a white solid, whose structure was assigned as *trans*-2-methoxy-3-hydroxy-2-phenylindan (**33**) on the basis of its physical properties and by comparison with an independently synthesized sample: mp 103–105°; ir (KBr) 6.18, 6.70, 6.89, 7.2, 7.91, 8.28, 9.41, 9.72, 10.32, 10.65, 10.89, 11.10, 11.48, 11.90, 12.30, 13.10, 13.32, 13.75, and 14.60 μ; NMR ($CDCl_3$) δ 3.10 (s, 3 H), 3.90 (broad s, 1 H), 4.93 (s, 2 H), and 6.8–7.8 (m, 9 H). An authentic sample of **33** was prepared by treating 200 mg of 2-phenylindene[66] (**34**) with 200 mg of *m*-chloroperbenzoic acid in 15 ml of methylene chloride at 0° for 12 hr. The organic layer was then washed with a 10% sodium bicarbonate solution followed by water. The methylene chloride solution was then dried over magnesium sulfate and the solvent was removed under reduced pressure to give 180 mg of a clear oil whose NMR spectrum indicated it to be 2,3-epoxy-2-phenylindan: NMR ($CDCl_3$) δ 3.42 (broad s, 2 H), 4.26 (s, 1 H), and 7.0–7.7 (m, 9 H). Conversion of this epoxide to methoxy alcohol **33** was achieved by dissolving the epoxide in methanol containing a trace of *p*-toluenesulfonic acid and allowing the solution to stir for 30 min. Removal of the solvent under reduced pressure gave a crystalline solid which was recrystallized from 95% ethanol to give methoxy alcohol **33**, mp 103–105°. This material was identical in every detail with the major product obtained from the irradiation of 3-phenylisochromene. A mixture melting point was undepressed at 103–105°.

4-Phenylisothiochromene (36) was prepared by adding 2.0 g of isothiochroman-4-one[67] in 10 ml of ether to a Grignard reagent prepared from 3.84 g of bromobenzene and 0.6 g of magnesium turnings in 30 ml of ether. The mixture was allowed to stir at room temperature for 2 hr and was then decomposed by pouring onto a 10% sulfuric acid solution on crushed ice. The ether layer was dried over magnesium sulfate and concentrated under reduced pressure to give 1.25 g of a yellow oil: ir (CCl_4) 2.90, 6.22, 6.70, 6.90, 7.84 μ; NMR (CCl_4) δ 2.7–4.2 (m, 5 H) and 6.8–7.5 (m, 9 H). The crude 4-phenylisothiochroman-4-ol was used without further purification. The oil was dissolved in 45 ml of glacial acetic acid which contained 5 ml of concentrated sulfuric acid and was allowed to stir at room temperature for 1 min. At the end of this time 70 ml of water was added and the aqueous solution was extracted with ether. The ethereal extracts were washed with 10% sodium bicarbonate followed by water. The organic phase was then dried over magnesium sulfate and the solvent was removed under reduced pressure to leave behind a yellow oil. This residue was purified by thick layer chromatography using a 5% ether–pentane mixture as the eluent. The major component amounted to 725 mg of a pale yellow oil whose structure was assigned as 4-phenylisothiochromene (**36**) on the basis of its physical properties: ir (CCl_4) 6.23, 6.72, 6.92, 7.08, and 10.96 μ; NMR (CCl_4) δ 3.86 (s, 2 H), 6.50 (s, 1 H), and 6.9–7.4 (m, 9 H); uv (methanol) 325 and 243 nm (ϵ 2800 and 7930); MS *m/e* 224, 223, 193, 155 (base), 122, 120, 118 (base), and 83.

Anal. Calcd for $C_{15}H_{12}S$: C, 80.31; H, 5.39; S, 14.29. Found: C, 80.03; H, 6.04; S, 14.06.

Irradiation of 4-Phenylisothiochromene in Methanol. A solution containing 189 mg of 4-phenylisothiochromene in 450 ml of methanol under a nitrogen atmosphere was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter for 1 hr. Removal of the solvent under reduced pressure gave a yellow oil which was subjected to thick layer chromatography using hexane as the eluent. The fastest moving band amounted to 16 mg of elemental sulfur, mp 118°. The second band contained 78 mg (51%) of a clear oil whose structure was assigned as 3-phenylindene (**37**): ir (CCl_4) 3.26, 6.34, 6.72, 6.86, 6.92, 7.20, and 10.25 μ; NMR ($CDCl_3$) δ 3.38 (d, 2 H, J = 2.0 Hz), 6.38 (t, 1 H, J = 2.0 Hz), and 7.0–7.6 (m, 9 H). This material was identical in every detail with an authentic sample of 3-phenylindene.[55] The third component isolated from the thick layer plate (12 mg) was starting material. The last band isolated from the thick layer plate contained 12 mg of a pale yellow oil (6%) whose structure was assigned as methyl phenyl (*o*-tolyl)thionoacetate (**38**) on the basis of its physical properties: ir (CCl_4) 3.22, 3.38, 6.20, 6.65, 6.85, 8.14, 8.40, 8.79, 9.90, 13.01, 13.40, 13.56, 13.90, and 14.38 μ; NMR ($CDCl_3$) δ 2.22 (s, 3 H), 4.03 (s, 3 H), 5.64 (s, 1 H), and 6.9–7.4 (m, 9 H); MS *m/e* 256, 224, 223, 181 (base), 169, 166, 165, and 161.

Quantum Yield Determinations. All quantitative measurements were made on a rotating assembly with a central light source (internal water-cooled mercury arc lamp, Hanovia Type L-450W). Samples in 13-mm Pyrex ampoules were placed in holders on the assembly approximately 6 cm from the immersion well. The light was filtered by circulation of 0.002 *M* potassium chromate in a 1% aqueous solution of potassium carbonate through the inner jacket to isolate the 3130-Å region of the medium-pressure mercury arc.[68] All studies were made at room temperature. Samples in 13-mm Pyrex test tubes were degassed to 5×10^{-3} mm in three freeze–thaw cycles and then sealed. Benzophenone–benzhydrol actinometry was used for quantum yield determinations.[69] After irradiation, the degree of reaction was determined by quantitative uv or vapor

phase chromatography. The conversions in the irradiations were run to 15% or less. The mass balance in these runs were generally better than 95%.

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Registry No.—**4,** 2513-25-9; **5,** 36839-05-1; **6,** 36913-69-6; **7,** 36852-12-7; **8,** 36852-14-9; **9,** 1128-92-3; **10,** 36852-15-0; **12,** 4222-08-6; **13,** 36839-06-2; **14,** 5882-21-3; **15,** 54193-66-7; **17,** 51870-64-5; **18,** 54193-67-8; **19,** 54193-68-9; **20,** 54193-69-0; **22,** 54193-70-3; **23,** 54193-71-4; **24,** 54193-72-5; **26,** 54193-73-6; **27,** 54193-74-7; **28,** 54193-75-8; **29,** 54193-76-9; **30,** 54193-77-0; **31,** 10425-96-4; **32,** 29539-10-4; **33,** 54193-78-1; **34,** 4505-48-0; **36,** 54193-79-2; **37,** 1961-97-3; **38,** 54193-80-5; 4-phenyl-3-chromanone, 17698-43-0; bromobenzene, 108-86-1; 3-phenylisochromanone, 32521-36-1; methyl iodide, 74-88-4; *cis*-4-methyl-3-phenyl-4-isochromanol, 54193-81-6; *trans*-4-methyl-3-phenyl-4-isochromanol, 54193-82-7; 3-phenyl-4-isochromanol, 32727-55-2; *trans*-2,3-dihydroxy-2,3-diphenylindan, 54193-83-8; 2,3-epoxy-2-phenylindan, 54193-84-9; isothiochroman-4-one, 4426-76-0; 4-phenylisothiochroman-4-ol, 54193-85-0.

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Carbon–Phosphorus Heterocycles. A New Route to Tetrahydrophosphinolines, Tetrahydroisophosphinolines, and Related Systems via Cyclization of Alkenyl-Substituted Phosphonium Salts with 115% Polyphosphoric Acid[1]

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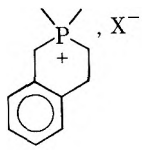
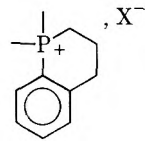
A convenient method of wide scope for the synthesis of the rare tetrahydroisophosphinolinium and tetrahydrophosphinolinium salts has been developed from readily available starting materials. Treatment of a variety of tertiary phosphines (all containing an aryl group and/or an arylmethyl group) with allylic type halides gave phosphonium salts containing a β-alkenyl substitutent. Cyclization of these salts occurred in the presence of 115% polyphosphoric acid (PPA) at 160° for 30 min to give the C–P heterocyclic systems in modest to good yields (24–82%). Work-up of the reaction mixtures simply involved addition to ice water. The resulting *homogeneous* solution was treated with KPF_6 (saturated aqueous solution) which caused the precipitation of the PF_6^- salt of the respective isophosphinolinium or phosphinolinium system. ^1H NMR, ^{31}P NMR, infrared and mass spectral and elemental analyses support the structures of these phosphorus analogs of the corresponding tetrahydroisoquinoline and tetrahydroquinoline heterocycles. Benzyldiphenylvinylphosphonium bromide (**3e**) cyclized at 300° with 115% PPA after 1.25 hr to give, after work-up, 1,2,3,4-tetrahydro-2,2-diphenylisophosphinolinium hexafluorosphate (**4e**, 51%). Thus, formation of the six-membered ring was favored over formation of the phospholane ring system. A mechanism is tentatively put forth to involve a rather classic electrophilic substitution in the cyclization process. The role of the anion(s) of PPA is unknown but probably involves direct association with the phosphonium cation prior to addition of KPF_6.

Carbon–phosphorus (C–P) heterocyclic systems that are the analogs of the quinoline and isoquinoline ring system have rarely been recorded.[3] A paucity of synthetic methods exists for these C–P heterocycles, but the procedures are fraught with tedious manipulations, uncommon starting materials, and long overall reaction times. A number of articles have appeared concerning phosphinolines[4] and isophosphinolines[5] in recent years, but no simple, systematic routes have been published from readily available precursors. We have discovered[6] that 1,2,3,4-tetrahydroisophosphinolines **1** and 1,2,3,4-tetrahydrophosphinolines **2** can be



1



2

prepared as phosphonium salts from simple open-chain precursors that can easily be synthesized from readily accessible reagents.

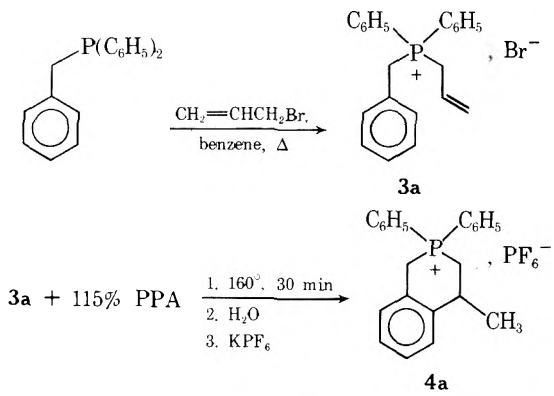
To illustrate, benzyldiphenylphosphine can be obtained as shown in an inverse Grignard flask and, without isola-

$$(C_6H_5)_2PCl + C_6H_5CH_2MgCl \xrightarrow{\text{ether}} (C_6H_5)_2PCH_2C_6H_5$$

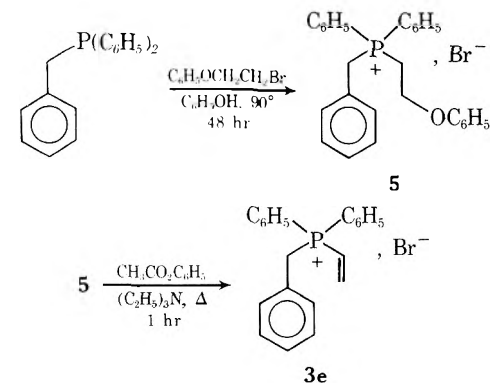
tion, can be quaternized with allyl bromide to yield allylbenzyldiphenylphosphonium bromide (**3a**). In the presence of 115% polyphosphoric acid (PPA)[7] at 160° for 30 min, phosphonium salt **3a** undergoes ring closure (Scheme I) to produce the 1,2,3,4-tetrahydro-4-methyl-2,2-diphenylisophosphinolinium hexafluorophosphate (**4a**) in good yield (75%) via addition of saturated aqueous KPF_6 to the mixture. Reprecipitation from methylene chloride by the slow addition of ether gave pure **4a**. Other examples of this novel cyclization are shown in Chart I with more detailed information on the properties of compounds listed in Tables I and II.

During the cyclization process, a gas is given off, presumably HBr.[8] On the assumption that protonation of **3a** by PPA occurs in such a manner so as to remove Br^- (lost as HBr) and to disrupt the alkene linkage also, the most logical second step is an electrophilic attack on the benzene ring. Loss of a proton to regenerate the aromatic ring could logically follow. The P^+ group is insulated from the aromatic ring by a methylene group and apparently has little effect on the cyclization.

Scheme I



Scheme II



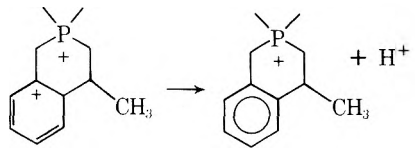
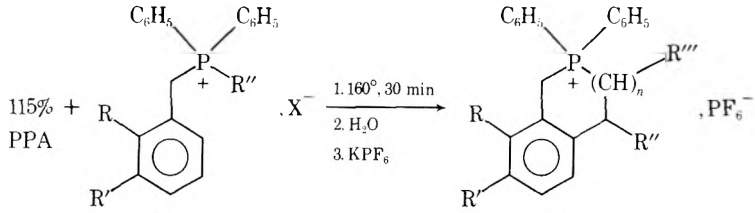


Chart I



Compd	R	R'	R''	X⁻	Compd	R	R'	R''	R'''	n
3b	H	CH_3	$-CH_2CH{=}CH_2$	Br	**4b**[a]	H	CH_3	CH_3	H	1
3c	H	H	$-CH_2CH{=}CHCH_3$	Br	**4c**	H	H	CH_3	H	2
3d	H	CH_3	$-CH_2CH{=}CHCH_3$	Br	**4d**	H	CH_3	CH_3	H	2
3e	H	H	$-CH{=}CH_2$	Br	**4e**[b]	H	H	H	H	1
3f	H	H		Br	4f	H	H	$-(CH_2)_3-$		1
3g	Benzo		$-CH_2CH{=}CH_2$	PF_6	**4g**	Benzo		CH_3	H	1
3h	Benzo			Cl	**4h**	Benzo		$-(CH_2)_3-$		1

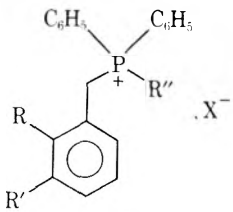
[a] Isolated as the bromide salt and was converted to the hexafluorophosphate derivative. [b] The reaction was performed at 300° for 1.25 hr.

The preference for a five- or six-membered ring being formed was examined with **3e**, although from theoretical principles both would have high-energy intermediate precursors. It was observed that **4e** was produced only when a temperature of 300°C was maintained for 1.25 hr. NMR analysis of the reaction mixture indicated that only a metathesis exchange took place at lower temperatures (160 and 180°, respectively).

Benzyldiphenylvinylphosphonium bromide (**3e**) was obtained from a modification of our procedure and one used by Shutt and Trippett[9] as shown in Scheme II. As before, the benzyldiphenylphosphine produced was not isolated but was allowed to react with β-bromophenetole to make the intermediate benzyl-β-phenoxyethyldiphenylphosphonium bromide (**5**). Compound **5** was then treated with a solution of ethyl acetate–triethylamine to generate **3e**.

Interestingly, compounds **3c** and **3d** underwent ring closure to produce the seven-membered rings, **4c** and **4d**, and *not* the six-membered ring. These cyclic compounds were identified by NMR (and infrared, mass spectral, and elemental analyses) owing to the characteristic doublet seen in the spectra for the methyl group on the saturated ring and not the ethyl substituent. With this in mind, we could assume that protonation had occurred at the γ carbon (in

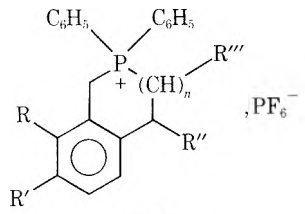
Table I



Compd	R	R'	R''	X⁻	Mp, °C	Quaternizing solvent (reaction time, hr)	Equiv of halide[a]	Yield, %	Molecular formula	Anal., % P	
3a[b]	H	H	$-CH_2CH{=}CH_2$	Br	201–203	Benzene (24)	2.49	52	$C_{22}H_{22}BrP$	Calcd	7.80
										Found	7.58
3b[b,c]	H	CH_3	$-CH_2CH{=}CH_2$	Br	173–175	Benzene (24)	1.84	48	$C_{23}H_{24}BrP$	Calcd	7.53
										Found	7.50
3c[b,c]	H	H	$-CH_2CH{=}CHCH_3$	Br	177–180	Toluene (24)	1.33	48	$C_{23}H_{24}BrP$	Calcd	7.53
										Found	7.64
3d[b,c]	H	CH_3	$-CH_2CH{=}CHCH_3$	Br	170–173	Ether–benzene (2.75:1) (48)	1.33	35	$C_{24}H_{26}BrP$	Calcd	7.28
										Found	7.19
3e[d]	H	H	$-CH{=}CH_2$	Br	220–222	Phenol (48)	1.0	62	$C_{21}H_{20}BrP$	Calcd	8.08
										Found	8.16
3f	H	H		Br	235–236	Benzene (24)	1.44	70	$C_{24}H_{24}BrP$	Calcd	7.33
										Found	7.20
3g	Benzo		$-CH_2CH{=}CH_2$	PF_6	158–161	Benzene (2.0)	1.1	43	$C_{26}H_{24}F_6P_2$	Calcd	12.10
										Found	11.81
3h	Benzo			Cl	223–226	Benzene (60)	1.41	65	$C_{28}H_{26}ClP$	Calcd	7.23
										Found	7.24

[a] Based on 1 equiv of phosphine. [b] Yield based on starting benzylic halide. [c] When ether is used as the quaternizing solvent, the yields of **3b–d** are decreased to 25, 26, and 29%, respectively. [d] Isolated as benzyl-β-phenoxyethyldiphenylphosphonium bromide and, upon treatment with ethyl acetate–triethylamine, converted to **3e**. Previously reported in ref 9.

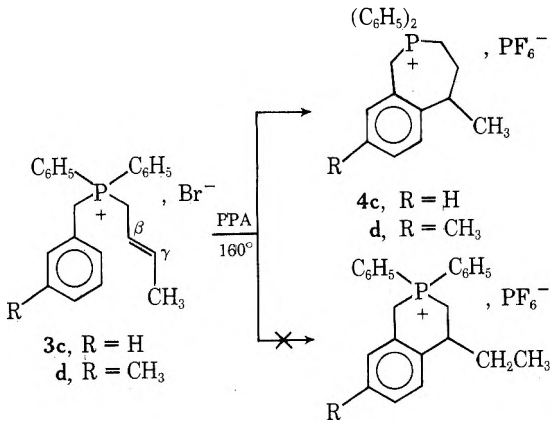
Table II



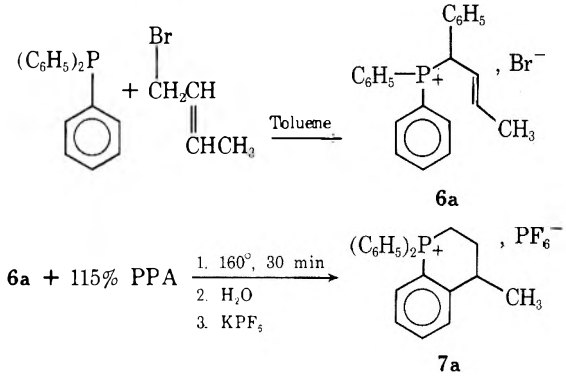
4a-h

Compd	R	R'	R''	R'''	n	Mp, °C	Yield, %	Molecular formula	Anal., % P
4a	H	H	CH_3	H	1	172.5–174.5	75	$C_{22}H_{22}F_6P_2$	Calcd 13.40 Found 13.09
4b[a]	H	CH_3	CH_3	H	1	185.5–187	28	$C_{23}H_{24}F_6P_2$	Calcd 13.00 Found 12.97
4c	H	H	CH_3	H	2	214–216	30	$C_{23}H_{24}F_6P_2$	Calcd 13.00 Found 12.88
4d	H	CH_3	CH_3	H	2	233–235	24	$C_{24}H_{26}F_6P_2$	Calcd 12.63 Found 12.69
4e	H	H	H	H	1	174–176	51	$C_{21}H_{20}F_6P_2$	Calcd 13.82 Found 13.61
4f[b]	H	H	$-(CH_2)_3-$		1	326–328	55	$C_{24}H_{24}BrP$	Calcd 7.33 Found 7.23
4g	Benzo		CH_3	H	1	219–220	55	$C_{26}H_{24}F_6P_2$	Calcd 12.10 Found 11.92
4h	Benzo		$-(CH_2)_3-$		1	264–266	25	$C_{28}H_{26}F_6P_2$	Calcd 11.52 Found 11.33

[a] Isolated as the bromide and converted to the hexafluorophosphate derivative. [b] Isolated as the bromide derivative.



Scheme III

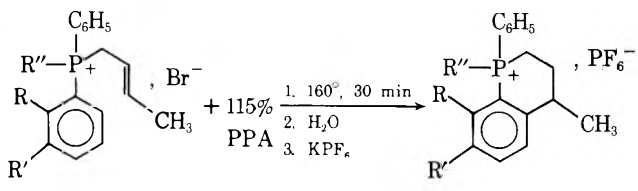


relation to the P atom). The suspected cation formed preferentially can possibly be defended on the grounds of greater hyperconjugative stabilization at the γ carbon because there are five hydrogens available as compared to just four adjacent hydrogens on the β carbon in the cation formed via protonation at the γ carbon in **3c** or **3d**. Moreover, protonation at the β carbon would also place the two positive centers further apart, possibly creating a more stable intermediate owing to less charge repulsion.

Surprisingly, this synthetic procedure was also found to be applicable to the preparation of the isomeric phosphinoline derivatives. For example, it was possible to react triphenylphosphine with halo alkenes, such as 1-bromo-2-butene, to give 2-butenyltriphenylphosphonium bromide[10] (**6a**) in high yield (94%). When treated with PPA (Scheme III), **6a** underwent ring closure to 1,2,3,4-tetrahydro-4-methyl-1,1-diphenylphosphinolinium hexafluorophosphate (**7a**) (82%). Additional examples are listed in Chart II along with more detailed information on the physical properties of the products and precursors in Tables III and IV.

Unlike the isophosphinoline system, the cyclic intermediate precursors suspected for the phosphinoline derivatives are not easily defended. The obvious difficulty with

Chart II



6b-d

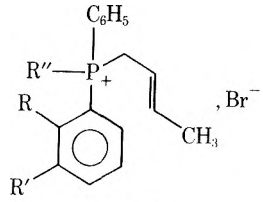
Compd	R = R'	R''
6b	H	CH_3
6c	H	C_2H_5
6d	Benzo	C_6H_5

7b-d

Compd	R = R'	R''
7b	H	CH_3
7c	H	C_2H_5
7d	Benzo	C_6H_5

applying current theory as a rationale is that the benzene ring is already bonded to a positively charged P atom. Intuitively, an intermediate such as represented by 8 seems untenable on the grounds of suspected strong electrostatic repulsion between like charges on adjacent groups. However, PPA anion (PPA^{n-}) very likely stabilizes the intermediate by association, since an excess of this anion is presumably available. This is supported by the observation that the entire reaction mixture is soluble in water. Only upon satura-

Table III

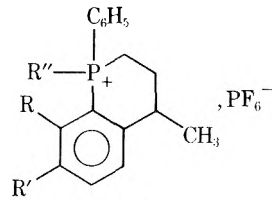


6a-d

Compd	R	R'	R''	Mp, °C	Quaternizing solvent (hr)	Equiv of halide[a]	Yield, %	Molecular formula	Anal., % P
6a[b]	H	H	C_6H_5	241–243	Xylene (19)	0.73	94	$C_{22}H_{22}BrP$	
6b	H	H	CH_3	187–189	Xylene (18)	0.73	88	$C_{17}H_{20}BrP$	Calcd 9.24 Found 9.32
6c	H	H	C_2H_5	198–200	Toluene (12)	1.43	77	$C_{18}H_{22}BrP$	Calcd 8.87 Found 9.15
6d	Benzo		C_6H_5	259.5–261	Benzene (12)	1.81	59	$C_{26}H_{24}BrP$	Calcd 6.92 Found 7.00

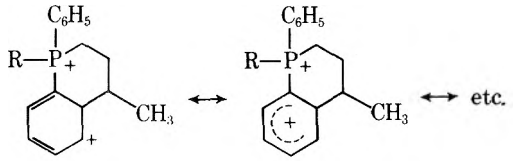
[a] Based on 1 equiv of phosphine. [b] This compound was previously reported in ref 10.

Table IV

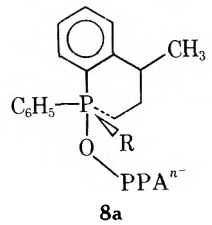


7a-d

Compd	R	R'	R''	Mp, °C	Yield, %	Molecular formula	Anal., % P
7a	H	H	C_6H_5	203.5–205	82	$C_{22}H_{22}F_6P_2$	Calcd 13.40 Found 13.42
7b	H	H	CH_3	179.5–182	67	$C_{17}H_{20}F_6P_2$	Calcd 15.48 Found 15.09
7c	H	H	C_2H_5	145–147	42	$C_{18}H_{22}F_6P_2$	Calcd 14.95 Found 14.90
7d	Benzo		C_6H_5	192–194.5	33	$C_{26}H_{24}F_6P_2$	Calcd 12.09 Found 11.99



8



8a

tion of the aqueous solution with the PF_6^- anion did the phosphonium salt precipitate (in the case of **4f**, a saturated solution of NaBr was added). Further speculation seems unwarranted on the mechanism until more data become available, although an intermediate like **8a** is also reasonable.

Structural identification of members of the isophosphinoline and phosphinoline ring systems rests on elemental, infrared, mass spectral,[11] and NMR analyses found in Tables I–V. The most revealing physical data came from extensive ^1H NMR and ^{31}P NMR studies. The NMR spectrum of **4g** showed the methylene protons (attached to the naphthalene group) as a doublet each with geminal coupling. There was also observed a J_{PCH} of 16.0 Hz; apparently the geminal coupling is a result of the electronic arrangement and stereochemistry of the newly formed ring fusion. The methylene group can be characterized as an ABX system[12] (X = P) with values of $\delta_A = 4.61$, $\delta_B = 5.28$, $J_{AB} = 16.0$, $J_{AX} = J_{BX} = 16.0$ Hz. The newly formed methyl group in **4g** appears as a doublet of doubets at δ 1.75 ($J_{PCCCH} = 7$, $J_{HCCH} = 2.0$ Hz) which could be the result of long-range P–H coupling. This phenomenon is not observed in **4c** (or **4d**) as the methyl group appears as a clean doublet at δ 1.48 ($J_{HCCH} = 7$ Hz) in the seven-membered rings. The presence of the methyl group in **4g** also eliminates the possibility of a seven-membered ring. The ^1H NMR spectrum of **4e** showed that the benzylic protons adjacent to phosphorus occurred as a doublet (even at 25-Hz sweep width) which suggests that the two rings are probably close to being coplanar.

The negative ^{31}P chemical shift values for the open-chain phosphonium compounds listed in Table V show the differences to be relatively small. These compare very well with many open-chain compounds,[13] but it should be noted that phosphonium salts have on rare occasions been re-

Table V
NMR Spectral Data for Reaction Products

Compd	Ir absorption spectra in KBr,[a] selected bands, cm^{-1}	^1H NMR spectral assignments, chemical shifts, δ[b]	^{31}P NMR, δ[c]
3a	1443 (s), 1114 (vs), 997 (m), 940 (s), 745 (vs), 691 (vs)	4.26 [d of d (J_{PCH} = 15, J_{HCCH} = 6 Hz), PCH_2CH, 2 H], 4.99 [d (J_{PCH} = 14 Hz), $C_6H_5CH_2P$, 2 H], 5.16–5.80 (m, $-CH{=}CH_2$, 3 H), 7.13 (s, C_6H_5, 5 H), 7.5–8.14 [m, $(C_6H_5)_2P<$, 10 H]	−23.96[i]
3b	1433 (s), 1111 (vs), 999 (m), 942 (m), 745 (s), 694 (s)	2.10 (s, CH_3, 3 H), 4.28 [d of d (J_{PCH} = 15, J_{HCCH} = 6 Hz), PCH_2CH, 2 H], 4.92 [d (J_{PCH} = 15 Hz), $ArCH_2P$, 2 H], 5.14–5.76 (m, $-CH{=}CH_2$, 3 H), 6.78 (s, ArH, 1 H), 6.99 (s, ArH, 3 H), 7.46–8.06 [m, $(C_6H_5)_2P<$, 10 H]	
3c	1443 (s), 1111 (vs), 997 (m), 980 (m), 752 (vs), 690 (vs)	1.24–1.64 (m, CH_3, 3 H), 4.15 [d of d (J_{PCH} = 15, J_{HCCH} = 7 Hz), PCH_2CH, 2 H], 4.91 [d (J_{PCH} = 15 Hz), $C_6H_5CH_2P$, 2 H], 4.90–5.96 (m, CH=CH, 2 H), 7.10 (s, C_6H_5, 5 H), 7.46–8.02 [m, $(C_6H_5)_2P<$, 10 H]	−24.79[i]
3d	1431 (s), 1110 (s), 998 (m), 976 (m), 741 (vs), 688 (vs)	1.24–1.70 (m, $CHCH_3$, 3 H), 2.08 (s, $ArCH_3$, 3 H), 4.17 [d of d (J_{PCH} = 15, J_{HCCH} = 7 Hz), PCH_2CH, 2 H], 4.86 [d (J_{PCH} = 15 Hz), $ArCH_2P$, 2 H], 4.90–6.0 (m, CH=CH, 2 H), 6.77 (s, ArH, 1 H), 6.98 (s, ArH, 3 H), 7.48–8.16 [m, $(C_6H_5)_2P<$, 10 H]	
3e	1433 (s), 1111 (s), 995 (m), 977 (s), 960 (vs), 691 (s)	5.07 [d (J_{PCH} = 15 Hz), $ArCH_2P$, 2 H], 5.91–6.62 (m, $CH{=}CH_2$, 2 H), 6.97–7.40 (m, ArH, $PCH{=}CH_2$, 6 H), 7.46–8.06 [m, $(C_6H_5)_2P<$, 10 H]	
3f	1431 (m), 1111 (s), 746 (s), 698 (s), 690 (s)	1.30–1.80 (m, cyclopentenyl ring, 1 H), 2.00–2.76 (m, cyclopentenyl ring, 3 H), 5.00 (br m, CH, 1 H), 5.06 [d of d (J_{PCH} = 14, J_{HCCH} = 4 Hz), $C_6H_5CH_2P$, 2 H], 5.91 (br s, CH=CH, 2 H), 7.07 (s, $C_6H_5CH_2$, 5 H), 7.44–8.06 (m, $(C_6H_5)_2P<$, 10 H)	
3g[d]	1435 (m), 1114 (s), 933 (m), 836 (vs), 732 (m), 682 (m)	3.79 [d of d (J_{PCH} = 15, J_{HCCH} = 6 Hz), PCH_2CH, 2 H], 4.83 [d (J_{PCH} = 15 Hz), $ArCH_2P$, 2 H], 5.18–5.84 (m, $CH{=}CH_2$, 3 H), 7.12–7.96 (m, ArH, 17 H)	
3h[e]	1437 (m), 1114 (m), 801 (s), 780 (s), 725 (vs), 692 (vs)	1.98–2.74 (m, CH_2CH_2, 4 H), 4.30–4.70 (m, CH, 1 H), 5.17 [d (J_{PCH} = 15 Hz), $ArCH_2P$, 2 H], 5.96 (br m, CH=CH, 2 H), 7.06–8.06 (m, ArH, 17 H)	
4a[f]	1439 (s), 1117 (s), 840 (vs), 743 (s), 689 (s)	1.56–1.80 [d of d (J_{PCCCH} = 6, J_{HCCH} = 2 Hz), CH_3, 3 H], 2.35–2.80 (m, CH, 1 H), 3.10–3.64 (m, CH_2, 2 H), 4.02 [d (J_{PCH} = 14 Hz), ArCHP, 1 H], 4.10 [d (J_{PCH} = 14 Hz), ArCHP, 1 H], 7.22–7.96 (m, ArH, 14 H)	−17.17[j]
4b[f]	1439 (s), 1117 (s), 844 (vs), 743 (s), 690 (s)	1.56–1.80 [d of d (J_{PCCCH} = 6, J_{HCCH} = 2 Hz), CH_3, 3 H], 2.30 (s, $ArCH_3$, 3 H), 2.41–2.80 (m, CH, 1 H), 3.10–3.56 (m, CH_2, 2 H), 3.99 [d (J_{PCH} = 14 Hz), ArCHP, 1 H], 4.05 [d (J_{PCH} = 14 Hz), ArCHP, 1 H], 7.08–7.96 (m, ArH, 13 H)	
4c[f]	1437 (s), 1116 (s), 840 (vs), 746 (s), 690 (s)	1.48 [d (J_{HCCH} = 7 Hz), CH_3, 3 H], 1.66–2.96 (m, CH_2CH_2, 4 H), 3.02–3.42 (m, CH, 1 H), 4.05 [t (J_{PCH} = 15 Hz), CH, 1 H], 4.52 [t (J_{PCH} = 15.0 Hz), CH, 1 H], 7.06–7.98 (m, ArH, 14 H)	−14.22[j]
4d[f]	1435 (s), 1110 (s), 838 (vs), 745 (s), 690 (s),	1.47 [d (J_{HCCH} = 7 Hz), CH_3, 3 H], 1.64–2.94 (m, CH_2CH_2, 4 H), 2.30 (s, CH_3, 3 H), 3.04–3.38 (m, CH, 1 H), 3.98 [t (J_{PCH} = 15 Hz), CH, 1 H], 4.47 [t (J_{PCH} = 15.0 Hz), CH, 1 H], 6.96 (s, ArH, 1 H), 7.24–8.02 (m, ArH, 12 H)	
4e[f]	1437 (s), 1116 (s), 840 (vs), 758 (s), 746 (s), 691 (s)	2.90–3.56 (m, CH_2CH_2, 4 H), 4.12 [d (J_{PCH} = 14 Hz), CH_2, 2 H], 7.20–7.88 (m, ArH, 14 H)	
4f[g]	1437 (s), 1115 (s), 758 (s), 683 (m)	1.69–2.82 [m, $-(CH_2)_3-$, 6 H], 3.30 (m, ArCH, 1 H), 4.05 [t (J_{PCH} = 16 Hz), ArCHP, 1 H], 4.5 (m, PCH, 1 H), 5.34 [t (J_{PCH} = 16, J_{HCH} = 1 Hz), ArCHP, 1 H], 6.7–8.3 (m, ArH, 14 H)	
4g[c]	1441 (m), 1406 (s), 1114 (s), 835 (vs), 742 (m), 685 (m)	1.75 [d of d (J_{PCCCH} = 7, J_{HCCH} = 2 Hz), CH_3, 3 H], 3.00–3.14 (m, CH, 1 H), 3.50–3.98 (m, CH_2, 2 H), 4.61 [t (J_{PCH} = 16.0 Hz), CH, 1 H], 5.28 [t (J_{PCH} = 16.0 Hz), CH, 1 H], 7.06–8.52 (m, ArH, 16 H)	

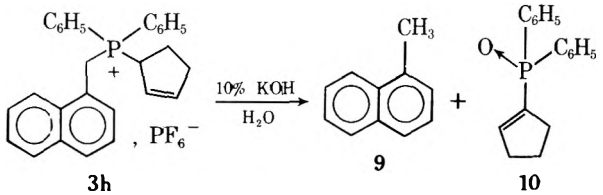
Table V
(Continued)

Compd	Ir absorption spectra in KBr,[a] selected bands, cm^{-1}	^1H NMR spectral assignments, chemical shifts, δ[b]	^{31}P NMR, δ[c]
4h[h]	1441 (s), 1397 (m), 1111 (s), 838 (vs), 731 (m), 686 (m)	2.04–3.00 [m, $-(CH_2)_3-$, 6 H], 3.64–3.96 (m, ArCH, 1 H), 4.06–4.40 (m, PCH, 1 H), 5.00 [t (J_{PCH} = 17 Hz), ArCHP, 1 H], 5.62 [t (J_{PCH} = 17 Hz), ArCHP, 1 H], 7.06–9.00 (m, ArH, 16 H)	
6a	1433 (s), 1110 (vs), 998 (m), 968 (m), 749 (s), 691 (s)	1.50–1.70 (m, CH_3, 3 H), 4.42–4.76 [d of d (J_{PCH} = 15, J_{HCCH} = 7 Hz), PCH_2CH, 2 H], 5.08–6.12 (m, CH=CH, 2 H), 7.54–8.0 (m, $(C_6H_5)_3P-$, 15 H)	−21.14[i]
6b	1433 (s), 1119 (vs), 996 (m), 977 (s), 760 (vs), 691 (s)	1.44–1.74 (m, $CHCH_3$, 3 H), 2.82 [d (J_{PCH} = 14 Hz), PCH_3, 3 H], 4.82 [d of d (J_{PCH} = 15, J_{HCCH} = 8 Hz), PCH_2CH, 2 H], 5.06–6.38 (m, CH=CH, 2 H), 7.54–8.2 (m, $(C_6H_5)_2P<$, 10 H)	−21.84[i]
6c	1433 (s), 1119 (vs), 975 (s), 767 (vs), 738 (vs)	1.06–1.48 [d of t (J_{PCCH} = 20, J_{HCCH} = 7 Hz), PCH_2CH_3, 3 H], 1.50–1.74 (m, $CHCH_3$, 3 H), 3.12–3.56 [s[l] (J_{PCH} = 13, J_{HCCH} = 7 Hz), PCH_2CH_3, 2 H], 4.25 [d of d (J_{PCH} = 15, J_{HCCH} = 7 Hz), PCH_2CH, 2 H], 5.02–6.2 (m, CH=CH, 2 H), 7.58–8.24 [m, $(C_6H_5)_2P<$, 10 H]	
6d	1431 (m), 1111 (s), 971 (s), 777 (s), 690 (s)	1.36–1.64 (m, CH_3, 3 H), 4.72 [d of d (J_{PCH} = 14, J_{HCCH} = 7 Hz), PCH_2CH, 2 H], 5.0–6.14 (m, CH=CH, 2 H), 7.34–8.46 (m, ArH, 17 H)	
7a[j]	1437 (s), 1115 (s), 840 (vs), 750 (s), 693 (s)	1.47 [d (J_{HCCH} = 7 Hz), CH_3, 3 H], 1.85–3.56 [m, (CH_2CH_2, CH), 5 H], 7.22–8.0 (m, ArH, 14 H)	−10.74[k]
7b[j]	1437 (m), 1119 (s), 840 (vs), 767 (s), 749 (s), 687 (s)	1.47 [d (J_{HCCH} = 6 Hz), CH_3, 3 H], 2.32–2.50 [2 d (J_{PCH} = 14 Hz), PCH_3, 3 H], 1.88–3.18 (m, CH_2CH_2, 4 H), 3.18–3.56 (m, CH, 1 H), 7.42–7.92 (m, ArH, 9 H)	−9.77[k]
7c[j]	1437 (m), 1114 (s), 840 (vs), 722 (s), 741 (s), 689 (s)	1.12–1.46 (m, PCH_2CH_3, 3 H), 1.45 [d (J_{HCCH} = 7 Hz), CH_3, 3 H], 1.98–3.10 [m (CH_2CH_2, PCH_2CH_3), 6 H], 3.18–3.52 (m, CH, 1 H), 7.42–7.92 (m, ArH, 9 H)	
7d[j]	1437 (m), 1111 (s), 840 (vs), 773 (s), 739 (s), 720 (m), 690 (s)	1.28 [d (J_{HCCH} = 7 Hz), CH_3, 3 H], 2.04–3.58 [m (CH_2CH_2, CH), 5 H], 7.03–8.38 (m, ArH, 16 H)	

[a] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. All compounds displayed medium to strong absorption in the regions 1431–1443 and 1110–1119 cm^{-1} which have often been assigned to the C_6H_5–P bond. Many examples are reported to support the assignment ranges but little definitive evidence is available to substantiate the correctness of the assignment; see L. C. Thomas, "Interpretation of the Infrared Spectra of Organophosphorus Compounds," Heyden, London, 1974. Chapter 15. [b] Spectra obtained on $DCCl_3$ solution of each compound with Me_4Si as internal standard; peak positions quoted in the case of doublets are measured from the approximate center, and relative peak areas are given as whole numbers. [c] ^{31}P resonance is relative to 85% H_3PC_4. [d] ^1H NMR spectra obtained in $DCCl_3$ with 4–5 drops of acetone-d_6 added. [e] NMR data was on the PF_6^- derivative in acetone-d_6. [f] ^1H NMR spectra obtained on $DCCl_3$ solution with 4–5 drops of CF_3CO_2H added. [g] Time averaged for 200 scans. [h] ^1H NMR spectra obtained in pyridine-d_5. Heteronuclear ^{31}P decoupling caused the collapse of the triplets at δ 5.00 and 5.62 to doublets (J = 17 Hz). Homonuclear decoupling gave a J_{PCH} = 17 Hz. [i] The spectra were obtained on samples (1.0 g) in $DCCl_3$ (4 ml). [j] The spectra were obtained on samples (1.0 g) in $DCCl_3$ (3 ml) and CF_3CO_2H (1 ml). [k] The spectra were obtained on samples (1.0 g) in CH_3CN (4.0 ml) with 5 drops of CF_3CO_2H added. The PF_6^- moiety has a value of δ +144.35 and δ +144.32 in **7a** and **7b**, respectively, compared to KPF_6 in H_2O (all compared to 85% H_3PO_4 standard external) which has a value of δ +144.68. [l] Appears as a sextet.

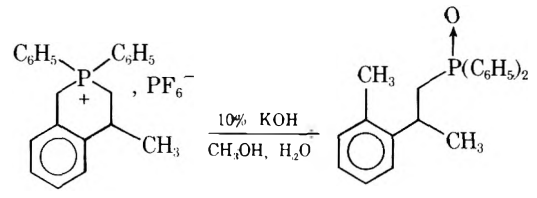
ported to have positive δ values. The cyclic derivatives also show expected shifts, but the variations could possibly be due to angular strain at phosphorus which could influence the symmetry around P and thus the shielding characteristics. Further work is obviously needed in this area before any quantitative judgments can be made.

Additional support for the structure identification of compounds **3h** and **4a** resulted from identification of the base hydrolysis products in each case. As a model for base



3h **9** **10**

hydrolysis, phosphonium salt **3h** gave 1-methylnaphthalene (**9**) and 1-cyclopentenyldiphenylphosphine oxide (**10**) in modest yields. Thus C—P bond cleavage at the ben-

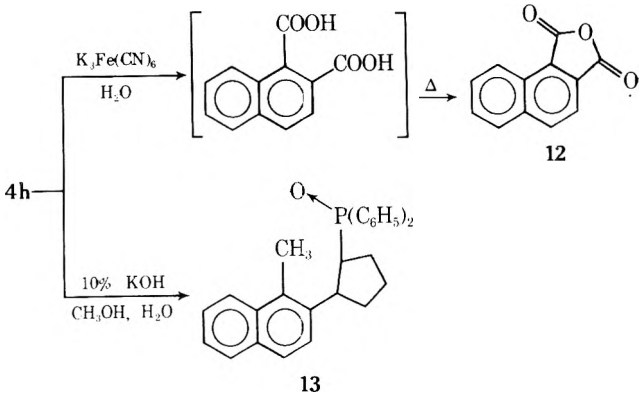


4a **11**

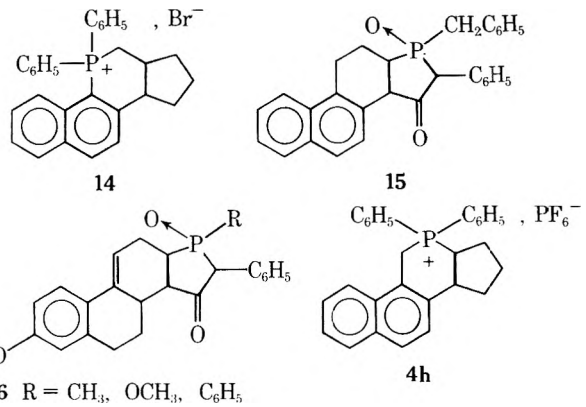
zylic position was found to take precedence as expected.[14] Similar results were observed in the preparation of **11**. Compound **9** was compared to the known compound while **10** and **11** were identified by elemental analyses and spectral data.

Oxidative degradation of **4h** with potassium ferricyanide and dehydration of the resulting diacid (Scheme IV) gave the known 1,2-naphthalene dicarboxylic anhydride (**12**), establishing that the new ring juncture was formed at the 2 position of the naphthalene ring. Further structural information came from hydrolysis of **4h** in 10% KOH (4:1 methanol–water), which cleaved the naphthylic C–P bond to give **13** in good yield. The NMR spectrum, infrared spectrum, and elemental analysis of **13** support the expected structure.

Scheme IV



Interest in heterosteroids as possible regulatory antagonists in metabolism has made the synthesis of new representatives of this class desirable. Although several attempts[15] to synthesize phosphasteroids (where carbon is replaced by phosphorus in the steroid skeleton) are recorded, only three examples have been reported in the literature to date. The synthesis of **14** (an 11-phosphasteroid)[16] and similar structures **15**[17] and **16**,[18] both possessing the



17-phosphasteroidal skeleton, were only very recently advanced. We report herein the synthesis of a fourth phosphasteroid, **4h**, where P is incorporated in the 12 position and several model compounds. The utility of heterophenanthrenes as precursors and model compounds for the synthesis of heterosteroids has been well recognized. However, few examples of C–P heterophenanthrenes are known[19] and the routes to these are often very tedious. Work is continuing on the extention of the method for the preparation of novel phosphorus heterocycles.

Experimental Section

General Data. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A unit as KBr pellets. ^1H NMR and ^{31}P NMR spectra were obtained with a XL-100(15) Varian spectrometer and run in $DCCl_3$ with tetramethylsilane as an internal standard unless otherwise indicated. Mass spectral analyses were performed on a CEC Model 21 HR unit. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Anhydrous solvents such as ether, benzene, toluene, and xylene were dried over sodium and filtered prior to use.

Starting Materials. The tertiary phosphines were either prepared by the classic Grignard reaction as described in the text (phosphines **3a–e**) or via a lithium cleavage process.[20c] One exception was 1-naphthyldiphenylphosphine, which was obtained by the reaction of 1-naphthylmagnesium chloride and diphenylphosphinous chloride and isolated and identified.[20a] Triphenylphosphine was commercially available. The 115% PPA was obtained from FMC Corp.[7]

The benzyl-substituted phosphonium salt **3f** was prepared from 3-cyclopentenyldiphenylphosphine[20c] and benzyl bromide. Standard apparatus used was a 300-ml, three-necked, inverse Grignard flask, addition funnel, mechanical stirrer, condenser, and a N_2 inlet. To this was attached a 300-ml, three-necked, round-bottomed flask, condenser, and a N_2 inlet. The preparation of allylbenzyldiphenylphosphonium bromide (**3a**) will be described as a general procedure.

Allylbenzyldiphenylphosphonium Bromide (3a). To 1.09 g (0.045 g-atom) of Mg in 20 ml of anhydrous ether was added a catalytic amount of iodine and ethyl bromide. After the reaction began, 5.7 g (0.045 mol) of benzyl chloride in 40 ml of ether was slowly added dropwise over a 15-min period followed by a 30-min period at reflux. To the Grignard mixture was slowly added 9.92 g (0.045 mol) of diphenylphosphinous chloride in 40 ml of ether over a 20-min period. This mixture was boiled for 1 hr after the final addition. In the lower, attached flask was placed 8.0 g (0.066 mol) of allyl bromide in 100 ml of anhydrous benzene. The benzene solution was heated to almost reflux, and the contents in the upper flask were added dropwise over a 2.5-hr period. When all the liquid in the upper flask had drained, it was rinsed with 25 ml of ether. The ether, via continued heating and a steady rate of N_2, was expelled from the lower flask. Allyl bromide (5.6 g, 0.046 mol) in 25 ml of benzene was added to the lower flask. The upper flask was removed, and the solution was boiled with stirring for 24 hr under N_2. A precipitate formed and was collected by vacuum filtration, dissolved in a minimum amount of H_2CCl_2, and then reprecipitated by the dropwise addition of ether until the solution became cloudy. After 24 hr, a white precipitate was collected by filtration and dried in vacuo to give 9.3 g (52%) of **3a**, mp 201–203°. Infrared, NMR, and analytical data are given in Tables I and V.

Ring Closures to Produce the Isophosphinolinium Salts. The general procedure will be illustrated with the preparation of **4a** (the most typical), **4b**, and **4e**.

1,2,3,4-Tetrahydro-4-methyl-2,2-diphenylisophosphinolinium Hexafluorophosphate (4a). In a 100-ml beaker was placed 60 ml of 115% PPA which was heated to 160°. Compound **3a** (2.0 g, 5 mmol) was added over a 10-min period followed by an additional 30 min of stirring. During the addition, a gas was given off, probably HBr.[8] The solution was cooled to 110–115° and slowly poured into 500 ml of ice water which resulted in a *homogeneous solution* upon stirring for 15 min. Precipitation of crude **4a** resulted upon the addition of 50 ml of a saturated KPF_6 solution. The crude, wet solid was collected by filtration and dissolved in a minimum amount of H_2CCl_2, and the water layer was separated. The solid was reprecipitated by the dropwise addition of ether until the solution became cloudy. A second reprecipitation from H_2CCl_2–ether gave 1.70 g (75%) of **4a**, mp 172.5–174.5°. Infrared, NMR, and analytical data are given in Tables II and V.

1,2,3,4-Tetrahydro-4,7-dimethyl-2,2-diphenylisophosphinolinium Hexafluorophosphate (4b). Phosphonium salt **3b** was slowly added to 120 ml of 115% PPA at 160° and, when the addition was complete, a stirring period of 45 min followed. When cooled to 110°, the solution was poured into 500 ml of ice water and stirring produced a homogeneous solution. A saturated NaBr solution (100 ml) was added, and the mixture was extracted with three 200-ml portions of H_2CCl_2 and dried ($MgSO_4$). The H_2CCl_2 solution was reduced to ca. 50 ml, and the dropwise addition of ether produced the crude bromide **4b**. The bromide proved exceptionally tedious to purify with much loss of product. Thus, this salt was dissolved in 90 ml of anhydrous methanol and addition of 30 ml of a saturated solution of KPF_6 with stirring produced a heavy precipitate. Purification by reprecipitation from H_2CCl_2–ether gave 1.30 g (28%) of **4b**, mp 185.5–187°. Infrared, NMR, and analytical data are given in Tables II and V.

1,2,3,4-Tetrahydro-2,2-diphenylisophosphinolinium Hexafluorophosphate (4e). To 70 ml of 115% PPA at 300° was added 2.0 g (5 mmol) of **3e** over a 10-min period followed by an additional

1.25 hr of stirring. The very dark solution was cooled to 120° and slowly poured into 250 ml of ice water. Continued stirring gave a clear solution that was filtered through a small piece of glass wool to remove a small amount of insoluble material. Upon addition of 35 ml of saturated KPF_6, a heavy precipitate separated that was extracted (owing to slow filtration) with two 200-ml and one 100-ml portions of H_2CCl_2. The solution was concentrated to ca. 40 ml followed by treatment with ether to produce crude **4e**. Infrared, NMR, and analytical data are given in Tables II and V.

Ring Closure to Produce the Phosphinolinium Salts. The general procedure will be illustrated with **7a**, which was typical of all systems studied.

1,2,3,4-Tetrahydro-4-methyl-1,1-diphenylphosphinolinium Hexafluorophosphate (7a). Compound **6a** (2.0 g, 5 mmol) underwent cyclization when treated with 60 ml of 115% PPA at 160° for 30 min. The crude heterocyclic salt **7a** was precipitated from 300 ml of water upon addition of 500 ml of a saturated KPF_6 solution. Two reprecipitations from H_2CCl_2–ether produced 1.9 g (82%) of **7a**, mp 203.5–205°. Infrared, NMR, and analytical data are given in Tables IV and V.

Base Hydrolysis of 3-Cyclopenten-1-yl(1-naphthylmethyl)-diphenylphosphonium Hexafluorophosphate (3h). The phosphonium compound **3h** (400 mg, 0.74 mmol) was boiled for 16 hr in 50 ml of methanol–water (4:1) containing 5 g of KOH. The mixture was cooled and 50 ml of water was added. The water layer was extracted with ether and then chloroform and, after drying ($MgSO_4$), gave 280 mg of residue. This residue was chromatographed over neutral alumina (benzene) to give 80 mg (76%) of 1-methylnaphthalene (**9**), identical with an authentic sample, and 130 mg (65%) of 1-cyclopentenyldiphenylphosphine oxide (**10**);[20c] ir ν 1600 (C=C), 1437, 1122 (P–C_6H_5), 1186 cm^{-1} (P → O); ^1H NMR (CCl_4) δ 2.00 [quartet (J = 7 Hz), CH_2, 2 H], 2.50 [m, $-(CH_2)_2-$, 4 H], 6.21 [d (J = 10 Hz), CH, 1 H], 7.20–7.80 (m, 2 C_6H_5, 10 H); mass spectrum (70 eV) m/e 268 (M^+).

Base Hydrolysis of 1,2,3,4-Tetrahydro-4-methyl-2,2-diphenylisophosphinolinium Hexafluorophosphate (4a). Compound **4a** (400 mg, 1 mmol) was heated in 40 ml of methanol–water (4:1) with 4 g of KOH for 12 hr. The solution was cooled and 50 ml of water was added. This was extracted with $HCCl_3$ and dried ($MgSO_4$). The residue was chromatographed an acidic alumina (Merck activity I) using benzene to give 217 mg (65%) of **11**: ir (film) ν 3450 (hydrate), 1439, 1121 (P–C_6H_5), 1188 cm^{-1} (P → O); ^1H NMR ($DCCl_3$) δ 1.34 [d (J = 7 Hz), CH_3, 3 H], 2.12 (s, CH_3, 3 H), 2.50 [d of d (J_{HCCH} = 6, J_{PCH} = 11 Hz), PCH_2CH, 2 H], 3.55 (m, CH, 1 H), 7.00–7.90 (m, aromatic H, 14 H); mass spectrum (70 eV) m/e 334 (M^+).

Anal. Calcd for $C_{22}H_{23}OP$: C, 79.02; H, 6.93. Found: C, 78.50; H, 7.36.

Oxidative Degradation of 4h. Preparation of 1,2-Naphthalenedicarboxylic Anhydride (12). The procedure was essentially that of Cope with some modifications.[21] The cyclic product **4h** (0.125 g, 0.23 mmol), 7.0 g of $K_3Fe(CN)_6$, and 1.25 g of KOH were heated at 70–75° 60 hr in 25 ml of water. The reaction mixture was filtered, carefully acidified (concentrated HCl), and extracted with ether. The residue from the ether solution was sublimed at 160° (0.2 mm) to give 5 mg (11%) of anhydride **12**, mp 162–165° (lit.[22] mp 168°). The low solubility of **4h** in water could explain the low yield of **12**.

Base Hydrolysis of 6,6a,7,8,9,9a-Hexahydro-6,6-diphenyl-5*H*-benzo[*h*]cyclopent[*c*]isophosphinolinium Hexafluorophosphate (4h). Compound **4h** (300 mg, 0.56 mmol) was heated for 14 hr in 40 ml of methanol–water (4:1) containing 4 g of KOH under N_2. An additional 20 ml of water was added and the mixture was extracted (3 × 25 ml of $HCCl_3$). The organic layer was dried ($MgSO_4$), and the residue from the chloroform solution was chromatographed over neutral alumina (benzene) to yield 180 mg (79%) of **13**: mp 168–169°; ir (KBr) ν 1429, 1116 (P–C_6H_5), 1174 cm^{-1} (P → O); ^1H NMR ($DCCl_3$) δ 2.10 [m, $-(CH_2)_3-$ 6 H], 2.62 (s, CH_3, 3 H), 2.95 (m, CH, 1 H), 3.60 (m, CH, 1 H), 7.30–8.00 (m, aromatics, 16 H); mass spectrum (70 eV) m/e 410 (M^+).

Anal. Calcd for $C_{28}H_{27}PO$: C, 81.91; H, 6.63; P, 7.56. Found: C, 81.84; H, 6.61; P, 7.72.

Registry No.—**3a**, 53201-22-2; **3b**, 54229-88-8; **3c**, 54229-89-9; **3d**, 54229-90-2; **3e**, 23901-74-8; **3f**, 54229-91-3; **3g**, 54229-93-5; **3h**, 54229-94-6; **4a**, 54229-96-8; **4b**, 54229-98-0; **4c**, 54230-00-1; **4d**, 54230-02-3; **4e**, 54230-04-5; **4f**, 54230-05-6; **4g**, 54293-27-5; **4h**, 54230-07-8; **5**, 23901-73-7; **6a**, 28975-45-3; **6b**, 54230-08-9; **6c**, 54230-09-0; **6d**, 54230-10-3; **7a**, 54230-12-5; **7b**, 54293-29-7; **7c**, 54230-14-7; **7d**, 54230-16-9; **10**, 38868-18-7; **11**, 54230-17-0; **12**, 5343-99-7; **13**, 54230-18-1; 1-naphthyl chloride, 90-13-1; 3-cyclopentenyldiphenylphosphine, 54230-19-2; benzyl bromide, 100-39-0; benzyl chloride, 100-44-7; diphenylphosphinous chloride, 1079-66-9; allyl bromide, 106-95-6; 1-bromo-2-butene, 4784-77-4; 3-methylbenzyl chloride, 620-19-9; 1-naphthylmethyl chloride, 86-52-2; β-bromophenetole, 589-10-6; ethyl acetate, 141-78-6; triphenylphosphine, 603-35-0; diphenyl-1-naphthylphosphine, 1162-90-9.

References and Notes

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Base-Catalyzed Reactions of α,β-Unsaturated Esters and Nitriles. II. Potassium-Catalyzed Di- and Trimerization of 2-Butenenitrile

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In the presence of a potassium–benzylpotassium catalyst system, at 110° and toluene as a solvent, 2-butenenitrile (**1**) undergoes oligomerization yielding 20–23% dimer, 2-ethylidene-3-methylglutaronitrile (**2**), and 67–75% cyclic trimer, identified as 1,3,5-tricyano-2,4,6-trimethylcyclohexane (**3**). Compound **2** is a mixture of the two possible geometric isomers; the component with a vinylic hydrogen cis to the conjugated cyano group represents 67% dimer. Trimer **3**, which contains a dominant stereoisomer (75–80%), yields on acid hydrolysis the monoamide of 2,4,6-trimethyl-1,3,5-cyclohexanetricarboxylic acid (**4**), rather than the free triacid. Resistance to complete hydrolysis is tentatively ascribed to the presence of a sterically hindered nitrile group in **3**. It is proposed that formation of **3** could be initiated either by α-vinylic or by allylic metalation of **1**, and that termination of the oligomerization process is caused by fast cyclization of an intermediate trimeric carbanion, followed by protonation.

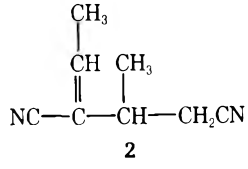
It was reported previously[1] that ethyl crotonate undergoes selective dimerization in the presence of a potassium–benzylpotassium catalyst to give the diethyl ester of 2-ethylidene-3-methylglutaric acid in nearly quantitative yield. This finding indicated that promoted alkali metal catalysts, previously used for dimerization[2,3] and aralkylation[4–7] of styrenes, as well as a variety of other processes,[8] could be conveniently employed for similar reactions of α,β-unsaturated esters. As an extension of these studies the potassium-catalyzed reactions of 2-butenenitrile (crotononitrile, **1**) were investigated with the objective of developing suitable procedures for selective oligomerization of α,β-unsaturated nitriles.

While high molecular weight polymerization and copolymerization reactions of **1** have been studied to some extent,[9–13] and a process for preparation of sterically regular polycrotononitrile has been reported,[14] there are only limited data on the oligomerization of this nitrile. An early study[15] indicates that in the presence of ethylmagnesium bromide **1** yields a mixture of oligomers, mainly a trimer, the structure of which could not be elucidated. It was subsequently reported[16] that monomer **1** is readily oligomerized in the presence of sodium ethoxide to give a mixture of dimeric, trimeric, and higher products of unspecified structure.

Experiments with **1** in the present study were carried out at 110°, using a large excess of toluene or methylcyclohexane as a solvent (**1**/solvent molar ratios of 1:6 to 1:10). About 0.2 g-atom of metallic potassium and 0.05 mol of *o*-chlorotoluene per mole of monomer **1** were used in the preparation of the potassium–benzylpotassium catalyst. Under these conditions (see Experimental Section), **1** reacts almost quantitatively to yield a mixture containing 20–23% of a dimer, 67–75% of a trimer, and 5–15% of unidentified high-boiling products. This product distribution is sharply different from that observed in the potassium-catalyzed reaction of ethyl crotonate, which yields almost exclusively a dimer under identical experimental conditions.[1]

In oligomerization experiments with sodium–benzylsodium as a catalyst, under otherwise identical conditions, the conversion of **1** is considerably lower (30–35%), while the dimer/trimer ratio remains similar to that observed with the potassium–benzylpotassium system.

The dimer of **1**, bp 82–83° (0.2 mm), was identified as 2-ethylidene-3-methylglutaronitrile (**2**), whereas the structure of the trimer, bp 152–155° (0.2 mm), was elucidated as that of 1,3,5-tricyano-2,4,6-trimethylcyclohexane (**3**).



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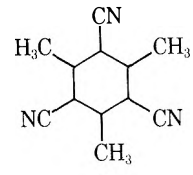
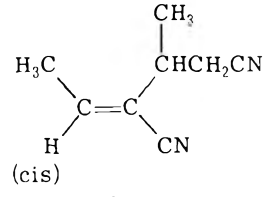


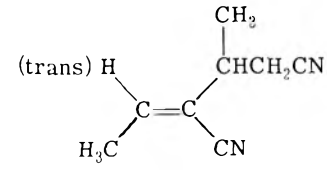
3

Compound **2** was identified by a combination of NMR, ir, and mass spectral analysis (see Experimental Section), and by conversion into derivatives.

Hydrolysis of **2** yielded 2-ethylidene-3-methylglutaric acid, identified by comparison with a reference sample obtained by independent means.[1] The distribution of **2** into the two possible stereoisomers **2a** and **2b** could not be determined by direct NMR analysis, since the differential shielding of cis and trans vinylic protons by a β-cyano group is only ca. 0.05 ppm.[17]



2a



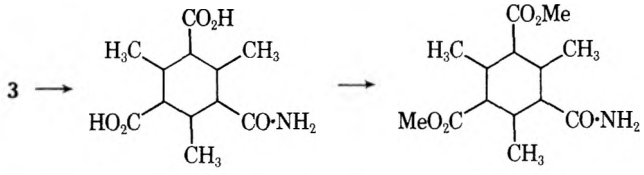
2b

Resolution of **2** into stereoisomers **2a** and **2b** was achieved by gas chromatography on a 300-ft capillary column coated with trifluoropropylmethylpolysiloxane. The molar ratio of **2a**:**2b** was 67:33. Structure assignment for the two stereoisomers was based on NMR analysis of the corresponding diester isomers, obtained by base hydrolysis of **2** under mild conditions and subsequent esterification with diazomethane. The differential shielding of the cis and trans vinylic protons by the β-carbomethoxy group in the produced dimethyl 2-ethylidene-3-methylglutarate was found to be 1.0 ppm, which allows for facile quantitative determination of the two stereoisomeric components.

Trimer **3** on gentle heating (80–100°) exhibits mercury-like mobility, viz., it does not wet glass, porcelain, and metal surfaces. Gas chromatographic analysis of **3** shows the presence of a dominant stereoisomer (75–80%), accompanied by small amounts of at least two other stereoisomeric components. The NMR, ir, and mass spectra of the tri-

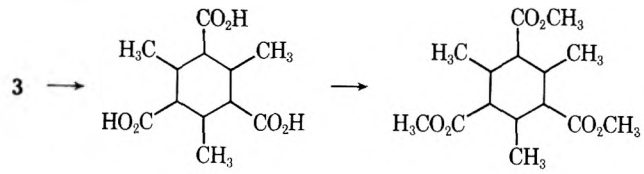
mer fully corroborated structure **3**, while the ^{13}C NMR spectrum indicated the absence of any significant amounts of an unsymmetrically substituted isomer, e.g., 1,2,4-tricyano-3,5,6-trimethylcyclohexane (see Experimental Section).

Hydrolysis of **3** with a 25% solution of sulfuric acid in glacial acetic acid yielded the monoamide of 2,4,6-trimethyl-1,3,5-cyclohexanetricarboxylic acid (**4**), which was subsequently transformed into the corresponding monoamide diester **5** by interaction with a diazomethane solution.



4 **5**

The NMR, ir, and mass spectra of the two derivatives were in agreement with structures **4** and **5** (see Experimental Section). Complete acid-catalyzed hydrolysis of **3** to the tricarboxylic acid **6** is extremely difficult and is practically not observed for reaction times of 20–24 hr. The reaction takes place to a very limited extent (10–15% by weight) at prolonged reaction time (>50 hr), and is accompanied by considerable loss of substrate.

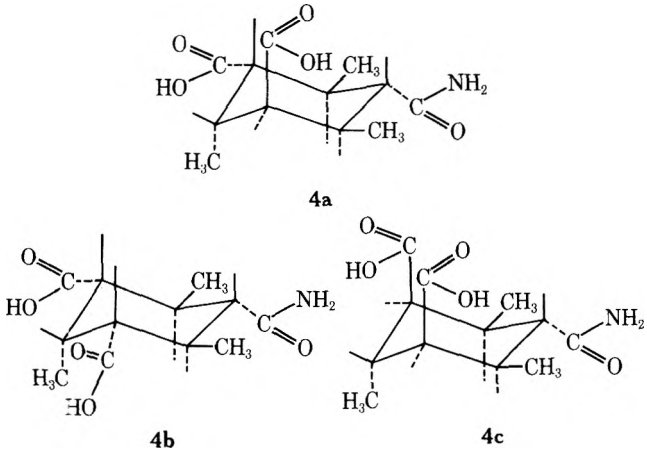


6 **7**

A sample of **6**, obtained by repeated fractional crystallization of the acid hydrolysis product (reaction time, 54 hr), was converted to the corresponding trimethyl ester **7** by reaction with diazomethane.

Separate experiments showed that basic reagents, e.g., potassium hydroxide in benzyl alcohol, are similarly ineffective for complete hydrolysis of **3**.

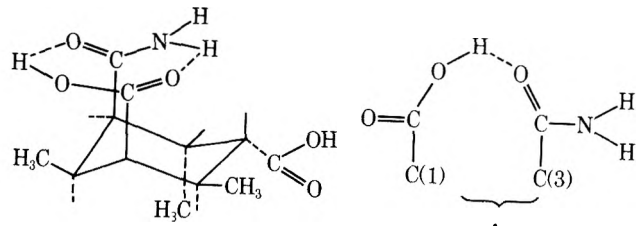
The observed phenomenon is probably related to the stereochemistry of compound **3**, as one of the three nitrile groups in the dominant stereoisomer could be sterically hindered. Examination of possible conformation models of the hydrolysis product **4** shows indeed that if an equatorial amide group is flanked by two equatorial methyl groups, as for instance in stereoisomers **4a**, **4b**, or **4c**, the approach to the former by the hydrolyzing species is sterically hindered.



4a **4b** **4c**

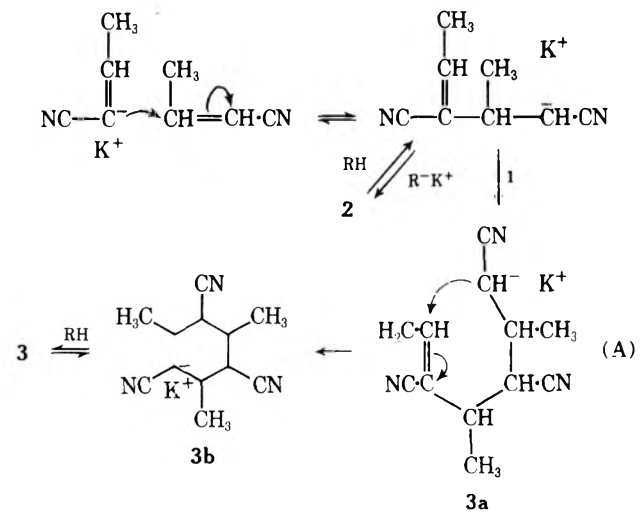
Isomers **4a**, **4b**, and **4c** are derivable from stereoisomeric forms of the original trinitrile **3**, containing (a) two equatorial and one axial cyano groups; (b) three equatorial cyano groups; and (c) one equatorial and two axial cyano groups, respectively. It should be noted that in the trinitrile precursors of stereoisomers **4a** and **4b** only one of the equatorial cyano groups is flanked by two equatorial methyl groups. Furthermore, models indicate that trinitrile stereoisomers corresponding to **4a** and **4b** have a minimal extent of steric interactions, and, therefore, should be energetically favored. The NMR spectra of esters **5** and **7**, derived from **4**, show two well-resolved signals for the two stereochemically distinct types of methyl groups[18] (in the ratio 2:1) in agreement with structures **4a**, **4b**, or **4c** (see Experimental Section).

An alternative but more remote possibility regarding the resistance of the trimer to complete hydrolysis is that the intermediate **4** contains an axial amido group which is stabilized by intramolecular hydrogen bonding[19] with a coaxial carboxylic group. Formation of a cyclic hydrogen bond complex, as in **4d** would require that the hydroxyl group, as well as the NH_2 group, rotate out of coplanarity with the respective carbonyl groups, which may be energetically feasible at the hydrolysis temperature employed (above 100°). Examination of models shows that single hydrogen bonding with preservation of coplanarity within (and between) the carboxylic and amide groups, as for instance in **4e**, is also possible, requiring only slight distortion of bond angles.



4d **4e**

By analogy with the mechanism proposed for the dimerization of ethyl crotonate,[1] the potassium-catalyzed reaction of **1**, leading to **2** and **3**, could be initiated by metalation at the α-vinylic position. Formation of higher oligomers is prevented by cyclization of an intermediate trimeric carbanion (**3a**) to give the resonance-stabilized trimer precursor **3b** (sequence A).

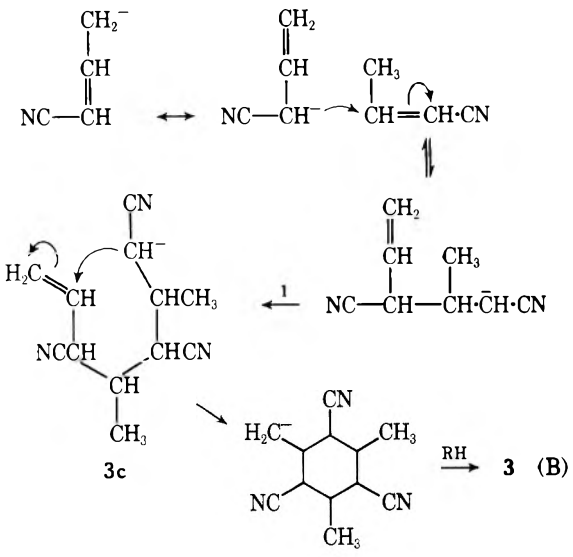


3b **3a**

Cyclization of unsaturated carbanions to resonance-stabilized tertiary carbanions, which are protonated to form five- or six-membered ring systems, has been found previously in the sodium-catalyzed reaction of α-methylstyrene.[3] On the other hand, the absence of any appreciable amount of an open-chain trimer of **1** in the reaction prod-

uct suggests that in the present case the trimerization and cyclization steps could proceed by a concerted mechanism, i.e., through an intermediate which is not a fully developed trimeric carbanion.

Alternatively, oligomerization of **1** could be initiated by allylic metalation. In such case formation of **3** may involve cyclization of a secondary trimeric carbanion (**3c**) to give an energetically favored primary carbanion (**3d**) as precursor of **3** (sequence B, K^+ omitted).

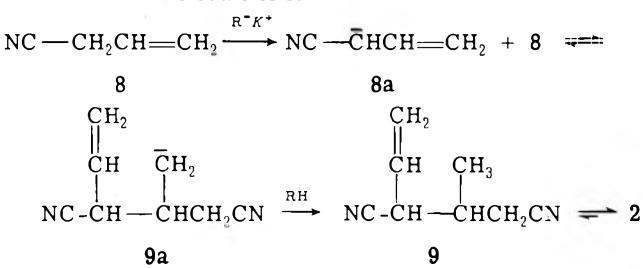


3c **3d**

Similar cyclizations of $\Delta^{4,5}$-, $\Delta^{5,6}$-, or $\Delta^{6,7}$-unsaturated carbanions, stabilized by charge delocalization, into localized primary carbanions which undergo fast irreversible protonation have been shown to occur in the potassium-catalyzed reaction of 1-phenyl-1,3-pentadiene, yielding 3-methyl-4-phenylcyclobutene,[2] as well as in the conversion of 6-phenyl-1-hexene and 7-phenyl-1-hexene to 1-phenyl-2-methylcyclopentane and 1-phenyl-2-methylcyclohexane, respectively.[20] Intramolecular cyclizations of ω-(3-pyridyl)-1-alkenes and ω-(4-pyridyl)-1-alkenes provide a further illustration of this type of carbanionic reaction.[21]

For comparison, experiments with 3-butenenitrile (allyl cyanide, **8**) as starting monomer were also carried out. It is found that, like **1**, compound **8** undergoes smooth reaction in the presence of potassium–benzylpotassium as catalyst (conversion, 80–85% at 110°; see Experimental Section), giving the same type of oligomers as obtained from **1**. However, gas chromatographic analysis of the product from **8** shows a dimer/trimer ratio of ca. 60:40 (% by weight), which is higher by a factor of about 8 compared to that found with **1**. Further, analysis of the unreacted monomer indicates that isomerization of **8** into the conjugated isomer **1**, during the oligomerization process, is incomplete.

The high dimer yield obtained from **8** may be due to fast protonation of a localized primary dimeric carbanion (**9a**) expected by interaction of the monomeric carbanion **8a** with a second molecule of **8**.



8 **8a** **9a** **9**

Metalation of **2**, followed by interaction with 2-butenenitrile (from isomerization of **8**), could give trimer **3** according to either sequence A or B. The low yield of **3** may be due to a low metalation rate of **2**, or to a relatively low concentration of 2-butenenitrile needed for the trimerization–cyclization step. Interaction of carbanion **9a**, or of the carbanion derived from **2**, with a third molecule of monomer **8**, followed by cyclization, should give cyclohexane derivatives possessing cyanomethyl substituents. No such compounds were detected in the product, indicating that the conjugated monomer **1**, rather than **8**, is involved in the final, trimerization–cyclization step.

It should be noted that the alkali metal catalyzed cyclotrimerization of **1** is different from base- or acid-induced cyclotrimerizations of aromatic nitriles, which involve participation of the cyano groups in the oligomerization process, and lead to 1,3,5-triazines.[22] The present process is also different from cyclotrimerization reactions involved in the termination of anionic oligomerization and polymerization processes of acrylates, initiated by organolithium or organomagnesium compounds. In such reactions initiation consists in addition of the organometallic initiator across the double bond of the monomer, while the termination step involves intramolecular nucleophilic attack on an ester group in the intermediate trimeric complex, leading to a cyclic β-keto ester.[23,24] In contrast, with promoted alkali metal catalysts there is no addition of the initiating species to the monomer, and oligomerization proceeds selectively with preservation of the ester or nitrile functional group.

Experimental Section

Materials. Crotononitrile (2-butenenitrile), supplied by Fluka A.G., was dried over anhydrous magnesium sulfate, and then distilled at 100 mm through a fractionating column. The purified (99.2%) monomer contained 76% cis and 24% trans isomer.

Allyl cyanide (3-butenenitrile), obtained from Borden Chemical Co., was dried and then redistilled at atmospheric pressure to give a sample of more than 99% purity.

Oligomerization Procedure. The preparation of the potassium–benzylpotassium catalyst, and a typical large-scale oligomerization experiment, were performed as follows.

Toluene (30 g) was introduced in a 500-ml three-neck flask equipped with a constant-rate dropping funnel, a reflux condenser, and a high-speed, 10,000 rpm stirrer provided with a metal dispersing blade. The apparatus was purged with dry nitrogen, 3 g (0.075 mol) of freshly cut potassium was added to the flask, and the mixture was brought to boiling and kept for 10 min without mixing. The molten metal was then stirred under reflux for 1 hr, and subsequently 2.5 g (0.02 mol) of o-chlorotoluene, dissolved in 10 g of toluene, was added dropwise to the fine dispersion, which acquired a black color at this stage. The catalyst preparation was completed by slowly adding (1 hr) another portion of toluene (120 g), while keeping the mixture under reflux.

Crotononitrile (25.2 g, 0.375 mol), dissolved in 45 g of toluene, was added at a constant rate to the stirred catalyst dispersion (45 min) and the mixing continued for another hour. A slow stream of nitrogen was kept throughout the experiment. The reaction mixture was quickly cooled to −5° and the catalyst decomposed by slowly adding 15 ml of absolute ethanol; decomposition above 0° causes side reactions. The product was washed with 10% aqueous hydrochloric acid, 10% aqueous sodium bicarbonate, and water, and finally dried over anhydrous magnesium sulfate. The solvent and unreacted monomer were removed at 100 mm and the remaining product (22.3 g, conversion 88.5%) was distilled to give a dimeric fraction, bp 80–85° (0.2 mm), 4.8 g (19.2%), a trimeric fraction, bp 150–155° (0.2 mm), 15.7 g (70.4%), and a high-boiling residue, ca. 1.5 g (ca. 7%).

2-Ethylidene-3-methylglutaronitrile (2). The dimeric product from several experiments was combined and redistilled to give a sample of **2** in more than 99% purity: bp 81–83° (0.2 mm); n^{25}D 1.4730; ir (neat) 852 ($R_1R_2C{=}CHR_3$, =C–H out-of-plane deformation),[25] 963, 1006, 1075, 1123, 1380 ($R_1R_2C{=}CHR_3$, =C–H in-plane deformation),[25] 1420, 1445, 1594–1628 (C=C, splitting due to conjugation with CN group), 2212 (conjugated CN), 2241 cm^{-1} (nonconjugated CN); ir ($CHCl_3$) 849 (=C–H out-of-plane deformation), 963, 1002, 1070, 1119, 1385 (=C–H in-plane deformation), 1423, 1455, 1597–1639 (C=C), 2198 (conjugated CN), 2228

(nonconjugated CN), 2905, 2955 cm^{-1}; NMR (CCl_4) δ 1.25 (d, 3, J = 6.3 Hz, CH_3 at C-3), 1.98 (d, 3, J = 7.0 Hz, $=CHCH_3$), 2.45 (d, 2, J = 5.7 Hz, $CHCH_2CN$), 2.5–3.0 (m, 1, H at C-3), 6.48 (q, 1, J = 7.1 Hz, $=CHCH_3$); m/e 134 (M^+).

Anal. Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.74; H, 7.36; N, 20.60.

Dimethyl 2-Ethylidene-3-methylglutarate (2c). Stereoisomeric Composition of Dimer 2. A 10-ml portion of 20% aqueous sodium hydroxide was added to 1.0 g (7.46 mmol) of **2**, and the mixture was refluxed for 24 hr. The hydrolysate was washed with ether to remove any unreacted **2**, acidified with aqueous hydrochloric acid, and then extracted with ether to give 2-ethylidene-3-methylglutaric acid, 1.04 g (6.05 mmol), 81%, identified by comparison with a reference sample.[1] A 0.40-g (2.32 mmol) portion of the acid, recrystallized from a mixture of carbon tetrachloride and ethyl acetate, was dissolved in ether and treated with an excess ethereal solution of diazomethane. The mixture was left for 4 hr, the solvent was removed, and the produced ester **2c**, 0.43 g (2.15 mmol), 93%, was subjected to quantitative NMR analysis in the 5.0–8.0-ppm region. The intensity of a quartet, centered at 6.8 ppm and due to the isomer with a vinylic hydrogen cis to the carbomethoxy group, relative to the intensity of a second quartet, centered at 5.8 ppm and due to the isomer with a vinylic hydrogen trans to the carbomethoxy group,[1] was 69:31, reflecting the distribution of the corresponding dinitrile stereoisomers **2a** and **2b** in the original dimeric fraction. Direct gas chromatographic analysis of dimer **2** on a capillary column (see Analytical) gave two well-resolved peaks in the ratio 67:33, in good agreement with the NMR determination.

1,3,5-Tricyano-2,4,6-trimethylcyclohexane (3). The redistilled trimer, bp 152–155° (0.2 mm), $n^{25}D$ 1.4950, $n^{30}D$ 1.4926, m/e 201 (M^+), was 99% pure and free of any dimer or higher oligomer.

Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.41; H, 7.49; N, 20.59.

Gas chromatography of **3** (see Analytical) reveals the presence of at least three stereoisomers, including a dominant component (75–80%): ir ($CHCl_3$) 966, 1390 (CH_3, symmetrical C–H deformation),[26] 1460 (CH_3, asymmetrical C–H deformation),[26] 2238 (CN stretching), 2910 (ring C–H stretching), 2960 cm^{-1} (CH_3, C–H stretching); NMR ($CDCl_3$) δ 1.38 (d superimposed on weaker m, 9, J = 6.2 Hz, $CHCH_3$), 1.9–2.3 (m, 3, CH_3CH), 2.5–3.0 (m, 3, NCCH).

The ^{13}C NMR spectrum of **3** shows a single line in the nitrile region, indicating the absence of any significant amounts of an unsymmetrically substituted isomer, containing separated as well as adjacent nitrile groups, e.g., 1,2,4-tricyano-3,5,6-trimethylcyclohexane, which should give rise to more than one signal in this region.

2,4,6-Trimethyl-1,3,5-cyclohexanetricarboxylic Acid Monoamide (4). A 5-g (0.025 mol) portion of trimer **3** was dissolved with gentle warming in 12 ml of glacial acetic acid, and to this was added 25 ml of concentrated sulfuric acid in 30 ml of water. The mixture was refluxed for 24 hr, and then cooled down to room temperature, diluted with 100 ml of saturated aqueous sodium chloride, and filtered, and the filtrate was continuously extracted with ether. The extract was treated with activated charcoal and silica gel, filtered, and dried. Removal of the solvent gave 4.6 g (0.018 mol), 72%, of crystalline monoamide **4**. Recrystallization from glacial acetic acid gave a pure sample of **4**: mp 274–276°; m/e 257 (M^+); ir (KBr) 1375 (CH_3, symmetrical C–H deformation), 1425 (CO_2H C–O– stretching),[27] 1460 (CH_3, asymmetrical C–H deformation), 1595 (NH_2 deformation), 1690 ($CONH_2$, C=O stretching),[27] 1715 (CO_2H, C=O stretching),[27] 2970, 3180–3300 (bonded N–H stretching),[27] 3490 cm^{-1} (OH stretching).

Anal. Calcd for $C_{12}H_{19}O_5N$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.10; H, 7.17; N, 5.18.

2,4,6-Trimethyl-3,5-dicarbomethoxy-1-cyclohexanecarboxamide (5). A 100-mg (0.388 mmol) portion of monoamide **4** was dissolved in 20 ml of absolute methanol, and the solution was treated with an excess ethereal solution of diazomethane. The mixture was left for 1 hr at room temperature, and the solvent was removed, leaving 108 mg (0.380 mmol), conversion 98%, of the esterified product **5**: m/e 285 (M^+); ir ($CHCl_3$) 1165 (CO_2Me, C–O– stretching), 1440, 1465, 1600 (NH_2 deformation), 1690 (C=O in $CONH_2$),[27] 1745 (C=O in CO_2Me),[27] 3000, 3500 cm^{-1} ($CONH_2$, nonassociated N–H stretching);[27] NMR ($CDCl_3$) δ 0.90 (d, 6, J = 6.2 Hz, CH_3), 1.05 (d, 3, J = 6.5 Hz, CH_3), 1.80–2.80 (m, 6, ring CH), 3.53 (s, 6, OCH_3), 5.28–5.76 (broad signal, 2, NH_2).

2,4,6-Trimethyl-1,3,5-cyclohexanetricarboxylic Acid (6). A 1.9-g (0.094 mol) portion of trimer **3** was dissolved with gentle heating in 8 ml of glacial acetic acid. To this was added 12.5 ml of concentrated sulfuric acid dissolved in 15 ml of water, and the mixture was refluxed for 24 hr. A fresh portion of 12.5 ml of sulfuric acid in 15 ml of water was added to the mixture and refluxing was continued for another 30 hr. After cooling, 30 ml of water was added, and the hydrolysate was filtered and then continuously extracted with ether for 4 days. The extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed, leaving a partially crystalline residue which after repeated fractional crystallization from glacial acetic acid gave 0.26 g (1.05 mmol, yield 11.2%) of acid **6**: mp 284–286°; m/e 258 (M^+); ir (KBr) 1460 (CH_2), 1720 (C=O), 2970, 3550 cm^{-1} (OH); NMR (pyridine) δ 0.9–1.5 (two closely spaced d, 9, CH_3), 2.3–3.4 (m, 6, ring CH), 11.1 (broad signal, 3, CO_2H).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.91; H, 7.18.

Trimethyl 2,4,6-Trimethyl-1,3,5-cyclohexanetricarboxylate (7). A 50-mg (0.194 mmol) portion of triacid **6** was dissolved in 10 ml of absolute methanol and treated with excess ethereal solution of diazomethane. The mixture was left for 1 hr at room temperature and the solvent was removed under vacuum, leaving 57 mg (0.190 mmol, yield 98%) of triester **7**: m/e 300 (M^+); NMR ($CDCl_3$) δ 0.87 (d, 6, J = 6.2 Hz, CH_3), 1.02 (d, 3, J = 6.6 Hz, CH_3), 1.9–2.9 (m, 6, ring CH), 3.58 (s, 9, OCH_3).

Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.70; H, 8.13.

The chemical shift difference between the two sharp, well-resolved doublets at 0.87 and 1.02 ppm, i.e., 0.15 ppm, is the expected one for equatorial and axial methyl groups in a symmetrically substituted cyclohexane.[18] The two signals provide further evidence for the absence of an unsymmetrical, 1,2,4-trimethyl-substituted component in the trimer, since the chemical shift difference for adjacent and separated methyls in such an isomer should be larger, and adjacent methyl substituents should produce methyl–methyl long-range coupling, i.e., a more complex pattern than observed.

Potassium-Catalyzed Oligomerization of 3-Butenenitrile (8). The preparation of the potassium–benzylpotassium catalyst, and the oligomerization of **8**, were carried out using the same procedure as described above for **1**.

In a typical experiment, 1.5 g (0.038 g-atom) of potassium, 1.25 g (0.01 mol) of *o*-chlorotoluene, and 75 g of toluene were used in the catalyst preparation, while 12.6 g (0.187 mol) of monomer **8** in 30 g of toluene was used in the oligomerization. The product, 9.65 g (conversion 76%), contained 63.0% of dimer **2**, 36.2% of trimer **3**, and ca. 0.8% of higher products, as determined by gas chromatography. The average oligomer distribution from several experiments was (% by weight) **2**, 61.0; **3**, 38.2; and higher components, ca. 0.8.

Analytical. Quantitative gas chromatography of oligomerization products was performed on a 6 ft × 0.125 in. column, packed with 10% UCC-W-982 silicone gum rubber, methyl vinyl type, on 80–100 mesh Diatoport S. Separation of **3** into stereoisomeric components was achieved on the same column, using slow programming in the 150–215° range. The resolution of **2** into stereoisomers **2a** and **2b** was carried out on a 300 ft × 0.01 in. Golay column, coated with QF-1 (trifluoropropylmethyl silicone), at 140° and a nitrogen pressure of 20 psi.

A Bruker 90, 90-MHz, Model HFX-10 high-resolution NMR spectrometer was used for measurement of the NMR spectra, while ir analysis was performed with a Perkin-Elmer Model 457A spectrophotometer.

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Registry No.—*cis*-**1**, 1190-76-7; *trans*-**1**, 627-26-9; **2a**, 22485-85-4; **2b**, 22485-84-3; *cis*-**2c**, 16657-04-8; *trans*-**2c**, 16657-03-7; **3**, 54181-86-1; **4a**, 54119-93-6; **4b**, 54163-74-5; **4c**, 54163-75-6; **5**, 54119-98-1; **6**, 54119-99-2; **7**, 54120-00-2; **8**, 109-75-1.

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Notes

Reductive Decyanation of β,γ-Epoxy Nitriles. A New Synthesis of β-Isopropylidene Alcohols

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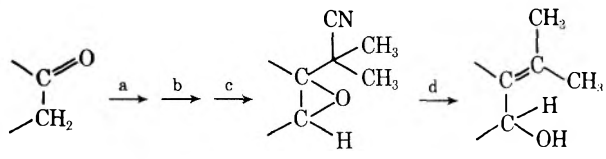
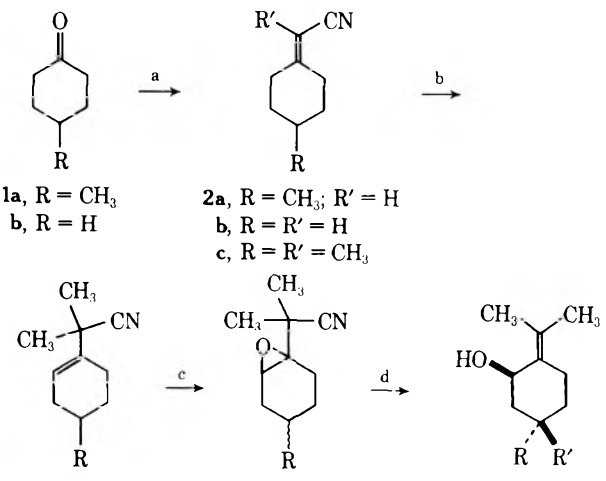
In the course of studies aimed at the synthesis of natural sesquiterpenoids we discovered that β,γ-epoxy nitriles underwent reductive decyanation–elimination to allylic alcohols upon treatment with sodium in liquid ammonia.[1] The epoxy nitriles could be prepared quite easily from ketones by a sequence involving (a) condensation with diethyl sodiocyanomethylphosphate, (b) geminal alkylation with methyl iodide, and (c) epoxidation with *m*-chloroperoxybenzoic acid (Scheme I). Since this initial discovery we have examined a number of additional substrates to ascertain the generality of the sequence and to optimize the reaction conditions. We have also carried out some preliminary studies of the oxidation of the allylic alcohol products. These results are reported herein.

Scheme I



Condensation of 4-methylcyclohexanone (**1a**) with diethyl sodiocyanomethylphosphonate afforded the nitrile **2a.** Alkylation of this nitrile in tetrahydrofuran using excess lithium diisopropylamide as the base and excess methyl iodide gave only the monomethylated conjugated nitrile **2c.** Presumably addition of the amide to the conjugated double bond effectively competes with proton abstraction, as is found for conjugated esters.[2] Schlessinger found that a 1:1 complex of lithium diisopropylamide and hexamethylphosphoric triamide (HMPA) showed a strong preference for proton abstraction in such cases.[2] Following his procedure we obtained an 80:20 mixture of di- and monomethylated product. However, with a 3:1 ratio of HMPA to base, dimethylation proceeded smoothly to give nitrile **3a.** Epoxidation of unsaturated nitrile **3a** afforded the epoxy nitrile **4a** as an apparent mixture of stereoisomers. Reduction–elimination of this mixture with sodium in liquid ammonia gave a roughly 2:1 mixture of alcohols **5a** and **5b,** *trans*- and *cis*-pulegol, in nearly 90% yield (Chart I).

Chart I[a]



1a, R = CH_3
b, R = H

2a, R = CH_3; R′ = H
b, R = R′ = H
c, R = R′ = CH_3

3a, R = CH_3
b, R = H

4a, R = CH_3
b, R = H

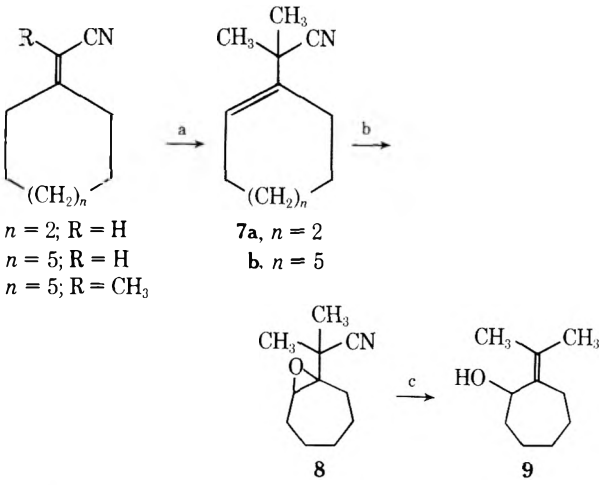
5a, R = CH_3; R′ = H
b, R = H; R′ = CH_3
c, R = R′ = H

[a] a, $NaCH(CN)PO(OEt)_2$; b, $(i\text{-}Pr)_2NLi$, CH_3I, HMPA; c, *m*-$ClC_6H_4CO_3H$; d, Na, NH_3.

Application of the above scheme to cyclohexanone (**1b**) afforded 2-isopropylidenecyclohexanol (**5c**) in 46% overall yield. Similarly, cycloheptanone was converted to 2-isopro-

pylidenecycloheptanol (**9**) in 44% overall yield (Chart II). Work on the cyclodecanone series had to be abandoned because conditions could not be found for effecting complete methylation of the cyclodecylidenenitrile **6b**. Our best attempt afforded a 3:1 mixture of dialkylated (**7b**) and monoalkylated (**6c**) products.

Chart II [a]



6a, $n = 2$; R = H
b, $n = 5$; R = H
c, $n = 5$; R = CH_3

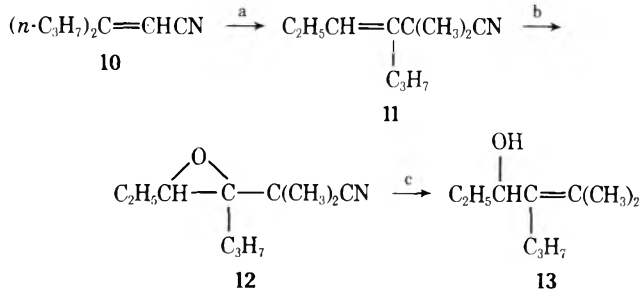
7a, $n = 2$
b, $n = 5$

8 **9**

[a] a, $(i\text{-Pr})_2NLi$, CH_3I, HMPA; b, $m\text{-}ClC_6H_4CO_3H$; c, Na, NH_3.

An acyclic example of the β-alkylidene alcohol synthesis is shown in Chart III. In this case all reactions proceeded smoothly and the alcohol **13** could be prepared in 55% overall yield starting with 4-heptanone. No attempt was made to ascertain the stereochemistry of unsaturated nitrile **11**.

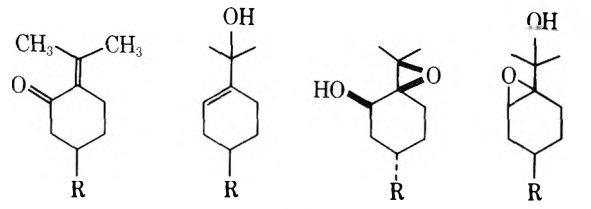
Chart III [a]



10 **11** **12** **13**

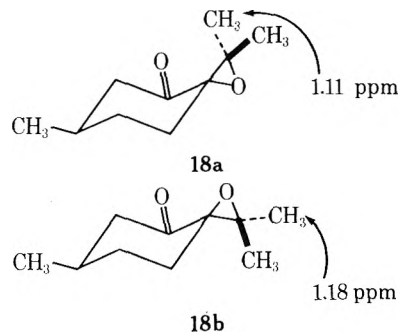
[a] a, $(i\text{-Pr})_2NLi$, CH_3I, HMPA; b, $m\text{-}ClC_6H_4CO_3H$; c, Na, NH_3.

We next examined the oxidation of these allylic alcohols to the isopropylidene ketones. This structural feature is found in a variety of cyclic and acyclic terpenes.[3,4] Attempts to oxidize the methyl isopropylidenecyclohexanol mixture **5a** and **5b** with various chromic acid reagents, including the chromium trioxide–pyridine complex,[5] led to extensive allylic rearrangement. Manganese dioxide showed greater promise, although the results varied considerably with the age of the oxidant. With a fresh batch of MnO_2 in cyclohexane we observed a rapid initial buildup of (±)-pulegone (**14a**) followed by a slow production of material with considerably longer gas chromatographic retention time. One of these products could be assigned the epoxy alcohol structure **16a** on the basis of spectral and gas chromatographic comparison with a sample prepared via epoxidation of the alcohol mixture **5a** and **5b** with *m*-chloroperoxybenzoic acid. Since *cis*-pulegol, obtained by reduction of (+)-pulegone with lithium aluminum hydride,[6] could be oxidized to pulegone in over 80% yield with MnO_2, the anomalous oxidation product **16a** must arise from the *trans*-pulegol (**5a**) present in the mixture. This presumption was further strengthened by the observation that epoxidation of *cis*-pulegol (**5b**) with *m*-chloroperoxybenzoic acid led to rearranged epoxy alcohol **17a** whereas the 2:1 mixture **5a,b** gave mainly the unrearranged epoxide **16a**.



14a, R = CH_3 **15a**, R = CH_3 **16a**, R = CH_3 **17a**, R = CH_3
b, R = H **b**, R = H **b**, R = H **b**, R = H

Further confirmation of structure **16a** for the epoxy alcohol obtained from either MnO_2 or *m*-chloroperoxybenzoic acid oxidation of *trans*-pulegol was secured through oxidation of **16a** with Collin's reagent to the known epoxy ketone **18a**.[7] Epoxidation of natural (+)-pulegone with alkaline hydrogen peroxide afforded the previously reported mixture of this epoxy ketone and the stereoisomer **18b**.[7] Additional support for these stereochemical assignments[7] was derived from the observed chemical shift of the epoxide methyl substituent syn to the ketone carbonyl. Models show that in the cis isomer **18a** this methyl grouping should fall within the shielding cone of the carbonyl grouping whereas the same methyl substituent should be deshielded by the carbonyl grouping in the trans isomer **18b**.[7]



18a

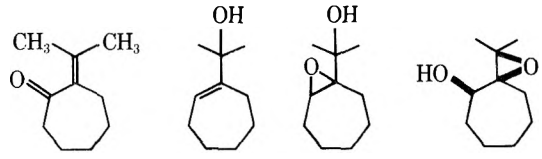
18b

The MnO_2 oxidation picture was further complicated by the finding that in benzene an older batch of the oxidant gave a mixture of pulegone (**14a**)[8] and the isomerized alcohol **15a** as the major products.[9] Only small amounts of longer retention time materials were produced under these circumstances. Again, a portion of the starting material (**5b**) underwent rapid oxidation to (±)-pulegone; the remainder (**5a**) slowly isomerized. The newer batch of MnO_2 oxidant yielded (±)-pulegone (**14a**) and epoxy alcohol **16a** but no allylic isomer **15a** in benzene. Evidently this remarkable olefin epoxidation reaction depends upon the exact nature of the MnO_2, which is possibly a function of its age. The allylic alcohol grouping no doubt also plays a part in the reaction, since a sample of 9-octalin was recovered unchanged after stirring with MnO_2 in benzene for several days.

Oxidation of 2-isopropylidenecyclohexanol (**5c**) with MnO_2 afforded only a trace of the ketone **14b**. The major product was rearranged alcohol **15b** or the epoxy alcohol **16b** depending upon the batch of MnO_2. Direct epoxidation of alcohol **14b** with *m*-chloroperoxybenzoic acid gave a mixture of isomeric epoxy alcohols **16b** and **17b**.

Oxidation of 2-isopropylidenecycloheptanol (**9**) with MnO_2 afforded the ketone **19** in over 20% yield and either rearranged alcohol **20** or an epoxy alcohol (possibly **21**) depending upon the batch of MnO_2. Direct epoxidation with *m*-chloroperoxybenzoic acid afforded authentic epoxy alco-

hol **22**, whose spectral properties differed from those of the MnO_2-derived material.



19 **20** **21** **22**

Experimental Section[10]

4-Methylcyclohexylideneacetonitrile (2a). The method of Wadsworth and Emmons[11] was employed. To 1.72 g (41.0 mmol) of ether-washed, 57% NaH in mineral oil under an argon atmosphere was added 100 ml of dry 1,2-dimethoxyethane (DME). Diethyl cyanomethylphosphonate (7.26 g, 41.0 mmol) in 20 ml of dry DME was added dropwise with cooling and stirring. After the evolution of hydrogen had ceased, 4.14 g (37.0 mmol) of 4-methylcyclohexanone was added and the reaction mixture was allowed to come to room temperature and to stir overnight. The mixture was poured into 200 ml of water and the product was isolated with ether, affording 3.99 g (80%) of the nitrile **2a:** bp 58–59° (0.5 mm); λ_{max} (film) 4.52, 6.13 μ; δ_{TMS} ($CDCl_3$) 0.92 (d, CH_3, J = 6 Hz), 1.03–3.13 (m, 9 H), 5.09 ppm (s, vinyl H).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.82; H, 9.94; N, 10.35.

Cyclohexylideneacetonitrile (2b). By the above procedure, 4.12 g of cyclohexanone gave 4.23 g (82%) of nitrile **2b:** bp 88–89° (6 mm); λ_{max} (film) 4.52, 6.12 μ; δ_{TMS} ($CDCl_3$) 1.47–1.88 (s, broad, 6 H), 2.07–2.66 (m, 4 H, allylic CH_2's), 5.05 ppm (m, vinyl H); reported bp 98–100° (12 mm).[12]

Cycloheptylideneacetonitrile (6a). By the above procedure 3.62 g of cycloheptanone gave 3.56 g (81.5%) of nitrile **6a:** BP 94–95° (0.5 mm); λ_{max} (film) 4.52, 6.19 μ; δ_{TMS} ($CDCl_3$) 1.35–2.03 (s, broad, 8 H), 2.24–2.86 (m, 4 H, allylic CH_2's), 5.20 ppm (m, vinyl H).

Anal. Calcd for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.76; H, 9.76; N, 10.32.

Cyclodecylideneacetonitrile (6b). By the above procedure 3.0 g of cyclodecanone gave 2.64 g (78%) of nitrile **6b:** bp 118–120° (0.5 mm); λ_{max} (film) 4.48, 6.14 μ; δ_{TMS} (CCl_4) 1.41–2.01 (m, 14 H), 2.01–2.71 (m, 4 H, allylic CH_2's), 5.20 ppm (s, vinyl H).

Anal. Calcd for $C_{12}H_{19}N$: C, 81.29; H, 10.80; N, 7.90. Found: C, 81.44; H, 11.01; N, 7.68.

3-Propyl-2-hexenenitrile (10). By the above procedure 4.21 g (37.0 mmol) of 4-heptanone gave 3.73 g (74%) of the nitrile **10:** bp 74–75° (0.5 mm); λ_{max} (film) 4.52, 6.15 μ; δ_{TMS} ($CDCl_3$) 0.75–1.05 (m, 6 H, CH_3's), 1.15–1.86 (m, 4 H, homoallylic CH_2's), 1.93–2.54 (m, 4 H, allylic CH_2's), 5.08 ppm (s, vinyl H).

Anal. Calcd for $C_9H_{15}N$: C, 78.78; H, 11.02; N, 10.21. Found: C, 78.96; H, 11.09; N, 10.25.

2-Methyl-2-(4-methyl-1-cyclohexenyl)propanenitrile (3a). The procedure of Herrmann, Kieczykowski, and Schlessinger[2] was modified. To a mixture of 21.3 ml (152 mmol) of diisopropylamine in 120 ml of dry tetrahydrofuran (THF), at 0° under an argon atmosphere, was added, via a syringe, 69.0 ml of 2.2 M butyllithium. After stirring for 15 min at 0° the mixture was cooled to −78° and 82 ml (456 mmol) of dry hexamethylphosphoric triamide (HMPA) was added. After 30 min at −78°, 5.14 g (38 mmol) of 4-methylcyclohexylideneacetonitrile (**2a**) was added in 20 ml of dry THF. After stirring for 15 min at −78° the mixture was quenched with excess methyl iodide (11.4 ml, 114 mmol) and allowed to slowly come to room temperature (1–2 hr). The mixture was poured into 150 ml of water and the product was isolated by extraction with ether. The combined ether extracts were washed with saturated ammonium chloride and with copious amounts of water. After drying and removal of the solvent, 4.67 g (76%) of the alkylated nitrile **3a** was obtained: bp 70–75° (0.5 mm); λ_{max} (film) 4.50, 7.25, 7.35 μ; δ_{TMS} (CCl_4) 0.94 (d, CH_3, J = 6 Hz), 1.41 (s, 6 H, *gem*-dimethyl), 5.84 ppm (m, vinyl H).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.92; H, 10.66; N, 8.52.

When the alkylation was performed as described above but with 27 ml (152 mmol) of HMPA an 80:20 mixture of nitriles **3a** and **2c** was obtained as evidenced by spectral and gas chromatographic analysis.

2-Methyl-2-(1-cyclohexenyl)propanenitrile (3b). By the procedure described above, 4.44 g of cyclohexylidenenitrile (**2b**) gave 5.23 g (79%) of alkylated nitrile **3b:** bp 67–68° (0.5 mm); λ_{max} (film) 4.49, 7.25, 7.35 μ; δ_{TMS} (CCl_4) 1.42 (s, 6 H, *gem*-dimethyl), 1.52–1.78 (m, 4 H), 1.88–2.20 (m, 4 H, allylic CH_2's), 5.86 ppm (m, vinyl H).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.30; H, 10.29; N, 9.34.

2-Methyl-2-(1-cycloheptenyl)propanenitrile (7a). By the procedure described above, 2.70 g of cycloheptylideneacetonitrile (**6a**) gave 2.82 g (86.5%) of nitrile **7a:** bp 78–80° (0.5 mm); λ_{max} (film) 4.55, 7.20, 7.30 μ; δ_{TMS} (CCl_4) 1.42 (s, 6 H, *gem*-dimethyl), 1.96–2.39 (m, 4 H, allylic CH_2's), 6.02 ppm (t, vinyl H).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.71; H, 10.58; N, 8.45.

3-Propyl-2,2-dimethyl-3-hexenenitrile (11). By the procedure described above, 2.75 g (20 mmol) of 3-propyl-2-hexenenitrile (**10**) gave 2.92 g (89%) of the alkylated nitrile **11:** bp 48–49° (0.5 mm); λ_{max} (film) 4.49, 7.20, 7.31 μ; δ_{TMS} (CCl_4) 1.52 (s, 6 H, *gem*-dimethyl), 1.83–2.60 (m, 4 H, allylic CH_2's), 5.35 ppm (t, J = 8 Hz, vinyl H).

Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 79.76; H, 11.79; N, 8.50.

2-Isopropylidene-5-methylcyclohexanol (5a,b). A solution of 4.0 g (24.6 mmol) of the cyclohexenylpropanenitrile (**3a**) and 8.5 g (49.2 mmol) of *m*-chloroperoxybenzoic acid (97%) in 100 ml of dichloromethane was stirred at room temperature overnight. The reaction mixture was poured into 25 ml of 10% sodium sulfite solution and the organic layer was separated, washed with water, and dried. The solvent was removed to give 4.3 g (98%) of epoxy nitrile **4a:** λ_{max} (film) 4.45, 7.20, 7.40 μ; δ_{TMS} (CCl_4) 0.88 (d, CH_3, J = 6 Hz), 1.29 and 1.32 (s, 6 H, *gem*-dimethyl), 3.13–3.30 ppm (m, 1 H).

The reduction procedure of Arapakos, Scott, and Hubert[13] was followed. To a solution of 3.8 g (167 mmol) of sodium in 250 ml of liquid ammonia was added 4.0 g (22.3 mmol) of the epoxy nitrile **4a** in 6 ml of dry ether. After 20 min excess ammonium chloride was added to discharge the blue color, the ammonia was evaporated, and the residue was dissolved in 200 ml of water. Extraction with ether afforded 3.0 g (87%) of the alcohol **5a,b:** bp 90–91° (0.5 mm); λ_{max} (film) 3.05, 6.00 μ; δ_{TMS} (CCl_4) 0.85 and 1.10 (d, J = 6 Hz, CH_3's in trans and cis isomers **5a** and **5b**), 1.66–1.80 (m, vinyl CH_3's), 4.48–4.84 ppm (m, carbinyl H's).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.73; H, 11.92.

2-Isopropylidenecyclohexanol (5c). Using the procedure described above, 4.12 g of cyclohexenyl nitrile **3b** gave 4.44 g of epoxy nitrile **4b:** λ_{max} (film) 4.50, 7.20, 7.30 μ; δ_{TMS} (CCl_4) 1.29 and 1.32 (s, 6 H, *gem*-dimethyl), 3.22 ppm (m, 1 H).

Reduction of the epoxy nitrile as described above gave the allylic alcohol **5c** in 84– yield. Purification was effected by sublimation (60°, 0.5 mm): mp 54–56°; λ_{max} (KBr) 3.15, 6.02 μ; δ_{TMS} (CCl_4) 1.64 and 1.71 (s, 6 H, CH_3's), 2.62 (s, 1 H, OH), 4.74 ppm (m, 1 H, carbinyl H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.84; H, 11.72.

2-Isopropylidenecycloheptanol (9). Using the procedure described above, 1.49 g of the cycloheptenyl nitrile **7a** gave 1.48 g (90%) of the epoxy nitrile **8:** δ_{TMS} (CCl_4) 1.30 (s, CH_3's), 3.07–3.24 ppm (m, 1 H).

Reduction of the epoxy nitrile afforded the allylic alcohol **9** in 70% yield: bp 100° (bath temperature) (5 mm); λ_{max} (film) 3.00, 6.00 μ; δ_{TMS} (CCl_4) 1.68 and 1.74 (s, 6 H, CH_3's), 4.40–4.74 ppm (m, carbinyl H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.89; H, 12.00.

4-Isopropylidene-3-hexenol (13). Using the above procedure, 2.23 g of 3-propyl-2,2-dimethyl-3-hexenylnitrile (**11**) gave 2.17 g (89%) of the epoxy nitrile **12:** λ_{max} (film) 4.50, 7.22, 7.37 μ; δ_{TMS} (CCl_4) 1.40 and 1.46 (s, 6 H, *gem*-dimethyl), 3.20 ppm (t, J = 6 Hz, 1 H).

Reduction of the epoxy nitrile **12** as described above gave the allylic alcohol **13** in 75% yield: bp 75–80° (bath temperature) (16 mm); λ_{max} (film) 2.92, 6.13 μ; δ_{TMS} (CCl_4) 1.66 (s, 6 H), 4.41 ppm (t, J = 6 Hz, carbinyl H).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.66; H, 13.16.

Oxidation of 2-Isopropylidene-5-methylcyclohexanol (5a,b). A. With Manganese Dioxide. A solution of 1.82 g (11.7 mmol) of 2-isopropylidene-5-methylcyclohexanol (**5a,b**) in 400 ml of cyclohexane was treated with four 20-g portions of powdered manganese dioxide over a 24-hr period until only a trace of starting alcohol could be detected in the gas chromatogram of an aliquot.

The mixture was filtered, the filter cake was washed with 400 ml of cyclohexane, and the filtrate was concentrated and distilled, giving 0.54 g (30%) of (±)-pulegone (**14a**), bp 85° (bath temperature) (0.4 mm), whose spectral properties and GC retention times matched those of an authentic sample of natural pulegone.[7]

The expended manganese dioxide was thoroughly extracted with ether in a Soxhlet extractor to give 0.72 g of epoxy alcohol **16a**, bp 90° (bath temperature) (0.4 mm). Redistillation (60°, 0.2 mm) gave a sample which crystallized upon standing. Recrystallization from hexane at 0° yielded colorless, cubic crystals, mp 43–44°.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.57; H, 10.66. Found: C, 70.43; H, 10.87.

When the above oxidation was performed in benzene with an older batch of MnO_2, gas chromatographic analysis showed a mixture of (±)-pulegone (35%), allylic alcohol **15a** (40%), and long retention time material (25%).

B. With *m*-Chloroperoxybenzoic Acid. To a solution of 0.68 g (4.4 mmol) of isomeric pulegols **5a** and **5b** in 50 ml of methylene chloride was added 1.04 g (6.65 mmol) of solid *m*-chloroperoxybenzoic acid. The mixture was stirred overnight, diluted with ether, and washed with sodium sulfite and sodium bicarbonate. Drying and removal of solvent under reduced pressure gave 0.75 g (100%) of an oily mixture of epoxy alcohols **16a** and **17a**: λ_{max} (film) 2.93, 6.89, 7.27, 9.63 μ; δ_{TMS} (CCl_4) 3.65 (m, carbinyl H of **16a**), 3.25 (m, carbinyl H of **17a**), 1.32 (s, *gem*-CH_3's of **16a**), 1.16 (s, *gem*-CH_3's of **17a**) 0.90 ppm (d, J = 6 Hz, CH_3 of **16a** and **17a**). Integration of the NMR spectrum indicated a 3:1 mixture of **16a** and **17a**.

Epoxidation of Allylic Alcohol 15a. The above procedure was applied to 0.93 g (6.0 mmol) of allylic alcohol **15a** to give 0.95 g (92%) of epoxy alcohol **17a** upon distillation (50°, 0.04 mm): λ_{max} (film) 2.93, 6.89, 7.45, 8.65, 10.46, 11.80 μ; δ_{TMS} (CCl_4) 3.25 (m, carbinyl H), 1.15 (s, *gem*-CH_3's), 0.90 ppm (d, J = 6 Hz, ring CH_3).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.57; H, 10.66. Found: C, 70.30; H, 10.83.

Epoxidation of Pulegone. To a stirred solution of 6.08 g (40.0 mmol) of (+)-pulegone (**14a**), 40 ml of methanol, and 11.5 ml of 30% hydrogen peroxide at 15° was added 3.3 ml of 6 *N* aqueous sodium hydroxide. After 3 hr water was added and the mixture was extracted with ether to give 6.04 g (90%) of epoxy ketones **18a** and **18b**: bp 65° (bath temperature) (0.2 mm); λ_{max} (film) 5.78, 6.85, 7.29 μ; δ_{TMS} (CCl_4) 1.36 (s, anti CH_3 of **18a** and **18b**), 1.18 (s, syn CH_3 of **18b**), 1.11 (s, syn CH_3 of **18a**), 1.08 ppm (d, J = 6 Hz, ring CH_3 of **18a** and **18b**).[7]

Oxidation of Epoxy Alcohol 16a. Collin's reagent was prepared from 1.20 g (12.0 mmol) of chromic anhydride and 1.86 ml (24.0 mmol) of pyridine.[5] To the stirred mixture was added 0.34 g (2.0 mmol) of epoxy alcohol **16a** (from MnO_2 oxidation of alcohol **5a,b**) in 5 ml of methylene chloride. After 15 min, the mixture was extracted with ether, washed with 5% NaOH, 5% HCl, $NaHCO_3$, and brine, and dried over magnesium sulfate to give 0.30 g of solid ketone **18a**. Crystallization from pentane afforded 0.15 g (45%) of needles: mp 77–78°; λ_{max} (film) 5.78, 6.85, 7.29 μ; δ_{TMS} (CCl_4) 1.36 (s, anti CH_3), 1.11 (s, syn CH_3), 1.08 ppm (d, J = 6 Hz, ring CH_3). An additional recrystallization from pentane gave the analytical sample, mp 78.5–79.5°.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.41; H, 9.59. Found: C, 71.67; H, 9.72.

The identical material, mp 78–79°, was obtained upon oxidation, as described above, of epoxy alcohol **16a** obtained from alcohol **5a,b** via *m*-chloroperoxybenzoic acid epoxidation.

Oxidation of 2-Isopropylidenecyclohexanol (5c). A. With Manganese Dioxide. A solution of 1.06 g (7.6 mmol) of 2-isopropylidenecyclohexanol (**5c**) in 250 ml of cyclohexane was stirred with 20 g of activated manganese dioxide at room temperature for 5 hr, at which time an additional 20 g of MnO_2 was added. Stirring was continued for 13 hr, the solid was filtered and washed with cyclohexane, and the filtrate was concentrated under reduced pressure. The residue was purified by thick layer chromatography on silica gel (20% ether–benzene development) and distillation (60°, 0.2 mm) to give 0.043 g (4%) of 2-isopropylidenecyclohexanone (**14b**):[4] λ_{max} (film) 5.92, 6.21 μ; δ_{TMS} (CCl_4) 1.90, 1.73 ppm (vinyl CH_3's).

Extraction of the solid manganese dioxide with ether afforded 0.44 g of epoxy alcohol **16b**: bp 80° (bath temperature) (0.2 mm); λ_{max} (film) 2.97, 10.03, 11.62 μ; δ_{TMS} (CCl_4) 3.60 (m, carbinyl H), 2.72 (s, OH), 1.27 ppm (s, *gem*-CH_3's).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.33. Found: C, 68.94; H, 10.55.

B. With *m*-Chloroperoxybenzoic Acid. According to the procedure outlined above for alcohol **5a,b**, 0.29 g (2.1 mmol) of 2-isopropylidenecyclohexanol (**5c**) afforded 0.32 g of epoxy alcohols **16b** and **17b**: λ_{max} (film) 2.95, 10.03, 11.60 μ; δ_{TMS} (CCl_4) 3.60 (m, carbinyl H of **16b**), 3.21 (m, carbinyl H of **17b**), 1.27 (s, *gem*-CH_3's of **16b**), 1.16, 1.10 ppm (*gem*-CH_3's of **17b**).

Oxidation of 2-Isopropylidenecycloheptanol (9). A. With Manganese Dioxide. The procedure described for alcohol **5a,b** was applied to 0.93 g (6.0 mmol) of 2-isopropylidenecycloheptanol (**9**) affording 0.19 g (21%) of ketone **19**: bp 80° (bath temperature) (0.2 mm); λ_{max} (film) 5.93, 6.24 μ; δ_{TMS} (CCl_4) 1.79, 1.74 ppm (s, vinyl CH_3's).

Extraction of the solid MnO_2 with ether yielded 0.15 g of oil containing ketone **19** plus alcoholic material whose NMR spectrum was compatible with a rearranged epoxy alcohol structure **21**: λ_{max} (film) 2.97, 5.93, 6.24 μ; δ_{TMS} (CCl_4) 3.21 (t, carbinyl H), 1.17, 1.10 ppm (*gem*-CH_3's).

B. With *m*-Chloroperoxybenzoic Acid. The procedure described for alcohol **5a,b** was applied to 0.60 g (3.9 mmol) of 2-isopropylidenecycloheptanol (**9**), affording 0.63 g (95%) of epoxy alcohol **22**: bp 80° (bath temperature) (0.2 mm); λ_{max} (film) 2.90 μ; δ_{TMS} (CCl_4) 3.61 (m, carbinyl H), 2.80 (s, OH), 1.31 ppm (s, *gem*-CH_3's).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.57; H, 10.66. Found: C, 70.71; H, 10.93.

Acknowledgments. We are indebted to the National Institutes of Health and the National Science Foundation for research grants (5-RO1-CA11089, National Cancer Institute, and GP-33276X, respectively). Initial studies on certain substrates described herein were conducted by Dr. R. D. Peveler and Mr. Paul A. Aristoff. A sample of *cis*-pulegol was provided by Miss Susan M. Cole.

Registry No.—**1a**, 589-92-4; **1b**, 108-94-1; **2a**, 54353-77-4; **2b**, 4435-18-1; **2c**, 54353-78-5; **3a**, 54353-79-6; **3b**, 54353-80-9; *cis*-**4a**, 54353-81-0; *trans*-**4a**, 54382-84-2; **4b**, 54353-82-1; **5a**, 18649-91-7; **5b**, 29910-20-1; **5c**, 54353-83-2; **6a**, 22734-05-0; **6b**, 54353-84-3; **7a**, 54353-85-4; **8**, 54353-86-5; **9**, 54353-87-6; **10**, 54353-88-7; **11**, 54353-89-8; **12**, 54353-90-1; **13**, 54353-91-2; (±)-**14a**, 3285-04-9; (+)-**14a**, 89-82-7; **14b**, 13747-73-4; **15a**, 25910-97-8; **16a**, 54382-85-3; **16b**, 54353-92-3; **17a**, 54382-86-4; **17b**, 54353-93-4; **18a**, 7599-91-9; **18b**, 13902-36-8; **19**, 23438-72-4; **21**, 54353-94-5; **22**, 54353-95-6; cycloheptanone, 502-42-1; diethyl cyanomethylphosphonate, 2537-48-6; cyclodecanone, 1502-06-3; 4-heptanone, 123-19-3; hexamethylphosphoric triamide, 49778-01-0; manganese dioxide, 1313-13-9; *m*-chloroperoxybenzoic acid, 937-14-4.

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(10) The apparatus described by W. S. Johnson and W. P. Schneider ["Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132] was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water and saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Infrared spectra were obtained with a Perkin-Elmer Model 137 spectrophotometer. Infrared absorptions are reported in wavelengths (μ) and are standardized with reference to the 6.24-μ peak

of polystyrene. Nuclear magnetic resonance spectra were recorded with a Varian T-60 spectrometer. Signals are reported as the chemical shift downfield from tetramethylsilane (TMS) in parts per million (ppm) of the applied field. The multiplicity of the peak is abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; and multiplet, m. Coupling constants are reported in hertz. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.

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Iodonium Ylides. Reactions of Phenyldimedonyliodone with Diphenylketene and Phenyl Isocyanate

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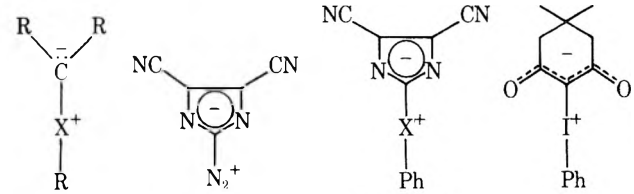
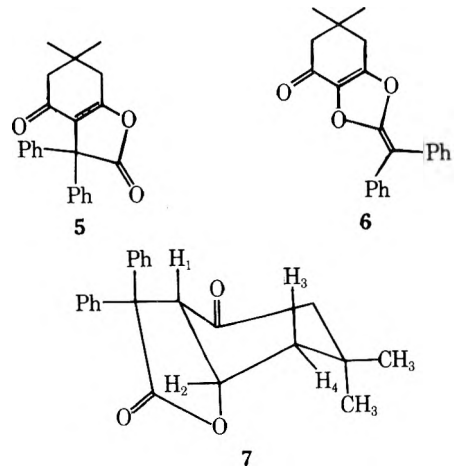
While the chemistry of phosphorous, nitrogen, and sulfur ylides has been studied extensively,[1] little is known of the halogen ylides. Halonium ylides of general structure **1** have been proposed when various carbenes are generated in the presence of alkyl and aryl halides,[2] but their high reactivity has largely precluded their isolation and study. We know of only one report concerning the formation of stable halonium ylides by carbene trapping. Sheppard and Webster[3] found that the thermal decomposition of 3,5-dicyanodiazoimidazole (**2**) in chlorobenzene, bromobenzene, or iodobenzene gave the corresponding chloronium, bromonium, and iodonium ylides **3a, 3b,** and **3c.** Some iodonium ylides have also been prepared by a different method which involves the treatment of various β-diketones and β-keto esters with aryliodoso compounds.[4,5] For example, phenyldimedonyliodone (**4**),[6,7] one of the most stable iodonium ylides, has been synthesized in high yield by condensation of iodosobenzene with dimedone in the presence of acetic anhydride.[5] However, chemical studies on **4** have been limited to its reactivity toward highly electrophilic agents and to its proclivity for nucleophilic cleavage and thermal decomposition and rearrangement.[6,8] We were, therefore, prompted to initiate a systematic study of **4** in order to *begin* to elaborate the chemical properties of halonium ylides. In this note, we describe reactions of **4** with two representative electrophilic heterocumulenes.



1 **2** **3a**, X = Cl; **b**, X = Br; **c**, X = I **4**

When phenyldimedonyliodone (**4**) was allowed to react with diphenylketene in dichloromethane at room temperature, lactone **5** and ketene acetal **6** were *isolated* in yields of 32 and 44% by column chromatography on Florasil. Iodobenzene is also formed in this reaction, and, in a control study, the yield of iodobenzene was determined by GLC analysis to be 99%. The structures of **5** and **6** were initially deduced from spectral (ir, NMR, uv, mass) and analytical (C, H) data.

The mass spectra of both compounds show the expected molecular ion peaks at *m/e* 332. However, while the parent ion peak in the spectrum of **5** is also the base peak, the base peak in the spectrum of **6** is at *m/e* 166 and must be that of a fragment ion derived from scission of the exocyclic carbon–carbon double bond. The ^{1}H NMR spectra of **5** and **6**



5 **6** **7**

are similar in that each exhibits a six-hydrogen singlet, a pair of two-hydrogen singlets, and a ten-hydrogen phenyl resonance. Their uv spectra are also similar, but the absorption maximum (α,β-unsaturated ketone) in the spectrum of **6** is red shifted by 11 mμ relative to that of **5.** The ir spectrum of **5** exhibits carbonyl bands at 5.50 (lactone) and 5.99 μ (ketone) while the ir spectrum of **6** shows a carbonyl band at 6.01 μ (ketone) and exocyclic double-bond absorption at 5.78 μ. Finally, the melting point of **6** is 60° higher than that of **5,** presumably because of its greater molecular symmetry.

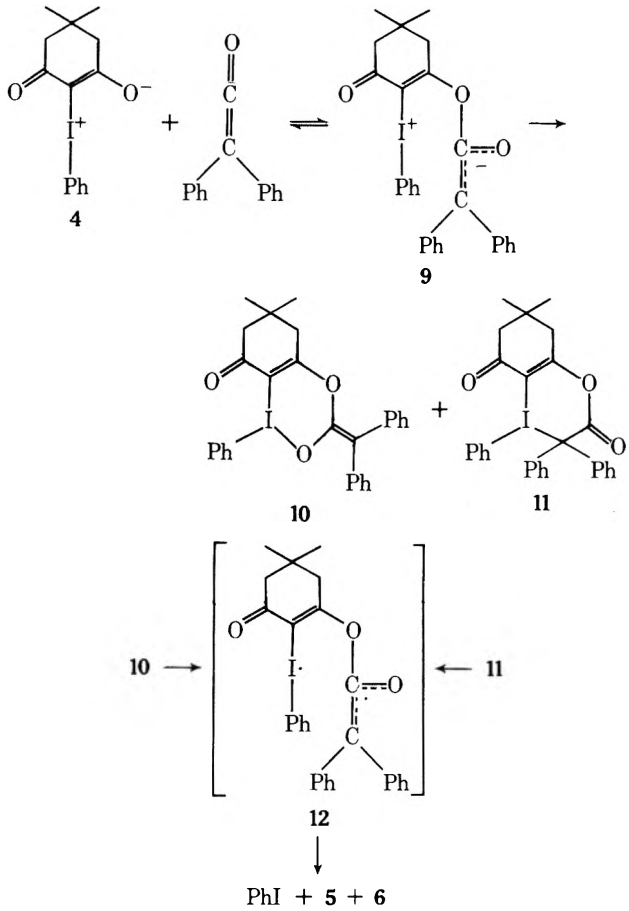
The structure assigned to **5** was confirmed by its catalytic hydrogenation in 54% yield to the saturated lactone **7,** which was in turn characterized by its elemental composition (C, H) and spectra (ir, NMR, uv, mass). In particular, the ir spectrum of **7** exhibits a carbonyl band at 5.72 μ as expected for a saturated γ-lactone while the uv spectrum shows only benzenoid absorption at 259 mμ (ϵ 633). The ^{1}H NMR spectrum of **7** exhibits *two* methyl singlets at δ 0.87 and 0.81, a ten-line multiplet at δ 5.0 (H-2, $J_{2,3} \simeq 11$, $J_{2,1} \simeq 8.5$, $J_{2,4} \simeq 6.5$ Hz), a doublet at δ 4.42 (H-1, $J_{1,2} \simeq 8.5$ Hz), and complex multiplets for the phenyl and methylene hydrogens. The doublet resonance for H-1 at δ 4.42 may seem anomalously downfield for a proton in that environment. However, inspection of Dreiding models indicates very clearly that H-1 lies in the deshielding region of one of the benzene rings.

The structure assigned to **6** was confirmed by oxidative cleavage of the exocyclic carbon–carbon double bond. When **6** was allowed to react with ozone and treated subsequently with basic hydrogen peroxide, benzophenone was isolated in 66% yield and characterized as its 2,4-dinitrophenylhydrazone. The ketene acetal proved remarkably resistant to hydrolysis. Even when **6** was warmed to dissolution in concentrated sulfuric acid and poured into water, it was recovered unreacted in 86% yield. The inertness of **6** toward hydrolytic cleavage may reflect the aromaticity of its conjugate acid **8.**

The production of iodobenzene, lactone **5,** and acetal **6** is a consequence of *formal* 1,3-addition of the dimedonyl unit in **4** to either the carbon–carbon or carbon–oxygen double bond of diphenylketene. There are not sufficient data to allow commitment to any one of several possible mechanisms for this reaction, but we would like to discuss specifically the mechanism shown in Scheme I. It seems reason-

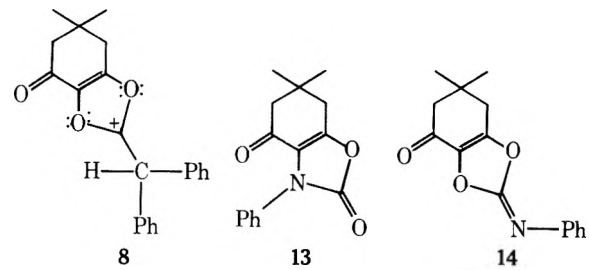
able to presume that the reaction is initiated by nucleophilic attack of **4** on diphenylketene to give betaine **9**. Although **5** and **6** might conceivably arise from **9** by direct displacement of iodobenzene from vinyl carbon, such a process seems unlikely. SN1 displacements at vinyl carbon are known,[9] but, in the case of **9**, this would require the formation of a *cyclic* vinyl cation with positive charge adjacent to carbonyl carbon. There also seems to be no special driving force for an addition–elimination sequence. The formation of iodine(III) heterocycles **10** and **11** by cyclization of betaine **9** and their subsequent homolytic decomposition through diradical **12** is a plausible source of the observed products. Such a reaction sequence finds precedent in a detailed study of iodine(III) compounds conducted by Beringer, Dehn, and Winicov.[10] For example, when diphenyliodonium chloride (100 mmol) was treated by those workers with ethylmagnesium bromide (200 mmol) in ether at −5°, the final products were iodobenzene (80 mmol), biphenyl (5 mmol), iodoethane (20 mmol), ethylbenzene (15 mmol), and benzene (95 mmol).[10]

Scheme I



When phenyldimedonyliodone (**4**) was allowed to react with phenyl isocyanate in dichloromethane at room temperature, only one "cycloadduct", assigned the oxazolinone structure **13**, was isolated in 44% yield. The structure of **13** was deduced from its elemental composition (C, H, N) and spectra (ir, NMR, uv). In particular, the ir spectrum of **13** exhibits two carbonyl bands at 5.94 (ketone) and 5.63 μ (azalactone).

If a homolytic decomposition mechanism such as that depicted in Scheme I were responsible for the genesis of **13**, the absence of the isomeric product **14** seems anomalous. We will, however, defer specific considerations regarding mechanism to a future report.



Experimental Section

General. NMR spectra were recorded on a Varian Model A-60 NMR spectrometer (relative to internal TMS), infrared spectra on a Perkin-Elmer Model 337 spectrophotometer, and ultraviolet spectra on a Cary 17 uv–visible–ir spectrophotometer. Mass spectra were recorded on a Du Pont 21-110C spectrometer. Peaks of fragment ions with intensities greater than 30% that of the base peak are reported Melting points are uncorrected. GLC analyses were conducted on a Hewlett-Packard Model 5750 gas chromatograph, a 6-ft column of 10% UCON W-98 on 80–100 mesh silica being utilized. Elemental compositions were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. Diphenylketene was prepared according to the method of Darling and Kidwell.[11] We thank Dr. Stephen D. Darling for a gift of some diphenylketene.

Reaction of Phenyldimedonyliodone (4) with Diphenylketene. A solution of diphenylketene (9.06 g, 46.6 mmol) and phenyldimedonyliodone (8.62 g, 25.2 mmol) in CH_2Cl_2 (80 ml) was allowed to stir for 5 days at room temperature. The CH_2Cl_2 was then evaporated *in vacuo*, and the remaining material resolved by column chromatography on Florisil (230 g). Twenty-five fractions of *ca.* 300 ml each were collected as the elution solvent was gradually changed from cyclohexane (fractions 1–9) to ether (fractions 10–21) to ethanol (fractions 22–25). Certain fractions were then combined, and the solvent was removed. The residues were triturated with cyclohexane or ether and finally analyzed by NMR spectroscopy. Fractions 3–12 yielded 2.686 g (32%) of lactone **5** as a crude yellow solid, and fractions 13–21 yielded 3.721 g (44%) of ketene acetal **6** as a crude white solid. Fractions 22–25 gave ca. 4 g of a brown, tacky substance apparently derived from diphenylketene.

Purification and Characterization of 5. The crude lactone **5** was recrystallized from cyclohexane–dichloromethane (2:1 v/v) as white needles and plates (2.307 g): mp 136–137°; ir ($CHCl_3$) 5.50 (lactone C=O), 5.99 and 6.07 μ (ketone C=O); NMR ($CDCl_3$) δ 7.28 (s, 10 H), 2.60 (s, 2 H), 2.32 (s, 2 H), 1.13 (s, 6 H); uv (CH_3OH) 252.5 mμ (ε 8.991×10^3); mass spectrum (70 eV) *m/e* (rel intensity) 332 (100), 304 (48), 303 (59), 178 (31); mol wt 332 (calcd, 332); (M + 1)/M, 24.11% (calcd, 24.16%).

Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.49; H, 6.06. Found: C, 79.32; H, 6.14.

Purification and Characterization of 6. The crude ketene acetal **6** was recrystallized from cyclohexane–dichloromethane (2:1 v/v) as fine white needles (2.973 g): mp 196–197°; ir ($CHCl_3$) 6.01 (C=O), 5.78 μ (exocyclic C=C); NMR ($CDCl_3$) δ 7.38 (m, 10 H), 2.78 (s, 2 H), 2.34 (s, 2 H), 1.16 (s, 6 H); uv (CH_3OH) 263 mμ (ε 1.0101×10^4); mass spectrum (70 eV) *m/e* (rel intensity) 332 (40), 166 (100), 165 (60); mol wt 332 (calcd, 332); (M + 1)/M, 23.1% (calcd, 24.16%).

Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.49; H, 6.06. Found: C, 79.31; H, 5.81.

Hydrogenation of 5. A solution of lactone **5** (1.752 g, 5.27 mmol) in ethyl acetate (40 ml) over 10% palladium on charcoal (0.351 g) was allowed to stir under hydrogen for 1 week at room temperature and atmospheric pressure. The catalyst and solvent were subsequently removed, leaving 1.973 g of a viscous liquid which partially solidified upon standing. Resolution of the crude product was effected by column chromatography on Florasil (150 g) as the elution solvent was gradually changed from cyclohexane to ether to ethyl acetate. Two cyclohexane fractions, two ether fractions, and one ethyl acetate fraction were collected. The solvent was removed from each fraction and the remaining material subjected to NMR analysis. Fraction 1 (0.453 g) was a wet solid which, after trituration with cyclohexane, yielded 0.308 g of lactone **7**. Fraction 2 (0.643 g) was fairly pure **7**. The crude solids from fractions 3 (0.250 g), 4 (0.106 g), and 5 (0.235 g) were not identified. Thus, the yield of lactone **7** was 0.951 g (54%).

Purification and Characterization of 7. The crude lactone **7** (0.951 g) was recrystallized from cyclohexane–dichloromethane

(1:1 v/v), yield 0.851 g: mp 164–166°; ir (KBr) 5.72 (lactone C=O), 5.91 μ (ketone C=O); NMR ($CDCl_3$) δ 7.85, 7.22 (complex multiplets, aromatic hydrogens), 5.0 (ten-line multiplet, H-2, $J_{2,3} \simeq 11.0$, $J_{2,1} \simeq 8.5$, $J_{2,4} \simeq 6.5$ Hz), 4.42 (d, H-1, $J_{1,2} \simeq 8.5$ Hz), 1.78 (m, $-CH_2-$ hydrogens), 0.87 (s, $-CH_3$), 0.81 (s, $-CH_3$); uv (CH_3OH) λ_{max} 259 mμ (ϵ_{max} 633), shoulders at 253 (567), 264 (560), and 270 (365); mass spectrum (70 eV) *m/e* (rel intensity) 334 (100), 290 (38), 289 (34), 274 (36), 206 (93), 205 (42), 166 (37), 91 (32); mol wt 334 (calcd, 334); (M + 1)/M, 26.9% (calcd, 24.3%).

Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 79.32; H, 6.51.

Ozonation of 6. A solution of ketene acetal **6** (0.126 g, 0.0379 mmol) and pyridine (5 ml) in dichloromethane (250 ml) was cooled to 0° and subjected to an ozone stream for 30 hr. Sodium hydroxide (5%, 40 ml) and hydrogen peroxide (30%, 2 ml) were then added, and the resulting two-phase mixture was refluxed for 16 hr. The aqueous and organic layers were then separated, and the aqueous layer was extracted with dichloromethane (2 × 100 ml). The extracts and the organic layer were combined, dried ($MgSO_4$), and concentrated in vacuo, leaving a yellow solid (0.086 g) shown by NMR analysis to consist of benzophenone and other unidentified materials. When an attempt to isolate benzophenone by preparative TLC failed, the crude product was dissolved in 95% ethanol (10 ml) and treated with fresh DNP reagent [2,4-dinitrophenylhydrazine (0.2 g), H_2O (1.5 ml), concentrated H_2SO_4 (1 ml), and 95% ethanol (5 ml)]. The resulting solution, upon standing overnight at room temperature, yielded an orange solid which was isolated by filtration and washed with cold 95% ethanol, wt 0.131 g. The crude solid was then purified by column chromatography on neutral alumina with 1:1 (v/v) cyclohexane–ether (400 ml) followed by ether (600 ml) as the elution solvents; 0.091 g of an orange powder (mp 234–236°) with an infrared spectrum identical with that of authentic benzophenone 2,4-dinitrophenylhydrazone was obtained (yield 66%). Recrystallization of this material from 1:1 (v/v) ethyl acetate–ethanol gave 0.083 g of orange crystals, mp 236–236.5° (lit.[12] mp 239°).

Reaction of 4 with Diphenylketene. Yield of Iodobenzene. A solution of diphenylketene (1.64 g, 8.44 mmol) in CH_2Cl_2 (10 ml) was added to a solution of **4** (1.71 g, 5.00 mmol) in CH_2Cl_2 (10 ml), and the resulting solution was diluted volumetrically with CH_2Cl_2 to 25 ml. The reaction mixture was allowed to stand for 4.5 days at room temperature. At the end of this time, a 10-ml volumetric aliquot was removed, added to 0.1781 g (1.327 mmol) of durene, and subjected to GLC analysis. Three separate injections gave the peak area ratios (as determined by planimeter integration) shown below.

Injection	Durene/iodobenzene
1	0.765
2	0.761
3	0.791

A known mixture of durene (1.96 mmol) and iodobenzene (2.07 mmol), when subjected to similar analysis, gave the following peak area ratios.

Injection	Durene/iodobenzene
1	1.078
2	1.129
3	1.075

Thus, the durene/iodobenzene peak area ratio must be multiplied by a factor of 0.867 to give the correct durene/iodobenzene mole ratio.

The yield of iodobenzene was, therefore, 99%.

Reaction of Phenyldimedonyliodone (4) with Phenyl Isocyanate. A solution of **4** (11.12 g, 32.5 mmol) and phenyl isocyanate (7.8 g, 65.5 mmol) in CH_2Cl_2 (120 ml) was allowed to stir for 4.5 days at room temperature. The CH_2Cl_2 was then evaporated in vacuo and the remaining wet, brown cake resolved by column chromatography on Florisil (225 g). Twenty-one fractions of ca. 300 ml each were collected as the elution solvent was gradually changed from cyclohexane (fractions 1–2) to ether (fractions 3–12) to CH_2Cl_2 (fractions 13–16) to ethanol (fractions 17–21). Various fractions were then combined, the solvent was removed, and the residues were triturated with ether and subjected to NMR analysis. Fractions 4–7 yielded 2.81 g of crude oxazolinone **13** as a white to faintly yellow solid. Fractions 9–14 yielded 4.85 g of a white solid (mp ~235°) identified as diphenylurea, and fractions 17–21 gave 2.65 g of unreacted **4**. The yield of **13** based on unrecovered **4** was 44%.

Purification and Characterization of 13. The crude oxazolinone **13** was recrystallized from cyclohexane–dichloromethane (1:1 v/v) as white needles: mp 122–123°; ir ($CHCl_3$) 5.63 (C=O), 5.94 μ (ketone C=O); NMR ($CDCl_3$) δ 7.37 (m, 5 H), 2.64 (s, 2 H), 2.37 (s, 2 H), 1.17 (s, 6 H); uv (CH_3OH) 276 mμ (ϵ 9.802 × 10^3).

Anal. Calcd for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.16; H, 5.83; N, 5.38.

Attempted Hydrolyses of 6. A. A solution of **6** (0.5 g, 1.50 mmol) in glacial acetic acid (25 ml) and water (2.5 ml) was heated to boiling for 10 min. The reaction mixture was then allowed to cool, poured into water (100 ml), and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated in vacuo, leaving 0.44 g (88%) of unreacted **6**.

B. A solution of **6** (1.2 g, 3.61 mmol) in dioxane (180 ml), water (19 ml), and concentrated hydrochloric acid (1 ml) was warmed on a steam bath for 2 hr. The dioxane was subsequently removed by evaporation at reduced pressure, and the remaining aqueous solution was extracted with ether. The ethereal solution was isolated, dried ($MgSO_4$), and concentrated in vacuo, leaving 1.01 g (84%) of unreacted **6**.

C. A solution of **6** (0.8 g, 2.41 mmol) in dioxane (100 ml), water (40 ml), and concentrated sulfuric acid (10 ml) was heated for 22 hr, and the reaction mixture was subsequently extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated in vacuo, leaving 0.71 g (89%) of unreacted **6**.

D. Ketene acetal **6** (0.3 g, 0.91 mmol) was added to concentrated sulfuric acid, and the mixture was warmed until solution was effected. The solution was then poured into water (100 ml) and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and concentrated in vacuo, leaving 0.26 g (87%) of unreacted **6**.

Synthesis of Phenyldimedonyliodone (4). Although the synthesis of **4** has been thoroughly described by other workers,[5,6] we employed the slightly modified procedure which follows.

A solution of 5.5 g (39.2 mmol) of dimedone (Eastman Chemical Co.) and 12 g (37.3 mmol) of iodosobenzene diacetate (Eastman Chemical Co.) in CH_2Cl_2 (200 ml) was allowed to stir for 15 min at room temperature. The reaction mixture was then washed with two 150-ml portions of 5% KOH and two 100-ml portions of saturated aqueous sodium chloride, filtered through anhydrous $MgSO_4$, and concentrated to dryness in vacuo. The pale yellow solid residue was triturated with ether and ultimately yielded 10.4 g (81%) of **4** as a white powder, mp 130° dec.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also wish to thank Dr. Stephen D. Darling and Dr. William G. Kofron for helpful discussions.

Registry No.—**4**, 35024-12-5; **5**, 54166-39-1; **6**, 54166-40-4; **7**, 54166-41-5; **13**, 54166-42-6; diphenylketene, 525-06-4; benzophenone 2,4-DNP, 1733-62-6; iodobenzene, 591-50-4; phenyl isocyanate, 103-71-9; diphenylurea, 102-07-8; dimedone, 126-81-8; iodosobenzene diacetate, 3240-34-4.

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(9) For example, see T. C. Clarke, D. R. Kelsey, and R. G. Bergman, *J. Am. Chem. Soc.*, **94**, 3626 (1972).
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An Anomalous Neber Reaction. A General Method for the Preparation of 3-Carboxy-1-naphthylamines

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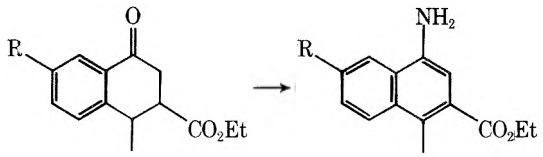
A need for 4-amino-1,6-dialkyl-2-naphthoate esters, to be used as intermediates in the synthesis of unsymmetrical 2,6-disubstituted naphthalene cyclophanes, and the ready availability of 3-carboalkoxy-1-tetralones[1,2] focused our attention on means of effecting the conversion of tetralone to naphthylamine (Scheme I).

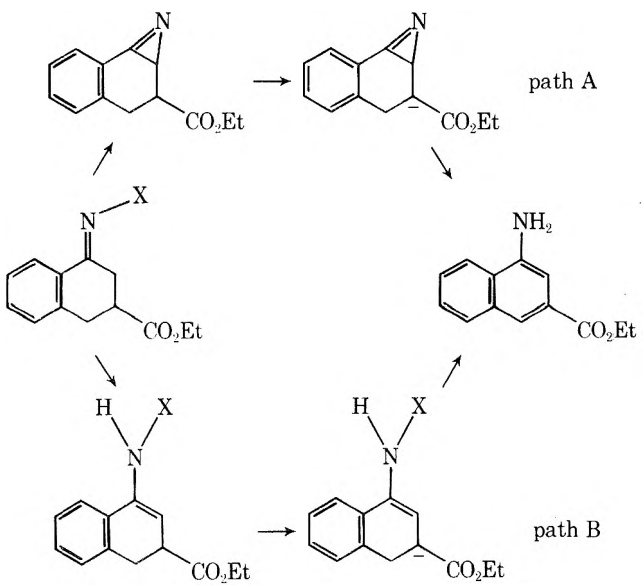
Scheme I



After a variety of more conventional approaches to this conversion had been examined with limited success, attempts were made to utilize the known acid-catalyzed transformation of tetralone oxime[3] or hydrazone derivatives[4] to naphthylamines, despite the low yields reported for most of these conversions. Perhaps because of the electron-withdrawing effect of the carboethoxy group, yields in our systems never exceeded 30% under all conditions tried with these reactions.

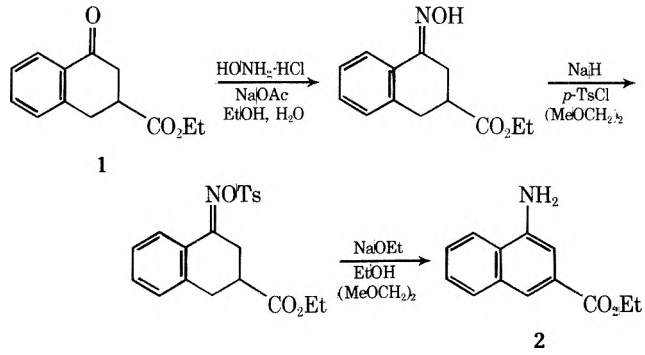
To our knowledge, a base-catalyzed conversion of 1-tetralone to 1-naphthylamine has not been reported, and indeed the Neber reaction of tetralone oxime tosylates is known to yield products other than naphthylamines under these basic conditions.[7] Nevertheless, the presence of the carboethoxy group seemed to offer potential activation for production of naphthylamine by one of the routes shown in Scheme II. We now report an effective base-catalyzed conversion of tetralone to naphthylamine.

Scheme II



The conversion of 3-carboethoxy-1-tetralones, e.g., **1**, to the corresponding oxime proceeded in excellent yield. The oxime tosylate was then prepared in anhydrous dimethoxyethane from the oxime, sodium hydride, and *p*-toluenesulfonyl chloride. Dilution of the crude tosylate solution with 2–3 equiv of sodium ethoxide in ethanol produced the aminonaphthoate **2** in good yield (Scheme III). A variety of 4-

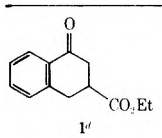
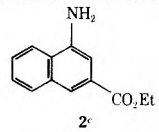
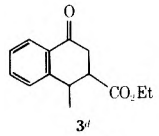
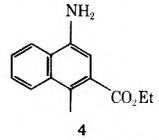
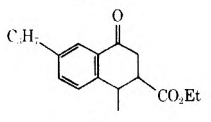
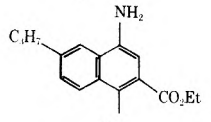
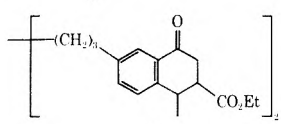
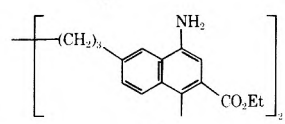
Scheme III



amino-2-naphthoates were thus prepared (Table I). Naphthylamines **2**, **4**, and **6** were consistently prepared in 70% yields. The yield of **8** is lower both because of its bifunctional nature and because of the impurity of tetralone **7**.

Optimization of conditions received some attention by an examination of oxime leaving group, base, and solvent. The *O*-tosyl group proved to be better than the *O*-methyl, *O*-acetyl, or *O*-trifyl leaving group. Aromatization of the *O*-methyl or *O*-acetyl oxime of **5** was possible in 30–50% yield utilizing lithium 2,2,6,6-tetramethylpiperidide[8] in large excess. The *O*-triflate rearranged prior to the addition of base. Of the bases examined, ethoxide or methoxide gave higher yields of naphthylamines than more highly hindered alkoxides, amine anion bases, or dimsyl anion. Ethoxide was chosen to minimize transesterification. Less basic tertiary amines were unreactive. Ethanol as solvent was superior to isopropyl alcohol, *tert*-butyl alcohol, *tert*-amyl alcohol, or dimethyl sulfoxide. Ethanol was also better than tetrahydrofuran–ethanol or ether–ethanol mixtures; however, a dimethoxyethane–ethanol (2:1 v/v) solvent mixture

Table I

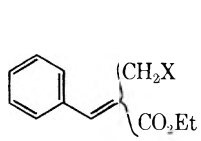
Tetralone	Amine[a]	% yield[b]
 1[d]	 2[c]	72
 3[d]	 4	72
 5[d]	 6	70
 7[e]	 8	20

[a] All amines are completely characterized spectroscopically and analytically. [b] Isolated yield. [c] Converted to amino acid, mp 205–207° (lit.[5] mp 204–206°). [d] Distilled tetralone. [e] Crude material.

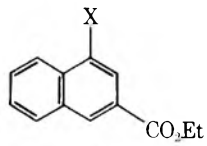
increased yields by 10–20%. Although some cooling is desirable for the mildly exothermic reaction, low temperature (−70°) offered no advantages. Finally, it was noticed that the rigorous exclusion of oxygen afforded a cleaner product.

The question of mechanism has not been studied in detail, and no firm conclusions can be drawn. The formation of **6** from **5** methoxyoxime and lithium 2,2,6,6-tetramethylpiperidide and mechanistic studies of the Neber reaction[6] suggest path B in Scheme II. Nevertheless, it is intriguing that optimum conditions for this reaction are very similar to those found for the closely related Neber conversion. A point which apparently has not been given prior attention is whether naphthylamines are formed from simple tetralone oxime tosylates under Neber conditions.[7] We have found that in fact 5–10% of 1-aminonaphthalene is formed from 1-tetralone oxime tosylate with sodium ethoxide in dimethoxyethane–ethanol. Clearly the carboethoxy group facilitates but does not induce the pathway to naphthylamines. Thus several different mechanisms may be involved in the naphthylamine formation.[9]

Other approaches to the formation of 4-amino-2-naphthoate esters were explored with very limited success. The dimethylenamine[10a] or pyrrolidine enamine[10b] of **5** could be prepared in low yield only with difficulty, and preliminary dehydrogenation experiments were not encouraging. The benzylamine Schiff base of **3** or **5** provided **4** or **6** in moderate yield (40–50%) after treatment with 10% palladium on carbon in refluxing mesitylene;[11] but under similar conditions the benzylamine Schiff base of **7** gave **8** in only 5% yield. Other attempts to aromatize the Schiff base of **3**, as well as **3** itself, failed to provide adequate yields of the corresponding aminonaphthalene or naphthol.[12] Despite a variety of precedents, direct cyclization of **9** to **10**[13] or of **11**–**14** to the corresponding naphthylamine[14,15] failed with one exception. Amide **14** capriciously provided up to 30% of amine **15** after treatment with phosphorus oxychloride.[15]



9, X = CO_2H
11, X = CN
12, X = $CONH_2$
13, X = CONHMe
14, X = $CONMe_2$



10, X = OAc
15, X = NMe_2

Experimental Section

General Procedure.[16] **Ethyl 4-Amino-1-methyl-2-naphthoate (4).** A solution of 0.350 g (1.50 mmol) of 3-carboethoxy-1-tetralone **3**, 0.115 g (1.1 equiv) of hydroxylamine hydrochloride, 0.132 g (1.1 equiv) of sodium acetate, and 10 ml of 80% ethanol was refluxed for 1 hr. The solution was partitioned between ether and water (25 ml each), and the layers separated. The aqueous layer was washed with additional ether (3 × 25 ml). The combined ether layers were then washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and condensed to provide a quantitative yield of the oily oxime: ir (film) 3400 and 1730 cm^{-1}. This crude oxime and 0.306 g (1.60 mmol) of *p*-tosyl chloride were dissolved in 20 ml of dry dimethoxyethane and treated with 0.090 g (1.87 mmol) of sodium hydride mineral oil dispersion.[17] The mixture was stirred under nitrogen for 17 hr, cooled to 0°, and treated with 10 ml of 0.6 *N* sodium ethoxide in ethanol.[18] The solution was stirred at 0° under nitrogen for an additional 2 hr and then subjected to the ether–water extractive work-up described above to provide crude oily amine. Purification by elution with 1:9 ethyl acetate–pentane from alumina provided 0.248 g (72%) of **4**: mp 73–74°; ir ($CHCl_3$) 3490, 3400, and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.77 (s, 3 H), 4.00 (s, 2 H), 4.37 (q, 2 H), 7.05 (s, 1 H), and 7.1–8.2 ppm (m, 4 H).

The hydrochloride salt was prepared by crystallization of **4** from ethanolic hydrochloric acid: mp 243–246°.

Anal. Calcd for $C_{14}H_{16}NO_2Cl$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.02; H, 6.08; N, 5.24.

Acknowledgment. Financial support from the National Science Foundation through Research Grant GP 33265X is gratefully acknowledged.

Registry No.—**1**, 22743-00-6; **2**, 54143-46-3; **3**, 54143-47-4; **4**, 54143-48-5; **4** HCl, 54143-49-6; **5**, 54143-50-9; **6**, 54143-51-0; **7**, 54307-68-5; **8**, 54143-53-2.

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(10) (a) W. H. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967); (b) U. K. Pandit et al., *Recl. Trav. Chim. Pays-Bas*, **89**, 1258 (1970).
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(14) (a) Trimethyloxonium fluoroborate: F. Johnson et al., *J. Org. Chem.*, **39**, 1434 (1974), and references cited therein. (b) Sulfuric acid: C. K. Bradsher et al., *J. Am. Chem. Soc.*, **78**, 2153 (1956). (c) Polyphosphoric acid: cf. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1. Wiley, New York, N.Y., 1968, p 899. (d) Polyphosphate ester: ibid., p 892; Vol. 2, p 333. (e) Phosphorus pentachloride: W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74–150 (1951). (f) Phosphorus pentachloride then aluminum chloride: D. H. Hey and J. M. Williams, *J. Chem. Soc.*, 1527 (1951).
(15) See ref 14e.
(16) This procedure is typical of those used for preparation of amines **2**, **4**, **6**, and **8** and provides comparable yields on a 0.1-mol scale. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 spectrometer at 60 MHz using tetramethylsilane as an internal standard. Infrared (ir) spectra were determined with a Perkin-Elmer 567 spectrometer. Melting points are uncorrected. Analyses were completed by Midwest Microlab, Ltd., Indianapolis, Ind. All new compounds have been adequately characterized. Reagent aluminum oxide for chromatography was purchased from Merck Chemical Division, Rahway, N.J.
(17) The sodium hydride was purchased from Alpha Ventron, Beverly, Mass., and washed with pentane after weighing, immediately prior to use.
(18) The reaction is relatively insensitive to concentration. During 0.1-mol scale reactions the tosylate and ethoxide concentrations were ten times greater. A volume ratio of 2:1 dimethoxyethane to ethanol is optimal.

Electrophilic Addition of $RPX_2/AlCl_3$ to Olefins. The Possibility of Phosphiranes

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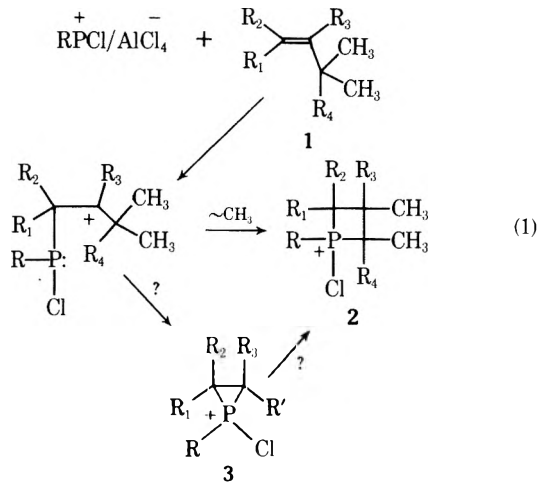
Received December 28, 1973

Small-ring heterocycles containing nitrogen, oxygen, or sulfur atom centers are rather common, whereas phosphorous analogs are obtainable only under special or awkward circumstances.[1,2,8] Phosphiranes are usually prepared by coupling vicinal dihalides with phosphides, while an unusual coupling reaction between $RPX_2/AlCl_3$ complexes and branched monoenes yields phosphetanes. Equation 1 summarizes this latter reaction and shows the breadth of ole-

fins which yield phosphetanes (via methyl migration),[2] but curiously, three-membered rings are not formed.[3] Our in-

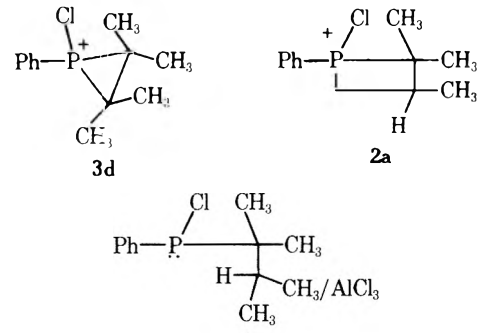


(1)

a, $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$
a′, $R_1 = R_2 = R_4 = H$; $R_3 = CH_3$
b, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$
c, $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$

terest in the synthesis and stability of small phosphorous systems[4] prompted us to evaluate this anomalous feature of that coupling reaction. We envisioned that phosphoranium ions (3) might be isolable intermediates in such reactions if suitable modifications were made in the character of the reagents. We report below our results of the reaction of $RPX_2/AlCl_3$ complexes with olefins such as 2,3-dimethyl-2-butene in which the surface to phosphetanes would not be expected to be open.

Employing a procedure similar to Cremer's[2d] we are able to isolate an adduct from mixing equal molar amounts of $PhPCl_2/AlCl_3$ with 2,3-dimethyl-2-butene followed by evaporation (at room temperature) of the CH_2Cl_2 solvent ca. 5–12 hr after mixing. The 100-MHz ^1H NMR ($CDCl_3$ solvent) of the residual viscous oil displayed aromatic H's (A = 5, broad multiplet, δ 7.0–8.3 ppm), a multiplet (A = 1, δ 2.4–2.9 ppm), and four single lines (A = 12, δ 1.15, 1.22, 1.57, and 1.90 ppm). Upon ^{31}P irradiation the low-field pair of this latter set collapsed to a single line (δ 1.77 ppm) while the remaining two transitions were unchanged. These spectra along with the ^{13}C NMR data of Table I were not consistent with either expected phosphiranium ion **3d** or known phosphetanium ion **2a** but instead required the acyclic structure **4** (isopropyl group, $^3J_{HH}$ = 7.0 Hz; *gem*-di-



methyls, $^3J_{PCCH_3}$ = 33 Hz and $^2J_{PCC}$ = 9.8 Hz; and quaternary C α to P, $^1J_{PC}$ = 26.9 Hz). Additional support for this assignment was afforded by H_2O quench of this salt, which yielded a phosphine oxide[5] **5** (ir P=O at 1205 cm^{-1}), and the mass spectrum, which showed a parent ion at *m/e* 244 (and a P + 2 of relative ⅓ intensity) and principal fragments *m/e* 204, 202; 162, 160; 125; and 85. Our assignment of **5** was confirmed by basic hydrolysis of this material to give known 1,2,2-trimethylpropylphenylphosphinic acid (**6**)[6] (Scheme I).

Close inspection of the ^1H NMR spectra of **4** and **5** and comparison of their respective CCH_3 regions was informative. Structures **4a** and **5** both contain a chiral phosphorous which should impart chemical nonequivalence to both sets of geminal methyls. Interestingly, the δ's for the methyls of each geminal set in the salt **4** were coincident. This can be rationalized either by a preponderance of **4b** (planar phosphorus) or by a rapid equilibration between **4a** and **4b**. That the equivalence in chemical shifts for the geminal

Scheme I

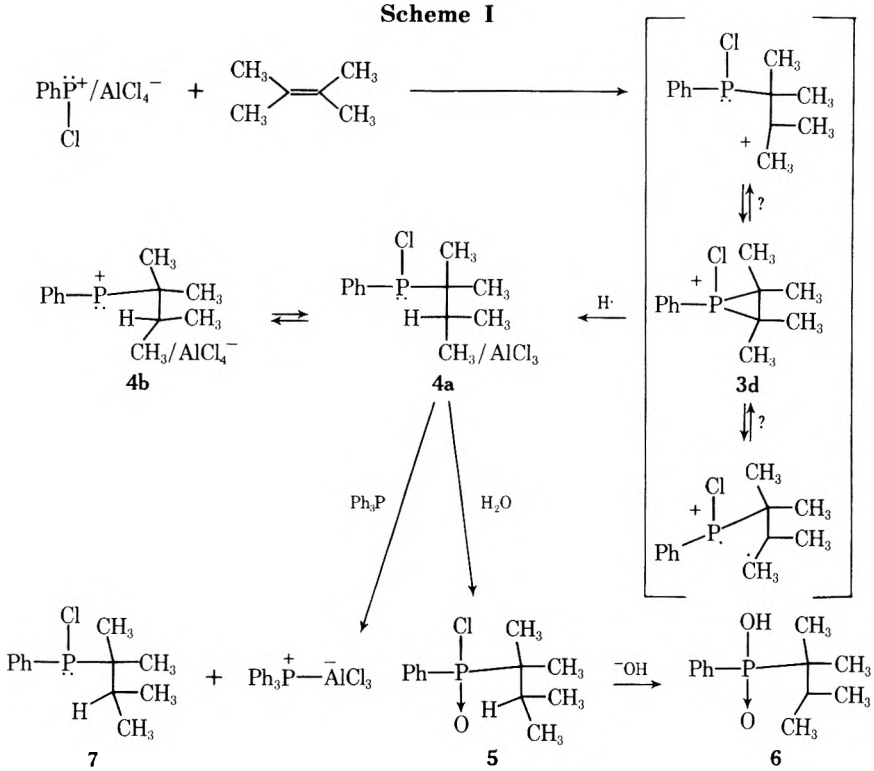
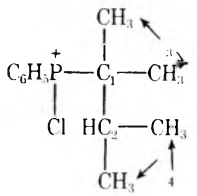


Table I
^{13}C NMR (25.1 MHz) Data for 4



Carbon	δ, ppm[a]	Multiplet pattern H decoupled	Multiplet pattern H coupled	$J(^{13}C-^{31}P)$[b]	$J(^{13}C-H)$[b]
1	51.9	d	d	26.9	
2	31.3	s	d		127
Me_3	16.9	d	dq	9.8	134
Me_4	17.6	s	q		134

[a] Relative to internal Me_4Si. [b] J value error ±1 Hz.

CH_3's in **4a** ⇄ **4b** is directly due to **4b** could be shown by the conversion of **4** to **7**. Treatment of **4** in CH_2Cl_2 with a equimolar amount of $(Ph)_3P$ followed by addition of pentane caused separation of $(Ph)_3P$–$AlCl_3$ with **7** remaining in solution. The aromatic H's were visible at 7.1–8.1 ppm and the CCH_3 region of the 100-MHz ^{31}P decoupled ^1H NMR of **7** displayed an overlapping six-line multiplet (A = 12) owing to observable nonequivalent δ's for the methyls of each geminal set: singlets at 0.86 and 1.10 ppm; two doublets (J = 7.0 Hz) with transitions at 1.09, 1.16, 1.11, and 1.18 ppm; and $^3J_{PCCH}$ = 9 and 16.5 Hz, could be measured without ^{31}P irradiation. Relative to **4** (but analagously to **7**) the ^1H NMR of **5** was more complex in the CCH_3 region, displaying ($CDCl_3$ solvent) a nine-line multiplet (A = 1.0, δ 1.90–2.40, $^3J_{HH}$ = 7.0, $^3J_{PCCH}$ = 14.0 Hz) and seven single lines (A = 12.3, δ 1.01, 1.06, 1.08, 1.13, 1.16, 1.31, 1.38; relative intensities 1:1:1:1:2:1:1) and aromatic H's (A = 3.1, δ 7.2–7.45; A = 1.8, δ 7.55–7.90). Decoupling at ^{31}P transformed the CCH_3 region into a six-line multiplet composed of two doublets ($^3J_{HH}$ = 7.0 Hz) with transitions at δ 1.01, 1.08, 1.06, and 1.13 ppm and singlets at 1.20 and 1.27 ppm (intensities 1:1:1:1:2:2). Comparison between the ^{31}P decoupled and nondecoupled spectra enabled assignment of $^3J_{PCCH_3}$ = 22 and 23 Hz and identity of a chiral P-carbon skeleton of P*–$C(CH_3)_2CH(CH_3)_2$ constitution.

In order to pinpoint the proton source in the formation of **4** and **5** the reaction sequence of Scheme I was repeated with several different deuterium sources added. Duplicate runs were carried out under the following conditions: (a) CD_2Cl_2 as solvent, (b) CD_3NO_2 as solvent, (c) $AlCl_3$ doped with D_2O with CH_2Cl_2 as solvent. The ^1H NMR and ^{13}C NMR spectra of intermediate **4** isolated from run c showed deuterium incorporation exclusively at the methine position, whereas runs under conditions a and b gave respectively no D incorporation and nonreproducible D incorporation.

A tentative mechanism which accounts for the formation of products **5**–**7** is summarized in Scheme I. The two most reasonable precursors to **4**, namely, a diradical phosphonium ion or a phosphine carbonium ion, are in principle distinguishable on the basis of the deuteration experiments reported above. Carbonium ion promoted H^- transfer from protic solvents is a rarity; however, trapping of carbon radicals by hydroxylic species has been observed.[7] Previous work on the addition of $RPX_3/AlCl_3$ to olefins provides a precedent for expecting 2-(phenylchlorophosphine)-1,2-dimethyl-1-butenium ion as an initial adduct in Scheme I.[2] Consequently, we favor the phosphonium diradical of Scheme I as a relay species between this adduct and the isolated species **4**. The apparent lability of the phosphiranium ion suggested by Scheme I is not completely unexpected, because phosphiranes are known to be thermally labile. For example, the phosphirane ring of 9-phenyl-9-phosphabicyclo[6.1.0]nonatriene requires a temperature of 70° to promote ring expansion to a phospholene derivative,[8] while phosphirane itself decomposes completely at room temperature (over 24 hr) to give ethylphosphine and other products.[2b] Phosphiranes with pentasubstituted phosphorus have been prepared but decompose rapidly at −78°, yielding ring-expanded products.[9] Recent theoretical calculations on three-membered phosphorus heterocycles predict decomposition energies consistent with the above trends.[10] Undoubtedly the stability of phosphoranium ions such as **3d** lies somewhere inbetween that of the pentacoordinate and the tricoordinate phosphorus derivatives. It may be possible, however, to stabilize the phosphoranium intermediates to ring opening by manipulation of substituents, especially since Cremer[2d] has noted an enhancement of lability to ring opening for pentamethyl phosphetanium ions vs. pentamethylphosphetanes, and in the former the rate of ring opening increases in the series $>P^+$–$(CH_3)Cl$, $>P^+$–$(Ph)Cl$, $>P^+Cl_2$.

Experimental Section

The NMR spectra were determined on a Jeol PS-100 NMR spectrometer operating on ^1H (continuous wave) at 100 MHz or ^{13}C (Fourier transform) at 25 MHz. The ^{13}C NMR ^1H coupled spectra were obtained via the alternatively pulsed ^1H technique of Ganson.[11] Aldrich Chemical Co. was the supplier of 2,3-dimethyl-2-butene, CD_2Cl_2 (99.5% D) was purchased from Merck Sharp & Dohme, and CD_3NO_2 (56% D) was prepared according to the literature.[12] All reactions were conducted under a nitrogen atmosphere.

2-(Chlorophenylphosphine)-2,3-dimethylbutane–$AlCl_3$ (4). To a chilled suspension of anhydrous aluminium chloride (0.4 g, 3.0 mmol) in CH_2Cl_2 (10 ml) was added dropwise phenylphosphonous dichloride (0.55 g, 0.4 ml, 3.0 mmol). The colorless mixture became homogeneous and clear after 5 min of stirring. While the mixture was still chilled 2,3-dimethyl-2-butene (0.25 g, 3.0 mmol) was added. A slight color developed at the point of contact of the olefin with the reaction mixture but it was quickly dissipated. After 5 hr of stirring at room temperature an aliquot taken for NMR showed essentially complete formation of **4**. Evaporation of the solvent in vacuo gave 0.7 g of a viscous liquid whose ^1H NMR and ^{13}C NMR spectra are reported in the text and Table I.

2-(Chlorophenylphosphine)-2,3-dimethylbutane-*d*–$AlCl_3$ (4-*d*). To anhydrous aluminum chloride (0.4 g, 3.0 mmol) in a chilled flask was added D_2O (40 μl, 2.0 mmol) and evolution of DCl could be observed. The CH_2Cl_2 solvent (10 ml) was added and the suspension had a yellow tinge. While the mixture was still chilled phenylphosphonous dichloride (0.55 g, 3.0 mmol) and 2,3-dimethyl-2-butene (0.25 g, 3.0 mmol) were added as described above. After stirring at room temperature overnight the solvent was evaporated to yield a viscous, colorless liquid. The ^1H NMR was the same as that described for **4** in the text with the exception of a singlet absorption for the $-C(CH_3)_2D$ function visible at 1.19 ppm (% D incorporation 55). The ^{13}C NMR, in which ^1H coupling remained, clearly showed the presence of the tertary C with a D attached (^{13}C NMR of **4** and **4-*d*** exhibited in the ^1H coupled spectra the following absorptions for C_2: **4**, a doublet at 33.7 and 28.6 ppm, J_{CH} = 127 Hz; **4-*d***, a doublet at 33.7 and 28.6 ppm and a broad peak at 32.0 ppm).

2-(Chlorophenylphosphine Oxide)-2,3-dimethylbutane (5). The reaction intermediate **4** prepared as above (in a 3-mmol run) could be converted to **5** by first redissolving the former in 10 ml of CH_2Cl_2 and pouring the mixture onto 50 g of ice. The organic phase was separated and washed with saturated $NaHCO_3$ (2 × 25 ml) and saturated NaCl (25 ml). The organic phase was dried with $MgSO_4$ and evaporated in vacuo, yielding **5** (0.26 g, 36% yield) which displayed a clean NMR as described in the text. Further purification could be effected by Kugelrohr, bp 110° (0.2 mm).

2-(Chlorophenylphosphine)-2,3-dimethylbutane (7). The reaction intermediate **4** (2.8 g, 7.1 mmol) prepared as above could be converted to **7** by first redissolving it in CH_2Cl_2 (20 ml) and

adding Ph_3P (1.9 g, 7.2 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred for 30 min and pentane (50 ml) was added, causing a yellow oil to deposit on the bottom of the flask. The solution was chilled and the organic phase was carefully drawn off. Evaporation of the solvent gave **7**, whose spectral properties are described in the text.

1,1,2-Trimethylpropylphenylphosphinic Acid (6). Compound **5** (200 mg, 0.83 mmol) was suspended in NaOH (10 ml of 5 *N* solution) and refluxed for 2 hr. Upon cooling white crystals of **8** were deposited (140 mg, 75% crude yield) whose ^1H NMR was in agreement with the literature.[6] Recrystallization from water gave needles, mp 94–95° (after drying) (lit. mp 91–93°).

Acknowledgment. I acknowledge support from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**4a**, 54193-52-1; **4a-*d***, 54193-53-2; **4b**, 54293-23-1; **4b-*d***, 54293-25-3; **5**, 54193-50-9; **6**, 28660-28-8; **7**, 54193-51-0; aluminum chloride, 7446-70-0; phenylphosphonous dichloride, 644-97-3; 2,3-dimethyl-2-butene, 563-79-1.

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(3) Other olefins, including 2-pentene, 2-methyl-2-butene, and 4-methyl-2-pentene, reportedly gave uncharacterized adducts in low yields.[2a]
(4) P. Crews and J. Engstrom, unpublished results.
(5) No attempt was made to exclude oxygen during the work-up; hence it is not surprising that the phosphine intermediate (i.e., **7**) is oxidized to **5**. Air oxidation of alkyl phosphines has long been recognized to be a facile process. As an example, Buckler [S. A. Buckler, *J. Am. Chem. Soc.*, **84**, 3093 (1962)] has shown that Bu_3P: can be rapidly air oxidized in organic or aqueous solvent to $Bu_3P \rightarrow O$.
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Polyfluorobenzopinacols

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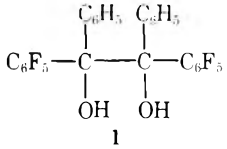
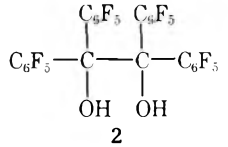
We report the preparation and chemical behavior of decafluorobenzopinacol (**1**)[2] and our attempts to prepare perfluorobenzopinacol (**2**), a compound which is still unknown.



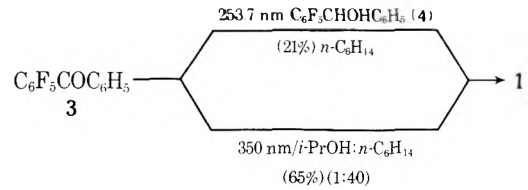
1



2

Decafluorobenzopinacol. Photochemical bimolecular reduction of pentafluorobenzophenone (**3**) by irradiation with 253.7-nm light in the presence of 2-propanol gave only an intractable tar. Under these conditions, benzophenone is converted to benzopinacol in high yield.[3] When 2-propanol was replaced by pentafluorobenzhydrol (**4**), the desired benzopinacol **1** was isolated in 21% yield. This conversion was more readily accomplished (65% yield) by irradiating **3** with 350-nm light in a 2-propanol–*n*-hexane (1:40) system (Scheme I).

Scheme I

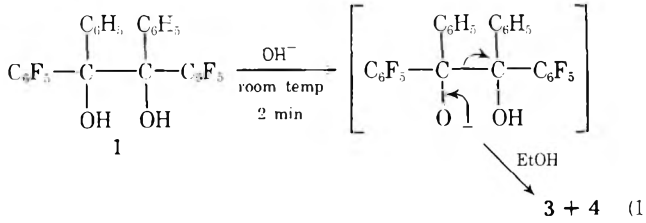


Compound **1** was also prepared by chemical reduction of **3** with zinc and acetic acid.[4] All of the samples of **1** exhibited a melting range of 153–156°. Mixture melting points showed no depression and the infrared spectra were identical. The wide melting range suggested the presence of a mixture of *dl* and meso forms, but attempts to separate components by chromatography on silica gel were unsuccessful.

Decafluorobenzopinacol (**1**) showed a remarkable reluctance to undergo the pinacol–pinacolone rearrangement under conditions in which most benzopinacols react with ease. No evidence of a rearrangement product could be detected on treatment with a wide range of mineral and organic acids. Frequently, fragmentation into **3** and **4** was observed (vide infra).

In considering the participation of **1** in this rearrangement, we must consider both the ease of formation of the electron-deficient carbenium ion center and the intrinsic migratory aptitudes of the phenyl and pentafluorophenyl groups in the subsequent 1,2 shift. From previous studies we would anticipate that phenyl would migrate without difficulty and much more readily than pentafluorophenyl.[5] The failure to observe a rearrangement product strongly suggests the dominance of the electron-withdrawing inductive effect of the pentafluorophenyl group (σ_I 0.25[7]) which so destabilizes the carbenium ion[8] as to preclude any migration. Resistance to rearrangement of 1,1,1,4,4,4-hexafluoro-2,3-diphenyl-2,3-butanediol was also attributed to the destabilizing influence of the trifluoromethyl group (σ_I 0.33–0.41[7]) to development of carbenium ion character.[9] Perfluoropinacol[10a] and the diol derived from octafluoroacetophenone[10b] behaved similarly.

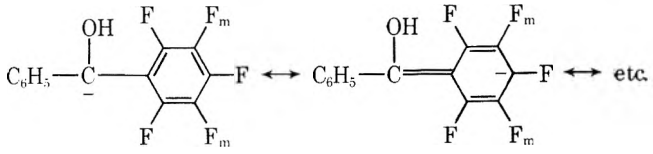
In contrast to its behavior in acidic medium, compound **1** reacted with exceptional facility when treated with 0.1 *N* ethanolic sodium hydroxide solution at room temperature to give an equimolar mixture of pentafluorobenzophenone (**3**) and pentafluorobenzhydrol (**4**) in nearly quantitative yield (eq 1).



1 (1)

Under the same conditions, benzopinacol failed to react, but, on heating, evidence of a similar cleavage was observed. This unusual reactivity of **1** in undergoing the cleavage is probably a reflection of the role of the C_6F_5 group in (1) enhancing the acidity of the hydroxyl group and (2) stabilizing the resulting anion of the benzhydrol. In

this regard, the meta fluorines (F_m) play a major role, consistent with the known stabilizing effect of fluorine attached to the carbon adjacent to a carbanionic center.[11]



Much more surprising than the *alkaline* cleavage were the observations that this fragmentation also proceeds under *acidic* conditions which normally lead to rearrangement to the pinacolone. Thus, nearly quantitative yields of **3** and **4** were obtained by heating **1** under reflux with iodine in glacial acetic acid, dilute sulfuric acid, and water–methanol. Under these latter conditions, we are likely dealing with thermal cleavage.

Perfluorobenzopinacol. All attempts to prepare perfluorobenzopinacol (**2**) from $(C_6F_5)_2C{=}O$ (**5**) by photochemical means were unsuccessful. Various light sources, solvents, and hydrogen donors (2-propanol, ether, benzene, *n*-hexane, cyclohexane, and tributyltin hydride[12]) were used. In general, polymeric residues were obtained, although some $(C_6F_5)_2CHOH$ (**6**) was isolated using $(n\text{-}C_4H_9)_3SnH$ at 350 nm. Subsequent to these studies, the clean photoreduction in 2-propanol of **5** to **6** was reported.[13] In contrast to these observations, perfluoropinacols are readily obtained by photoinitiated bimolecular reduction of hexafluoroacetone and octafluoroacetophenone.[10]

An attempt to convert **5** to **2** by chemical reduction, using "magnesium subiodide",[14] was unsuccessful. Treatment of **5** with sodium amalgam in tetrahydrofuran gave a deep blue mixture which exhibited ESR signals, suggesting the formation of the ketyl, $(C_6F_5)_2\dot{C}\text{–}O^-Na^+$, the precursor of the desired dimer **2**, which, however, was not isolated after acidification. Finally, in contrast to the behavior of **3**, compound **5** was reduced almost quantitatively to **6** with zinc and acetic acid.

Dimerization of the intermediate radical $(C_6F_5)_2\dot{C}\text{–}OH$ or ketyl may be particularly difficult owing to C–F dipole–dipole repulsions of the ortho fluorines as the two pairs of C_6F_5 groups come into close proximity. The shifting of the odd-electron density to ortho or para fluorines has also been suggested to explain the absence of dimerization.[13]

Experimental Section

Melting points are uncorrected and were obtained on an Electrothermal melting point apparatus. Infrared spectra were obtained on a Beckman Ir-8 infrared spectrophotometer or a Perkin-Elmer Model 137 Infracord spectrometer using sodium chloride cells with a path length of 0.1 mm. Ultraviolet spectra were measured on a Cary Model 14 spectrophotometer.

Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Ill., and M-H-W Laboratories, Garden City, Mich.

Fluorinated starting materials were purchased from Pierce Chemical Co., Rockford, Ill.

2,3,4,5,6-Pentafluorobenzhydrol (4). This compound, mp 46–47°, was obtained in 76% yield from benzaldehyde and pentafluorophenylmagnesium bromide by a previously reported procedure.[15]

Decafluorobenzhydrol (6). This compound, mp 75–77°, was prepared in 83% yield according to a procedure described previously.[15]

2,3,4,5,6-Pentafluorobenzophenone (3). This compound, mp 33–34°, was obtained in 80% yield by oxidation of **4** with chromium trioxide in glacial acetic acid, as described previously.[15]

Decafluorobenzophenone (5). This compound, mp 90–92°, was prepared in 74% yield by chromic acid oxidation of **6** as described previously.[15]

1,2-Diphenyl-1,2-bis(pentafluorophenyl)ethanediol (1). A. By Photolysis of 2,3,4,5,6-Pentafluorobenzophenone (3) with 2,3,4,5,6-Pentafluorobenzhydrol (4) in *n*-Hexane. Pentafluorobenzophenone (1.2 g, 0.0044 mol) and 1.5 g (0.0055 mol) of pentafluorobenzhydrol were dissolved in a minimum amount of *n*-hexane (10 ml) containing a small drop of glacial acetic acid. This solution, contained in a quartz tube, was flushed with nitrogen for 20 min, then irradiated with ultraviolet light (253.7 nm, Srinivasan-Griffin reactor) for 20 hr at room temperature under a nitrogen atmosphere. A white, crystalline material, which deposited at the bottom of the reaction vessel, was filtered off, washed with *n*-hexane, and dried. The product, the decafluorobenzopinacol **1**, weighed 0.5 g (21%), mp 140–143°. It readily dissolved in ether, and was deposited as a fine, white powder upon addition of *n*-hexane to the ethereal solution. Several purifications from ether–hexane raised the melting point to 153–156°: ir ($CHCl_3$) 3620, 1525, 1490 cm^{-1}.

Anal. Calcd for $C_{26}H_{12}O_2F_{10}$: C, 57.15; H, 2.21. Found: C, 57.21; H, 2.41.

B. By Photolysis of 2,3,4,5,6-Pentafluorobenzophenone (1) in Isopropyl Alcohol and *n*-Hexane. A solution containing 1 g (0.00368 mol) of pentafluorobenzophenone, 1 drop of glacial acetic acid, 0.5 ml (0.008 mol) of isopropyl alcohol, and 20 ml of *n*-hexane was irradiated (350 nm), following the general procedure described above. The yield was 0.65 g (65%). The product was identified as **1** by melting point, mixture melting point, and infrared spectrum.

When this reaction was carried out in isopropyl alcohol only, without using *n*-hexane, only polymeric residue was obtained. The nature of this oily residue was not identified.

However, when the photochemical reaction was carried out using only *n*-hexane as solvent, the desired product was obtained in about 20% yield.

C. By Reduction of 2,3,4,5,6-Pentafluorobenzophenone with Zinc. To 18 g (0.0663 mol) of pentafluorobenzophenone, dissolved in 72 ml of glacial acetic acid, was added 36 g of zinc powder in ten portions over a period of 30 min while the reaction mixture was stirred vigorously and kept below 40° by means of a cold-water bath. External cooling was not needed after all of the zinc powder had been added. The thick reaction mixture was stirred for about 24 hr at room temperature. Then 500 ml of cold water was added to the mixture, and the resulting solids were filtered off, air dried, and extracted with acetone (150 ml). The acetone extract was filtered and evaporated to give 16.4 g of crude product. The crude decafluorobenzopinacol so obtained was further purified by dissolving in a minimum amount of ether and reprecipitating by addition of *n*-hexane. The final yield was 11.2 g (62%) of white powder, which had a melting point and infrared spectrum identical with those of the material prepared photochemically. There was no depression in a mixture melting point determination.

Reactions of Decafluorobenzopinacol (1). In 0.1 *N* Sodium Hydroxide. When 0.5 g of **1** was added to 10 ml of 0.1 *N* sodium hydroxide solution in 95% ethanol, the solid dissolved immediately. The solution became moderately warm and gave a transient blue color. Within 2 min, the alkaline solution was neutralized with dilute hydrochloric acid. The material isolated from this reaction gave an infrared spectrum identical with that of an authentic mixture of pentafluorobenzophenone and pentafluorobenzhydrol. The yield was nearly quantitative.

As a control experiment, 1.0 g of benzopinacol was mixed with 20 ml of base for 2 min. No liberation of heat was observed. Benzopinacol (0.96 g) was recovered. However, when the same mixture was heated under reflux for 2 min, the product obtained was shown by infrared analysis to be a mixture of benzophenone and benzhydrol.

In Acetic Acid with Iodine. **1** (3 g, 0.0055 mol) was dissolved in 10 ml of glacial acetic acid and a small amount (0.04 g) of iodine was added. The pink solution was heated under reflux for 5 min. The solvent and most of the iodine were removed under reduced pressure, and the resulting viscous residue was taken up in 30 ml of ether and washed with water containing a pinch of sodium bisulfite. The ethereal layer was washed with water, dried (magnesium sulfate), filtered, and evaporated to give a clear semisolid, which solidified slowly on cooling in the refrigerator. This product (2.7 g) had an infrared spectrum identical with that of an equimolar mixture of pentafluorobenzophenone and pentafluorobenzhydrol.

The mixture of products thus obtained was separated into its components by column chromatography. About 1 g of product was dissolved in a minimum volume of *n*-hexane and added to a 20-cm column of alumina (25 g, acidic, pH 4). The column was then slowly eluted with *n*-hexane (200 ml) and then with benzene (200 ml). Most of the pentafluorobenzophenone was found in the first 100-ml fraction of *n*-hexane. Pentafluorobenzhydrol was readily eluted with benzene. Pentafluorobenzophenone and pentafluorobenzhy-

drol so separated were positively identified by melting points and infrared spectra. Similar behavior was observed on heating compound 1 for 24 hr with dilute sulfuric acid, trifluoroacetic, trichloroacetic, formic, and oxalic acids, and water–methanol (50:50, v/v).

In Concentrated Sulfuric Acid. When 0.5 g of 1 was mixed with 10 ml of concentrated sulfuric acid, the white powder appeared to be completely insoluble. The heterogeneous mixture became light orange in color after a few days of vigorous mixing at room temperature. The mixture was then slowly added into a large amount of cracked ice. A white solid separated immediately. About 0.4 g of material was isolated and identified as starting material by mixture melting point and comparison of infrared spectra. In fuming sulfuric acid (30%), only a water-soluble white solid was obtained.

Attempted Preparation of Perfluorobenzopinacol (2). Photochemical. Photochemical reactions were carried out in a manner similar to that described previously. Only intractable tar was obtained when decafluorobenzophenone (5) was irradiated in isopropyl alcohol, *n*-hexane, isopropyl alcohol–*n*-hexane, or cyclohexane, with ultraviolet light at 350 nm. Tar formation appeared to be even more extensive when 253.7-nm light was used. A mixture of decafluorobenzophenone and decafluorobenzhydrol in *n*-hexane was also irradiated, but the resulting material neither solidified nor could it be distilled in vacuo. The reaction of decafluorobenzophenone with tributyltin hydride in benzene or acetonitrile was carried out according to the procedure described by Hammond.[12] No solid could be isolated, even after column chromatography.

Reaction with Zinc. To a glacial acetic acid solution (5 ml) containing 1 g of decafluorobenzophenone was added 2 g of zinc powder and the mixture was stirred vigorously for 24 hr at room temperature. The reaction mixture was poured into a large volume of cold water. The resulting solid, together with zinc, was collected by filtration, dried, and extracted with ether. From the ether layer was isolated 0.9 g of white solid. This compound was identified as decafluorobenzhydrol (6) by mixture melting point and by its infrared spectrum.

Reaction with Sodium Amalgam. Decafluorobenzophenone (2.7 g) and sodium amalgam (2%, 54 g) were mixed vigorously in 54 ml of tetrahydrofuran under a nitrogen atmosphere. The reaction mixture turned to a red-wine color in a few minutes, then blue after 2 hr, and was deep red after 24 hr. The blue mixture exhibited ESR signals. Only a dark-brown, oily residue was obtained after the reaction mixture was decomposed with dilute acetic acid.

Reaction with "Magnesium Subiodide". This procedure was based on the method described by Gomberg and Bachmann.[14] Decafluorobenzophenone (3.64 g, 0.01 mol), dissolved in 5 ml of benzene, was added into "magnesium subiodide", prepared from magnesium powder (0.486 g suspended in 12.5 ml of ether or THF) and 1.4 g of iodine. This mixture was gently refluxed for 1 day, but all of the starting ketone was recovered.

Registry No.—1, 54293-20-8; 3, 1536-23-8; 4, 1944-05-4; 5, 853-39-4; 6, 1766-76-3; sodium hydroxide, 1310-73-2; iodine, 7553-56-2; zinc, 7440-66-6.

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Carbon-13 Nuclear Magnetic Resonance Spectra of 2*H*-1-Benzopyran-2-ones (Coumarins) in Chloroform and Sulfuric Acid

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Coumarins appear extensively in nature as photosensitizing agents[1] and have recently been employed as blue-green laser dyes.[2] Our interest in the photobleaching of laser dyes has prompted us to examine the carbon-13 NMR spectra of coumarins in neutral and acidic solvents. Ultimately, it is the structure, electronic distribution, and environment of the dye which determine its photostability. The lifetime of laser dyes could be improved if these factors could be understood and controlled. The carbon-13 chemical shift can be a reliable indicator of the ground-state electronic environments of carbon atoms in molecules[3] and should provide valuable insight into the nature of the coumarin structure.

Results

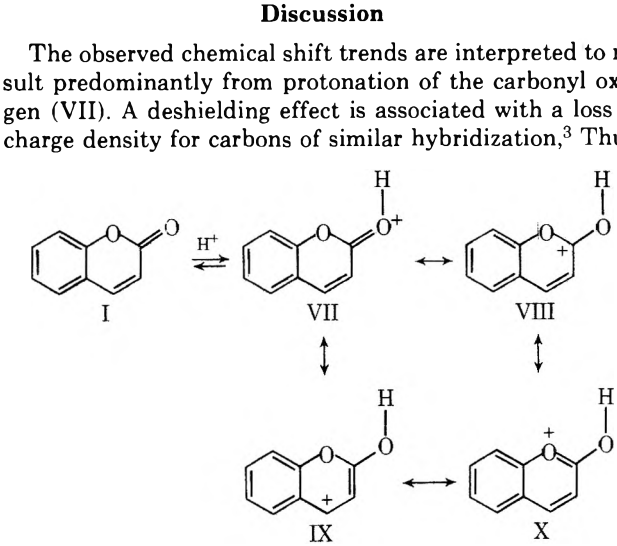
Table I gives the carbon-13 chemical shifts obtained in $CHCl_3$ and 96% H_2SO_4, as well as the chemical shift difference, Δ, between these two solvents. Assignments of resonance positions to individual carbon atoms were based on known substituent effects,[4] splitting patterns in proton-coupled spectra, and internal consistency. A positive Δ indicates that the resonance is deshielded in H_2SO_4 relative to $CHCl_3$.

There is a general deshielding pattern (+Δ) for all carbons except C-3, which is shielded for coumarins I–III and V. With few exceptions, most notably coumarin VI, the aromatic carbon resonances are deshielded 0–9 ppm. Larger deshielding trends of between 10 and 20 ppm are observed for C-2 and C-4 with the shift of C-4 always larger than that of C-2. A shielding of 2–6 ppm for C-3 is observed for I–III and V while C-3 is deshielded in IV and VI.

The one-bond carbon–hydrogen coupling constants, $^1J_{CH}$, are included in parentheses in Table I as well as their difference in neutral and acidic solvent. In general, the value of $^1J_{CH}$ is larger in 96% H_2SO_4 solution. Peak assignments were aided by noting that the $^1J_{CH}$ of C-3 was frequently about 10 Hz larger than the remaining $^1J_{CH}$ values.

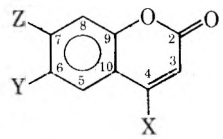
Discussion

The observed chemical shift trends are interpreted to result predominantly from protonation of the carbonyl oxygen (VII). A deshielding effect is associated with a loss of charge density for carbons of similar hybridization,[3] Thus,



large contributions from resonance forms VIII and IX, which place positive charge at C-2 and C-4, can be used to

Table I
Carbon-13 Chemical Shifts and One-Bond Carbon–Hydrogen Coupling Constants for Substituted Coumarins



					Chemical shift ($^1J_{CH}$)[a]											
	X	Y	Z		C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	X	Z	
I	H	H	H	A	172.8	110.4 (182)	159.2 (170)	131.6 (179)	130.7 (168)	138.9 (176)	119.1 (162)	153.7	121.8			
				N[b]	159.6	115.7 (172)	142.7 (164)	127.3 (163)	123.6 (163)	130.9 (163)	115.7 (164)	153.1	118.1			
				Δ	13.2	−5.3 (10)	16.5 (6)	4.3 (16)	7.1 (5)	8.0 (13)	3.4 (−2)	0.6	3.7			
II	H	Cl	H	A	173.0	112.1 (182)	157.7 (173)	130.4 (172)	136.3	138.5 (173)	120.8 (172)	152.1	122.7			
				N	159.6	117.6 (175)	141.9 (166)	126.8 (167)	129.4	131.4 (168)	118.0 (169)	152.1	119.6			
				Δ	13.4	−5.5 (7)	15.8 (7)	3.6 (5)	6.9	7.1 (5)	2.8 (3)	0	3.1			
III	H	H	OH	A	172.3	106.3 (183)	158.9 (164)	133.8 (170)	120.5 (169)	164.1	105.1 (167)	155.9	117.3			
				N[c]	162.0	112.0 (173)	144.8 (164)	129.7 (163)	113.8 (163)	162.4	103.0 (162)	156.4	112.3			
				Δ	10.3	−5.7 (10)	14.1 (0)	4.1 (7)	6.7 (6)	1.7	2.1 (5)	−0.5	5.0			
IV	OH	H	H	A	172.6	90.4 (175)	177.6	126.0 (175)	129.8 (170)	139.2 (172)	119.1 (164)	154.5	116.2			
				N[c]	160.4	89.3 (167)	163.8	121.2 (170)	121.7 (164)	130.4 (164)	114.3 (166)	151.5	114.1			
				Δ	12.2	1.1 (8)	13.8	4.8 (5)	8.1 (6)	8.8 (8)	4.8 (−2)	3.0	2.1			
V	CH_3	H	OH	A	171.1	106.4 (178)	173.7	130.2 (169)	120.2 (164)	163.2	105.3 (170)	155.2	117.7	21.2		
				N[c]	158.6	108.4 (170)	152.9	124.3 (163)	111.1 (164)	159.3	100.4 (163)	151.3	110.1	16.4		
				Δ	12.5	−2.0 (8)	20.8	5.9 (6)	9.1 (0)	3.9	4.9 (7)	3.9	7.6	4.8	$-CH_2-$	$-CH_3$
VI	CH_3	H	Et_2N	A	170.4	110.5 (169)	171.1	130.0 (172)	121.8 (169)	150.9	112.7 (172)	141.9	122.5	19.5	55.6	9.6
				N	161.6	108.0 (173)	152.5	125.0 (159)	108.0 (159)	150.1	97.1 (159)	155.5	108.4	18.1	43.8	12.3
				Δ	8.8	2.5 (−4)	18.6	5.0 (13)	13.8 (10)	0.8	15.6 (13)	−13.6	14.1	1.4	11.8	−2.7

[a] Chemical shifts are reported in parts per million relative to Me_4Si. $^1J_{CH}$ values are contained in parentheses and are given in hertz. A = 96% H_2SO_4 solutions; N = $CHCl_3$ solutions; Δ = (A − N) is the chemical shift or coupling constant difference. [b] C-6 has been erroneously assigned in L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972. Spectrum 333. [c] Dimethyl sulfoxide added to enhance solubility.

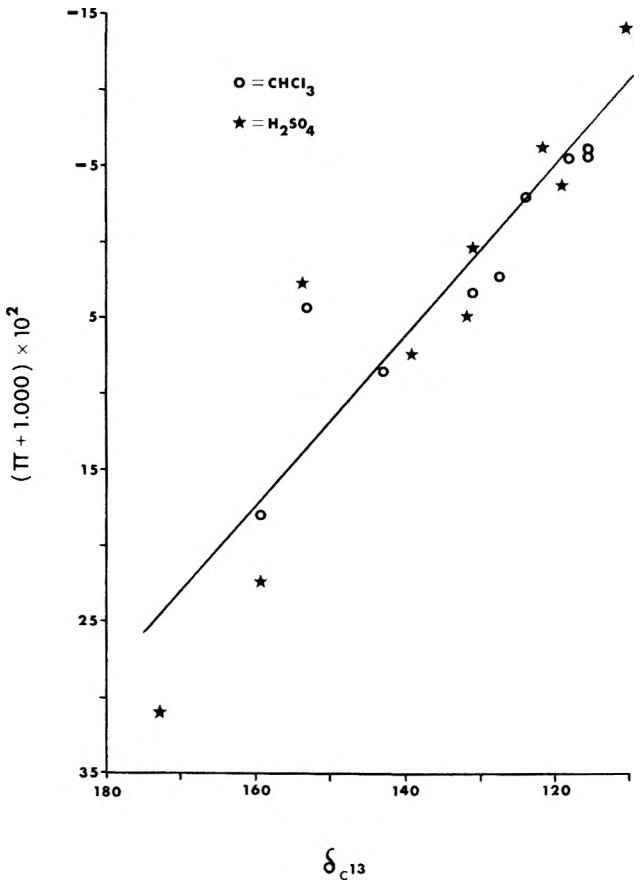


Figure 1. Plot of π charge density vs. carbon-13 chemical shift for coumarin and protonated coumarin.

rationalize the deshielding noted for these carbons. The chemical shift changes are smaller than those observed for protonated unsaturated aldehydes and ketones.[5]

The effects at C-3 are taken to indicate a substantial contribution from resonance form IX, in which C-3 is now β to two vinylic oxygens whose shielding influence[6] opposes the deshielding effect of the adjacent positive charge[7] at C-4. For coumarins I–III and V the shielding effect predominates, whereas for coumarins IV and VI deshielding is observed.

Protonation of the ether oxygen as well as significant contributions from resonance form X appear to be excluded because of the relative constancy of the C-9 chemical shift. Interestingly, resonance forms analogous to X have been shown to contribute significantly in the case of acyclic, saturated esters.[8] Evidently, in the coumarin structure, charge delocalization over the double bond is preferred rather than charge stabilization by the ether oxygen lone pairs.

Chemical shift changes associated with the aromatic ring are taken to be a result of further inductive and positive charge delocalization effects at these carbons. The aromatic carbon chemical shifts for coumarin VI appear to be more grossly affected compared with the rest of the series. This indicates that these carbons experience a stronger perturbation of their electronic environments which may be due to additional protonation at nitrogen. The chemical shift changes for the diethylamino group carbons are consistent with nitrogen protonation. Furthermore, spectroscopic studies of coumarin VI in acidified solution were interpreted in terms of protonation of the diethylamino group.[2]

The increase in $^1J_{CH}$ upon protonation indicates that charge is being lost at the carbon atoms.[9] The changes in $^1J_{CH}$ do not parallel the changes in chemical shift, presumably because the coupling constant is sensitive to other factors such as bond distance, hybridization, and bond polarization.[10] Long-range carbon–hydrogen couplings were observed but are not tabulated because of uncertainties in assignment.

In order to establish a more quantitative relationship between the carbon-13 chemical shifts and charge densities, the electron densities of carbon atoms in coumarin and protonated coumarin were calculated using the CNDO/2 method.[11] A good correlation between chemical shift and total charge or π charge densities was obtained. Figure 1 shows the plot of chemical shift vs. π charge density (ρ = 0.915).

The reactivity of some coumarins has already been reasonably explained by using various MO indices.[12] The establishment of a chemical shift–charge density relationship enables one to investigate the use of carbon-13 chemical shifts as an aid in the prediction and explanation of phenomena which depend on electron distribution. For example, the reactivity of the coumarins toward nucleophilic attack at C-2 can be assessed by assuming that the Δ's of Table I represent the difference between ground- and transition-state-like charge distributions. The order of susceptibility to nucleophilic attack would be predicted to be II $\approx$ I > V $\approx$ IV > III > VI. This order is in qualitative agreement with the kinetic results obtained for the ring fission of analogous coumarins.[13]

Although the exact photobleaching mechanism of laser dyes has not been determined, it appears to involve a nonreversible photochemical reaction and depends, in a complex fashion, on such factors as pH, concentration, and solvent.[14] If the mechanism involves the nucleophilic attack by solvent on a photoexcited molecule, the correlation developed here may be applicable, and aid in the design of improved coumarin laser dyes. However, carefully controlled photobleaching studies must be made available which further elucidate the photobleaching mechanism before this can be rigorously pursued. Assuming that the correlation can be applied, it is noteworthy that coumarin VI would be predicted to be the most stable dye in this series. In practice, coumarins substituted in the 7 position with dialkylamino groups are very stable laser dyes.[2]

Experimental Section

All chemicals were commercially available and used without further purification. Carbon-13 NMR spectra were obtained on a Varian HA-100 spectrometer modified for pulsed operation and equipped with an external fluorine-19 lock.[15] The spectrometer was operated at 25.15 MHz and the probe temperature was 36 ± 2°. Signals were accumulated in a Nicolet 1074 signal averager and Fourier transformed by a PDP-8/L computer. Coupling constants were measured from spectra recorded under gated-decoupling conditions.[16]

Saturated $CHCl_3$ solutions were used and chemical shifts converted to the tetramethylsilane (Me_4Si) scale by the relationship $\delta_{Me_4Si} = \delta_{CHCl_3} + 77.1$. In some cases dimethyl sulfoxide was added to enhance solubility. Spectra were also obtained using 3 *M* solutions of the coumarins in 96% H_2SO_4. Chemical shifts in 96% H_2SO_4 were measured relative to external benzene and converted to the Me_4Si scale using $\delta_{Me_4Si} = \delta_{C_6H_6} + 128.7$.

Standard bond lengths and angles[11] were used in the CNDO/2 calculations.[17]

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Registry No.—I, 91-64-5; II, 2051-59-4; III, 93-35-6; IV, 1076-38-6; V, 90-33-5; VI, 91-44-1.

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Chromate Oxidation of Alkylpyrazines

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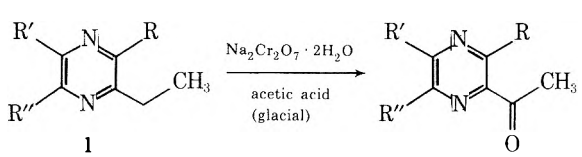
The most convenient preparation of acetylpyrazines previously reported in the literature is a two-step synthesis consisting of a treatment of alkylpyrazines with *N*-bromosuccinimide (NBS), followed by oxidation to the corresponding ketones using either sodium 2-propanenitronate or pyridine 1-oxide.[1] We have now found that 2,3-dialkylpyrazines can be oxidized in one step by sodium dichromate in acetic acid, in good yields, to the corresponding 2-acyl-3-alkylpyrazines. When the 3 position is not substituted, the acylpyrazines are obtained only in very low yields.

These results were rather surprising as attempts to oxidize alkylpyridines with chromic acid were reported to proceed violently and lead to no identifiable products.[2]



1 2

As is shown in Table I, oxidation of 2-ethyl-3-methylpyrazine (**1a**), 2,3-diethylpyrazine (**1b**), and a mixture of 2-ethyl-3,5-dimethylpyrazine (**1c**) and 2-ethyl-3,6-dimethylpyrazine (**1d**) with sodium dichromate in acetic acid gave the corresponding 2-acetylpyrazines **2a, 2b** and a mixture of **2c** and **2d.** When 2-ethyl-5-methylpyrazine (**1e**) and ethylpyrazine (**1f**) were oxidized by the same procedure, the ketones **2e** and **2f** were obtained in only very low yield.

As the alkylpyrazines are expensive and are partially destroyed during the oxidation, it was found more economical to halt the oxidation when approximately one-half of the substrate was oxidized. The alkylpyrazines were easily separated from the ketones by distillation. Increasing the amount of oxidizing agent increased the amount of the ketone but also increased the destruction of the substrate.

Table I

		Yield, %[3]
1a, R = CH_3; R′ = H; R″ = H	**2a**	53
1b, R = Et; R′ = H; R″ = H	**2b**	67
1c (d), R = CH_3 (CH_3); R′ = CH_3 (H); R″ = H (CH_3)	**2c** (d)	57
1e, R = H; R′ = CH_3; R″ = H	**2e**	9
1f, R = H; R′ = H; R″ = H	**2f**	1

Application of this procedure to alkylpyridines led to almost total destruction. Oxidation of 4-ethyl-3-methylpyridine and 4-ethylpyridine gave the corresponding ketones in 5 and 4% yield, respectively. When 3-ethyl-4-methylpyridine and 2-ethylpyridine were oxidized, no identifiable products were obtained.

Experimental Section

All the NMR spectra were run on a Varian HA-100 spectrometer. All chemical shifts are reported in parts per million (δ) relative to Me_4Si. The mass spectra were run on CEC Model 21-103C and AEI MS9 mass spectrometers. Mass spectral major fragmentation peaks are listed in decreasing order of intensity.

2-Acetyl-3-ethylpyrazine (2b). 2,3-Diethylpyrazine (**1b,** 1088 g, 8 mol) was heated to 118°, and a solution of sodium dichromate dihydrate (1500 g) in glacial acetic acid (3000 g) was added in 3 hr with agitation at 118°. Agitation was continued for another 1 hr at 118°, when GLC analysis (20 ft × 0.25 in., 20% Carbowax 20M column) indicated that the reaction mass contained 50% ketone **2b** and 50% starting material **1b.** The reaction mass was then cooled and quenched in 12 l. of water. The solution was extracted four times with toluene (1000 g), and the combined extracts were washed once with water (5 l.) and with 5% sodium carbonate solution (1500 g). The solvent was removed in vacuo, and the residue was fractionated to give starting material **2a** (481.4 g, 3.54 mol) and ketone **2b** (447.0 g, 2.98 mol): yield 67%; bp 77° (6 mm); NMR 1.28 (3 H, t, $-CH_2CH_3$), 2.68 [3 H, s, $-(C{=}O)CH_3$], 6.15 (2 H, q, $-CH_2CH_3$), 8.46 (1 H, d, ArH), 8.60 ppm (1 H, d, ArH); mass spectrum *m/e* 150 (molecular ion), 107, 43, 52, 108.

Anal. Calcd for $C_8H_{10}ON_2$: *m/e* 150.0793. Found: *m/e* 150.0787.

2-Acetyl-3-methylpyrazine (2a). By the above procedure, except that the reaction was run at 80°, oxidation of 2-ethyl-3-methylpyrazine (**1a,** 165 g, 1.35 mol) with a solution of sodium dichromate dihydrate (780 g) in glacial acetic acid (1560 g) gave starting material **1a** (47.6 g, 0.39 mol) and ketone **2a** (69.4 g, 0.51 mol): yield 53%; bp 71° (6 mm); NMR 8.60 (1 H, d, ArH), 8.46 (1 H, d, ArH), 2.71 [3 H, s, $-(C{=}O)CH_3$], 2.82 ppm (3 H, s, $-CH_3$); mass spectrum *m/e* 136 (molecular ion), 43, 94, 93, 42, 67.

Anal. Calcd for $C_7H_8ON_2$: *m/e* 136.0637. Found: *m/e* 136.0642.

2-Acetyl-3,5-dimethylpyrazine (2c) and 2-Acetyl-3,6-dimethylpyrazine (2d). By the same procedure, treatment of a mixture of 2-ethyl-3,5-dimethylpyrazine (**1c**) and 2-ethyl-3,6-dimethylpyrazine (**1d**) (1142 g, 8.4 mol) with a solution of sodium dichromate dihydrate (1575 g) in glacial acetic acid (3150 g) at 80° gave a mixture of starting material **1c** and **1d** (649.0 g, 4.77 mol) and a mixture of ketones **2c** and **2d** (312.6 g, 2.08 mol): yield 57%; bp 70° (7 mm); NMR (mixture) 8.32 (1 H, s, ArH), 2.73 [3 H, s, $-(C{=}O)CH_3$], 8.52 (1 H, s, ArH), 2.74 [3 H, s, $-(C{=}O)CH_3$], 2.46 or 2.66 ppm (3 H each, 2 s, $-CH_3$); mass spectrum *m/e* 150 (molecular ion), 108, 107, 66, 122, 81.

Anal. Calcd for $C_8H_{10}ON_2$: *m/e* 150.0793. Found: *m/e* 150.0790.

2-Acetyl-5-methylpyrazine (2e). By the previous procedure, oxidation of 2-ethyl-5-methylpyrazine (**1e,** 19.5 g, 0.16 mol) with a solution of sodium dichromate dihydrate (30 g) in glacial acetic acid (60 g) gave starting material **1e** (8.2 g, 0.07 mol) and ketone **2e** (1.1 g, 0.008 mol): yield 9%; bp 80° (8 mm); mp 55–56°; NMR 2.60 (3 H, s, $-CH_3$), 2.64 [3 H, s, $-(C{=}O)CH_3$], 8.46 (1 H, s, ArH), 9.08 ppm (1 H, s, ArH); mass spectrum *m/e* 136 (molecular ion), 43, 94, 93, 39, 67.

Anal. Calcd for $C_7H_8ON_2$: *m/e* 136.0637. Found: *m/e* 136.0631.

Acetylpyrazine (2f). By the same procedure except that the reaction was run at 116°, treatment of ethylpyrazine (**1f,** 17.3 g,

0.16 mol) with a solution of sodium dichromate dihydrate (30 g) in glacial acetic acid (60 g) gave starting material **1f** (2.03 g, 0.019 mol) and ketone **2f** (0.27 g, 0.002 mol): yield 1%; bp 72° (15 mm); mp 76–77° (lit.[4] mp 76–78°); NMR 2.69 [3 H, s,-(C=O)CH_3], 8.60 and 8.71 (2 H, 2 d, ArH), 9.22 ppm (1 H, s, ArH); mass spectrum *m/e* 43, 122 (molecular ion), 80, 79, 52, 53.

Acknowledgment. I wish to express my appreciation to Dr. W. I. Taylor for his interest in this work. I also wish to thank Mr. M. Jacobs for the NMR analyses, Ms. A. Sanderson for the mass spectral analyses, and Mr. H. Bondarovich for the high-resolution mass spectral analyses.

Registry No.—**1a**, 15707-23-0; **1b**, 15707-24-1; **1c**, 27043-05-6; **1d**, 13360-65-1; **1e**, 13360-64-0; **1f**, 13925-00-3; **2a**, 23787-80-6; **2b**, 32974-92-8; **2c**, 54300-08-2; **2d**, 54300-09-3; **2e**, 22047-27-4; **2f**, 22047-25-2; sodium dichromate dihydrate, 7789-12-0.

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Sulfonation of Unsaturated Compounds. II. Isolation and Characterization of a Carbyl Sulfate

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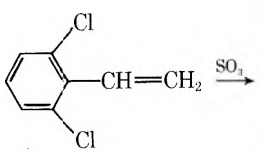
Cyclic sulfonate–sulfate anhydrides **2** (carbyl sulfates) have been proposed as intermediates in some sulfonations of olefins[1] with sulfur trioxide. Evidence for these intermediates comes from the identification of isolated products, usually after alkaline hydrolysis of the sulfonation mixture. In some cases, the carbyl sulfate has been isolated as a crystalline product[2] from a sulfonation mixture. However, these carbyl sulfates have not been characterized directly and no spectral data are available for them.

Using 2,6-dichlorophenylethylene (**1**) to avoid side products resulting from sulfonation into the phenyl ring, it is possible to isolate a pure carbyl sulfate. Dropwise addition of olefin **1** into liquid sulfur dioxide in 1,2-dichloroethane gave the carbyl sulfate **2** in 96% yield. Spectral and analytical data support the assignment of structure **2**.



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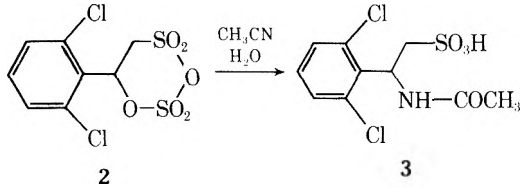

2 **3**

The carbyl sulfate can also be obtained from the sulfur trioxide–dioxane adduct as sulfonating agent, but in lower yields.

Carbyl sulfate **2** reacted readily with wet acetonitrile to give the β-aminosulfonic acid **3** through a Ritter-type reaction.[3] Treatment of **2** with aqueous alkali, pyridine, and piperidine gave mixtures of sulfate and sulfonate salts.

Experimental Section

1-(2,6-Dichlorophenyl)-1-sulfate-2-sulfonate Anhydride (Carbyl Sulfate, 2). Method A. Freshly distilled sulfur trioxide (Sulfan, Allied Chemicals), 2.6 g (0.032 mol), was added to 25 ml of dry 1,2-dichloroethane at 0°. To this solution 2,6-dichlorostyrene (5.5 g, 0.032 mol) in 12.5 ml of 1,2-dichloroethane was added dropwise over 25 min at 2–6° with stirring. A precipitate of **2** started to appear immediately. After 12 min of stirring 50 ml of pentane was added and the solution was filtered. The product was washed with pentane–1,2-dichloroethane (1:1) and pentane to yield 5.2 g of the thermally unstable carbyl sulfate **2**: 96%; mp 81.5–83.5°; ir (KBr) 3020, 1580, 1447, 1422, 1380, 1250, 1231, 1215, 1190, 957, 913, 749 cm^{-1}; NMR (DMSO-d_6) δ 7.35 (m, 3 H), 6.35 (m, 1 H), 3.55 (m, 2 H); mass spectrum *m/e* 174, 172 (M − $2SO_3$), 139, 137 (M − $2SO_3$ − Cl), 80 (SO_3), 64 (SO_2); neut equiv, calcd 333.17; found (tritration with 0.05 *N* NaOH in xylene–isopropyl alcohol, 1:1), 335.

Anal. Calcd for $C_8H_6Cl_2O_6S_2$: C, 28.84; H, 1.82; Cl, 21.29; S, 19.25. Found: C, 29.18; H, 2.12; Cl, 21.62; S, 19.55.

Method B. The dioxane–sulfur trioxide complex[4] was prepared from 2.30 g (0.0288 mol) of sulfur trioxide and 2.53 g (0.0288 mol) of dioxane in dry 1,2-dichloroethane (27.5 ml). A solution of 5.5 g (0.032 mol) of **1** in 12.5 ml of 1,2-dichloroethane was added dropwise over 25 min with stirring at 2–4°. After 15 min of stirring, pentane (45 ml) was added and the mixture was allowed to stand in the cold overnight. Filtration and washing as described gave 3.05 g (63.7%) of **2**.

2-(2,6-Dichlorophenyl)-2-(*N*-acetamido)ethanesulfonic Acid (3). A solution of 0.6 g (0.002 mol) of **2** in 15 ml of wet acetonitrile was refluxed for 2 hr. Cooling and filtration gave 0.121 g of **3**: 21.6%; ir (KBr) 3255, 3095, 1670, 1560, 1450, 1250, 1205, 1007, 722 cm^{-1}; NMR (D_2O) δ 7.38 (m, 3 H), 6.27 (m, 1 H), 3.61 (m, 2 H), 2.07 ppm (s, 3 H); mass spectrum *m/e* 174, 172 (M − $CH_3CONHSO_3H$), 139, 137 ($C_6H_3Cl_2CHCH_2$ − Cl), 102 ($C_6H_3Cl_2CHCH_2$ − 2Cl), 101, 64; neut equiv, calcd, 312.18; found (tritration), 308.

Anal. Calcd for $C_{10}H_{11}Cl_2NO_4S$: C, 38.54; H, 3.55; N, 4.51; S, 10.27. Found: C, 38.64; H, 3.44; N, 4.55; S, 10.27.

Acknowledgment. This work was supported by the Sloan Basic Research Fund. One of us (U.Z.) thanks the Iad Avi Hayishuv Foundation, Israel, and the Hebrew Technical Institute, New York, N.Y., for financial support.

Registry No.—**1**, 28469-92-3; **2**, 54276-72-1; **3**, 54276-73-2; SO_3, 7446-11-9; acetonitrile, 75-05-8; 1,2-dichloroethane, 107-06-2.

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Ionization Constants and Volumes of Highly Hindered Pyridines in Methanol[1]

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Although the pK_a's of several 2,6-dialkylpyridinium hydrochlorides have been reported, there is no single com-

plete set of data for the series hydrogen, methyl, ethyl, isopropyl, and *tert*-butyl in a single solvent. In the course of another study,[2] we prepared this series of pyridines and measured both the ionization constants and the ionization volumes in methanol at 25°. We present the data here, and note that the latter data permit some insight into the trend in the former.

Experimental Section

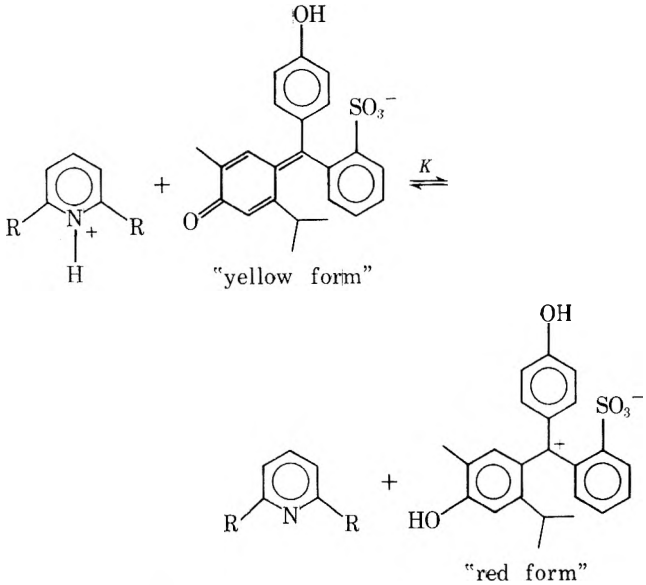
The pyridines were obtained as described.[2]

Thymol Blue was obtained from J. T. Baker, and used without purification. For the pK_a measurements, the spectra of the red and yellow forms of Thymol Blue, of the pyridines, and of their hydrochlorides were measured in methanol solution at 25.00 ± 0.05° by means of a Cary 14, with special attention to the wavelength regions of 250–275 and 545–555 nm. Five-milliliter samples of methanolic solutions of Thymol Blue and of the pyridine of accurately known strength (about 10^{-3} to 10^{-4} *M*) were pipetted into a 25-ml volumetric flask. A hydrochloric acid solution in methanol was added to give the appropriate color (by eye). The flask was thermostated at 25.00° and filled to the mark.

The optical densities in the long wavelength region were used to calculate the ratio of the indicator species;[3] the actual concentrations were also calculated and used in turn to furnish the ratio of free to protonated base. These calculations were repeated for several wavelengths; reproducibility was generally about 1% for the indicator and somewhat less than that for the pyridine. The pK_a is then calculated as shown below. The error in pK_a due to ionic strength effects is less than 0.05,[4] hence less than that in the pK_a reported for Thymol Blue. The density measurements were carried out as before;[2] the hydrochloride solutions were obtained by mixing equivalent quantities of base and hydrochloric acid solutions by means of a microburette.

Results and Discussion

The pK_a values are based on the competition for protons between a given pyridine and the indicator Thymol Blue.[5]



For this equilibrium

$$K = \frac{[B][InH]}{[BH^+][In^-]} = K_{a(BH^+)}/K_{a(InH)}$$

The pK_a of the indicator is known[4] to be 4.7, so that we may write

$$pK_a = 4.7 - \log K$$

The advantage of the indicator method is that it can be carried out spectrophotometrically with very low concentrations at an ionic strength of 10^{-4} or less with good accuracy, provided that K is not too greatly different from unity. The difference in pK_a between the pyridines can then be determined to better than 0.1 unit. Our observations with 2,6-diisopropylpyridine may serve as an example. Twelve measurements were made in which the $[In^-]/[InH]$ ratio was varied over an eightfold range, giving a value of K_{av} of 0.0123 ± 0.0006, so that $pK_a = 4.7 + (1.91 \pm 0.02)$. The final results are shown in Table I.

In one case a direct comparison can be made: when R = H, our result is in excellent agreement with the one reported.[6] The general trend is also in agreement with results obtained by others. We subscribe to the interpretation that protonation is facilitated by α-carbon substitution because of inductive electron donation, and that it can be hindered in some way by increasing substitution and crowding. When R = *t*-Bu, there is no longer any possibility of rotating the hindering methyl groups out of the way, and the change in pK_a is then especially severe.[7] The detailed nature of the hindrance—whether to solvation, H bonding, or bonding—is touched on further below.

Basically, two methods are available for the measurement of ionization volumes. In one of these, use is made of the effect of pressure on the pK_a via the relation

$$\Delta V_i = 2.303RT\,\partial pK_a/\partial p$$

Thus, one could measure the spectra of mixtures of a given pyridine and Thymol Blue under pressure; however, the pressure dependence of $pK_a(InH^+)$ in methanol is not known for Thymol Blue or any other suitable indicator. A disadvantage of the method is, furthermore, that only a difference in volume is obtained and information whether any trends are due to changes in volume of the free base or conjugate acid remains hidden. We furthermore noted that mercury (required to keep the solution of interest separated from hydraulic fluid) is rapidly attacked by methanolic hydrogen chloride to give a species absorbing at 238 nm (neither basic methanol solutions nor those acidic with perchloric acid behave this way), and hence we abandoned this approach. In the other method, one determines ΔV_i as the net sum of several partial molar volumes at infinite dilution, such that the species add up to the ionization reaction under consideration. Errors due to dissociation of the conjugate acids become appreciable at very low concentration, and hence the pycnometric technique was used. The measurements are summarized in Figure 1, and the results are shown in Table II.

The ionization volumes given are calculated on the assumption that $\phi_V°$ for hydrochloric acid in methanol is −5.3 cm^3/mol,[10] and by making use of the known $\phi_V°$ values of the pyridines in methanol.[2] All of them are positive, presumably a reflection of the fact that the charge in the pyridinium ions must to some degree be delocalized; we have reviewed the evidence bearing on this point elsewhere.[11] They are also remarkably independent on interference by 2,6-alkyl groups except for *tert*-butyl; $\Delta V_i°$ for 2,6-di-*tert*-butylpyridinium hydrochloride is by all odds the largest known volume change for proton transfer.[12] Obviously a large fraction of this change can be attributed to the apparent difficulty of the neutral base to be hydrogen bonded in that case.[2]

Finally, a further comment on the pK_a's of these compounds is in order. The declines in pK_a, absent or small at first but then steep at *tert*-butyl, may be caused by steric hindrance to solvation or to steric compression of the conjugate acid itself.[13] The former explanation has been favored by Wepster,[14] and by McDaniel;[8] the latter author found that the changes in pK_a became more pronounced if the solvent is systematically varied from water to aqueous alcohol, or from methanol to 2-propanol. On the other hand, Brown[7] has favored the idea of sterically compressed

Table I
pK_a Values of 2,6-Dialkylpyridinium Hydrochlorides in Several Solvents at 25°

Substituent	Methanol	50% Aqueous Ethanol	Water	Registry no.
H	5.37,[a] 5.4[b]	4.38[c]	5.22[e]	628-13-7
Me	6.86[a]	5.77[c]	6.72[e]	15439-85-7
Et	6.9[b]			54384-36-0
i-Pr	6.6[b]	5.34[c]		54384-37-1
t-Bu	4.2[b]	3.65,[d] 3.58[c]		54384-38-2

[a] Reference 6. [b] This work. [c] Reference 7. [d] Reference 8. [e] Reference 9.

Table II
Partial Molal Volumes of the Pyridinium Hydrochlorides at Infinite Dilution, and the Ionization Volumes in cm³/mol in Methanol at 25.00°

Substituent	Φ_V°	ΔV_I°
H	63.69 ± 0.22	+9.8
Me	97.72 ± 0.19	+8.1
Et	128.39 ± 0.29	+10.0
i-Pr	164.36 ± 0.31	+10.8
t-Bu	196.02 ± 0.17	+22.0

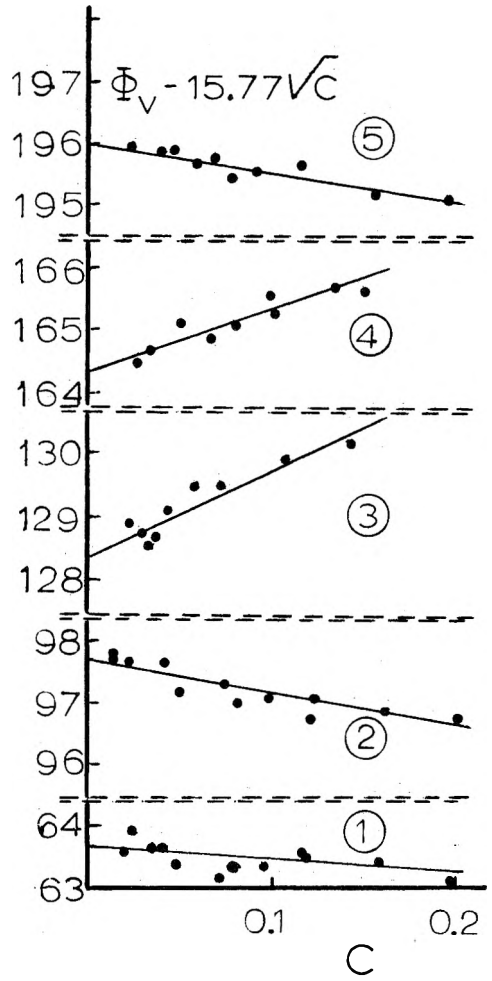


Figure 1. The approach at 25.00° in methanol of the partial volumes of the 2,6-disubstituted pyridinium hydrochlorides to their limiting values: (1) R = H; (2) R = Me; (3) R = Et; (4) R = *i*-Pr; (5) R = *t*-Bu.

pyridinium ions primarily on the grounds that the change at *tert*-butyl is so much more dramatic than with the other alkyl groups. He includes a stressed NH–SOH hydrogen bond as a possibility in his point of view. Our volume data do not allow a clear choice to be made between Brown's two possibilities; however, they do cast doubt on the hindered solvation. Solvation of ions is normally accompanied by a large volume decrease, and if this electrostriction were absent or greatly diminished in the *tert*-butyl cation, this should surely be reflected in an ionization volume much less than that of the lower homologs. What is observed is a volume change much *larger*, and even if allowance is made for the inability of the solvent to form hydrogen bonds with the neutral base, one would still have to conclude that there is no evidence for a conspicuous lack or absence of electrostriction around the cation.

Acknowledgment. This work was generously supported by the National Science Foundation.

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Blocking and Deblocking of α-Methylene-γ-butyrolactones[1]

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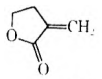
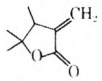
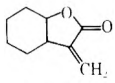
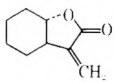
Recent reports in the literature have been concerned with the use of protecting groups which prevent Michael-type additions of nucleophilic reagents to the reactive sites of α-methylene lactones. These include dimethylamine,[3] thiols (1-propanethiol,[4] cysteine[5]), and phenylselenium anion.[6] We wish to report that sodium thiophenoxide can be employed in a high-yield reaction as a reagent for blocking α-methylene lactones. In addition, the removal of the β-phenylthio blocking group for regeneration of the α-methylene unit can be readily accomplished in high yield (see Table I) employing an alternate method from that previously utilized for β-thio adducts. Previously deblocking of a β-thio adduct required conversion to its corresponding

Table I

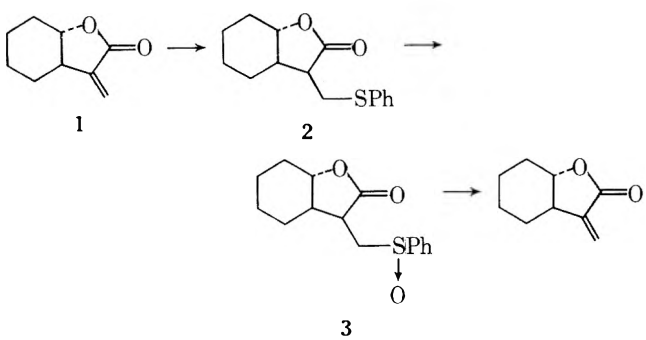
α-Methylene lactone	Registry no.	Yield[a] of β-thiophenyl adduct, %	Registry no.	Yield[a] of sulfoxide, %	Registry no.	Yield[a] of regenerated α-methylene lactone, %
	547-65-9	98	54353-61-6	95	54353-65-0	98
	49576-63-8	98.5	54353-62-7	99	54353-66-1	97
	16822-06-3	99	54353-63-8	99	54353-67-2	95
	3727-53-5	98	54353-64-9	97	54353-68-3	90

[a] Reported yields are based on isolated pure material.

sulfonium salt followed by β-elimination with aqueous sodium bicarbonate.[4]

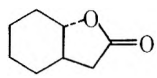
The blocking, deblocking sequence reported herein involves (a) addition of sodium thiophenoxide to the α-methylene lactone, (b) oxidation of the initially formed sulfide to its sulfoxide, and (c) thermal elimination of benzenesulfenic acid[7] (see Scheme I). Unlike our experience with

Scheme I



phenylselenium anion as a reagent for protecting the α-methylene function of lactones, the yields reported herein for the Michael addition are all nearly quantitative. Oxidation to the sulfoxide proceeds in greater than 95% yield with sodium metaperiodate at 0°. Heating the sulfoxide in toluene for 5 hr followed by evaporation of the solvent and distillation regenerates the α-methylene unit. Table I lists several other systems on which we have successfully carried out this sequence of reactions.

In principle, alkylation of a lactone enolate with iodomethyl phenyl sulfide should lead directly to a blocked α-methylene lactone. We have attempted to alkylate lactone **4** under conditions reported to give high yields of alkylated



products with alkyl iodides.[8] At best only a 20% yield of **2** could be realized employing **4** and iodomethyl phenyl sulfide. Attempts to improve this alkylation are in progress.

Experimental Section[9]

Addition of Sodium Thiophenoxide to α-Methylene Lactone 1. A solution of *trans*-butyrolactone **1** (106 mg, 0.7 mmol) in 2.0 ml of absolute ethanol was added at 0° to a solution of sodium thiophenoxide in absolute ethanol [prepared from sodium (25.8 mg, 1.12 mmol), ethanol (2.0 ml), and benzenethiol (308 mg, 2.8 mmol)]. The mixture was stirred at 0° for 1 hr. The reaction was quenched by the addition of acetic acid (4 drops) and water. Extraction with ether followed by washing of the combined ethereal extracts with water and brine afforded the crude β-thiophenyl adduct **2**. Purification by passage through a short column of silica gel resulted in 180 mg (98%) of pure material, mp 76.5–77°, which was homogeneous by TLC analysis (silica gel–methylene chloride). The NMR and ir spectra revealed lack of α-methylene protons [ir (CCl_4) 1775 and 1580 cm^{-1}].

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.69; H, 6.92. Found: C, 68.83; H, 6.80.

Oxidation of Sulfide 2. A solution of sulfide **2** (131 mg, 0.5 mmol) in 7.0 ml of methanol containing 0.5 ml of benzene was treated at 0° with sodium metaperiodate (139 mg, 0.65 mmol) in 3.0 ml of water. After stirring for ca. 50 hr, the product was extracted with methylene chloride several times. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo, affording 188 mg of crude sulfoxide. Chromatography on silica gel [elution with benzene–ethyl acetate (1:1)] gave 135 mg (97%) of the β-phenylsulfinyl compound **3** which was homogeneous by TLC analysis (silica gel–methylene chloride) [ir (CCl_4) 3050, 1775, 1580, 1045 cm^{-1}].

Regeneration of α-Methylene Lactone 1 via Thermolysis. A solution of the β-phenylsulfinyl lactone **3** (135 mg, 0.48 mmol) in 5.0 ml of toluene was heated at ca. 107° for 5 hr. Evaporation of the solvent under reduced pressure afforded a crude oil (135 mg) which after distillation [75° (bath temperature), 0.2 mmHg] resulted in 66 mg (90%) of pure α-methylene-γ-butyrolactone **1**. The NMR and ir spectra were identical with those previously recorded[10] [ir (CCl_4) 1767 and 1668 cm^{-1}; NMR (CCl_4) δ 5.91 (C=CH_2, doublet, J = 3 Hz, 1 H), 5.34 (C=CH_2, doublet, J = 3 Hz, 1 H), 3.9–3.4 (broad, CHO–)].

Acknowledgment. We thank the National Cancer Institute (Public Health Service Research Grant RO1 CA 13689-03) and Eli Lilly & Co. for generous support of our research. We thank Messrs. Steven Burke and Nebojsa Marinovic for preparing the starting α-methylene lactones.

Registry No.—Sodium thiophenoxide, 930-69-8.

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4-Oxahomoadamantane from Intramolecular, Nucleophilic Participation by Hydroxyl under Hofmann Elimination Conditions[1,2]

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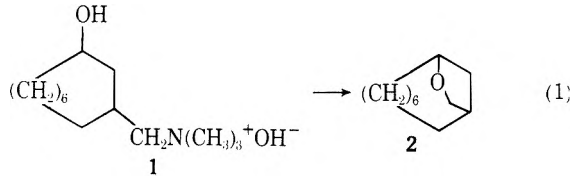
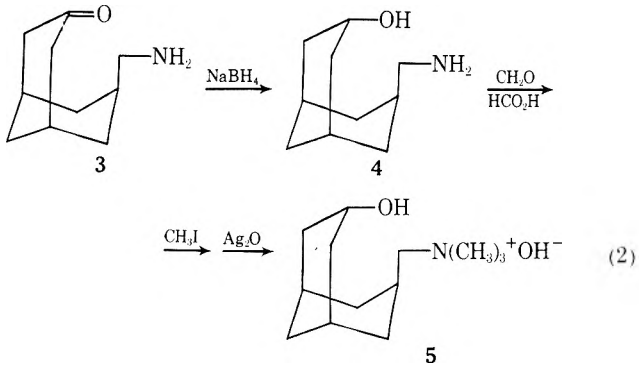
We are prompted by a recent report[3] to communicate our results on intramolecular, nucleophilic displacement under Hofmann elimination conditions. Hirsch and coworkers obtained[3] **2** (five-membered ring formation, 33% yield) by decomposition of the quaternary hydroxide **1** (eq 1) along with lesser quantities of other products.



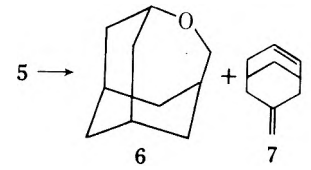
1 2 (1)

We investigated **5**, which was synthesized from *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (**3**)[4,5] according to eq 2. Thermolysis of crude **5** produced 4-oxahomoadamantane[6,7] (**6**, seven-membered ring formation, 19% overall yield from **3**) and minor amounts of 7-methylenebicyclo[3.3.1]non-2-ene[5] (**7**, 2% overall yield from **3**) (eq 3).



3 4 5 (2)

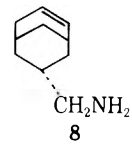
Since nucleophilic displacement of tertiary amines is known[8] to compete with straightforward elimination, this type of intramolecular alkylation process involving the alkoxide form of **5** appears reasonable.



6 7 (3)

A number of analogous examples are recorded in the prior literature.[8] The six-membered ether, thebenone, was generated from tetrahydrothebainonemethine by a similar process involving the phenolic hydroxyl. In addition, β-amino alcohol precursors gave rise to epoxides from participation by the neighboring hydroxyl group. Formation of *trans*-β-methylstyrene oxide from the quaternary hydroxide derived from ephedrine serves to illustrate. In the previous work,[3,8] cyclization involved formation of three-, five-, and six-membered rings.

Diolefin **7** most likely is formed by dehydration of **4** in the presence of formic acid, followed by exhaustive methylation and Hofmann elimination. Compound **4** is known to undergo partial dehydration to the corresponding amino alkene **8**[7] on exposure to 20% formic acid (1 day at reflux).[2,9]



8

Experimental Section

Compound **3** (9.3 g, 0.055 mol) was reduced in ethanol with sodium borohydride to the corresponding endo alcohol **4**.[10] After addition of water, the product was extracted with chloroform. Evaporation of the dried solution provided the desired material, which was subjected to the Hofmann elimination procedure.[5] The intermediates were not purified. A white, solid product, 4-oxahomoadamantane (**6**, 1.32 g, 17% overall yield from **3**) sublimed into the condenser during reaction. Identification was effected by comparison with spectral data for the authentic material.[6,11] The distillate from pyrolysis was extracted with ether. The organic layer was washed with dilute hydrochloric acid, then with water, dried, and freed of solvent. GLC analysis of the liquid product (0.3 g) revealed the presence of **6** (40%) and **7** (60%, 2% overall yield from **3**).

Acknowledgment. We thank Mr. T. A. Wnuk for helpful discussions.

Registry No.—**3**, 34650-78-7; **4**, 21933-00-6; **5**, 54517-88-3; **6**, 21898-86-2; **7**, 37439-70-6.

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Mechanism of the Lithium Aluminum Hydride Reduction of a Nonenolizable β Diketone[1]

Summary: The possible stereospecific lithium aluminum hydride ($LiAlH_4$) and lithium tri(*tert*-butoxy)aluminum hydride [$LiAl(O\text{-}t\text{-}Bu)_3H$] reductions of 2,2-dimethylindandione have been examined and the experimental conditions governing the range of the isomer distribution are described.

Sir: We have reinvestigated a previous report by Alder and Fremery[2] concerning the $LiAlH_4$ reduction of a nonenolizable β diketone, 2,2-dimethylindandione. The authors reported the product as a single compound; however, stereochemistry was not mentioned. Under Alder's reaction conditions of excess $LiAlH_4$ in refluxing diethyl ether, we obtained an approximately 1:1 mixture of *cis*- and *trans*-2,2-dimethylindandiol.

Akhtar and Marsh[3] have reported the $LiAlH_4$ (excess)/diethyl ether reduction of cholestan-5α-ol-3-one. To explain the preponderance of the cis product, cholestane-3α,5α-diol, the authors favored the formation of a complexed intermediate at the 5-hydroxyl position, thus forcing subsequent attack from the less hindered β side.

The minor product, cholestane-3β,5α-diol, may arise by at least two different pathways. One involves an intramolecular hydride transfer and another, an attack of a second $LiAlH_4$ molecule from the α side.

We attempted to determine if the second reduction step for such nonenolizable β diketones to the *trans*-diol is uniquely governed by steric approach control[4] or if an intramolecular hydride transfer occurs. Insights into the reaction mechanism were obtained by varying the equivalent ratio of the reactants and by using different reaction temperatures.

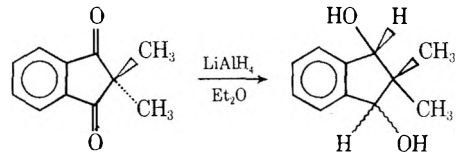
It became necessary to determine if kinetic control was operational under all the widely diverse conditions of reactant ratios and temperatures employed in this study. Each individual isomeric composition was determined at at least three different reaction times. They always agreed to within 2%. Therefore it is experimentally verified that no equilibration of products was taking place under any set of experimental conditions used.

The isomeric composition was determined by two procedures. Addition of the lanthanide shift reagent, $Eu(fod)_3$,[5] caused the methyl resonances of the two isomeric compounds to be sufficiently separated so that the an integration could be performed. The diols were also converted into their silyl ethers by treatment with a mixture of hexamethyldisilazane and trimethylchlorosilane.[6] The silylated ethers were separated by gas chromatography to evaluate the isomeric composition. Experimental agreement between the two methods was 3%.

By varying either the equivalent ratio of ketone to hydride or the temperature of the medium, the isomeric composition of the products was considerably altered. The results of these experimental variations are tabulated in Table I. The following trends are evident. As the equivalent amount of hydride is decreased, the relative amount of *trans*-diol increases. As the temperature of the reaction is decreased, the amount of *trans*-diol increases.

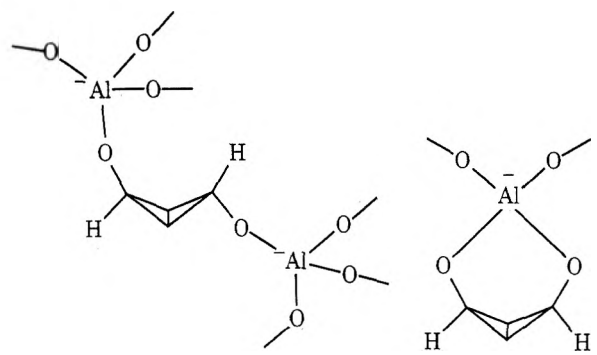
If the "Non-Crossing Rule"[7] were obeyed and if the product stabilities were known, then varying the temperature would lend insights into the relative importance of product development control vs. steric approach control. From the data it appears that no such insights may easily be gained because the relative amount of the isomers varied from one side of 50% to the other. It is reasonable to designate the *trans*-aluminate as the less stable product and to assign the *cis*-aluminate as the more stable product if their structures are as shown.

Table I



Ratio[a] of ketone:$LiAlH_4$	% relative isomers: At 34° Cis	At 34° Trans	At −78° Cis	At −78° Trans
0.5	53.6[b,c]	46.3	56.1[c,d]	43.7
1.0	35.5[b,e]	64.3	12.7[d,f]	87.1
2.0	28.8[b,g]	71.0	7.0[d,h]	92.8

[a] Equivalent reduction ratio (ERR). [b] Upon completion of hydride addition, immediate hydrolysis. [c] 100% conversion, based on NMR. [d] 3-hr reaction time, followed by hydrolysis. [e] 75% conversion, based on NMR. [f] 78% conversion, based on NMR. [g] 75% conversion, based on NMR. [h] 94% conversion, based on NMR.

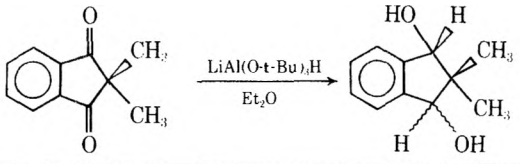


trans cis

If the above designations are valid, then the following conclusions may be drawn. As the amount of hydride, or the temperature is decreased, one finds a tendancy toward more of the trans product. Thus, excess $LiAlH_4$ favors product development control while minimal $LiAlH_4$ favors steric approach control. Likewise high temperature favors product development control while low temperature favors steric approach control.

In accounting for the trans product, the possibility of an intramolecular hydride reduction must be considered. Indeed, with less available hydride in solution, the tendency for intermolecular attack is lessened. If an intramolecular hydride transfer is operational, it should become more favored as the equivalent amount of $LiAlH_4$ is decreased, thus resulting in more trans product. This is the observed trend. However, it must be mentioned that it is currently accepted that, owing to a disproportionation mechanism,[8]

Table II



Ratio[a] of ketone:LiAl-(O-*t*-Bu)$_3$H	% relative isomers: At 34° Cis	At 34° Trans	At −78° Cis	At −78° Trans
0.03	98.2	1.7[b,c]		
0.5	62.3	37.5[b,c]		97[d,g]
1.0		97[b,e]		97[d,g]
2.0		97[b,f]		97[d,g]

[a] Equivalent reduction ratio (ERR). [b] 24-hr reaction time, followed by hydrolysis. [c] 95% conversion, based on NMR. [d] 6-hr reaction time, followed by hydrolysis. [e] 77% conversion, based on NMR. [f] 66% conversion, based on NMR. [g] 25% conversion based on NMR.

reductions with $LiAlH_4$ generally proceed uniquely from AlH_4^{-1} and not the mixed alkoxy hydrides, e.g., $AlH_2(OR)_2^{-1}$.

To exclude an intramolecular hydride transfer pathway, all but one of the hydrides on the reducing agent must be replaced. Reduction with LiAl(O-*t*-Bu)$_3$H fulfills this requirement. Examination of Table II reveals that as the equivalent amount of LiAl(O-*t*-Bu)$_3$H is decreased the *trans*-diol increases. Presumably the *trans*-diol results from the approach of a second LiAl(O-*t*-Bu)$_3$H from the same side as the bulky alkoxyaluminum function. Since the data from the $LiAlH_4$ reductions parallels that of the LiAl(O-*t*-Bu)$_3$H, we see no need, at least at present, to invoke an intramolecular hydride transfer to explain the *trans*-diol in the $LiAlH_4$ case.

In both the $LiAlH_4$ and LiAl(O-*t*-Br)$_3$H cases, it is possible that the carbonyl function first reduced may act as a neighboring group.[9] This group may then preferentially solvate the next reducing anion species, thus steering it in so that the trans product is formed. This explanation is consistent with the results obtained with minimal hydride and at low temperatures.

We are currently investigating 3-hydroxy-2,2-dimethylindanone under the same reaction conditions. Its aluminate is a possible intermediate in the reduction of 2,2-dimethylindandione. Experimental details and the completed work on this study will be reported at a later date.

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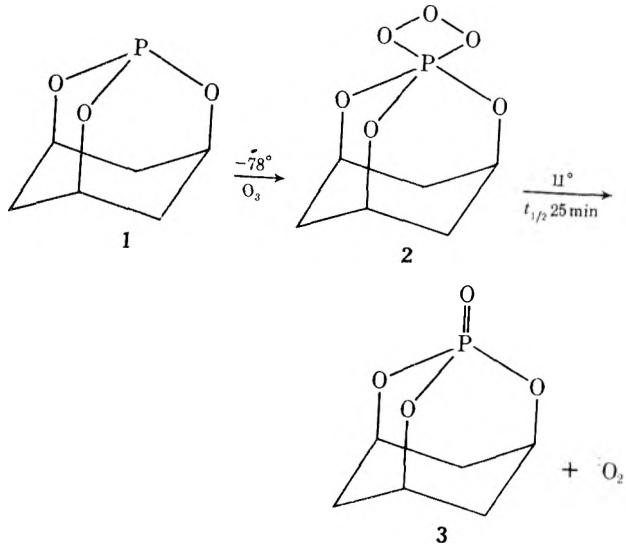
1-Phospha-2,8,9-trioxaadamantane Ozonide. A Convenient Source of Singlet Molecular Oxygen[1]

Summary: Thermal decomposition of 1-phospha-2,8,9-trioxaadamantane ozonide produces singlet molecular oxygen in quantitative yield (k_1 = 1.01 × 10^{-3} sec^{-1} at 18° in CH_2Cl_2).

Sir: The reactions of singlet molecular oxygen ($^1O_2$) with various organic substrates have been extensively investigated in recent years.[2] The possible role of $^1O_2$ in biological oxidation processes has also been of interest.[3] Singlet oxygen can be generated by photosensitization and by chemical methods such as the spontaneous decomposition of phosphite ozonides. Murray[4] and coworkers have shown that triphenyl phosphite ozonide decomposes at −30° to yield $^1O_2$ which may be trapped by an acceptor in solution. However, separation of the oxidation products from the triphenyl phosphate is often difficult. In addition, triphenyl phosphite ozonide is not sufficiently stable to permit storing this reagent conveniently.

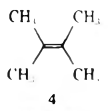
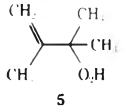
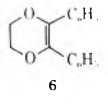
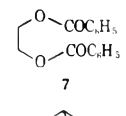
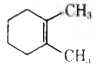
It has been suggested that polycyclic phosphite ozonides should exhibit unusual stability as a result of restricted pseudorotation.[5,6] We wish to report that the adduct **2** obtained from the addition of ozone to 1-phospha-2,8,9-trioxaadamantane (**1**)[7] is a relatively stable ozonide which decomposes quantitatively to $^1O_2$ and phosphate **3**.



Singlet oxygen exhibits three modes of reaction with alkenes: 1,4 cycloaddition with conjugated dienes to yield cyclic peroxides, the "ene" reaction to form allylic hydroperoxides, and 1,2 cycloaddition to give 1,2-dioxetanes which subsequently cleave to carbonyl-containing products. Examples of these reactions using the ozonide **2** as the source of $^1O_2$ are summarized in Table I. A trapping experiment using a 5:1 excess of acceptor **8** gave a 95% yield of the product **9** based on ozonide **2**. One criterion for the intermediacy of singlet oxygen in a reaction is the product distribution obtained from 1,2-dimethylcyclohexene (**10**).[8] Decomposition of **2** in the presence of **10** in CH_2Cl_2 yields a ratio of the two hydroperoxides **11** and **12** which is consistent with the formation of free $^1O_2$ in the reaction.

In a typical experiment, a 0.12 *M* solution of the ozonide **2** in CH_2Cl_2 was prepared by the slow addition of a solution of 0.24 g (1.5 mmol) of **1** in 3 ml of CH_2Cl_2 to 10 ml of CH_2Cl_2 at −78° continuously saturated with ozone. After the addition is complete, dry nitrogen is bubbled through the solution to remove the excess ozone. A solution of the singlet oxygen acceptor in 1 ml of CH_2Cl_2 is added to an al-

Table I
Oxidations with 1-Phospha-2,8,9-trioxaadamantane Ozonide (2)

Singlet oxygen acceptor	Products	Acceptor concn, M	Ozonide concn, M	% yield (isold) [a, b]
 4	 5	0.11	0.11	52
		0.11	0.22	77
 6	 7	0.11	0.22	82
 8	 9	0.11	0.11	56
		0.11	0.33	89
		0.55	0.11	95[c]
	 11[d]			95
 10	 12[d]	0.11	0.11	5

[a] Products were identified by comparison with authentic samples. [b] The isolated yields are based on starting alkene. [c] Yield based on ozonide 2. [d] Products from this reaction were analyzed by gas chromatography as the alcohols obtained by triphenylphosphine reduction of 11 and 12.

Table II
First-Order Rate Constants for the Decomposition of 2 in CH_2Cl_2

T, °C	k_1, sec^{-1}	$t_{1/2}$, min
18.2	1.07×10^{-3}	10.8
10.9	4.63×10^{-4}	24.9
3.3	2.55×10^{-4}	90.6
1.1	9.94×10^{-5}	116
−4.4	6.97×10^{-5}	166

Table III
Transition-State Parameters for Decomposition of 2 in CH_2Cl_2

E_a	19.1 ± 1.2 kcal mol^{-1}
Log A	11.45
$\Delta G^{\ddagger}(9°)$	20.3 kcal mol^{-1}
$\Delta H^{\ddagger}(9°)$	18.6 kcal mol^{-1}
$\Delta S^{\ddagger}(9°)$	−6.3 eu

iquot of the ozonide solution at −78°. The resultant solution is then allowed to warm to ambient temperature over a period of 30 min. The CH_2Cl_2 is removed under vacuum and the residue treated with CCl_4 to give a CCl_4 solution of the product. The phosphate 3 is almost totally insoluble in CCl_4.

The rate of decomposition of 2 in CH_2Cl_2 has been measured at a series of temperatures by following the oxygen evolution.[9] The first-order rate constants are given in Table II. These data were used to calculate the activation energy and the transition-state parameters for decomposition (Table III). We, therefore, find that 1-phospha-2,8,9-trioxaadamantane ozonide (2) is 106 times more stable at −5° than triphenyl phosphite ozonide and 1.4 times more stable than the ozonide from the bicyclic phosphite, 1-ethyl-4-phospha-3,5,8-trioxabicyclo[2.2.2]octane.[5,6,10]

Of further interest is the fact that 2 is soluble in water and can be used as a source of singlet oxygen in H_2O. These experiments will be described shortly.

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An Asymmetric Synthesis of 2-Substituted γ-Butyrolactones and 2-Substituted 1,4-Butanediols

Summary: The preparation of the titled compounds has been accomplished in 64–73% optical purity using low temperature alkylation of chiral oxazolines.

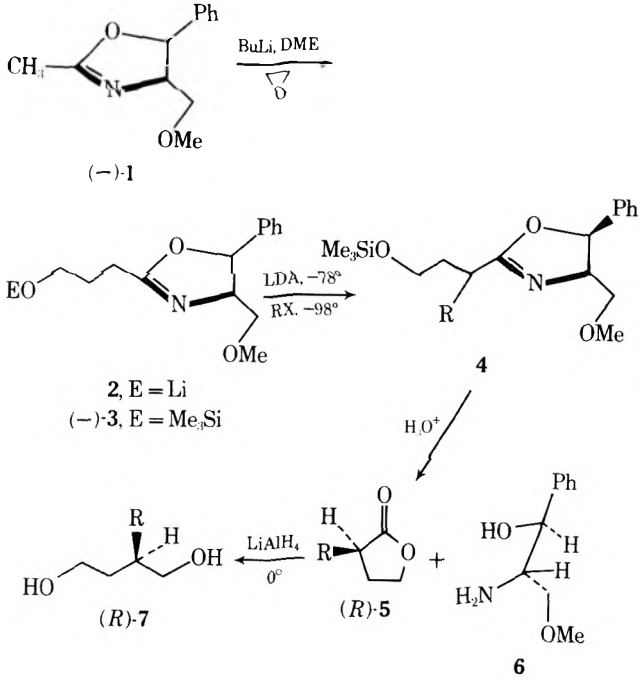
Sir: The recently demonstrated utility of (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline (1) as a precursor to (*R*)- and (*S*)-dialkylacetic acids in 60–80% enantiomeric purity[1] has the potential to reach a variety of chiral molecules. We wish to further demonstrate that efficient avenues to lactones and 1,4-diols of high optical purity are also possible via this technique. As in previous examples,[2] the chiral amino alcohol **6** is recovered without loss of optical purity and may be recycled to oxazoline **1**.

Treatment of **1** with *n*-butyllithium (−78°) in dimethoxyethane (DME) followed by addition of ethylene oxide (5 equiv, −78°, then 18 hr at 0°) produced the lithio salt **2** which was directly treated with chlorotrimethylsilane furnishing the oxazoline trimethyl silyl ether **3** [80%; 150° (0.01 Torr); ir (film) 1670 cm^{-1}; NMR (CCl_4) δ 7.27 (s, 5), 5.2 (d, 1), 4.0 (m, 1), 3.8–3.2 (m, 4), 3.38 (s, 3), 2.4 (br t, 2), 1.85 (m, 2), 0.09 (s, 9); $[\alpha]^{23}_{589}$ −41.6° (*c* 9.8, $CHCl_3$)]. The latter now represents the starting material for all of the chiral substituted lactones and butanediols (vide infra). Addition of 1.05 equiv of lithium diisopropylamide (LDA) to **3** (−78°, THF, 30 min) formed the deep yellow anion whose solution was cooled to −98° (liquid N_2–MeOH) and treated with 1.05 equiv of the alkyl halide;[3] the temperature was maintained for 1–2 hr and then allowed to warm slowly to ambient. After quenching (saturated NH_4Cl) and ethereal extraction, the crude alkylated oxazolines **4** (~100%) were hydrolyzed without further purification (4.5 *N* HCl, 15 min, reflux) to the 2-substituted

Table I
Asymmetric Synthesis of (*R*)-γ-Butyrolactones 5 and (*R*)-1,4-Butanediols 7

Compd	R	Yield, %[a]	$[\alpha]^{23}_{589}$ (*c* EtOH)	Optical purity, %	CD, $[\theta]_{218\ nm}$ (CH_3CN)
(*R*)-5	Me	58	+13.80 (10.0)	64.2[b]	−1430[g]
(*R*)-5	Et	68	−7.65 (9.8)		−1750
(*R*)-5	*n*-Pr	75	−8.05 (5.7)	73.3[c]	−1870
(*R*)-5	Allyl	60	−16.50 (4.8)	72.0[c]	−1730
(*R*)-5	*n*-Bu	71	−7.30 (9.7)		−1600
(*R*)-7	*n*-Pr	90[d]	+3.47 (neat)	73.3[e]	
(*R*)-7	Allyl	92[d]	+3.60 (neat)	72.0[f]	

[a] Yields of 5 based upon 3 unless otherwise noted. [b] T. Kaneko, K. Wakabayashi, and H. Katsura [*Bull. Chem. Soc. Jpn.*, 35, 1149 (1932)] report $[\alpha]^{15}D$ −21.5 (c 5.5, EtOH). [c] Based upon the optical purity of the corresponding 1,4-butanediols 7 which must be a minimum value since some racemization of 5 during the reduction is possible. [d] Based upon 5. [e] Literature value[5] +4.73° (neat). [f] Literature value[5] +5.0° (neat) [g] Molecular ellipticities were determined on a Varian-Cary Model 61 CD instrument. Units are degrees centimeter squared/decimole.



γ-butyrolactones 5, all of which possessed the *R* configuration (Table I).[4] Since the absolute configuration and maximum rotation was known only for 2-methyl-γ-butyrolactone (5, R = Me), and a variety of chiral shift reagents failed to provide enantiomeric compositions for the lactones, it was necessary to correlate 5 by other methods. This was readily done by reducing ($LiAlH_4$, 0°, Et_2O) the 2-(*n*-propyl)- and 2-allylbutyrolactones to their corresponding 1,4-butanediols 7 which had been previously described by Freudenberg and Lwowski.[5] The facile conversion of 5 to 7 now makes chiral 1,4-butanediols readily accessible in optical purity comparable to those of the lactones. Furthermore, since the lactones 5 were all of the *R* configuration, as indicated by their comparable CD characteristics, the diols (+)-7 can now be assigned the *R* configuration.[6]

The production of *R* lactones via this method is consistent with the mechanism proposed in our earlier report.[1] Reversal of the order of introduction of substituents on (−)-1 would presumably lead to the *S* lactones. Work is continuing toward further utility of this asymmetric synthesis and the potential incorporation of chiral 1,4-butanediols as precursors to chiral polyethers and polyesters.

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

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A Rapid Procedure for the Hydrolysis of Amides to Acids

Summary: The hydrolysis of amides to acids by aqueous sodium peroxide (in less than 2 hr at 50–80°) in high yield and with little decarboxylation of the acid is reported.

Sir: The conversion of amides to carboxylic acids is considered a routine procedure but in practice it is not always straightforward.[1] Often vigorous conditions[2] and strong catalysts such as concentrated sulfuric or phosphoric acid[3] and strong alkali hydroxides are needed to effect the hydrolysis. In general, the yields of these reactions are fair to good but occasionally the severe reaction conditions cause decomposition of the desired acid. For example, we have found that the usual hydrolytic conversions of heterocyclic carboxamides to the corresponding acids are particularly difficult because the acids are prone to decarboxylation. To circumvent this problem a new method was developed. Specifically, we have found sodium peroxide (caution—see final paragraph for warning for using peroxides) to be a superior reagent for the mild hydrolysis of heterocyclic amides and other amides in general. The reaction is rapid and can be carried out at relatively low temperatures. We would like to recommend it as a simple, nonstringent general procedure.

Table I
Yields of Acid from the Hydrolysis of Amides with Sodium Peroxide

Amide	Acid isolated	Amine isolated	Absolute yield, %
$C_6H_5CONH_2$	$C_6H_5CO_2H$		85
$3\text{-}CH_3OC_6H_4CONH_2$	$3\text{-}CH_3OC_6H_4CO_2H$		81
$4\text{-}CH_3OC_6H_4CONH_2$	$4\text{-}CH_3OC_6H_4CO_2H$		88
$2,6\text{-}(CH_3)_2C_6H_3CONH_2$	$2,6\text{-}(CH_3)_2C_6H_3CO_2H$		88
$C_6H_4\text{-}1,3\text{-}(CONH_2)_2$	$C_6H_4\text{-}1,3\text{-}(CO_2H)_2$	NH_3	95
$C_6H_5CH_2CONH_2$	$C_6H_5CH_2CO_2H$		94
2-Pyrazinamide	2-Pyrazinoic acid		81
3-Hydroxy-2-pyrazinamide	3-Hydroxy-2-pyrazinoic acid		73
2-Picolinamide	2-Picolinic acid		89
$C_{11}H_{23}CONH_2$	$C_{11}H_{23}CO_2H$		83
$(CH_3)_2CHCONH_2$	$(CH_3)_2CHCO_2H$		78
$CH_3CONHC_6H_5$		$C_6H_5NH_2$	89
$C_6H_5CONHCH_3$	$C_6H_5CO_2H$		83
$C_{11}H_{23}CONH\text{-}n\text{-}C_4H_9$	$C_{11}H_{23}CO_2H$		87
$CH_3CON(CH_3)C_6H_5$		$C_6H_5NH(CH_3)$	89
$C_6H_5CONHC_6H_5$			No reaction
$C_6H_5CON(CH_2CH_3)_2$			No reaction

$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}NHR' + Na_2O_2 \xrightarrow{H_2O} \xrightarrow{HCl} RCO_2H + R'NH_2$$

An aqueous suspension of the amide is treated with 1 equiv of sodium peroxide at 50° (or more conveniently on a steam bath). The amide rapidly dissolves and ammonia (for primary amides) is evolved. After 60 min, the reaction is essentially complete and only marginal yield increases are observed if heating is continued for another hour. Isolation of the acid is accomplished by careful neutralization of the reaction mixture and yields are usually greater than 85% (Table I). Primary, secondary, and tertiary amides are all hydrolyzed and either the acid or the amine can be recovered. Only extremely water-insoluble amides failed to react and, although ethanol can be substituted as solvent for some of the reactions, it was of no value in these cases. This appears to be the only restriction on the generality of the reaction. Very little decomposition of any of the acids was observed. The high yields for 2-pyrazinoic acid, 3-hydroxy-2-pyrazinoic acid, 2-picolinic acid, and 2,6-dimethylbenzoic acid should be especially noted since these acids are difficult to obtain in good yields from their amides by conventional hydrolysis methods.

The mechanism of the reaction has not been elucidated but the consumption of peroxide corresponds to the yield of acid (see Table II). One equivalent of peroxide is necessary to give complete hydrolysis and decreasing peroxide gives a proportionate decrease in yield. Peroxides have not been used to hydrolyze amides previously although hydrogen peroxide was suggested as a method to digest proteins.[4] A mechanism was not discussed but it may be that the α effect[5] makes the peroxide ion extremely nucleophilic, increasing the rate of reaction with the poorly electrophilic amide carbonyl groups. We have prepared the corresponding peroxycarboxylates and found them to decompose cleanly to the acid at the temperatures involved. Because of the known oxidizing power of peroxides, it might alternately be suggested that an oxidative hydrolysis is involved. Nitriles can be hydrolyzed to hydroxamic acids and thence to carboxylic acids with hydrogen peroxide.[6] A similar process could be occurring with sodium peroxide. However, nitrobenzene is derived from the amine portion of *N*-phenylamides when treated with hydrogen peroxide[7] and other amides show extensive degradation of the amine.[8] In all of our examples either ammonia (as opposed to hydroxylamine) or the amine from secondary or tertiary amides was isolated. Other oxidative mechanisms may be occurring but without further data we favor accelerated hydrolysis as the most plausible explanation at this time.

$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}NH_2 + HO_2^- \longrightarrow R\text{—}\overset{\overset{O^-}{|}}{\underset{\underset{O\text{—}OH}{|}}{C}}\text{—}NH_2 \longrightarrow R\text{—}\overset{\overset{O}{\|}}{C}\text{—}O_2^- + NH_3$$

Table II
Comparison of Reaction Time, Yield, and Loss of Peroxide for Benzamide and Sodium Peroxide

Time, min	Acid yield, %[a]	Peroxide remaining, %
15	32	43
30	52	11
45	70	1
60	87	0
120	94	0

[a] Acid yield is amount isolated which could lag behind conversion as indicated by loss of peroxide.

The following example for pyrazinamide will illustrate the general procedure. Pyrazinamide (2.0 g, 0.0165 mol) is suspended in 50 ml of water and the mixture placed on the steam bath. Sodium peroxide (1.29 g, 0.0165 mol) is then added portionwise with care [the reaction of sodium peroxide with water can be exothermic and reactions reminiscent of metals in water have been observed with large-scale mixtures (>1 mol) of amides and sodium peroxide]. Ammonia can be detected being evolved with a piece of moist pH paper. After heating for 2 hr, the resulting solution is cooled to 0° and carefully acidified dropwise with concentrated hydrochloric acid. The crystals are separated by filtration to yield 1.9 g (94.2%) of pyrazinoic acid, mp 222–225° (lit.[9] mp 225°).

As in all reactions involving peroxides and organic compounds, caution should be exercised and all new reactions performed first on a small scale. No serious incidents occurred in any of the reactions that we have run but the observation of a transitory metalloid-type intermediate dictates that utmost safety precautions be followed.

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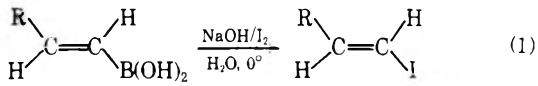
Reaction of Alkenylboronic Acids with Bromine in the Presence of Sodium Methoxide and Methanol. A Simple One-Stage Synthesis of α-Bromo Acetals

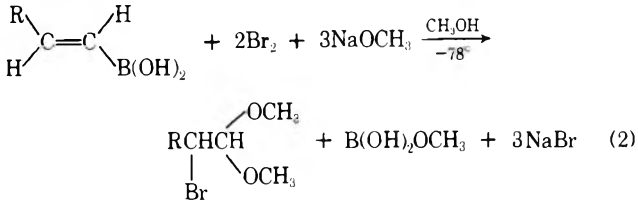
Summary: Alkenylboronic acids add bromine rapidly at −78° in the presence of sodium methoxide in methanol to give the corresponding α-bromo dimethyl acetals in good yield.

Sir: Alkenylboronic acids are readily available via the hydrolysis of the catechol esters produced by the hydroboration of alkynes with catecholborane.[1] We recently reported that such *trans*-1-alkenylboronic acids are converted by iodine under the influence of base into the corresponding *trans*-1-alkenyl iodides of >99% stereochemical purity in almost quantitative yield[2] (eq 1).



(1)

We undertook to prepare the corresponding bromides by an analogous procedure using bromine. However, the results proved unsatisfactory. For example, the addition of bromine to a solution of *trans*-1-octenylboronic acid in aqueous sodium hydroxide at 0° gave a 65:35 mixture of *cis*- and *trans*-1-octenyl bromide in a yield of ~50%, along with 25% *n*-octylaldehyde. A possible route to the aldehyde is oxidation of the vinylboronic acid by sodium hypobromite.[3] Consequently, we examined the use of sodium methoxide in methanol at −78° as a means of avoiding this side reaction.[2] Unexpectedly, the reaction produced 38% new product, the α-bromo dimethyl acetal, together with 8% *cis*-1-octenyl bromide and 10% *trans*-1-octenyl bromide. It seems clear that the formation of the α-bromo dimethyl acetal will require at least 3 equiv of sodium methoxide and 2 equiv of bromine (eq 2).



(2)

In exploring this new reaction, three different procedures were examined. Procedure A involves the addition of two equivalents of bromine in dichloromethane to a solution of *trans*-1-octenylboronic acid and 3 equiv of sodium methoxide in methanol at −78°. Procedure B involves the addition of *trans*-1-octenylboronic acid to a solution of 2 equiv of bromine and 3 equiv of sodium methoxide in methanol at −78°. Procedure C involves the addition of a cold solution of *trans*-1-octenylboronic acid and a 1 *M* equiv of sodium methoxide in methanol to a solution of 2 equiv of bromine and 2 equiv of sodium methoxide in methanol at −78°. The results are summarized in Table I.

Table I
Reaction of *trans*-1-Octenylboronic Acid with Bromine in the Presence of Sodium Methoxide at −78°

Procedure	α-Bromo acetal, %	*cis*-1-Octenyl bromide, %	*trans*-1-Octenyl bromide, %
A	80	2	16
B	63	19	16
C	92	0	4

Bromination of a series of *trans*-1-alkenylboronic acids was carried out by procedure C to produce the corresponding α-bromo dimethyl acetals. The results are summarized in Table II.

Table II
Preparation of α-Bromo Acetals by the Bromination of *trans*-1-Alkenylboronic Acids in the Presence of Sodium Methoxide at −78°

Alkyne	Alkenylboronic acid, %[a]	α-Bromo dimethyl acetal, %[b]
1-Hexyne	90	92,[c] 82[d]
1-Octyne	90	92,[c] 82[d] (72,[c] 55[d])
3-Chloro-1-pentyne	92	90,[c] 82[d]
Cyclohexylethyne	93	88,[c] 81[d]
3,3-Dimethylbutyne	94	52,[c] 49[d]

[a] See ref 1. Isolated yields. [b] The yields are by GLPC analysis. The values in parenthesis are isolated yields. [c] Based on alkenylboronic acid. [d] Based on alkyne.

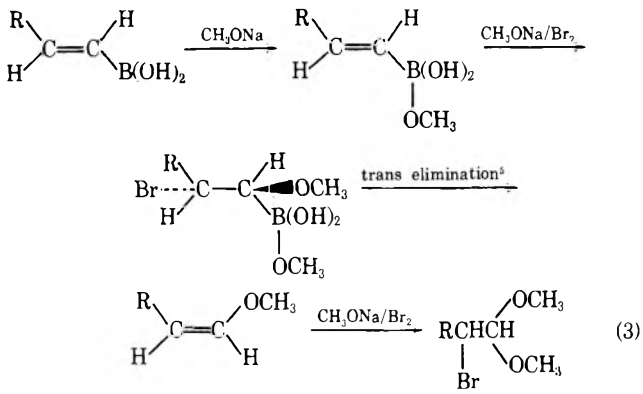
One exception to the generality of this procedure was observed. *trans*-2-Phenyl-1-ethyleneboronic acid was converted by procedure C to give a product which was not the 2-bromo acetal. This product is under investigation.

The following experimental procedure (procedure C) was used. In a 250-ml flask were placed 100 mmol of *trans*-1-octenylboronic acid[1] and 100 ml of absolute methanol; 100 mmol of a solution of sodium methoxide in methanol (33.4 ml of 3.0 *M*) was added at 0°. The solution was maintained at 0°. In another 500-ml flask were placed 200 ml of absolute methanol and 200 mmol of sodium methoxide solution in methanol (66.8 ml, 3.0 *M*). The mixture was cooled to −78°, 200 mmol of bromine (10.4 ml) was added over 30 min, and the pale yellow colored solution was stirred for 15 min. To this solution was added through a double-ended needle under nitrogen pressure over 30 min the solution of *trans*-1-octenylboronic acid and sodium methoxide in methanol previously prepared. The reaction mixture was stirred for 30 min at −78° and then brought to room temperature. The product was extracted with 400 ml of *n*-pentane and 200 ml of water saturated with sodium chloride. The water layer was further extracted with *n*-pentane (200 ml × 2). The combined pentane extract was washed with 100 ml of water and dried over anhydrous magnesium sulfate. Following removal of the solvent, pure α-bromooctylaldehyde dimethyl acetal, bp 68° (0.15 mm), was obtained in 72% yield. The identification of the compound was carried out by a comparison of its ir, ^{1}H NMR, and mass spectra with those of an authentic sample.[4]

An attempt to use the catechol ester directly resulted in a very poor yield of the product (16%).

Although we have not yet attempted to make a specific study of the mechanism of this synthesis of α-bromo acetals, it is evident that the reaction possesses highly interesting characteristics. For example, if the sodium methoxide is omitted, only traces of the α-bromo dimethyl acetal are produced.

It seems probable that the reaction proceeds via (a) the trans addition of the elements of methyl hypobromite, (b) the formation of the alkenyl methyl ether by trans elimination of boron and bromine, and (c) addition of the elements of methyl hypobromite to the methyl ether (eq 3).



(3)

The synthesis of α-bromo acetals has been achieved by a variety of procedures. These may be summarized briefly as follows: (a) direct bromination of the aldehyde, followed by the treatment with alcohol;[6] (b) addition of bromine to the enol acetate in alcohol;[7] (c) 1,4 addition of organoboranes to 2-bromoacrolein, followed by conversion of the product to the acetal;[8] (d) halogenation of the aldehyde with cupric halides in alcohol.[4,9]

The reaction of terminal alkenylboronic acids with bromine in the presence of sodium methoxide in methanol provides a new simple route to the α-bromo dimethyl acetals from the corresponding acetylenes.

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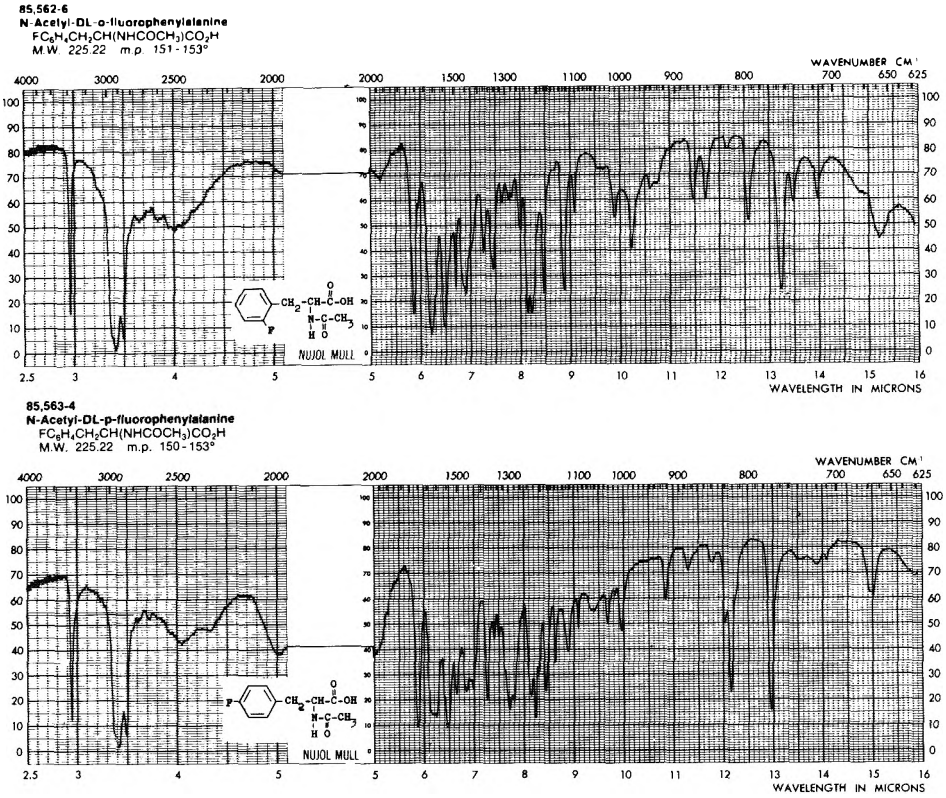

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