

Transformations of Sesqui- and Diterpenes

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The acid-catalyzed rearrangements of the sesquiterpenes thujopsene and humulene were studied, in detail, and the mechanism of the stepwise rearrangements established. The acid-catalyzed

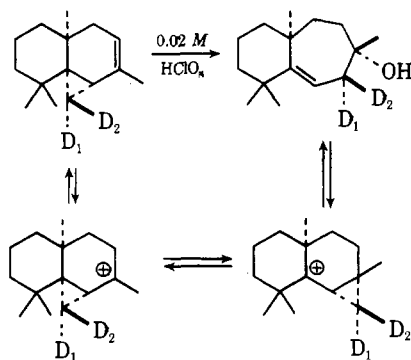
and photochemically induced rearrangements of the monocyclic diterpene cembrene were investigated and the structures of the cyclized products established.

In accepting the Ernest Guenther Award I should like to express my appreciation to Fritzsche, Dodge, & Olcott who sponsor this award directed toward the chemistry of essential oils and related natural products. I should also like to express my appreciation to my coworkers who have pursued the projects I shall discuss today. As you shall see, these associates have applied all the modern tools and thoughts to their projects, showing that to obtain the maximum reward from a research study a wide range of knowledge is essential. I should also like to thank the National Science Foundation, the Hoffmann-La Roche Foundation, and the Givaudan Corporation for their support.

This award was first given in 1948 to John L. Simonsen and, in his presentation award talk, details of the distribution of various terpenoid substances in essential oils were discussed. Through the past 25 years, a variety of subjects has been discussed in the award addresses. Today I should like to return again to the chemistry of components of essential oils.

A close relationship exists between natural products and mechanistic organic chemistry since the wide variety of structural changes such compounds undergo either first call attention to a new type of rearrangement process or else offer a system of known stereochemistry which can serve as the best model for mechanistic studies of various organic reactions. Let us first consider the chemistry of the cyclopropylcarbinyl system.

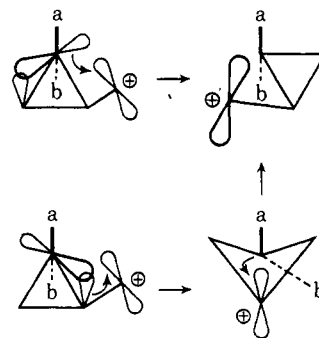
Thujopsene, a tricyclic sesquiterpene which is a constituent of the wood oils and of the heartwood of many genera belonging to the natural order Cupressales, possesses a cyclopropylcarbinyl system. It was first shown by Nagahama



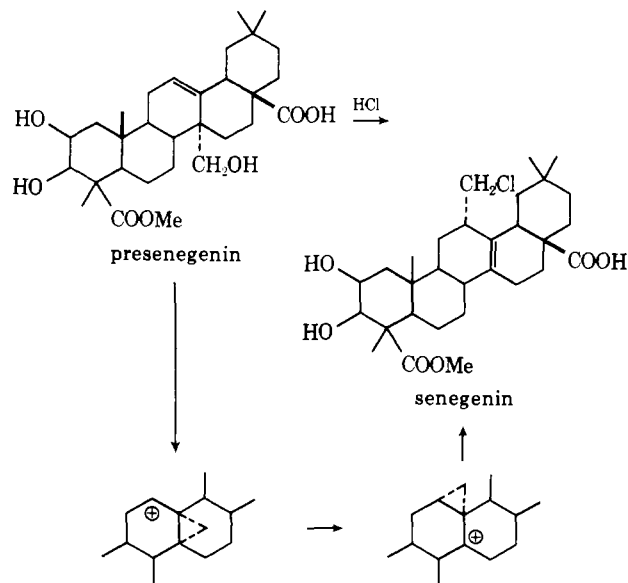
(1960)¹ that this hydrocarbon, upon treatment with mild acid, gave the rearranged (and also naturally occurring) alcohol widdrol in modest yield (25%). The usual mechanistic pathways were suggested for this familiar cyclopropyl-homoallylic rearrangement but when such suggestions were considered in detail, clearly the process was more complex. Since we had previously achieved a simple stereospecific synthesis of thujopsene,² the dideutero materi-

al was prepared.³ The results obtained from the rearrangement clearly established that the overall arrangement process proceeded *via* a cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement.³ This was the first established example of such a process in a complex natural product. The stereochemical details of the rearrangement processes were next established and it was found, using stereospecifically deuterium-labeled material, that the rearrangement was completely stereospecific, *i.e.*, when you follow the fate of d_2 through the processes its stereochemical identity is retained.⁴

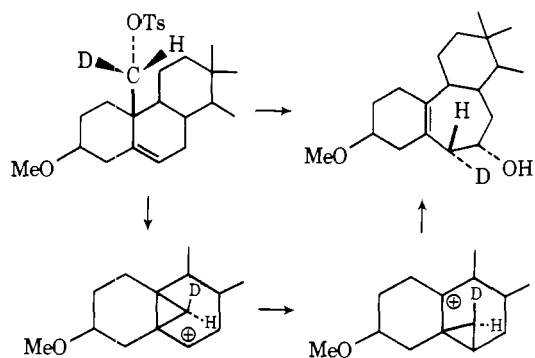
Such a result is in agreement with recent studies by various investigators who have shown that the overall cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement must occur by a direct conversion involving the small back lobe of the back bond or by a series of 1,2 shifts of the cyclopropane bonds *via* a "puckered" cyclobutonium ion.⁵



Subsequent to these studies, other workers have found this stereospecific rearrangement to occur in other natural products. de Mayo⁶ and Pelletier⁷ have reported that

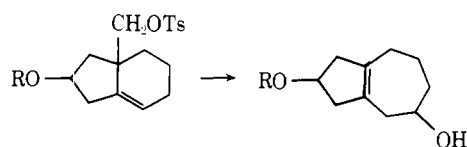


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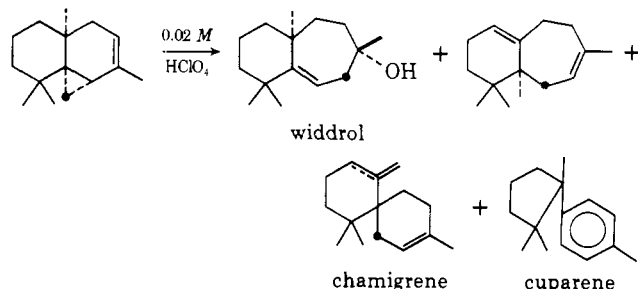
under the usual acidic isolation conditions the triterpene presenegenin rearranges *via* a series of cyclopropylcarbinyll rearrangements to senegenin. Tadanier⁸ and Arigoni⁹ in their studies of 19-hydroxy steroids also have shown that the rearrangement is stereospecific *via* two isolatable cyclopropylcarbinyll intermediates.

Most recently, this rearrangement process has been ap-



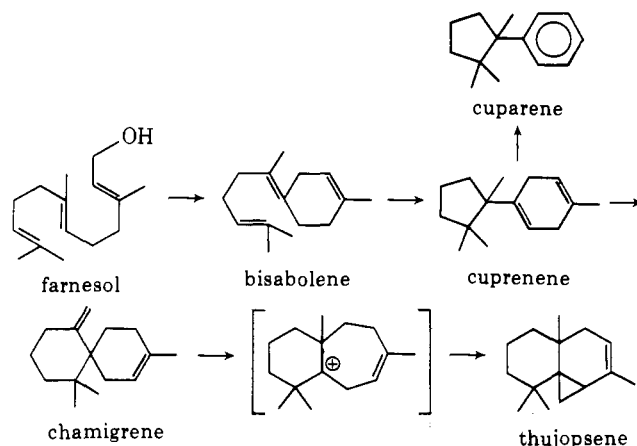
plied to the synthesis of hydroazulenic sesquiterpenes.¹⁰ Thus, the stereospecificity of the rearrangement process shown in thujopsene studies has now been shown to be of widespread generality.

Let us now turn our attention to some competing rearrangement reactions which have recently been shown to be of great interest. When this same perchloric acid-catalyzed reaction is followed in more detail, it is found that two hydrocarbons build up. One is a ring-expanded diene with a methyl group rearrangement.¹¹ It is of interest to note that using deuterium-labeled thujopsene it was shown that this product is directly formed from the initial cyclopropylcarbinyll carbonium ion since the deuterium label stays intact. The second product is a mixture of α - and β -chamigrenes, naturally occurring sesquiterpenes found to occur along with thujopsene in the leaf oil of *Chamaecyparis taiwanensis*.¹² A minor amount of a third hydrocarbon is formed, this material being cuparene, a sesquiterpene occurring along with thujopsene in Hiba wood oil. These results are of interest since by this acid-

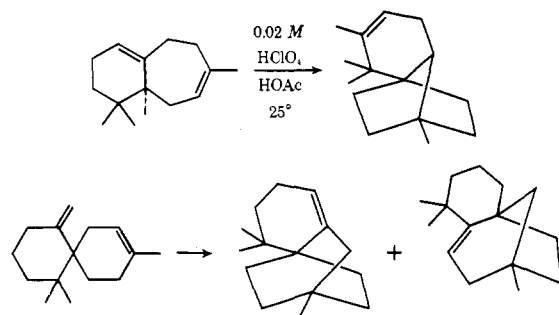


catalyzed process we have been able to achieve the postulated biogenetic sequence by which these materials are formed in nature. Thus, farnesol is postulated to be ring closed first to bisabolene which then closes to cuprenenes. These materials then, by dehydrogenation, give rise to cuparene or, by rearrangement, to chamigrene. This later material is postulated to be the precursor of the thujopsene.

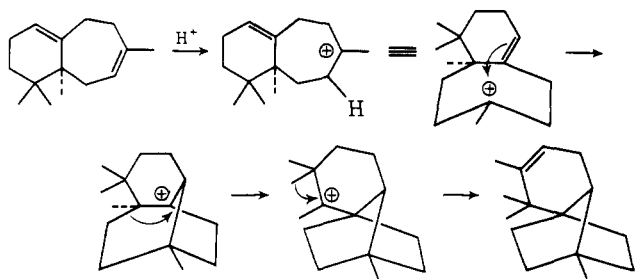
With these findings it was of interest to see what further cyclized products could be formed from these two new materials. It was found that by using 0.02 M HClO_4 in acetic acid at 25°, the methyl-rearranged diene went to a new tricyclic hydrocarbon.¹³ Under the same conditions



the chamigrenes went to a mixture of two other tricyclic hydrocarbons.¹² The structure of the product from methyl-rearranged diene was proved by degradation and by partial synthesis in my laboratories and the structures of the two materials from the chamigrenes were established by Daeniker, Hochstetler, Kaiser, Kitchens, and Blount at the Givaudan and Hoffmann-La Roche laboratories.¹⁴



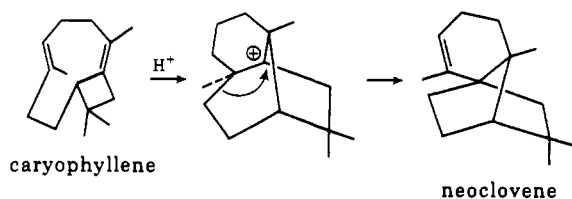
The mechanism of the formation of these materials is interesting. The transformation of the rearranged diene



proceeds *via* protonation of the lesser hindered double bond in the seven-membered ring to generate the tertiary cation, which cyclizes to yield the bridgehead cation. This strained cation then can undergo a Wagner-Meerwein rearrangement to the less strained tertiary carbonium ion which now is not part of the bicyclo[2.2.1]heptane ring system. A subsequent methyl migration then yields another tertiary cation which, upon loss of a proton, can give rise to the final product. This suggested mechanism employing this series of intermediates does not necessarily provide, step by step, the driving force for the overall rearrangement; the intermediate's only function is to provide a route to the final product whose low free energy content provides the driving force for the overall reaction. Undoubtedly, the major feature of this transformation which accounts for the low free energy content of the tricyclic olefin relative to the starting diene is the net transformation of one carbon-carbon double bond into two carbon-carbon single bonds. Such a conversion is estimated to be exothermic by 18–20 kcal/mol. This decrease in thermochemical energy compensates for the increased

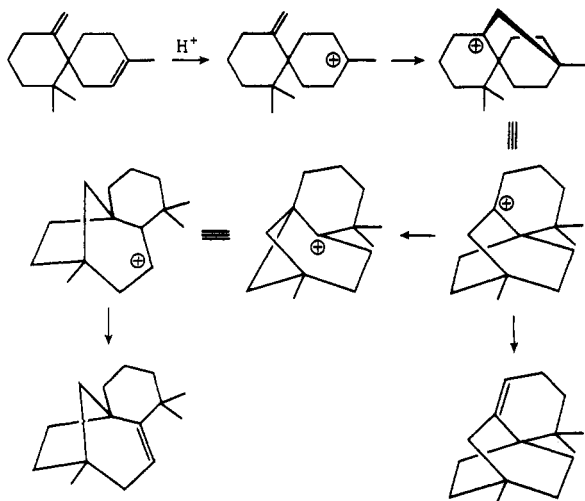
strain of the bicyclo[2.2.1]heptane nucleus, i.e., 14–18 kcal/mol.

It is of interest to note that the reaction pathway by which caryophyllene is thought to be converted under aci-



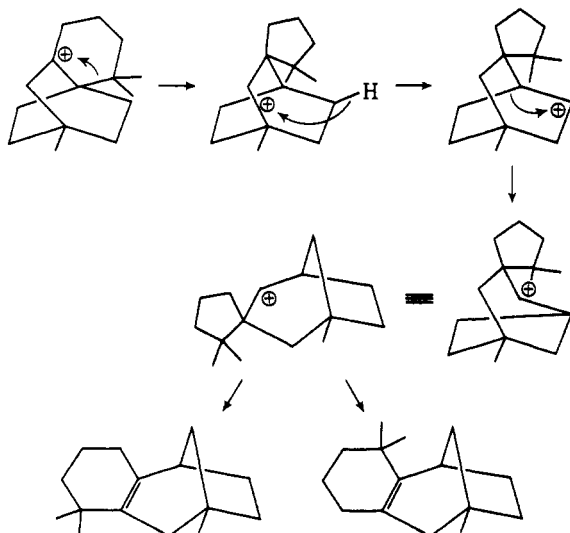
dic conditions into neoclovene is similar to the above route postulated for the thujopsene rearrangement. These two examples clearly illustrate the importance of considering the balance of energies in different species and calls attention to the utility of considering a strained intermediate like a bridgehead carbonium ion in conjunction with the overall energy balance of the molecule.

The reaction of β -chamigrene is less complicated. The



initial protonation at the endocyclic double bond is expected since it is known from the chemistry of this hydrocarbon that it is the lesser hindered double bond. Ring closure now forms a bicyclo[2.2.2]octyl cation which, by loss of a proton, gives one hydrocarbon and by a Wagner-Meerwein 1,2 shift leads to the other hydrocarbon.

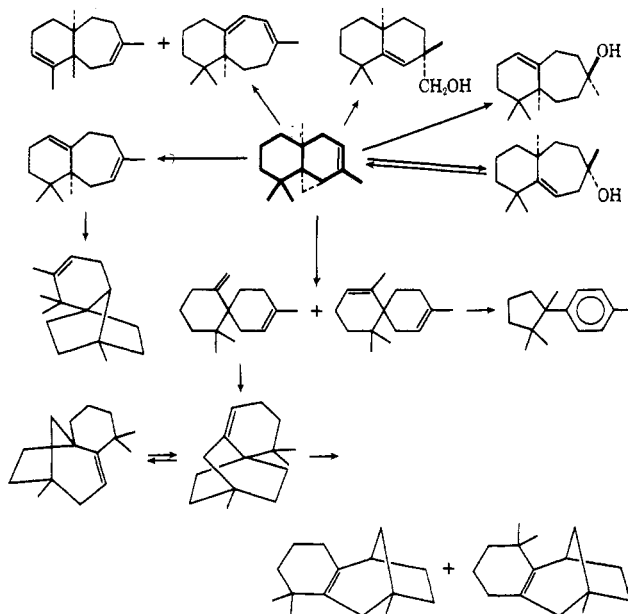
These latter two hydrocarbons are strained and, when



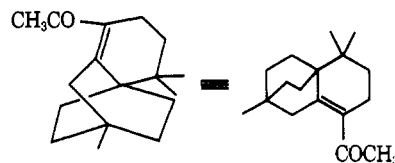
allowed to react with 0.02 M HClO_4 in refluxing acetic acid, underwent further rearrangement. The rearrangements proceed by a series of 1,2 migrations and again we see that the rearrangement process proceeds *via* a bridgehead carbonium ion. In this case the bicyclo[2.2.2]octyl

cation has a strain energy of only 17.3 kcal/mol as compared to 31.7 kcal/mol for the bicyclo[2.2.1]heptane ion. The bicyclo[3.2.1]octyl cation has a strain energy of 18.7 kcal/mol and so, in this latter series of rearrangements, the intermediates (or activated complexes) are of an energy such that it is reasonable for a rearrangement to proceed through them.

To place all of these results in the proper context, let us see a summary of the rearrangements which start from *cis*-thujopsene. It is seen that this series of rearrangements is probably the most extensive of any known sesquiterpene.

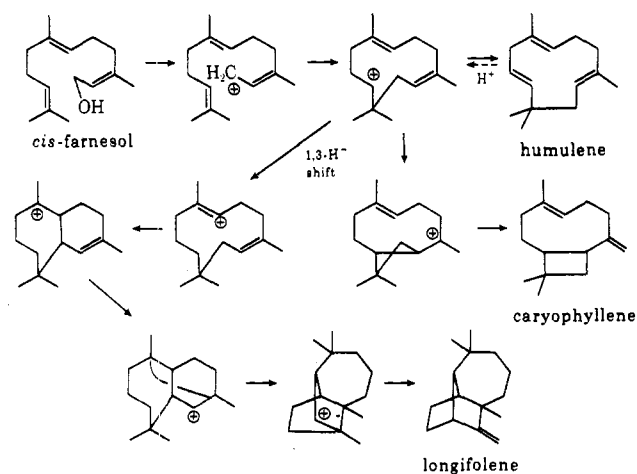


In addition to the fundamental interest in skeletal rearrangements and possible biogenetic relationships, this series of rearrangements has a commercial interest. In 1961, Runeberg¹⁵ showed that thujopsene was a constituent of American cedarwood oil, an important oil in the fragrance industry. Among the numerous derivatives of this oil which are utilized in perfumery is a ketone mixture obtained by acetylation of the hydrocarbon fraction of this oil with acetic anhydride and a Lewis acid catalyst. The product possesses a warm woody odor and is sold under various trade names in the fragrance industry. The workers at the Givaudan Corp., Daeniker, Hochstetler, Kaiser, and Kitchens, studied this problem in detail and showed that the desired ketone was derived from thujopsene.¹⁴



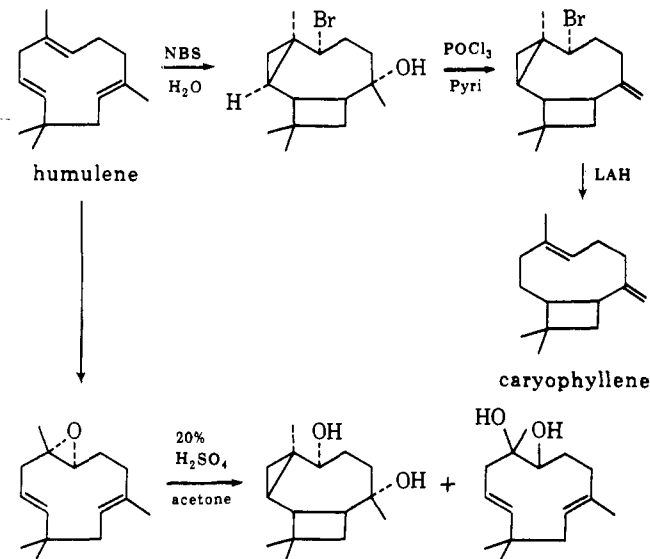
With our previous knowledge of the acid-catalyzed rearrangement of this hydrocarbon it was evident that there was a wide choice of rearrangement products which could be acetylated and they showed that the product was derived from the hydrocarbon which came *via* the chamigrene route. Their work aided ours in that the establishment of the structure of the ketone gave us proof of a postulated intermediate in our overall rearrangement scheme.

The finding that by controlled acid-catalyzed rearrangement of thujopsene we were able to mimic the postulated biogenetic pattern encouraged us to study another system. The Hendrickson Biogenetic Hypothesis, related to the bi- and tricyclic sesquiterpenes, summarizes a series of conversions worthy of study.



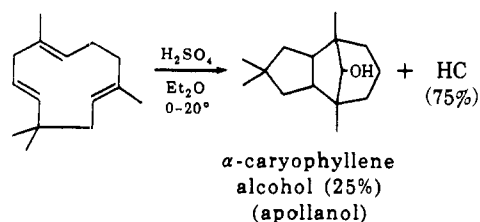
A key intermediate derived from farnesol is the 11-membered ring carbonium ion. This ion is related to the natural sesquiterpene from hop oil, humulene. Thus, it might be possible that by selective protonation of humulene one could obtain the same ion and the reactions of the ion followed. For example, this ion as shown is suggested to be the precursor of caryophyllene by simple ring closure and of longifolene by a series of ring closures and 1,2 migrations much like what we have discussed for thujopsene.

Many workers have studied the cyclization of humulene and their results have tended to support the biogenetic hypotheses. For example, humulene, upon reaction with hypobromous acid, gave rise to the bromohydrin resulting from transannular reaction.¹⁶ This bromohydrin could, in turn, be converted into caryophyllene. A similar reaction



sequence was obtained from the epoxide.¹⁷ Based upon these results it was suggestive that humulene, upon protonation, should give rise to the related alcohol which, in turn, would rearrange to caryophyllene.

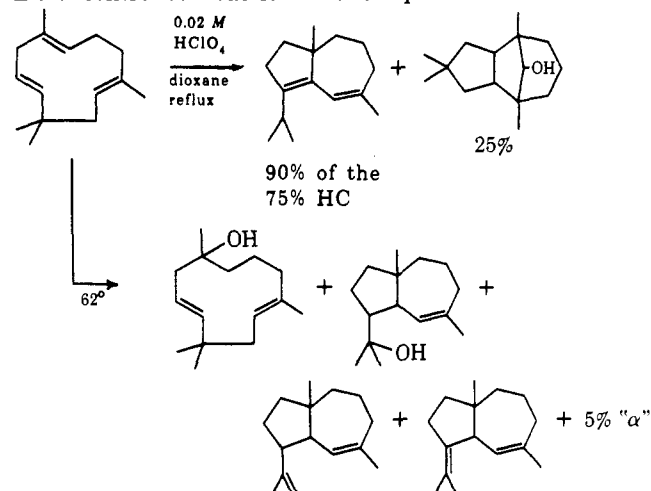
On the other hand, acid-catalyzed rearrangement of hu-



mulene had been studied by many workers and recently Nikon reinvestigated the reaction.¹⁸ He found that hu-

mulene, when allowed to react with concentrated H_2SO_4 in ether at low temperature, gave a solid alcohol in 25% yield and it was shown to have the interesting tricyclic ring structure. The 75% hydrocarbon fraction was not studied.

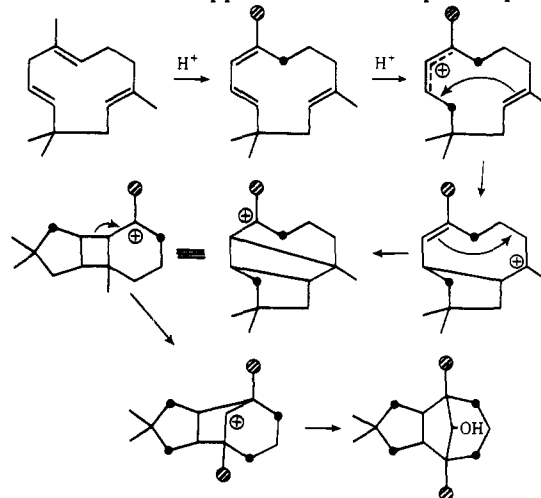
Our studies, as with thujopsene, were directed toward a more controlled reaction and all products were investi-



gated.¹⁹ The humulene we employed was kindly supplied by the Glidden Co. Using 0.02 M $HClO_4$ in refluxing dioxane, it was found that 25% of α -caryophyllene alcohol was still obtained and that the 75% yield of hydrocarbon was more than 90% of one compound. When the conditions of Nikon¹⁸ were used, similar results were obtained. The structure of the hydrocarbon was established by degradation and it was shown to be a hydroazulene, a structure having no relationship to that of the alcohol. This new structure results from one ring closure and one 1,2 migration.

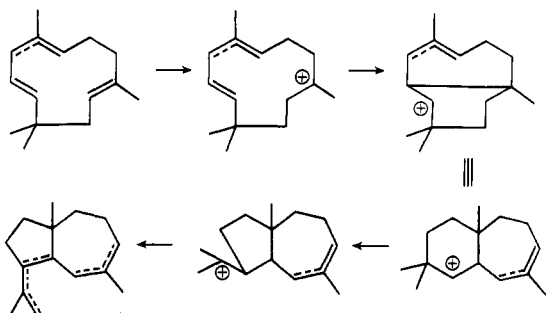
In order to obtain more detail as to its formation, the reaction conditions were modified and it was established that the first product was humulol, formed by hydration of the most reactive double bond. This material exists in equilibrium with humulene. Very early in the reaction another alcohol appears and this was shown to be related to the hydroazulene nucleus. This alcohol then dehydrates to form two other olefinic isomers. Under these conditions, these two olefins are relatively stable and only under the more vigorous conditions does the rearrangement to the conjugated diene continue. Thus, the acid-catalyzed rearrangement of humulene does not yield any of the expected biogenetic related products. It is of particular interest to note the different reaction course followed using the other Lewis acids, and in those cases the nature of the initial reaction complex must call for homoallylic participation.

The mechanisms of these transformations in acid are of interest since there appear to be two separate pathways.



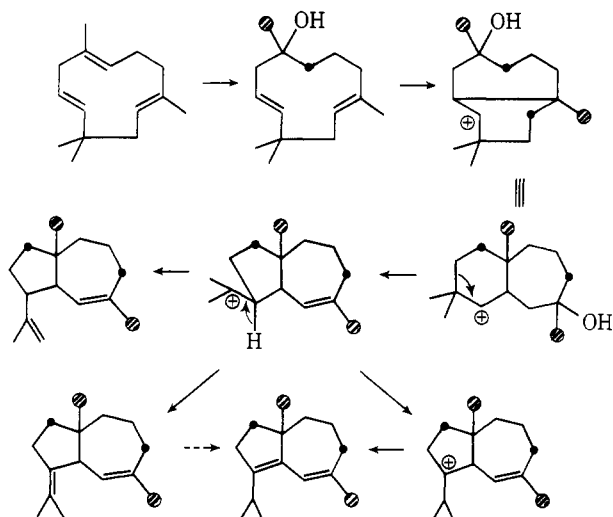
Nickon has established the reaction mechanism for the formation of α -caryophyllene alcohol. It was suggested that the first step was to move the two double bonds into conjugation, followed by protonation of the conjugated diene to give the allylic carbonium ion. This ion then ring closes and the resulting carbonium ion, in turn, cyclizes to give the tricyclic cation. This activated complex, in turn, undergoes a 1,2 migration and the product is formed by hydration of the final carbonium ion. This mechanism calls for the introduction of a proton at one site to yield the conjugated diene and that once this diene is formed a second addition of a proton occurs and there is no stable intermediate between this cation and the final product. Recently this has been shown to be the case by evaluation of the ^{13}C spectrum of the material prepared in D_2SO_4 .²⁰ It is possible to locate the carbon atoms which hold a deuterium and, as shown, the predicted distribution was found.

Turning to the present work,¹⁹ at first sight there ap-



pear to be many possible pathways but when you consider them in detail it is found that all but one involve anti-Markownikoff addition of a proton. The gross concept requires that first ring closure to a 6,7-bicyclic system occur and then that ring contraction of the six-membered ring with extrusion of the isopropyl group take place.

There are two aspects of this gross mechanism which require evaluation. First if, as in the Nickon process, the first step is conjugation of the double bond to form the conjugated diene, then it is difficult to explain how protonation could preferentially occur on the required isolated double bond. On the other hand, if the conjugation did not occur first, then a reason must be found for preferential protonation at a position known not to be the most reactive. The following detailed process is given to account for these deficiencies.

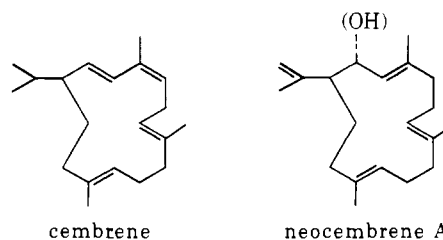


The rapid formation of humulol suggests that hydration of the double bond competes with the migration. This reaction now blocks that position and permits the second protonation to occur at the desired position for it is now the lesser hindered double bond. The formation of the fused 6,7 ring system occurs, and next ring contraction

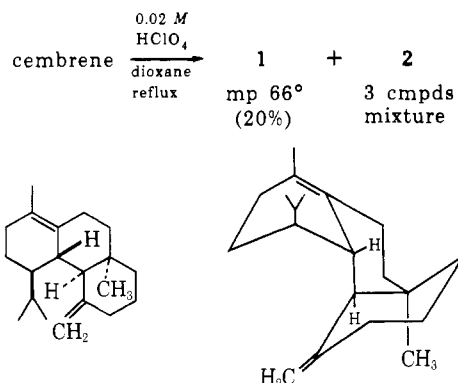
with concomitant dehydration occurs. The most obvious fate for the carbonium ion is to lose a proton and yield the two isomeric nonconjugated dienes. Finally, migration into conjugation takes place.

We also have examined the ^{13}C nmr spectrum of the deuterated final product and the deuteria are as indicated, in agreement with the postulated mechanism. The surprising result, however, is the almost total absence of deuterium on the isopropyl group, since it was anticipated that the two isomers with the isolated double bonds would be the precursors of the final products. Clearly, this result indicated that the majority of the final product arises *via* an internal 1,2-hydride shift without the intervention of the other isomeric olefins. The material used in this study was prepared under the more forcing conditions and thus this migration must be preferred to hydration of the carbonium ion which takes place under the less vigorous conditions. These results show the utility of ^{13}C nmr for the study of mechanisms.

Next, it was of interest to study the diterpene equivalent of humulene. The naturally occurring nucleus in this series is the 14-membered ring system, cembrene. Our earlier work established the structure of the first example in this series, the hydrocarbon cembrene, a material widely occurring in the oleo resins of the haploxylen subgenus of pines.²¹ Recently, the related neocembrene A has been isolated from other conifers,²² from the gum resin extract of an Indian tree (*Commiphori inukul*),²³ and from the Australian termite.²⁴ Our studies were carried out with cembrene.

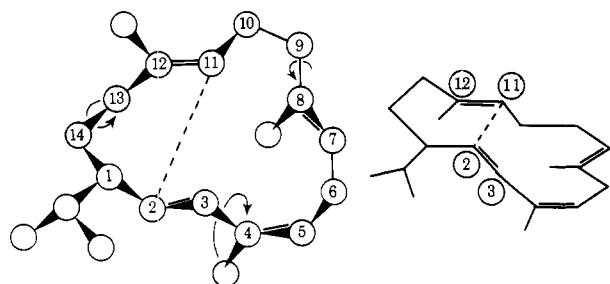


We have only made preliminary studies in this series but the results are worthy of discussion.²⁵ As expected, acid-catalyzed reactions are more complicated in this larger ring and, after 1 hr, two main fractions were obtained by the normal separation procedures. The first fraction crystallized but the second fraction, upon vpc analysis using a 500-ft capillary column, was shown to be a mixture of three compounds. The structure of the crystalline material was determined by Dr. William Thiessen at the Oak Ridge National Laboratory and was found to be of the hydrophenanthrene ring system.²⁶ This structure showed some interesting features. In the crystal the isopropyl groups adopt an axial conformation due to the extreme steric hindrance between it and the exocyclic methylene group. This type of steric repulsion is typical of a 4,5-disubstituted phenanthrene series.

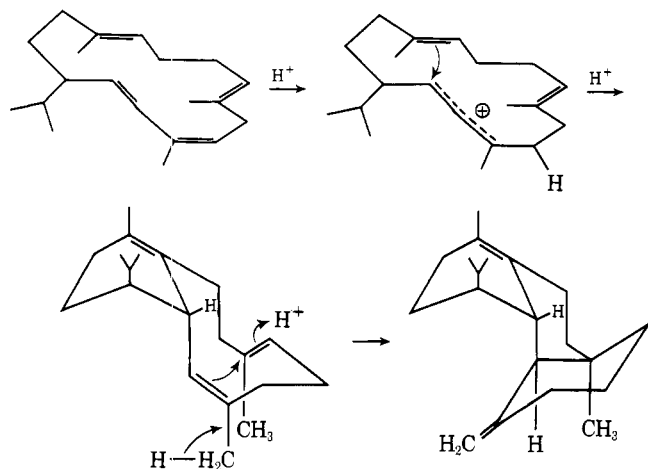


It is worthy to discuss the mechanism of this transformation since again it appears to be a stepwise process.

First let us look at the conformation of cembrene in the crystal. One sees it is arranged so that the required carbon



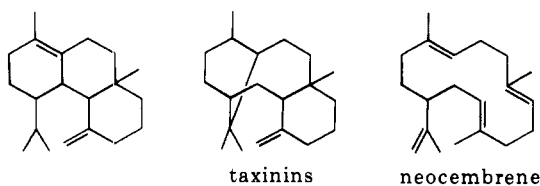
atoms for ring closure, say C-2 and C-11, are in the proper vicinity for bonding but to achieve proper bonding it is essential to rotate bonds 3,4, 8,9, and 13,14 to get a conformation which brings the atoms within bonding distance. In this conformation the diene adopts an *s-cis* arrangement.



As expected, protonation occurred at the diene and at that end of the system which yields the more stable allyl carbonium ion. In this ion, C-2 can readily attack C-11 and make the first ring; however, the resulting carbonium ion must yield a stable intermediate, since the final structure cannot be derived by ring closure of this ion.

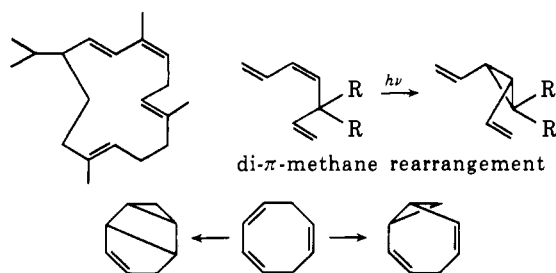
The intermediate diene has been sought but we have been unsuccessful in obtaining evidence of its presence. Nevertheless, this diene, upon protonation, can yield the product. In this diene, if one examines Dreiding models, it is evident that one double bond must be *cis* in order to minimize repulsion in the transition state between the developing methylene group and the already formed ring. We have not done a detailed ^{13}C nmr spectral analysis of the deuterated product.

The resemblance of this structure and that of the naturally occurring taxins (taxane) is worthy of mention. It is

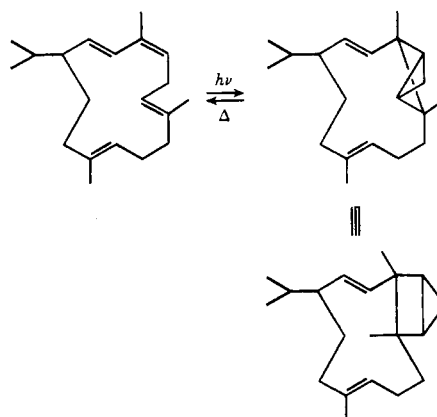


seen that the ring system is clearly related to the acid rearrangement product and, in fact, if you examine the structure of neocembrene you see that it could be the direct precursor of the taxinin nucleus.

Finally, I should like to discuss the photochemistry of cembrene. It is readily seen that the arrangements of the double bonds are those which can lead to a di- π -methane rearrangement, *i.e.*, a process in which one gets an overall 1,2 migration with the formation of a cyclopropane ring.



When the similar chromophoric system is contained in a ring system, it is found that two possible processes now occur, the di- π -methane rearrangement and a [2 + 2] cycloaddition to form a housane type of structure.



In the case of cembrene, there is only one major product, it being formed in greater than 60% yield and shown to have the housane structure.²⁷ The material, upon heating to 180°, reversed to cembrene.

It is evident that by carefully choosing your natural product not only can interesting new potential synthetic and mechanistic chemistry be developed but it also is possible to perform biogenetic types of syntheses of other natural products.

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Dihydrobenzenes in Synthesis in Terpene Related Areas

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1-Methoxycyclohexa-1,4-dienes obtained by metal-ammonia reductions of anisole derivatives are useful in synthesis because of their nature both as enol ethers and as dienes. Dihalocarbene adducts give rise eventually either to tropones or to methylated cyclohexanones according to subsequent manipulations. Introduction of angular methyl groups can be accomplished efficiently in

this manner. They readily directly form Diels-Alder adducts derived from the isomeric 1,3-dienes. These adducts can be ring-opened by acid to 4-substituted cyclohexenones, a procedure used in stereoselective syntheses of (\pm)-juvabione and of (\pm)-nootkatone. Synthetic capabilities of tricarbonylcyclohexadieneiron derivatives are introduced.

Instead of recounting only some finished syntheses I thought it might be more useful to terpene chemists interested in synthesis to draw attention to some general approaches which have been perhaps insufficiently used. The references given are only to my own work, which was in all cases the earliest in the area discussed. In a number of instances later work has been published by others.

The basis of the subject is the ready availability of cyclohexa-1,4-dienes and particularly the 1-methoxy derivatives from the reduction of aromatic compounds by metal-ammonia-alcohol combinations (*e.g.*, Birch and Subba Rao, 1972). This work was originally aimed at making 19-nortestosteroids, since the methoxydienes are enol ethers and can be hydrolyzed first to $\beta\gamma$ - and to $\alpha\beta$ -unsaturated cyclohexenones. The initial work culminated in the total synthesis of 19-nortestosterone (Birch, 1950a), the first totally synthetic potent androgen, and later led to analogs of other steroid hormones, including oral contraceptives. Direct reductions of aromatic rings or reductions followed by hydrolysis to ketones have been extensively used in connection with terpenoid synthesis, the first examples being concerned with piperitone and γ -curcumene (Birch and Mukherji, 1949). This is too well known to merit further discussion here except to note that the approach has largely eliminated the need for high pressure hydrogenations of aromatic rings and also permits a considerable degree of steric control.

Further to the production of cyclohexenones, copper-catalyzed Grignard reagent additions (Birch and Robinson, 1943; Birch and Smith, 1962; Kharasch and Tawney, 1941) to an enone system permit introduction of quaternary carbon atoms, including angular methyl groups. Such an introduction into, for example, a 2-octalone was early shown (Birch and Robinson, 1943; Birch and Smith, 1962) to result in a cis ring junction, which somewhat limits applications in the terpene field. More recent modifications, using notably lithium copper dialkyl reagents,

have shown considerable synthetic scope for the procedure.

The 1-methoxycyclohexa-1,4-dienes are at the same time vinyl ethers and dienes, and one or other or both of these features explains their reaction capabilities in synthesis. A general feature of their nature as vinyl ethers is the high reactivity of that double bond toward electrophilic reagents. One example is the acid hydrolysis shown in Figure 1. Another important feature is that if in consequence of this reactivity a new carbon-carbon bond is formed as part of a ring to the center carrying OMe, a ring bond is readily broken by reactions calculated to produce a carbonium ion on this particular carbon as a consequence of interaction with the unshared electrons on the oxygen. Two important synthetic examples of this type of fission will be quoted. The first consists of a very facile synthesis of tropone derivatives, exemplified by the synthesis of nezukone shown in Figure 2 (Birch and Keeton, 1968). The other is connected with the Diels-Alder reactions discussed later. Such reactions occur less readily or not at all in the absence of OR.

Reaction of the electron-deficient carbene occurs somewhat selectively in this case on the enol ether bond and much more selectively in cases where the second double bond is less activated by substitution. Removal of halide anion by a silver cation or by heating in quinoline provokes the ring fission shown. The intermediate oxonium salt undergoes hydrolysis and with double bond shifts and hydrogen bromide elimination the action of silver fluoroborate experimentally gives directly the tropone in high yield. Several other examples are shown in Figure 3 (Birch *et al.*, 1965). Although such syntheses could probably be carried out by standard ring expansions, brominations, dehydrobrominations, etc., the present procedure is a three-step one from an aromatic compound and is probably the easiest tropone synthesis available.

Dimethoxy derivatives can lead to cyclooctane derivatives or ring-closed derivatives of these, again in high yields (Figure 4) (Birch and Keeton, 1971; Birch *et al.*, 1964a).

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