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A STUDY OF SOME TERPENE OXIDES:
CONFORMATIONAL EFFECTS IN SUBSTITUTED CYCLOHEXENE OXIDES

By

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1963

A STUDY OF SOME TERPENE OXIDES:
CONFORMATIONAL EFFECTS IN SUBSTITUTED CYCLOHEXENE OXIDES

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July 30, 1963
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Date: July 30, 1963

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The author wishes to express his sincere appreciation to Dr. E. Earl Royals for his guidance, assistance and his encouragement through this work.

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CHAPTER I

INTRODUCTION

Limonene and α-pinene are widely distributed in nature and are produced economically in commercial quantities. The epoxidation of these compounds may be carried out by several methods, the peracetic acid epoxidation process being the commercial method of choice.

The epoxides of limonene, carvomenthene and α-pinene have found uses as organic intermediates on a very limited scale. Consequently, the stereochemistry of these epoxides and their reaction products has been generally ignored until recently. From the stereochemistry of the reaction products of substituted cyclohexene epoxides, it is possible to show that substituents may fix the conformation of the cyclohexane ring, thus determining which carbon-oxygen bond will be broken in the opening of the epoxide.

In this work a study of the acid catalyzed hydration and rearrangements of _d_-limonene monoxide in a sulfuric acid - water system was carried out. Similar preliminary work was also done on α-pinene oxide in an attempt to find an economical route to pinol. The stereochemistry of the products obtained by the action of acetic acid on the epoxides of *d*-limonene, *d*-carvomenthene and *dl*-α-pinene was investigated. The pyrolysis of the resultant hydroxy-acetates and the stereochemistry of the products obtained was also investigated.

Limonene monoxide prepared by peracid epoxidation was shown to be a mixture of two isomers. Both a chemical and physical method for the determination of the relative amounts of the two isomers present have been presented. The stereospecific synthesis of each of the two isomers of limonene monoxide was carried out.

The reactions of limonene monoxide with lithium aluminum hydride and with powdered sodium were reinvestigated.

Cis- and *trans*-carveol, and *trans*-*iso*carveol, were prepared stereospecifically. Hydrogenation of each of these materials gave results incompatible with the structural assignments of the carvomenthols of Bose (1). On the basis of this and other evidence, the carvomenthols were assigned their proper stereochemistry. The conformational assignments of the carvomenthols were shown to be in complete accord with all of the available experimental evidence.

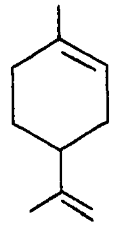
The synthesis of several substituted 6-oxa-bicyclo-[3.2.1]-oct-3-enes was undertaken in an attempt to shed some light on the internal ether - aromaticity competition during the formation of pinol type systems. A correction of a proposed mechanism for the formation of pinol from α-terpineol dibromide was shown.

In the course of the synthetic steps leading to the substituted 6-oxa-bicyclo-[3.2.1]-oct-3-enes, several diene syntheses of interest were carried out. Diene syntheses were also attempted on substituted enol acetates. Dehydroacetic acid was isolated from an attempted addition of the enol acetate of ethyl acetoacetate to cyclopentadiene. This acid and its methyl and ethyl esters (enol ethers) were studied in order to ascertain the structure of these compounds.

CHAPTER II

HISTORICAL

The structures of limonene (I) and α-pinene (II) were ascertained around the turn of the century. While it is impossible to adequately summarize here the prolonged investigations carried out on these hydrocarbons during the early years of terpene chemistry, it is sufficient to say that the elucidation of the structures of these compounds were two of the major problems upon which much of the chemistry of cyclic terpenes rested.



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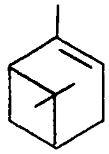

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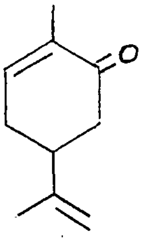
The important evidence which allowed the elucidation of the structure of the optically active limonene (the racemic form is commonly known as dipentene) was its relationship to carvone (III) and α-terpineol (IV). Limonene readily formed a crystalline nitrosochloride (2) which, when treated with base, was converted into carvone oxime.

The presence of an isopropenyl group in dihydrocarvone (V), prepared by the sodium - alcohol reduction of carvone, was established by its oxidative degradation (3,4). Furthermore, α-terpineol was shown to give limonene on dehydra-



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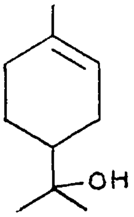

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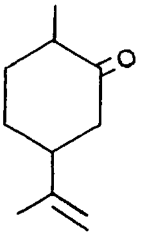


(V)

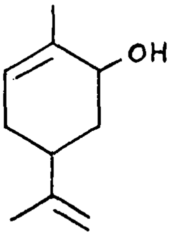
tion (5). These experiments formed the basis of the structure proof for limonene. The synthesis of dipentene has confirmed the structural assignment (6,7).

Limonene is abundant in nature, being the main constituent of the terpene fraction of a number of oils, among them, the oils of bergamot, orange, lemon, dill and caraway (8,9).

No terpene occurs more widely distributed in nature than α-pinene. It is the main constituent of turpentine and is found in most of the essential oils of the _Coniferae_. The term "pinene" was given by Wallach (10) to the hydrocarbon fraction of the oil turpentine, b.p. 155-65°, but the name α-pinene is now reserved for a single terpene hydrocarbon.

As the author has reviewed the structure proof of α-pinene in an earlier work (11), this shall not be repeated here. Several reviews are available dealing with the structure proofs and general reactions of limonene (12,13, 14) and α-pinene (15,16,17). The natural sources and general properties have also been conveniently tabulated (18).

The autoxidation of limonene has been thoroughly studied under varying conditions. Blumann and Zeitschel (19) have shown that the autoxidation of dipentene in moist air gives dl-carveol (VI) and dl-carvone (III) (20). Horne (21) has pointed out that the literature on the autoxidation of limonene might mislead one to believe that carveol and carvone are formed in good yields, while in actuality this is not the case.



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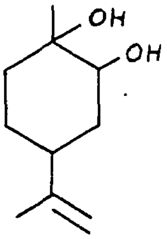

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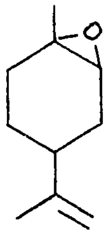
For many years the presumption was that the primary products of the autoxidation of limonene was the glycol (VII), from which carveol was obtained upon dehydration of the tertiary hydroxyl group (23). However, in light of the studies on the autoxidation of cyclohexene, the methyl cyclohexenes and other cyclic olefins (23,24,25), it would be more reasonable to picture the reaction as proceeding through the hydroperoxide intermediate. Japanese workers have reported that the air autoxidation of limonene afforded less than a 20% concentration of the hydroperoxide (26). The rate of formation of the hydroperoxide was enhanced by benzoyl peroxide or heavy metal salts, but this had no effect on the percent of hydroperoxide formation.

The most complete analysis of the product mixture obtained from the autoxidation of limonene was reported in a series of patents to the Glidden Co. (27,28). The hydroperoxides formed in the autoxidation were reduced under alkaline conditions and the volatile organic material subjected to fractional distillation. Limonene (I), limonene-1,2-oxide (VIII), limonene-8,9-oxide (IX), <u>cis</u>- and <u>trans</u>-2,8-<u>p</u>-menthadien-1-ol, <u>cis</u>- and <u>trans</u>-carveol (VI), carvone (III) and an unidentified fraction were isolated. From the aqueous alkaline solution a mixture of organic acids was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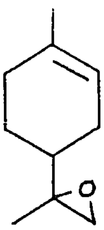
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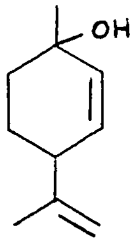

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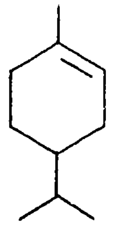
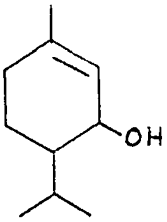

(XI)

recovered. In the autoxidation of carvomenthene (XI) and α-terpineol (IV), the corresponding analogues of the compounds isolated from the autoxidation of limonene were obtained (27,28). Schmidt has confirmed the formation of *dl*-carvone and *dl*-carveol and has also isolated a crystalline limonene-1,2-diol (8-*p*-menthene-1,2-diol) (VII) (29) as well as limonene monoxide (30). This glycol was identical to that obtained from hydration of limonene monoxide. The limonene monoxide and limonene-1,2-diol were optically active. Schenk, Eggert and Denk (25) have shown that limonene hydroperoxide is photosensitive and apparently goes through an allylic radical rearrangement to give racemization. This leads to the conclusion that the formation of *dl*-carveol and *dl*-carvone from limonene proceeds through the allylic hydroperoxide intermediate while the formation of the other, optically active, products presumably follows a course which involves direct addition of active oxygen to the olefinic linkage. The limonene-1,2-glycol was considered to be a *trans*-diol since the opening of the oxide ring would be expected with an inversion of configuration. This conclusion corrected Schmidt's earlier erroneous *cis* assignment (21,29-31).

The recent literature contains several reports of kinetic studies of the autoxidation of limonene under varying conditions (21,26,33,34).

Carvomenthene (XI) which may conveniently be prepared by the partial hydrogenation of limonene (35-41) has been shown to yield piperitol (XII) on autoxidation in the presence of catalysts, but gives carvotanacetol (XIII) in the absence of catalysts (42). As was previously mentioned, carvomenthene oxide (XIV) and <u>cis</u>- and <u>trans</u>-2-<u>p</u>-menthen-1-ol (XV) have also been obtained (27,28).



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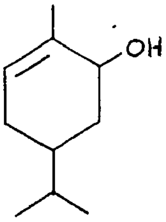

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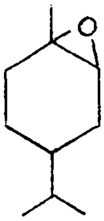

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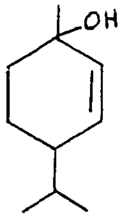
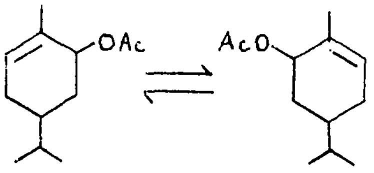
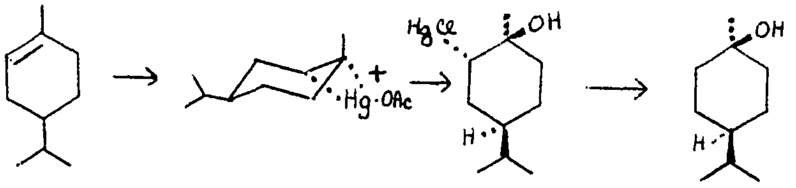


(XV)

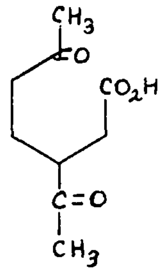
The oxidation of both limonene and carvomenthene by other reagents has proven to be of considerable interest. The action of mercuric acetate, $Hg(OAc)_2$, on limonene and carvomenthene in benzene has been thoroughly investigated (43-45), the products formed being carveyl acetate and carvotanacetol acetate respectively. It is interesting to note that the mechanism of the reaction of both mercuric acetate and lead tetraacetate with carvomenthene must require a step which will cause racemization in the resultant molecules as the optically active olefin gave a racemic product (45). The racemization could quite conceivably be similar to that for the hydroperoxide of limonene (25,30), presumably by passing through an allylic rearrangement. The allylic rearrangement of acetates is a commonly occurring phenomena and has been used to advantage in a number of cases (46). Whether the rearrangement is radical in nature or ionic has not been ascertained.



The action of mercuric acetate on carvomenthene in aqueous media has been shown to yield trans-p-menthan-1-ol (XVI) upon reduction of the mercurial (47).



While mercuric acetate gave carveyl acetate from limonene, the action of lead tetraacetate showed attack at the isopropenyl olefin (48). First investigated by Ward (49), the products remained unidentified until Aratani (48) reinvestigated this reaction. The main products identified were the diacetates of 1-p-menthen-8,9-diol and 1,8(10)-p-menthadien-9-ol. Thus lead tetraacetate preferentially attacked the double bond outside the ring rather than the endocyclic olefin.



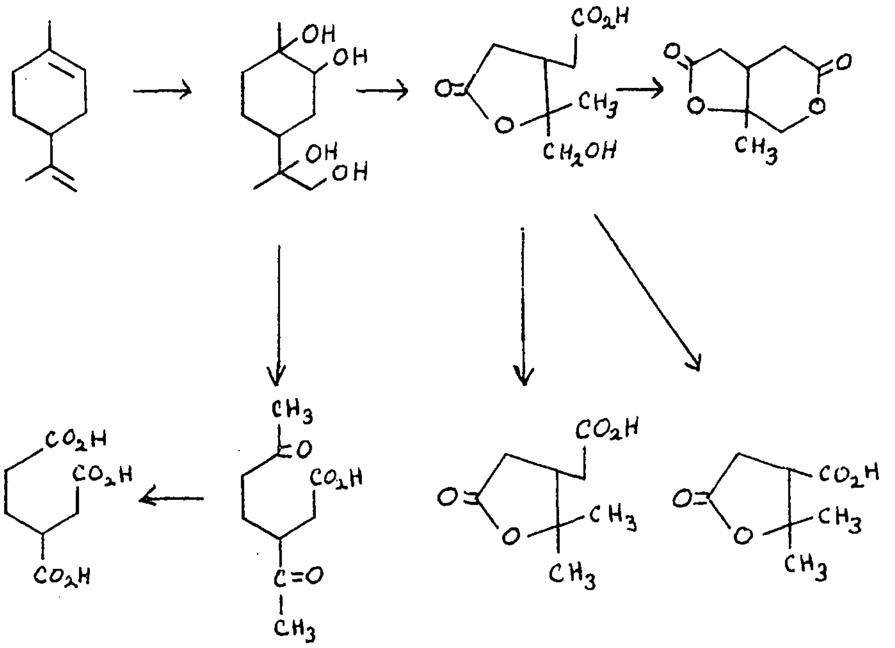
(XVII)

The ozonization of limonene led to the expected diketonic acid (XVII) which was identical to an acid previously obtained by Tiemann and Semmler (50). More recently the oxidative degradation of the mono- and diozonide of limonene, as well as that of carvomenthene ozonide, have been studied (51).

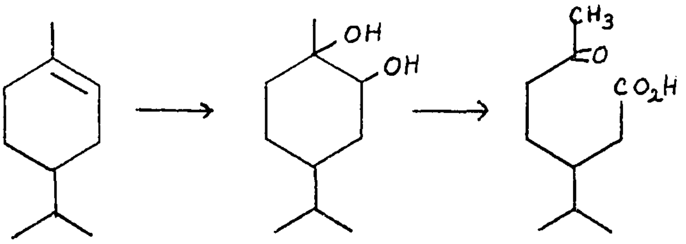
The action of chromyl chloride has been reported (52, 53) to form an addition compound, $C_{10}H_{16} \cdot 2CrO_2Cl_2$. On decomposition with water a mixture of α-p-tolyl propaldehyde and p-tolyl methyl ketone were formed.

The oxidation of limonene with potassium permanganate solutions has been studied by a number of workers (50,54-56) and apparently proceeds by the scheme outlined on the following page.

The action of dilute permanganate on carvomenthene gave a cis-1-hydroxy-carvomenthol (cis-p-menthane-1,2-diol (XVIII) (30). More vigorous oxidation results in oxidation to the keto acid (XIX).

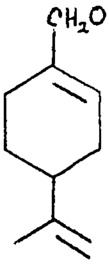


The electrolytic oxidation of dipentene has been studied by Glasstone and Stanley (58).



(XVIII) (XIX)

Several conflicting results with regard to the oxidation products of limonene with selenium dioxide have been reported. Schmidt (59) reported the sole product that was isolated to be perillyl alcohol (XX), while Sebe (60) has found p-cymene along with other oxidation products.



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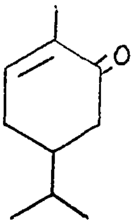

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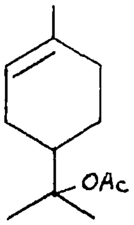

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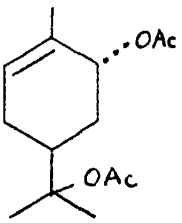
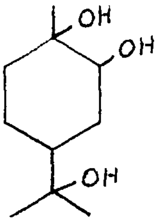


(XXIII)

Perillyl alcohol was ruled out as one of the oxidation products by Zacharewicz (61). However, the chromic acid oxidation product of his primary alcohol gave a semicarbazone, m.p. 199°. The oxidation product of perillyl alcohol is dihydrocuminic aldehyde, semicarbazone, m.p. 198-198.5° (62). Carvotanacetone (XXI) was reported as the product of the selenium dioxide oxidation of carvomenthene (63,64). In connection with the selenium dioxide oxidation of olefins of this type it was interesting to note that α-terpinyl acetate (XXII) gave <u>trans</u>-sobrerol diacetate (XXIII) when run in an acetic acid - acetic anhydride solvent (65). From the published results it was apparent that this oxidation can yield a variety of products under differing conditions. The reported results were, in many cases, subject to doubt and should be reinvestigated.

The oxidation with Beckman's chromic acid mixture yielded homoterpinyl methyl ketone (XXIV) (66). The first product of the reaction was α-terpineol which was then oxidized to the ketolactone by way of the triol (IVa) intermediate. More recently the oxidation of limonene and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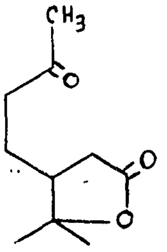
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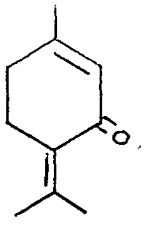
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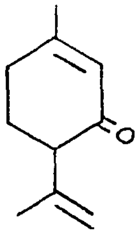
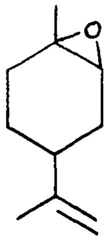

(XXVI)

carvomenthene has been carried out with t-butyl chromate. Limonene yielded 21% carvone along with homoterpinyl methyl ketone, piperitenone (XXV) and isopiperitenone (XXVI) (67). Fujita and Matsuura (68) have reported a 57% yield of carvotanacetone as the sole product of the t-butyl chromate oxidation of carvomenthene, while Dupont, Dulon and Mondou (69) reported a mixture of piperitone (31%) and carvotanacetone (14%) as the products.

The oxidation of limonene and carvomenthene with reagents which cause epoxidation and hydroxylation were of special interest in this work.

Epoxidation may be defined as the reaction in which olefinic unsaturation is directly converted into a three membered cyclic ether. Generally this transformation is achieved by use of an organic peracid (70,71). A great deal of literature on epoxides and their formation has been made available during the past fifteen years due to the great industrial effort to find chemical intermediates for polymer sysntheses (72,73). No attempt will be made to discuss the general procedures for epoxidation as they have been adequately reviewed elsewhere (74).

The epoxidation of limonene was studied by Prileschaev (75) using perbenzoic acid as the epoxidizing agent. Prileschaev isolated both the monoxide (VIII) and the dioxide (XXVII). Meerwein, Ogait, Prang and Serini (57), who performed kinetic studies on the epoxidation of a number of terpenes including limonene, showed that the initial product formed was limonene monoxide (limonene-1,2-oxide). Arbuzow and Mikhailow (76) obtained limonene monoxide in 63% yield with both perbenzoic and peracetic acids in ethereal solution. The epoxidation of d-limonene has been done previously in this laboratory by Horne (21) and by Harrell (77,78) using monoperphthalic acid. Recently Goryaev, Tolstikov, and El'chibekova (79) have modified the procedure for the preparation of monoperphthalic acid developed by Royals and Harrell (78), shortening the time required for its preparation. More recently the epoxida-



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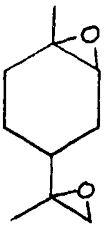
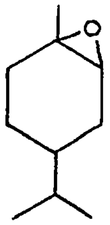


(XXVII)

tion of limonene has been reported by Schmidt (29), Greenspan and Linder (80), Pigulevski and Khokhryakov (81), Kuczynski and Piatkowski (82) and Kergomard and Geniex (83). Blum reported the preparation of limonene monoxide in 50% yield using succinyl peroxide (84). Commercially limonene monoxide has been prepared by peracetic acid oxidation in yields up to 90% (85,86). The further epoxidation of limonene monoxide yields the dioxide (57,75).

As was previously mentioned, limonene monoxide has been isolated as an autoxidation product of limonene (27, 28,30). It has also been isolated by distillation from the essential oils of C. densiflorus (87).

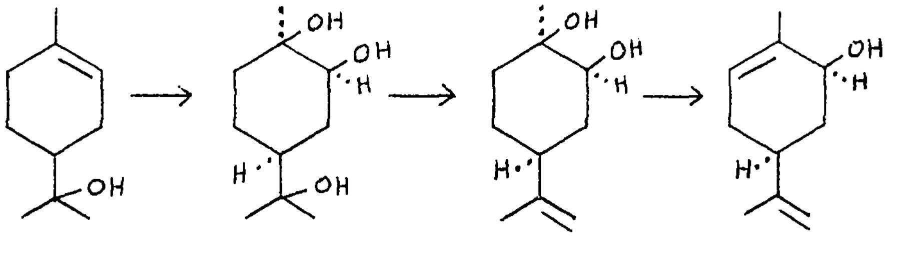
Carvomenthene oxide (XIV) has been conveniently prepared by the catalytic hydrogenation of limonene monoxide using Raney nickel or platinum oxide as the catalyst (80, 88,89) or by the action of epoxidizing agents on carvomenthene (90,91).



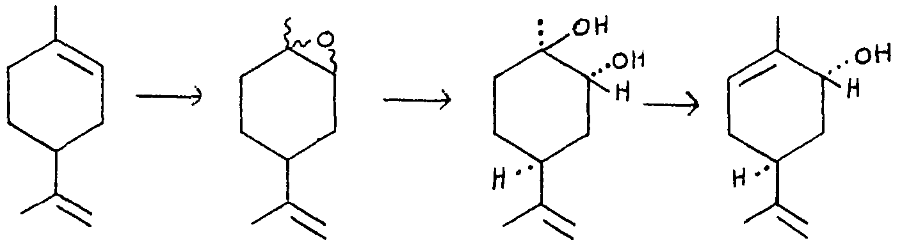
(XIV)

Until recently the only studies on limonene monoxide were those involving further epoxidation (75,76,92) and those in which the epoxide has been hydrated to produce limonene-1,2-diol (21,29,30,57,75).

The preparation of limonene-1,2-diol (8-p-menthene-1,2-diol) was first accomplished by Ginsberg (93). α-terpineol was oxidized to p-menthane-1,2,8-triol with dilute potassium permanganate as described by Wallach (94) and the corresponding triacetate formed. The pyrolysis of this triacetate afforded a fraction consisting of a diacetate which on saponification gave a diol isomeric with sobrerol, melting at 63-64°. This glycol gave a p-menthane-1,2,8,9-tetrol on dilute permanganate oxidation thus indicating that the glycol was an 8-p-menthene-1,2-diol. The acid catalyzed hydration of limonene monoxide gave a different glycol than that obtained by Ginsberg (29,75). The stereochemistry of the two glycols was determined by Blumann and Wood (95) and elaborated by Schmidt (30). The hydroxylation of olefins with dilute permanganate gives cis-glycols (96) whereas the hydration of a cis-epoxide generally gives a trans-glycol (97). This being the case, by forming the diacetate of the two limonene-1,2-diols and preferentially pyrolyzing the tertiary acetate, the carveyl acetates were obtained. A fraction corresponding to cis-carveyl acetate was the pyrolysis product obtained from the glycol (VIIa) prepared by permanganate epoxidation. Trans-carveyl acetate was the product from the glycol (VIIb) prepared by hydration of limonene oxide. The carveyl acetates were identified by saponification to their respective cis- (VIa) and trans- (VIb) carveols. Sword (98) has



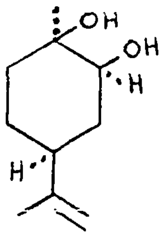
(VIIa) (VIa)



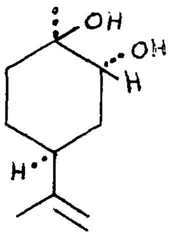
(VIIb) (VIb)

reported the preparation of what was undoubtedly the trans-limonene-1,2-diol (VIIb) by treating d-limonene with a hydrogen peroxide - acetic acid mixture and saponification of the resultant product. The hydroxylation of limonene to the trans-limonene-1,2-diol (VIIb) has more recently been carried out by Royals and Harrell (78) and by Newhall (99) using tungsten trioxide and performic acid respectively.

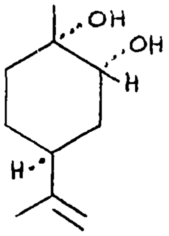
Of the eight possible optically active and four inactive modifications for the limonene-1,2-diols, only three active and two inactive forms of (VIIa) and (VIIb) are known (30).



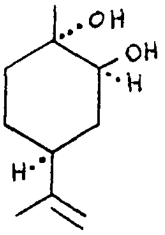
(VIIa)



(VIIb)

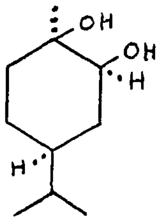


(VIIc)

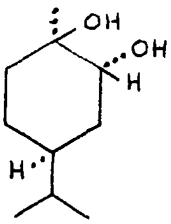


(VIId)

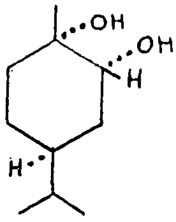
The corresponding *p*-menthane-1,2-diols (1-hydroxy-carvomenthols) (XVIII) have been more throughly investigated and the stereochemistry correctly assigned (30,100-102). However, the nomenclature, based on the incorrect structural assignments of two of the carvomenthols is in error (100). In the discussion, evidence will be presented which will clarify this situation and bring all of the terpenes whose nomenclature is based on the carvomenthols under the proper heading.



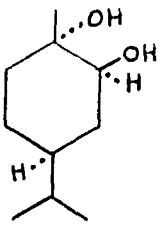
(XVIIIa)



(XVIIIb)



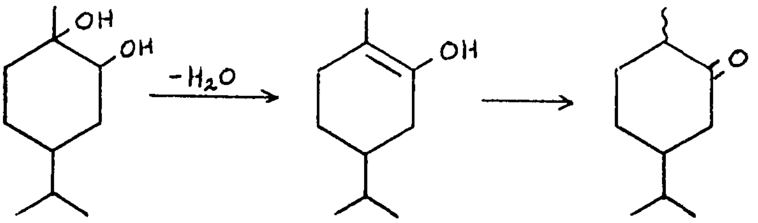
(XVIIIc)



(XVIIId)

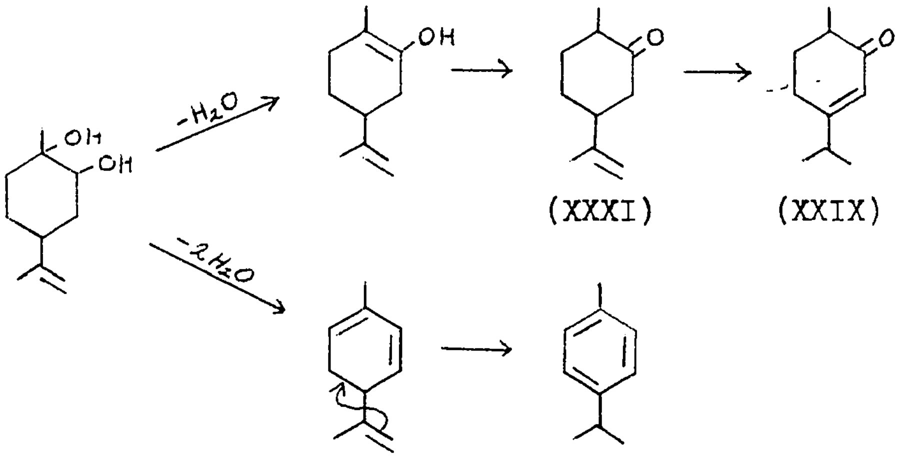
*Neo*limonene-1,2-diol (1-hydroxy-*neo*dihydrocarveol) (VIIb) was first converted into *neo*menthane-1,2-diol (1-hydroxy-*neo*carvomenthol) (XVIIIb) by hydrogenation (57).

It has also been obtained by the hydration of carvomenthene oxide (30,100). A second *trans*-diol, *neoiso*menthane-1,2-diol (1-hydroxy-*neoiso*carvomenthol) (XVIIId) was isolated in small amounts from the mother-liquor of such an oxide hydration by Jefferies and Milligan (100). The direct hydroxylation of carvomenthene with performic acid has been reported to give the two *trans*-diols (99,102). Hydroxylation (30,102) with dilute permanganate gave menthane-1,2-diol (1-hydroxy-carvomenthol) (XVIIIa). This isomer was also obtained by Jefferies and Milligan (100) by treatment of carvomenthene with iodine - silver acetate - water; by treatment with *t*-butyl hydroperoxide, and by inversion of the bromohydrins derived from carvomenthene oxide. These three methods also yielded the fourth isomer, *iso*menthane-1,2-diol (1-hydroxy-*iso*carvomenthol) (XVIIIc) in the reaction mixtures. Hydroxylation of carvomenthene with osmium tetroxide and esterification gave *iso*menthane-1,2-diol as the di-*p*-nitrobenzoate. The stereochemistry of the *p*-menthane-1,2-diols was unequivocally determined by chemical and infrared evidence (30,100,101).



(XXVIII)

Dehydration of the four p-menthane-1,2-diols with sulfuric acid gave carvomenthone (XXVIII) as the only identifiable product in each case (57,100). Dehydration of the limonene-1,2-diols (21,28,78) gave carvenone (XXIX) and p-cymene (XXX). The carvenone was presumably formed

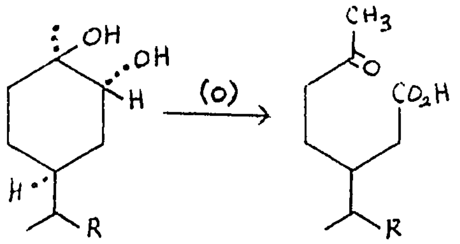


(XXXI) (XXIX)

(XXX)

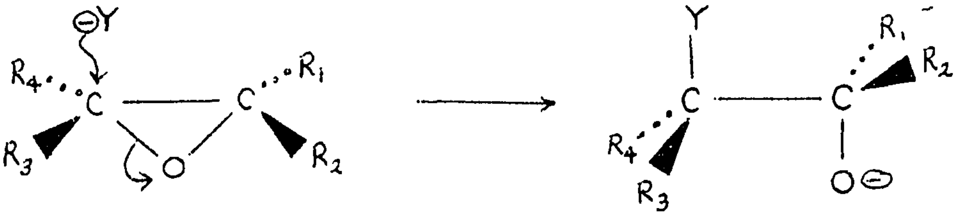
through the dihydrocarvone (XXXI) intermediate.

Mild oxidation of neolimonene-1,2-diol, and of the corresponding saturated glycol, have been reported to yield the expected keto acids.



The reactions of limonene monoxide should combine the reactivity of an epoxide moity with that of a double bond. However, only relatively few reactions of limonene monoxide have been reported. In many of the reported cases, the epoxide provided a mixture of isomers, the identification of which was incomplete. This, coupled with the misinterpretation of results, has led to a number of incorrect conclusions regarding the stereochemistry of reaction products. Part of the difficutly in this field was that insufficient evidence was available from which to draw analogies with regard to both the reactions of substituted cyclohexene epoxides and the stereochemistry of the resultant products.

Before taking up the general reactions of the epoxides of limonene, carvomenthene and α-pinene, it is necessary to digress from the literature of these hydrocarbons and their epoxides to that of epoxides in general (97). In the majority of cases, attack of the epoxide with nucleophilic reagents is considered to be an SN_2 process. From the point of view of mechanism the stereochemical evidence is quite revealing. In SN_2 reactions, inversion occurs because of the approach of the reagent on the side opposite the leaving group. Therefore inversion of configuration is the expected result of an SN_2 mechanism, but is incompatible for an SN_1 mechanism. (In acid catalyzed reactions the epoxide oxygen is initially protonated, but the process is otherwise the same). There are, of course, a few examples of ring opening reactions which give retention of configuration. These are usually found in cases where neighboring group effects play an important role.

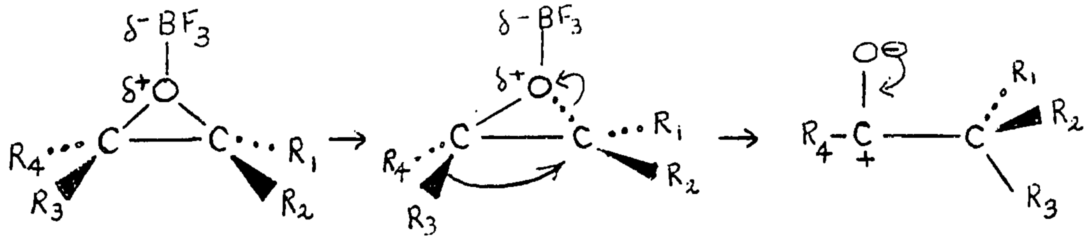


The orientational results with alkyl and cycloalkyl substituted epoxides have shown that the incoming reagent normally attacks the least substituted position (primary steric effect) unless there are marked polar or conjugative effects. While exceptions to this have appeared in the work of Mousseron (102-111) on the epoxides of the cyclohexane and cyclopentane series, aspects of this work were disputed by three groups of later investigators (112-114) and further substantiation has been considered necessary. Notable in this work was the lack, in many cases, of the determination of the stereochemistry of the reaction products.

The reactions studied so far have involved attack on an epoxide carbon atom by an external nucleophilic reagent.

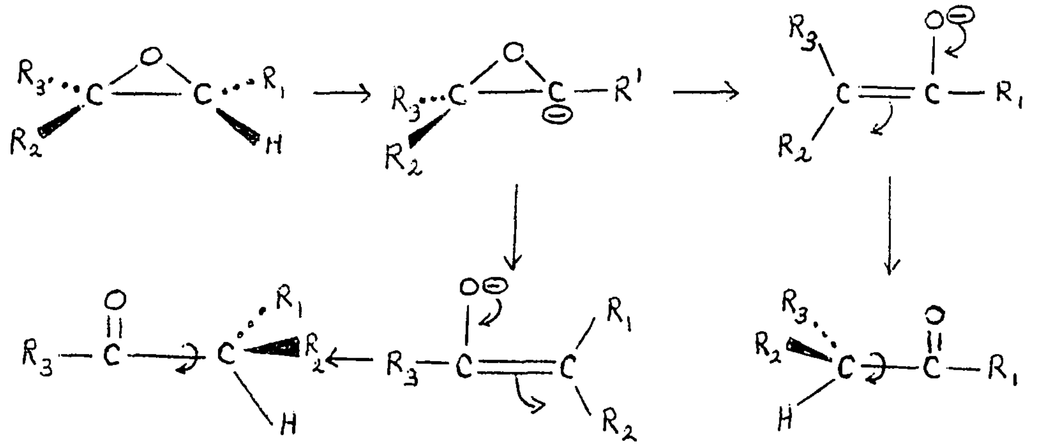
If such a reagent is not available, its place may be taken by a substituent in the epoxide molecule. This migration usually gives rise to a carbonyl group in the resultant molecule. In some cases ring expansion or contraction may accompany the rearrangement.

Rearrangements of epoxide molecules are usually catalyzed by Lewis acids, but also may be brought about by heat alone. As the reactions are normally catalyzed by a Lewis acid (e.g., BF_3-etherate), the entity that undergoes rearrangement is not the epoxide, but rather its complex.



The course of the rearrangement is governed by two factors: the direction of ring opening and the relative migratory aptitude of the substituent groups. Electron releasing groups facilitate the breaking of the carbon - oxygen bond to which they are attached, often determining the direction of the ring opening. Once the direction of ring opening has been decided, there remains a choice between migration of the two substituents, above, R_3 or R_4. This is decided by the relative migratory aptitudes of the groups. This order is generally aryl > acyl > H > ethyl > methyl.

Some epoxides rearrange to carbonyl compounds under the influence of basic catalysts. In these cases the products may be different from those obtained under acid conditions. Two related mechanisms, either of which may be followed in a particular case, have been put forth.



In systems, such as the steroid epoxides, where the ring system is conformationally homogeneous, the stereochemical results of the epoxide reactions are readily discernible (115). The direction of the epoxide ring opening is such that they invariably give diaxial products. This rule has been stated for the steroids by Fürst and Plattner (116) and extended to certain sugar epoxides by Mills (117). This rule is: "Either electrophilic or nucleophilic

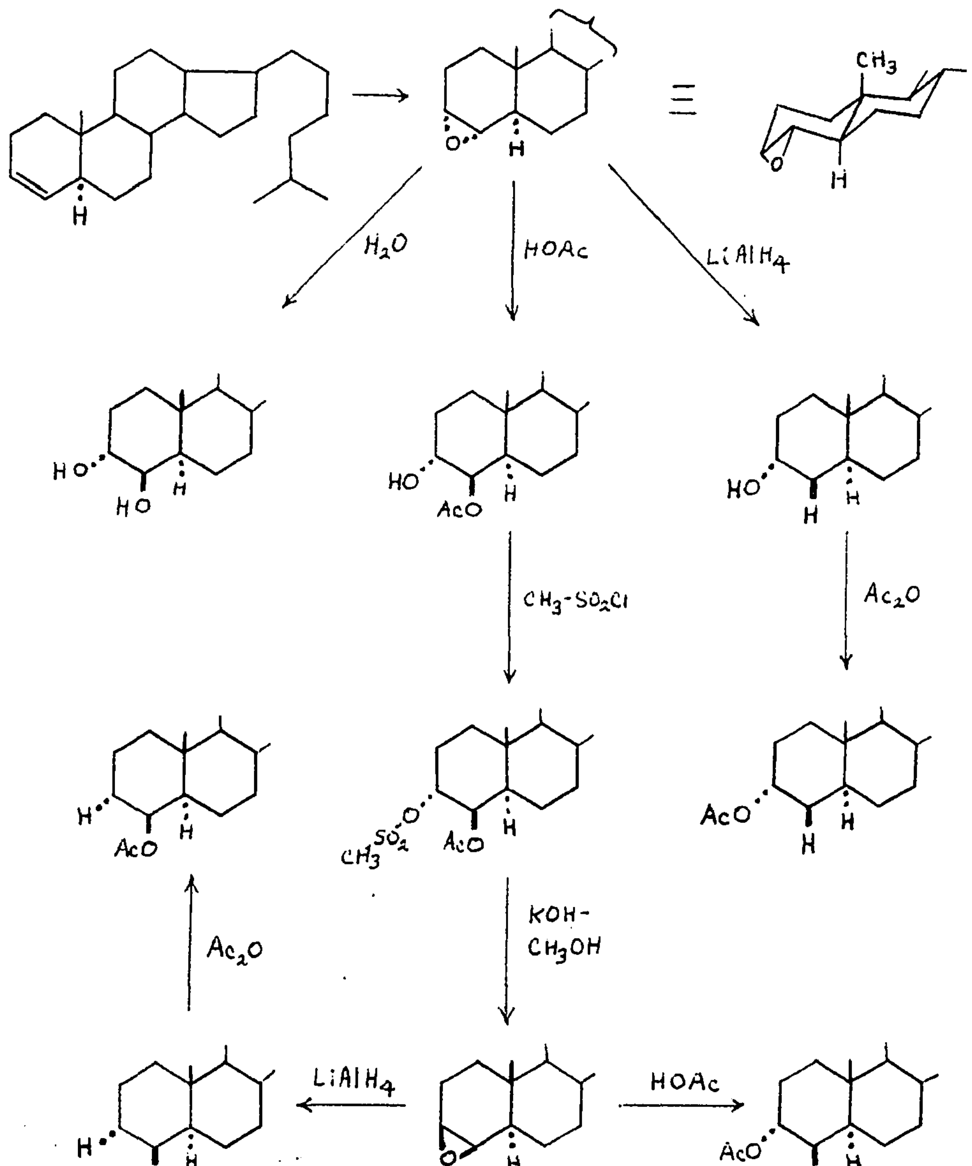


FIGURE 1

RULE OF DIAXIAL OPENING AND CLOSING IN THE 3β,4β-EPOXYCHOLESTANE SYSTEM opening of epoxides affords mainly the diaxial product". The reactions of 3β,4β-epoxycholestane (118) are typical (Figure 1).

It is not immediately obvious why diaxial rather than diequatorial ring opening occurs. Either method would give inversion of configuration at the point of attack. The fact that inversion does occur indicates that the opening proceeds by an SN_2 mechanism. Assuming that the structure of cyclohexene oxide (vide infra) is unchanged when it becomes part of a steroid epoxide, schemes may be written for the action of p-toluenesulfonic acid with 2α-3α-epoxycholestane to give either a diaxial or diequatorial product (Figure 2). "It has been assumed that the stable chair conformation of the cyclohexane ring is partly reestablished in the transition states. The fact that only the diaxial product is obtained must mean that the diaxial transition state is more stable than the diequatorial one. That this is so can probably be attributed to the more nearly linear nature of the partial bonds in the diaxial transition state, and also to the fact that the reagent is in the same plane as the epoxide ring in the diaxial transition state (since partial reestablishment of the chair conformation of the six membered ring must mean that the partial bonds of this transition state have achieved some equatorial character)" (97).

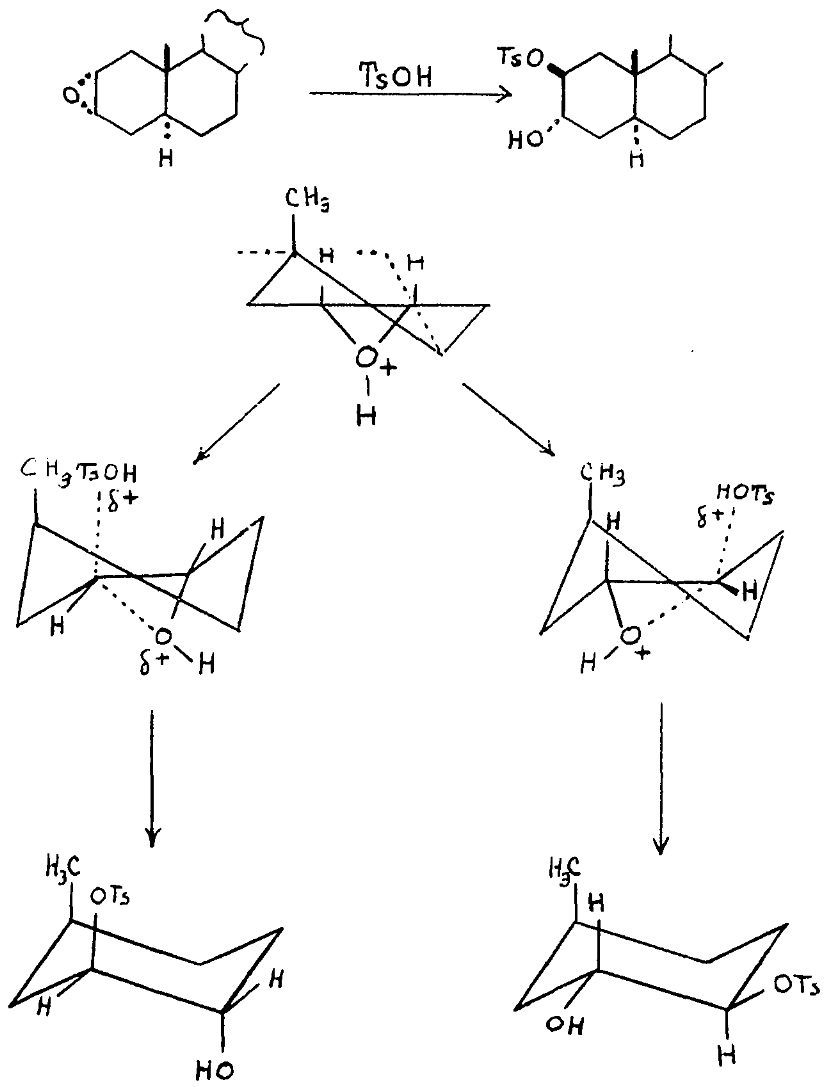
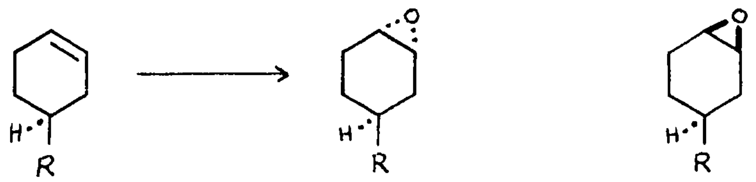


FIGURE 2

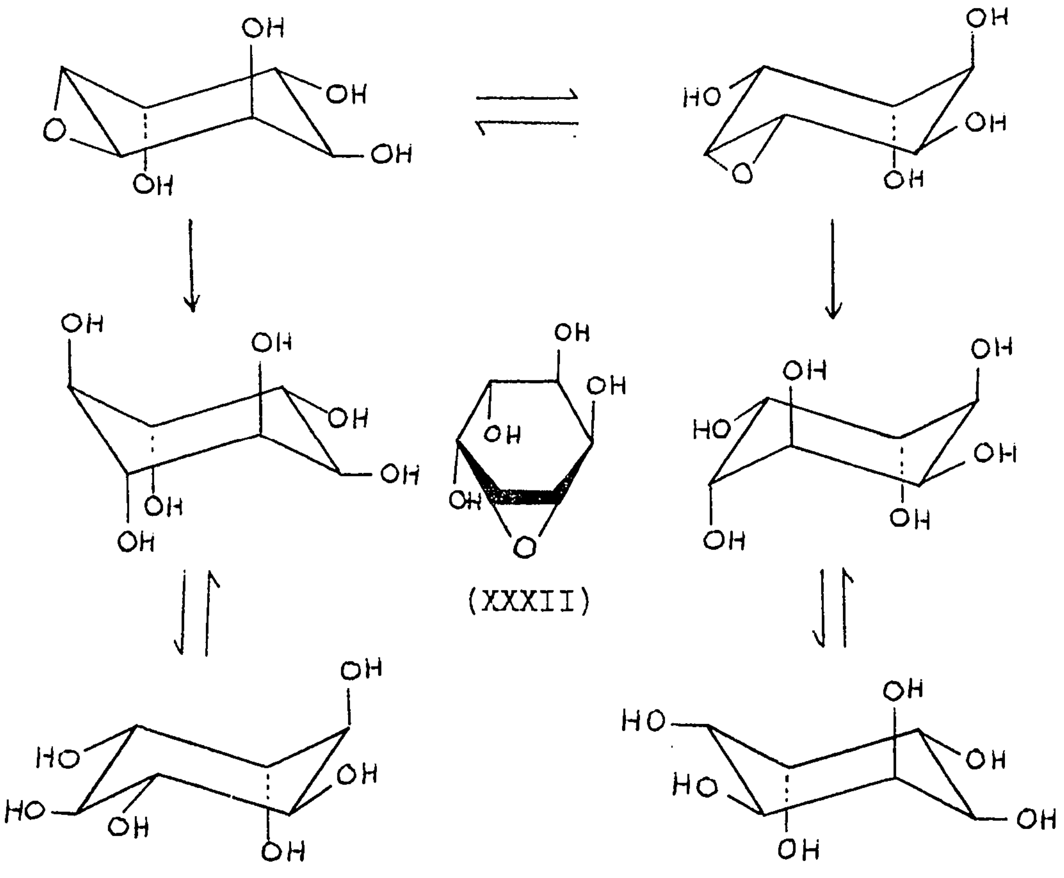
TRANSITION STATES FOR THE OPENING OF THE EPOXIDE RING IN RING A OF 2α-3α-EPOXY-CHOLESTANE

While occasionally diequatorial products are formed, these are exceptional cases which can usually be explained by the presence of factors causing destabilization of the diaxial transition state.

This brings to debate the case of substituted cyclohexene epoxides such as the limonene and carvomenthene oxides. Is the ring opening determined by the conformational influences of the substituents or by the primary steric effect? This problem is complicated by the fact that the epoxides formed by the peracid epoxidation procedures could conceivably be, and often are, mixtures of the two possible epoxides (82,119-121). A further complication arises in a case where the substituted cyclohexene epoxide may interconvert between the two chair conformations. An example of this last complication is the anhydroinositols. 1,2-anhydro<u>allo</u>inositol (XXXII) theoretically may take up either of the two chair conformations and if the Fürst - Plattner rule holds, the two possible products, <u>neo</u>- (XXXIII) and (<u>L</u>)-inositol (XXXIV) should be formed. It was found by Angyal (122,123) that these two products were formed in nearly equal amounts,



indicating interconversion of the conformations. Angyal therefore contended that the apparent exceptions from the Fürst - Plattner rule in monocyclic compounds were not due to "equatorial opening", but to the reaction of the epoxide in its other possible conformation.



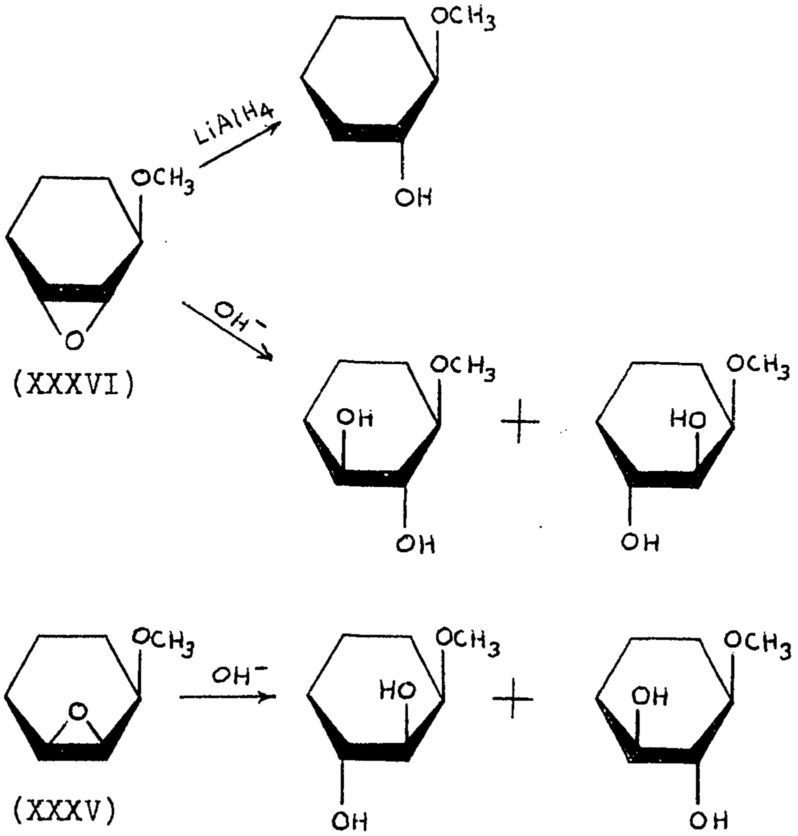
(XXXII)

(XXXIV) (XXXIII)

Angyal warned, however, that predictions about the direction of ring opening might not always be reliable because it would be difficult to presuppose the conformation in which the epoxide would react.

While a number of substituted cyclohexene epoxides have been prepared and their reactions investigated, the stereochemistry of the resultant products was generally ignored (97). However, several notable examples are available.

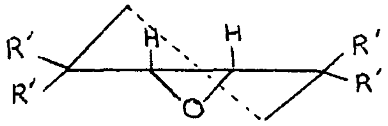
Lemieux, Kullnig and Moir (124) have reported a study of cis- and trans- isomers of 3-methoxy-cyclohexene oxide, (XXXV) and (XXXVI) respectively.



(XXXVI)

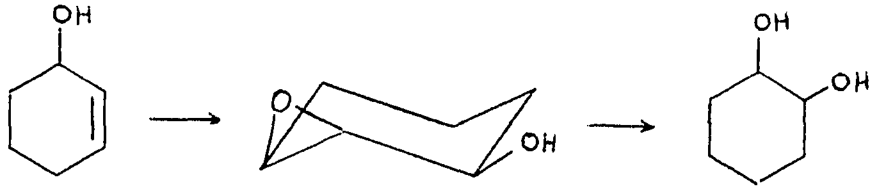
(XXXV)

From the reported results it was apparent that, at least in the case of the trans- isomer (XXXVI), conventional conformational effects played a negligible role. However, this was a system in which the methoxyl substituent, being relatively small, was quite likely affected to an extent by being alpha to the epoxide ring, and vice - versa. The epoxide ring tends to "flatten out" the cyclohexane ring in the same way as an olefinic linkage, causing the ring to occupy a "half - chair" conformation (125).

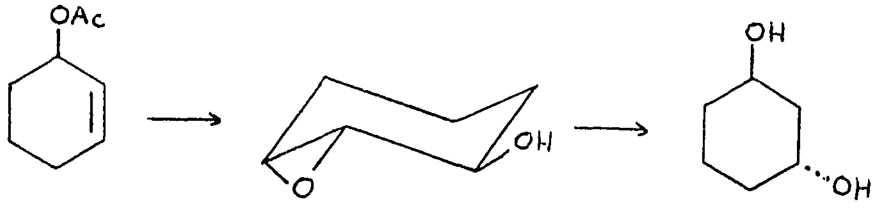


Therefore, the substituents on the carbons alpha to an olefinic or epoxy linkage are imperfectly staggered and do not occupy the normal equàtorial and axial positions; these substituents are said to be "quasiequàtorial" or "quasiaxial". While substituents in the "quasiequàtorial" position are more stable than those in the "quasiaxial" position (115) they do not contribute as much to the conformational stability as do substituents further removed. It is quite feasible that this and the relatively small size of the substituent allows the electronic effect of the electronegative methoxyl group to dominate the orientation of the ring opening. In the case of the cis- isomer (XXXV), the conformational and electronic effects compliment each other.

In the case of the lithium aluminum hydride ($LiAlH_4$) reduction of the cis- (XXXVII) and trans- (XXXVIII) epoxides of 3-hydroxy-cyclohexene, conformational factors appear to play the decisive role (126,127). The formation of the epoxide by peracid epoxidation of 3-hydroxy-cyclohexene gave the cis- epoxide. Reduction with lithium aluminum hydride proceeded by diaxial opening, the conformation being "fixed" by the hydroxyl group.

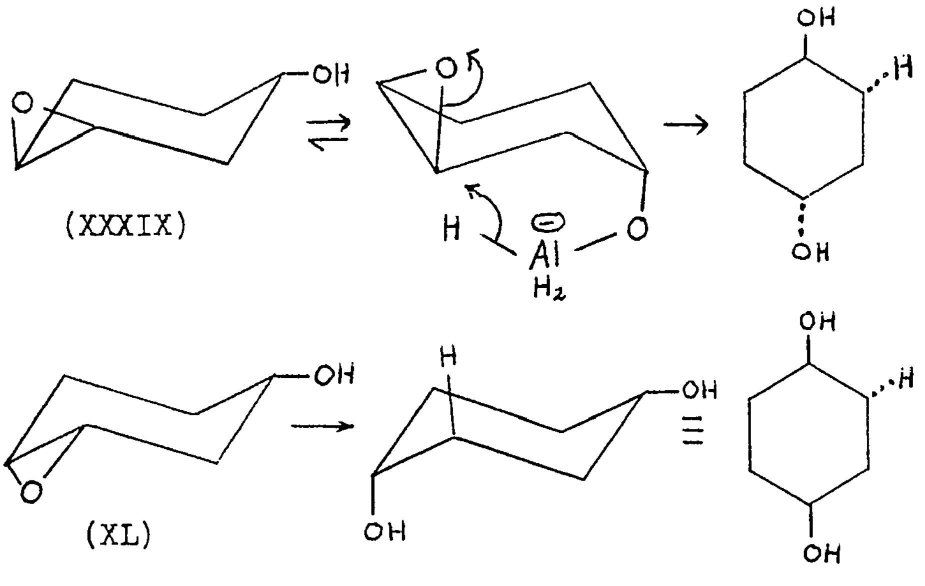


(XXXVII)



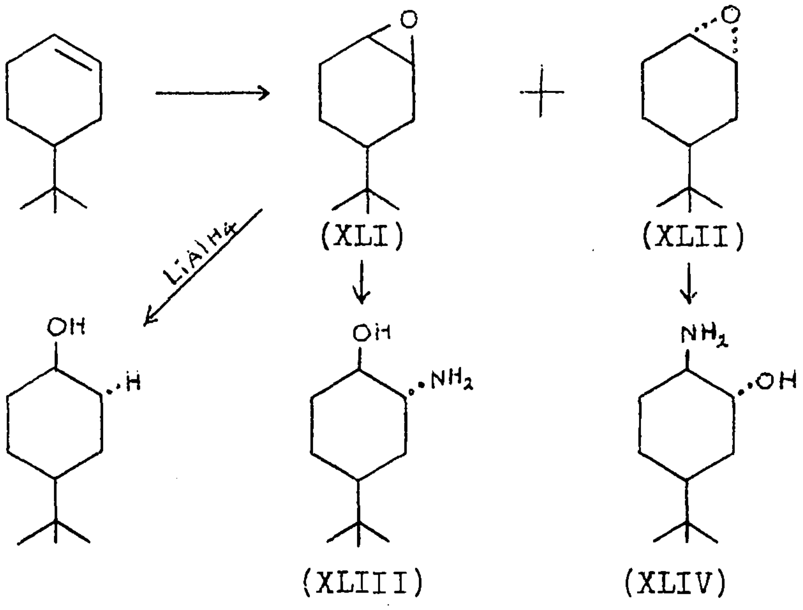
(XXXVIII)

The allylic acetate gave predominately the trans- epoxide which was converted to the epoxy alcohol (XXXVIII) and reduced as before. Again conformational effects determined the product. The ability of the "small" hydroxyl group to anchor the conformation may well be due to the complex which the hydroxyl can form with the aluminum hydride. Such a complex can also lead, in some cases, to anomalous results. A case in point was the reduction of the trans- epoxide of 4-hydroxy-cyclohexene (XXXIX) which proceeded with intramolecular assistance. Conformational effects determined the product of the cis- epoxide (XL).



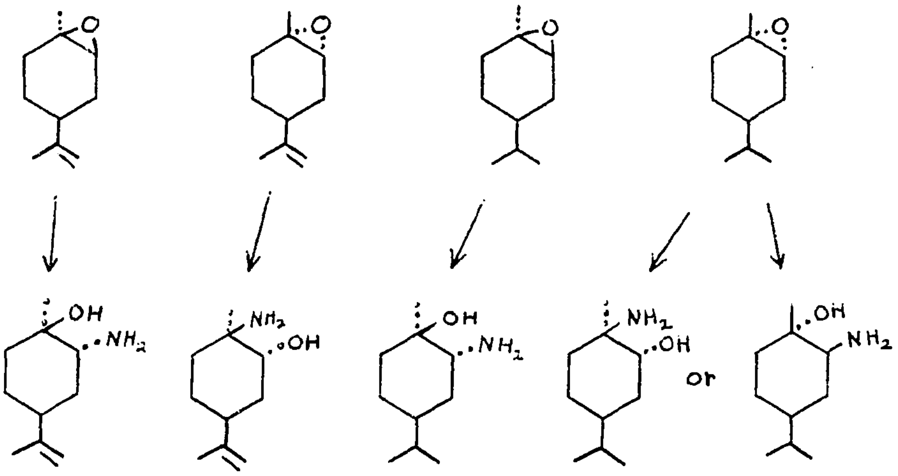
Recently the epoxidation of 4-t-butyl-cyclohexene with perbenzoic acid has been reported to yield a mixture of the cis- (XLI) and trans- (XLII) epoxides (128). When heated with ammonia, a mixture of amino alcohols was obtained. The infrared spectrum of the product contained only a single peak in the hydroxyl stretching region, at

3626 cm^{-1} , corresponding to a free (axial) hydroxyl group (129,130). This proved the absence of any but the diaxial isomers, (XLIII) and (XLIV), showing that attack had taken place stereospecifically, in the sense of the rule of diaxial opening. The 2-amino-4-*t*-butyl-cyclohexanol was



separated by derivitization and regenerated. Conversion to the pure *cis*- epoxide was accomplished by pyrolysis of the quaternary trimethyl ammonium base. Reduction of the pure *cis*- epoxide with lithium aluminum hydride gave the *cis*-4-*t*-butylcyclohexanol, expected on the basis of conformational analysis.

The reaction of limonene monoxide, $[\alpha]_D +65^\circ$, with ammonia was reported by Pigulevski and Kohkryakov (81) to give a hydroxy amino derivative which was tentatively assigned the structure of 2-amino-1-hydroxy-8-p-menthene. However, since limonene oxide, prepared from peracid epoxidation, has been found to be a mixture of the two possible isomers, it is almost a certainty that this was a mixture of the two amino alcohols, (XLV) and (XLVI).



(XLV) (XLVI) (XLVIII) (XLIX) (XLVII)

Evidence for the formation of two amino alcohols has been furnished by Newhall (91) who found that the action of ammonia (or amines) on a mixture of cis- and trans-carvomenthene oxide gave a mixture of trans- amino alcohols. The configuration of the trans-2-amino-1-hydroxy-p-menthane (1-hydroxy-neocarvomenthylamine) (XLVII) was established by an independent synthesis. The structure of the second amino alcohol was assigned as (XLVIII) on the assumption that the epoxide ring cleavage proceeded exclusively in one direction (primary steric effect). However, trans-1-amino-

2-hydroxy-p-menthane (1-amino-neocarvomenthol) (XLIX) would be the expected product if conformational requirements were the determining factor. The basis of Newhall's assumption was a preliminary report (131) that the cleavage of the carvomenthene oxides by ethyl alcohol with a basic catalyst yielded exclusively 2-ethoxy-1-hydroxy-p-menthane. It has since been shown (132,133) that the action of ethyl alcohol - sodium ethoxide on the limonene monoxides gives both 2-ethoxy-1-hydroxy-, and the 1-ethoxy-2-hydroxy-8-p-menthene. Acetylation and pyrolysis of the corresponding acetate mixture confirmed the position assignments. Due to the ambiguity of the abstract (132,133) it was impossible to ascertain whether the carvomenthene oxides gave a similar mixture. It is plausible to assume that they did. This being the case, it would appear that conformational effects outweigh any primary steric effects, thus causing diaxial opening of the epoxide ring. Therefore, Newhall's second amino alcohol was more likely (XLIX) than (XLVIII).

That the limonene monoxides open stereospecifically was shown by the elegant work of Pigulevski (135) and of Kuczynski and Piatokowski (82,119) with the lithium aluminum hydride reduction of the two limonene monoxides. More recently the action of sodium powder on the limonene monoxides has been shown to be stereospecific (135). These two reactions have been reinvestigated and will be dealt with further in the discussion.

It was necessary to bring to the fore some of the most recent work on the limonene and carvomenthene oxides, as well as the other epoxides mentioned, in order to become acquainted with the basic concepts which govern the reactions of substituted cyclohexene epoxides.

The initial work on the reactions of limonene monoxide with acidic reagents was carried out by Royals and Harrell (77,78). These workers showed that under acid conditions (e.g., sulfuric acid) limonene monoxide isomerized to dihydrocarvone and carvenone. The treatment of limonene monoxide with glacial acetic acid - sodium acetate led to the formation of the monoacetate of 8-p-menthene-1,2-diol in 82% yield. That this product contained at least some of the 2-acetoxy-1-hydroxy-8-p-menthene was shown by boric acid dehydration to give carveyl acetate, along with p-cymene and dihydrocarvone. Dehydration of the monoacetate with p-toluenesulfonic acid monohydrate in benzene gave only carvenone and p-cymene. Limonene oxide gave 36% dihydrocarvone when refluxed in benzene with freshly fused zinc chloride. By passing limonene monoxide over alumina at 310-325° a mixture of dihydrocarvone and carvenone was obtained. An attempted heat isomerization yielded no isolable product other than unreacted limonene monoxide at

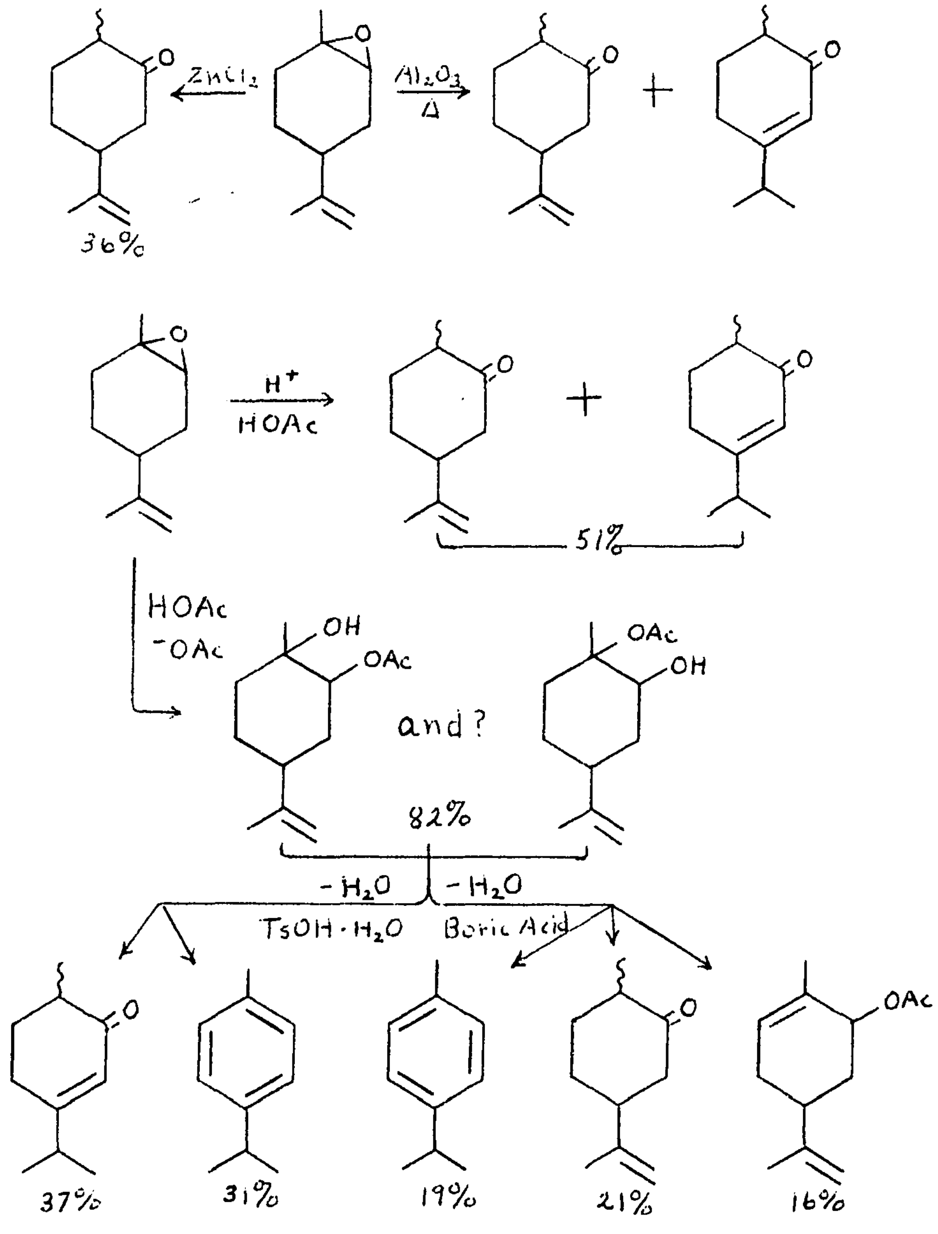
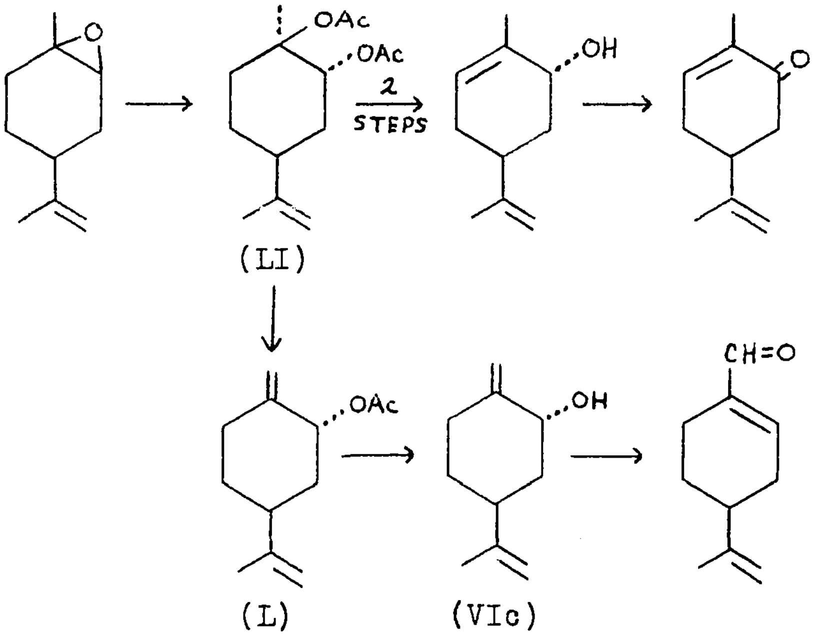


FIGURE 3

REACTIONS OF LIMONENE MONOXIDE (ROYALS AND HARRELL)

415-430°.

Linder and Greenspan (86) were able to effect the synthesis of carvone from limonene monoxide in an overall yield of 7% by the method outlined below:



The carvone obtained was off odor. This was undoubtedly due to the fact that not only carveyl acetate but also *iso*carveyl acetate (L) (136) would be expected from the pyrolysis of 1,2-diacetoxy-8-*p*-menthene (LI). On hydrolysis *iso*carveol (VIc) would also be present along with carveol, and under the oxidation procedure described the *iso*carveol would yield perillyl aldehyde (87) as the contaminant in the carvone. This would explain the off odor.

Nearly simultaneously, Kergomard and Geniex (83) reported the preparation and pyrolysis of the diacetate. The reported products were dihydrocarvone and cis-carveyl acetate. An elaborate explanation was offered to explain the epimerization of the expected axial acetete (trans-carveyl acetate) to the equatorial acetate (cis-carveyl acetate). It appears, however, that they were confused in their discussion, since in the experimental section they proved that the product obtained was the trans-carveyl acetate (by way of the dinitrobenzoate of the carveol).

Kergomard and Geniex (86) have also reported the treatment of limonene monoxide with alumina under slightly different conditions than those described by Royals and Harrell (78). They obtained dihydrocarvone, carveol and polymer; from carvomenthene oxide, carvomenthone and carvotanacetol were obtained.

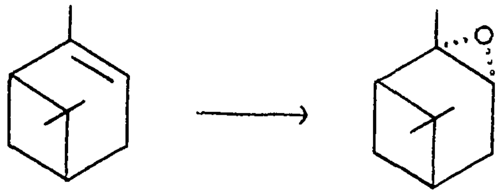
Booth (137) has recently reported the pyrolysis of limonene monoxide in the temperature range 200-550°. For example; d-limonene monoxide pyrolyzed at 260-265° for 35 hours. The pyrolysis product was fractionally distilled to yield 5-7% dihydrocarvone, 3-5% l-carvone, 2-4% l-carveol and 11-13% d-cis-isocarveol.

The catalytic hydrogenation of limonene monoxide is reported to initially give carvomenthene oxide (83,131).

Furakawa (138) found that a carvomenthol was formed with absorbtion of two moles of hydrogen to one mole of limonene oxide. Kergomard and Geniex (139,140) have reported the carvomenthol to be nearly all *iso*carvomenthol. However the sample obtained was impure and no alcohol derivatives were formed. They reported the oxidation product to be *iso*carvomenthone. An explanation was offered to rationalize the exclusive formation of *iso*carvomenthol. This explanation cannot be considered valid since it (a) assumes that limonene monoxide is one isomer and (b) assumes the incorrect structures for *iso*- and *neoiso*carvomenthol. Pigulevski and Kozhim (90) hydrogenated carvomenthene oxide using palladium hydroxide in acetic acid. They recovered a complex mixture which contained *d*-*neo*carvomenthol, *l*-carvomenthol, *p*-menthan-1-ol, *trans*-*p*-menthane, *d*-carvomenthone and *d*-*iso*carvomenthone as well as the high boiling monoacetate of *p*-menthane-1,2-diol. It was shown that the action of the palladium hydroxide in acetic acid caused the isomerization to carvomenthone. The hydroxyacetate was formed by the addition of acetic acid to the epoxide.

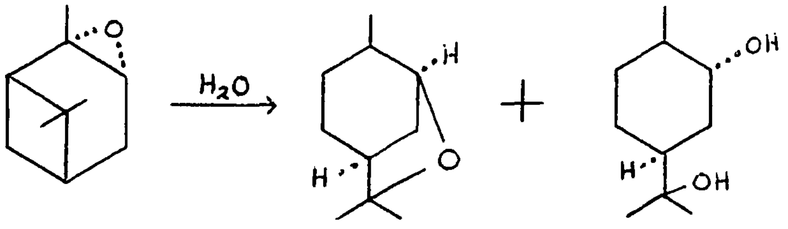
The synthesis of 1-acetyl-4-*iso*propyl-1-cyclopentene from limonene monoxide has constituted a proof of structure (141) of the natural ketone obtained from *Spanish Eucalyptus Globulus* (142).

The oxidation of α-pinene has been thoroughly reviewed by Simonsen and Owen (15) through 1947. Several outstanding contributions have been made since this review, notably the work of the Glidden group on the autoxidation of α-pinene (27) and that of Whitman (46) on the mechanism of the lead tetraacetate oxidation of α-pinene.



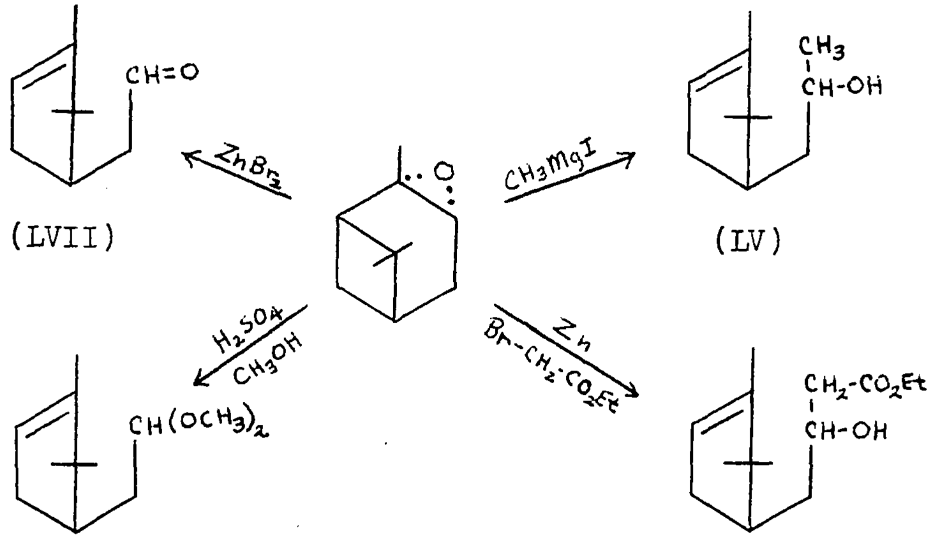
(LII)

The epoxidation of α-pinene, first done by Prileschaev (75), have been investigated by a number of workers (77,78,139,143-145). The stereochemical course of the epoxidation of α-pinene with peracids undoubtedly gives only <u>cis</u>-α-pinene oxide (LII), as has been observed in the analogous pinol system (147), because of steric hindrance.



(LIII) (LIV)

Nametkin and Jaceva (147) postulated that the primary hydration product was pinol, since when α-pinene oxide was heated with water at 115-120°, pinol (LIII) was obtained along with sobrerol (LIV). This may or may not be the case. Hydration with dilute acid yielded _trans_-sobrerol in nearly quantitative yields (143,144,148). Likewise, _trans_-sobrerol was formed in basic aqueous media (149).



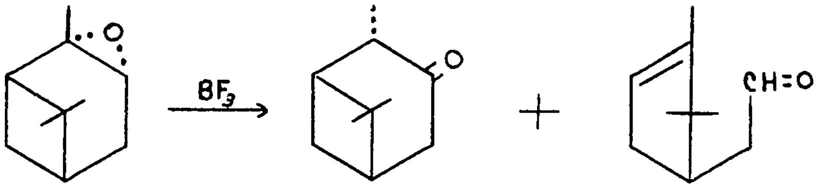
(LVII) (LV)

(LVIII) (LVI)

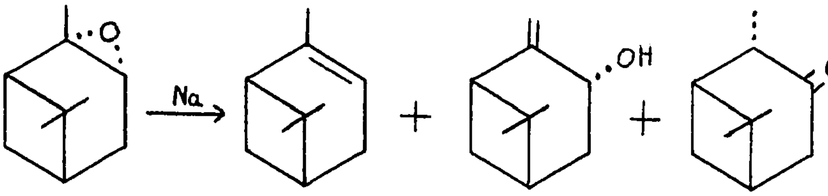
α-pinene oxide gave a substituted campholenol (LV) with Grignard reagents (150,151) and in the Reformatsky reaction (LVI) (152). Similarly α-pinene oxide was isomerized to campholenic aldehyde (LVII) by zinc bromide (152,153) and to the dimethyl acetal (LVIII) by a sulfuric acid - methanol solution (154). Arbuzow and Mikhailow (144) have reported the formation of a glycol monoacetate on treatment of α-pinene with peracetic acid in chloroform, and that a similar product was obtained by the treatment of α-pinene oxide with acetic acid. Royals and Harrell (78) found that with glacial acetic acid, α-pinene oxide was principally isomerized to campholenic aldehyde. A high boiling, crude hydroxyacetate was also a product of this reaction. α-pinene oxide when refluxed with acetic anhydride has been found to give campholenic aldehyde, sobrerol diacetate, <u>trans</u>-carveyl acetate and several other unidentified compounds (155,156).

The pyrolysis of α-pinene oxide has been reported to give pinocamphone (LIX) and carveol (157).

Recently McCullagh (158) has shown that <u>trans</u>-pinocamphone and campholenic aldehyde were the products of the



(LIX)

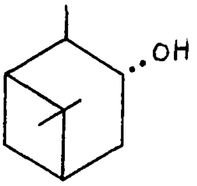


(LX)

boron trifluoride - etherate isomerization of α-pinene oxide in benzene.

Powdered sodium in benzene gave mainly α-pinene with some trans-pinocarveol (LX) and trans-pinocamphone (159).

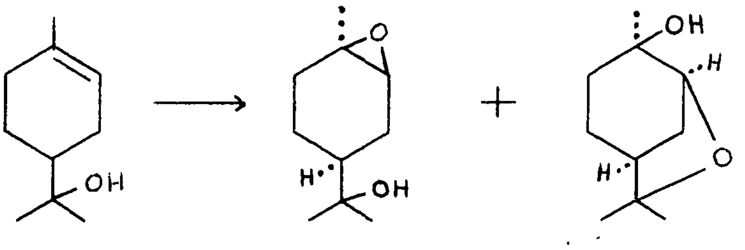
The hydrogenation of α-pinene oxide with Raney nickel catalyst has been investigated by Isaeva and Arbuzow (160) and Kergomard and Geniex (139). The main product of the reduction was isopinocampheol (LXI) (139), although a second alcohol and some pinocamphone (160) were detected. Kergomard and Geniex postulated alcoholic epimerization to explain the stereochemistry of the isopinocampheol obtained. This postulation was not necessary since Bose's assignments for iso- and neoisopinocampheol were incorrect (161) by his own admission (162).



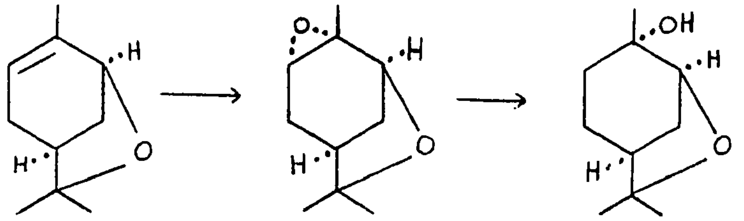
(LXI)

6-OXA-BICYCLO-[3,2,1]-OCT-3-ENES

The preparation of substituted 6-oxa-bicyclo-[3.2.1]-oct-3-enes has been limited for nearly 75 years to that of pinol (11), although a mention was made of homopinol by Wallach (163). The literature on pinol has been thoroughly reviewed by this author in a previous work (11). It is pertinent, however, to mention at this point the work of Piatkowski and Kuczynski (164,165) with regard to their studies of the stereochemical course of epoxidations. It was found that the epoxidation of α-terpineol yielded two products, trans-1,2-epoxy-p-menthan-8-ol (LXII) and trans-1-hydroxy-dihydropinol (LXIII) (164).



(LXII) (LXIII)



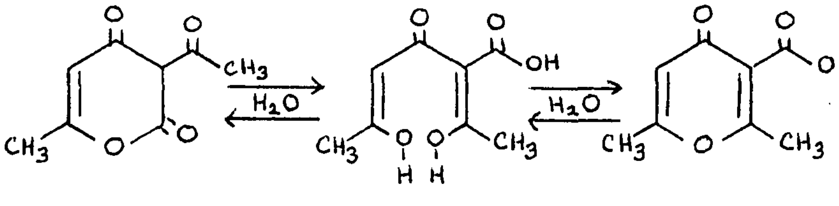
(LXIV) (LXV)

The epoxidation of pinol yielded only cis-1,2-epoxy-dihydropinol (LXIV) (147). Lithium aluminum hydride reduction of this epoxide gave cis-1-hydroxy-dihydropinol (LXV).

DEHYDROACETIC ACID

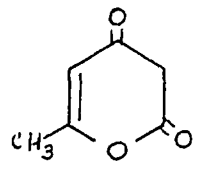
Dehydroacetic acid may be formed by the action of dehydrating agents on acetoacetic ester or by acetic anhydride on acetone dicarboxylic acid. It has been converted into a large variety of compounds such as diacetylacetone, pyridines, etc. Besides its interesting chemistry the sodium salt has found wide use as a food additive.

The structure of dehydroacetic acid was demonstrated by the observation that isomerization to 2,6-dimethyl-4-pyrone-3-carboxylic acid (LXVI) with hot, 85% sulfuric acid was easily explained in terms of the Feist (165,166) structure (LXVII).

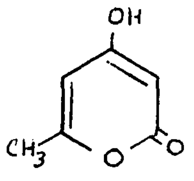


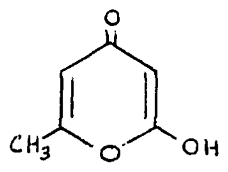
(LXVII) (LXVI)

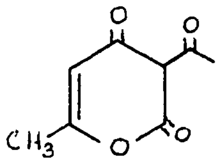
A recent reexamination of structure (LXVII) by Berson (167) has confirmed the structure of the carbon skeleton of dehydroacetic acid as formulated. The striking similarity of the ultraviolet absorbtion spectra of dehydroacetic acid and its ethyl ester (enol ether) provided compelling evidence that dehydroacetic acid was completely enolized in solution. The bathochromic shifts of the maxima in the spectra of dehydroacetic acid (λmax 310 mμ) and the dehydroacetate ion, relative to the maxima for triacetic lactone (LXVIII) (λmax 283 mμ) and the triacetic lactonate ion (λmax 278 mμ), are consistent with that expected for the addition of the chromophorically active acetyl group in the enol variants of the Feist structure (LXVII).



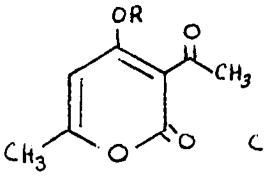
(LXVIII)



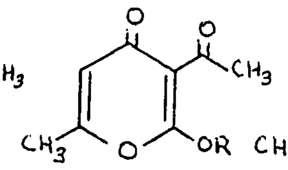




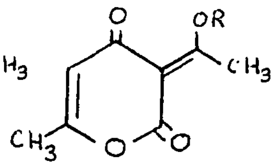
(LXVII)



(LXVIIa)



(LXVIIb)



(LXVIIc)

It was noted that the maximal absorbtion for the dehydroacetate and triacetic lactonate ions occurred at shorter wave lengths than for the corresponding un-ionized acids. This was in contrast to the observed bathochromic effect of ionization of simple β-dicarbonyl systems (168). On the basis of the absorbtion data, Berson indicated that the conversion of dehydroacetic acid to its ethyl ester occurred with a minimal structural change, i.e., with simple replacement of the hydrogen with an ethyl group. The observations that the ester did not consume alkali upon titration, nor give a positive ferric chloride test, and exhibited no change in its ultraviolet spectral characteristics led Berson to favor the enol variants (LXVIIb) and (LXVIIc) on the basis that (LXVIIa) might concievably show acidic properties since the methyl group would be conjugated with both the lactone and the side chain carbonyl groups. A choice between the three enols was not made, however, because of a lack of further evidence.

CHAPTER III

DISCUSSION OF RESULTS

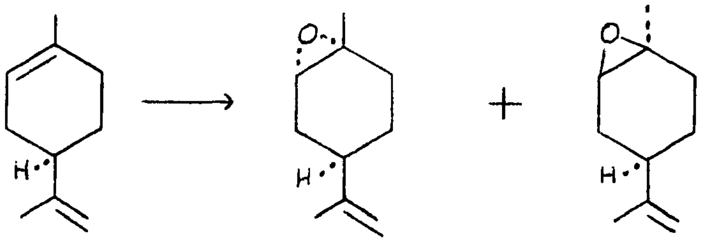
Limonene monoxide, carvomenthene oxide and α-pinene oxide are compounds which offer great promise as intermediates in the synthesis of other oxygenated terpenes. Both limonene monoxide and α-pinene oxide are available commercially or they may be conveniently prepared in the laboratory. Carvomenthene oxide is easily prepared by the partial hydrogenation of limonene monoxide.

These epoxides offered the opportunity to study the ring opening of unsymmetrical epoxides situated on substituted cyclohexane rings. This situation afforded a severe test for the Fürst-Plattner rule in the case of monocyclic systems. Secondly, while many of the reactions investigated have previously been reported, the identification of some of the reaction products, and in particular the stereochemistry of the products, has been lacking. It has been the attempt of this research to fill these gaps.

LIMONENE MONOXIDE AND CARVOMENTHENE OXIDE

A commercial grade of d-limonene monoxide was purified by fractional distillation to remove the d-limonene impurity. As the d-limonene obtained had an $[\alpha]_D$+110° (or better), the d-limonene monoxide prepared from it was considered to be nearly optically pure. The fraction, b.p. 92-94°/20 mm., α_D^{25}+59.20°, n_D^{25} 1.4654, was pure d-limonene monoxide as indicated by gas - liquid phase chromatography (GLPC).

The limonene monoxide* prepared by peracid epoxidation procedures, as was that above, has been shown to be a mixture of the cis- (VIIIa) and trans- (VIIIb) isomers by Kuczyński and Piatkowski (82,119). Therefore, the d-limonene monoxide was fractionally distilled at atmospheric pressure (under nitrogen) in an attempt to separate the two isomers. Since both isomers showed as a single peak on GLPC, the distillation was followed by the observed optical rotation and refractive index of each cut. The fraction, b.p. 197°, α_D^{25}+50.80°, n_D^{25} 1.4640 (cut #10) and b.p. 198°,



(VIIIa) (VIIIb)

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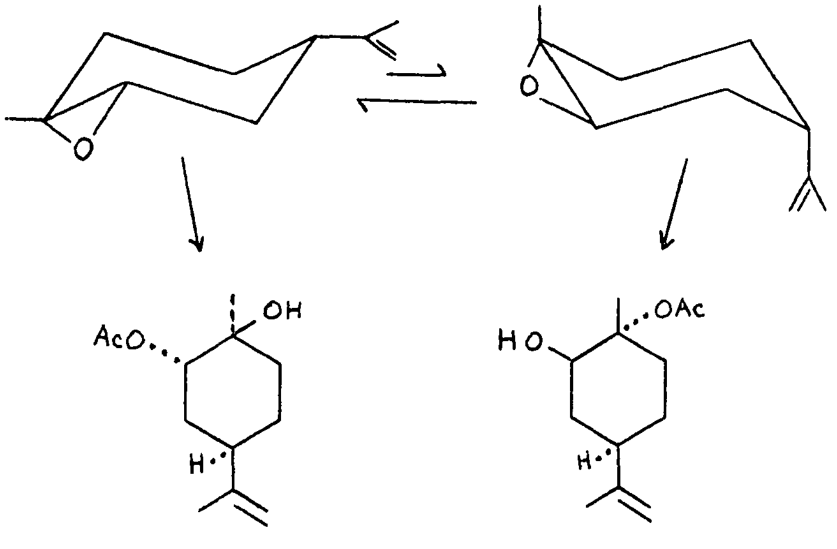
*The absolute configurations of the terpenes are illustrated throughout the discussion on the basis of their relationship to d-limonene, whose absolute configuration has been established (169).

$\alpha_D^{25}+75.34^\circ$, n_D^{25} 1.4665 (cut #35), were as near to purity as could be obtained. The cut #35 was essentially pure *d*-*trans*-limonene monoxide. The lower boiling fraction, however, was subsequently shown to be quite impure.

In testing the Fürst-Plattner rule, the reactions of an isomeric mixture of epoxides was considered to be meaningful only if the distinction could be made among the reaction products as to which product(s) came from each of the two isomers. Therefore, it was advantageous to undertake the stereospecific synthesis of pure *cis*- and pure *trans*-limonene monoxide.

The synthesis of *d*-*trans*-limonene monoxide was carried out according to the method of Kuczńyski and Piatkowski (82,119). The first stage of this synthesis afforded the initial evidence that conformational influences direct the opening of the epoxide ring in the limonene monoxides. The mixture of *d*-limonene monoxides, $\alpha_D^{25}+59.20^\circ$, was hydrated with a 1% sulfuric acid - water solution to give a single glycol isomer, *neo*limonene-1,2-diol dihydrate. This glycol dihydrate was recrystallized from chloroform, from which the water of hydration was easily separated. The *neo*limonene-1,2-diol, m.p. 70-71°, $[\alpha]_D^{25}+55^\circ$ (acetone), was then subjected to *p*-toluenesulfonyl chloride in pyridine to form the monotosylate (LXIX) (1-hydroxy-2-tosyl-8-*p*-menthene), $\alpha_D^{24}+51.05^\circ$, n_D^{24} 1.4944. Refluxing the monotosylate in methanolic - potassium hydroxide yielded 92% *d*-*trans*-limonene monoxide, b.p. 78.5-80.5°/10 mm., $\alpha_D^{24}+83.22°$, n_D^{24} 1.4657.

The reaction of *d*-*trans*-limonene monoxide with a glacial acetic acid - sodium acetate solution gave a mixture of hydroxyacetates. The hydroxyacetate mixture was indirectly identified by GLPC to be a 9 : 1 ratio of two isomers. These isomers were subsequently shown to be 90% of a *trans*-2-acetoxy-1-hydroxy-8-*p*-menthene (1-hydroxy-*neo*dihydrocarveyl acetate) (LXX) and 10% of a *trans*-1-acetoxy-2-hydroxy-8-*p*-menthene (1-acetoxy-*neoiso*dihydrocarveol) (LXXI), by analysis of the pyrolysis products. The two isomers arise from the two possible conformations that *trans*-limonene monoxide can assume in the transition state during the oxirane opening and provides confirmation



(LXX) (LXXI)

that the Furst-Plattner rule holds for trans-limonene monoxide. The suggestion of Angyal (122) explains the formation of the small amount of tertiary acetate formed, in that the formation of the diequatorial product arose from an initial diaxial oxirane ring opening with subsequent inversion of the less stable conformation to the more stable. That the conformation with the methyl and isopropenyl group equatorial afforded the more stable conformation in the transition state was indicated by the very high percentage of 1-hydroxy-neodihydrocarveyl acetate obtained.

The preparation of d-cis-limonene monoxide (VIIIa) gave somewhat more difficulty. Several attempts to prepare the tosylate of 1-hydroxy-neodihydrocarveyl acetate failed. Methane sulfonyl chloride in pyridine, however, converted this hydroxyacetate into impure 1-mesyl-neodihydrocarveyl acetate (LXXII). The impure mesylate was then refluxed with methanolic - potassium hydroxide. Four products were obtained; d-neolimonene-1,2-diol (18%), trans-carveol and trans-isocarveol (38%) and d-cis-limonene monoxide (29%). The d-neolimonene-1,2-diol was formed from hydrolysis of unreacted 1-hydroxy-neodihydrocarveyl acetate present in the mesylate as an impurity. The observed carveols were not unexpected by-products of the reaction since the action of strong bases often causes elimination reactions of

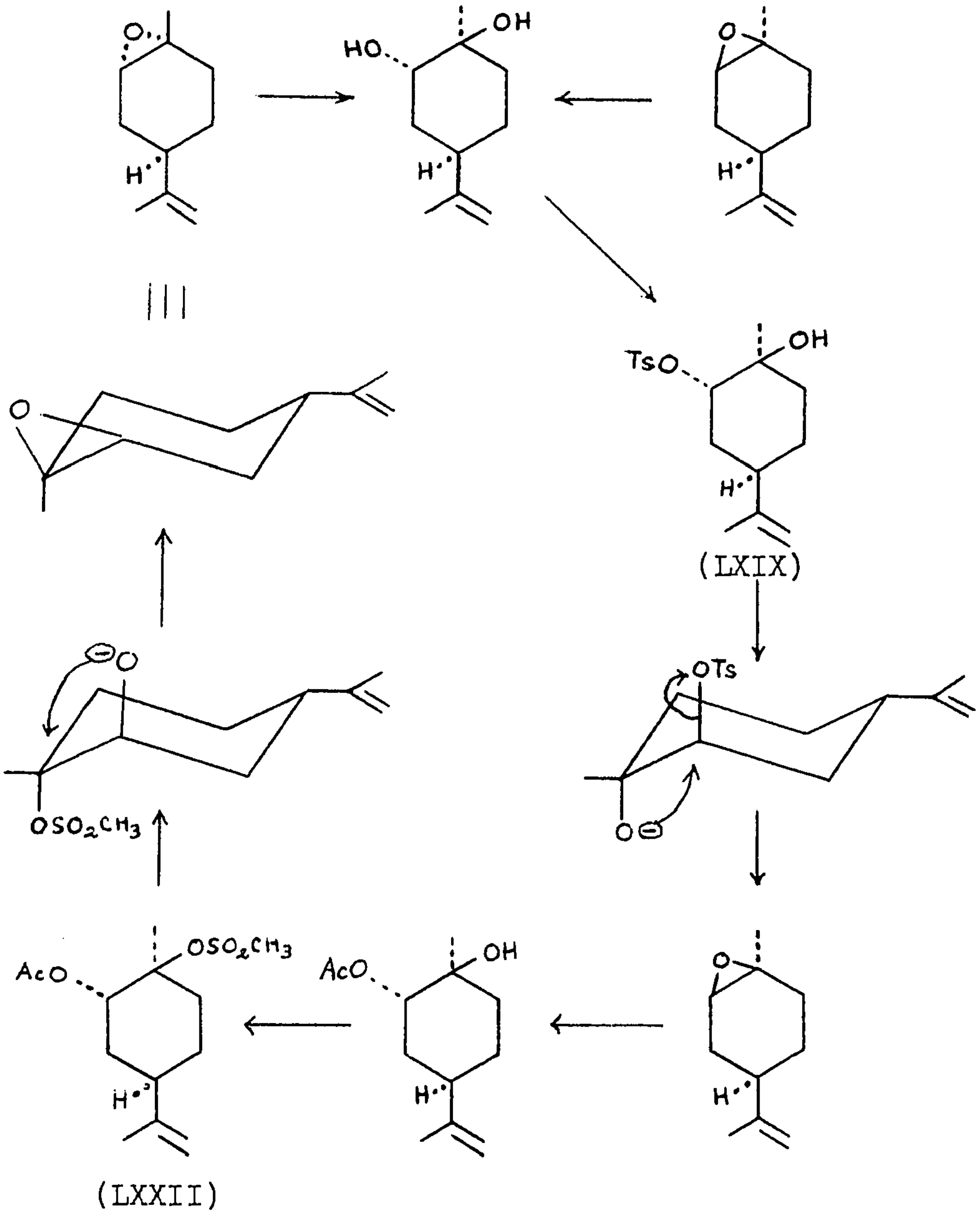


FIGURE 4

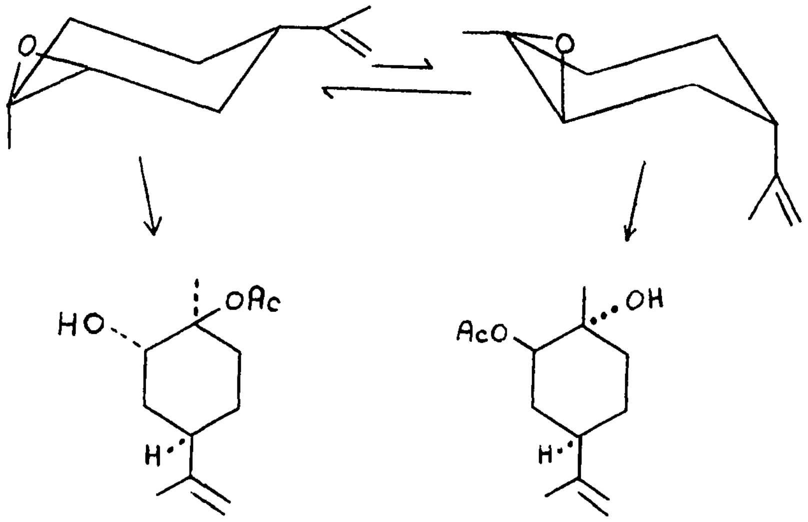
PREPARATION OF CIS- AND TRANS-LIMONENE MONOXIDES mesylates and tosylates to occur. Since such eliminations are generally "trans", no dihydrocarvone was formed. The reaction of interest was the formation of *d*-*cis*-limonene monoxide which had b.p. 96-98°/26 mm., $\alpha_D^{23.5}$ +36.00°, $n_D^{23.5}$ 1.4683.

In the formation of the *trans*- epoxide, the anion of the alpha, *trans* hydroxyl group displaced the neighboring tosylate group to form the oxirane ring. The same process occurred for the formation of the *cis*- epoxide, but in this case acetate hydrolysis and anion formation had to occur prior to the epoxide closing. That such a two stage reaction must occur undoubtedly enhanced the predominant formation of the carveols.

The hydration of the *d*-*cis*-limonene monoxide to *d*-*neo*-limonene-1,2-diol completed the cycle (Figure 4). Conversions of one isomeric epoxide into another, as was illustrated by this cycle, have been done previously in the steroid series (118) and more recently in a monocyclic system (170).

The reaction of *d*-*cis*-limonene monoxide with a glacial acetic acid - sodium acetate solution appeared to give *trans*-1-acetoxy-2-hydroxy-8-*p*-menthene (1-acetoxy-*neo*dihydrocarveol) (LXXIII) in at least 95% purity. This was one of the most dramatic cases of conformational effects determining the direction of the epoxide opening. If the primary steric effect were the determining factor, the expected product would have been a *trans*-2-acetoxy-1-hydroxy-8-*p*-menthene (specifically 1-hydroxy-*neoiso*dihydrocarveyl acetate) (LXXIV). None of this isomer was found. This isomer could have also formed from the transition conformations in which the isopropenyl group would be axail. This conformation was the least thermodynamically stable one and therefore it was not too surprising that none (or little) of the product arising from this conformation was formed.

Since the epoxides appeared to open stereospecifically there was little question as to the stereochemistry of the products. That the stereochemical assignments for the hydroxyacetates obtained from the limonene monoxides were



(LXXIII) (LXXIV)

correct was born out by the observed stereochemistry of the pyrolysis products of these compounds.

The analysis of a sample of d-limonene monoxide for the percentage of each isomer was now possible by polarimetry. Having assumed the density differences to be negligible in this calculation, the percentages were found from the equation:

$$(x)\ 36.0 + (y)\ 83.2 = \text{observed optical rotation}$$

$$100x = \%\ \underline{d}\text{-}\underline{cis}\text{-limonene monoxide, } \alpha_D^{24} + 36.0^\circ$$

$$100y = \%\ \underline{d}\text{-}\underline{trans}\text{-limonene monoxide, } \alpha_D^{24} + 83.2^\circ$$

The commercial sample obtained from peracid epoxidation, $\alpha_D^{25}+59.2^\circ$, was thus a mixture of 50.5% cis- and 49.5% trans-limonene monoxide. A second physical method was initially employed for analysis which would be satisfactory for racemic or partially racemic samples, also. Observations of the nuclear magnetic resonance spectrum of the neat liquid of the limonene monoxide mixture showed a ratio of 50.5 : 49.5 of the single methyl peaks of the two isomers at -70 cps (-1.16 ppm) from TMS (internal standard). The ratio was obtained by measurement of the area under the methyl peaks.

A slightly less exact method of analysis involved reacting the epoxide mixture with glacial acetic acid - sodium acetate to form the hydroxyacetates. The hydroxyacetate mixture thus obtained was hydrogenated and the resultant saturated hydroxyacetate mixture subjected to GLPC. The ratio of the hydroxyacetates from the two isomers was 52 : 48.

The hydroxyacetate mixture obtained from peracid d-limonene monoxide was subjected to vapor phase pyrolysis at varying temperatures. These results are tabulated in Table I. It was found that between 370° and 396°, under the prescribed conditions, preferential pyrolysis of the trans-1-acetoxy-2-hydroxy-8-p-menthenes occurred and the trans-2-acetoxy-1-hydroxy-8-p-menthene was recovered unchanged. The unchanged hydroxyacetate was easily separated from the neutralized pryolysate by distillation. The pyrolysate contained at least five components as indicated by GLPC. Fractional distillation yielded the first two components, isodihydrocarvone and dihydrocarvone (XXXI), as one, b.p. 85-87°/8 mm., α_D^{25}+21.80°, n_D^{25} 1.4714, although it was possible to see the two isomers on GLPC. These were identified by preparation of the 2,4-dinitrophenylhydrazone, m.p. 147-149°, and the semicarbazone, m.p. 189°. The infrared spectrum was identical to that of an authentic sample.

The third component, b.p. 102°/10 mm., α_D^{25}+82.00°, $n_D^{25.5}$ 1.4925 gave a 3,5-dinitrobenzoate, m.p. 69-69.5°. The physical constants of this alcohol and its derivatives in-

TABLE I

RATIO OF PYROLYSIS PRODUCTS OF TRANS-1-ACETOXY-2-HYDROXY-8-p-MENTHENES

Temperature	Dihydrocarvone[a]	Trans-iso-carveol	Trans-carveol	Cis-carveol
342° [b]	-	-	-	-
370°	16.7%	40.7%	38.8%	3.8%
396°	20.4%	41.4%	35.2%	3.0%
436° [c]	26.6%	35.7%	34.6%	3.1%
450° [d]	26.8%	22.1%	16.7%	2.4%

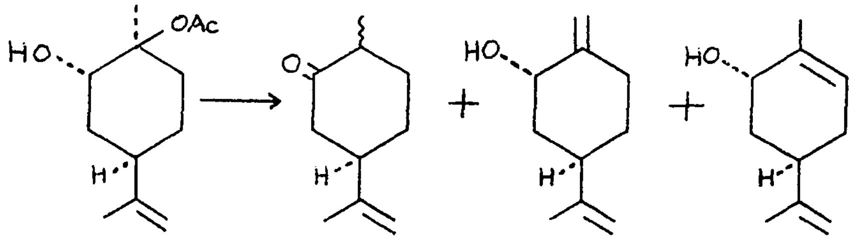
[a] This value is the combined total of dihydrocarvone and isodihydrocarvone.

[b] Negligible pyrolysis occurred.

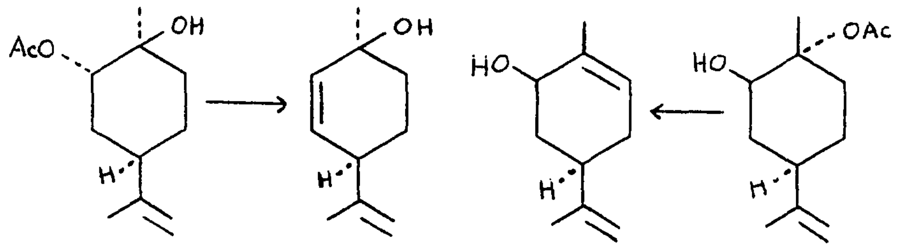
[c] Neglecting pyrolysis of 2-acetoxy-1-hydroxy-8-p-menthene.

[d] 31% of mixed hydrocarbons and other low boiling decomposition products present.

dicated that it was the same as the *cis*-1(7)8,-*p*-menthadien-2-ol isolated by Naves and Grampoloff (87) from the essential oils of *Cymbopogon densiflorus*. This was further



(XXXI) (VIc) (VIb)



(Xa) (VIa)

confirmed by the infrared spectrum which was identical to that reported. The assignment of this alcohol, hereafter referred to as an *iso*carveol, as the *cis*- isomer, however, was in error. The incorrect assignment was based on the isolation of *iso*carvomenthol as a hydrogenation product. Although no reference for the carvomenthol assignments used was noted, the assignments were those first postulated by Bose (1) in which the assignments for *iso*- and *neoiso*-carvomenthol were reversed on the basis of very tenuous evidence. The *iso*carvomenthol, in truth, indicated that the isomer was *trans*. Furthermore, since the 1-acetoxy-

*neo*dihydrocarveol was formed stereospecifically from the *cis*-limonene monoxide, the stereochemistry was expected to have the secondary hydroxyl group *trans* to the isopropenyl group. Further confirmation of the stereochemistry for the *trans*-*iso*carveol (VIc) was furnished by the identification of the *l*-*trans*-carveol (VIb) fraction, b.p. 106°/10 mm., α_D^{25} -181.80°, n_D^{25} 1.4934, which comprised the other major component. The *l*-*trans*-carveol furnished a 3,5-dinitrobenzoate, m.p. 111°. The *trans*-*iso*carveol and *trans*-carveol fractions each gave a mixture of *iso*- and *neo*carvomenthol on hydrogenation. *Cis*-carveol (VIIa), b.p. 108°/10 mm., was found in a very small yield, due to the small percentage of 1-acetoxy-*neoiso*dihydrocarveol formed from the other, less stable, conformation of the *trans*-limonene monoxide. This carveol was identified by GLPC and by its infrared spectrum compared to an authentic sample, prepared from the lithium aluminum hydride reduction of *l*-carvone according to Reitsema (171).

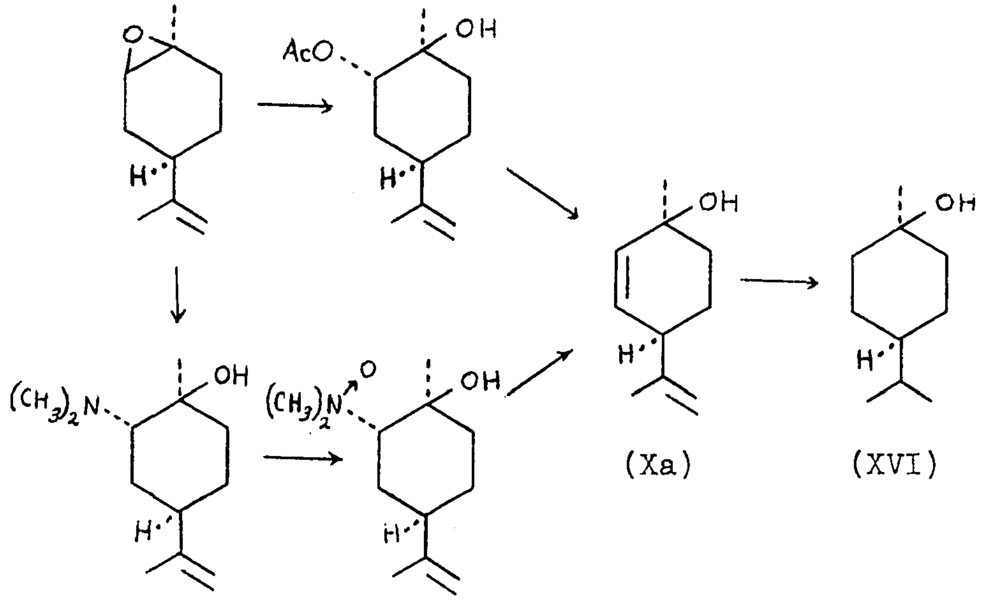
The *l*-*trans*-carveol obtained from pyrolysis of 1-acetoxy-*neo*dihydrocarveol was oxidized in 79% yield to carvone, identified by GLPC, its infrared and ultraviolet spectra and its 2,4-dinitrophenylhydrazone, m.p. 186°. It was noticed that under the acid conditions of oxidation some of the unreacted *trans*-carveol was isomerized to *cis*-carveol.

The first reported isolation of an *iso*carveol was that of Blumann and Wood (95) who pyrolyzed the diacetate of *neo*limonene-1,2-diol and obtained the *iso*carveyl acetate which gave an impure *iso*carveol upon saponification. This was probably the same isomer, *trans*-*iso*carveol, as was obtained here. The melting point of their 3,5-dinitrobenzoate, however, was curiously high.

The 1-hydroxy-*neo*dihydrocarveyl acetate formed from the *trans*-limonene monoxide was pyrolyzed at 455° under the prescribed conditions to give *trans*-2,8-*p*-menthadien-1-ol (Xa), b.p. 81-83°/7 mm., α_D^{26}+46.70°, n_D^{26} 1.4826, as the only observed product. The physical constants and infrared spectrum compare to those reported. On hydrogenation pure *trans*-*p*-menthan-1-ol (XVI) was obtained as indicated by GLPC and its 3,5-dinitrobenzoate, m.p. 82-83°.

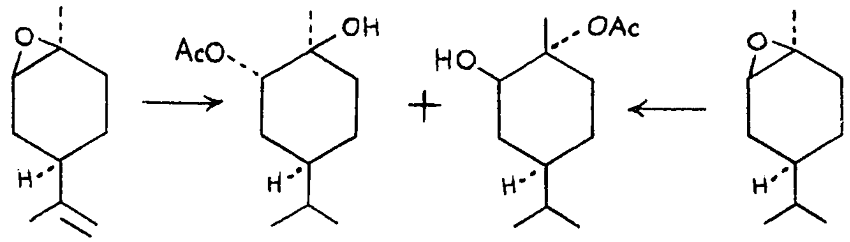
Kuczyński and Zabza (172) have recently obtained identical results by pyrolysis of the N-oxide of the 2-(N,N-dimethyl-amino)-1-hydroxy-8-*p*-menthene formed from *d*-*trans*-limonene monoxide. They obtained *d*-*trans*-2,8-*p*-menthadien-1-ol of a somewhat higher optical purity than that reported here. The physical constants of their alcohol were as follows: b.p. 69-70°/2.5 mm., d_4^{20}0.9429, n_D^{20} 1.4900, $[\alpha]_D^{20}$+68.9°.

The liquid phase pyrolysis of the hydroxyacetate obtained from the peracid limonene monoxides differed markedly from that occurring in the vapor phase. The tertiary acetates gave mainly dihydrocarvone and very little of the carveols. The secondary acetate, however, gave 2,8-p-menthadien-1-ol as before.

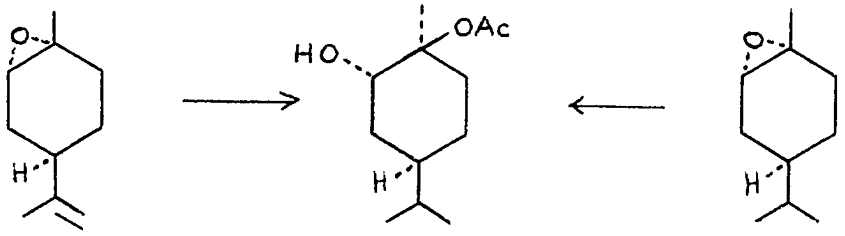


The action of acetic acid - sodium acetate on the carvomenthene oxides gave results analogous to those for the limonene monoxides.

The carvomenthene oxides employed in this work were prepared by hydrogenation of the limonene monoxides in ethyl acetate using platinum oxide as catalyst. The per-acid limonene monoxides gave a carvomenthene oxides fraction, b.p. 133-135°/7 mm., n_D^{25} 1.4629, α_D^{25}+56.80°. This epoxide mixture afforded essentially the same ratio of hydroxyacetates as did the limonene monoxides. It was



(LXXVII) (LXXVI)



(LXXV)

therefore possible to obtain the same hydroxyacetate mixture by hydrogenation of the limonene hydroxyacetates.

The pyrolysis of the saturated hydroxyacetate mixture was not as selective as in the case of the limonene hydroxyacetates in that at the temperatures required to completely pyrolyze the tertiary acetate a small percentage of the secondary acetate was also pyrolyzed. The ratios of the pyrolysis products of the trans-1-acetoxy-2-hydroxy-p-menthanes (91% 1-acetoxy-neocarvomenthol (LXXV) and 9% 1-acetoxy-neoisocarvomenthol (LXXVI)) are tabulated in Table II.

The pyrolysis products were separated by fractional distillation. The fraction, b.p. 72°/4 mm., n_D^{23} 1.4596, $\alpha_D^{23}+14.60^\circ$, corresponded to a mixture of d-carvomenthone and *d*-*iso*carvomenthone (XXVIII), semicarbazone m.p. 176-177°. The second fraction was identified as the previously unreported *d*-*trans*-*iso*carvotanacetol (XIIIc), b.p. 98-100°/ 10 mm., n_D^{25} 1.4765, α_D^{25}+62.91°, which afforded a 3,5-dinitrobenzoate, m.p. 80.5-81.5°. The infrared spectrum indicated a terminal methylene group. Hydrogenation gave the same mixture, *iso*carvomenthol and *neo*carvomenthol, as was obtained from *trans*-*iso*carveol. The third fraction, b.p. 101-102°/10 mm., $n_D^{23.5}$ 1.4772, $\alpha_D^{23.5}$ -164.80°, was *l*-*trans*-carvotanacetol (XIIIa). While no claim was made to the optical purity of this fraction, it certainly had a higher optical rotation than any sample previously reported, as far as could be ascertained. The *l*-*trans*-carvotanacetol afforded a 3,5-dinitrobenzoate m.p. 115°. Hydrogenation gave a mixture of *iso*- and *neo*carvomenthol, similar to that obtained from *trans*-carveol. A small amount of what was assumed to be *cis*-carvotanacetol (XIIIb) was observed on GLPC of the crude pyrolysate, but this component was not isolated for identification.

Pyrolysis of the 2-acetoxy-1-hydroxy-*p*-menthane (1-hydroxy-*neo*carvomenthyl acetate) (LXXVII) afforded only *trans*-2-p-menthen-1-ol (XVa), n_D^{25} 1.4674, α_D^{25}-13.02°. This alcohol gave *trans*-*p*-menthan-1-ol on hydrogenation.

The lithium aluminum hydride reduction of *cis*- and *trans*-limonene monoxide has been reported to give *trans*-β-

TABLE II

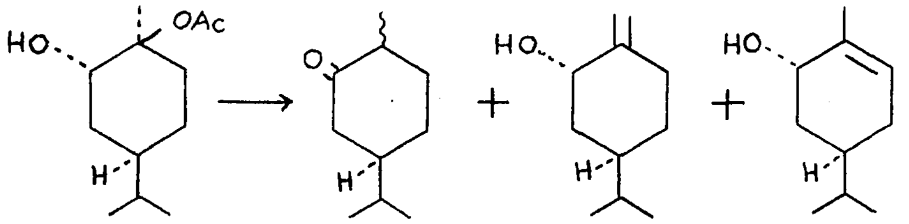
RATIO OF PYROLYSIS PRODUCTS OF *TRANS*-1-ACETOXY-2-HYDROXY-*p*-MENTHANES

Temperature	Carvomenthone[a]	*Trans*-*iso*-carvotanacetol	*Trans*-carvotanacetol	*Cis*-carvotanacetol
375° [b]	29.6%	30.0%	36.6%	3.8%
392° [c]	27.7%	30.3%	38.5%	3.5%
400° [c]	29.4%	31.2%	36.2%	3.2%

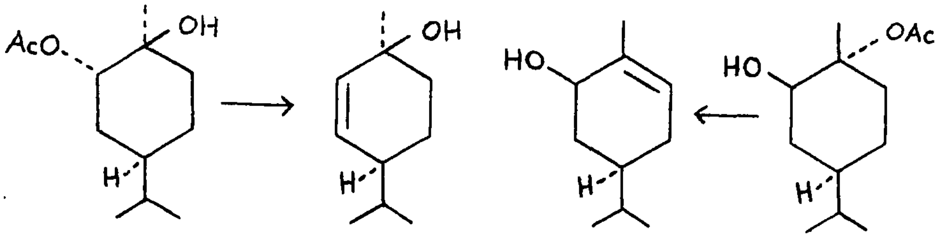
[a] This value is the combined total of carvomenthone and isocarvomenthone.

[b] Product ratio is from hydroxyacetate pyrolyzed, as incomplete pyrolysis occurred at this temperature.

[c] Neglecting pyrolysis of 2-acetoxy-1-hydroxy-*p*-menthane which occurred to a small extent.

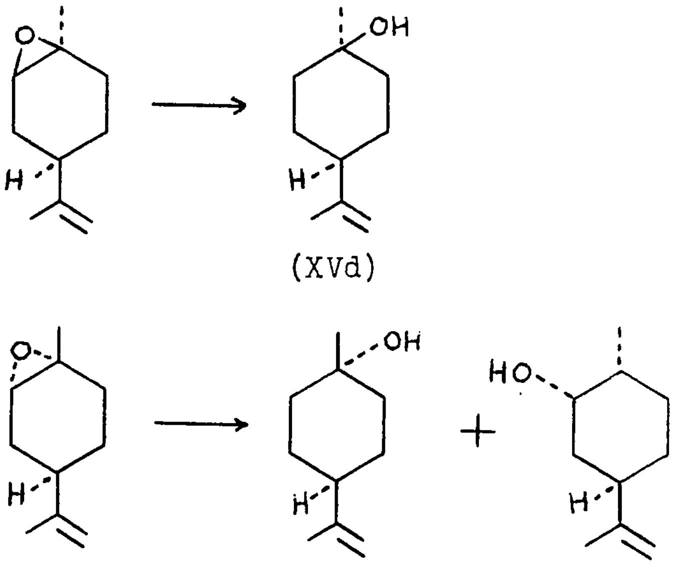


(XXVIII) (XIIIc) (XIIIa)



(XVa) (XIIIb)

terpineol (XVd) (from the *trans*- isomer) and *neo*dihydrocarveol (XVc) (from the *cis*- isomer) as the major products, as well as a small amount of *cis*-β-terpineol (XVe) (82, 119,135). This reaction was carried out in order to obtain an authentic sample of *neo*dihydrocarveol for comparison in subsequent experiments. The mixture obtained was analyzed by GLPC and the products identified by fractional distillation and isolation. The product mixture (74% recovery) contained 9% limonene monoxide (mainly *cis*-isomer), 48% *trans*-β-terpineol, 5% *cis*-β-terpineol, 29% *neo*dihydrocarveol and 9% of two other unidentified products. This product ratio was quite similar to that previously reported. It was interesting to note that the trans-limonene monoxide reacted faster and more stereospecifically than the cis- isomer.



(XVd)

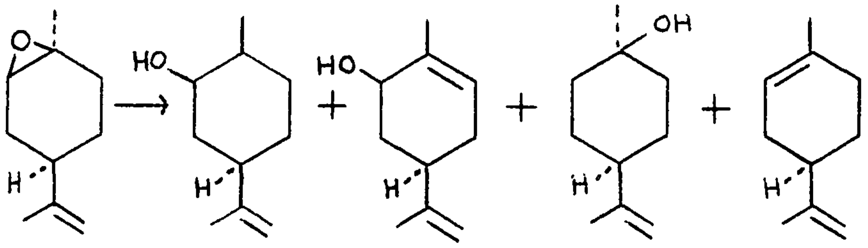
(XVe)

(XVc)

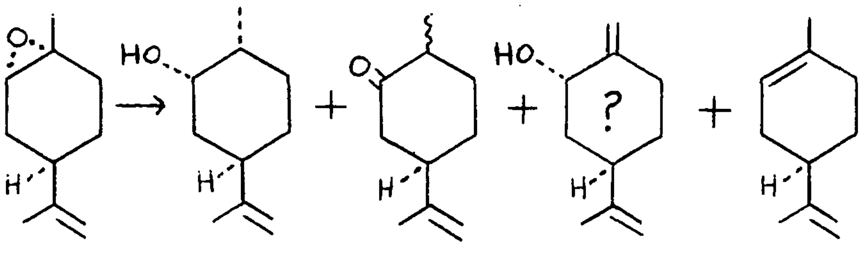
The reaction conditions for the lithium aluminum hydride reduction of the limonene monoxides were quite different from that of the glacial acetic acid - sodium acetate solution used in the previous ring opening study. It is apparent, however, that in both cases the conformational effects of the substituents on the monocyclic cyclohexene epoxide are the predominate influence on the direction of the epoxide ring opening. It would appear that the Fürst-Plattner rule of diaxial opening applies to monocyclic systems as well as those in which the ring conformation is fixed by fusion to other rings. The examples presented in this research are the severest tests to date of this principle in a monocyclic system inasmuch as the systems studied present a direct competition between the primary steric effect and the conformational effects.

The reaction of sodium powder on the limonene monoxides exemplified the fact that the solvent used can have a large effect on the course of epoxide reactions. A mixture of limonene monoxides was allowed to react with sodium powder in diethyl ether. The two main reaction products, besides polymer, were dihydrocarvone and trans-β-terpineol in a ratio of 7 : 3. A very small amount of dihydrocarveol (XVb), also, was detected by GLPC as well as a small hydrocarbon fraction. This result was in sharp contrast to the results of Chabudzynski (135) using benzene as the solvent. Reinvestigation of this reaction with benzene as the solvent proved fruitful in that the isolation of the "cis-isocarveol" formed was distinctly different from the material isolated by Naves and Grampoloff (87), contrary to what was reported by Chabudzynski.

The isolated material was 30% polymer and 70% volatile oils. The volatile component contained three main products; trans-β-terpineol, dihydrocarvone (cis and trans), and "cis-isocarveol". Minor components included limonene monoxide, limonene, neodihydrocarveol, trans-isocarveol (?), cis-carveol and several other unidentified substances. It was possible to isolate the three major components as well



(XVb)

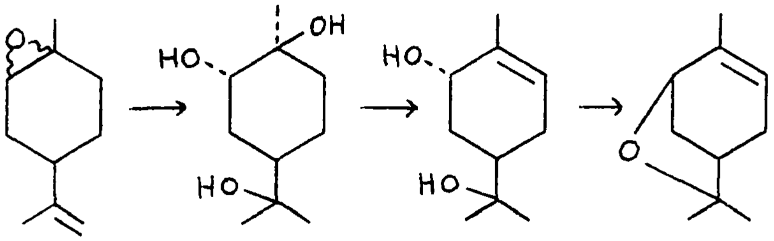


as the *cis*-carveol in a fair state of purity. The "*cis*-*iso*carveol" obtained had a b.p. 98°/10 mm., n_D^{25} 1.4775, α_D^{25} -16.35°. This fraction appeared to contain approximately 10% impurity and it is quite likely that the optical rotation would be of a magnitude of α_D-35° were the sample completely pure. This "*iso*carveol" had a similar, but different, infrared spectrum than that reported for the *trans*- isomer (87). The 3,5-dinitrobenzoate had a m.p. 122-122.5° compared to the 69-69.5° reported for the other isomer. Hydrogenation did not give *iso*carvomenthol as reported (135) but rather only carvomenthol. From the information available it would appear that the component identified as *cis*-*iso*carveol was really *l*-dihydrocarveol, which Chabudzynski reported was not present in the reaction mixture. While a trace (approximately 2-3%) of what might have been *trans*-*iso*carveol was present in the reaction of the mixed limonene monoxides, it was absent in the reaction of pure *trans*-limonene monoxide.

There was no doubt that the *cis*- isomer reported by Chabudzynski (135) was not the same as that reported by Naves and Grampoloff (87). The evidence presented in this research indicated that the isomer of Naves and Grampoloff was the *trans*- isomer and that of Chabudzynski was *l*-dihydrocarveol (XVb).

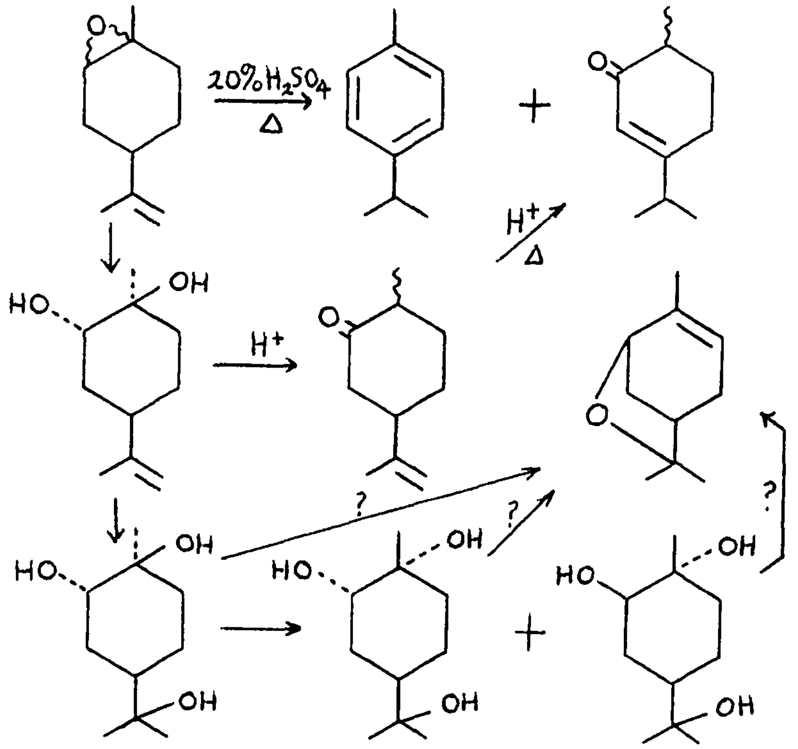
The result of sodium powder on pure *trans*-limonene monoxide was analyzed by GLPC and was as reported (135), except that *cis*-carveol was also present among the reaction products and the product identified as *cis*-*iso*carveol was *l*-dihydrocarveol.

The hydration of the limonene monoxides to *neo*limonene-1,2-diol with 1% sulfuric acid was one of the first reactions observed with this compound. The fact that the peracid limonene monoxide is a mixture of *cis*- and *trans*-isomers, and that only one hydration product is obtained, should have been the first indication that the opening of the epoxide ring proceeded by the Fürst-Plattner rule. Unfortunately, it was only recently realized that limonene monoxide existed as two isomers. It has also been found that the action of sulfuric acid under more vigorous conditions affords dihydrocarvone and carvenone (77,78). The action of acid hydration and isomerization of limonene monoxide has had only cursory examination, however. It was considered feasible that under the proper acid reaction conditions limonene monoxide might be made to form pinol by the route shown. Therefore, a study of the hydration and acid isomerization of limonene monoxide was undertaken.

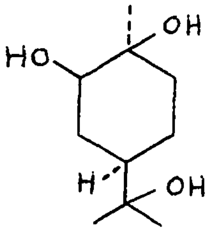


Approximately forty experiments were carried out under varying conditions. In most cases the results were quite similar. It was found that in hot, refluxing 20% sulfuric acid the peracid limonene monoxides gave 39% carvenone and 39% p-cymene. As it was wished to avoid the formation of these two compounds, the initial addition of the limonene monoxides was conducted at ice bath temperature, in the majority of experiments; thereafter, the temperature was raised as desired. With 15-35% sulfuric acid and raising the temperature to approximately 27° for a reaction time of eight to sixty-four hours, two fractions were obtained; (a) an organic layer which contained dihydrocarvone and carvenone as the major components with pinol and p-cymene as minor components, and (b) a water soluble fraction which consisted of an alcohol identified as 1,8-dihydroxy-neocarvomenthol (IVb), the hydration product of neolimonene-1,2-diol. With increasing reaction time the proportion of carvenone increased while that of dihydrocarvone decreased. At higher acid concentrations, 40-65% sulfuric acid, the experiments gave progressively more carvenone and less dihydrocarvone in the volatile organic layer. In the aqueous phase three distinctly different alcohols were now detected, one optically active and two optically inactive. It was found that with an increase in the reaction time the amount of these two latter alcohols increased while that of the optically active alcohol decreased. The yields, based on limonene monoxide, varied widely. It was found that the alcohol yields were generally in the range of 20-40% with yields of the volatile components ranging from 20-50%. The optically active alcohol, m.p. 136°, $[\alpha]_D^{25}$+55° (acetone), was identified as d-1,8-dihydroxy-neocarvomenthol; the same isomer found by Schmidt (30) on hydration of neolimonene-1,2-diol. The isomers, m.p. 114.5-115.5° and 154-156°, were optically inactive and gave distinctly different infrared spectra. Dilute potassium permanganate oxidation of dl-α-terpineol afforded the dl-1,8-dihydroxy-carvomenthol (IVa), m.p. 122°, which gave an infrared spectrum different from the three alcohols above.

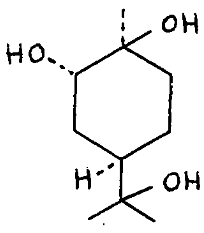
Formic acid - hydrogen peroxide oxidation of dl-α-terpineol afforded a small amount of impure dl-1,8-dihydroxy-neocarvomenthol, m.p. 110-111°, identified by its infrared spectrum. Characterization of the d-1,8-dihydroxy-neocarvomenthol was further afforded by its oxidation to homoterpinyl methyl ketone.



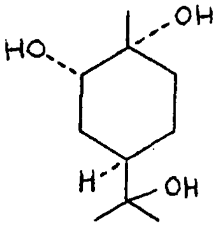
From the limited information available, it would appear that the isomers, m.p. 114.5-115.5° and 154-156°, were dl-1,8-dihydroxy-isocarvomenthol (IVc) and dl-1,8-dihydroxy-neoisocarvomenthol (IVd), although at the present time it is impossible to designate with certainty which structure belongs to which isomer. The formation of these compounds presumably occurs by way of the intermediate carbonium ions with subsequent reformation of the alcohols.



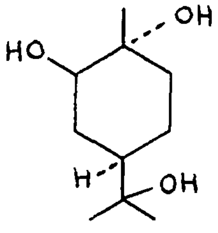
(IVa)



(IVb)



(IVc)



(IVd)

The reaction of peracid limonene monoxide with boron trifluoride - etherate in benzene was found to yield carvenone in 45.5% yield; however, with dimethyl sulfoxide as the solvent a 50% yield of dihydrocarvone was formed with no appreciable carvenone.

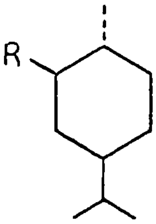
Pyrolysis of limonene monoxide at 546° gave dihydrocarvone as the main product with a small amount of mixed alcohols.

*Neo*limonene-1,2-diol, formed by hydration of the oxirane linkage of the limonene monoxides, gave 1-hydroxy-*neo*carvomenthol upon hydrogenation. The literature on the 1-hydroxy-carvomenthols has been confused by the use of Bose's carvomenthol assignments (1) in that the nomenclature sometimes belies the assigned structure. This confusion also led Naves and Grampoloff (87) to assign the *cis* conformation to *trans*-*iso*carveol. Although an overwhelming amount of evidence is available which contradicts two of these assignments, they do not appear to have been challenged. The literature, in fact, is a mass of confusion because the assignments of Bose are used by some investigators while others use the assignments given by Simonsen and Owen (173). For this reason, it was deemed essential to clarify, once and for all, the stereochemistry of the carvomenthols.

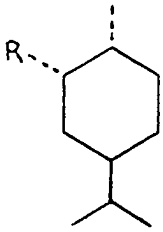
ON THE STRUCTURE OF THE CARVOMENTHOLS

The configurations of the carvomenthols have been the subject of disagreement for a number of years (1,173). Theory predicts the existence of four racemic carvomenthols and eight optically active forms. Characterization of four stereoisomeric carvomenthols, in a state of purity, was accomplished by Johnston and Read (174). Simonsen and Owen assigned the structures of the carvomenthols on the basis of the known relationship between the carveols and carvomenthones with the carvomenthols. Subsequent work by Schmidt has extended this relationship to the four dihydrocarveols and the sobrerols (175-177). Although the Auwers-Skita rules must be applied with caution to 1,3-disubstituted cyclohexane derivatives, nearly all the evidence for the structures of cis- and trans-carveol concur with the structures assigned on this basis.

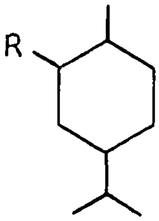
The evidence of Bose for the structures of the carvomenthols was based upon the reactions of the three known carvomenthylamines with nitrous acid. Mills (178) and Bose (179) independently have shown that equatorial amines react cleanly with nitrous acid to give equatorial alcohols with very little olefin formation. Axial amines give mainly olefin and some mixed alcohols. On the basis of conformational analysis, as well as the Auwers-Skita rule, carvomenthone was considered to have the methyl and isopropyl groups <u>trans</u> and in the equatorial positions. Formation of carvomenthone oxime and the subsequent reduction with sodium in alcohol afforded 95% carvomenthylamine and 5% <u>neo</u>carvomenthylamine (180). As the method of reduction generally provided the more stable isomer, Bose considered the carvomenthylamine to have all of the substituents equatorial. This was confirmed by the action of nitrous acid which gave nearly all carvomenthol. The <u>neo</u>carvomenthylamine, with the isopropyl and methyl groups equatorial, must therefore have the amino group axial. This was born out by predominant olefin formation on reaction with nitrous acid. The oxime of <u>iso</u>carvomenthone, where the methyl and isopropyl groups are <u>cis</u>, gives only <u>iso</u>carvomenthylamine. Bose assumed that the isopropyl group fixed the conformation of the cyclohexane ring and was in the equatorial position. This would require the methyl group to be axial. Since the action of nitrous acid on *iso*carvomenthylamine gave mainly *iso*carvomenthol with very little olefin, the conformation was considered to have the amino group equatorial. Thus Bose assigned the structures to the carvomenthylamines, and by analogy to the carvomenthols, as follows: carvomenthylamine (LXXVIII) and carvomenthol (LXXIX), *neo*carvomenthylamine (LXXX) and *neo*carvomenthol (LXXXI), *iso*carvomenthylamine (LXXXII) and *iso*carvomenthol (LXXXIII), and *neoiso*carvomenthylamine (LXXXIV) and *neoiso*carvomenthol (LXXXV). Unfortunately



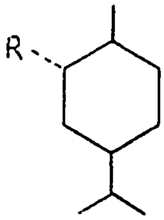
(LXXVIII, R=NH_2)
(LXXIX, R=OH)



(LXXX, R=NH_2)
(LXXXL, R=OH)



(LXXXII, R=NH_2)
(LXXXIII, R=OH)

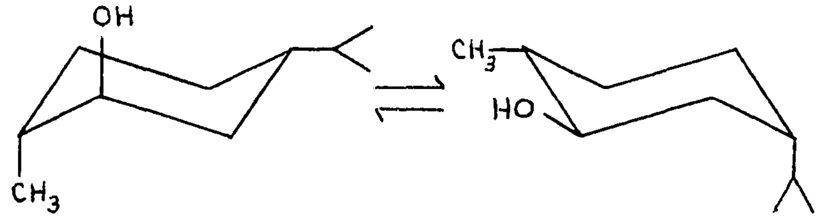


(LXXXIV, R=NH_2)
(LXXXV, R=OH)

*neoiso*carvomenthylamine was not available for reaction with nitrous acid for comparison. The configurations of carvomenthylamine, carvomenthol, *neo*carvomenthylamine and *neo*-

carvomenthol were identical to those deduced by McNiven and Read (181). Bose stated that since isocarvomenthol was esterified at a faster rate than was neocarvomenthol, this was evidence for the correctness of the conformation assigned to isocarvomenthol.

The error in Bose's argument was that the presence of an isopropyl group on a cyclohexane ring does not necessarily fix the conformation, as has so often been assumed. Recently the isopropyl group has been shown to have the same magnitude as the methyl or ethyl group in affecting the ring conformation (182.184). It is in quite a different class from the t-butyl group. Thus, while contributing to the ring conformation, the isopropyl group can not be considered bulky enough to cancel the effects of the other substituents. Therefore, the structure which Bose assigned as neoisocarvomenthol may take up the alternative conformation in which the isopropyl group is axial and the methyl and hydroxyl groups are equatorial. Were this the case with the corresponding amine, then this conformation could also



predominately give the corresponding alcohol on reaction with nitrous acid. Considering this, it is impossible to conclude which assignment is iso- and which is neoisocarvomenthol solely on the basis of the action of nitrous acid on isocarvomenthylamine. The argument that the relative rates of esterification of neocarvomenthol and isocarvomenthol support the structures of Bose was refuted by the same arguments that Eliel (185) applied to the isomeric menthols.

The inconsistencies of these carvomenthol assignments, which arise from hydrogenation studies on the carveols, fall into place if the assignments of Bose for isocarvomenthol and neoisocarvomenthol are reversed. There are three major pieces of evidence which support the reversal of assignments; (1). The relationship between the sobrerols, dihydrocarveol hydrates, dihydrocarveols and carvomenthols shown by Schmidt. This includes the relative hydrolysis rates of related structures which support such a reversal of assignments. (2). The molecular rotation values of the carvomenthols which are as predicted for carvomenthol, neocarvomenthol and neoisocarvomenthol (using the stereochemistry which Bose assigned as isocarvomenthol). However, the value for isocarvomenthol indicates that it exists in nearly equal amounts of the two possible conformations (186) (as was predicted above from purely conformational arguments). (3) Hydrogenation studies of the carveols, originally done by Johnston and Read, using palladium on charcoal as a catalyst, also contradicts Bose's assignments of _iso_- and _neoiso_carvomenthol. A more complete study was carried out in this laboratory. The hydrogenations of _cis_- and _trans_-carveol, _trans_-_iso_carveol, _trans_-carvotanacetol and _trans_-_iso_carvotanacetol were studied. That these compounds were as postulated was based on the methods of preparation, derivatization and comparison with authentic samples whenever possible. The solvent used was ethyl acetate with platinum oxide as the catalyst. In order to ascertain whether the solvent or catalyst caused isomerization of either the starting materials or the saturated alcohols produced, the following tests were made: (1). The unsaturated alcohols were shaken with the solvent and catalyst for approximately twelve house. (2). The individual carvomenthols were shaken in a similar manner. No isomerization occurred in either case. The hydrogenation results were analyzed by GLPC and the percentages calculated in Table III. This evidence indicated that _iso_carvomenthol has structure (LXXXV) and _neoiso_carvomenthol has structure (LXXXIII).

The consideration that the structures of these two carvomenthols, _iso_- and _neoiso_-, were still questionable has often been overlooked in the course of structure proofs

TABLE III

HYDROGENATION OF UNSATURATED ALCOHOLS

Alcohol	Carvomenthol	*Neo*-carvomenthol	*Iso*-carvomenthol	*Neoiso*-carvomenthol
Cis-carveol	49%	-	-	51%
Trans-carveol	-	63%	37%	-
Trans-*iso*carveol	-	24.5%	75.5%	-
Trans-carvotanacetol	-	64%	36%	-
Trans-*iso*-carvotanacetol	-	25%	75%	-

TABLE IV

HYDROGENATION OF LIMONENE MONOXIDES[a]

Catalyst	PtO_2	Raney Nickel W-7	Raney Nickel W-5
Temperature	30°	100°	100°
Pressure	60 p.s.i.	2000 p.s.i.	2000 p.s.i.
Carvomenthene oxide	100%	-	-
*Neo*carvomenthol	-	3.8%	6.1%
Carvomenthol		49.4%	48.8%
*Iso*carvomenthol			
*Neoiso*carvomenthol	-	27.3%	25.7%
p-menthan-1-ol	-	19.5%	19.4%

---

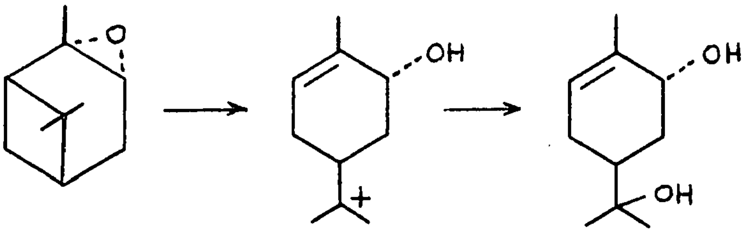
[a] 50-50 mixture of *cis*- and *trans*- isomers from peracid epoxidation.

(87,139,140), although the inconsistencies of Bose's assignments were early recognized (180). The hydrogenation with Raney nickel catalyst of the limonene monoxides, and therefore also the carvomenthene oxides, was reported to give only isocarvomenthol by Kergomard and Geniex (139, 140). Reinvestigation with both W-5 and W-7 Raney nickel afforded substantially different results in this laboratory. The results are tabulated in Table IV.

The nomenclature used throughout this work was based on the carvomenthol assignments given above.

α-PINENE OXIDE

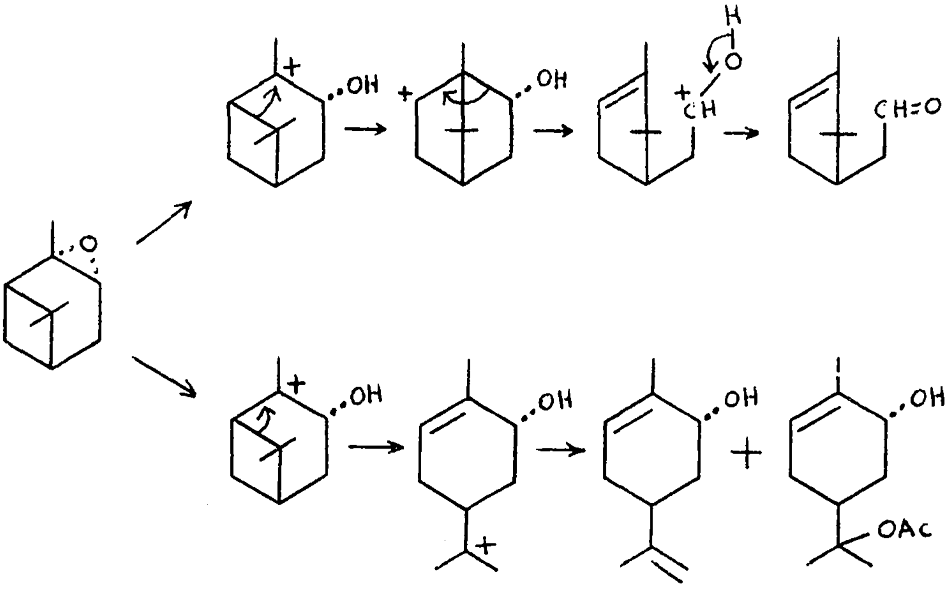
Sobrerol exists in the cis and trans forms, giving rise to four optically active and two racemic modifications. α-pinene oxide forms only the trans modification upon hydration. Even though there is some rearrangement during this transition, it is obvious that the original oxirane oxygen had to be in a position trans to the gem-dimethyl grouping of the cyclobutane ring. For consistent nomenclature the oxide should therefore be called cis-α-



pinene oxide, cis referring to the methyl at the 2-position and the gem-dimethyl side of the cyclobutane ring.

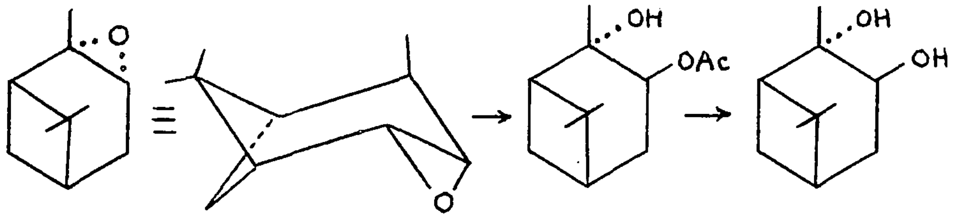
While trans-sobrerol is more reluctant to form pinol than is the cis modification, it may still be produced. Therefore, reactions of α-pinene oxide in acid media were investigated. It was found that strong acid media formed a complex mixture of what appeared to be mainly campholenic aldehyde, some pinocamphone and a small amount of pinol, along with a considerable amount of resinous material. When dl-α-pinene oxide was hydrated with dilute acid to dl-trans-sobrerol, m.p. 131-132°, and the acid concentration raised after the sobrerol formation, pinol was formed in 65% yield along with a small amount of p-cymene.

Royals and Harrell (77,78) reported that α-pinene oxide with glacial acetic acid - sodium acetate formed campholenic aldehyde along with an unidentified, impure, hydroxyacetate which has been assumed to be 6-acetoxy-8-hydroxy-1-p-menthene (187). Reinvestigation of this reaction afforded 39% campholenic aldehyde, b.p. 80°/10 mm., n_D^{25} 1.4630; 17.1% trans-carveol, b.p. 76°/4 mm., n_D^{25} 1.4949; and 20.5% of a hydroxyacetate, b.p. 127-133°/4 mm., n_D^{25} 1.4813. The aldehyde was characterized by its 2,4-dinitrophenylhydrazone, m.p. 110-111°, and its semicarbazone, m.p. 138.5-140°. The dl-trans-carveol afforded a 3,5-dinitrobenzoate, m.p. 118-118.5°. Hydrolysis of the hydroxyacetate gave *dl*-*trans*-sobrerol, m.p. 128-129°, which showed no depression on admixture with an authentic sample. From mechanism considerations the hydroxyacetate would be expected to be *trans*-8-acetoxy-6-hydroxy-1-*p*-menthene (LXXXVI) instead of that which had previously been assumed (187). This was confirmed by pyrolysis of the hydroxyacetate to give *dl*-*trans*-carveol, identified by GLPC, its infrared spectrum and the 3,5-dinitrobenzoate, m.p. 119°.



(LXXXVI)

It was considered feasible, although unlikely, that the hydroxyacetate might have arisen if the oxide opening had occurred by the breaking of the axial C-O linkage. This would have afforded the monoacetate of α-pinene glycol (LXXXVII). Anticipating this possibility, the α-pinene glycol was prepared by the method of Schmidt (188), which consisted of the permanganate oxidation of α-pinene to the cis-1-hydroxy-pinocamphone and reduction with lithium aluminum hydride. As it turned out, this was not necessary since none of the monoacetate of the α-pinene glycol was formed.



(LXXXVII)

It appeared that the equatorial bond in cis-α-pinene oxide preferentially opened the oxirane ring, after which the observed rearrangements occurred. It was questionable, however, as to whether conformational influence was the contributing factor. It was quite possible that the driving force in this reaction was the carbonium ion formation. Nevertheless, this oxide underwent the same cleavage of the equatorial C-O linkage as had been observed in most of the cyclohexene oxide series, corresponding to the Fürst-Plattner rule of diaxial opening. This, however, was considered to be a special case. The conformation of cis-α-pinene oxide was considered to be fixed due to the unfavorable steric interactions that would occur in the alternate conformation.

SUBSTITUTED 6-OXA-BICYCLO-[3.2.1]-OCT-3-ENES

In a previous work this author studied the reactions of 1,2-dibromo-8-hydroxy-p-menthane with various bases. It was found that strong basic reagents gave pinol (4,7,7-trimethyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) while weaker bases afforded p-cymene as the product. It was erroneously postulated that the ether formation preceded the tertiary bromide elimination in the pinol formation. A reinvestigation of the action of basic reagents on 6-bromo-8-hydroxy-1-p-menthene has refuted this claim. The previous error was undoubtedly due to the instability of the allylic bromide, which rapidly decomposes to p-cymene at room temperature. The results of this reinvestigation are tabulated in Table V.

The effect of the alkyl substituents on the basicity of the hydroxyl group was of interest. Therefore, preparation of a series of substituted 6-oxa-bicyclo-[3.2.1]-oct-3-enes by the dibromide intermediates was undertaken. By studying this reaction with various bases, it was possible to observe the internal ether - aromaticity competition.

In order to obtain the dibromide precursors of the pinol analogs, it was necessary to synthesize the desired α-terpineol analogs (LXXXVIII, LXXXIX, XC and XCI).

TABLE V

REACTION OF BASES ON α-TERPINEOL MONOBROMIDE (6-BROMO-8-HYDROXY-1-p-MENTHENE)

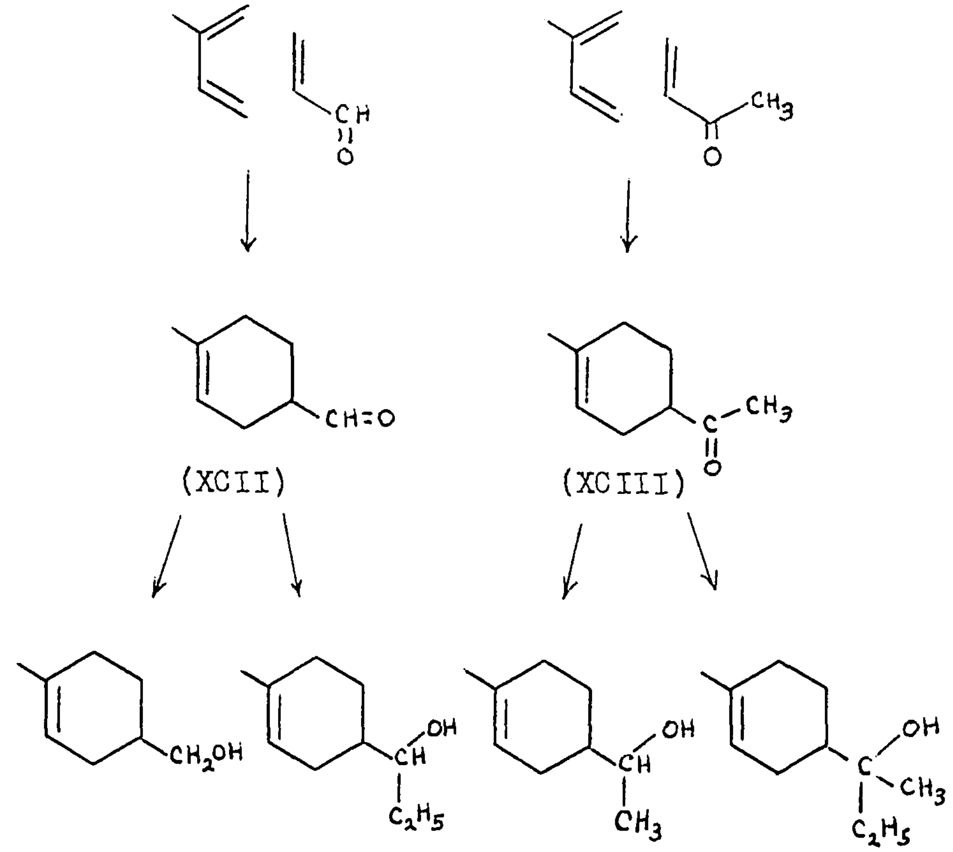
Basic Reagent	Solvent[a]	Product ratio pinol %	: p-cymene %
Sodium ethoxide	ethyl alcohol[b]	98	2
Sodium hydroxide	ethyl alcohol[b]	95	5
Sodium methoxide	methyl alcohol[b]	72	28
Pyridine	benzene[b]	0	100
2% sodium bicarbonate solution[c]		-	-

[a] All solvents were anhydrous except the bicarbonate solution.

[b] Reaction temperature: 65-75°.

[c] The product obtained was dl-trans-sobrerol, m.p. 128°; reaction temperature was 25°.

The preparation of dinor-α-terpineol (LXXXVIII) was approached by attempting a Diels-Alder diene synthesis, employing isoprene as the diene and allyl alcohol as the dienophile. A number of runs were made at increasing temperatures, but nothing other than starting material was obtained. Using acrylonitrile as the dienophile, 4-cyano-1-methyl-cyclohex-1-ene was obtained, b.p. 85-93°/20 mm., n_D^{20} 1.4723, in an 83% yield. Since the addition of acrolein



(XCII) (XCIII)

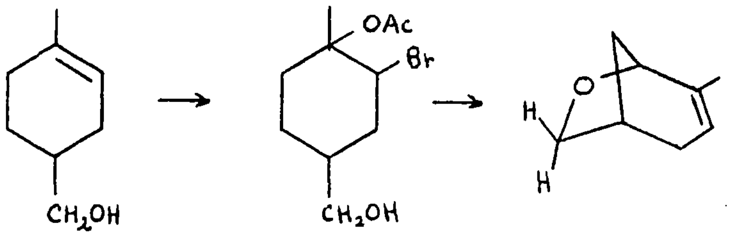
(LXXXVIII) (XC) (LXXXIX) (XCI)

was considered to be a more direct approach, this was the dienophile which was finally employed. Isoprene and acrolein formed the adduct 1-methyl-4-formyl-cyclohex-1-ene (XCII) in 84% yield. This adduct, b.p. 64°/10 mm., n_D^{23} 1.4711, was characterized by the preparation of its semicarbazone, m.p. 142.5-144° and its 2,4-dinitrophenylhydrazone, m.p. 165.5-166.5°. Lithium aluminum hydride furnished a 96% yield of two materials; 87% of dinor-α-terpineol (LXXXVIII), b.p. 90°/10 mm., n_D^{25} 1.4810, 3,5-dinitrobenzoate m.p. 111-112°, and 9% of an unidentified material, b.p. 89°/10 mm., which was purified by GLPC to give n_D^{25} 1.4603. This latter material had a carbonyl group which showed at 5.71 microns in the infrared. From the GLPC this second fraction was thought to be two different compounds which were not separated. No further work was done on this.

Alder and Vogt (189) prepared nor-α-terpineol (LXXXIX) by addition of methyl magnesium halide to 1-methyl-4-formyl-cyclohex-1-ene. For convenience, the problem was approached from another route in this laboratory. The Diels-Alder addition of isoprene and methyl vinyl ketone afforded 1-methyl-4-acetyl-cyclohex-1-ene (XCIII) in better than 90% yield. It was found by GLPC that less than 3% 1-methyl-5-acetyl-cyclohex-1-ene was formed. The 1-methyl-4-acetyl-cyclohex-1-ene, b.p. 79-80°/10 mm., $n_D^{22.5}$ 1.4703, was characterized by the preparation of its semicarbazone, m.p. 148.0-148.5° and the 2,4-dinitrophenylhydrazone, m.p. 116°. Lithium aluminum hydride reduction gave nor-α-terpineol, b.p. 93°/9 mm., n_D^{24} 1.4792, in 90% yield. This alcohol gave a 3,5-dinitrobenzoate, m.p. 95-96°.

The approach used in the synthesis of iso- and homo-α-terpineol, (XC) and (XCI) respectively, involved addition of the corresponding aldehyde and ketone, previously produced in the Diels-Alder syntheses to ethyl magnesium bromide. This gave iso-α-terpineol (1-methyl-[4-α-hydroxy-propyl]-cyclohex-1-ene), b.p. 82-85°/3 mm., n_D^{25} 1.4808, 3,5-dinitrobenzoate, m.p. 111-113°, in 81.5% yield and homo-α-terpineol (1-methyl-[4-α-hydroxy-α-methyl-propyl]-cyclohex-1-ene), b.p. 89-92°/3 mm., n_D^{25} 1.4836, 3,5-dinitrobenzoate - oil, in 87.5% yield.

Bromination of dinor-α-terpineol with pyridinium bromide perbromide in acetic acid according to the method of Lombard and Heywang (190) gave what was apparently the 1-acetoxy-2-bromo derivative (XCIV). This compound gave



(XCIV) (XCV)

dinorpinol (4-methyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) (XCV) with strong bases, but went unchanged when reacted with pyridine. Due to this undesirable acetylation during the bromination, this method was discarded. More satisfactory results were obtained with the terpineol analogs by addition of a bromine - carbon tetrachloride solution to a carbon tetrachloride solution of the olefinic alcohol, at ice bath temperatures. This procedure gave very clean products. The carbon tetrachloride was removed under vacuo prior to use of the dibromide.

The reactions of these dibromides with strong bases gave the corresponding pinol analogs. Weak bases were reluctant to cause aromatization and did not form the pinol analogs, but gave the allylic bromides instead. As with α-terpineol dibromide other high boiling products were produced. In these cases, however, the products were "cleaner" and were identified as high boiling alcohols. The results of the studies regarding the aromatization-internal ether formation are tabulated for dinor-α-terpineol dibromide in Table VI and for nor-α-terpineol dibromide in Table VII. The iso- and homo-α-terpineol dibromides were converted into the corresponding pinol analogs by strong bases. The physical properties of the 6-oxa-bicyclo-[3.2.1]-oct-3-enes produced in this study are tabulated in Table VIII.

TABLE VI

REACTION OF BASES WITH DINOR-α-TERPINEOL DIBROMIDE[a]

Basic Reagent		Solvent	Product ratio *dinor*-pinol %	: *p*-xylene %
Sodium ethoxide	100%	ethyl alcohol	100	0
Sodium methoxide	100%	methyl alcohol	98-100	0-2
Sodium hydroxide	85%	methyl alcohol	83	17
Pyridine	100%	methyl alcohol	0	100[b]

[a] The reaction temperatures were between 68° and 75°.

[b] While *p*-xylene was formed, the main product was the allylic bromide.

TABLE VII

REACTION OF BASES WITH *NOR*-α-TERPINEOL DIBROMIDE[a]

Basic Reagent	Solvent	Product ratio	
		*nor*pinol % :	4-ethyl-toluene %
Sodium ethoxide	100% ethyl alcohol	98-100	0-2
Sodium methoxide	100% methyl alcohol	95	5
Sodium hydroxide	85% methyl alcohol	90	10
Pyridine[b]	100% methyl alcohol	-	-

[a] The reaction temperatures were between 68° and 75°.
[b] The only product formed was the allylic bromide.

TABLE VIII

PROPERTIES OF PINOLS
(SUBSTITUTED 6-OXA-BICYCLO-[3.2.1]-OCT-3-ENES)

Compound	B.P.	n_D^{25}
l-pinol[a]	64-65°/11 mm.	1.4698
dl-pinol[b]	61-62°/10 mm.	1.4725
dl-dinorpinol (XCV)	55-56°/10 mm.	1.4777
dl-norpinol (XCVI)	60-61.5°/12 mm.	1.4708
dl-isopinol (XCVII)	85-88°/14 mm.	1.4690
dl-homopinol (XCVIII)	70°/10 mm.	1.4725

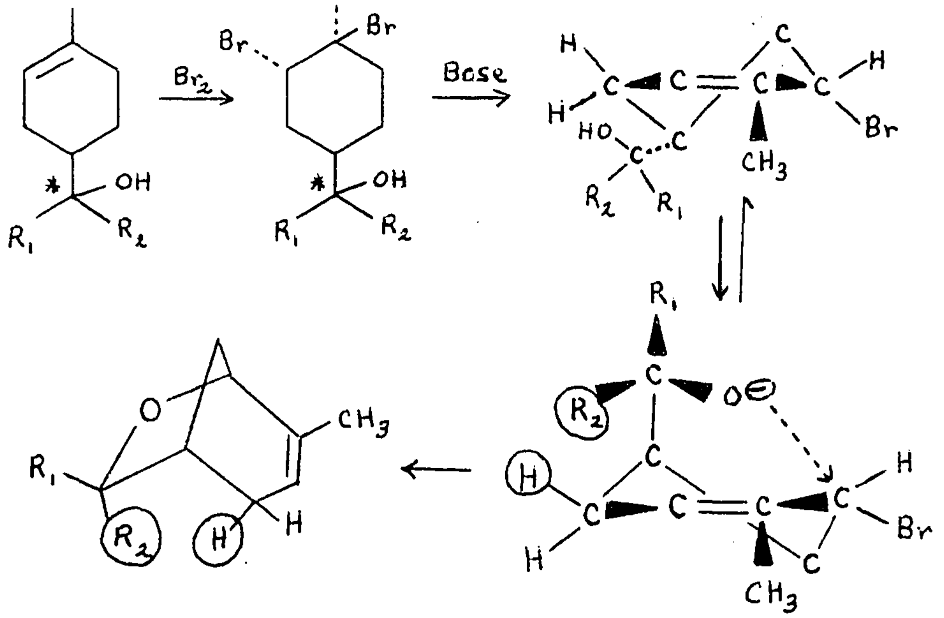
[a] d_4^{20} 0.9423, α_D-87.5°, index of refraction at 20° (190).
[b] d_4^{20} 0.9420.

It was apparent from the studies of the dibromo-alcohols, that the base strength played an important role in the ether formation. This was indicated dramatically in previous work (11) and still held in the cases studied here. While the aromatic compounds were reluctant to form with the dinor- or nor-α-terpineol dibromides (except in acid media or when heated), it appeared that formation of the allylic dibromide was an intermediate step in the formation of the internal ethers.

The formation of the two possible stereoisomeric racemates occurred with norpinol (XCVI). No attempt was made to separate the two isomers. It was noted that the two isomers were not formed in equal amounts. This would be due to the unfavorable steric interactions in the transition state of the isomer which was formed to a lesser extent. This would also explain the presence of the nearly equal amount of high boiling alcohols formed in the reactions producing the iso- and homopinols, (XCVII) and (XCVIII) respectively.

Since the starting materials for nor-, iso-, and homopinol are racemic, this would mean that only 50% of the starting material would be sterically favored to form the pinol analogs (due to the asymmetry about the hydroxyl-carbon). From a study of molecular models, it seemed likely that the pinol isomers whose formations were sterically favored would be the isomers which have the largest substituent in the exo position.

Each of the pinols formed a complex with ferricyanic acid.



(XCV); $R_1 = R_2 = H$

(XCVI); $R_1 = CH_3$, $R_2 = H$ and $R_1 = H$, $R_2 = CH_3$

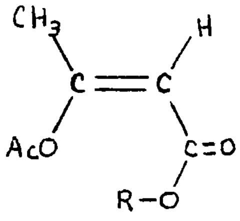
(XCVII); $R_1 = C_2H_5$, $R_2 = H$ (and $R_2 = C_2H_5$, $R_1 = H$?)

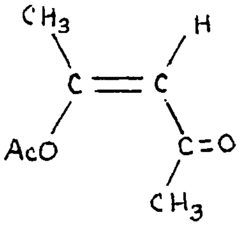
(XCVIII); $R_1 = C_2H_5$, $R_2 = CH_3$ (and $R_2 = C_2H_5$, $R_1 = CH_3$?)

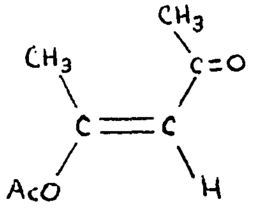
DEHYDROACETIC ACID

In the course of the research dealing with the Diels-Alder synthesis, a number of unsuccessful attempts were made to add enol acetates to cyclopentadiene.

The preparation of the enol acetates of 2,4-pentandione, ethyl acetoacetate and methyl acetoacetate were carried out. It was found that the esters of acetoacetic acid formed only a single isomer, probably the <u>cis</u> enol acetates, whereas 2,4-pentandione afforded the two possible, <u>cis</u> and <u>trans</u>, isomers. The properties of these enol acetates are tabulated in Table IX. This appeared to be the first report of the two isomeric enol acetates 2,4-pentandione (2-acetoxy-2-penten-4-ones). The α-isomer appeared to be the predominant one. Since the keto - enol equilibria of the acetoacetic esters have been shown to have the enol completely in the <u>cis</u> configuration, whereas acetylacetone can exist in both the <u>cis</u> and <u>trans</u> configurations in the enol form, this might indicate that the configurations of the enol acetates formed follows that of the enol itself.


(cis)


(cis)


(trans)

The NMR spectrum of the α- isomer showed a splitting ($J \sim 0.7$ cps) of the vinyl methyl group by the vinyl proton, while this was not observed for the β- isomer.

Also, the vinyl methyl group was approximately 7 cps further downfield in the α- compound than in the β- isomer. This was analogous to the dehydroacetic acid system, which showed a splitting where the vinyl proton and vinyl methyl were cis. Unfortunately, the NMR spectra for the enol acetates of methyl and ethyl acetoacetate were of such poor quality that no worthwhile data was obtained. Also, analogies of vinyl compounds with cyclic systems must be considered as "dangerous" in such a structure proof. Because of this, and the absence of further physical data, the assignments of the enol acetates as cis or trans must be considered as pure conjecture until further proof is available.

In the course of the attempted addition of the enol acetate of ethyl acetoacetate to cyclopentadiene, a solid, m.p. 110°, identified as dehydroacetic acid was isolated. No Diels-Alder adduct was formed. Under the vigorous experimental conditions, the enol acetates apparently underwent self-condensation to give ethyl acetate and dehydroacetic acid.

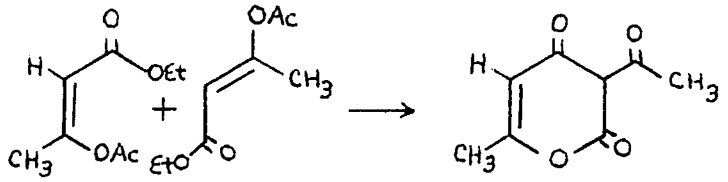
The carbon skelton of dehydroacetic acid has been rigorously established along with the determination that the acid exists (at least in solution) in the enol form (167). The question which remained unanswered was which enol form the acid and its enol ethers possessed.

TABLE IX

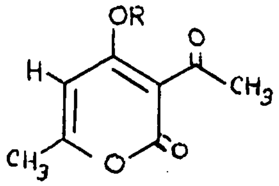
PROPERTIES OF ENOL ACETATES

Compound	B.P.	n_D^{25}	λmax (mμ)[a]
3-acetoxy-methyl-crotonate	86°/10 mm.	1.4428	210
3-acetoxy-ethyl-crotonate	83°/5 mm.	1.4423	209
α-2-acetoxy-2-penten-4-one	85-86°/10 mm.	1.4500	232.5
β-2-acetoxy-2-penten-4-one	87°/10 mm.	1.4493	226

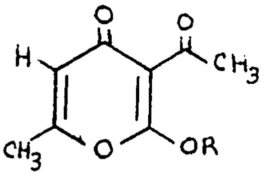
[a] Spectra taken in 95% ethanol; mean deviation ± 1.0 m



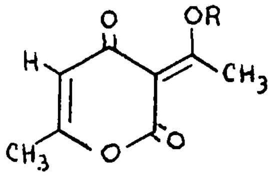
The problem was approached by a study of the spectral properties of dehydroacetic acid and its derivatives. Berson's (167) assumption, deduced from the similar ultraviolet spectra of dehydroacetic acid and its enol ether, that the structure of the ether and acid was the same except for the replacement of the acid proton with an alkyl group was considered to be valid in the absence of any contradictory evidence.



(LXVIIa)



(LXVIIb)



(LXVIIc)

Dehydroacetic acid was prepared according to the method of Arndt (191) and the sodium and silver salts were prepared. The action of methyl or ethyl iodide on the dry silver salt readily formed the respective esters (enol ethers). The ultraviolet spectra of these are tabulated

TABLE X

ULTRAVIOLET SPECTRAL DATA OF DEHYDROACETIC ACID AND ITS DERIVATIVES[a]

Compound	λ max (mμ)[b]	Log ϵ
Dehydroacetic Acid	222.5	3.99
	311.0	4.05
Sodium Dehydroacetate	230.0	4.22
	295.5	3.92
Silver Dehydroacetate	229.0	4.21
	297.0	3.92
Methyl Dehydroacetate	224.5	3.98
	314.5	3.94
Ethyl Dehydroacetate	225.5	3.96
	313.5	3.91

[a] Spectra taken in 95% ethanol.

[b] Mean deviation ± 1.0 mμ

TABLE XI

INFRARED SPECTRAL DATA OF DEHYDROACETIC ACID

Compound	λ max (microns)
Dehydroacetic acid	5.70(s), 5.75(m)[a], 6.06(s), 6.16(m), 6.40(s), (CCl_4). 5.82(s), 6.06(s), 6.16(m), 6.42(s), (Nujol). 5.78(s), 6.05(s), 6.17(m), 6.40(s), (KBr).
Sodium Dehydroacetate	5.93(s), 6.02(s), 6.25[a], 6.34(s), 6.51(ms), (KBr). 5.93(s), 6.02(s), 6.31(m), 6.34(s), 6.51(ms), (Nujol).
Silver Dehydroacetate	5.95(s), 6.08(s), 6.41(s), (Nujol). 5.93(s), 6.03(s), 6.35(s), 6.52(m), (KBr).
Methyl Dehydroacetate	5.78(s), 5.83(s)[a], 5.89(s)[a], 6.08(m), 6.56(m), (CCl_4). 5.78(ms)[a], 5.86(s), 5.98(s), 6.09(m), 6.66(s), (Nujol). 5.76(ma)[a], 5.83(s), 5.95(s), 6.06(m), 6.64(s), (KBr).
Ethyl Dehydroacetate	5.79(s), 5.87(s)[a], 6.07(m), 6.53(ms), (CCl_4). 5.83(s)[a], 5.89(s), 6.09(m), 6.54(s), (Nujol). 5.69(m), 5.83(s), 5.89(s)[a], 6.07(m), 6.54(s), (KBr).

[a] Shoulder

(s) strong, (m) medium intensity.

in Table IX and the infrared spectra in the carbonyl - olefin region are tabulated in Table X. The infrared and ultraviolet spectra would tend to rule out structure (LXVIIb) on the basis of comparison with other derivatives of 2,4-pyrandiones (192,193). A tabulation of such derivatives is included in the Appendix for comparison. This did now, however, rule out structure (LXVIIc), although the striking similarities of the spectral properties of (LXVIIa) to known compounds favored this structure.

The problem was unequivocally solved by analysis of the nuclear magnetic resonance spectra of dehydroacetic acid and its derivatives. Dehydroacetic acid gave a NMR spectrum with peaks at -135 cps (-2.25 ppm), which corresponded to the methyl group at the 6-position. This was split ($J = 0.81$ cps) by the olefinic proton. The peak at -154 cps (-2.57 ppm) was a sharp singlet corresponding to the acetyl methyl group. The quartet at -347 cps (-5.78 ppm) corresponding to one proton was the vinylic proton split by the methyl group at the 6-position. When dehydroacetic acid was dissolved in deuterium oxide and the solution made basic by sodium deuteroxide, the peak at -154 cps (-2.57 ppm) disappeared due to the rapid exchange of the acetyl methyl hydrogens with deuterium. This, however, proved little, for if structure (LXVIIc) were the correct one, under the conditions used, exchange would undoubtedly have also taken place. When ethyl dehydroacetate was shaken with deuterium oxide and sodium deuteroxide,. exchange of the replaceable hydrogens of the acetyl methyl group was observed. This would tend to rule out structure (LXVIIc) as a possibility. It would thus appear that (LXVIIa) was the enol structure for the enol ethers, if not dehydroacetic acid itself. This evidence still left the outside possibility that (LXVIIb) (which was ruled out on the basis of infrared evidence) could feasibly be the structure if the acetyl group caused an abnormal shift in the observed infrared spectrum. Therefore, ethyl dehydroacetate was hydrogenated in ethyl alcohol using 5% palladium on charcoal as the catalyst. This yielded a dark, viscous oil which gave an ultraviolet λmax 264.5 m and infrared absorbtions at 5.81(m), 6.04(s), 6.19(s) and 8.00(s) microns. This material gave a strong positive ferric chloride test. The NMR spectrum showed the absence of the O-ethyl grouping indicating that the enol ether was cleaved during the hydrogenation. The 6-methyl group was now present as a doublet at -82 cps (-1.37 ppm), while the acetyl methyl showed as a singlet at -116 cps (-1.93 ppm) which readily exchanged deuterium with deuterium oxide in the presence of sodium deuteroxide. A single proton showed up at -248 cps (-4.13 ppm) as a multiplet, corresponding to the 6-position hydrogen. The remaining hydrogens appeared as non-resolvable multiplets. The absence of two extra protons in the region occupied by the single proton on the C-O carbon rules out (LXVIIb). The spectral data presented constitutes a proof of the enol structure of ethyl dehydroacetate, and if the assumption of the direct relationship of the ether and acid is valid, of dehydroacetic acid (LXVIIa).

CHAPTER IV

EXPERIMENTAL

All melting points and boiling points are uncorrected. Optical rotations were measured on a Josef and Jan Fric polarimeter using a 1 dm. tube. Refractive indices were measured on a Bausch and Lomb, Abbe-3L, refractometer. Analyses by gas - liquid phase chromotography (GLPC) were done by using a Wilkins Aereograph Master Model A-100 instrument equipped with a 10-ft., ¼-in., column packed with a Carbowax - 20M substrate on firebrick. Infrared analyses were carried out using a Perkin-Elmer Model 21 and Model 137 spectrophotometer. Ultravoilet spectra were obtained on a Beckman Model DB spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer. Chemical shifts are reported in both cycles per second (cps) and parts per million (ppm) downfield from tetramethylsilane using deuterated chloroform as solvent, unless otherwise noted.

The pyrolysis apparatus consisted of a pyrex tube, 1-in., O.D., mounted vertically in a 1-ft. Hoskins electric furnace. The column was packed with 6 mm. glass beads to a height of ½-in. and with 1/8-in. Pyrex helices to a height of 17-in. The bottom of the column was connected to a 30 cm. West condenser which was fitted with a 250 ml. flask with a side arm, cooled in a dry ice - acetone bath. To this side arm was attached a trap and a bubbler. At the top of the column, a nitrogen inlet and an addition funnel were placed. The addition funnel was also equipped with a nitrogen inlet. The ester flow rate was adjusted by a stainless steel needle valve. The temperature was measured by a thermometer inserted to a depth of approximately 10-in. in the glass helices.

Derivatives were prepared by the methods presented by Vogel (194) with the following modification; all derivatives were recrystallized from ethanol or ethanol - water solutions at least twice. Melting points were taken in capillary tubes on a Mel-Temp melting point apparatus.

Analyses were done by Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, 164 Banbury Road, Oxford, England.

Purification of d-limonene monoxide (VIII). 1.50 Kg. of commercial grade d-limonene monoxide obtained from Food Machinery and Chemical Corporation, n_D^{20} 1.4697, $\alpha_D^{27}+63.33^\circ$ (neat) (prepared by peracid oxidation), was fractionally distilled over a 3-ft. spinning band column to remove the small percentage of d-limonene present. Two fractions were obtained; (1). d-limonene, b.p. 70°/20 mm., $\alpha_D^{28}+99.06^\circ$ (neat) and (2). *d*-limonene monoxide, b.p. 92-94°/20 mm., α_D^{25}+59.20° (neat), n_D^{25} 1.4654. The distillation was followed by GLPC analysis and the fractions reported were pure. 150 g. of the pure *d*-limonene monoxide was subjected to fractionation over a 3-ft., metal helice packed, Todd column equipped with an automatic fraction cutting distilling head, at atmospheric pressure under nitrogen. Thirty-five cuts were arbitrarily taken. The distillation was followed by the observed optical rotation and refractive index of each cut. Cut #10, b.p. 197°, α_D^{25}+50.80° (neat), n_D^{25} 1.4640, was impure *d*-*cis*-limonene monoxide. Cut #35, b.p. 198°, α_D^{25}+75.34° (neat), n_D^{25} 1.4665, was essentially pure *d*-*trans*-limonene monoxide (Lit. (119): b.p. 66°/3.5 mm., $[\alpha]_D^{20}$+83.70°, n_D^{20} 1.4668, d_4^{20} 0.9303). 110 g. distilled over the range 196-198°. 40 g. was left in the distillation pot as a dark resinous mass which had the distinct spearmint odor characteristic of carvone. There was no separation of the two isomers when analyzed by GLPC over a number of different substrates.

d-neolimonene-1,2-diol (VIIb). 500 g. of commercial grade limonene monoxide, n_D^{20} 1.4697, α_D^{27}+63.33°, was mixed with 2500 ml. of 6% sulfuric acid at ice bath temperature and stirred for 5 hours. The solution was filtered to remove the crude *neo*limonene-1,2-diol dihydrate. After washing with ice water, the glycol was taken up in 1200 ml.

of hot chloroform from which the water of hydration readily separated. The hot chloroform was separated from the water and the neolimonene-1,2-diol crystallized to give 375 g. (67%) of material, m.p. 70.0-70.5°, $[\alpha]_D^{25}$+55° (acetone), (Lit. (30): m.p. 72-73°, $[\alpha]_D$+48°). Anal. Calculated for $C_{10}H_{18}O$: C, 70.55%; H, 10.66%. Found: C, 70.13%; H, 10.75%.

d-1-hydroxy-2-tosyl-8-p-menthene (LXIX). d-neo-limonene-1,2-diol (41.3 g.) was added to a solution of 49.8 g. p-toluenesulfonyl chloride in 100 ml. of dry pyridine. The flask was sealed and the solution stirred at 25° for 48 hours. The reaction was worked up by pouring into a cracked ice - hydrochloric acid solution and extracted with four 75 ml. portions of ether. The ethereal solution was washed with 50 ml. portions of dilute hydrochloric acid, saturated sodium bicarbonate solution and water. The ethereal portion was dried over anhydrous sodium sulfate. The ether was removed under vacuo leaving 43.0 g. (58%) of crude 1-hydroxy-2-tosyl-8-p-menthene. A small portion (8.0 g.) was purified by distillation over a modified Hickman still to yield 7.0 g., n_D^{24} 1.4944, α_D^{24}+51.05° (neat).

d-trans-limonene monoxide (VIIIb). To a solution of 13.5 g. of potassium hydroxide in 100 ml. of methanol was added 35.0 g. of the crude d-1-hydroxy-2-tosyl-8-p-menthene. The reaction immediately became milky in appearance. The reaction was stirred for 30 minutes at room temperature. The reaction mixture was poured into water and extracted five times with 50 ml. portions of ether. The ethereal solution was washed with a 50 ml. portion of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the material distilled to yield 16.6 g. (96%) d-trans-limonene monoxide, b.p. 78.5-80.5°/10 mm., n_D^{24} 1.4657, α_D^{24} +83.22° (neat). Anal. Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.91%; H, 10.50%.

Reaction of d-trans-limonene monoxide with glacial acetic acid - sodium acetate. 500 mg. of d-trans-limonene monoxide, n_D^{25} 1.4665, α_D^{25} +75.34°, was added to a solution of 1.50 g. sodium acetate in 10 ml. of glacial acetic acid. The reaction was stirred at room temperature for 48 hours. The reaction was worked up by pouring into 300 ml. of water and neutralizing the solution with sodium bicarbonate. The aqueous solution was then extracted seven times with 30 ml. portions of ethyl acetate. This was washed with a 50 ml. portion of water and dried over sodium sulfate. The ethyl acetate solution was hydrogenated at 60 p.s.i. on the Paar hydrogenation apparatus using 0.3 g. of platinum oxide as the catalyst. This was done in order to obtain the carvomenthene hydroxyacetates for GLPC analysis since the limonene hydroxyacetates were held on the substrate. The carvomenthene hydroxyacetates were obtained by removing the catalyst by filtration and evaporating the solvent under reduced pressure. The carvomenthene hydroxyacetates (400 mg.), n_D^{25} 1.4596, were analyzed by GLPC. Analysis indicated the hydroxyacetates to be 90% 2-acetoxy-1-hydroxy-p-menthane (1-hydroxy-neocarvomenthyl acetate) and 10% 1-acetoxy-2-hydroxy-p-menthane (1-acetoxy-neoisocarvomenthol). An authentic sample of 1-hydroxy-neocarvomenthyl acetate was used as an internal standard. This indicated that the hydroxyacetates initially formed were 90% 1-hydroxy-neodihydrocarveyl acetate (LXX) and 10% 1-acetoxy-neoisodihydrocarveol (LXXI).

Reaction of peracid d-limonene monoxide with glacial acetic acid - sodium acetate. 76.0 g. of peracid d-limonene monoxide, n_D^{25} 1.4654, α_D^{25}+59.20°, was added to a solution of 41.0 g. sodium acetate in 500 g. glacial acetic acid, with stirring. The temperature rose to approximately 37° but was cooled to 27° and the reaction mixture was stirred at this temperature for a period of 68 hours. The reaction mixture was poured into approximately 2000 ml. of water and extracted seven times with 75 ml. portions of ether. The ethereal solution was neutralized with a saturated sodium bicarbonate solution, washed with 75 ml. of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the limonene hydroxyacetates distilled over a range 132-138°/7 mm. to give 96.0 g. (90.5%) of material, n_D^{25} 1.4742, α_D^{25}+53.60° (neat). Hydrogenation of a small portion in ethyl acetate, as described previously, and analysis by GLPC indicated that the original hydroxyacetate consisted of 46.4% 1-hydroxy-neodihydrocarveyl acetate (LXX), 5.1% 1-acetoxy-neoisodihydrocarveol (LXXI) and 48.5% of 1-acetoxy-neodihydrocarveol (LXXIII).

Pyrolysis of mixed limonene hydroxyacetates. 90.0 g. of mixed limonene hydroxyacetates, b.p. 114°/3 mm., n_D^{25} 1.4750, α_D^{25}+56.80° (neat), prepared as above from peracid limonene monoxide, was pyrolyzed at 370°. The ester was dropped on the pyrolysis column at a rate of 1 drop/27 seconds. The pyrolysate was taken up in ether and washed with a saturated sodium bicarbonate solution until neutralized and then washed once with a 50 ml. portion of water. The solvent was removed under reduced pressure and the pyrolysate distilled over a simple cold finger distilling head under reduced pressure. Two main fractions were collected; (1). b.p. 85-126°/6-8 mm. (32 g.) and (2). 126-130°/6 mm. (35 g.). Analysis of the first fraction by GLPC indicated that there were five components (see Table I). Fractionation of the first cut over a 3-ft. spinning band column yielded the first two components as a single fraction, b.p. 85-87°/8 mm., n_D^{25} 1.4714, α_D^{25}+21.80° (neat), identified as a mixture of isodihydrocarvone and dihydrocarvone (XXXI) by its semicarbazone, m.p. 189° and its 2,4-dinitrophenylhydrazone, m.p. 147-149° (Lit. (195): n_D^{20} 1.4717, α_D -17.75°, d^{19} 0.928, semicarbazone m.p. 189-191°, for l-isomers). The infrared spectrum and GLPC retention times were identical to that of an authentic sample. Anal. Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.77%; H, 10.92%. The third component, b.p. 102°/10 mm., $n_D^{25.5}$ 1.4925, α_D^{25} +82.00° (neat), gave a 3,5-dinitrobenzoate, m.p. 69-69.5°. The physical constants and infrared spectrum indicated that this was identical with the "cis"-1(7),8-p-menthadiene-2-ol isolated by Naves and Grampoloff (Lit. (87): b.p. 71-72°/3 mm., d_4^{20} 0.9457, n_D^{20} 1.4955, $[\alpha]_D$ +94.3°, 3,5-dinitrobenzoate m.p. 69-69.5°). Anal. Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.67%; H, 10.86%. Hydrogenation of a 1.0 g. portion of this alcohol in 25 ml. of ethyl acetate with 0.1 g. platinum oxide catalyst at 60 p.s.i. on the Paar hydrogenation shaker gave a 1.0 g. mixture of 24.5% neocarvomenthol and 75.5% isocarvomenthol as analyzed by GLPC using authentic samples as internal standards. The hydrogenation product was distilled over a modified Hickman still to yield a carvomenthol sample, n_D^{25} 1.4630, α_D^{25} +21.06°. Preparation of the 3,5-dinitrobenzoate by means of the acid chloride in pyridine gave a crystalline derivative, m.p. 111°, corresponding to that of isocarvomenthol. (Lit. (196):

m.p. 111°). The pyrolysis product was thus identified as *d-trans*-1(7),8-*p*-menthadiene-2-ol (*d-trans-iso*carveol) (VIc). The fourth component, b.p. 106°/10 mm., n_D^{25} 1.4934, α_D^{25}-181.80° (neat) was identified as *l-trans*-carveol (VIb) (Lit. (195): b.p. 102.2-102.4°/10 mm., n_D^{25} 1.4942, $[\alpha]_D^{25}+213^{\circ}6$ for *d*-isomer). *Anal.* Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.96%; H, 10.80%. This alcohol gave a 3,5-dinitrobenzoate, m.p. 111° (Lit. (195): m.p. 111.5°). The *l-trans*-carveol gave 63% *neo*carvomenthol and 37% *iso*carvomenthol on hydrogenation in ethyl acetate as described for *trans-iso*carveol. Analysis was done by GLPC using authentic samples as internal standards. The fifth component, b.p. 108°/10 mm. was identified by GLPC and its infrared spectrum as impure *cis*-carveol (VIa) by comparison with an authentic sample. Pyrolyses at 342°, 396°, 436° and 450° were carried out in a similar manner. The results are tabulated in Table I.

The second fraction from the crude distillation was *trans*-2-acetoxy-1-hydroxy-8-*p*-menthene (1-hydroxy-*neo*dihydrocarveyl acetate) (LXX). Redistillation gave a pure fraction, b.p. 143°/10 mm., n_D^{25} 1.4728, α_D^{25}+73.50° (neat). This hydroxyacetate formed a 3,5-dinitrobenzoate, m.p. 161-162°. *Anal.* Calculated for $C_{12}H_{20}O_3$: C, 67.89%; H, 9.50%. Found: C, 67.63%; H, 9.56%.

Liquid phase pyrolysis of mixed limonene hydroxy-

acetates. 25 g. of a mixture of limonene hydroxyacetates was distilled over a 3-ft. spinning band column under nitrogen at atmospheric pressure. The crude pyrolysate, b.p. 70-220°, was analyzed by GLPC and neglecting the acetic acid formed, the reaction mixture consisted of 40% dihydrocarvone, 40% 2,8-p-menthadien-1-ol and 20% carveols. The hydroxyacetate pyrolyzed was not analyzed prior to its pyrolysis and thus the composition was not necessarily the same as reported for the limonene hydroxyacetates previously described.

Preparation of 1-cis-carveol (VIa). 45.0 g. l-carvone, n_D^{25} 1.4967, α_D^{25}-58.47° (neat), was reduced with lithium aluminum hydride according to the procedure of Reitsema (171) to give 40.5 g. (89%) crude l-carveol, n_D^{23} 1.4940, α_D^{25}-32.40° (neat) which was distilled to give 39.9 g. l-carveol, n_D^{25} 1.4955, α_D^{25}-32.74° (neat) which was shown by GLPC analysis to be 94.4% l-cis-carveol and 5.6% l-trans-carveol.

Pyrolysis of d-1-hydroxy-neodihydrocarveyl acetate (LXX). Pyrolysis of d-1-hydroxy-neodihydrocarveyl acetate (34.0 g.) at 455°, the ester dropping on the pyrolysis column at a rate of 1 drop/30 seconds, yielded a crude pyrolysate which was taken up in 200 ml. ether and neutralized with a saturated sodium bicarbonate solution. The ethereal solution was then washed with 50 ml. of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the pyrolysate distilled to give 21 g. (86.5%) of crude *d*-*trans*-2,8-p-menthadien-1-ol (Xa), b.p. 90-101°/10 mm., n_D^{25} 1.4838, α_D^{25}+41.62° (neat). Fractionation over a 3-ft. spinning band column yielded a cut, b.p. 81-83°/7 mm., n_D^{26}1.4826, α_D^{26}+46.70° (neat) (Lit. (87,172): b.p. 68-69°/3 mm., d_4^{20}0.9429, n_D^{20}1.4900, $[\alpha]_D^{20}$+68.9°). *Anal*. Calculated for $C_{10}H_{16}O$: C, 78,89%; H, 10.59%. Found: C, 79.06%; H, 10.75%. The infrared spectrum corresponded to that reported (87). Hydrogenation by the procedure previously described for *trans*-*iso*carveol, gave *trans*-*p*-menthan-1-ol, which was purified by distillation over a modified Hickman still to give 2.3 g., n_D^{24}1.4564 α_D^{24}+0.83° (neat) (Lit. (87): b.p. 67-68°/3 mm., n_D^{20}1.4600, α_D^{20}+0.02°). The *trans*-*p*-menthan-1-ol gave a 3,5-dinitrobenzoate, m.p. 82-83° (Lit. (87): m.p. 83-83.5°). The infrared spectrum of the *trans*-*p*-menthan-1-ol was identical to that reported (87). Analysis by GLPC showed this alcohol to be better than 95% pure.

Oxidation of l-trans-carveol. 3.00 g. of *l*-*trans*-carveol, from the pyrolysis of l-acetoxy-*neo*dihydrocarveol, was slowly dropped into a solution of 4.00 g. chromic anhydride in a solution of 10 ml. acetone, 25 ml. water and 5 ml. ether which had been precooled to 10°. The addition rate was such that the temperature never rose above 15°.

The reaction was then stirred, at 15°, for a period of 10 hours. The ether layer was separated and the aqueous phase extracted three times with 25 ml. ether. The ethereal layers were combined and washed with 25 ml. portions of water, sodium bicarbonate and water again. The ethereal layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield 2.60 g. of a yellow oil which was shown by GLPC analysis to be a mixture of 61% carvone, 32% trans-carveol and 7% cis-carveol. The carvone had an ultraviolet λmax at 235 mμ and gave a 2,4-dinitrophenylhydrazone, m.p. 186° (Lit. (195): m.p. 189°). The yield of carvone (1.57 g.), based on the percent carveol reacted, was 79%.

d-cis-limonene monoxide (VIIIa). 21.2 g. of 1-hydroxy-neodihydrocarveyl acetate was added to a solution of 12.0 g. menthane sulfonyl chloride in 45 ml. of dry pyridine at 15° and the reaction vessel sealed. The temperature was allowed to rise to 25° and the reaction stirred for 58 hours. The reaction mixture was then poured into a cracked ice - hydrochloric acid solution and extracted three times with 50 ml. portions of ether. The ethereal layer was then washed once with 50 ml. of a saturated sodium bicarbonate solution and one time with a 50 ml. portion of water. The ethereal layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield

24.5 g. of crude trans-1-mesyl-2-acetoxy-8-p-menthene (LXXII), n_D^{23} 1.4787, α_D^{23} -7.38° (neat). 20.0 g. of the crude mesylate was added to a solution of 12.0 g. postassium hydroxide in 100 ml. of 75% methanol. The reaction was stirred for 48 hours at room temperature. The reaction mixture was then poured into 700 ml. of water and extracted four times with 50 ml. portions of ether. The ethereal portions were washed twice with 50 ml. portions of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield a liquid which contained crystalline material. 50 ml. of pentane was added, causing a mass of crystals to precipitate. The crystals were filtered and the pentane removed from the liquid portion under reduced pressure. The crystals, (2.10 g.), m.p. 55-57°, were recrystallized from a benzene - pentane solution to give neolimonene-1,2-diol (18%), m.p. 68-69°, identical with an authentic sample. No melting point depression occurred on admixture and the infrared spectra were identical. Distillation of the liquid on a microware distillation head equipped with a 5-in. vigreaux column gave 3.10 g. d-cis-limonene monoxide (29%), b.p. 96-98°/26 mm., $n_D^{23.5}$ 1.4683, $\alpha_D^{23.5}$ +36.00° (neat), and 4.00 g. of mixed trans-carveol and trans-isocarveol (38%), b.p. 96-115°/10 mm., $n_D^{23.5}$ 1.4894, $\alpha_D^{23.5}$ +119.00° (neat). The limonene monoxide and carveols were identified by GLPC and their infrared spectra compared to peracid limonene monoxide and authentic samples of the carveols. 1.0 g. of *d*-*cis*-limonene monoxide was hydrated in 10 ml. of 1% sulfuric acid to yield *neo*limonene-1,2-diol dihydrate which upon loss of the water of hydration and recrystallization from benzene - pentane gave *d*-*neo*limonene-1,2-diol, m.p. 70-71°, $[\alpha]_D^{25}$ +53° (acetone).

Reaction of d-cis-limonene monoxide with glacial acetic acid - sodium acetate. 600 mg. of *d*-*cis*-limonene monoxide was mixed with 10 ml. of glacial acetic acid and 1.0 g. sodium acetate and the reaction mixture was allowed to stir for 48 hours. The reaction mixture was then poured into 50 ml. of water and extracted seven times with 10 ml. portions of ethyl acetate. The ethyl acetate portions were washed with a saturated sodium bicarbonate solution until neutral and then with a 40 ml. portion of water. The ethyl acetate layer was dried over anhydrous sodium sulfate. Hydrogenation, as was described for the hydroxyacetates formed from *trans*-limonene monoxide, yielded a hydroxyacetate that was shown to be at least 95% pure by GLPC and was identified as the 1-acetoxy-2-hydroxy-*p*-menthane (1-acetoxy-*neo*carvomenthol) indicating the limonene hydroxyacetate to be 1-acetoxy-*neo*dihydrocarveol (LXXIII). Identification was made by use of internal standards which had been identified by their pyrolysis products. An attempt to prepare the 3,5-dinitrobenzoate of the 1-acetoxy-neocarvomenthol was unsuccessful.

Carvomenthene oxides (XIV). 15.2 g. (0.10 mole) of peracid limonene monoxide, b.p. 92-94°, n_D^{25} 1.4654, α_D^{25}+59.20° (neat) was placed in 250 ml. of ethyl acetate with 0.5 g. of platinum oxide and hydrogenated at 60 p.s.i. on the Paar hydrogenation apparatus. When an 8 p.s.i. pressure drop had occurred (corresponding to a 0.10 mole absorbtion of hydrogen), the hydrogenation was stopped. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. Distillation of the carvomenthene oxides produced, gave a nearly quantitative yield of epoxide, b.p. 72-75°/10 mm., n_D^{25} 1.5404, α_D^{25}+51.46° (neat). This corresponded to an approximately 1 : 1 ratio of cis- and trans-carvomenthene oxide, since the ratio of the limonene monoxides was known.

Reaction of the carvomenthene oxides with glacial acetic acid - sodium acetate. 77.0 g. of peracid carvomenthene oxide, from the hydrogenation of peracid limonene monoxide above, was added to a solution of 41.0 g. sodium acetate in 350 ml. glacial acetic acid and the resultant solution stirred for a period of 68 hours at room temperature. The reaction mixture was poured into 1500 ml. of water and extracted seven times with 50-75 ml. portions of ether. The ethereal layers were combined and neutralized with a saturated sodium bicarbonate solution. The neutralized ethereal layer was washed twice with 100 ml. portions of water and dried over anhydrous sodium sulfate. The ether was removed under vacuo and the crude hydroxyacetates distilled over a simple cold finger still to give 91.2 g. (86%) of mixed hydroxyacetates, b.p. 120-136°/7 mm. (mainly 133-135°/7 mm.), n_D^{25} 1.4629, $\alpha_D^{25}+56.80°$ (neat). Analysis by GLPC showed the hydroxyacetate mixture to consist of 46.5% 1-hydroxy-neocarvomenthyl acetate (LXXVII), 5.3% 1-acetoxy-neoisocarvomenthol (LXXVI) and 48.2% of 1-acetoxy-neocarvomenthol (LXXV). As this was essentially the same ratio as was obtained upon hydrogenation of the mixed limonene hydroxyacetates, a second method of preparation was afforded.

Pyrolysis of mixed carvomenthene hydroxyacetates. 240 g. of a mixed carvomenthene hydroxyacetate fraction, b.p. 140-141°/10 mm., n_D^{23} 1.4616, $\alpha_D^{23}+57.80°$ (neat), prepared by hydrogenation of the limonene hydroxyacetates, was pyrolyzed at 392°. The ester was dropped on the pyrolysis column at a rate of 1 drop/27 seconds. The pyrolysate was taken up in ether and neutralized with a saturated sodium bicarbonate solution. The ether layer was then washed with two 50 ml. portions of water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the pyrolysate distilled over a simple cold finger distilling head to give two fractions; (1). b.p. 87-130°/6-7 mm. (86 g.) and (2). b.p. 132-135°/8 mm (98 g.). Analysis of the first cut by GLPC indicated the presence of at least six constituents (see Table II). Fractional distillation of the first cut over a 3-ft. spinning band column initially yielded a fraction, b.p. 57-70°/4 mm. which was subsequently shown to be impure 2-p-menthen-1-ol by GLPC using an authentic sample as an internal standard. The first major component, b.p. 72°/4 mm., n_D^{23} 1.4596, α_D^{23}+14.60° (neat) corresponded to a mixture of d-isocarvomenthone and d-carvomenthone (XXVIII). Anal. Calculated for $C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 77.29%; H, 11.56%. This component was identified by GLPC and its infrared spectrum compared to an authentic sample. The ketone formed a semicarbazone, m.p. 176-177°, (Lit. (195): n_D^{30} 1.4531, d_{30}^{30}0.900, $[\alpha]_D^{30}$-9.33°, for the l-isomer). The third component, b.p. 98-100°/10 mm., n_D^{25} 1.4765, α_D^{25}+62.91° (neat) was identified as the previously unreported d-trans-1(7)-p-menthen-2-ol (d-trans-isocarvotanacetol) (XIIIc). The alcohol gave a 3,5-dinitrobenzoate, m.p. 80.5-81.5°. The infrared spectrum with absorbtions at 3.25 and 6.03 microns was indicative of a terminal methylene group. Anal. Calculated for $C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 77.22%; H, 11.94%. Hydrogenation, as described for trans-isocarveol, gave 25% neocarvomenthol and 75% isocarvomenthol, as indicated by

GLPC analysis using authentic samples as internal standards. The fourth component, b.p. 101-102°/10 mm., $n_D^{23.5}$ 1.4772, $\alpha_D^{23.5}$ -164.80° (neat), corresponded to l-*trans*-carvotanacetol (XIIIa) and formed a 3,5-dinitrobenzoate, m.p. 115°, (Lit. (196): b.p. 101°/13 mm., n_D^{20} 1.4800, $[\alpha]_D^{17}$+100.5°; (197): 3,5-dinitrobenzoate, m.p. 109-110°). *Anal*. Calculated for $C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 77.86%; H, 11.98%. Hydrogenation, as described previously for *trans*-*iso*carveol, gave 64% *neo*carvomenthol and 36% *iso*carvomenthol. Analysis was done by GLPC using authentic samples as internal standards. The last component of the pyrolysate was assumed to be *cis*-carvotanacetol (XIIIb), by analogy with the pyrolysis of the limonene hydroxyacetates, although it was not isolated. Similar pyrolyses of the 1-acetoxycarvomenthols at 375° and 400° are tabulated in Table II.

The second cut from the crude distillation of the pyrolysate, b.p. 132-135°/8 mm., n_D^{25} 1.4606, α_D^{25}+70.90° (neat) corresponded to 1-hydroxy-*neo*carvomenthyl acetate (LXXVII). This hydroxyacetate appeared to be homogeneous by GLPC analysis. The hydroxyacetate formed a 3,5-dinitrobenzoate, m.p. 155-155.5°. It was noted that for both the limonene hydroxyacetates and the carvomenthene hydroxyacetates, that when the infrared spectra were taken neat, two carbonyl bands appeared at 5.74 and 5.79 microns, whereas in carbon tetrachloride solution only a single band at 5.75 microns occurred.

d-1-hydroxy-neocarvomenthyl acetate (XXVIII). 2.0 g. of 1-hydroxy-*neo*dihydrocarveyl acetate, b.p. 143°/10 mm., n_D^{20} 1.4750, α_D^{25}+73.50° (neat) was placed in 100 ml. ethyl acetate with 0.5 g. platinum oxide catalyst and hydrogenated at 60 p.s.i. on the Paar hydrogenation apparatus. The catalyst was removed by filtration and the solvent removed under reduced pressure. The crude hydroxyacetate was distilled over a modified Hickman still to yield 2.0 g. of 1-hydroxy-*neo*carvomenthyl acetate, n_D^{26} 1.4583, α_D^{26}+81.00° (neat). *Anal.* Calculated for $C_{12}H_{22}O_3$: C, 67.25%; H, 10.35%. Found: C, 67.72%; H, 10.48%.

Pyrolysis of 1-hydroxy-neocarvomenthyl acetate. 19.0 g. of 1-hydroxy-*neo*carvomenthyl acetate was pyrolyzed at 450°, under the prescribed pyrolysis conditions. The ester was dropped on the pyrolysis column at a rate of 1 drop/27 seconds. The crude pyrolysate was taken up in ether and neutralized with a saturated sodium bicarbonate solution. The ethereal layer was then washed with a 50 ml. portion of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, leaving 11.3 g. (84%) of crude *l*-*trans*-2-*p*-menthen-1-ol (XVa). Distillation over a modified Hickman still gave 8.7 g. of material, n_D^{25} 1.4674, α_D^{25}-13.02° (neat) (Lit. (27,28): b.p. 85°/10 mm., n_D^{25} 1.4698, $[\alpha]_D^{25}$-17.2°, d^{25} 0.915, f.p. 6-8°). *Anal.* Calculated for

$C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 78.01%; H, 11.60%. Hydrogenation of 2.5 g. l-trans-2-p-menthen-1-ol, by the procedure described for trans-isocarveol, gave 2.2 g. of material after distillation over a modified Hickman still, n_D^{23} 1.4555, α_D^{23} +2.30°. Analysis by GLPC indicated the sample contained approximately 5% impurity. This trans-p-menthan-1-ol gave a 3,5-dinitrobenzoate, m.p. 83° (Lit. (87): m.p. 83-83.5°).

Lithium aluminum hydride reduction of peracid limonene monoxide. 47.0 g. of peracid limonene monoxide, n_D^{25} 1.4654, α_D^{25} +59.20° (neat) was dropped into a slurry of 3.10 g. of lithium aluminum hydride in 130 g. of dried diethyl ether with stirring. The reaction was refluxed for 36 hours. After cooling to room temperature, water was added dropwise until a flocculent precipitate formed. The precipitate was filtered and washed with 50 ml. of ether. The solvent was removed from the filtrate under reduced pressure and the resultant product distilled over a 3-ft. spinning band column. Analysis of the crude product by GLPC prior to distillation indicated two major components and four minor components. The percentage composition was determined to be 9% cis-limonene monoxide, 48% trans-β-terpineol, 5% cis-β-terpineol, 29% neodihydrocarveol and 9% of two unidentified products. The products were identified by distillation and isolation. The first component, b.p. 85-

90°/10 mm., n_D^{23} 1.4650, α_D^{23}+38.50° (neat) corresponded to *d*-*cis*-limonene monoxide. This was indicated by GLPC and its infrared spectrum compared to an authentic sample. The second component, b.p. 100°/10 mm., n_D^{23} 1.4740, α_D^{23}+0.02° (neat, supercooled), m.p. 31°, was *trans*-β-terpineol (XVd) (Lit. (82): b.p. 97°/17 mm., n_D^{20} 1.4747, d_4^{20} 0.9197, m.p. 32°). *Anal.* Calculated for $C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 77.57%; H, 12.09%. The third component was tentatively assigned as *cis*-β-terpineol (XVe), b.p. 104.5°/10 mm., n_D^{23} 1.4763 (Lit. (82): b.p. 78°/1.5 mm., n_D^{20} 1.4793, d_4^{20} 0.9258). The fourth component, b.p. 107°/8 mm., n_D^{23} 1.4784, α_D^{23}+29.60° (neat), was *d*-*neo*dihydrocarveol (XVc) (Lit. (175): b.p. 96-97°/9 mm., d^{15} 0.930, n_D^{20} 1.4802, $[\alpha]_D$-32.5° for the *l*-isomer). Hydrogenation of *d*-*neo*dihydrocarveol, as described for *trans*-*iso*carveol, gave *neo*carvomenthol as the only product. Analysis was by GLPC using an authentic sample as an internal standard. Several other unidentified products were present in the fraction, b.p. 108-111°/9 mm. 36.3 g. (74%) of distillate was obtained.

Reaction of peracid limonene monoxide with sodium powder in benzene. 152 g. of peracid limonene monoxide, b.p. 92-94°/20 mm., n_D^{25} 1.4641, α_D^{25}+60.75° (neat) was slowly added to a slurry of 92 g. of 50% sodium powder dispersion in 500 ml. of dry benzene. The reaction became quite hot and ran out of control, with the subsequent loss of some of the reaction mixture. The reaction was then refluxed for 10 hours. After cooling, the excess sodium was reacted with methanol. The reaction mixture was poured into 1000 ml. of water and the organic phase separated. The aqueous phase was extracted seven times with 75 ml. portions of ether which were combined with the organic layer. The ethereal solution was then washed with 150 ml. portions of dilute hydrochloric acid, saturated sodium bicarbonate and water. The organic phase was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resultant product distilled. 68.0 g. of distillate, b.p. 84-125°/8 mm. and 28.0 g. of pot residue were obtained. This corresponded to 29.5% polymer and mineral oil and 70.5% distillate of the organic material recovered. The crude distillate was then fractionated over a 3-ft. spinning band column. Prior to fractionation the distillate was analyzed by GLPC, the products each being individually identified by use of an authentic sample as an internal standard, when available. The analysis showed 7.1% limonene, 1.7% unidentified hydrocarbon, 3.0% limonene monoxide, 21.0% <u>trans</u>-β-terpineol, 23.0% dihydrocarvone, 4.5% <u>neo</u>-dihydrocarveol (?), 23.6% dihydrocarveol, 3.2% <u>trans</u>-<u>iso</u>-carveol (?), 7.6% unidentified alcohols and 5.3% <u>cis</u>-carveol. Fractionation allowed the isolation in a relatively pure state of *trans*-β-terpineol, b.p. 99-100°/10 mm., n_D^{25} 1.4736, α_D^{25}+0.08° (neat, supercooled), m.p. 30°, identified by GLPC and its infrared spectrum compared to the authentic sample prepared from the lithium aluminum hydride reduction. The second major component, b.p. 104°/10 mm., n_D^{25} 1.4700, α_D^{25}+16.35° (neat), was identified by GLPC and its infrared spectrum to be *d*-*iso*dihydrocarvone and *d*-dihydrocarvone. The third component, b.p. 108°/10 mm., n_D^{25} 1.4775, α_D^{25}-16.35° (neat) contained about 10% of an impurity. This material gave a 3,5-dinitrobenzoate, m.p. 122-122.5°. Hydrogenation of a sample gave nearly pure carvomenthol, as identified by GLPC and its infrared spectrum compared to an authentic sample. *Anal.* Calculated for $C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 78.13%; H, 12.25%. This corresponded to a slightly impure sample of *l*-dihydrocarveol (XVb) (Lit. (175): b.p. 99-102°/9 mm., d^{15} 0.924, n_D^{20} 1.4778, α_D+31°, 3,5-dinitrobenzoate, m.p. 122-123°, for the *d*-isomer). The top fraction, b.p. 110-114°/10 mm., was regarded as a slightly impure sample of *cis*-carveol on the basis of GLPC and its infrared spectrum compared to an authentic sample. This fraction gave an impure 3,5-dinitrobenzoate, m.p. 86-88° (Lit. (195): m.p. 92.0-92.5°).

Reaction of d-trans-limonene monoxide with sodium powder and benzene. 2.0 g. of pure *d*-*trans*-limonene monoxide was added to 1.0 g. of 50% sodium dispersion in 20 ml. of dry benzene. The reaction mixture was heated to reflux for a period of 30 minutes. The reaction was cooled and an excess of ethanol added as rapidly as possible. The reaction was then poured into 500 ml. of water. The reaction mixture was extracted with four 50 ml. portions of ether. The ethereal layer was washed with 50 ml. portions of dilute hydrochloric acid, saturated sodium bicarbonate solution and water; it was then dried over anhydrous sodium sulfate. The solvent was removed under *vacuo* and the crude oil subjected to analysis by GLPC using internal standards for identification. The following components were present; limonene, a trace of a second hydrocarbon, limonene monoxide, *trans*-β-terpineol (major component), dihydrocarveol, and *cis*-carveol.

Reaction of peracid limonene monoxide with sodium powder in diethyl ether. 16.2 g. of peracid limonene monoxide was added to a solution of 9.2 g. of 50% sodium powder slurry in 100 ml. of dry ether. The reaction mixture was refluxed for 24 hours. After cooling, the excess sodium was reacted with methanol. The reaction mixture was poured into water and the aqueous phase extracted three times with 75 ml. portions of ether. The ethereal extracts were washed with 75 ml. portions of dilute hydrochloric acid, a 5% sodium bicarbonate solution

solution and water. The ethereal solution was removed under vacuo and the residue distilled to give 16.0 g. of distillate, 68-110°/7 mm. Analysis of the distillate by GLPC indicated 61% dihydrocarvone, 25% trans-β-terpineol, 5% cis-carveol, 4% dihydrocarveol, and 10% hydrocarbons (mainly limonene).

Reaction of peracid limonene monoxide with refluxing 20% sulfuric acid. 24.0 g. of peracid limonene monoxide was rapidly dropped into 150 ml. of vigorously refluxing 20% sulfuric acid. The reaction was refluxed for 4 hours, cooled and poured into 500 ml. of water. The oil layer was separated and the aqueous phase extracted five times with 50 ml. of ether. The organic phases were combined and neutralized with a sodium carbonate solution. The ethereal phase was then washed with 50 ml. of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure leaving a crude oil which yielded 20.9 g. of distillate, b.p. 45-98°/5 mm. GLPC analysis indicated that the distillate consisted of 43.5% p-cymene and 56.5% carvenone. Fractionation over a 3-ft. spinning band column gave a fraction (8.2 g.), b.p. 53-60°/10 mm., n_D^{25} 1.4935, which corresponded to a 39% yield of p-cymene. A fraction (9.4 g.), b.p. 87-95°/10 mm., n_D^{25} 1.4818, α_D^{25}+1.20° (neat) corresponding to a 39% yield of carvenone, was obtained. These products were identified by GLPC and their infrared spectra compared to authentic samples. The carvenone gave a 2,4-dinitrophenylhydrazone, m.p. 163-165°.

Hydration and acid isomerization of peracid limonene monoxide. Procedures and results are given for typical runs. The sulfuric acid concentration was varied in 5% increments from 20-65%.

Typical procedure. 76.0 g. of peracid limonene monoxide was slowly dropped into a solution of sulfuric acid at 0-5° over a $2\frac{1}{2}$ hour period. The reaction was then allowed to stir for a period of 8-72 hours after addition. The reaction temperature was allowed to rise to room temperature approximately 6 hours after addition. The reaction mixture was poured into cracked ice and neutralized with solid potassium carbonate. The potassium sulfate formed was filtered and washed with absolute ethanol. The aqueous phase was extracted three times with 100 ml. of ether, the ether layer washed with 50 ml. of water and dried over anhydrous sodium sulfate. The ethanol washings were combined with the aqueous phase and evaporated. The aqueous phase generally yielded a heavy viscous oil containing alcohols and residual water. The aqueous oil was subjected to continuous chloroform extraction for 48 hours. Any solid alcohols were then crystallized from the chloroform and recrystallized from ethyl acetate. The ethereal solution was distilled, after removal of solvent, under reduced pressure.

Typical results. A 50% acetic acid - 15% sulfuric acid solution, reacted for 48 hours, yielded 6 g. dihydrocarvone, 15 g. 1,8-dihydroxy-neocarvomenthol, m.p. 136°, and 20 g. of an alcohol, m.p. 302°, which after 6 months melted at 147-149°. Recrystallization of this fraction yielded an alcohol, m.p. 155-156°.

A 20% sulfuric acid solution, reacted for 24 hours, yielded 7 g. of liquid organic material which consisted of dihydrocarvone > carvenone > pinol > p-cymene. The alcoholic fraction yielded 37 g. of crude 1,8-dihydroxy-neocarvomenthol, m.p. 126-128°.

A 35% sulfuric acid solution, reacted for a period of 8 hours, gave 20.5 g. of liquid organic material which analysis by GLPC showed to be mainly dihydrocarvone > carvenone > p-cymene and pinol, along with trace amounts of several low boiling unidentified materials. The water soluble fraction yielded 25 g. of crude triol, m.p. 118-120°, which after four recrystallizations melted at 135-136°.

A 50% sulfuric acid solution, reacted for 18 hours, yielded 40 g. of liquid which consisted of 35% carvenone, 25% dihydrocarvone, 25% pinol and 10% p-cymene as well as 5% unidentified material. Analysis was done by GLPC using authentic samples as internal standards. The aqueous phase was lost on this run.

A 50% sulfuric acid solution, stirred at approximately 5° for 18 hours, gave 29 g. of liquid material consisting of dihydrocarvone > carvenone > pinol > p-cymene. This experiment gave 15 g. of alcohols which yielded three crops on recrystallization; (1). m.p. 90-95°, (2). m.p. 115-122°, (3). m.p. 146-148°. Chromatography over basic alumina (pH 8) using chloroform as the elutant of crops (1). and (2). yielded alcohols melting at 114.5-115.5° and 136° respectively. Recrystallization of (3). from ethyl acetate yielded an alcohol, m.p. 155-156°.

Identification of products. Combination of the liquid organic material from several runs gave enough material to conveniently fractionate the reaction products over a 3-ft. spinning band column. The fraction, b.p. 68-69.5°/20 mm., n_D^{25} 1.4938, corresponded to p-cymene. The second component, b.p. 69-72°/20 mm., n_D^{25} 1.4739, was pinol (contaminated with some p-cymene). The third component, b.p. 97-105°/20 mm., n_D^{25} 1.4701, α_D^{25}+12.43° (neat), was dihydrocarvone. This fraction on redistillation gave material, b.p. 92°/9 mm., n_D^{20} 1.4709, α_D^{20}+15.75° (neat). The fourth component, b.p. 110-115°/20 mm., was carvenone which on redistillation gave material, b.p. 81°/5 mm., n_D^{20} 1.4825, α_D^{20}+1.14° (neat). The dihydrocarvone fraction gave a 2,4-dinitrophenylhydrazone, m.p. 148-149°. The carvenone fraction gave a 2,4-dinitrophenylhydrazone, m.p. 165°. All samples were identified by GLPC and their infrared spectra compared to authentic samples. The alcohol derivative, m.p. 136°, $[\alpha]_D^{25}+55^\circ$ (acetone), corresponded to the 1,8-dihydroxy-neocarvomenthol (IVb) (Lit. (30): m.p. 136°, $[\alpha]_D^{25}+54^\circ$ (acetone)). Anal. Calculated for $C_{10}H_{20}O_3$: C, 63.80%; H, 10.71%. Found: C, 63.89%; H, 10.80%. The alcohol, m.p. 114.5-115.5°, $[\alpha]_D^{25}\pm0^\circ$, gave an infrared spectrum different from that of the other 1,8-dihydroxy-carvomenthols. Analysis indicated this to be a hydrate. Anal. Calculated for $C_{10}H_{20}O_3\cdot\frac{1}{2}H_2O$: C, 60.88%; H, 10.73%. Found: C, 60.79%; H, 10.93%. The alcohol, m.p. 155-156°, $[\alpha]_D^{25}\pm0^\circ$, gave an infrared spectrum different from the other 1,8-dihydroxy-carvomenthols (p-menthane triols). Anal. Calculated for $C_{10}H_{20}O_3$: C, 63.80%; H, 10.71%. Found: C, 63.33%; H, 10.75%.

Oxidation of 1,8-dihydroxy-neocarvomenthol (IVb). 1.88 g. of 1,8-dihydroxy-neocarvomenthol was dissolved in a 20 ml. solution of 1 : 2 ether-acetone and a solution of 2.00 g. chromic anhydride in 22.5 ml. of 10% sulfuric acid was dropped in over a 15 minute period. The temperature was controlled at 25-30° by means of a cold water bath. The reaction was then stirred at room temperature for 6 hours. The ether layer was separated from the aqueous phase. The aqueous phase was extracted twice with 20 ml. of ether. The ethereal layers were combined, neutralized with a saturated sodium bicarbonate solution, washed with 20 ml. of water and dried over anhydrous sodium sulfate. The ether was evaporated to yield 1.20 g. of crude l-homoterpinyl methyl ketone (XXIV), m.p. 40.5°, $[\alpha]_D^{25}$-40° (acetone). The lactone melted at 45° upon recrystallization (Lit. (29): m.p. 47°, $[\alpha]_D$-42° (acetone)). The infrared spectrum showed bands at 5.61 and 5.81 microns, indicative of a keto-lactone.

dl-1,8-dihydroxy-carvomenthol (IVa). 73.0 g. of dl-α-terpineol, b.p. 98-99°/10 mm., n_D^{20} 1.4830, was added in five 15 g. portions to a solution of 75 g. potassium permanganate in 2500 ml. of water, cooled to 5°. The temperature was maintained at 5-8° during the 4 hour reaction time. The purple permanganate color changed to brown as the manganese dioxide was produced. The manganese dioxide was filtered and the aqueous solution evaporated after extracting once with 100 ml. of ether to remove any unreacted α-terpineol. When the volume was reduced to approximately 700 ml., the aqueous phase was subjected to continuous extraction with chloroform for a 48 hour period. The alcohol was crystallized from the chloroform and recrystallized from ethyl acetate to give pure dl-1,8-dihydroxy-carvomenthol, m.p. 122° (Lit. (196): m.p. 121-122°). This alcohol gave a different infrared spectrum from the three 1,8-dihydroxy-carvomenthols described above.

Oxidation of dl-α-terpineol with formic acid - hydrogen peroxide. To a mixture of 77 g. *dl*-α-terpineol and 500 ml. 89% formic acid was added 60 g. of 30% hydrogen peroxide over a 15 minute period. The reaction was stirred for 12 hours at 30°. The reaction was then heated to 55-60° and the formic acid removed under *vacuo*. When most of the formic acid had been removed, the flask was charged with 80 ml. of 20% sodium hydroxide and gently refluxed for 20 minutes. The reaction was then cooled and neutralized with dilute hydrochloric acid. The liquid was then evaporated under reduced pressure and the residue extracted four times with 150 ml. of ether. The extracts were dried over anhydrous sodium sulfate. The solvent was removed under vacuo and the residue distilled to give 53 g. of material, b.p. 110-165°/5 mm., which was arbitrarily cut into three fractions. The low boiling fraction, b.p. 110-140°/5 mm., contained carbonyl compounds as indicated by the infrared spectrum. The high boiling fraction, 160-165°/5 mm., set up to a hard, resinous substance of amber like appearance. From this fraction, 0.4 g. of triol, m.p. 94°, was crystallized from ethyl acetate. This material gave an infrared spectrum identical to that of *d*-1,8-dihydroxy-*neo*carvomenthol. A crude sublimation gave the alcohol in what was still probably a slightly impure state, m.p. 111°. No attempt was made to further purify this substance or improve the oxidation procedure.

Hydrogenation of d-neolimonene-1,2-diol. Hydrogenation of 2.5 g. of d-neolimonene-1,2-diol by the procedure described for trans-isocarveol, gave 2.5 g. of crude d-1-hydroxy-neocarvomenthol. On recrystallization from the benzene - petroleum ether, the alcohol melted at 88°, $[\alpha]_D^{25}+48^\circ$ (acetone) (Lit. (30): m.p. 88°, $[\alpha]_D+44^\circ$).

Isomerization of peracid limonene monoxide with boron trifluoride - etherate in benzene. 100 g. of peracid limonene monoxide was added to 400 g. of dry benzene containing 3.0 g. of predistilled boron trifluoride - etherate and gently refluxed for 24 hours. After 8 hours another 3.0 g. of boron trifluoride - etherate was added. The reaction turned black after about 3½ hours. After cooling, the benzene solution was repeatedly washed with 100 ml. portions of saturated sodium bicarbonate and water. The organic phase was dried over anhydrous sodium sulfate, the solvent removed under reduced pressure and the resultant product distilled. 50 g. of material, b.p. 94-98°/7 mm., was obtained which on redistillation gave, nearly quantitatively, a material, b.p. 94°/7 mm., n_D^{25} 1.4805, $\alpha_D^{25}+1.86^\circ$ (neat). Anal. Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.34%; H, 10.53%. This corresponded to a 45.5% yield of pure carvenone as analyzed by GLPC. 11 g. of high boiling alcohols were obtained and 45 g. of resinous material remained as pot residue.

Isomerization of peracid limonene monoxide with boron trifluoride - etherate in dimethyl sulfoxide. Peracid limonene monoxide, 61.0 g., was added to a solution of 0.4 ml. of boron trifluoride - etherate in 160 ml. of predistilled dimethyl sulfoxide. The reaction was stirred for 48 hours, with the reaction temperature being maintained at approximately 85°. Every 12 hours an additional 0.2 ml. of boron trifluoride - etherate was added. The reaction was cooled, poured into water and the organic layer separated. The aqueous phase was extracted several times with ether and the organic phases combined, washed with water, saturated sodium bicarbonate solution and water again. The ethereal phase was dried over anhydrous sodium sulfate, the solvent removed under vacuo and the product distilled to yield 30.6 g. (50%) of dihydrocarvone, b.p. 95-98.5°/10 mm., $n_D^{25.5}$ 1.4763, $\alpha_D^{25.5}$ +15.70° (neat). Redistillation gave a fraction, b.p. 69-70°/5 mm., $n_D^{23.5}$ 1.4695, $\alpha_D^{23.5}$ +18.00° (neat). The residue consisted of high boiling (polymeric?) alcohols. The dihydrocarvone was identified by GLPC and its infrared spectrum compared to an authentic sample.

Pyrolysis of peracid limonene monoxide. Several pyrolyses were carried out from 500-550°. Below 500° little pyrolysis occurred. A typical run is described. 25 g. of peracid limonene monoxide was dropped on the pyrolysis column (540°) at a rate of 1 drop/40 seconds. The pyrolysate consisted of 10 g. of low boiling products (among them, isoprene and water) which collected in the dry ice - acetone trap. The less volatile components were distilled to yield 11.0 g. of nearly pure dihydrocarvone, b.p. 80-87°/5 mm., n_D^{25} 1.4784, α_D^{25} +19.6° (neat) and 1.5 g. of mixed carveols. No limonene monoxide was present. At lower temperatures, pyrolysis was often incomplete.

Hydrogenation of peracid limonene monoxide with Raney nickel. 30.0 g. of limonene monoxide was placed in a glass liner with 100 ml. of absolute ethanol and approximately 4 g. of Raney nickel. The glass liner was placed in a high pressure hydrogenation apparatus under 2000 p.s.i. of hydrogen and heated to 100°. The apparatus was shaken for 36 hours, cooled and the liner removed. The Raney nickel was removed by filtration and the alcohols poured into 700 ml. of water. The aqueous phase was extracted five times with 75 ml. of ether. The ether phase was washed once with 75 ml. of water and dried over anhydrous sodium sulfate. The solvent was removed under *vacuo* and the alcohol mixture subjected to analysis by GLPC. The *iso*carvomenthol and the carvomenthol isomers, while readily distinquishable on the chromatograms, overlapped and their percentages are reported together. In both cases, *iso*carvomenthol was the predominant isomer. The results are tabulated in Table IV.

Hydrogenation of unsaturated alcohols. The procedure used for trans-isocarveol was the one employed. The unsaturated alcohols were also shaken in the presence of the catalyst (no hydrogen) for 12 hours and then analyzed by GLPC. Similarly, the saturated alcohols were individually shaken for 12 hours in the presence of the catalyst (hydrogen) and then analyzed by GLPC. No isomerization occurred in either case. The percentages of the resultant carvomenthols are tabulated in Table III.

Conversion of dl-cis-α-pinene oxide into pinol (4,7,7-trimethyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene). To 720 g. of water and 160 ml. ethanol, precooled to 5°, was added precooled dl-cis-α-pinene oxide (304 g.). The solution was vigorously stirred, maintaining the temperature between 5° and 10°. 720 g. of concentrated sulfuric acid was slowly added over an 8 hour period, the reaction temperature being maintained by means of an ice - salt bath. The reaction was then stirred for 24 hours between 5° and 10°. The temperature was allowed to rise to 27° and the reaction stirred for 12 hours more. The organic layer was separated and the aqueous phase diluted with ice water and extracted five times with 150 ml. of ether. The organic phases were combined and neutralized with a sodium carbonate solution. The organic phase was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the reaction distilled, yielding 249 g. of distillate, b.p. 60-110°/15 mm. Redistillation gave 203 g. (66.5%) of nearly pure pinol, b.p. 60-63°/10 mm., n_D^{25} 1.4718. Analysis by GLPC of the crude distillate indicated the presence of a very small amount of p-cymene and some high boiling materials (possibly carveols). (Note: in the reaction described, after the addition of about 10 g. of acid, the appearance of sobrerol was in evidence. Removal of a small aliquot gave crystals of dl-trans-sobrerol which melted at 131-132° after several recrystallizations from ethyl acetate). Product identification was effected by GLPC and the infrared spectrum compared to an authentic sample. The inverse addition was carried out, but gave campholenic aldehyde and pinocamphone as well as pinol and a considerable amount of resinous material.

Reaction of dl-cis-α-pinene oxide with glacial acetic acid - sodium acetate. 136.0 g. of distilled dl-cis-α-pinene oxide, b.p. 63-65°/10 mm., n_D^{25} 1.4670, was slowly dropped into a slurry of 123 g. of sodium acetate in 600 g. of glacial acetic acid over a 2½ hour period. The temperature rose to approximately 40° during this time. The reaction was stirred for 72 hours, during which time the temperature dropped to 27°. The reaction mixture was poured into 1000 ml. of water, the oil layer separated and the aqueous phase extracted three times with 100 ml. of ether.

The organic phases were neutralized with a saturated sodium bicarbonate solution and thrice washed with 75 ml. portions of water. The ethereal phases were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the product distilled over a 3-ft. spinning band column to give 53.0 g. of campholenic aldehyde (39%), b.p. 80°/10 mm., n_D^{25} 1.4630, which gave a yellow 2,4-dinitrophenylhydrazone, m.p. 110-111° and a semicarbazone, m.p. 138.5-140° (Lit. (78): n_D^{32} 1.4607, semicarbazone, m.p. 139.5-140.5°). Anal. Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.61%; H, 10.63%. The second component (26.0 g.), b.p. 76°/4 mm., n_D^{25} 1.4949, was identified as dl-trans-carveol (17.1%). This alcohol gave a 3,5-dinitrobenzoate, m.p. 118-118.5° (Lit. (195): n_D^{19} 1.4956, 3,5-dinitrobenzoate, m.p. 119°). Anal. Calculated for $C_{10}H_{16}O$: C, 78.89%; H, 10.59%. Found: C, 78.48%; H, 10.55%. It afforded GLPC evidence and an infrared spectrum identical to an authentic sample of d-trans-carveol. The third component (43.5 g.), b.p. 127-133°/4 mm., n_D^{25} 1.4813, was the monoacetate of sobrerol (8-acetoxy-6-hydroxy-1-p-menthene) (LXXXVI) (20.5%) which gave a 3,5-dinitrobenzoate, m.p. 130.5-132°. Hydrolysis of 0.4 g. with 4 ml. of 50% potassium hydroxide in 10 ml. of a 20% ethanol solution afforded dl-trans-sobrerol, m.p. 128-129° which was undepressed on admixture with an authentic sample. Anal.

Calculated for $C_{12}H_{20}O_3$: C, 67.89%; H, 9.50%. Found: C, 68.24%; H, 9.72%.

Pyrolysis of 8-acetoxy-6-hydroxy-1-p-menthene (LXXXVI). 6.00 g. of the sobrerol monoacetate, produced above, was dropped at a rate of 1 drop/25 seconds on the pyrolysis column (370°). The pyrolysis product was taken up in ether, neutralized with a saturated sodium bicarbonate solution, washed with water and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude product (4.24 g.), identified by GLPC as trans-carveol, was distilled on a modified Hickman still to give 3.78 g. of dl-trans-carveol, n_D^{25} 1.4959, 3,5-dinitrobenzoate m.p. 119°. This gave an infrared spectrum identical with an authentic sample. GLPC analysis indicated the crude pyrolysate to be better than 90% trans-carveol.

Hydroxylation of d-α-pinene. 68 g. of d-α-pinene, n_D^{25} 1.4635, α_D^{25} +16.65° (neat), was added in four aliquots to a solution of 79 g. of potassium permanganate in 2000 ml. of water, between 0° and 5°. The reaction was stirred for 8 hours at this temperature. The manganese dioxide formed was filtered and the aqueous phase reduced to 200 ml. by evaporation. The aqueous phase was subjected to a continuous chloroform extraction for 36 hours. The chloroform layer yielded an oil, tan in color, (5.70 g.) which was subjected to distillation over the modified Hickman still to yield a colorless oil, n_D^{25} 1.4882, $[\alpha]_D^{25}$ -14.2° (acetone) which was indicated to be cis-1-hydroxy-pinocamphone (188) by its infrared spectrum.

Lithium aluminum hydride reduction of cis-1-hydroxy-pinocamphone. 250 mg. of the hydroxy-ketone was dissolved in 200 ml. of dry ether (in a beaker) and approximately 200 mg. of lithium aluminum hydride added. The ether was filtered to remove any solid, a little water was added and the solution dried over anhydrous sodium sulfate. Evaporation of the ether yielded 210 mg. of alcohol, of which about 80 mg. was an oil. The solid gave a m.p. 140-143°. Infrared spectral evidence indicated both materials were alcoholic (no carbonyl bands). The solid was identified as impure α-pinene glycol (LXXVII) (188).

4-cyano-1-methyl-cyclohex-1-ene. 15.0 g. of isoprene, 16.0 g. of acrylonitrile, 40 ml. of toluene and 0.10 g. of hydroquinone were placed in a glass liner in a steel, high pressure, apparatus and heated to 135° under 2000 p.s.i. of an inert gas (hydrogen) for 18 hours. The apparatus was cooled and the products distilled. Distillation gave 21.1 g. 4-cyano-1-methyl-cyclohex-1-ene (82%), b.p. 85-93°/20 mm., n_D^{20} 1.4723.

1-methyl-4-formyl-cyclohex-1-ene (XCII). 73.0 g. of isoprene and 59.0 g. of predistilled acrolein were placed in the glass liner with 0.10 g. hydroquinone. This was placed in the high pressure bomb under 2000 p.s.i. (hydrogen) and heated to 125° for 7 hours. Distillation of this product afforded 110 g. of material, b.p. 45-47°/5 mm., (84.4%) identified as 1-methyl-4-formyl-cyclohex-1-ene. Redistillation gave b.p. 64°/10 mm., n_D^{23} 1.4711 (Lit. (189): b.p. 70-71°/14 mm.). The aldehyde gave a semicarbazone, m.p. 142.5-144° (Lit. (189): m.p. 144°), and a 2,4-dinitrophenylhydrazone, m.p. 165.5-166.5°.

Dinor-α-terpineol (LXXXVIII). To 22.8 g. of lithium aluminum hydride, slurried in 2000 ml. of anhydrous ether, was added 248 g. of 1-methyl-4-formyl-cyclohex-1-ene so as to keep the reaction refluxing gently. The reaction was refluxed for 2 hours after addition was complete. Water was then added dropwise until a white, flocculent precipitate formed. The precipitate was filtered by means of a buchner funnel. The ethereal solution was stripped of solvent under reduced pressure. The colorless oil was crudely distilled yielding 242 g. (96%) of alcohol. GLPC analysis showed two components in about a 91 : 9 ratio. Distillation afforded the main component, dinor-α-terpineol, b.p. 90°/10 mm., n_D^{25} 1.4810. This alcohol gave a 3,5-dinitrobenzoate, m.p. 111-112°. The second component, b.p. 89°/10 mm., n_D^{25} 1.4603, was isolated by GLPC. The infrared spectrum of the unknown compound had a carbonyl band at 5.71 microns. GLPC analysis showed that this may have been two products, although it was impossible to confirm this with the data available.

<u>1-methyl-4-acetyl-cyclohex-1-ene (XCIII)</u>. 30.0 g. of methyl vinyl ketone and 35.0 g. of isoprene with 0.10 g. hydroquinone were placed in a high pressure bomb under 2000 p.s.i. of hydrogen and heated to 175° for 18 hours. Distillation of the product obtained gave 59 g. of crude 1-methyl-4-acetyl-cyclohex-1-ene (93%), b.p. 63-68°/5 mm. Redistillation gave material, b.p. 79-80°/10 mm., $n_D^{22.5}$ 1.4703, which formed a semicarbazone, m.p. 148-148.5° (Lit. (189): m.p. 149°) and a 2,4-dinitrophenylhydrazone, m.p. 116°. Analysis of the crude distillate by GLPC indicated less than 3% of 1-methyl-5-acetyl-cyclohex-1-ene.

<u>Nor-α-terpineol (LXXXIX)</u>. 276.0 g. of 1-methyl-4-acetyl-cyclohex-1-ene was added to a slurry of 22.8 g. of lithium aluminum hydride in 2000 ml. of anhydrous ether at such a rate as to maintain gentle reflux. The reaction was refluxed for 1 hour after completion of ketone addition. The reaction was then cooled and water added dropwise until a white, flocculent precipitate formed. The precipitate was filtered off, the solvent removed under reduced pressure and the product distilled. Distillation gave 250 g. (89.5%) of <u>nor</u>-α-terpineol, b.p. 90-95°/9 mm., n_D^{25} 1.4788, which on redistillation gave a b.p. 93°/9 mm., n_D^{24} 1.4792. This alcohol gave a 3,5-dinitrobenzoate, m.p. 95-96°.

Anal. Calculated for $C_9H_{16}O$: C, 77.09%; H, 11.50%. Found: C, 77.26%; H, 11.57%.

Iso-α-terpineol (XC). A solution of 60.0 g. ethyl bromide in 70.0 g. dry ether was slowly added over a 2 hour period to 14.60 g. of predried magnesium turnings (under nitrogen) at a rate such that gentle reflux was maintained. After addition was complete, the reaction was stirred for 30 minutes while the temperature was lowered to 5° be means of an ice - salt bath. 1-methyl-4-formyl-cyclohex-1-ene (62.0 g.) in 75 ml. of ether was then added over an 80 minute period, maintaining the temperature between 5° and 15°. The reaction was stirred for 30 minutes after addition was complete. The reaction was then poured into an ice - 10% sulfuric acid solution. The oil layer that formed was separated and the aqueous phase was extracted four times with 125 ml. of ether. The extractions were washed with two 125 ml. portions of water and dried over anhydrous potassium carbonate. The solvent was removed under reduced pressure and the product distilled, b.p. 82-85°/3 mm., n_D^{25} 1.4808, to yield 63 g. (81.5%) of iso-α-terpineol (1-methyl-[4-α-hydroxy-propyl]-cyclohex-1-ene). The alcohol gave a 3,5-dinitrobenzoate, m.p. 111-113°. Anal. Calculated for $C_{10}H_{18}O$: C, 77.87%; H, 11.76%. Found: C, 77.80%; H, 11.74%.

Homo-α-terpineol (XCI). A solution of 127 g. of ethyl bromide and 200 ml. of dry ether was slowly added to 30.5 g. of predried magnesium turnings so as to maintain a gentle reflux, cooling when necessary with an ice bath. When addition was complete, the reaction was stirred for 35 minutes and then a mixture of 138 g. of 1-methyl-4-acetyl-cyclohex-1-ene in 300 ml. of dry ether was added at a rate such that gentle reflux was maintained. The reaction was heated at reflux for 1 hour after addition was completed. After the reaction was cooled, the reaction was worked up as for iso-α-terpineol. 163 g. of crude material was recovered before distillation. Distillation afforded 147 g. (87.5%) homo-α-terpineol, b.p. 89-92°/3 mm., n_D^{25} 1.4836. The alcohol failed to give a crystalline 3,5-dinitrobenzoate. Anal. Calculated for $C_{11}H_{20}O$: C, 78.51%; H, 11.98%. Found: C, 78.58%; H, 11.88%.

Bromination of dinor-α-terpineol (LXXXVIII) with pyridinium bromide perbromide. To 138 g. of dinor-α-terpineol in 665 ml. of glacial acetic acid was added, scoopwise, 386 g. of pyridinium bromide perbromide, prepared according to the method of Fieser (198), over a 40 minute period at room temperature. The solution took on a yellow-orange color. The reaction was then poured into 1500 ml. of water and the oil layer that formed was separated. The aqueous phase was extracted twice with 150 ml. of ether. The oil was then taken up in ether and repeatedly washed with water and a dilute sodium bicarbonate solution. The neutralized ether layer was dried over anhydrous sodium sulfate and stored in the refrigerator. After the solvent was removed, the infrared spectrum showed a strong carbonyl absorbtion at 5.73 microns. Reacting what was thus assumed to be a bromoacetate (24 g.) in pyridine (68 g.) at 35° for 24 hours gave the bromoacetate back unchanged. This material distilled with negligible decomposition at b.p. 150-153°/6 mm., n_D^{24} 1.5232. Similar results were obtained in refluxing methanol - piperidine. Analysis would indicate that this was impure bromoacetate. Anal. Calculated for $C_{10}H_{17}OBr$: C, 45.29%; H, 6.46%. Found: C, 39.11%; H, 5.44%. When 128 g. of this "bromoacetate" was added to a refluxing sodium ethoxide (32.2 g.) - absolute ethanol (475 ml.) solution, 39 g. of dinorpinol (4-methyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) (XCV) was obtained, b.p. 56-67°/ 10 mm., n_D^{25} 1.4772. The remainder was left in the pot as high boiling residue on distillation. Because of the undesirable acetylation during bromination, this bromination procedure was not used further.

Bromination procedure for terpineol analogs. The olefins were mixed in a 1 : 10 ratio, by volume, with carbon tetrachloride. The solution was then cooled to about 5° and a 1 : 1 bromine - carbon tetrachloride solution was added dropwise (1 mole of bromine for 1 mole of olefin).

The bromides were stored in solution, under refrigeration, until just prior to use. The carbon tetrachloride was stripped off under vacuo and the dibromides were used in their crude forms. The results were very clean in every case.

Reactions of dibromo-alcohols with basic reagents. The procedure for the reaction of the dibromo-alcohols with bases was as follows. The ratio of equivalents of base to the bromine equivalent was a 2 : 1 excess of base. The base was in a 0.50 molar concentration in the respective solvents. The dibromide was dropped into the base solution at the prescribed temperatures and stirred for a period of 8 hours. The reaction was cooled and poured into water, extracted with ether, washed with water, dried over anhydrous sodium sulfate, the solvent removed and the results analyzed by GLPC. While only the aromatic and pinol compounds were reported in the product ratio, this was not to imply that the reported ratios were actual yields. In the case of weak bases the allylic bromide was the primary product. Large scale runs were carried out only to isolate reaction products for identification purposes. When the dibromides were heated or reacted with acids, the aromatic product was observed. Authentic samples of the purified pinol analogs, isolated from large scale runs, and of the aromatics, obtained commercially, were used in the GLPC analyses as internal standards.

6-bromo-8-hydroxy-1-p-menthene was prepared as described previously (11) and used immediately after preparation. The results are tabulated in Table V. The results for dinor-α-terpineol dibromide are in Table VI and for nor-α-terpineol dibromide in Table VII.

Dinorpinol (4-methyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) (XCV). 17.25 g. of sodium was dissolved in 280 g. of pre-dried tertiary butyl alcohol. The temperature was raised to 65° and 64.5 g. of dinor-α-terpineol dibromide was slowly dropped in over a 3 hour period. The reaction was stirred for 2 hours after addition and then cooled. The reaction mixture was poured into 700 ml. of water and extracted seven times with 75 ml. of ether. The ethereal solution was washed four times with 100 ml. of water and then dried over anhydrous sodium sulfate. Distillation gave 17.8 g. (64.5%) dinorpinol, b.p. 55-56°/10 mm., n_D^{25} 1.4777. This was identical to the material previously obtained from the "bromoacetate". The dinorpinol formed a crystalline complex with ferricyanic acid, and a crude dibromide melted at 46-48°.

Norpinol (4,7-dimethyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) (XCVI). 335 g. of nor-α-terpineol dibromide was slowly added to solution of 237 g. of sodium methoxide in 600 ml. of absolute ethanol, refluxing gently. The reaction time was 8 hours. The reaction was worked up as for dinorpinol. Distillation gave 95 g. of crude norpinol, b.p. 50-115°/12 mm. Fractionation gave 65 g. of norpinol, b.p. 60-61.5°/12 mm., n_D^{25} 1.4708, corresponding to a 43% yield. The remaining materials were high boiling alcohols (via infrared). The GLPC analysis indicated that the two possible isomeric norpinols were present in about a 3 : 2 ratio. The mixed norpinols gave a crystalline complex with ferricyanic acid.

Isopinol (4-methyl-7-ethyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) (XCVII). 55.0 g. of iso-α-terpineol dibromide was dropped into a refluxing solution of 36 g. sodium ethoxide in 250 ml. of absolute ethanol and refluxed for 8 hours. The reaction was worked up as described for dinorpinol. Distillation afforded 13 g. (48%) of isopinol, b.p. 85-88°/14 mm., n_D^{25} 1.4690. A second fraction (7.5 g.) consisting of high boiling alcohol(s), b.p. 97-138°/14 mm., was obtained. Analysis of the isopinol fraction showed only a single peak on GLPC, but this does not rule out the possibility of the two possible isomers being present. The isopinol(s) formed a crystalline complex with ferricyanic acid.

Homopinol (4,7-dimethyl-7-ethyl-6-oxa-bicyclo-[3.2.1]-oct-3-ene) (XCVIII). 174 g. of homo-α-terpineol dibromide was dropped into a refluxing solution of 95 g. sodium methoxide in 730 ml. of absolute ethanol. The reaction was refluxed for 8 hours. The reaction was worked up as for dinorpinol. Distillation gave 40.5 g. of homopinol (46%), b.p. 77-96°/15 mm., and 44 g. of high boiling alcohols, b.p. 96-135°/10 mm. Redistillation of the first fraction gave homopinol, b.p. 70°/10 mm., n_D^{25} 1.4725. Homopinol formed a crystalline derivative with ferricyanic acid.

3-acetoxy-methyl-crotonate (enol acetate of methyl acetoacetate). 348 g. of methyl acetoacetate and 360 g. of isopropenyl acetate were mixed together and 3 ml. of concentrated sulfuric acid added dropwise with stirring. The reaction mixture was then refluxed, and the acetone formed was distilled off. The reaction became black in color. After 2½ hours, the reaction mixture was distilled from the pot under reduced pressure. 389 g. of colorless liquid was obtained which was then fractionated on a 3-ft. spinning band column. This gave 52 g. of methyl acetoacetate, b.p. 42-84°/10 mm. and 306 g. of 3-acetoxy-methyl-crotonate, b.p. 86°/10 mm., n_D^{25} 1.4428. This corresponds to a 78.5% yield based on the methyl acetoacetate reacted. The infrared spectrum and ultraviolet spectrum (λmax 210 mμ) were recorded. Anal. Calculated for $C_7H_{10}O_4$: C, 53.16%; H, 6.37%. Found: C, 53.60%; H, 6.59%.

3-acetoxy-ethyl-crotonate (enol acetate of ethyl acetoacetate). 396 g. of ethyl acetoacetate and 347 g. of isopropenyl acetate were mixed and 3 ml. of concentrated sulfuric acid added dropwise. The reaction was then carried out as for 3-acetoxy-methyl-crotonate. 590 g. of crude distillate gave 149 g. of ethyl acetoacetate and 404 g. of enol acetate on fractionation, corresponding to a 97% yield based on the ethyl acetoacetate reacted. The enol acetate, b.p. 83°/5 mm., n_D^{25} 1.4423 (Lit. (199): b.p. 89-90°/10 mm., n_D^{30} 1.4675) gave an ultraviolet λmax at 209 mμ. Anal. Calculated for $C_8H_{12}O_4$: C, 55.80%, H, 7.03%. Found: C, 56.12%; H, 7.16%.

Cis- and trans-2-acetoxy-2-penten-4-one (enol acetate of acetylacetone). 350 g. of isopropenyl acetate and 300 g. of 2,4-pentandione (acetylacetone) were mixed together and 3 ml. of concentrated sulfuric acid added dropwise. The reaction was carried out as for 3-acetoxy-methyl-crotonate. 416 g. of crude material was obtained which was fractionated to give acetylacetone and the enol acetate of 2,4-pentandione. GLPC analysis indicated the enol acetate to be a 67 : 33 ratio of two isomers. These isomers were separated by fractionation to give α-2-acetoxy-2-penten-4-one, b.p. 85-86°/10 mm., n_D^{25} 1.4500, ultraviolet λ max at 232.5 mμ and β-2-acetoxy-2-penten-4-one, b.p. 87°/10 mm., n_D^{25} 1.4493, ultraviolet λmax at 226 mμ. Anal. Calculated for $C_7H_{10}O_3$: C, 59.14%; H, 7.09%. Found: C, 59.27%; H, 7.25%.

Hydrogenation of 3-acetoxy-methyl-crotonate. 25 g.

of the enol acetate was placed in a glass liner with 200 ml. of ethyl acetate and 0.7 g. platinum oxide and shaken under 60 p.s.i. of hydrogen. The reaction absorbed 22 p.s.i. of hydrogen (0.29 mole). The catalyst was removed by filtration and the material distilled at atmospheric pressure. Three fractions were obtained: (1). ethyl acetate, (2). methyl-n-butyrate, b.p. 102°, and (3). acetic acid, b.p. 118°. The methyl-n-butyrate was identified by GLPC and its infrared spectra compared to an authentic sample.

Attempted diene synthesis of cyclopentadiene and 3-acetoxy-ethyl-crotonate (enol acetate of ethyl acetoacetate. 61.2 g. of the enol acetate was mixed with 19.8 g. of freshly distilled cyclopentadiene and 0.2 g. hydroquinone. The reaction mixture was placed in a high pressure bomb, in a glass liner, and heated to 190° for 20½ hours under 2000 p.s.i. of hydrogen. Upon removal from the bomb, 4 g. of polymer was filtered off and the liquid was distilled yielding cyclopentadiene and a high boiling fraction. The high boiling material was fractionated to give 35 g. of unreacted enol acetate and 6.3 g. of white crystalline material, b.p. 126°/7 mm., m.p. 99-100°. The solid melted at 108° after several recrystallizations from carbon tetrachloride. The solid was identified as dehydroacetic acid, giving no melting point depression on admixture with an authentic sample. The authentic sample was prepared by the method of Arndt (191).

Sodium salt of dehydroacetic acid. The preparation of the sodium salt was effected by the gradual addition of slightly more than one equivalent of a sodium hydroxide solution to one equivalent of dehydroacetic acid in a saturated water solution. Immediately upon addition of the base, salt formation occurred. A little ethanol was added and the salt was filtered, washed with ethanol, and recrystallized from a water - ethanol solution. For the ester syntheses, commercial sodium dehydroacetate, obtained from Aceto Chemical Co., was employed.

Silver salt of dehydroacetic acid. An aqueous solution of purified sodium dehydroacetate was added to a concentrated silver nitrate solution, in excess, with stirring. The silver salt was filtered and washed with ice water, filtered and dried. The salt turned dark on drying.

Dehydroacetic acid esters (enol ethers). The dry silver salt of dehydroacetic acid was refluxed for several hours in an excess of the alkyl iodide of the desired ester. The excess alkyl iodide was distilled off and the residue taken up in hot carbon tetrachloride from which the esters were crystallized. The methyl dehydroacetate melted at 91-92° (Lit. (200): m.p. 93-95°) after several recrystallizations. The ethyl ether (ester) melted at 90-91°

(Lit. (201): m.p. 93-94°). The ultraviolet spectra of the acid and its derivatives agree well with the literature (187) (see Table X). The infrared spectra in the carbonyl-olefin region are tabulated in Table XI. The nuclear magnetic resonance spectra are given in the Appendix. The solvent used for the NMR spectra was deuterated chloroform, with the exception of that of the sodium salt which was taken in deuterium oxide. The deuterium exchange experiments were carried out by placing the samples in a deuterium oxide - sodium deuteroxide solution and shaking for 10-15 minutes prior to taking the spectra. It was noted that in the case of ethyl dehydroacetate, a secondary reaction took place at the same time that exchange of the acetyl methyl was occurring. However, it was easy to differentiate the two compounds in the spectra.

Hydrogenation of ethyl dehydroacetate. 2.5 g. of ethyl dehydroacetate was hydrogenated at 60 p.s.i. on the Paar hydrogenation shaker using 0.5 g. of 5% palladium on charcoal as catalyst in 35 ml. of absolute ethanol. The catalyst was removed by filtration and the ultraviolet spectrum of the ethanol solution gave a λmax at 264.5 mμ. Removal of the solvent under reduced pressure afforded a dark oil which gave a strong, positive ferric chloride test in both water and alcohol. The infrared spectrum gave λmax 5.81(w-m), 6.04(s), 6.19(s), 8.00(s) microns in carbon tetrachloride solution. The first carbonyl absorbtion was shifted when the oil was run neat; λmax 5.75 microns and intense. The NMR spectrum was taken in both deuterated chloroform and deuterium oxide. A deuteration experiment was carried out. The NMR spectra are given in the Appendix. The absence of the ethyl group was obvious in the NMR spectra, indicating enol ether cleavage. The spectra are discussed in Chapter III.

CHAPTER V

SUMMARY

1. The stereospecific preparation of d-cis- and d-trans-limonene monoxide was carried out. The stereochemistry of the hydroxyacetates formed from the limonene monoxides and carvomenthene oxides was determined by pyrolysis of the respective hydroxyacetates. The pyrolysis of the hydroxyacetates readily distinguished the tertiary and secondary acetates formed from the epoxides. The Fürst-Plattner rule was found to be valid for substituted monocyclic cyclohexene epoxides. The stereochemistry of the pyrolysis products of the limonene hydroxyacetates indicated that the "cis"-1(7),8-p-menthadien-2-ol reported by Naves and Grampoloff (87) had the trans configuration. The lithium aluminum hydride and sodium powder reductions of the limonene monoxides were reinvestigated. The selective and total hydrogenations of the peracid limonene monoxides were effected. The acid hydration and isomerization products of the peracid limonene monoxides were identified as carvenone, d-dihydrocarvone, p-cymene, pinol, d-1,8-dihydroxy-neocarvomenthol and two optically inactive alcohols, tentatively assigned as dl-1,8-dihydroxy-isocarvomenthol

and dl-1,8-dihydroxy-neoisocarvomenthol.

2. A study of the hydrogenation products of the carveols, coupled with the known relationships of the carvomenthols, indicated that the configurations of iso- and neoiso-carvomenthol, assigned by Bose (1), should be reversed.

3. Pinol was prepared in 65% yield from α-pinene oxide. The products, and the stereochemistry thereof, obtained from the action of acetic acid - sodium acetate on α-pinene oxide were identified as campholenic aldehyde, trans-carveol and trans-8-acetoxy-6-hydroxy-1-p-menthene.

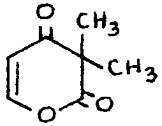
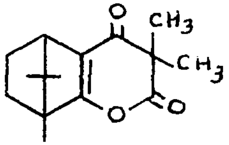
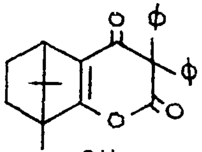
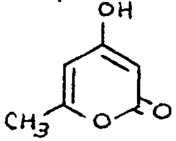
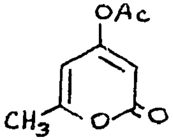
4. A series of α-terpineol analogs were synthesized; their dibromides were prepared and subjected to reaction with various bases. The internal ether - aromaticity competition was studied. The reinvestigation of the action of bases on 6-bromo-8-hydroxy-1-p-menthene refuted the mechanism of pinol formation previously postulated (11). A series of pinol analogs (substituted 6-oxa-bicyclo-[3.2.1]-oct-3-enes) were synthesized.

5. A study of the spectra of ethyl dehydroacetate, and its hydrogenation product, unambiguously determined the structure of the parent enol ether.

APPENDIX

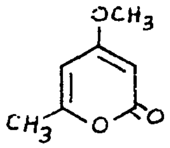
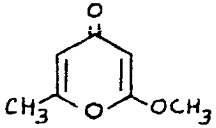
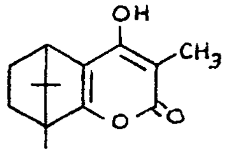
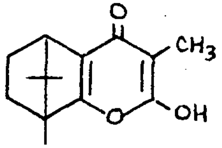
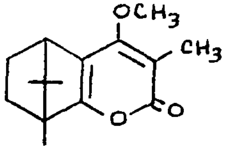
APPENDIX

SPECTRAL PROPERTIES OF 2,4-PYRANDIONE DERIVATIVES

Compound	Infrared λmax (microns)	Ultraviolet λmax (mμ)	Reference
	5.58, 5.91, 6.16 (CH_2Cl_2)	250 (7,400)	192
	5.58, 5.99, 6.15 (CH_2Cl_2)	282 (7,050)	192
	5.61, 5.98, 6.15 (CH_2Cl_2)	293 (6,700)	192
	5.83, 6.02, 6.15, 6.30, 6.51 (KBr)	283 (6,000)	192
	5.61, 5.75, 6.06, 6.35 (CH_2Cl_2)	294 (6,890)	192

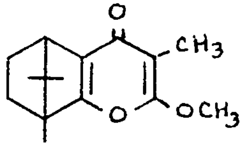
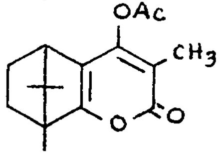
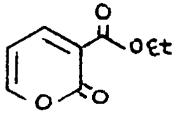
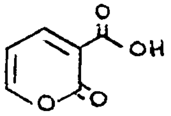
(continued)

APPENDIX (continued)

Compound	Infrared λmax (microns)	Ultraviolet λmax (mμ)	Reference
	5.84^a, 5.88, 6.09, 6.41 (CH_2Cl_2)	280 (6,300)	192
	5.98, 6.15, 6.28 (CH_2Cl_2)	240 (13,000)	192
	-	311 (10,300)	192
	6.03^a, 6.39 (KBr)	-	192
	5.93, 6.22, 6.55 (CH_2Cl_2)	320 (9,800)	192

(continued)

APPENDIX (continued)

Compound	Infrared λmax (microns)	Ultraviolet λmax (mμ)	Reference
	6.03, 6.19, 6.25, 6.33 (CH_2Cl_2)	256 (27,300)	192
	5.64, 5.86, 6.15, 6.38 (CH_2Cl_2)	324 (10,500)	192
	5.65, 5.85, 6.15, 6.45, 8.10 9.10 (Neat)	309 (7,050)	193
	5.71, 6.02, 6.46, 8.08, 9.98 (Nujol)	313 (14,800)	193

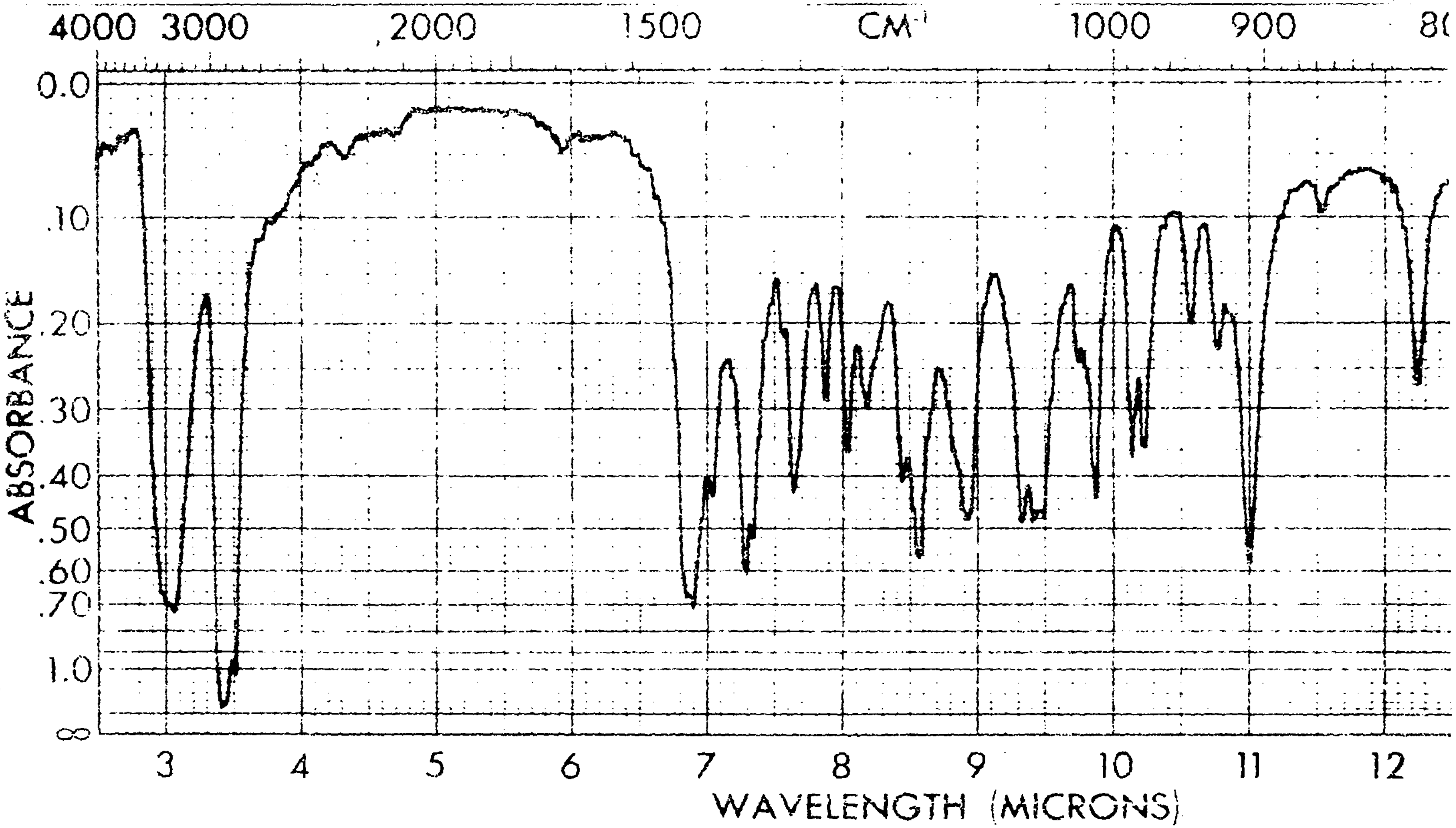
[a] Shoulder

APPENDIX

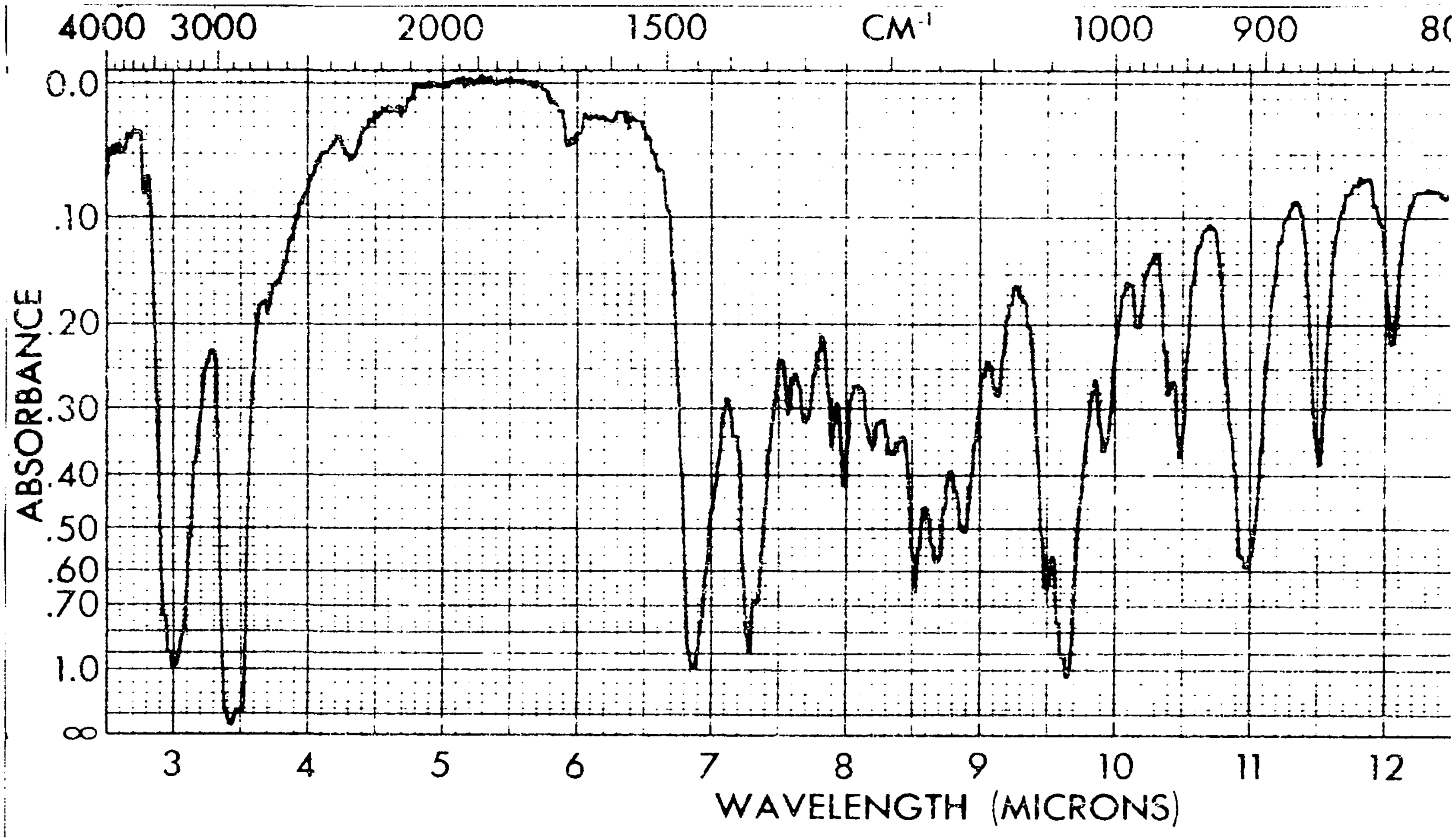
EXPERIMENTAL INFRARED SPECTRAL DATA

The following spectra were obtained in Nujol on a Perkin-Elmer, Model 137 spectrophotometer fitted with sodium chloride optics and cells.

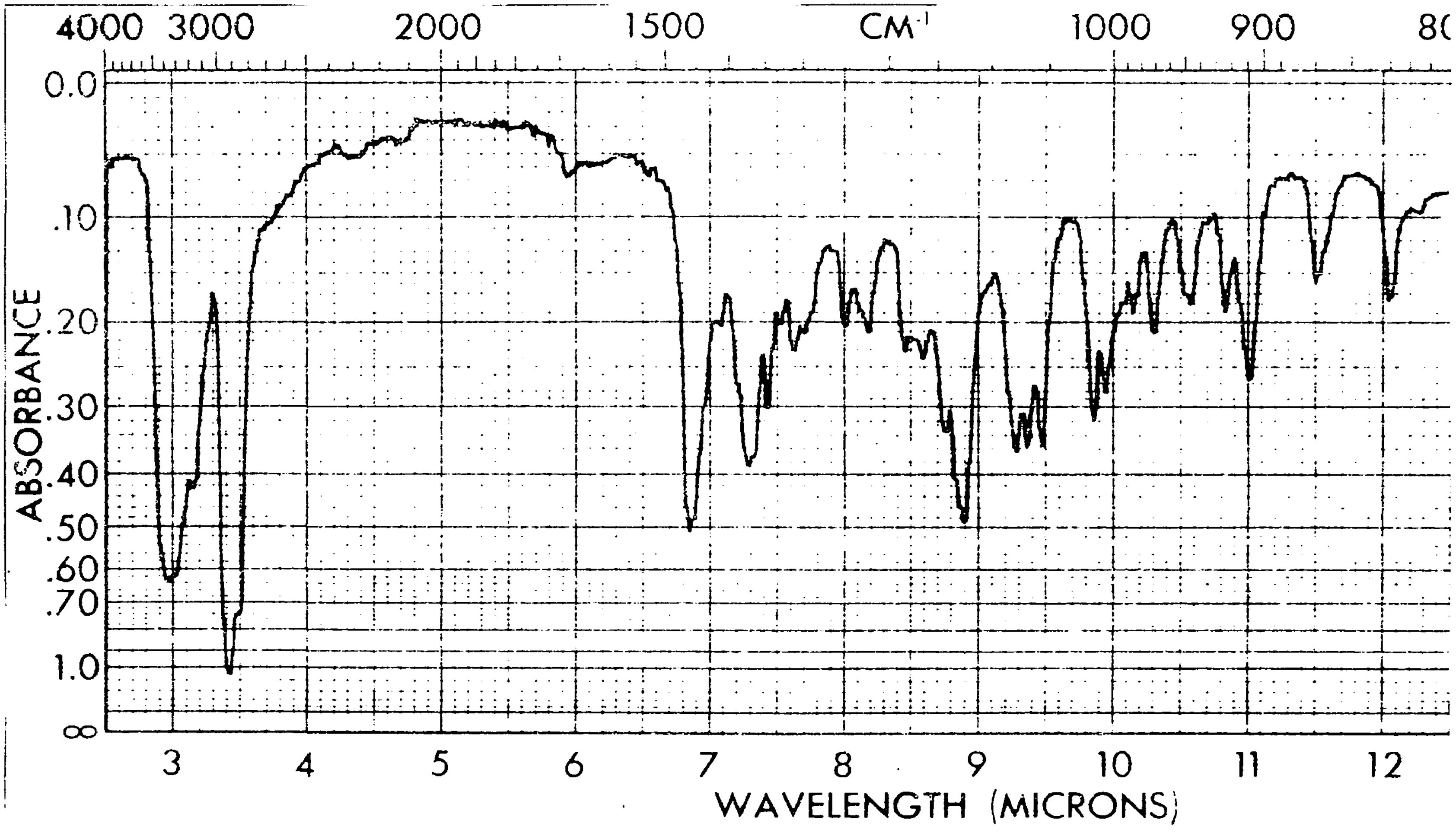
dl-1,8-DIHYDROXY-CARVOMENTHOL, M.P. 122° (IN NUJOL).



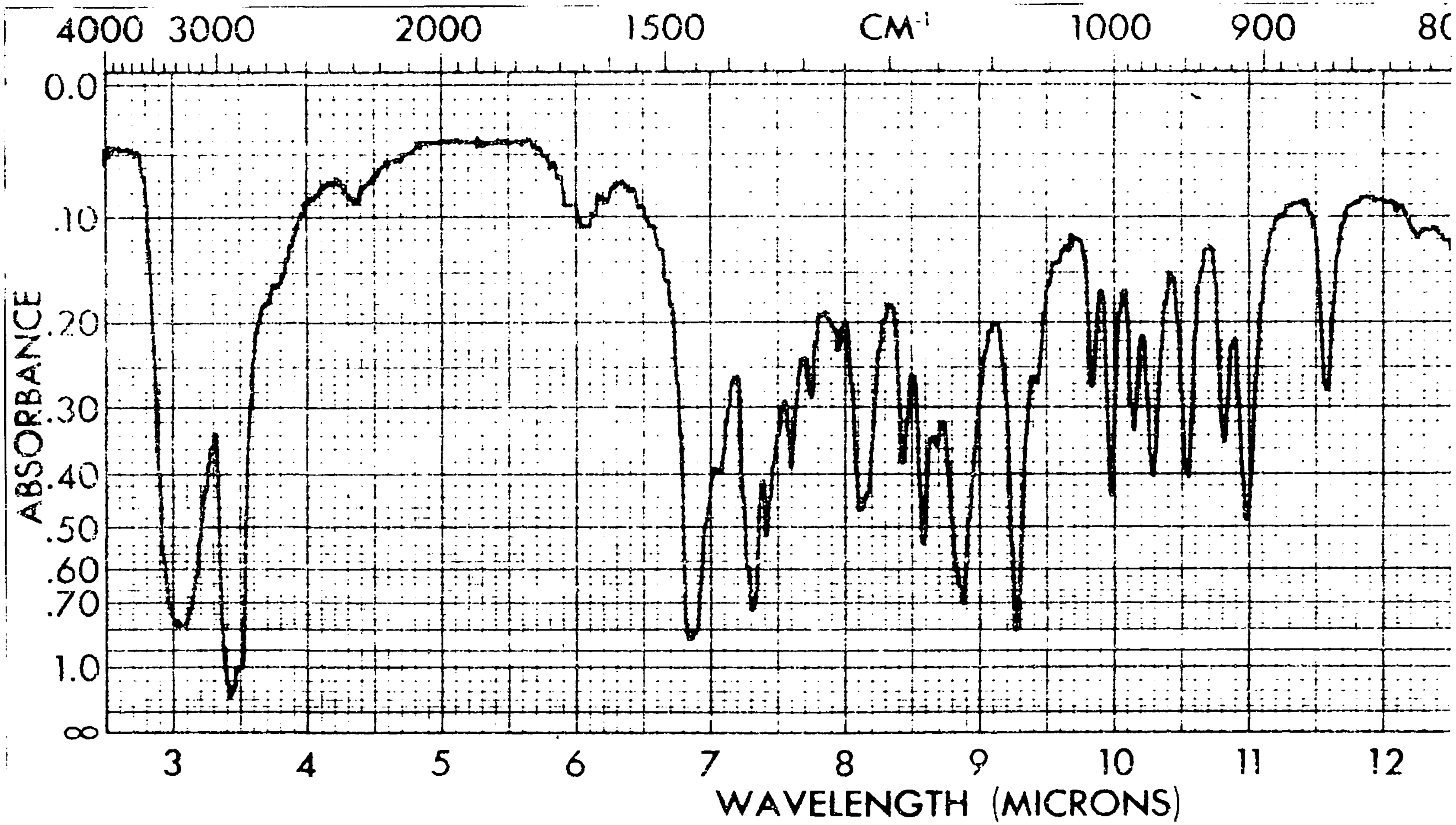
d-1,8-DIHYDROXY-NEOCARVOMENTHOL, M.P. 136° (IN NUJOL).



dl-1,8-DIHYDROXY-*ISO*CARVOMENTHOL(?), M.P. 155-156° (IN NUJOL).



dl-1,8-DIHYDROXY-NEOISOCARVOMENTHOL(?), M.P. 114.5-115.5° (IN NUJOL).

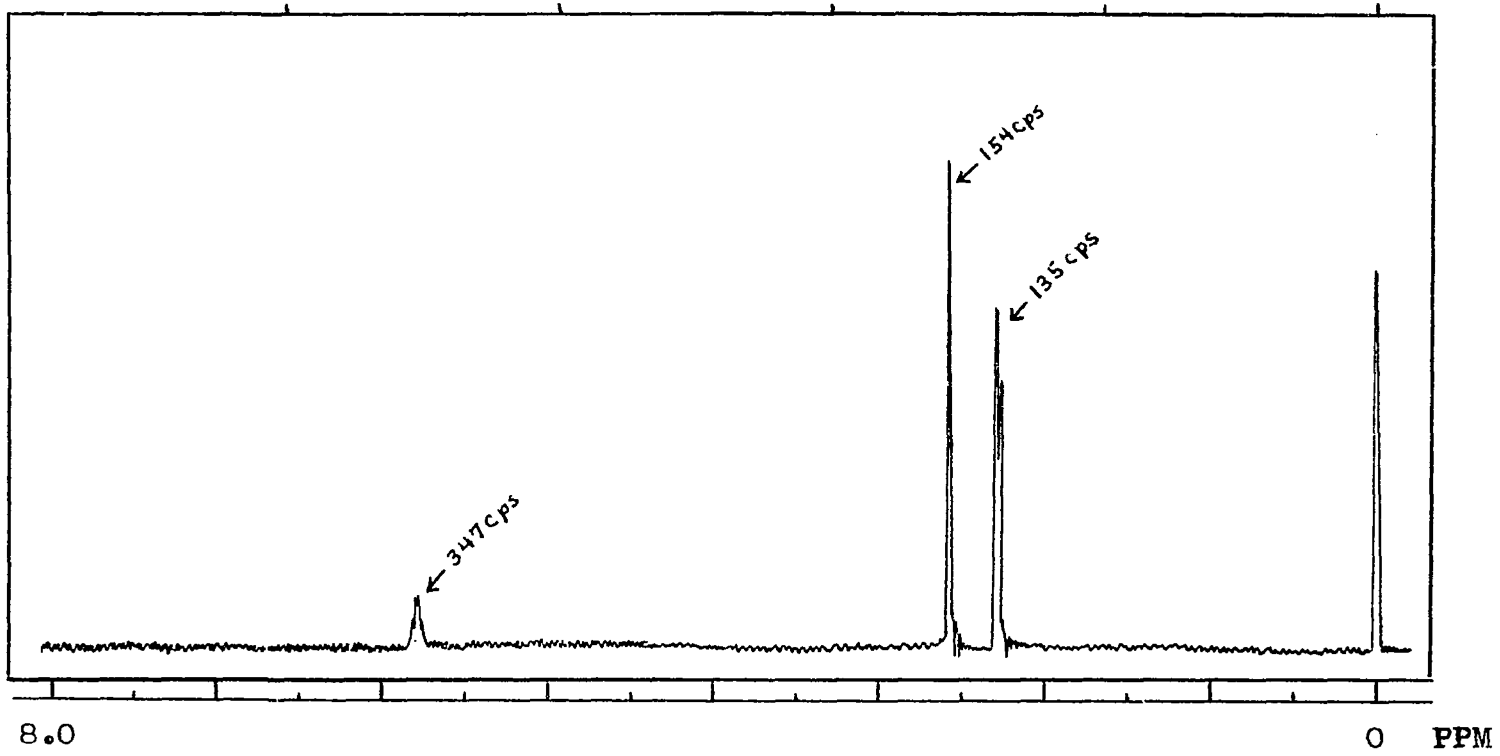


APPENDIX

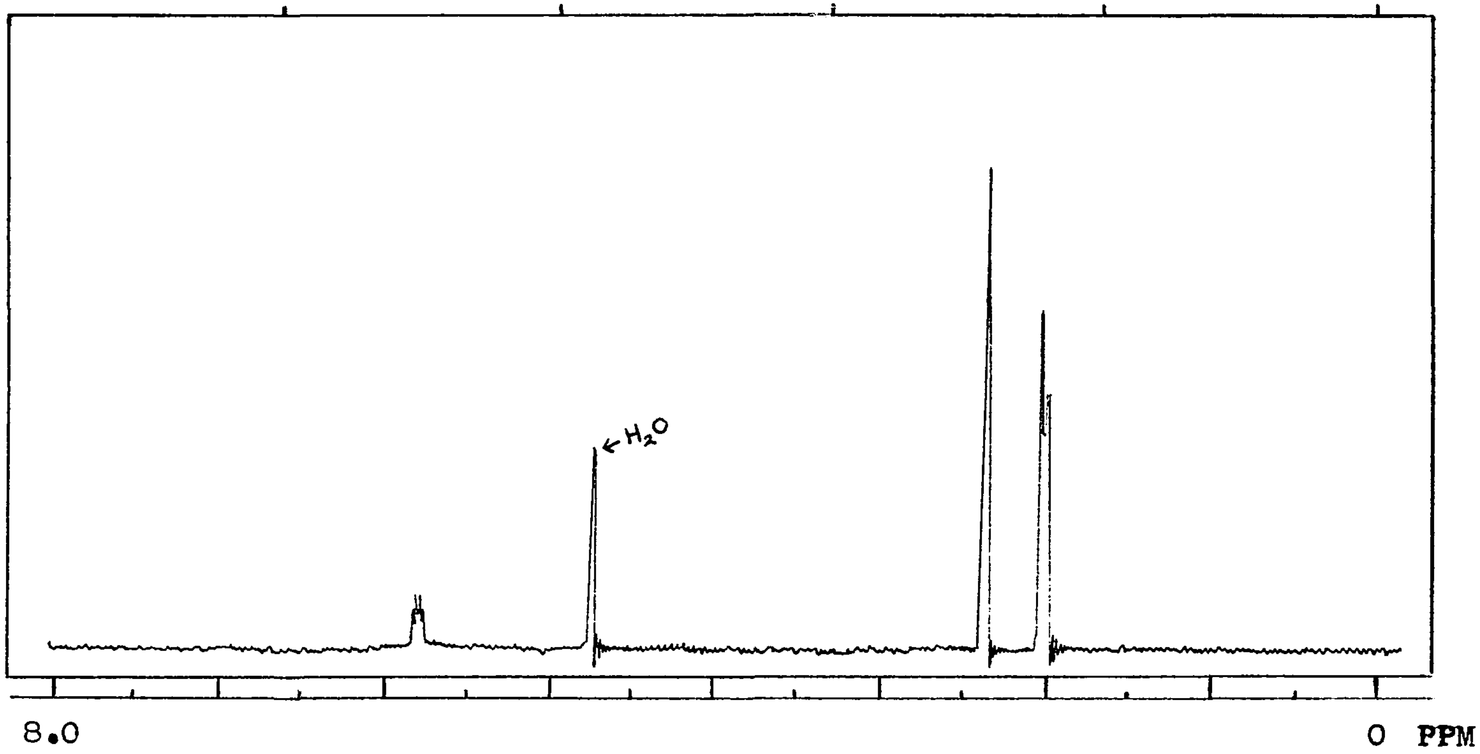
EXPERIMENTAL NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA

The following spectra were obtained on a Varian Model A-60 nuclear magnetic resonance spectrometer. Tetramethylsilane was used as an internal reference except for spectra run in deuterium oxide solvent.

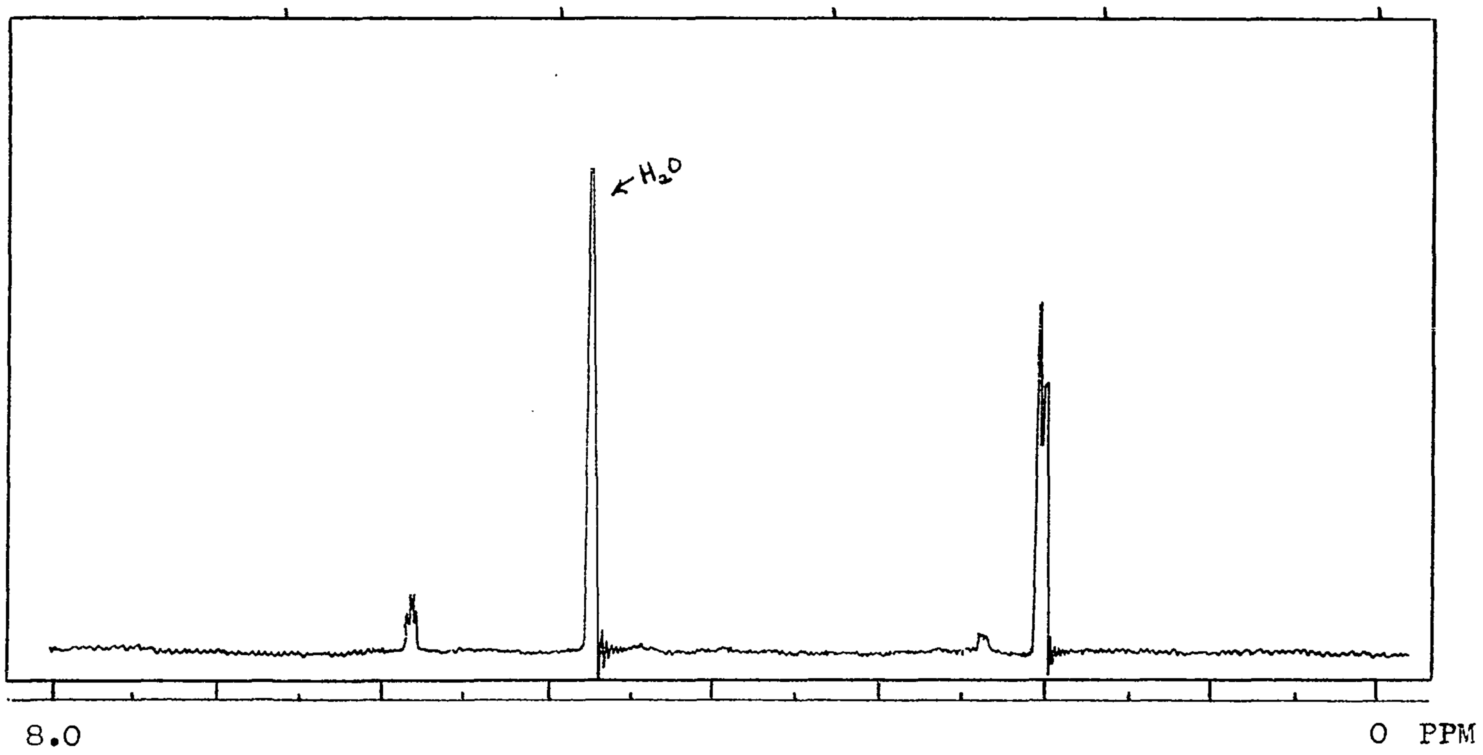
DEHYDROACETIC ACID (IN $CDCl_3$).



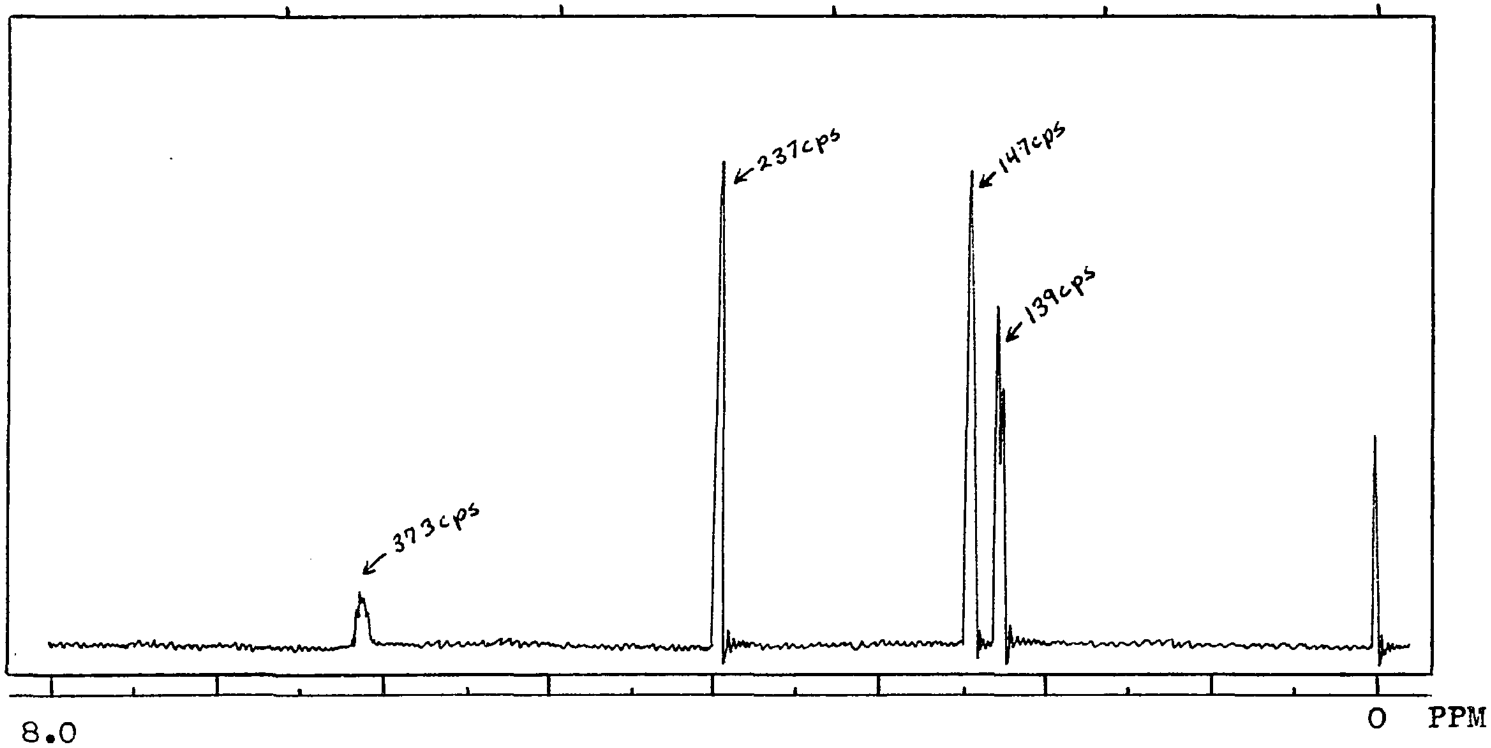
SODIUM DEHYDROACETATE (IN D_2O).

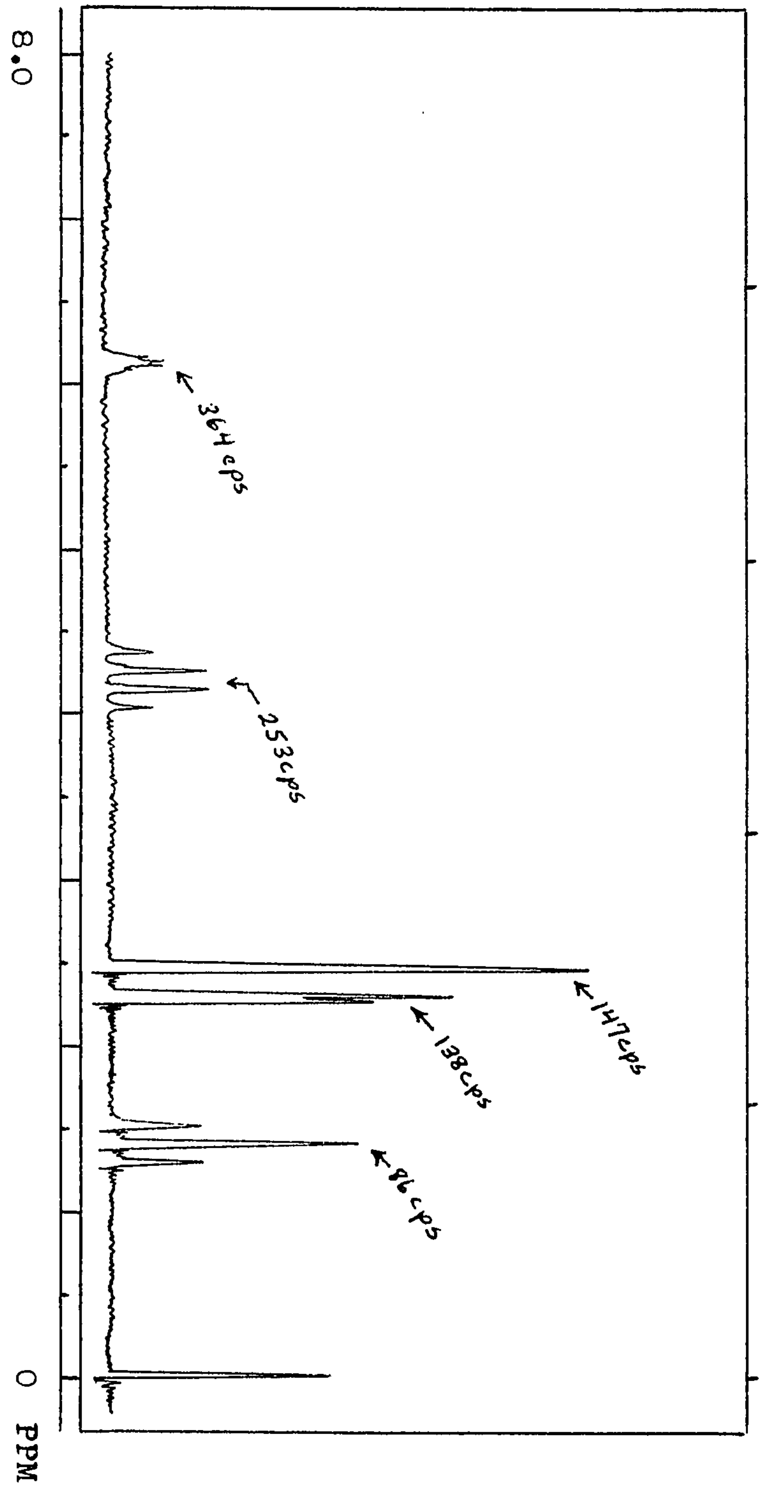


DEUTERATED SODIUM DEHYDROACETATE (IN D_2O).



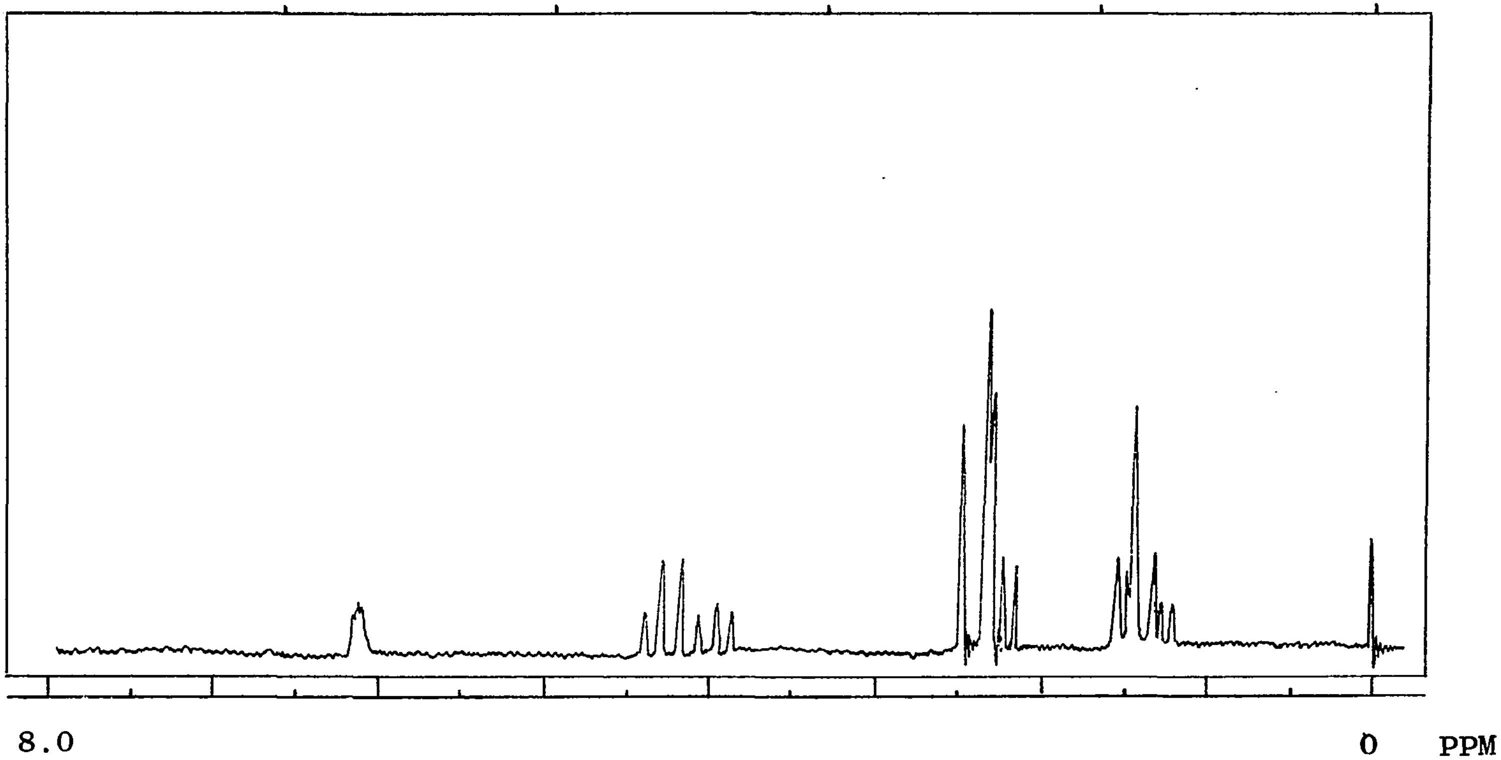
METHYL DEHYDROACETATE (IN $CDCl_3$).



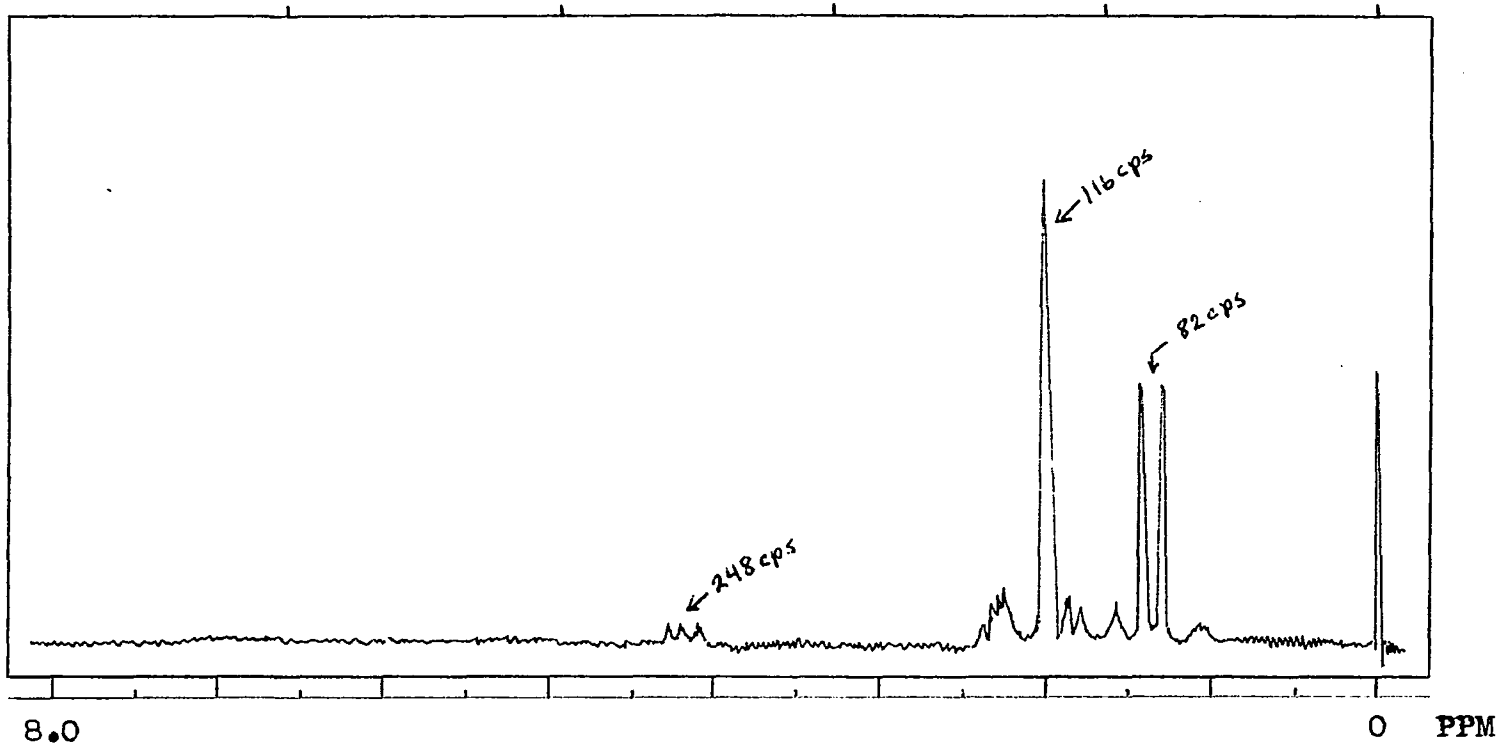


ETHYL DEHYDROACETATE (IN $CDCl_3$).

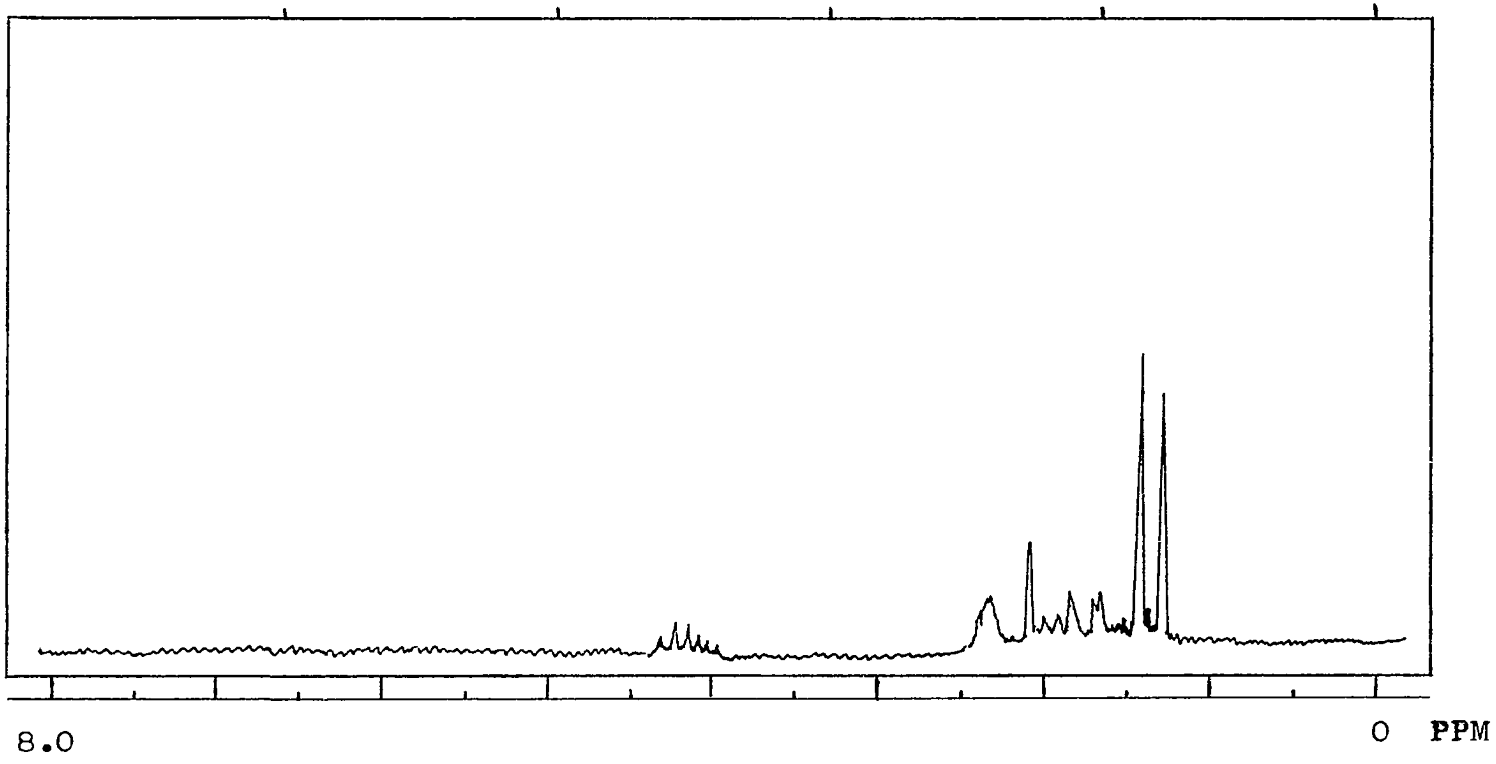
PARTIALLY DEUTERATED ETHYL DEHYDROACETATE (IN $CDCl_3$).



HYDROGENATION PRODUCT FROM ETHYL DEHYDROACETATE (IN CCl_4).



DEUTERATED HYDROGENATION PRODUCT FROM ETHYL DEHYDROACETATE (IN D_2O).



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BIOGRAPHICAL SKETCH

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